RANG & DALE’S
Pharmacology
Flash Cards Updated Edition

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HOW TO USE THESE CARDS:

The cards are in sets that accord with the chapters in Rang & Dales’ ‘Pharmacology’ and Dale & Haylett’s ‘Pharmacology Condensed’ and references to relevant pages in these books are given throughout.

The first card in a set has a diagram of the patho-physiological processes of the chapter topic (e.g. thrombosis, analgesia, malaria etc.) and at the top of the card the name of a drug (A) that modifies those processes. The back of the card has the essential details of drug A – actions, mechanism of action, pharmacokinetic aspects, adverse effects, the names of similar drugs and important aspects of clinical use.

In the second card, drug A is placed in context in the diagram and another drug (B) is listed, with its essential details on the back. Drugs are added cumulatively to the diagram in subsequent cards in the set.

The final card in a set will usually include all the drugs mentioned and either allow space for personal notes or provide some challenging questions on the uses of the drugs.

It is expected that students will use the cards for private revision and this is facilitated (on trains/ buses etc.) by the provision of a punched hole and ring which allows particular sets or batches to be separated and easily carried. The cards can also be used in Q/A group sessions.
Pharmacology is not a conceptually difficult subject like theoretical physics or higher mathematics. The only problem in studying pharmacology is that a great many facts and hard-to-remember drug names have to be mastered. To get to grips with the subject it is essential to appreciate how drugs work; and to do this it is necessary to understand the underlying pathophysiological processes on which they act. Once you’ve covered the detail from lectures and textbooks, there is then the problem of making sure the information stays securely and accessibly in your memory for when you need it later in your professional life. And to do this efficiently you need to know what the essential points about any drug are, so that with these you will be able, by association, to call up fuller details.

Our cards follow fairly closely the sequence of chapters in Rang & Dale (7th edition) and Dale and Haylett (2nd edition). On the front of each card there is a drug name and a diagram showing the relevant pathophysiological processes it affects (e.g. noradrenergic transmission, heart failure etc); the essential information about the drug appears on the back.

The crucial facts about each drug are thus shown in the context of its mechanism of action, so that the user can lodge them securely in his/her mind, as pointers to the more detailed material buried ‘deeper’.

The cards could also (whisper it) help with revising for exams.

ACKNOWLEDGEMENTS

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</tr>
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<td>very low density lipoprotein</td>
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Pilocarpine

Cholinergic pharmacology

Simple figure of cholinergic transmission with potential sites of drug action

AcetylCoA

CoA

Exocytosis choline + acetate

Choline + acetate

ACh

ACh

ACh

Nicotinic receptors in:
neuromuscular junction
autonomic ganglia
adrenal medulla
CNS neurones

Acetylcholinesterase

Muscarinic receptors in:
smooth muscle
cardiac muscle
glands
CNS neurones

Acts on, causes,
gives rise to
Movement
**Actions**  Parasympathomimetic actions: contracts smooth muscle (e.g. gut, bladder, pupil); decreases rate and force of heart beat; glandular secretion (e.g. salivary, sweat, gastric acid); inhibits neurotransmitter release.

**MOA**  Action in glaucoma is due to interaction with M₃ receptors which couple to G_q to increase cellular IP₃ and DAG concentrations. Constriction of pupil aids drainage of aqueous humour and lowers intraocular pressure.

**Abs/Distrb/Elim**  For glaucoma pilocarpine is given as eye drops and actions last for a day. A slow delivery system placed under the eyelid acts for several days.

**Clinical use**  Glaucoma (narrow and wide angle). Bethanechol to stimulate bladder emptying or to improve gut motility.

**Adverse effects**  Blurred vision (contraction of ciliary muscle). Otherwise few unwanted effects because of very limited systemic absorption of topically applied drug. Bethanechol may produce bronchoconstriction.
Cholinergic pharmacology

Atropine

1. Pilocarpine

\[ \text{Exocytosis} \text{ choline} + \text{acetate} \]

\[ \text{Choline carrier} \]

\[ \text{AcetylCoA} \]

\[ \text{Acetylcholinesterase} \rightarrow \text{choline} + \text{acetate} \]

\[ \text{Nicotinic receptors in:} \]

- neuromuscular junction
- autonomic ganglia
- adrenal medulla
- CNS neurones

\[ \text{Muscarinic receptors in:} \]

- smooth muscle
- cardiac muscle
- glands
- CNS neurones

\[ \text{Acts on, causes, gives rise to} \]

\[ \text{Movement} \]

Pilocarpine
Muscarinic receptor antagonist (Similar drugs: dicycloverine, oxybutinin, tropicamide)

**Atropine**

*Actions* Inhibits secretions (salivary, bronchial, sweat, gastric acid, etc.). Tachycardia. Relaxes smooth muscle (causing inhibition of peristalsis, pupillary dilation, paralysis of accommodation, etc.). Antiemetic (CNS effect).

*MOA* Competitive reversible antagonism at all muscarinic receptors.

*Abs/Distrb/Elim* Given orally. Half-life 3h.


*Adverse effects* Constipation, hyperthermia (reduced sweating), dry mouth, urinary retention, blurred vision, raised intraocular pressure, CNS excitement (delerium, hallucinations).

R&D 7e Ch 13, pp 159-160; D&H 2e Ch 10, pp 28-31
Scopolamine (hyoscine)

Cholinergic pharmacology

Simple figure of cholinergic transmission with potential sites of drug action

- **Acetylcholine (ACh)**
  - Synthesized from choline and acetate
  - Acts on nicotinic and muscarinic receptors
  - Cleared by acetylcholinesterase

**Nicotinic receptors**
- Neuromuscular junction
- Autonomic ganglia
- Adrenal medulla
- CNS neurones

**Muscarinic receptors**
- Smooth muscle
- Cardiac muscle
- Glands
- CNS neurones

**Drugs and their effects**
- **Pilocarpine**: Stimulates ACh release
- **Atropine**: Blocks ACh receptors
**Scopolamine**

**Actions**  Inhibits secretions (salivary, bronchial, sweat, gastric acid etc.). Tachycardia. Relaxes smooth muscle (causing inhibition of peristalsis, pupillary dilation, paralysis of accommodation etc.). CNS actions: antiemetic, amnesic.

**MOA**  Competitive reversible antagonism at all muscarinic receptors.

**Abs/Distrb/Elim**  Oral admin. T_{0.5} 4h. Also administered as transdermal patch for effects lasting 2–3 days.

**Clinical use**  Main use is in motion sickness. Adjunct for anaesthesia (amnesia, inhibition of secretions and of bronchoconstriction, reduction of post-operative vomiting). Urinary incontinence.

**Adverse effects**  Constipation, dry mouth, urinary retention, blurred vision, raised intraocular pressure, drowsiness.
Succinylcholine (suxamethonium)

Cholinergic pharmacology

Simple figure of cholinergic transmission with potential sites of drug action

- Acetylcholine (ACh)
- CoA
- Acetyl-CoA
- Choline carrier

Nicotinic receptors in:
- neuromuscular junction
- autonomic ganglia
- adrenal medulla
- CNS neurones

Muscarinic receptors in:
- smooth muscle
- cardiac muscle
- glands
- CNS neurones

Acetylcholinesterase

Exocytosis

Acts on, causes, gives rise to

Movement

Pilocarpine

Atropine, scopolamine
**Actions**  Short-lasting paralysis of skeletal muscle.

**MOA**  Action on nicotinic receptors produces a maintained depolarization of the muscle membrane. This inactivates the Na\(^+\) channels, which propagate the action potential throughout the muscle. Action potentials fail to spread along the muscle fibres preventing muscle contraction in response to motor nerve activity.

**Abs/Distrb/Elim**  Given i.v. Hydrolysed by plasma cholinesterase within a few minutes. (A small percentage of people have an enzyme with much lower activity and action is prolonged.)

**Clinical use**  Short-lasting paralysis to aid tracheal intubation and for short operative procedures. Action is not reversed by anticholinesterases.

**Adverse effects**  Hyperkalaemia (with possible cardiac arrhythmia). Hypotension. Bradycardia. Muscle pain (resulting from spasm during the initial depolarisation). Raised intraocular pressure. Malignant hyperthermia (rarely, when used with halothane).
Cholinergic pharmacology

Pancuronium

1.05

Simple figure of cholinergic transmission with potential sites of drug action

- **AcetylCoA**
- **CoA**
- **Exocytosis** choline + acetate
- **ACh**
- **ACh**
- **ACh**
- **Nicotinic receptors in:**
  - neuromuscular junction
  - autonomic ganglia
  - adrenal medulla
  - CNS neurones
- **Muscarinic receptors in:**
  - smooth muscle
  - cardiac muscle
  - glands
  - CNS neurones

- **Succinylcholine**
- **Pilocarpine**
- **Atropine, scopolamine**

- **Acts on, causes, gives rise to** Movement

- **Acetylcholinesterase**

- **Choline carrier**

- **CAT**

- **Movement**
**Actions**  Paralysis of skeletal muscle.

**MOA**  Reversible competitive antagonism at muscle-type nicotinic receptors. Inhibits binding of ACh to the receptors at the muscle end-plate. End-plate potential fails to reach threshold for initiation and propagation of the action potential along the muscle fibre. Action reversed by anticholinesterases (e.g. neostigmine 1.07).

**Abs/Distrb/Elim**  Given i.v. Half-life 2–3h. Substantial renal excretion (duration increased in renal failure).

**Clinical use**  In general anaesthesia – aids tracheal intubation, provides muscle relaxation for general surgery and aids mechanical ventilation.

**Adverse effects**  Tachycardia (muscarinic antagonist action).

**Special points**  Tubocurarine is the archetypal non-depolarizing neuromuscular blocker, but it has more side effects, such as bronchoconstriction due to histamine release, and is now rarely used.
Simple figure of cholinergic transmission with potential sites of drug action

- **Nicotinic receptors in:**
  - neuromuscular junction
  - autonomic ganglia
  - adrenal medulla
  - CNS neurones

- **Muscarinic receptors in:**
  - smooth muscle
  - cardiac muscle
  - glands
  - CNS neurones

- **Choline carrier**
- **Exocytosis**
- **AcetylCoA**
- **Acetylcholinesterase**
- **CoA**
- **ACh**

- **Arrows:**
  - Black: Acts on, causes, gives rise to
  - Red dashed: Movement

- **Drugs:**
  - **Succinylcholine**
  - **Pancuronium**
  - **Atropine, scopolamine**
  - **Pilocarpine**
**Actions**  Paralysis of skeletal muscle.

**MOA**  Reversible competitive antagonism at muscle-type nicotinic receptors. Inhibits binding of ACh to the receptors at the muscle end-plate. End-plate potential fails to reach threshold for initiation and propagation of the action potential along the muscle fibre. Action reversed by anticholinesterases (e.g. neostigmine 1.07).

**Abs/Distrb/Elim**  Given i.v. Half-life 30min. Eliminated mainly by a spontaneous chemical reaction (Hofmann elimination) in the plasma which makes duration of action relatively independent of renal function.

**Clinical use**  In general anaesthesia – aids tracheal intubation, provides muscle relaxation for general surgery and aids mechanical ventilation. Cisatracurium is one of the 10 isomers of atracurium and is replacing it in clinical use.

**Adverse effects**  Minor effects attributed to histamine release.
**Neostigmine**

Cholinergic pharmacology

Simple figure of cholinergic transmission with potential sites of drug action

- Acetylcholine (ACh) is released during exocytosis.
- ACh acts on nicotinic and muscarinic receptors.
- Nicotinic receptors are found in the neuromuscular junction, autonomic ganglia, adrenal medulla, and CNS neurones.
- Muscarinic receptors are found in smooth muscle, cardiac muscle, glands, and CNS neurones.

**Drugs and Their Actions:**

- **Succinylcholine**: Acts on, causes movement.
- **Pancuronium, atracurium**: Acts on, causes paralysis.
- **Neostigmine**: Acts on, causes, gives rise to parasympathomimetic effects.
- **Acetylcholinesterase (CAT)**: Breaks down ACh.
- **Atropine, scopolamine**: Acts on, causes antimuscarinic effects.
**Actions** Parasympathomimetic: increased peristalsis; increased secretions; bradycardia; bronchoconstriction; decreased intraocular pressure. At the neuromuscular junction – fasciculation and increased twitch tension. CNS – agitation and dreaming.

**MOA** Reversible inhibition of acetylcholinesterase reduces breakdown of ACh at cholinergic nerve-endings, so potentiating transmitter action. Binds to both esteratic and anionic sites in the enzyme. The esterase is carbamylated.

**Abs/Distrb/Elim** Given i.v. (to reverse neuromuscular block), by mouth (for myasthenia gravis). Mostly ionised, so low oral bioavailability and poor penetration of the blood–brain-barrier. Half-life 1h.


**Adverse effects** May exacerbate asthma. Unwanted parasympathomimetic actions can be reduced by atropine (1.02).
Cholinergic pharmacology

1.08 Edrophonium

Simple figure of cholinergic transmission with potential sites of drug action

- Acts on, causes, gives rise to
- Movement

Choline carrier

ACh

AcetylCoA

Exocytosis

Nicotinic receptors in:
- neuromuscular junction
- autonomic ganglia
- adrenal medulla
- CNS neurones

Muscarinic receptors in:
- smooth muscle
- cardiac muscle
- glands
- CNS neurones

Acetylcholinesterase

choline + acetate

Succinylcholine +

Pancuronium, atracurium -

Neostigmine -

Pilocarpine +

Atropine, scopolamine -
**Anticholinesterase (Similar drugs: neostigmine, physostigmine)**

**Edrophonium**

**Actions**  
At the neuromuscular junction – fasciculation and increased twitch tension. Parasympathomimetic – increased peristalsis, increased secretions, bradycardia, bronchoconstriction.

**MOA**  
Reversible inhibition of acetylcholinesterase reduces the breakdown of ACh at cholinergic nerve-endings, so potentiating neurotransmission. Edrophonium binds only to the anionic site in the esterase. The binding is mainly electrostatic and reverses readily.

**Abs/Distrb/Elim**  
Given i.v. or i.m. Short duration of action (10min).

**Clinical use**  
Diagnosis of myasthenia gravis. To confirm that a proper dose of neostigmine or pyridostigmine is being used in the treatment of myasthenia gravis. Action too short for therapeutic use.

**Adverse effects**  
May exacerbate asthma. Unwanted parasympathomimetic actions can be reduced by atropine (1.02).

---

*R&D 7e Ch 13, pp 168-169; D&H 2e Ch 10, pp 28-31*
Simple figure of cholinergic transmission with potential sites of drug action

- **Cholinergic pharmacology**

**Echothiophate**

- **Actions**:
  - Atropine, scopolamine
  - Pancuronium, atracurium
  - Succinylcholine
  - Pilocarpine
  - Neostigmine, edrophonium
  - Atropine, scopolamine

- **Sites of Action**:
  - **Nicotinic receptors**:
    - Neuromuscular junction
    - Autonomic ganglia
    - Adrenal medulla
    - CNS neurones
  - **Muscarinic receptors**:
    - Smooth muscle
    - Cardiac muscle
    - Glands
    - CNS neurones

- **Chemical Processes**:
  - **Exocytosis**: Choline + Acetate → AcetylCoA
  - **Acetylcholinesterase**: ACh → Choline + Acetate

- **Other**:
  - CoA
  - AcetylCoA
  - CAT

---

**Legend**:
- → Acts on, causes, gives rise to
- ← Movement

---

**Note**:
- The diagram illustrates the simplified process of cholinergic transmission and the potential sites of drug action.
**Actions**  Parasympathomimetic – increased peristalsis, increased secretions, bradycardia, bronchoconstriction, decreased intraocular pressure. At the neuromuscular junction – fasciculation and increased twitch tension. With nerve gases (e.g. sarin) persistent potentiation of ACh action leads to paralysis and death.

**MOA**  Irreversible inhibition of acetylcholinesterase potentiates actions of released ACh at cholinergic nerve-endings. Binds to enzyme’s esteratic site causing irreversible phosphorylation. (Pralidoxime, a cholinesterase reactivator, can reverse the phosphorylation.)

**Abs/Distrb/Elim**  Most are readily absorbed through the skin, gut and lungs. (Protective clothing needed to avoid absorption of insecticides and nerve gases.) Long-acting.

**Clinical use**  Glaucoma.

**Adverse effects**  May exacerbate asthma. Unwanted parasympathomimetic actions can be reduced by atropine (1.02).
**Summary**

1. **Cholinergic pharmacology**

   - **Atropine**, **scopolamine**
   - **Pancuronium**, **atracurium**

   **AcetylCoA**

   - **Choline**
   - **Acetylcholine (ACh)**
   - **Carrier**

   **Nicotinic receptors in:**
   - neuromuscular junction
   - autonomic ganglia
   - adrenal medulla
   - CNS neurones

   **Muscarinic receptors in:**
   - smooth muscle
   - cardiac muscle
   - glands
   - CNS neurones

   **Simple figure of cholinergic transmission with potential sites of drug action**

   - **Exocytosis: choline + acetate**
   - **Acetylcholinesterase**
   - acts on, causes, gives rise to
   - **Movement**

   - **Succinylcholine**
   - **Pancuronium**, **atracurium**
   - **Neostigmine**, **edrophonium**, **echothiophate**
   - **Pilocarpine**
   - **Atropine**, **scopolamine**
The figure gives a simple outline of noradrenergic transmission

- Tyrosine is converted to Dopamine by Dopa decarboxylase.
- Dopamine is taken up by the Noradrenergic varicosity.
- Dopamine acts on Smooth muscle cell via β2 receptors, causing relaxation.
- Dopamine acts on Cardiac muscle cell via β1 receptors, increasing rate and force.
- NA (noradrenaline) is released from the Noradrenergic varicosity.
- NA acts on Smooth muscle cell via α1 receptors, causing contraction.
- NA acts on Cardiac muscle cell via β1 receptors, increasing rate and force.
- Uptake 1 removes NA from the synaptic cleft.
**Actions**  Bronchodilatation. (Minimal action on heart: ↑rate and force). Relaxes uterine smooth muscle.

**MOA**  ↓calcium-mediated contraction in bronchioles. ↑cAMP which activates protein kinase A (PKA). PKA inhibits myosin light chain kinase (MLCK) – the mediator of contraction.

**Abs/Distrib/Elim**  By inhalation for asthma: Salbutamol: short-acting (3–5h), can be given i.v. Salmeterol: long-acting (8–12h). Ritodrine: by infusion for premature labour. All mainly excreted unchanged.

**Clinical use**  Asthma (main use). Salbutamol and terbutaline for the acute attack; salmeterol for nocturnal asthma, exercise-induced asthma and for long-term therapy. Chronic obstructive pulmonary disease (COPD): salbutamol, terbutaline or salmeterol (with ipratropium; card 12.05).

**Adverse effects**  Tremors, tachycardia, sometimes dysrhythmias, nervousness, some peripheral dilatation.

**Special points**  Hypertensive crisis if used with MAO inhibitor. MAOIs also potentiate CNS stimulant actions.
The figure gives a simple outline of noradrenergic transmission.
**Actions**
Reduces BP in hypertensive patients by ↓causing: cardiac output ↓renin release ↓CNS-mediated sympathetic activity
In angina slows heart and reduces metabolic demand.

**MOA**
Block of the action of endogenous and exogenous agonists on β₁-receptors.

**Abs/Distrb/Elim**
Absorbed orally; plasma t½ 4h; metabolised by liver.

**Clinical use**

**Adverse effects**
Dangerous: bronchconstriction in asthma, in emphysema; potential heart block or heart failure in patients with coronary disease; decreased sympathetic warning to hypoglycemia in diabetic patients. Inconvenient: cold extremities, fatigue.

**Special points**
Atenolol is water-soluble, can enter the CNS and may cause nightmares. Oxprenolol has some intrinsic sympathomimetic activity and thus causes less bradycardia and less coldness of hands and feet.

---

**References**
R&D 7e Ch 14, p 187-188; D&H 2e Ch 11, pp 32-35
The figure gives a simple outline of noradrenergic transmission

Tyrosine → DOPA → Dopa decarboxylase → Dopamine → NA

Noradrenergic varicosity

Dopamine

NA

α₂

Uptake 1

β₁

RATE

FORCE

Cardiac muscle cell

RELAXATION

Smooth muscle cell

α₁

β₂

Propranolol, oxprenolol

Salbutamol, terbutaline, salmeterol

Atenolol, metoprolol, propranolol, oxprenolol

+ Uptake 1

- Uptake 1

Acts on, causes, gives rise to

Movement
Agonist at \(\alpha\)- and \(\beta\)-receptors

**Epinephrine**

**Actions**  
\(\alpha_1\): vasoconstriction (thus \(\uparrow\)BP); contraction of uterus, GIT sphincters, bladder sphincter, radial iris muscle.  
\(\alpha_2\): inhibition of lipolysis, inhibition of NA release.  
\(\beta_1\): increased heart rate; \(\beta_2\): bronchodilation, vasodilation with decrease in diastolic blood pressure.

**MOA**  
At \(\alpha_1\)-receptors: Activation of phospholipase C with generation of IP\(_3\) (which increases intracellular calcium and thus force of contraction).  
At \(\beta_2\)-receptors: increase cAMP activates protein kinase A. In smooth muscle PKA reduces the contractile action; in cardiac muscle it increases intracellular calcium and thus the force of the contraction.

**Abs/Distrb/Elim**  
Given i.m. or s.c. Plasma \(t_{1/2}\) 2min. Metabolised by monoamine oxidase and catechol-O-methyl transferase.

**Clinical use**  
Asthma, anaphylactic shock, cardiac arrest. Also added to local anaesthetic solutions.

**Adverse effects**  
Tachycardia, raised BP, anxiety.

**Special points**  
Phenylephrine and oxymetazoline are similar drugs except that they are \(\alpha_1\)-selective.
The figure gives a simple outline of noradrenergic transmission.
An $\alpha_1$-receptor antagonist (Similar drugs: doxazosin, terazosin, tamsulosin)

**Prazosin**

**Actions**
- Vasodilatation and thus ↓ blood pressure
- ↑ Heart rate (a reflex $\beta_1$-receptor response to the ↓ BP)
- ↓ Bladder sphincter tone
- Inhibition of hypertrophy of smooth muscle of bladder neck and prostate capsule.

**MOA**
- Block of the action of endogenous and exogenous agonists on $\alpha_1$-receptors. Tamsulosin is an $\alpha_{1A}$-receptor antagonist.

**Abs/Distrb/Elim**
- **Prazosin**: absorbed orally; plasma half-life 3–4h; metabolised by liver, extensive first-pass metabolism.
- **Tamsulosin**: absorbed orally; plasma half-life 10–15h; metabolised by liver. **Doxazosin** half-life 22h.

**Clinical use**
- For severe hypertension: Prazosin, doxazosin (in combination with other agents; see CVS card 6.06). For benign prostatic hypertrophy: tamsulosin; prazosin, doxazosin also used.

**Adverse effects**
- **Prazosin**: orthostatic hypotension, dizziness; hypersensitivity reactions; insomnia; sometimes priapism. **Tamsulosin** can also cause abnormal ejaculation and back pain.

R&D 7e Ch 14, p 187; D&H 2e Ch 11, pp 32-35
The figure gives a simple outline of noradrenergic transmission.

- Tyrosine is converted to DOPA by Dopa decarboxylase.
- DOPA is converted to dopamine by Dopa decarboxylase.
- Dopamine is further converted to noradrenaline (NA).
- Noradrenergic varicosity is involved in the transmission.

- Noradrenergic varicosity releases noradrenaline (NA).
- Noradrenaline (NA) can act on α1 and β1 receptors.
- Noradrenaline (NA) can also be released by epinephrine (adrenaline).
- Propranolol, oxprenolol, salbutamol, terbutaline, salmeterol can affect noradrenergic transmission.
- Prazosin, doxazosin, tamsulosin can affect noradrenergic transmission.
- Atenolol, metoprolol, propranolol, oxprenolol can affect noradrenergic transmission.

The diagram shows the interaction of these compounds and receptors in the noradrenergic system.
**Actions**  A cardiac stimulant: it increases contractility and thus cardiac output. It has less effect on heart rate and there is little vasoconstriction.

**MOA**  Acts mainly on $\beta_1$-receptors causing G-protein-mediated increase of cAMP which increases calcium influx in the cardiac myocytes. Minimal effect on $\beta_2$-receptors.

**Abs/Distr/Elim**  Given i.v.; plasma $t_{1/2}$ 2min Inactivated by MAO and COMT.

**Clinical use**  Cardiogenic shock. Decompensated congestive cardiac failure.

**Adverse effects**  Dysrhythmias.

---

R&D 7e Ch 21, p 252; D&H 2e, Ch 11, pp 32-35
The figure gives a simple outline of noradrenergic transmission.
Phenylephrine

**Actions**  Vasoconstriction; nasal decongestion; dilatation of pupil without effect on accommodation.

**MOA**  Causes release of calcium from the sarcoplasmic reticulum. The increased calcium activates the contractile mechanism.

**Abs/Distrb/Elim**  Given intranasally or topically in the eye, plasma half-life 3h, (longer in the elderly).

**Clinical use**  As nasal decongestant; for opthalmoscopy.

**Adverse effects**  Hypertension, reflex bradycardia.

R&D 7e Ch 14, pp 182t-184t; D&H 2e Ch 11, pp 32-35
The figure gives a simple outline of noradrenergic transmission.
**Actions**  Block of $\alpha_1$-receptor effects: vasodilatation and postural hypotension. Block of $\alpha_2$ effects: reduced NA action on $\alpha_2$ receptors on the varicosity, increases release of NA from varicosity which can cause tachycardia and increased cardiac output.

**MOA**  Binds covalently (and therefore irreversibly) to $\alpha$ receptors and blocks NA action, but phentolamine’s action is reversible.

**Abs/Distrb/Elim**  Plasma half-life 3h, (longer in the elderly). Given orally; plasma half-life $\sim$12h; action lasts longer (up to several days) because of irreversible binding to receptor.

**Clinical use**  Used in the treatment of phaeochromocytoma.

**Adverse effects**  Postural hypotension and tachycardia.
The figure gives a simple outline of noradrenergic transmission.

Noradrenergic transmission involves the conversion of Tyrosine to DOPA by Dopa decarboxylase. DOPA is then converted to Dopamine, which is stored in Noradrenergic varicosity. Dopamine can be further converted to Noradrenaline (NA) by Dopa decarboxylase. NA can be released or taken up by the cell. NA acts on various receptors to cause contractions or relaxations in cardiac and smooth muscle cells. The figure also shows the effects of different drugs on these receptors.
Amfetamine

**Actions**  Releases NA from the varicosity therefore has similar actions to NA and epinephrine, but weaker:
- \( \alpha_1 \) receptor stimulation: \( \rightarrow \) vasoconstriction \( \rightarrow \) increased BP.
- \( \beta_2 \) receptor stimulation: \( \rightarrow \) bronchodilatation.
- \( \beta_1 \) stimulation: \( \rightarrow \) increased heart rate.
Is also a potent CNS stimulant.

**MOA**  Taken up by Uptake 1 into the varicosity, then into the vesicle by exchange with NA; the NA, now loose in the cytoplasm, is then released by exchange with amfetamine at Uptake 1.

**Abs/Distrb/Elim**  Absorbed orally; plasma half-life: ~ 12h. Excreted unchanged in urine.

**Clinical use**  Narcolepsy, hyperactivity in children.

**Adverse effects**  Increased BP, tachycardia, insomnia, psychosis with excessive doses.

**Special points**  Tolerance, dependence and addiction can develop. (Ephedrine is not addictive).

---

R&D 7e Ch 14, p 191; D&H 2e Ch 11, pp 32-35
The figure gives a simple outline of noradrenergic transmission.

Noradrenergic transmission involves the conversion of tyrosine to DOPA, followed by dopamine synthesis. Dopamine can then be converted to NA (noradrenaline) in the varicosity. NA is released into the synapse and acts on α and β receptors to cause contraction or relaxation of muscle cells. Drugs such as amfetamine, ephedrine, and salbutamol displace NA, while propranolol and oxprenolol inhibit its release. Dopamine and dobutamine can also stimulate uptake 1 of NA. The figure highlights the complex interplay of neurotransmitters and receptors in regulating cardiovascular function.
**Cocaine**

**Actions and MOA**  
Sympathomimetic action: Inhibition of uptake of NA by Uptake 1 leads to increased NA effects (notably vasoconstriction).  
For mechanism of local anaesthetic action see local anaesthetic card 28.03

**Abs/Distrb/Elim**  
See CNS stimulants and psychotomimetics card 27.02.

**Clinical use**  
Local anaesthetic.

**Adverse effects**  
See CNS stimulants and psychotomimetics card 27.02.

**Drugs with similar action**  
*Other drugs inhibiting Uptake 1:* phenoxybenzamine (main action: alpha blocker), tricyclic antidepressants. *Other local anaesthetics:* see local anaesthetic set (28)

**Special points**  
Cocaine is a widely used drug of addiction. The vasoconstriction caused by its Uptake 1 blocking action can lead to necrosis of the nasal septum in cocaine addicts who snort it.

---

R&D 7e Ch 47, pp 587-588; D&H 2e Ch 43, p 99
The figure gives a simple outline of noradrenergic transmission.
**Actions**  Reduces release of NA. Lowers blood pressure.

**MOA**  Acts mainly in the CNS. Is taken up into adrenergic neurones and converted into false transmitter methylnoradrenaline (methylnorepinephrine). This is released and acts on the alpha-2 adrenoceptors decreasing the release of NA.

**Abs/Distrb/Elim**  Given orally, actively transported into CNS neurones. Plasma half-life ~ 2h; duration of action ~ 24h.

**Clinical use**  Hypertension in pregnancy.

**Adverse effects**  Hypotension, transient sedation, dry mouth, diarrhoea, hypersensitivity reactions.
The figure gives a simple outline of noradrenergic transmission.
Adjunct to levodopa treatment  

**Carbidopa**

**Actions and MOA** Levodopa is used to treat Parkinsonism, but in the GIT and periphery it is metabolised by DOPA decarboxylase which reduces the dose available to the CNS. Furthermore, the resulting dopamine has unwanted effects.

Carbidopa inhibits DOPA decarboxylase increasing the availability of levodopa to the CNS and reducing its dopamine-mediated side effects. See CNS card 20.01.

**Abs/Distrb/Elim** Usually given in combination with levodopa in the treatment of Parkinsonism. Carbidopa can’t cross the blood – brain barrier so it affects only the peripheral metabolism of levodopa.

**Clinical use** An adjunct in treatment of Parkinsonism.

**Adverse effects** Hypotension, transient sedation, dry mouth, diarrhoea, hypersensitivity reactions.
The figure gives a simple outline of noradrenergic transmission

Noradrenergic transmission involves the conversion of Tyrosine to Dopamine through the action of Dopa decarboxylase. Dopamine then acts on noradrenergic varicosity, leading to the release of NA.

- **Tyrosine** leads to the production of Dopamine through Dopa decarboxylase.
- Dopamine is moved and acts on, leading to relaxation or contraction of smooth muscle cells and cardiac muscle cells.
- Various medications influence NA levels and actions, impacting smooth muscle and cardiac muscle cell activities.

Key points:
- **Tyrosine** is converted to **Dopamine**.
- Dopamine activates **NA** release.
- **Phenylephrine** and **Epinephrine** have opposing effects on smooth muscle and cardiac muscle cells.
- **Carbidopa** and **Methyldopa** inhibit NA activity.
- **Amfetamine**, **ephedrine**, and **salbutamol** displace NA.
- **Propranolol**, **atenolol**, and **oxprenolol** inhibit NA effects.
- **Phenoxybenzamine**, **methyldopa**, and **atropine** inhibit NA uptake.
- **Atenolol** and **metoprolol** inhibit NA action.
- **Epinephrine** and **dopamine** are transported into the cell.
- **Prazosin**, **doxazosin**, and **tamsulosin** inhibit NA action.

Diagram highlights the complex interactions between neurotransmitters and medications, emphasizing the regulation of smooth muscle and cardiac muscle cell activities.

**Summary**

Noradrenergic transmission plays a crucial role in various physiological processes, including blood pressure regulation, cardiovascular function, and smooth muscle contraction. Understanding the mechanisms and effects of noradrenergic transmission is essential for the development of effective therapeutic strategies.
Add the drugs dealt with in the NA cards in the relevant places.

<table>
<thead>
<tr>
<th>Adrenoceptor agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
</tr>
<tr>
<td>?, ?</td>
</tr>
<tr>
<td>?, ?</td>
</tr>
</tbody>
</table>

Note that (?) indicates a drug not dealt with in the cards; have a go at giving the names.
### Adrenoceptor agonists

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Phenylephrine, Oxymetazoline</td>
<td>Clonidine</td>
<td>Dobutamine, Dopamine</td>
<td>Salbutamol, Terbutaline, Ritodrine, Salmeterol</td>
</tr>
<tr>
<td></td>
<td>Methoxamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noradrenaline (Norepinephrine; MethylNoradrenaline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenaline (Epinephrine)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Add the drugs dealt with in the NA cards in the relevant places

| Adrenoceptor antagonists |
|---------------|---------------|---------------|---------------|
| $\alpha_1$    | $\alpha_2$    | $\beta_1$    | $\beta_2$    |
| $\text{?}, \text{?}, \text{?}$ | (?)          | $\text{?}, \text{?}$ | (?)          |

Note that (?) indicates a drug not dealt with in the cards; have a go at giving the names.
Adrenoceptor antagonists

<table>
<thead>
<tr>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin, Doxazosin, Tamsulosin</td>
<td>Yohimbine**</td>
<td>Atenolol, Metoprolol</td>
<td>Butoxamine**</td>
</tr>
<tr>
<td>Phenoxybenzamine, Phentolamine</td>
<td></td>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Labetalol*</td>
</tr>
</tbody>
</table>

* Not dealt with in the cards. **Not used clinically.
Mediators of inflammation 1: prostanoids (in grey boxes), leukotrienes (in dashed boxes) and PAF (in dotted box)

Phospholipid

Arachidonate

*Cyclo-oxygenases (COX-1, COX-2)*

Phospholipase A₂

Lyso-glyceryl-phosphorylcholine

5-Lipoxygenase

**Phospholipid**

**Cyclo-oxygenases (COX-1, COX-2)**

**Phospholipase A₂**

Lyso-glyceryl-phosphorylcholine

**5-Lipoxygenase**

**PAF**

*vasodilator; ↑vasc. permeability; bronchoconstrictor; chemotaxin*

**LTA₄**

*chemotaxin*

**LTA₄**

**TXA₂**

*thrombotic; vasoconstrictor*

**Cyclic endoperoxides**

**PGI₂**

*vasodilator; hyperalgesic; ↓platelet aggregation*

**PGF₂α**

*bronchoconstrictor; myometrial contraction*

**PGD₂**

*vasodilator; ↓platelet aggregation*

**PGE₂**

*vasodilator; hyperalgesic*

**LTC₄**

*bronchoconstrictors; increase vascular permeability*

**LTD₄**

**LTC₄**

**LTD₄**

**LTC₄**

**LTD₄**

**LTC₄**

**LTD₄**

**LTC₄**

**LTD₄**

**LTC₄**

**LTD₄**
**Actions**
Reduces inflammation, is analgesic for inflammatory pain, is antipyretic (i.e. reduces raised temperature).

**MOA**

**Abs/Distrb/Elim**
Given orally, half-life 2h.

**Clinical use**
Inflammatory conditions (e.g. rheumatoid disease, osteoarthritis, musculo-skeletal disorders); dysmenorrhoea.

**Adverse effects**
Gastrointestinal disturbances including gastric bleeding; headache, dizziness less commonly, allergic reactions occasionally; renal toxicity rarely.

**Special points**
Increased adverse effects if combined with other NSAIDs. Used to close patent ductus arteriosus.

**Similar drugs**
Diclofenac: (moderate potency, half-life 1–2h). Ketoprofen (half-life ~2h); Naproxen (more potent, half-life 10–14h); ketorolac (half-life 4–10h, COX-1 selective); piroxicam (half-life 57h, GIT toxicity common, COX non-selective).

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*R&D 7e Ch 26, p 319t; D&H 2e Ch 16, pp 42-43*
Inflammation and anti-inflammatory drugs

Aspirin

Mediators of inflammation 1: prostanoids (in grey boxes), leukotrienes (in dashed boxes) and PAF (in dotted box)

**Phospholipid**

- **Cyclo-oxygenases (COX-1, COX-2)**
- **5-Lipoxygenase**
- **Lyso-glyceryl-phosphorylcholine**

**Arachidonate**

- **Phospholipase A₂**

**Cyclic endoperoxides**

- **PGI₂** (vasodilator; hyperalgesic; ↓ platelet aggregation)
- **PGF₂α** (bronchoconstrictor; myometrial contraction; ↓ platelet aggregation)
- **PGD₂** (vasodilator; ↓ platelet aggregation)
- **PGE₂** (vasodilator; hyperalgesic)

**TXA₂** (thrombotic; vasoconstrictor)

**LTA₄**

- **LTA₄** → **LTA₄** → **LTB₄** (chemotaxin)

**PAF** (vasodilator; ↑ vasc. permeability; bronchoconstrictor; chemotaxin)

**NSAIDs:**

- e.g. ibuprofen
- Others: diclofenac, ketoprofen, naproxen, ketorolac

**Others:**

- ibuprofen
- diclofenac
- ketoprofen
- naproxen
- ketorolac

**PGI₂** (vasodilator; hyperalgesic; ↓ platelet aggregation)

**PGF₂α** (bronchoconstrictor; myometrial contraction)

**PGD₂** (vasodilator; ↓ platelet aggregation)

**PGE₂** (vasodilator; hyperalgesic)

**TXA₂** (thrombotic; vasoconstrictor)

**LTA₄** (chemotaxin)

**LTB₄** (chemotaxin)

**LTC₄** (bronchoconstrictors; increase vascular permeability)

**LTD₄**
Actions  Reduces inflammation, is analgesic for inflammatory pain, is antipyretic (i.e. reduces raised temperature). Inhibits platelet aggregation (see card 10.01).

MOA  Irreversible acetylation of cyclo-oxygenases; weakly COX-1 selective.

Abs/Distrb/Elim  Given orally. Half-life only 30min – rapid hydrolysis to salicylate but effects last longer because the COX has been inactivated and new enzyme must be produced.

Clinical use  Main use: as antithrombotic in myocardial infarction (see card set 7). Other NSAIDs are preferred for anti-inflammatory action and analgesia in musculo-skeletal conditions.

Adverse effects  Gastrointestinal disturbances, especially gastric bleeding. In high dosage can cause ‘salicylism’ (tinnitus, vertigo, reduced hearing); allergic reactions occasionally; renal toxicity rarely. Can cause the potentially fatal Reye’s syndrome (encephalopathy & liver disorder) in children after a viral infection.

Special points  Should not be used in children. Can cause increased effect of warfarin resulting in bleeding. Should not be used for gout because it reduces urate excretion & interferes with the action of uricosuric agents.
Mediators of inflammation 1: prostanoids (in grey boxes), leukotrienes (in dashed boxes) and PAF (in dotted box)

**Phospholipid**

**Arachidonate**

**Cyclo-oxygenases (COX-1, COX-2)**

**Lyso-glyceryl-phosphorylcholine**

**Cyclic endoperoxides**

**5-Lipoxygenase**

**PAF** (vasodilator; ↑vasc. permeability; bronchoconstrictor; chemotaxin)

**TXA$_2$** (thrombotic; vasoconstrictor)

**PGI$_2$** (vasodilator; hyperalgesic; ↓platelet aggregation)

**PGF$_{2\alpha}$** (bronchoconstrictor; myometrial contraction)

**PGD$_2$** (vasodilator; ↓platelet aggregation)

**PGE$_2$** (vasodilator; hyperalgesic)

**LTA$_4$, LTB$_4$, LTC$_4$, LTD$_4$** (bronchoconstrictors; increase vascular permeability)

**NSAIDs:**
- e.g. ibuprofen
- Others: diclofenac, ketoprofen, naproxen, ketorolac, aspirin
**Actions**  Analgesic and antipyretic (i.e. reduces raised temperature). Has little anti-inflammatory action.

**MOA**  Inhibition of COX-1, COX-2 and also the recently identified COX-3 which occurs predominantly in the CNS.

**Abs/Distrb/Elim**  Given orally, half-life 2–4h, inactivated in the liver.

**Clinical use**  Mild to moderate pain, especially headache. It is the most commonly used NSAID.

**Adverse effects**  Few and uncommon with therapeutic doses. Toxic doses cause firstly nausea and vomiting and then 24h later potentially fatal liver toxicity.
Mediators of inflammation 1: prostanoids (in grey boxes), leukotrienes (in dashed boxes) and PAF (in dotted box)

- Phospholipid
  - Phospholipase A₂
  - Arachidonate
    - Cyclo-oxygenases (COX-1, COX-2)
    - Cyclic endoperoxides
      - PG₁₂ (vasodilator; hyperalgesic; ↓ platelet aggregation)
      - PGF₂α (bronchoconstrictor; myometrial contraction)
      - PGD₂ (vasodilator; ↓ platelet aggregation)
      - PGE₂ (vasodilator; hyperalgesic)
    - TXA₂ (thrombotic; vasoconstrictor)
    - LTA₄
      - LTA₄ (chemotaxin)
      - LTC₄ (bronchoconstrictors; increase vascular permeability)
      - LTD₄
    - 5-Lipoxygenase
      - PAF (vasodilator; ↑ vasc. permeability; bronchoconstrictor; chemotaxin)

- NSAIDs
  - COX-non-selective: ibuprofen, aspirin, paracetamol
A ‘coxib’ non-steroidal anti-inflammatory drug (Similar drugs: etoricoxib, parecoxib)

Celecoxib

**Actions**  Analgesic, antipyretic and anti-inflammatory actions. No antiplatelet action.

**MOA**  Selective inhibition of COX-2 – the enzyme that is induced in areas of inflammation. Celecoxib is 10–20 x more active on COX-2 than COX-1 – the constitutive enzyme that generates physiologically important prostaglandins.

**Abs/Distrb/Elim**  Given orally, half-life ~11h, inactivated in the liver.

**Clinical use**  Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis. (No cardioprotective effect because no antiplatelet action.)

**Adverse effects**  Fewer adverse gastrointestinal effects than the traditional NSAIDs. Some renal toxicity because COX-2 occurs constitutively in the kidney.

R&D 7e Ch 26, p 325; D&H 2e Ch 16, pp 42-43
What group of drugs can inhibit the production of all the inflammatory mediators below?

**Mediators of inflammation 1: prostanoids (in grey boxes), leukotrienes (in dashed boxes) and PAF (in dotted box)**

**Phospholipid**

- **Cyclo-oxygenases (COX-1, COX-2)**
  - NSAIDs
    - COX-non-selective: ibuprofen, aspirin, paracetamol
    - COX-2 selective: Celecoxib

**Cyclic endoperoxides**

- **PGI₂** (vasodilator; hyperalgesic; ↓platelet aggregation)
- **PGF₂α** (bronchoconstrictor; myometrial contraction)
- **PGD₂** (vasodilator; ↓platelet aggregation)
- **PGE₂** (vasodilator; hyperalgesic)

**Lyso-glyceryl-phosphorylcholine**

- **5-Lipoxygenase**
  - **LTA₄**
  - **LTA₄** (chemotaxin)
  - **LTC₄** (bronchoconstrictors; increase vascular permeability)
  - **LTD₄** (vasodilator; ↓permeability; bronchoconstrictor)

- **PAF** (vasodilator; ↑vasc. permeability; bronchoconstrictor; chemotaxin)
Glucocorticoids can inhibit the production of all the inflammatory mediators below:

- **Glucocorticoids also inhibit induction of:**
  - Cyclo-oxygenases (COX-1, COX-2)
  - Phospholipase A₂
  - 5-Lipoxygenase

**NSAIDs**
- COX-non-selective: ibuprofen, aspirin, paracetamol
- COX-2 selective: Celecoxib

**Cyclo-oxygenases** (COX-1, COX-2)
- TXA₂ (thrombotic; vasoconstrictor)
- PGE₂ (vasodilator; hyperalgesic)
- PGD₂ (vasodilator; myometrial contraction)
- PGF₂α (bronchoconstrictor; myometrial contraction)
- PGF₁α (vasodilator; hyperalgesic; ↓platelet aggregation)

**5-Lipoxygenase**
- LTA₄
- LTB₄ (chemotaxin)
- LTC₄ (bronchoconstrictors; increase vascular permeability)
- LTD₄

**Phospholipid**
- Lyso-glyceryl-phosphorylcholine
- Phospholipase A₂

**Cyclo-oxygenases (COX-1, COX-2)**
- Lipocolipids (vasodilator; hyperalgesic; ↓platelet aggregation)

**R&D 7e Ch 26, pp 318-335; D&H 2e Ch 29, pp 70-71**
The figure shows the pathophysiology of rheumatoid joint damage

CD4 T cells become activated and stimulate macrophages, osteoblasts and fibroblasts

IL-1 = interleukin-1, TNF-α = tumour necrosis factor-alpha (the main pro-inflammatory cytokines)
An immunosuppressive disease-modifying antirheumatoid drug (DMARD) **Methotrexate**

**Actions** Has marked anti-inflammatory action in rheumatoid disease. Methotrexate (MTX) is cytotoxic in the larger doses used to treat cancer.

**MOA** Is a folate antagonist and thus interferes with thymidylate synthesis (which is essential for DNA synthesis).

**Abs/Distrb/Elim** Given orally; has active metabolite; both MTX and metabolite are poly-glutamated (PgMTX). Half-life 6–9h.

**Clinical use** Drug of first choice for rheumatoid arthritis; also used in psoriasis, ankylosing spondylitis, polymyositis and vaculitis. MTX is also an anti-cancer agent.

**Adverse effects** Gastrointestinal disturbances, dose-related liver toxicity. Bone marrow depression and pneumonitis can occur.

R&D 7e Ch 26, p 327; D&H 2e Ch 46, p 105, Appendix A3
The figure shows the pathophysiology of rheumatoid joint damage.

- Immunosuppressant DMARD methotrexate
- CD4 Th0 → Activated Th1 cell
- Osteoclast
- Fibroblast
- Collagenase
- Macrophage

Release of other inflammatory cytokines and chemokines

Erosion of cartilage and bone: JOINT DAMAGE
**Actions**  Produces remission of active rheumatoid arthritis. According to X-rays, disease progression is reduced.

**MOA**  In the colon the salicylic acid moiety is released, is absorbed and has anti-inflammatory action.

**Abs/Distrb/Elim**  Given orally; only ~15% is absorbed in the GIT. Half-life 6–16h.

**Clinical use**  Rheumatoid arthritis, juvenile arthritis, inflammatory bowel disease.

**Adverse effects**  Nausea & vomiting, headaches, rashes. Rarely bone marrow dyscrasias, liver dysfunction. About a third of patients discontinue the drug because of adverse effects.
The figure shows the pathophysiology of rheumatoid joint damage.

**Immunosuppressant DMARD methotrexate**

- $\text{T CD4} \rightarrow \text{Th0} \rightarrow \text{Activated Th1 cell} \rightarrow \text{Macrophage}

**Release of other inflammatory cytokines and chemokines**

- IL-1, TNF-$\alpha$

**Influx of inflammatory cells**

**Erosion of cartilage and bone: JOINT DAMAGE**

**DMARDS: Methotrexate, sulfasalazine**
**Actions**  Modifies the immune reaction underlying rheumatoid arthritis through an inhibitory action on activated T cells.

**MOA**  Gives rise to a metabolite that inhibits dihydroorotate dehydrogenase; this results in inhibition of T-cell proliferation and decreased production of autoantibodies by B cells.

**Abs/Distrb/Elim**  Absorbed orally. The metabolite undergoes enterohepatic cycling, half-life thus ~18 days.

**Clinical use**  Rheumatoid arthritis. Particularly effective in combination with methotrexate.

**Adverse effects**  ~25% of patients get diarrhoea. Increased BP, weight gain can occur. The long half-life can lead to cumulative toxicity.
The figure shows the pathophysiology of rheumatoid joint damage

- **Immunosuppressant DMARD** methotrexate

- **T CD4** gives rise to
  - **Th0**
  - **Activated Th1 cell**
    - **Macrophage**
      - IL-1
      - TNF-α
      - Release of other inflammatory cytokines and chemokines
      - Influx of inflammatory cells
      - Erosion of cartilage and bone: JOINT DAMAGE

- **DMARDs**: Methotrexate, sulfasalazine, **leflunomide**
**Actions**  Reduces joint inflammation and symptoms of rheumatoid arthritis. Reduces symptoms of Crohn’s disease.

**MOA**  It is a monoclonal antibody against TNF-\(\alpha\) that binds with the TNF-\(\alpha\) and prevents its interaction with cell surface receptors in inflammatory cells.

**Abs/Distrb/Elim**  Given by i.v. infusion every 4 weeks. Half-life 9–12 days.

**Clinical use**  Active rheumatoid arthritis – usually combined with methotrexate if other DMARDs haven’t worked. Ankylosing spondylitis and psoriatic arthritis – if other therapy hasn’t worked.

**Adverse effects**  Nausea, vomiting, headache, upper respiratory tract infections with cough. Because of inactivation of macrophages latent TB and other conditions (e.g. hepatitis B) could be reactivated. Blood dyscrasias can occur. Antibodies against infliximab may be produced.

**Similar drugs**  *Adalimumab* is also an anti-TNF-\(\alpha\) antibody (half-life 10–20 days, MTX reduces clearance).  *Etanercept* another anti-TNF-\(\alpha\) antibody (given subcut. twice a week; half-life ~5 days).
What group of drugs inhibits mediator release from the macrophage?

**The figure shows the pathophysiology of rheumatoid joint damage**

- **Immunosuppressant DMARD methotrexate**

  - Activated Th1 cell
  - Macrophage

- **Anti-TNF agents** e.g. **infliximab** etanercept

  - Release of other inflammatory cytokines and chemokines

- **DMARDS: Methotrexate, sulfasalazine, leflunomide**
Glucocorticoids

Other DMARDS

Anti-TNF agents

Anti-IL1 agents

E.g. anakinra

R&D 7e Ch 26, pp 327-328; D&H 2e Ch 17 pp 44-45, Appendix A3

Erosion of cartilage and bone: JOINT DAMAGE

DMARDS: Methotrexate, sulfasalazine, leflunomide, anticytokine agents, gold compounds (auranofin, aurothiomalate), hydroxychloroquine, penicillamine

Tmargin

CD4

Th0

Activated Th1 cell

Macrophage

IL-1

TNF-α

Osteoclast

Fibroblast

Collagenase

Influx of inflammatory cells

Release of other inflammatory cytokines and chemokines

= gives rise to

= releases

= acts on
The figure shows the final metabolic pathway in the production of uric acid

**GOUT** is due to the overproduction of uric acid leading to arthritis due to deposition of urate crystals in the joints. Phagocytes engulf the crystals and release inflammatory mediators.
Allopurinol

**Actions**  Reduces uric acid concentration in the body.

**MOA**  Inhibits xanthine oxidase and also the biotransformation of purines to xanthine.

**Abs/Distrb/Elim**  Given orally; well absorbed; converted to alloxanthine which has a half-life of ~18–30h and is the moiety that inhibits xanthine oxidase.

**Clinical use**  To prevent episodes of gout.

**Adverse effects**  Gastrointestinal disturbances. Rashes and blood dyscrasias can occur.

**Special points**  Allopurinol is not used to treat acute attacks of gout – these are treated with NSAIDs. Allopurinol interferes with the metabolism of oral anticoagulants and can increase the effect of azathioprine and cyclophosphamide.

**Similar drugs**  Probenicid is similar in that it is also uricosuric but it acts by increasing uric acid excretion through an effect on the proximal tubule in the nephron; only used to prevent gouty attacks.

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R&D 7e Ch 26, pp 331-332; D&H 2e Ch 16, p 43
The figure shows the final metabolic pathway in the production of uric acid.

Gout is due to the overproduction of uric acid leading to arthritis due to deposition of urate crystals in the joints. Phagocytes engulf the crystals and release inflammatory mediators.
Colchicine

*Actions*  It decreases the pain and inflammation of gouty arthritis.

*MOA* Inhibits migration into gouty joints of neutrophils by binding to tubulin and preventing its polymerisation into microtubules. Neutrophils are reduced to moving with a ‘drunken walk’. It also decreases production of the chemokine leukotriene B₄.

*Abs/Distrb/Elim*  Given orally, well-absorbed; half-life 9h.

*Clinical use*  To prevent episodes of gout.

*Adverse effects*  Diarrhoea and sometimes nausea and vomiting. Blood dyscrasias can occur.

*Special points*  It can increase the bone marrow depression caused by other drugs.
Drugs affecting the immune response

**Ciclosporin**

4.01

**Antibody-mediated reactions**

- B → P
- B → MB
- Memory B cell

**Cell-mediated reactions**

- Th1 → MT
- Memory T cell
- Th1 → Th1
- Macrophage-activating cytokines & other cytokines
- Tc → Kill virally infected cells

T = T cell, Th = T helper cell, B = B cell
**Actions**
Reduces cell-mediated immune (CMI) responses; lesser effect on antibody-mediated responses. Interferes with antigen-induced T-cell differentiation and the clonal proliferation of T cells and thus the development & activation of cytotoxic T cells and of other T cells responsible for CMI responses.

**MOA**
It complexes with cyclophilin to inhibit calcineurin which normally activates the transcription of interleukin-2 (IL-2).

**Abs/Distrb/Elim**
Given orally or by i.v. infusion. Tissue concentration is $3 \times$ that in the plasma. Metabolised in the liver by the P450 3A enzyme system.

**Clinical use**
Used to prevent rejection of organ and tissue transplants & for prevention of graft v host disease. Can be useful in autoimmune diseases. Often used in combination with glucocorticoids or methotrexate.

**Adverse effects**
Nephrotoxicity. Can cause hypertension & hepatotoxicity and sometimes GIT disturbances, tremor, hirsutism, paraesthesia, gum hypertrophy.

**Special points**
Multiple interactions with other drugs.

**Similar drug**
Tacrolimus: indirectly inhibits calcineurin; more potent than ciclosporin with similar adverse effects – myelosuppression etc. but greater neurotoxicity.

R&D 7e Ch 26, pp 328-329; D&H 2e Ch17, pp 44-45
Drugs affecting the immune response

**Azathioprine**

**Cell-mediated reactions**
- CD4
- CD8
- CD2

**Antibody-mediated reactions**
- B
- MB
- P
- Plasma cell
- Memory B cell

**Immunosuppressants:** Ciclosporin

T = T cell, Th = T helper cell, B = B cell
**Actions**  Reduces the clonal proliferation of T and B cells during the induction phase of the immune response.

**MOA**  Interferes with purine synthesis and has cytotoxic action on dividing cells.

**Abs/Distrb/Elim**  Given orally or by i.v. infusion. Metabolised to mercaptopurine (mcp) which is the cytotoxic moiety acting by interfering with purine nucleotide metabolism. Mcp is inactivated by xanthine oxidase.

**Clinical use**  Used to prevent rejection of organ and tissue transplants & for prevention of graft v host disease. Also used in chronic inflammatory and autoimmune diseases (e.g. rheumatoid arthritis).

**Adverse effects**  Myelotoxicity (dose-related). GIT disturbances, hypersensitivity reactions (skin rashes, arthralgia etc.).

**Special points**  Blood should be monitored for myelosuppression.
Drugs affecting the immune response

Mycophenolate mofetil

**Antibody-mediated reactions**
- Plasma cell → Releases antibodies
- Memory B cell

**Cell-mediated reactions**
- Memory T cell
- Macrophage-activating cytokines & other cytokines
- Kill virally infected cells

**Immunosuppressants**: Ciclosporin, azathioprine

- T = T cell, Th = T helper cell, B = B cell
**Actions**  Selectively restrains the clonal proliferation of T and B cells and reduces the production of cytotoxic T cells.

**MOA**  Inhibits de novo purine synthesis specifically in T and B lymphocytes (other cells can generate purines by another pathway).

**Abs/Distrb/Elim**  Given orally or by i.v. infusion. Metabolised to mycophenolic acid which is the active moiety which interferes with purine nucleotide metabolism.

**Clinical use**  Used to prevent rejection of organ transplants usually in combination with ciclosporin and glucocorticoids. Also used in autoimmune diseases (e.g. rheumatoid arthritis).

**Adverse effects**  GIT, CVS & respiratory system disturbances, hepatitis, pancreatitis, tremor, dizziness, flulike syndrome.

**Special points**  Treatment requires specialist supervision.

R&D 7e Ch 26, p 330; D&H 2e Ch 17, pp 44-45
Drugs affecting the immune response

Immunosuppressants: Ciclosporin, sirolimus, azathioprine, mycophenolate mofetil

Antibody-mediated reactions

- B → P → Plasma cell → Releases antibodies
- B → MB → Memory B cell

Cell-mediated reactions

- Th1 → MT → Memory T cell
- Th1 → Th1 → Macrophage-activating cytokines & other cytokines
- Tc → Kill virally infected cells

T = T cell, Th = T helper cell, B = B cell
**Actions**  Inhibits the clonal proliferation of T and – more particularly – B cells; decreases immunoglobulin production.

**MOA**  Blocks the response of precursor cells to interleukin-2 (IL-2) (by binding a cytosolic protein FK-binding protein 12) and thus preventing activation of T & B cells.

**Abs/Distrb/Elim**  Given orally; metabolised by P450 3A in the liver – therefore many drug interactions.

**Clinical use**  Used to prevent rejection of organ transplants (particular renal because, unlike ciclosporin, it has no renal toxicity) usually in combination with ciclosporin or glucocorticoids.

**Adverse effects**  Myelosuppression (important), hyperlipidaemia, venous thromboembolism, diarrhoea, rash, osteonecrosis.

**Special points**  Drug concentrations in the blood need to be monitored.
Drugs affecting the immune response

**Glucocorticoid** (e.g. prednisolone)

### Drugs affecting the immune response

**Immunosuppressants:** Ciclosporin, sirolimus, azathioprine, mycophenolate mofetil, **sirolimus**

**Antibody-mediated reactions**
- B → P → Plasma cell → Releases antibodies
- B → MB → Memory B cell

**Cell-mediated reactions**
- Th1 → MT → Memory T cell
- Th1 → Th1 → Macrophage-activating cytokines & other cytokines
- Th1 → Tc → Kill virally infected cells

**Antigen-presenting cell**
- IL-2 → Th2
- IL-2 → Th1
- IL-2 → Memory T cell

**Antigen**
- CD4
- CD8

T = T cell, Th = T helper cell, B = B cell
An anti-inflammatory/immunosuppressant glucocorticoid (GC) Prednisolone

**Actions**
Inhibits clonal proliferation of T & B cells and macrophage activation. (Other actions: reduction in chronic inflammation, autoimmune and hypersensitivity reactions; various metabolic effects; negative feedback action on ant. pituitary and hypothalamus. (see card 16.01)

**MOA**
GCs interact with intracellular receptors to inhibit the transcription of specific genes that code for various cytokines esp. IL-2. (see card 16.02)

**Abs/Distrb/Elim**
Given orally or by injection, topically. The main effects occur only after 2–8 h because protein synthesis of mediators and enzymes is required (see card 16.02).

**Clinical use**
To prevent rejection of organ transplants and to treat rejection episodes. Also used for inflammatory, see hypersensitivity and autoimmune conditions (see card 16.01)

**Adverse effects**
Used long-term it causes:
- suppression of response to infection
- suppression of endogenous GC synthesis
- osteoporosis
- growth suppression in children
- iatrogenic Cushing’s syndrome (see card 16.03 for pictorial expression of Cushing’s syndrome).
**Drugs affecting the immune response**

- **Cetirizine**

**Cell-mediated reactions**
- T = T cell, Th = T helper cell, B = B cell

**Antibody-mediated reactions**
- Releasing antibodies
- Plasma cell
- Memory B cell
- Memory T cell
- Macrophage-activating cytokines & other cytokines
- Kill virally infected cells

**Immunosuppressants**
- Ciclosporin
- Sirolimus
- Azathioprine
- Mycophenolate mofetil
- Sirolimus
- Glucocorticoids (GCs)
**Actions**  Inhibits H₁-receptor actions and thus reduces immediate hypersensivity reactions.

**MOA**  Competitive inhibitor of histamine at H₁-receptors on smooth muscle.

**Abs/Distrb/Elim**  Given orally well absorbed, doesn’t cross the blood–brain barrier, metabolised in the liver, excreted in the urine.

**Clinical use**  Hypersensitivity reactions – hay fever, urticaria, some drug allergies, insect bites, pruritus.

**Adverse effects**  Effects due to action on peripheral muscarinic receptors (dry mouth; sometimes blurred vision, constipation, urine retention).

**Special points**  It doesn’t cross into the CNS therefore little or no sedation.
Drugs affecting the immune response

Promethazine

Cell-mediated reactions

Antibody-mediated reactions

Immunosuppressants: Ciclosporin, sirolimus, azathioprine, mycophenolate mofetil, sirolimus, glucocorticoids

Antigen-presenting cell

T = T cell, Th = T helper cell, B = B cell
**Actions**  Inhibits H₁-receptor actions and thus reduces immediate hypersensivity reactions; has anticholinergic action, some local anaesthetic action, weak α-adrenoceptor antagonism and fairly marked sedative effect.

**MOA**  Competitive inhibitor of histamine at H₁-receptors on smooth muscle etc.

**Abs/Distrb/Elim**  Given orally or by deep i.m. injection or by slow i.v. injection; enters the CNS.

**Clinical use**  Hypersensitivity reactions – hay fever, urticaria; premedication; sedation; emergency treatment of anaphylaxis; motion sickness.

**Adverse effects**  Anticholinergic action on peripheral muscarinic receptors (dry mouth; sometimes blurred vision, constipation, urine retention); headache, drowsiness.

**Special points**  Injection can be painful.
**What antihistamines are used for motion sickness?**

**Drugs affecting the immune response**

**Antibody-mediated reactions**

1. IgE antibodies (abs) attach to mast cell
2. Allergen bridges 2 IgE abs
3. H is released & acts on histamine receptor

**Cell-mediated reactions**

**Immunosuppressants:** Ciclosporin, sirolimus, azathioprine, mycophenolate mofetil, sirolimus, glucocorticoids

**T = T cell, Th = T helper cell, B = B cell**
Antihistamines

- **Promethazine** (as specified on cards 4.07 & 14.08)
- Cyclizine
- Cinnarizine

*But a more efficient drug is*

- Hyoscine, a muscarinic antagonist (see card 1.03)

  which can be given by transdermal patch as well as orally.
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.
**Actions**  Antidysrhythmic.

**MOA**  Belongs to class 1a of the Vaughan Williams classification. Blocks open and inactivated Na\(^+\) channels in the cell membrane (‘use-dependent’ action) to reduce the rate of phase 0 depolarisation thus causing an increase in the effective refractory period and slowed AV conduction. Also produces some slowing of action potential repolarisation (a class III action).

**Abs/Distrib/Elim**  Oral and i.v. admin. \(T_{0.5}\) 5–10h. Half is excreted unchanged by kidney; half is metabolised in liver.

**Clinical use**  Supraventricular and, more usually, ventricular dysrhythmia.

**Adverse effects**  Atropine-like effects: blurred vision, dry mouth, constipation, urinary retention. Negative inotropic action. Procainamide has less antimuscarinic action than either disopyramide or quinidine. The class III actions of these drugs may lead to torsade de pointes.

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R&D 7e Ch 21, p 255t; D&H 2e Ch 18, pp 46-47
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.
**Actions**  Antidysrhythmic, local anaesthetic (see card 28.01)

**MOA**  Belongs to class 1b of the Vaughan Williams classification. Blocks open and inactivated Na\(^+\) channels in the cell membrane (shows ‘use-dependence’, so more likely to act in damaged, depolarised tissue). Na\(^+\) channel block reduces the rate of phase 0 depolarisation, increasing the effective refractory period and slowing AV conduction.

**Abs/Distrib/Elim**  Given i.v. (Very high first-pass metabolism precludes oral admin.). Short T\(_{0.5}\) – 2h. Subject to cytochrome P450 metabolism. Mexiletine and tocainide are orally active.

**Clinical use**  Treatment and prevention of ventricular fibrillation especially following infarction. Also digoxin-induced dysrhythmias.

**Adverse effects**  Unwanted CNS effects include drowsiness, tremors and convulsions.

R&D 7e Ch 21, p 256; D&H 2e Ch 18, pp 46-47
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.

Disopyramide, lidocaine

- 0 Fast depolarisation
- 1 Rapid partial repolarisation
- 2 Plateau
- 3 Main repolarisation
- 4 Pacemaker depolarisation

Sympathetic activity

Membrane potential (mV)
**Flecainide**

**Actions**  Antidysrhythmic.

**MOA**  Belongs to class 1c of the Vaughan Williams classification. Preferential block of open Na\(^+\) channels. Reduces the rate of phase 0 depolarisation causing an increase in the effective refractory period and slowed AV conduction. Associates with and dissociates from sodium channels more slowly than either la or lb agents.

**Abs/Distrib/Elim**  Oral admin. \(T_{0.5}\) 20h. Mostly excreted unchanged in urine. Propafenone is metabolised more rapidly by the liver and has a shorter \(T_{0.5}\) (5–10h).

**Clinical use**  Prevention of paroxysmal atrial fibrillation. Severe ventricular dysrhythmia, unresponsive to other agents.


R&D 7e Ch 21, pp 255-256; D&H 2e Ch 18, pp 46-47
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.
**Propranolol**

**Actions**  Antidysrhythmic. (Also antihypertensive, antianginal.) Blocks actions of catecholamines on β-adrenoceptors (see card 2.02).

**MOA**  Blocks sympathetic drive, reducing pacemaker activity (phase 4) and increasing AV conduction time. Reduces the slow inward Ca\(^{2+}\) current which affects phase 2 of the action potential. Propranolol has additional class I action. Esmolol and atenolol are β\(_1\) selective.

**Abs/Distrib/Elim**  Oral admin. T\(_{0.5}\) s: propranolol – 4h, atenolol – 6h, esmolol – 10min.

**Clinical use**  Reduction of mortality after infarct (where dysrhythmias have a sympathetic input). Paroxysmal atrial fibrillation. Esmolol’s short T\(_{0.5}\) allows its use by i.v. infusion for emergency treatment of supraventricular dysrhythmias.

**Adverse effects**  Bronchoconstriction in asthmatic patients. Cardiac slowing with possible heart block. Propranolol has CNS effects: depression, sedation and sleep disturbances.

R&D 7e Ch 21, p 257; D&H 2e Ch 18, pp 46-47
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.
**Actions**  Antidysrhythmic.

**MOA**  Class III drugs block $K^+$ channels in the cell membrane to delay repolarization and increase action potential duration. This increases the refractory period. Amiodarone also blocks $Na^+$ channels and $\beta$-adrenoceptors so has class I and class II actions. Sotalol also has class II actions.

**Abs/Distrib/Elim**  Long acting; extensive tissue binding, $t_{1/2}$ several weeks. Sotalol and ibutilide have half-lives of 5–10h.

**Clinical use**  One of the most effective antidysrhythmics. Atrial fibrillation and flutter, ventricular ectopic beats and tachyarrhythmias. Ibutilide i.v. for acute treatment of atrial fibrillation and flutter.

**Adverse effects**  Torsades de pointes. (Less likely with amiodarone than other class III drugs.) Amiodarone may cause pulmonary fibrosis, liver damage, photosensitive skin rashes and thyroid malfunction.
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.

- **Disopyramide, lidocaine, flecainide**: Block 1 Rapid partial repolarisation.
- **Propranolol**: Block Sympathetic activity and 0 Fast repolarisation.
- **Amiodarone**: Block 3 Main repolarisation and 4 Pacemaker depolarisation.

Membrane potential (mV):
- **+30**
- **0**
- **-60**
**Actions**  Antidysrhythmic. (Also antianginal and antihypertensive.) Blocks Ca\(^{2+}\) channels in both cardiac and smooth muscle so has both negative inotropic and smooth muscle relaxant actions.

**MOA**  Blocks L-type, voltage-gated, Ca\(^{2+}\) channels which are important in the action potential plateau and in particular affects action potential propagation in the SA and AV nodes. Shows use-dependence so is more active in tachyarrhythmias. Decreases automaticity and slows AV conduction.

**Abs/Distrib/Elim**  Oral (less commonly i.v.) admin. t\(_{1/2}\) 6–8h.

**Clinical use**  Supraventricular tachycardias. Control of ventricular rate in atrial fibrillation.

**Adverse effects**  Side effects due to smooth muscle relaxation: hypotension and dizziness, ankle oedema, constipation. Unwanted cardiac actions include heart block and bradycardia.

R&D 7e Ch 21, p 257-258; D&H 2e Ch 18, pp 46-47
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.

Membrane potential (mV)

-60 0  +30

1. Rapid partial repolarisation
2. Plateau
3. Main repolarisation
4. Pacemaker depolarisation

Sympathetic activity

Propranolol

Disopyramide, lidocaine, flecainide

Amiodarone

Verapamil
**Actions**  Antidysrhythmic.

**MOA**  Activates G-protein-coupled adenosine receptors. Action (on A₁ receptors) is due to inhibition of Ca²⁺ channel opening and increased K⁺ channel opening (the effect is analogous to the action of ACh on cardiac muscarinic receptors). Important actions are its negative chronotropic action on the SA node and slowed AV conduction.

**Abs/Distrib/Elim**  Given i.v. Short duration of action. T₀.₅ 10secs.

**Clinical use**  Termination of paroxysmal supraventricular tachycardia.

**Adverse effects**  Side effects (e.g. flushing, chest pain, dyspnoea, bronchospasm) are short-lived because of rapid elimination of adenosine.
Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.

- **1 Rapid partial repolarisation**
  - **Disopyramide, lidocaine, flecainide**
  - **Propranolol**
  - **Sympathetic activity**
  - **Adenosine**

- **2 Plateau**
  - **Verapamil**

- **3 Main repolarisation**
  - **Amiodarone**

- **4 Pacemaker depolarisation**
**Actions**  Antidysrhythmic. Osmotic purgative

**MOA**  Slows AV node conduction. Reduces increased cardiac excitability due to hypomagnesaemia, which is common after heart operations. The cellular mechanism of action is not established but is likely to involve effects on membrane ion permeability or transport.

**Abs/Distrib/Elim**  Given i.v.

**Clinical use**  Prevention of supraventricular tachycardia and ventricular arrhythmias after bypass surgery. Ventricular dysrhythmias due to digoxin toxicity. Management of torsades de pointes.

**Adverse effects**  Muscle weakness.

R&D 7e Ch 21, p 368; D&H 2e Ch 18, pp 46-47
The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension.

CNS

Peripheral sympathetic system releases noradrenaline, which

Stimulates the heart, increasing:

Cardiac output

Constricts blood vessels increasing:

Peripheral resistance

Plasma volume, which affects

Baroreceptor discharge

Affects

Renin

Angiotensin I (AT I) Angiotensinogen

ACE

Angiotensin II (AT II), whichstimulates secretion of

Aldosterone, which decreases constricts blood vessels and increases
**Actions**  
Lowers blood pressure by decreasing vasoconstrictor tone, also by reducing cardiac load.

**MOA**  
Inhibits angiotensin-converting enzyme thus reducing synthesis of vasoconstrictor angiotensin II. This decreases aldosterone secretion, resulting in increased salt and water excretion, indirectly decreasing plasma volume and cardiac load (see card 6.02).

**Abs/Distrb/Elim**  
All are given orally. Captopril: half-life ~2h. Lisinopril: half-life 12h. Enalapril is a prodrug converted to an active moiety by liver enzymes.

**Clinical use**  
Hypertension; heart failure; ventricular dysfunction following myocardial infarction; diabetic nephropathy.

**Adverse effects**  
Hypotension; dry cough, angioedema. Renal failure can occur.

**Special points**  
Hyperkalaemia can occur if given with potassium-sparing diuretics. The dry cough and angioedema are due to the drugs producing bradykinin by stimulating the kallikrein-kinin system.

R&D 7e Ch 22, pp 274-275; D &H 2e Ch 17, pp 44–49
The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension.

- CNS
- Peripheral sympathetic system releases noradrenaline, which
  - Stimulates the heart, increasing: Cardiac output
  - Constricts blood vessels, increasing: Peripheral resistance

Together these control BLOOD PRESSURE, which affects
- Renal blood flow, which affects Salt and water excretion, which affects

- Renin release
- Angiotensin I (AT I)
- Angiotensinogen
- Angiotensin II (AT II), which stimulates secretion of Aldosterone, which decreases

ACE Inhibitors (e.g. captopril, enalapril)
**Actions**  Lowers blood pressure by decreasing vasoconstrictor tone.

**MOA**  Blocks the action of angiotensin II on the angiotensin II (AT$_1$ subtype) receptor.

**Abs/Distrb/Elim**  Given orally. Half-life 1–2h; half-life of metabolite 3–4h.

**Clinical use**  Hypertension; congestive heart failure; nephropathy.

**Adverse effects**  Hypotension, dizziness. Hyperkalaemia can occur.

**Special points**  Doesn’t cause the dry cough or angioedema seen with the ACE inhibitors.
The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension.

CNS

Peripheral sympathetic system releases noradrenaline, which

Stimulates the heart, increasing:

Cardiac output

Constricts blood vessels, increasing:

Peripheral resistance

Plasma volume, which affects

Baroreceptor discharge

Affects

Renin

Angiotensinogen

Angiotensin I (AT I)

Angiotensin II (AT II), which stimulates secretion of

Aldosterone, which decreases

Salt and water excretion, which affects

Renal blood flow, which affects

BLOOD PRESSURE, which affects

Baroreceptor discharge

ACE

ACE Inhibitors (e.g. captopril, enalapril)

Losartan (AT II receptor antagonist)
**Actions**  Vascular dilatation lowers blood pressure. Amlodipine & nifedipine dilate arterial resistance vessels. (Verapamil acts mainly on the heart, slowing the rate; see card 5.06).

**MOA**  Block voltage-gated calcium channels in vascular smooth muscle inhibiting calcium influx and thus contraction.

**Abs/Distrb/Elim**  Given orally. Half-life of amlodipine 35h, of nifedipine 2h. Verapamil undergoes first-pass metabolism; half-life ~ 4h.

**Clinical use**  Hypertension; angina pectoris.

**Adverse effects**  Nifedipine & amlodipine: reflex tachycardia, hypotension and headache due to vasodilatation.

**Special points**  Grapefruit juice increases the effects.
The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension.

- **Peripheral sympathetic system** releases noradrenaline, which
  - Stimulates the heart, increasing: **Cardiac output**
  - Constricts blood vessels, increasing: **Peripheral resistance**

Together these control **BLOOD PRESSURE**, which affects
- **Renal blood flow**, which affects
- **Salt and water excretion**, which affects

- **Baroreceptor discharge**
- **Plasma volume, which affects**

**Angiotensin I (AT I)**
- **Angiotensinogen**
- **Renin release**
- **Angiotensin II (AT II)**, which
  - Stimulates secretion of **Aldosterone**, which decreases
  - Constricts blood vessels and increases

**ACE Inhibitors (e.g. captopril, enalapril)**

**Losartan (AT II receptor antagonist)**

**CNS**

**Vasodilators:**
- Calcium channel blockers (e.g. amlodipine)
**Actions**  Marked long-lasting vascular dilatation; lowers blood pressure.

**MOA**

**Abs/Distrb/Elim** Given orally. Half-life ~ 4h.

**Clinical use** Very severe hypertension.

**Adverse effects** Salt & water retention and tachycardia and angina (therefore given with a loop diuretic and a beta blocker). Hirsutism.

**Special points** Also used topically to treat baldness.

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**R&D 7e Ch 22, p 272; D&H 2e Ch 19, p 49**
The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension.

- **CNS**
  - Peripheral sympathetic system releases noradrenaline, which
    - Stimulates the heart, increasing: **Cardiac output**
    - Constricts blood vessels increasing: **Peripheral resistance**
  - Together these control **BLOOD PRESSURE**, which affects
    - Renal blood flow, which affects **Salt and water excretion**, which affects
    - Renin release

- **Baroreceptor discharge**
  - Affects

- **Plasma volume, which affects**
  - Affects

**ACE**

Angiotensin I (AT I) → Angiotensin II (AT II), which stimulates secretion of **Aldosterone**, which decreases

**ACE Inhibitors** (e.g. captopril, enalapril)

**Losartan** (AT II receptor antagonist)

Vasodilators: Calcium channel blockers (e.g. amlodipine), **minoxidil**

CVS antihypertensive drugs

Hydralazine
**Actions**  Relaxes arterial smooth muscle lowering blood pressure.

**MOA** Interferes with the release of Ca$^{++}$ from the sarcoplasmic reticulum in vascular smooth muscle cells.

**Abs/Distrb/Elim**  Given orally. Half-life ~ 1-3h.

**Clinical use**  Very severe hypertension – particularly in pregnancy.

**Adverse effects**  Palpitations, hypotension, GIT disturbances, dizziness, allergic reactions (which can be severe with long-term use)
The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension. Important drugs in bold.

**Angiotensinogen**

**Angiotensin I (AT I)**

**Angiotensin II (AT II)**, which stimulates secretion of **Aldosterone**, which decreases

**CNS**

**Peripheral sympathetic system** releases noradrenaline, which

**Constricts blood vessels** increasing:

**Plasma volume**, which affects

**Cardiac output**

Stimulates the heart, increasing:

**Peripheral resistance**

**Plasma volume**, which reduces

**Renin**

**Renin release**

**Salt and water excretion**, which affects

**Renal blood flow**, which affects

**Blood Pressure**, which affects

**Cardiac output**

**Peripheral resistance**

**Plasma volume**, which reduces

**Vasodilators:**

- Calcium channel blockers (e.g. amlodipine), **Hydralazine**
- **ACE Inhibitors** (e.g. captopril, enalapril)
- Losartan (AT II receptor antagonist)
OTHER ANTIHYPERTENSIVE DRUGS

Important drugs in bold. For details see the cards specified

**Angiotensinogen**

Angiotensin II (AT II), which stimulates secretion of

**Aldosterone**, which decreases

**Renin**

**Angiotensin I (AT I)**

ACE

**Angiotensin II (AT II)**, which

stimulates secretion of

constricts blood vessels and increases

**Plasma volume**, which affects

**Cardiac output**

**Peripheral sympathetic system releases noradrenaline**, which

**Stimulates the heart**, increasing:

**Cardiac output**

**Constricts blood vessels**, increasing:

**Peripheral resistance**

**Salt and water excretion**, which affects

**Renin release**

**Renin**

**Renal blood flow**, which affects

**Blood Pressure**, which affects

**Beta blockers** decrease

**Spironolactone blocks aldosterone receptors** and thus increases:

**α₂-Adrenoceptor agonists** (e.g. methyl-dopa)

decrease sympathetic outflow

**β₁-Adrenoceptor blockers** (e.g. metoprolol, atenolol)

**Diuretics** (e.g. thiazides furosemide)

decrease increase

**α₁-Adrenoceptor antagonists** (e.g. terazosin)

**Adrenoceptor antagonists** (e.g. atenolol)

decrease sympathetic outflow

**Peripheral sympathetic system**

release noradrenaline, which

**Stimulates the heart**, increasing:

**Cardiac output**

**Constricts blood vessels**, increasing:

**Peripheral resistance**

**Salt and water excretion**, which affects

**Renin release**

**Renin**

**Renal blood flow**, which affects

**Blood Pressure**, which affects

**Beta blockers** decrease

**Spironolactone blocks aldosterone receptors** and thus increases:
The figure below outlines the pathophysiology of angina and myocardial infarction.
**Actions** Dilates and relaxes arterial resistance vessels and coronary arteries and thus (i) reduces cardiac work and metabolic demand and (ii) increases the perfusion and oxygenation of heart muscle; see Fig. 1.

**MOA** Inhibits voltage-gated calcium channels and reduces the contractile process; see Fig. 2.

**Abs/Distrb/Elim** Given orally. Elimination half-lives: nifedipine ~2h, amlodipine ~40h, verapamil 6h, diltiazem 4h.

**Clinical use** To prevent angina (nifedipine, diltiazem). For hypertension; see card 6.03. For dysrhythmias: verapamil (see card 5.06).

**Adverse effects** Nifedipine: flushing & headache and with chronic use – ankle swelling. Verapamil: constipation (an effect on GIT smooth muscle) and sometimes heart failure.

*R&D 7e Ch 18, pp 294-296; D&H 2e Ch 20, pp 294-296*
The figure below outlines the pathophysiology of angina and myocardial infarction.

- Atherosclerotic plaque
  - Decreased myocardial perfusion
    - Angina
  - Plaque rupture, thrombosis
    - Block of coronary artery
      - Potential dysrhythmias
      - Myocardial infarction
        - Ventricular dysfunction
          - Shock
        - PAIN!
          - Increased sympathetic activity

- Nifedipine, Diltiazem
**Vasodilator drug (Similar drug: isosorbide mononitrate)**

**Glyceryl trinitrate**

---

**Actions** Dilates and relaxes vascular (especially venular) smooth muscle and thus (i) reduce cardiac work and therefore metabolic demand and (ii) increase the perfusion and oxygenation of heart muscle; see Fig. 1

**MOA** Gives rise to nitric oxide (NO) in the cell which activates protein kinase G (PKG) and reduces contraction; Fig. 2.

---

**Abs/Distrb/Elim** Glyceryl trinitrate: sublingual tablet or spray, acts immediately; effects last ~30 mins. Can be given by transdermal patch – effects last 24h. Can be given i.v. Isosorbide mononitrate: given orally; half-life 4h; slow-release preparation available.

**Clinical use** Given sublingually to prevent/treat stable angina; glyceryl trinitrate is given i.v. to treat unstable angina. (Nitrates are also used in chronic heart failure; see card 8.02).

**Adverse effects** Headache due to vasodilatation; postural hypotension due to ↓vasomotor tone; prolonged usage leads to tolerance; methaemoglobinaemia (rare) with continued high doses.

---

**Fig. 1**

- Venous capacitance vessels
- Arterial resistance vessels
- Coronary vessels
- HEART
- Nitrates dilate
- these and reduce preload
- these and reduce afterload

**Fig. 2**

- Guanylyl cyclase
- GTP → cGMP
- PKG
- Nitrates
- Inhibits
- Reduces
- Kinase
- Myosin
- MyosinP
- Ca²⁺ → Contraction
What groups of drugs are used clinically to treat the pathophysiological
conditions shown in the dashed box below?

The figure below outlines the pathophysiology of angina and myocardial infarction.

- **Atherosclerotic plaque**
  - Decreased myocardial perfusion
  - **Angina**
    - Nifedipine, Diltiazem
    - Glyceryl trinitrate, isosorbide mononitrate
  - **Plaque rupture, thrombosis**
  - Block of coronary artery
  - **Myocardial infarction**
    - Potential dysrhythmias
    - Ventricular dysfunction
    - PAIN!
      - Shock
    - Increased sympathetic activity
Myocardial infarction is a medical emergency requiring hospitalisation.

- Statins (see card 9.01)
- β-adrenoceptor antagonists (see card 2.02)
- ACE inhibitors (see card 6.01)
- Anti-platelet agents (see section 10)
- Anticoagulants (see card 10.09)
- Thrombolytic agents (see card 10.05)

Atherosclerotic plaque → Plaque rupture, thrombosis → Block of coronary artery → Myocardial infarction

Potential dysrhythmias

Increased sympathetic activity

Opioids (see cards 26.01–26.03)

Myocardial infarction → Ventricular dysfunction

PAIN! → Shock
The pathophysiology of heart failure – showing the autocatalytic (positive feedback) mechanisms

Myocardial disease, hypertension, vascular disease can cause:

- Increased pre-load
  - Exacerbates
  - Cardiac failure
    - i.e. reduced cardiac output, which leads to:
      - Decreased renal blood flow
      - Renin release
      - Angiotensinogen
      - Renin
      - Angiotensin I
      - ACE
      - Angiotensin II
      - Aldosterone release, which increases
- Increased after-load
  - Exacerbates
  - Increased peripheral resistance
  - Vasoconstriction
  - Oedema (peripheral and pulmonary)
  - Increased central venous pressure
  - Increased plasma volume

- Reduced tissue perfusion
- Increased peripheral resistance
- Increased plasma volume
- Oedema (peripheral and pulmonary)

Increased pre-load exacerbates Cardiac failure, i.e. reduced cardiac output, which leads to:

Decreased renal blood flow
- Renin release
- Angiotensinogen
- Renin
- Angiotensin I
- ACE
- Angiotensin II
- Aldosterone release, which increases

Increased after-load exacerbates

Increased central venous pressure
- Oedema (peripheral and pulmonary)
- Increased plasma volume

Cardiac failure

Oedema (peripheral and pulmonary)
- Increased central venous pressure
- Increased plasma volume

Increased pre-load exacerbates

Increased after-load exacerbates
**Actions**  

**MOA**  
Inhibits Na\(^+\)/K\(^+\) ATPase in plasma membrane. The increased intracellular Na\(^+\) reduces Ca\(^++\) extrusion thus increasing \([\text{Ca}^{++}]_i\)

**Abs/Distrb/Elim**  
Given orally, usually with a loading dose; renal excretion; plasma half-life ~36h.

**Clinical use**  
Atrial fibrillation. Heart failure (if diuretics and ACE inhibitors haven’t worked).

**Adverse effects**  
Dysrhythmias, due to block of AV conduction and ectopic pacemaker action; yellow vision; nausea and vomiting.

**Special points**  
Narrow margin between effective dose and toxic dose. Decreased plasma K\(^+\) increases toxicity due to competition between K\(^+\) and digoxin for the Na\(^+\)/K\(^+\) ATPase.

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R&D 7e Ch 21, p 258; D&H 2e Ch 21, pp 53-55
What groups of drugs would be clinically useful at the sites shown with a question mark. Have a go at giving examples.

Myocardial disease, hypertension, vascular disease can cause:

- Increased pre-load
- Increased central venous pressure
- Oedema (peripheral and pulmonary)
- Increased plasma volume
- Decreased renal blood flow

Cardiac failure i.e. reduced cardiac output, which leads to:

- Reduced tissue perfusion
- Vasoconstriction

Increased after-load

Increased peripheral resistance

Retention of salt and water

Aldosterone release, which increases

Renin release

Angiotensinogen

Angiotensin I

Angiotensin II

Inotropic agents e.g. digoxin increase output

Inotropes

Increased after-load

Increased peripheral resistance
Drugs used in the treatment of heart failure

Myocardial disease, hypertension, vascular disease can cause:

- Increased pre-load
- Increased central venous pressure
- Oedema (peripheral and pulmonary)
- Increased plasma volume

**Cardiac failure** i.e. reduced cardiac output, which leads to:

- Decreased renal blood flow
- Renin release
- Retention of salt and water

**Diuretics:** Furosemide, thiazides (see Card set 13)

**Vasodilators,** e.g. hydralazine (see Card set 6)

**Vasodilators**
- e.g. dobutamine, a β-1 agonist with inotropic action, used in acute heart failure. Beta blockers have negative inotropic actions but are sometimes used if there is sympathetic over-activity

**ACE inhibitors,** e.g. captopril. enalapril (see card set 6)

* Increased after-load
- Increased peripheral resistance
- Increased pre-load
- Inotropic agents *
- e.g. digoxin increase output

**Renin**

**Angiotensinogen**

**Angiotensin I**

**Angiotensin II**

**Aldosterone release,** which increases

- Reduced tissue perfusion
- Oedema (peripheral and pulmonary)
- Increased plasma volume

---

R&D 7e Ch 22, pp 278-280; D&H 2e Ch 21, pp 53-55
Cholesterol and lipoprotein metabolism

**Endogenous pathway**

LDL (low density lipoproteins) carry cholesterol (C) to the tissues. VLDL (very low density lipoproteins) carry triglycerides (TG) and free fatty acids to the tissues.

HDL = high density lipoproteins; ACoA = acetyl Coenzyme A; CE = cholesteryl esters.

To ↓LDL and ↑HDL slows atheroma progress.

**Exogenous pathway**

Portal vein

Bile duct

Bile acids

Intestine

Dietary fat

C + Fatty acids + Glycerol

LDL (low density lipoproteins) carry cholesterol (C) to the tissues.

VLDL (very low density lipoproteins) carry triglycerides (TG) and free fatty acids to the tissues.

HDL = high density lipoproteins; ACoA = acetyl Coenzyme A; CE = cholesteryl esters.

To ↓LDL and ↑HDL slows atheroma progress.
Simvastatin

**Actions**  
Lowers LDL-C. Also produces some lowering of plasma triglyceride and some increase in HDL-C.

**MOA**  
Specific reversible competitive inhibition of the rate-limiting enzyme HMG-CoA-reductase and thus ↓hepatic C synthesis which up-regulates LDL-receptor synthesis and causes ↑clearance of LDLC from plasma into liver cells.

**Abs/Distrb/Elim**  
Given orally; undergoes first-pass metabolism; inactive until biotransformation in the liver. Plasma half-life: 1–3h.

**Clinical use**  
Hypercholesterolaemia. Used to prevent atherosclerosis in patients with high C serum levels and to prevent cardiac infarction in patients who already have atherosclerosis.

**Adverse effects**  
Usually mild: muscle pain, GIT disturbances, insomnia, rash.  
Rarer severe effects: severe myositis (risk increased if given with fibrates); angioedema.

**Special points**  
Statin action is increased by Estimibe.

R&D 7e Ch 23, p 289; D&H 2e Ch 22, pp 56-57
Cholesterol and lipoprotein metabolism

**Endogenous pathway**
- Liver
  - ACoA
  - HMG-CoA reductase
  - MVA
  - LDL receptors
  - Endocytosis by liver cells
- LDL
  - VLDL
  - CE > TG
  - Chylomicron remnant
  - CE > TG
- LDL
  - CE
- HDL
  - CE
- Chylomicron
  - Formation
  - Absorption into lymphatics
- Intestine
  - Bile duct
  - Portal vein
- Cholesterol
  - HDL
  - LDL
  - VLDL

**Exogenous pathway**
- Dietary fat
  - + Glycerol
  - Intestine
  - Chylomicron remnant
  - CE > TG

**Statins**
- E.g. simvastatin
- Decrease synthesis of C
- Increase uptake of LDL

**Other pathways**
- Vascular endothelium
  - Lipoprotein lipase
  - CE > TG
  - Chylomicrons
  - TG > CE

**Other processes**
- C from cell turnover
- Uptake of C
- Free fatty acids
- Peripheral tissues
**Actions**  Fibrates cause: a marked decrease in plasma VLDL and thus triglyceride; a modest decrease in LDL-C; a small increase in HDL-C.

**MOA**  Fibrates ↑transcription of the genes for *lipoprotein lipase* and for the apoproteins apoA1 and apoA5 which are ligands for specific receptors. Fibrates ↑LDL-C uptake by the LDL-C receptors.

**Abs/Distrb/Elim**  Given orally, well absorbed; metabolised to glucuronide conjugates excreted via the kidney.

**Clinical use**  Used for mixed dyslipidemia (i.e. ↑in both plasma TGs and C); also in cases with low HDL and thus ↑risk of atheroma.

**Adverse effects**  GIT upsets; rash; moderate increased risk of gall stones; myositis — which can be severe.

**Special points**  Avoid use of statins with fibrates.
Cholesterol and lipoprotein metabolism

**Endogenous pathway**
- LDL receptors
- HMG-CoA reductase
- ACaA
- MVA
- Bile acids and C
- LDL
- VLDL
- HDL
- Lipoprotein lipase
- Chylomicron remnant
- Chylomicrons
- Vascular endothelium

**Exogenous pathway**
- Portal vein
- Bile duct
- Bile acids
- Intestine
- Dietary fat
- C + Fatty acids + Glycerol

**Signs and symbols**
- Statins e.g. simvastatin, decrease synthesis of C
- Fibrates increase uptake of LDL
- Fibrates decrease secretion
- Fibrates enhance

**Processes**
- Endocytosis by liver cells
- Endogenous pathway
- Exogenous pathway
- HMG-CoA reductase
- MVA
- LDL receptors
- VLDL
- HDL
- Lipoprotein lipase
- Cholesterol from cell turnover
- Uptake of C
- Free fatty acids
- Free fatty acids
- CE
- TG
- CE
**Actions**  Specifically inhibits the absorption of cholesterol from the intestine. Main effect: decrease of plasma LDL concentration.

**MOA**  Blocks a sterol carrier protein in the brush border of enterocytes and thus reduces the amount of biliary and dietary C delivered to the liver via chylomicrons. This results in a ↓ in the liver’s C store, an ↑ in hepatic LDL absorption and ↑ clearance of LDL-C from the plasma.

**Abs/Distrb/Elim**  Given orally, activated in the liver, reaches maximum concentration in 2h after which it undergoes enterohepatic cycling and is gradually excreted in the faeces. Plasma half-life: 22h.

**Clinical use**  Hypercholesterolaemia, usually as adjunct to a statin.

**Adverse effects**  These are few. GIT upsets may occur as may headache, rashes and myalgia.

**Special points**  Plasma concentrations are ↑ by fibrates and ↓ by colestyramine.
**Cholesterol and lipoprotein metabolism**

**Endogenous pathway**
- **Bile acids and C**
  - Endocytosis by liver cells
  - LDL receptors
- **ACoA**
  - HMG-CoA reductase
- **MVA**
  - Liver

**Exogenous pathway**
- **Bile duct**
  - Portal vein
  - Bile acids
  - Dietary fat
  - Intestine
  - Chylomicron formation
  - Chylomicrons
    - TG > CE
    - Cholesterol remnants
    - CE > TG
  - VLDL
    - C
    - TG > CE
    - LDL
    - CE
  - HDL
    - CE

- **Lipoprotein lipase**
  - Free fatty acids
  - CE
  - HDL
  - LDL
  - TG
  - CE
  - Lipid transport

**Statins e.g. simvastatin, decrease synthesis of C**
- **Statins and fibrates increase uptake of LDL**
- **Fibrates decrease secretion**
- **Ezetimibe inhibits absorption of cholesterol**
- **HDL**
  - CE
  - Uptake of C
  - Free fatty acids
  - C from cell turnover
  - Vascular endothelium
  - Peripheral tissues
**Actions**  This is a bile acid binding resin whose main action is to decrease LDL cholesterol.

**MOA**  It is a positively charged drug that binds the negatively charged bile acids inhibiting their absorption. This reduces the pool of bile acids in the liver which decreases the hepatic store of C. This in turn stimulates the synthesis of LDL receptors which results in increased uptake of LDL into liver cells. The drug also lowers C by decreasing its absorption from the GIT.

**Abs/Distrb/Elim**  It is given orally and is not absorbed so there are no adverse systemic effects.

**Clinical use**  Hypercholesterolaemia, often used with a statin.

**Adverse effects**  GIT disturbances: constipation and bloating, sometimes diarrhoea.

**Special points**  Prevents absorption of fat-soluble vitamins, statins, gemfibrozil and other drugs (e.g. digoxin, thiazides, thyroxine, steroids, iron salts, folic acid).
Cholesterol and lipoprotein metabolism

**Endogenous pathway**
- **Statins** e.g. simvastatin, decrease synthesis of C
  - Statins and fibrates increase uptake of LDL
- LDL receptors
  - Endocytosis by liver cells
- ACoA
- HMG-CoA reductase
  - MVA
- Bile acids and C
- Liver

**Exogenous pathway**
- Portal vein
- Bile duct
  - Chylomicron formation
- Dietary fat
  - Intestine
  - Cholesterol
  - Fatty acids
  - Glycerol
- Lipoprotein lipase
  - VLDL
    - TG > CE
    - LDL
    - TG > CE
    - HDL
    - CE
    - Uptake of C
    - Free fatty acids
    - Free fatty acids
    - CE
    - CE
    - CE
    - CE
    - Vascular endothelium
    - Peripheral tissues

**Colesyramine,** colestipol (resins) bind bile acids
- Ezetimibe inhibits absorption of cholesterol
- Fibrates decrease absorption of cholesterol
- Fibrates enhance secretion
- Fibrates decrease synthesis of C
- Statins e.g. simvastatin, decrease synthesis of C
A vitamin (B3) that has lipid-lowering action

**Nicotinic acid**

**Actions & MOA**
Increases HDL. Decreases plasma triglyceride synthesis and reduces the release of VLDL from the liver which results in decreased plasma triglycerides and LDL levels.

**Abs/Distrb/Elim**
Given orally; excreted in the urine.

**Clinical use**
As an adjunct to a statin in dyslipidaemia, or when a statin is contraindicated.

**Adverse effects**
Vasodilatation (with uncomfortable flushing); GIT disturbances, pruritus, rashes. Less commonly: palpitations, dyspnoea, headache, giddiness, peripheral oedema. High doses can impair liver function as well as glucose tolerance and can precipitate gout.

**Special points**
Unwanted effects can limit its clinical use. Pretreatment with ibuprofen can reduce the flushing.
**Cholesterol and lipoprotein metabolism**

### Endogenous pathway

- **Bile duct**: Bile acids
- **Portal vein**: Bile acids
- **Endocytosis by liver cells**: Bile acids and C
- **Lipoprotein lipase**: Chylomicron formation
- **Lipoprotein receptors**: Endocytosis by liver cells
- **HMG-CoA reductase**: Decrease synthesis of C
- **Statins e.g. simvastatin**: Decrease synthesis of C
- **Statins and fibrates**: Increase uptake of LDL
- **Fibrates and nicotinic acid**: Decrease secretion
- **Ezetimibe**: Inhibits absorption of cholesterol
- **Fibrates and nicotinic acid**: Decrease synthesis of C

### Exogenous pathway

- **Intestine**: Dietary fat, C + Fatty acids + Glycerol
- **Vascular endothelium**: CE > TG
- **CE**: Lipoprotein lipase
- **TG > CE**: Chylomicrons
- **LDL**: TG > CE
- **HDL**: CE
- **LDL receptors**: Endocytosis by liver cells
- **VLDL**: TG > CE
- **ACoA**: HMG-CoA reductase
- **MVA**: Liver
- **C from cell turnover**: Uptake of C
- **Free fatty acids**: Vascular endothelium

### Summary

- **Cholestyramine, colestipol (resins)** bind bile acids
- **Statins**: Decrease synthesis of C
- **Fibrates**: Decrease synthesis of C
- **Ezetimibe**: Inhibits absorption of cholesterol
- **Fibrates and nicotinic acid**: Decrease secretion
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)
A non-steroidal drug with antithrombotic and anti-inflammatory properties

**Actions**  Antiplatelet (also analgesic and anti-inflammatory).

**MOA**  Irreversibly inactivates (COX-1); alters balance between TXA₂ and PGI₂ in the platelet/vascular endothelium axis.

**Abs/Distrib/Elim**  Given orally in small doses. Excretion in urine, increased if urine is alkalinised.

**Clinical use**  In the context of thrombosis; to reduce risk of myocardial infarction or transient ischaemic attacks; intermittent small doses given orally decrease platelet TXA₂ without significantly reducing endothelial PGI₂. Also used to treat acute stroke.

**Adverse effects**  Gastrointestinal bleeding because the cytoprotective action of PGs (namely ↓ acid secretion, ↑ mucus & bicarbonate) is decreased; bronchospasm in some individuals. Toxic doses cause respiratory alkalosis followed by acidosis.

**Special points**  Interactions: effects increased by anticoagulants & thrombolytic drugs.

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R&D 7e Ch 24, pp 302-304; D&H 2e Ch 23, pp 58-59
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)

Antiplatelet agents: aspirin

Atherosclerotic plaque (Plaque rupture)

Platelet adhesion, activation, aggregation

Fibrinogen binding to platelet GPIIb/GPIIIa receptors

Thrombus

Activation of clotting factors, tissue factor, XIIa, Xa, Ila, etc.

Fibrin forms the framework of the thrombus

Fibrin degradation products

Trapped blood cells

Plasminogen

Plasmin

Plasminogen activator

Artery wall
Actions  It prevents platelet activation.

**MOA**  It irreversibly inhibits the binding of ADP to the purine receptor on platelets thus inhibiting ADP-mediated platelet activation and interfering with GpIb/IIa-mediated platelet aggregation.

Abs/Distrib/Elim  Given orally, loading dose first then once daily. Metabolised to an active compound. Because action is irreversible, the effects last several days until platelets are replaced.

Clinical use  Prevention & treatment of myocardial infarction & other vascular disorders. Often given with aspirin.

Adverse effects  Unwanted effects: bleeding; GIT discomfort; rashes. Rarely neutropaenia.

Special points  Effects ↑ by other antithrombotic drugs. Interactions: inhibits metabolism of NSAIDs, phenytoin.

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**Diagram:**

- Platelets, activated by adherence, release ADP, 5-HT, TXA₂
- ADP acts on ADP receptors in other platelets activating them to express GP IIb/IIIa receptors
- Clopidogrel selectively blocks ADP receptors
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)

Antiplatelet agents: aspirin, clopidogrel

Plasminogen → Plasmin

Plasminogen activator

Artery wall

Fibrin degradation products

Fibrin

Activation of clotting factors, tissue factor, XIIa, Xa, IIa, etc.

Platelet adhesion activation aggregation

Trapped blood cells

Atherosclerotic plaque

Plaque rupture

Thrombus

Platelet

Activation

Aggregation

Clotting factors

Pulmonary embolism

Pulmonary embolism prevention
**Actions**  
It inhibits platelet activation.

**MOA**  
Abciximab is a monoclonal antibody Fab fragment against the platelet GP IIb/IIIa receptor. It binds and inactivates the receptor preventing the binding of fibrinogen thus inhibiting platelet aggregation.

**Abs/Distrib/Elim**  
Given by i.v. injection. Half life 10–30min.

**Clinical use**  
Adjunct to heparin and aspirin in high-risk patients undergoing coronary angioplasty (an operation to unblock coronary artery). Prevents restenosis and reinfarction.

**Adverse effects**  
Bleeding; thrombocytopenia.

**Special points**  
For specialist use. Used just once because of immunogenicity. Drug with similar action: eptifibatide, a peptide sequence from a GPIIb/IIIa receptor ligand.
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)

Atherosclerotic plaque

Plaque rupture

Platelet adhesion

Activation of clotting factors,
tissue factor, Xlla, Xa, IIa, etc.

FIBRIN forms the framework of the THROMBUS

Trapped blood cells

Fibrin degradation products

Plasminogen

Plasmin

Antiplatelet agents: aspirin, clopidogrel, abciximab

Artery wall
**Actions**  It inhibits platelet aggregation.

**MOA**  Has vasodilator activity; prevents platelet adenosine uptake & cyclic GMP phosphodiesterase action.

**Abs/Distrib/Elim**  Given orally, usually as a modified release preparation.

**Clinical use**  Used with aspirin for secondary prevention of ischaemic stroke & transient ischaemic attacks.

**Adverse effects**  Headache (common); GIT disturbances; hypotension, hypersensitivity reactions.
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)
**Actions & MOA**  It enzymically activates plasminogen to give plasmin which digests fibrin & fibrinogen, lysing the clot.

**Abs/Distrib/Elim**  Given by i.v. injection or infusion; short half-life.

**Clinical use**  Myocardial infarction, deep vein thrombosis, pulmonary embolism, acute ischaemic stroke.

**Adverse effects**  Bleeding (most important), reperfusion dysrhythmias, nausea & vomiting, hypersensitivity reactions.

**Special points**  It needs to be given within 12 hours of the onset of the condition, preferably within 1 hour.

**Similar drug**  Retepase (long half-life).
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)

- Antiplatelet agents: aspirin, clopidogrel, abciximab, dipyridamole

- Fibrinolytic Agents: alteplase, reteplase

Atherosclerotic plaque

- Plaque rupture

- Activation of clotting factors, tissue factor, Xllla, Xa, lla, etc.

- Fibrin forms the framework of the THROMBUS

- Trapped blood cells

- Fibrin degradation products

- Artery wall

- Plasminogen

- Plasmin

- Plasminogen activator
An antifibrinolytic agent

Tranexamic acid

**Actions & MOA**  It inhibits plasminogen activation and thus prevents fibrinolysis.

**Abs/Distrib/Elim**  Given orally and by i.v. injection or infusion.

**Clinical use**  To reduce haemorrhage following dental extraction or prostatectomy. For menorrhagia, epistaxis, hereditary angioedema, thrombolytic overdose.

**Adverse effects**  GIT disturbances. Rare: hypersensitivity skin reactions, disturbed colour vision.

R&D 7e Ch 24, p 307; D&H 2e Ch 23, pp 58-59
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)

Platelet adhesion
Activation aggregation

Activation of clotting factors, tissue factor, Xlla, Xa, Ila, etc.

Fibrin forms the framework of the thrombus

Fibrin degradation products

Thrombus

Fibrinolytic Agents
alteplase, reteplase

Plasminogen

Plasmin

Antifibrinolytic agent
tranexamic acid

Antiplatelet agents:
aspirin, clopidogrel, abciximab, dipyridamole

Trapped blood cells
**Action**  It inhibits blood coagulation.

**MOA**  Accelerates action of antithrombin III (ATIII) increasing its inactivation mainly of factors IIa (thrombin) & Xa; also affects IXa, XIa, & XIIa.

**Abs/Distrib/Elim**  Given by subcut. or by i.v. injection. Elimination half-life 40–90min; renal excretion.

**Clinical use**  To treat deep vein thrombosis, pulmonary embolism, unstable angina, acute peripheral arterial occlusion.

**Adverse effects**  Main adverse effect: bleeding. Thrombocytopenia, hypersensitivity reactions, osteoporosis.

**Special points**  Dosage is adjusted according to the activated partial thromboplastin time. Overdose treated with protamine sulfate.

**Similar drugs**  Low molecular weight heparins.
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein).

Antiplatelet agents: aspirin, clopidogrel, abciximab, dipyridamole

Fibrinolytic Agents alteplase, reteplase

Antifibrinolytic agent tranexamic acid

Fibrin degradation products

Atherosclerotic plaque Plaque rupture

Platelet adhesion activation aggregation

Activation of clotting factors, tissue factor, XIIa, Xa, IIa, etc.

FIBRIN forms the framework of the THROMBUS

Fibrinolytic Agents

Anticoagulants heparin

Thrombus

Trapped blood cells

Plasminogen Plasmin

Plasminogen activator

Artery wall
**Action**  It inhibits blood coagulation.

**MOA**  Accelerates action of antithrombin III (ATIII) increasing its inactivation of Factor Xa.

**Abs/Distrib/Elim**  Given by subcut. injection. Elimination half-life 130–180 min; renal excretion.

**Clinical use**  To prevent venous thromboembolism. To treat deep vein thrombosis, pulmonary embolism, myocardial infarction, unstable angina.

**Adverse effects**  Main adverse effect: bleeding. Less likely than heparin to cause thrombocytopenia, hypersensitivity reactions, osteoporosis.

**Special points**  No need to monitor the activated partial thromboplastin time. Overdose treated with protamine sulfate.

**Similar drugs**  Other low molecular weight heparins: e.g. bemiparin, dalteparin.

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### BLOOD COAGULATION

- **Atherosclerotic plaque or damaged endothelium**
- **The in vivo pathway**
  - VIIa (tissue factor)
  - XIIa
  - Xla
  - IXa
  - Factor X
  - Xa
- **The in vitro contact system**
  - Ca $^{2+}$ + Factor Va + phospholipid
  - Factor II (prothrombin)
  - IIa (thrombin)
  - Heparin + ATIII

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R&D 7e Ch 24, p 299; D&H 2e Ch 23, pp 58-59
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein).

Antiplatelet agents: aspirin, clopidogrel, abciximab, dipyridamole

Fibrinolytic Agents alteplase, reteplase

Antifibrinolytic agent tranexamic acid

Activation of clotting factors, tissue factor, XIIa, Xa, IIa, etc.

Fibrin forms the framework of the thrombus

Trapped blood cells

Fibrinolytic Agents alteplase, reteplase

Antiplatelet agents: aspirin, clopidogrel, abciximab, dipyridamole

Fibrin degradation products

Anticoagulants heparin enoxaparin
An oral anticoagulant

**Warfarin**

**Action**
It inhibits blood coagulation.

**MOA**
Inhibits the reduction of vitamin K and thus prevents the γ-carboxylation of the glutamate residues in factors II, VII, IX & X – shown in red in the figure.

**Abs/Distrib/Elim**
Given orally. Onset slow because the circulating γ-carboxylated factors have to be degraded.

**Clinical use**
To treat deep vein thrombosis, pulmonary embolism. To prevent embolisation in atrial fibrillation.

**Adverse effects**
Bleeding; treated by giving natural Vit K or fresh plasma or coagulation factor concentrates.

**Special points**
Prothrombin time must be monitored. Action increased (with ↑ risk of bleeding) by many drugs e.g. ciprofloxacin, aspirin. Action decreased (with ↓ risk of clotting) by many drugs e.g. rifampicin.

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R&D 7e Ch 24, pp 300-301; D&H 2e Ch 23, pp 58-59
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)

Antiplatelet agents: aspirin, clopidogrel, abciximab, dipyridamole

Fibrinolytic Agents alteplase, reteplase

Antifibrinolytic agent tranexamic acid

Plasminogen ——> Plasmin

Artery wall

Atherosclerotic plaque

Plaque rupture

Platelet adhesion
activation aggregation

Fibrin forms the framework of the THROMBUS

Trapped blood cells

Activation of clotting factors, tissue factor, XIIa, Xa, IIa, etc.

Anticoagulants: heparin, enoxaparin, warfarin

Fibrin degradation products

Plasminogen activator

Anticoagulants are used mainly for thromboembolism in ... ? ... vessels because ... ... ?

Antiplatelet drugs are used mainly for thromboembolism in ... ? ... because ... ... ?
The diagram used on the front faces of this set of cards was a schematic diagram of an arterial thrombus showing – for simplicity – both platelet aggregation/activation and blood coagulation contributing to the thrombus.

Anticoagulants (e.g. warfarin, heparin, low molecular weight heparins which modify blood coagulation and inhibit the formation of fibrin) are used mainly for thromboembolism in veins because venous thrombi consist largely of a fibrin mesh with platelets and blood cells trapped inside it.

Antiplatelet drugs (e.g. aspirin, clopidogrel which modify platelet aggregation and activation) are used mainly for thromboembolism in arteries because arterial thrombi have a large platelet component with not much contribution from blood coagulation. Anticoagulants have little effect on arterial thrombi.
The diagram shows the events leading up to platelet aggregation.

- Platelet adhesion and activation
- GPIIb/IIIa receptor activation
- Release of ADP
- Synthesis of TXA₂
- AGGREGATION
The main examples of drugs that affect platelet aggregation at the site indicated. There are, of course, others.

- **Abciximab**: Release of ADP, aggregation, and activation.
- **Clopidogrel**: GPIIb/IIIa receptor activation.
- **Aspirin**: Inhibits synthesis of TXA₂.
- **Dipyridamole**: Inhibits synthesis of TXA₂.

Release of ADP → GPIIb/IIIa receptor activation → Platelet adhesion and activation → AGGREGATION
Synthesis of nucleotide thymidylate (dTMP)

\[ \text{dTMP} \rightarrow \text{dUMP} \]

\[ \text{DHFR} \rightarrow \text{FH}_4 \rightarrow \text{FH}_2 \rightarrow \text{FH}_4 + 1\text{-carbon unit} \]

\[ \text{dTMP synthetase} \]

\[ \text{dTMP (aka TMP)} = \text{thymidylate} \]
\[ \text{DHFR} = \text{dihydrofolate reductase} \]
\[ \text{FH}_2 = \text{dihydrofolate} \]
\[ \text{FH}_4 = \text{tetrahydrofolate} \]
\[ \text{dUMP (aka UMP)} = \text{uridylate} \]
**Actions & MOA** Folic acid is essential for DNA synthesis and cell proliferation. In the tetrahydrofolate (FH\(_4\)) form it is a cofactor in the synthesis of purines and pyrimidines being particularly important in thymidylate synthesis.

**Abs/Distrib/Elim** Given orally, it is absorbed by active transport into intestinal mucosal cells where it is reduced to FH\(_4\) then methylated to methyl-FH\(_4\) which passes into the plasma and from thence into cells. The functionally inactive methyl-FH\(_4\) is demethylated in a Vit B\(_{12}\)-dependent reaction (see card 11.03).

**Clinical use** To treat megaloblastic anaemias caused by folate deficiency. To prevent the development of folate deficiency in susceptible individuals (e.g. pregnant women, premature infants, patients with severe chronic haemolytic anaemias). To treat toxicity caused by methotrexate (a folate antagonist).

**Adverse effects** Rare; occasionally GIT disturbances.

**Special points** Should not be used in undiagnosed megaloblastic anaemias because if the anaemia is due to Vit B\(_{12}\)-deficiency the anemia may improve but the neurological lesions will persist and could get worse.
Synthesis of nucleotide thymidylate (dTMP)

- **Folic acid**
- **FH₂**
- **FH₄** + 1-carbon unit
- **dTMP**
- **dUMP**

**Symbols and abbreviations:**
- DHFR = dihydrofolate reductase
- FH₂ = dihydrofolate
- FH₄ = tetrahydrofolate
- dTMP (aka TMP) = thymidylate
- dUMP (aka UMP) = uridylate

**Equations:**
- DHFR → FH₂ → FH₄ + 1-carbon unit → Thymidylate synthetase → dTMP
- DHFR → FH₂ → FH₄ + 1-carbon unit → Thymidylate synthetase → dUMP
Restores the blood picture in megaloblastic anaemias (e.g. pernicious anaemia) and results in partial to full recovery of the neurological syndrome (subacute combined degeneration of the spinal cord).

It is necessary for the conversion of methyl-tetrahydrofolate (methyl-FH$_4$) to tetrahydrofolate (FH$_4$) which is essential for thymidylate synthesis and thus for DNA synthesis.

Given by i.m. injection.

To treat pernicious anaemia and other causes of vitamin B$_{12}$ deficiency.

Nausea, dizziness, headache and hypersensitivity reactions; hypokalaemia at start of treatment.

Cyanocobalamin.
Role of Vit B\textsubscript{12} (hydroxocobalamin) in reactions necessary for synthesis of thymidylate (dTMP)

DHFR = dehydrofolate reductase, \( \text{FH}_2 \) = dihydrofolate, \( \text{FH}_4 \) = tetrahydrofolate. dUMP = uridylate, dTMP = thymidylate
A recombinant growth factor controlling erythropoiesis

**Epoetin**

**Actions & MOA**  It binds to receptors on committed erythrocyte progenitor cells stimulating proliferation and differentiation.

**Abs/Distrib/Elim**  Given by subcut. or i.v. injection.

**Clinical use**  To treat the anaemia of chronic renal failure and of AIDS; to alleviate anaemia caused by cytotoxic anticancer drugs; to prevent anaemia in premature infants.

**Adverse effects**  GIT disturbances; hypertension.
Growth factors controlling haemopoiesis

- IL = interleukin
- SCF = stem cell factor

**Stem cell**
- Erythropoietin
- Monocyte-granulocyte precursor
  - Neutrophils
  - Eosinophils
  - Basophils
- IL-2
- IL-4

**Committed progenitor cells**
- SCF, IL-3, IL-6, IL-1

**Cytokines**
- Thrombopoietin
- Erythropoietin
- Megakaryocyte
- Platelets
- Erythrocytes
- Monocytes
- T lymphocytes
- B lymphocytes
Recombinant human granulocyte-colony-stimulating factor

**Actions & MOA**  Interacts with specific receptors on myeloid progenitor cells causing proliferation and differentiation. It can mobilise haemopoietic stem cells from bone marrow to blood.

**Abs/Distrib/Elim**  Given by subcut. injection, subcut infusion or i.v. injection.

**Clinical use**  Neutropenia associated with cytotoxic cancer chemotherapy, bone marrow transplantation or HIV infection.

**Adverse effects**  GIT disturbances, bone pain, muscle pain, fever, rash, alopecia.

**Similar drug**  Lenograstim.

**Special points**  For use only by experienced clinicians.
Growth factors controlling haemopoiesis

- **Committed progenitor cells**
  - **SCF, IL-3, IL-6, IL-1**
  - **Thrombopoietin**
    - **Megakaryocyte** → **Platelets**
  - **Erythropoietin**
    - **Megakaryocyte** → **Erythrocytes**
  - **Monocyte-granulocyte precursor**
    - **Filgrastim**
      - **Neutrophils**, **Eosinophils**, **Basophils**
    - **IL-2** → **T lymphocytes**
    - **IL-4** → **B lymphocytes**

**Cytokines**

**IL** = interleukin

**SCF** = stem cell factor
A haematinic agent

**Ferrous sulfate**

*R&D 7e Ch 25, p 311; D&H 2e Ch 24, p 60*

It is used in haemoglobin production in red blood cell precursors in the bone marrow.

**Abs/Distrib/Elim**  Given orally.

**Actions & MOA**  It is used in haemoglobin production in red blood cell precursors in the bone marrow.

**Clinical use**  Iron-deficiency anaemia.

**Adverse effects**  Dose-related GIT disturbances – nausea, epigastric pain, abdominal cramps, diarrhoea.

**Drugs with similar action**  Ferrous fumarate, ferrous gluconate – given orally. Iron dextran given by deep i.m. injection or slow i.v. infusion.

**Special points**  Iron toxicity both acute (due to excessive ingestion of iron salts) or chronic (e.g. from repeated blood transfusions) is treated with the iron chelator desferrioxamine.

*R&D 7e Ch 25, p 311; D&H 2e Ch 24, p 60*
Ferric iron (Fe$^{3+}$) enters the body in the diet, is converted in the GIT into ferrous iron (Fe$^{2+}$), which is absorbed into the mucosal cells by active transport and from thence into the plasma.

In the plasma, iron is bound to transferrin and most is used in rbc generation in the bone marrow.

The body cannot excrete iron but 1mg per day is lost mainly through sloughing of ferritin-containing GIT mucosal cells.

Iron is stored as ferritin or haemosiderin, mainly in mononuclear phagocytes (mnp) and liver.

**Absorption in food**

1mg per day

**Ferrous sulfate**

**Plasma (4mg)**

**Tissues (150mg)**

Iron is present in myoglobin, in cytochromes and other enzymes

**Bone marrow:**

in rbc precursors (150mg)

**Stores in mnp (1000mg)**

Hb in rbc (3000mg)
Folic acid is usually given to pregnant women as a supplement – to prevent the development of neural tube defects (e.g. spina bifida) in the foetus.

Iron is also important in pregnant women but whether it should be given as a supplement is controversial; there are two schools of thought:

- Some authorities believe that a good diet containing iron-rich foods is preferable to using oral iron salts because these can result in adverse effects to both mother and foetus, and that iron supplements should not be given unless iron levels are low due to dietary factors or blood loss (e.g. from haemorrhoids, GIT ulcers etc.)

- Some authorities recommend that all pregnant women take 27mg a day of iron as a supplement.
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack**  
(bronchial hyper-reactivity and spasm)

- **Triggers:** Allergen (e.g. pollen, animal dander)  
  Air pollutants, viral infection

- **Mast cell spasmogens:** (e.g. histamine, LTC₄, LTD₄ etc.)

- **Chemotaxins:** (e.g. LTB₄, cytokines etc.)

  - **Smooth muscle**  
    - **Mucosa**  
    - **Bronchospasm**

  - **Normal bronchiole**

**Delayed phase of the asthma attack**  
(bronchial hyper-reactivity, spasm and airway inflammation)

- **Influx/activation of inflammatory cells,** (e.g. eosinophils, monocytes, T cells etc.)  
  which release leukotrienes, cytokines, eosinophil proteins etc.

  - **Bronchospasm**  
    - **wheezing, cough**

  - **↑ of hyper-reactivity & inflammation**

  - **Mucus**
Actions: Bronchodilatation – a physiological antagonist of spasmogenic mediators; minimal action on heart: ↑rate and force.

MOA: ↓calcium-mediated contraction in bronchioles. ↑cAMP which activates protein kinase A (PKA). PKA inhibits myosin light chain kinase (MLCK) – the mediator of contraction.

Abs/Distrb/Elim: By inhalation for asthma. Short-acting (3–5h); can be given i.v. in acute severe asthma. Mainly excreted unchanged.

Clinical use: For the acute asthmatic attack – used ‘as needed’. To prevent exercise-induced asthma. For chronic obstructive airways disease.

Unwanted effects: Tremors, tachycardia, sometimes dysrhythmias, nervousness, some peripheral dilatation.

Special points: Selective β₂-agonists are first-line drugs for the acute phase i.e. the acute attack; ineffective on the delayed phase.
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack** (bronchial hyper-reactivity and spasm)
- **Triggers:** Allergen (e.g. pollen, animal dander) || Air pollutants, viral infection
- Mast cell spasmogens (e.g. histamine, LTC₄, LTD₄ etc.) ➔ release ➔ Chemotaxins (e.g. LTB₄, cytokines etc.) ➔ Bronchospasm

**Normal bronchiole**

**Delayed phase of the asthma attack** (bronchial hyper-reactivity, spasm and airway inflammation)
- **Influx /activation of inflammatory cells,** (e.g. eosinophils, monocytes, T cells etc.) ➔ release leukotrienes, cytokines, eosinophil proteins etc. ➔ which cause:
  - Bronchospasm ➔ wheezing, cough
  - ↑ of hyper-reactivity & inflammation

**Salbutamol reverses the bronchospasm**

**Mucosa**

**Smooth muscle**
A long-acting selective $\beta_2$-agonist (similar drug: formoterol. See also card 2.01)

**Salmeterol**

*Actions* Bronchodilatation – a physiological antagonist of spasmogenic mediators. (Minimal action on heart: $\uparrow$ rate and force).

**MOA** $\downarrow$ calcium-mediated contraction in bronchioles. $\uparrow$cAMP which activates protein kinase A (PKA). PKA inhibits myosin light chain kinase (MLCK) – the mediator of contraction.

**Abs/Distrb/Elim** By inhalation for asthma. Long-acting (8–12h); Mostly metabolised by P450 with significant amount lost in faeces.

**Clinical use** To prevent bronchconstriction with exercise-induced asthma or at night in patients needing prolonged bronchodilator therapy. For chronic obstructive pulmonary disease.

**Unwanted effects** Tremors, tachycardia, sometimes dysrhythmias, nervousness, some peripheral vasodilatation.

**Special points** Not used for the acute attack; not given ‘as needed’ but regularly as adjunct to corticosteroids.
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack**
(bronchial hyper-reactivity and spasm)

- Triggers: Allergen (e.g. pollen, animal dander)  
- Air pollutants, viral infection

Mast cell spasmogens
(e.g histamine, LTC₄, LTD₄ etc.)

Chemotaxins
(e.g. LTB₄, cytokines etc.)

![Smooth muscle](image)

**Mucosa**

![Bronchospasm](image)

Normal bronchiole

Salbutamol & salmeterol reverse bronchospasm

**Delayed phase of the asthma attack**
(bronchial hyper-reactivity, spasm and airway inflammation)

- Influx /activation of inflammatory cells, (eosinophils, monocytes, T cells etc.) which release leukotrienes, cytokines, eosinophil proteins etc.
- Which cause:
- Bronchospasm wheezing, cough
- ↑of hyper-reactivity & inflammation

Mucus
**Actions**  Bronchodilatation. (Also stimulates CNS and CVS.)

**MOA**  Inhibits phosphodiesterase PDE4 thus ↑cAMP (and ?cGMP) thus relaxing smooth muscle. Inhibition of PDE4 in inflammatory cells can ↓mediator release.

**Abs/Distrb/Elim**  Sustained-release preparations given orally. Plasma half-life (~8h) is ↑by liver disease, cardiac failure & viral infection and ↓by heavy smoking & drinking. Plasma level is ↓by rifampicin, phenytoin, carbamazepine and ↑by erythromycin, diltiazem, fluconazole and caffeine. Aminophylline can be given i.v.

**Clinical use**  A second-line drug for chronic asthma not adequately controlled by β₂-agonists. Aminophylline i.v. is used for severe acute asthma.

**Unwanted effects**  GIT disturbances, tachycardia, anxiety. High plasma levels can cause serious dysrhythmia or seizures.

**Special points**  Plasma levels should be monitored.
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack**
(bronchial hyper-reactivity and spasm)

- Triggers: Allergen (e.g. pollen, animal dander) Air pollutants, viral infection

- Mast cell spasmogens (e.g. histamine, LTC4, LTD4 etc.)

- Chemotaxins (e.g. LTB4, cytokines etc.)

**Delayed phase of the asthma attack**
(bronchial hyper-reactivity, spasm and airway inflammation)

- Influx /activation of inflammatory cells, (eosinophils, monocytes, T cells etc.) which release leukotrienes, cytokines, eosinophil proteins etc. which cause:

- Bronchospasm
- Wheezing, cough
- ↑ of hyper-reactivity & inflammation

**Triggers:** Salbutamol, salmeterol, theophylline

**Smooth muscle**

**Mucosa**

**Normal bronchiole**

**Bronchospasm**

**↑ of hyper-reactivity & inflammation**

**Mucus**
A leukotriene receptor antagonist (Similar drug: zafirlukast)

**Actions**  Reverses bronchoconstriction. Relaxes airway smooth muscle in mild asthma.

**MOA**  The drug is an antagonist at the cysteinyl leukotriene receptor, \((\text{CysLT}_1)\) on which the bronchospasmic mediators \(\text{LTC}_4\), \(\text{LTD}_4\) and \(\text{LTE}_4\) act. It can ↓ both the early- and late-phase responses to inhaled allergen.

**Abs/Distrb/Elim**  Given orally. Metabolised in liver and excreted mainly in bile; half-life 3–5h.

**Clinical use**  A third-line drug for asthma, used as adjunct to inhaled corticosteroids and long-acting \(\beta_2\)-agonists. Effective in aspirin-induced asthma.

**Unwanted effects**  Few.

**Special points**  Easy for children to take.
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack**
(bronchial hyper-reactivity and spasm)

- **Triggers:**
  - Allergen (e.g. pollen, animal dander)
  - Air pollutants, viral infection

- **Mast cell spasmogens**
  - (e.g. histamine, LTC₄, LTD₄ etc.)

- **Chemotaxins**
  - (e.g. LTB₄, cytokines etc.)

- **Montelukast**

- **Smooth muscle**

- **Bronchospasm**

- **Mucosa**

- **Normal bronchiole**

- **Salbutamol, salmeterol theophylline reverse bronchospasm**

**Delayed phase of the asthma attack**
(bronchial hyper-reactivity, spasm and airway inflammation)

- **Influx /activation of inflammatory cells,**
  - (eosinophils, monocytes, T cells etc.)
  - Which release leukotrienes, cytokines, eosinophil proteins etc.
  - Which cause:
    - Bronchospasm
    - Wheezing, cough
    - ↑ of hyper-reactivity & inflammation

- **Mucus**
**Actions** Bronchodilatation by inhibiting acetylcholine-mediated bronchoconstriction and mucus secretion. No effect on the late phase.

**MOA** Competitively antagonises acetylcholine action on muscarinic receptors.

**Abs/Distr/Elim** Given by inhalation; the action lasts for 3–5h.

**Clinical use** For asthma as adjunct to β₂-agonist & corticosteroids; for chronic obstructive pulmonary disease.

**Unwanted effects** Few.

**Special points** Useful in patients intolerant of β₂-agonists.
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack**
(bronchial hyper-reactivity and spasm)

- **Triggers:** Allergen (e.g. pollen, animal dander), Air pollutants, viral infection
- Mast cell spasmogens (e.g. histamine, \( \text{LTC}_4, \text{LTD}_4 \) etc.)
- Chemotaxins (e.g. \( \text{LTB}_4 \), cytokines etc.)

**Delayed phase of the asthma attack**
(bronchial hyper-reactivity, spasm and airway inflammation)

- Influx/activation of inflammatory cells, (e.g. eosinophils, monocytes, T cells etc.) which release leukotrienes, cytokines, eosinophil proteins etc. which cause:
- Bronchospasm, wheezing, cough
- ↑ of hyper-reactivity & inflammation

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**Immediate phase**:
- Normal bronchiole
- Smooth muscle
- Mucosa
- Bronchospasm
- Salbutamol, salmeterol, theophylline, **ipratropium** reverse bronchospasm

**Delayed phase**:
- Montelukast
- Mucus
An antiasthmatic corticosteroid (Similar: budesonide; fluticasone, hydrocortisone)

**Beclometasone**

**Actions** Reduces hyper-reactivity and decreases the inflammatory delayed phase. No effect on the immediate phase. (See also card 16.01.)

**MOA** Reduces the activation of inflammatory cells and the release of mediators especially cytokines (see cards 4.05 & 16.02).

**Abs/Distrb/Elim** Given by inhalation with metered-dose inhaler; the full action takes weeks to occur.

**Clinical use** Added to bronchodilator therapy if this is inadequate. An i.v. glucocorticoid (e.g. hydrocortisone) is life-saving in acute severe asthma (status asthmaticus).

**Unwanted effects** Hoarse voice; oral candidiasis (thrush).

**Special points** Regular high doses of inhaled corticosteroids can be absorbed and cause adrenal suppression and other adverse effects (see card 16.03).

R&D 7e Ch 27, p 343; D&H 2e Ch 25, pp 62-63
**Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways**

**Immediate phase of the asthma attack**
(bronchial hyper-reactivity and spasm)

- **Triggers:** Allergen (e.g. pollen, animal dander)
- Air pollutants, viral infection

**Mast cell spasmogens**
(e.g. histamine, LTC₄, LTD₄ etc.)

**Chemotaxins**
(e.g. LTB₄, cytokines etc.)

**Beclometasone inhibits**

- Bronchospasm
- wheezing, cough

**Smooth muscle**

**Mucosa**

**Normal bronchiole**

**Delay phase of the asthma attack**
(bronchial hyper-reactivity, spasm and airway inflammation)

- **Influx /activation of inflammatory cells,**
  (eosinophils, monocytes, T cells etc.)
- which release leukotrienes, cytokines, eosinophil proteins etc.
  which cause:

  - Bronchospasm
  - wheezing, cough
  - ↑ of hyper-reactivity & inflammation

- **Triggers:** Salbutamol, salmeterol, theophylline, ipratropium reverse bronchospasm

- **Beclometasone**
**Actions**  Reduces plasma IgE levels and decreases magnitude of both early and late phases.

**MOA**  It is a monoclonal antibody that inhibits the binding of IgE to mast cells (and eosinophils) thus reducing mediator release.

**Abs/Distrb/Elim**  Given subcutaneously at 2–4 week intervals.

**Clinical use**  For persistent allergic asthma not completely controlled with inhaled corticosteroid plus long-acting $\beta_2$-agonist.

**Unwanted effects**  Hypersensitivity reactions.

**Special points**  Needs expert administration.
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack**
(bronchial hyper-reactivity and spasm)

- Triggers: Allergen (e.g. pollen, animal dander) Air pollutants, viral infection
- Mast cell spasmogens (e.g. histamine, LTC₄, LTD₄ etc.)
- Chemotaxins (e.g. LTB₄, cytokines etc.)
- Montelukast

**Delayed phase of the asthma attack**
(bronchial hyper-reactivity, spasm and airway inflammation)

- Influx /activation of inflammatory cells, (eosinophils, monocytes, T cells etc.) which release leukotrienes, cytokines, eosinophil proteins etc. which cause:
  - Bronchospasm wheezing, cough
  - ↑ of hyper-reactivity & inflammation

**Triggers:**
- Salbutamol, salmeterol, theophylline, ipratropium reverse bronchospasm
- Beclometasone inhibits
- Omalizumab

**Smooth muscle**
**Mucosa**
**Normal bronchiole**

**Mucus**
**Cromoglicate**

**Actions**  Moderate inhibition of allergen – and exercise-induced asthma and bronchial hyperreactivity – but not in all patients. No effect on bronchial spasm.

**MOA**  Inhibits mast cell degranulation and the response of sensory C fibres to irritants (early phase) and eosinophil activation (delayed phase) possibly by an action on chloride channels in the plasma membranes.

**Abs/Distrb/Elim**  Given by powder inhalation.

**Clinical use**  Prophylaxis of asthma, mainly in older children. To reduce symptoms of allergic rhinitis.

**Unwanted effects**  Irritation of throat by the powder.

**Special points**  None.

R&D 7e Ch 27, p 343; D&H 2e Ch 25, p 63
Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways

**Immediate phase of the asthma attack** (bronchial hyper-reactivity and spasm)
- **Triggers:** Allergen (e.g. pollen, animal dander), Air pollutants, viral infection
- **Mast cell spasmogens** (e.g. histamine, \( \text{LTC}_4, \text{LTD}_4 \) etc.)
- **Chemotaxins** (e.g. \( \text{LTB}_4 \), cytokines etc.)
- **Smooth muscle**
- **Mucosa**
- **Normal bronchiole**
- **Bronchospasm**
- **Salbutamol, salmeterol, theophylline, ipratropium reverse bronchospasm**

**Delayed phase of the asthma attack** (bronchial hyper-reactivity, spasm and airway inflammation)
- **Triggers:** Allergen (e.g. pollen, animal dander), Air pollutants, viral infection
- **Influx /activation of inflammatory cells,**
  (eosinophils, monocytes, T cells etc.)
- **Chemotaxins** (e.g. \( \text{LTB}_4 \), cytokines, eosinophil proteins etc.)
- **Beclometasone inhibits**
- **Bronchospasm**
- **Wheezeing, cough**
- **↑ of hyper-reactivity & inflammation**
- **Mucus**

**Cromoglicate** can inhibit
Based on the cards you've done, work out the possible names of drugs A, B, C etc, in the five-step programme given below, and specify the mode of administration.

Step 1  Patient is started on Drug A. How would A be given?

Step 2  If drug A is needed more often than specified in Step 1, add Drug B.
        How would B be given?

Step 3  If asthma is not adequately controlled, add Drug C. How would it be given?

Step 4  If asthma is still not adequately controlled, add other drug(s). How would it/they be given?

Step 5  If asthma is still not adequately controlled, add another drug. How would it be given?
How might the main drugs given here be introduced gradually in a patient whose asthma is difficult to control?

**Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways**

**Immediate phase of the asthma attack**
(bronchial hyper-reactivity and spasm)

- Triggers: Allergen (e.g. pollen, animal dander), Air pollutants, viral infection
  - Mast cell spasmogens (e.g. histamine, \( \text{LTC}_4, \text{LTD}_4 \) etc.)
  - Chemotaxins (e.g. \( \text{LTB}_4 \), cytokines etc.)

**Delayed phase of the asthma attack**
(bronchial hyper-reactivity, spasm and airway inflammation)

- Triggers: Salbutamol, salmeterol, theophylline, ipratropium reverse bronchospasm
  - Beclometasone inhibits
  - Montelukast
  - Omalizumab

**Immediate and delayed phases**

- Bronchospasm
- Wheezing, cough
- Influx /activation of inflammatory cells, (eosinophils, monocytes, T cells etc.) which release leukotrienes, cytokines, eosinophil proteins etc. which cause:
  - Bronchospasm
  - \( \uparrow \) of hyper-reactivity & inflammation

- Salbutamol, salmeterol, theophylline, ipratropium reverse bronchospasm
- Beclometasone
- Cromoglicate can inhibit
Step 1  Patient is started on a short-acting bronchodilator such as salbutamol. Taken by inhalation ‘as needed’ – up to once daily.

Step 2  If inhalation of the short-acting bronchodilator is needed more than once a day, regular inhaled beclometasone is added.

Step 3  If the asthma is not adequately controlled, a long-acting bronchodilator (salmeterol) taken regularly by inhalation is added rather than increasing the doses of beclometasone.

Step 4  If the asthma is still not adequately controlled, oral theophylline or montelukast is added – or the dose of inhaled beclometasone is increased.

Step 5  If the asthma is still not adequately controlled, a regular single daily dose of an oral corticosteroid (e.g. prednisolone) is added.
Kidney

Diagram of the nephron with 3 tubular cells shown enlarged as a basis for specifying drug action

Bowman’s capsule

Proximal tubule (shown straightened out)

Na⁺/K⁺ ATPase moving Na⁺ out into the interstitium and K⁺ into the cell

Symporter moving Na⁺, K⁺ and 2Cl⁻ from lumen into cell

Symporter moving K⁺ and Cl⁻ out of cell into interstitium

Medullary loop

Co-transporter moving Na⁺ and Cl⁻ from lumen into cell

Na⁺ channel

Aldosterone mediator activates ADH acts on V₂ receptors to increase permeability

Distal convoluted tubule (shown straightened out)

Collecting tubule

Na⁺/K⁺ ATPase moving Na⁺ out into the interstitium and K⁺ into the cell

Co-transporter moving Na⁺ and Cl⁻ from lumen into cell

Symporter moving K⁺ and Cl⁻ out of cell into interstitium

Na⁺ channel

Aldosterone mediator activates ADH acts on V₂ receptors to increase permeability

Diagram of the nephron with 3 tubular cells shown enlarged as a basis for specifying drug action

Symporter moving Na⁺, K⁺ and 2Cl⁻ from lumen into cell

Co-transporter moving Na⁺ and Cl⁻ from lumen into cell

Symporter moving K⁺ and Cl⁻ out of cell into interstitium

Na⁺ channel

Aldosterone mediator activates ADH acts on V₂ receptors to increase permeability
A loop diuretic (Similar drug: bumetanide)

**Furosemide**

**Actions** Causes copious urine production by inhibiting NaCl reabsorption in the thick ascending loop. Increases excretion of Ca\(^{2+}\) and Mg\(^{2+}\), decreases excretion of uric acid.

**MOA** Inhibits the Na\(^{+}\)/K\(^{+}\)/2Cl\(^{-}\) co-transporter in the luminal membrane by combining with the chloride binding site.

**Abs/Distrb/Elim** Given orally (can be given i.v. in emergencies), well absorbed, reaches site of action by being secreted into the proximal tubule. Half-life 90min.

**Clinical use** Pulmonary oedema, chronic heart failure, ascites due to liver cirrhosis, hypercalcaemia, hyperkalaemia.

**Adverse effects** Hypokalaemic alkalosis; hyperuricaemia (can precipitate gout); hypovolaemia and hypotension in elderly patients; reversible ototoxicity.

R&D 7e Ch 28, pp 353-354; D&H 2e Ch 26, pp 64-65
Diagram of the nephron with 3 tubular cells shown enlarged as a basis for specifying drug action

- **Bowman’s capsule**
- **Proximal tubule (shown straightened out)**
- **Medullary loop**
- **Ascending loop (thick segment)**
- **Distal convoluted tubule (shown straightened out)**
- **Collecting tubule**

**Furosemide**

- **Na⁺ channel**
- **Aldosterone mediator activates ADH acts on V₂ receptors to increase permeability**

**Diagram Description**

- The nephron is diagrammed, showing the movement of ions and water through the different tubular segments.

**Key Points**

- **Hydrochlorothiazide** influence on kidney function, particularly on reabsorption and secretion processes.
- **Furosemide** action and its effect on electrolyte transport.

**Pharmacological Mechanisms**

- Ion transport mechanisms in different tubular segments, with specific emphasis on the effects of aldosterone and ADH.
- Role of drugs like Hydrochlorothiazide and Furosemide in altering ion balance and fluid management.

**Clinical Relevance**

- Understanding the nephron’s structure and function is crucial for pharmacology, particularly in conditions like hypertension and heart failure, where renal sodium and water management is critical.

**Educational Notes**

- This diagram is a valuable educational tool for visualizing the complex interplay of ions and water in the nephron.
- It highlights the importance of osmoregulation and the role of hormones like ADH and aldosterone in sodium and water reabsorption.

**Additional Information**

- **Kidney** function, particularly in the context of electrolyte balance and fluid homeostasis, is a fundamental concept in medical sciences.
**Actions**  Causes moderate degree of diuresis by inhibiting NaCl reabsorption in the distal tubule. Increases K⁺ and H⁺ excretion. Decreases excretion of Ca²⁺ and uric acid; increases excretion of Mg²⁺. Some vasodilator action.

**MOA**  Inhibits the Na⁺/Cl⁻ co-transporter in the luminal membrane of the distal convoluted tubule.

**Abs/Distrb/Elim**  Given orally; reaches site of action by being secreted into the proximal tubule. Half-life 90min.

**Clinical use**  Hypertension. Also mild heart failure; nephrogenic diabetes insipidus; kidney stones.

**Adverse effects**  Potassium loss; metabolic alkalosis; hyperuricaemia (can precipitate gout); increased insulin requirement; erectile dysfunction.
Diagram of the nephron with 3 tubular cells shown enlarged as a basis for specifying drug action.

- **Bowman’s capsule**
- **Proximal tubule (shown straightened out)**
- **Ascending loop (thick segment)**
- **Medullary loop**
- **Distal convoluted tubule (shown straightened out)**
- **Collecting tubule**

**Drug Action Diagram**:

- **Furosemide**
- **Hydrochlorothiazide, bendroflumethiazide**
- **Na⁺ channel**
- **Aldosterone mediator activates ADH acts on V₂ receptors to increase permeability**

**Drug Mechanisms**:

- **Aldosterone**
- **ADH acts on V₂ receptors**
- **Na⁺ channel**
- **H₂O channel**
- **K⁺ channel**
- **2Cl⁻ channel**

**Processes**:

- **Na⁺ transport**
- **K⁺ transport**
- **Cl⁻ transport**
- **H₂O transport**
**Amiloride**

**Actions**
Inhibits sodium reabsorption in the distal nephron; has limited diuretic efficacy. Reduces K⁺ excretion.

**MOA**
Inhibits the sodium channel in the luminal membrane of the collecting tubule, reducing sodium influx.

**Abs/Distrb/Elim**
Given orally. Triamterene has more rapid onset and shorter duration of action than amiloride.

**Clinical use**
Given with K⁺-losing diuretics (thiazides, loop diuretics) to limit K⁺ loss.

**Adverse effects**
Hyperkalaemia; may cause acidosis.
Diagram of the nephron with 3 tubular cells shown enlarged as a basis for specifying drug action

- **Bowman’s capsule**
- **Proximal tubule** (shown straightened out)
- **Medullary loop**
- **Ascending loop (thick segment)**
- **Distal convoluted tubule** (shown straightened out)
- **Collecting tubule**

**Na⁺**, **K⁺**, **Cl⁻**, **H₂O**

- **Na⁺ channel**
- **Aldosterone mediator activates ADH acts on V₂ receptors to increase permeability**
- **Amiloride, triamterene**
- **Hydrochlorothiazide, bendroflumethiazide**

**Spironolactone**

**Furosemide**
**Potassium-sparing diuretic (Similar drug eplerenone)**

**Spironolactone**

**Actions**  Inhibits sodium reabsorption in the distal nephron; has limited diuretic efficacy. Reduces $K^+$ excretion.

**MOA**  It is a competitive antagonist of aldosterone; causes diuresis by preventing the production of the aldosterone mediator that normally causes influx of sodium by activating the sodium channel in the luminal membrane of the collecting tubule.

**Abs/Distrb/Elim**  Given orally, gives rise to active metabolite, canrenone, which has a plasma half-life of 16h. Eplerenone has no active metabolite and a shorter half-life.

**Clinical use**  Hypertension, given with $K^+$-losing diuretics (thiazides, loop diuretics) to limit $K^+$ loss. Primary and secondary hyperaldosteronism.

**Adverse effects**  Hyperkalaemia; hyperchloraemic acidosis. Can cause gynaecomastia (less likely with eplerenone).
Diagram of the nephron with 3 tubular cells shown enlarged as a basis for specifying drug action

- **Bowman’s capsule**
- **Proximal tubule** (shown straightened out)
- **Ascending loop (thick segment)**
- **Medullary loop**
- **Distal convoluted tubule** (shown straightened out)
- **Collecting tubule**

**Na⁺** channel

**K⁺** channel

**Cl⁻** channel

**H₂O** channel

**Furosemide**

**Hydrochlorothiazide, bendroflumethiazide**

**Amiloride, triamterene**

**Spironolactone is an aldosterone antagonist**

**Aldosterone mediator activates Spironolactone**
**Actions**  Increases the amount or water excreted by the kidney; has a smaller effect on sodium excretion.

**MOA**  It is an inert compound that passes across into the filtrate at the glomerulus and is not resorbed. Acts in those parts of the nephron that are freely permeable to water.

**Abs/Distrb/Elim**  Given intravenously, not metabolised, excreted in about 30min.

**Clinical use**  Cerebral oedema; increased intraocular pressure.

**Adverse effects**  Temporary expansion of the extracellular fluid compartment and hyponatraemia due to osmotic extraction of intracellular water. Pulmonary oedema may occur.
What drug will turn the urine alkaline?

**Diagram of the nephron with 3 tubular cells shown enlarged**

- **Bowman’s capsule**
- **Proximal tubule** (shown straightened out)
- **Medullary loop**
- **Ascending loop (thick segment)**
- **Distal convoluted tubule** (shown straightened out)
- **Collecting tubule**

**Mannitol** increases osmotic pressure

**Na^+**, **K^+**, **Cl^−**

**Furosemide**

**Aldosterone mediator activates**

**Spironolactone** is an aldosterone antagonist

**Hydrochlorothiazide, bendroflumethiazide**

**Na^+** channel

**Amiloride, triamterene**
Alkalization of the urine

- **Bowman’s capsule**
- **Proximal tubule** (shown straightened out)

**Mannitol** increases osmotic pressure

- **Medullary loop**
- **Ascending loop (thick segment)**
- **Distal convoluted tubule** (shown straightened out)
- **Collecting tubule**

- **Na⁺**, **K⁺**, **Cl⁻**, **P**
- **Na⁺ channel**, **H₂O channel**

**Mannitol**

- Furosemide

**Potassium or sodium citrate**
- *Given orally. Adverse effects: mild diuresis, hyperkalaemia with high doses*

**Hydrochlorothiazide, bendroflumethiazide**

**Amiloride, triamterene**

**Spironolactone** is an aldosterone antagonist

**Aldosterone mediator** activates

Spironolactone is an aldosterone antagonist

*Given orally. Adverse effects: mild diuresis, hyperkalaemia with high doses*

R&D 7e Ch 28, pp 356-357
Factors influencing gastric HCl secretion and the development of gastric ulcers

*Helicobacter pylori* → Gastrin release

Gastrin → Gastrin receptor (G)

Histamine → Histamine receptor (M)

Arachidonate → Arachidonate receptor

Vagus nerve → Muscarinic receptor (M)

Ulcer → Mucosal damage

Gastric mucosa

PP → Proton pump

C → K⁺-Cl⁻ symport carrier

G → Gastrin receptor

H₂ → Histamine receptor

M → Muscarinic receptor

PG → Prostaglandin receptor

NSAIDs → NSAIDS are ulcerogenic

ACh → Muscarinic receptor

Vagus nerve

Gastric lumen
**Actions**  Inhibits gastric acid secretion. Inhibits action of histamine released from mast cell-like cells in the gastric mucosa. Partially inhibits acid secretion stimulated by gastrin or vagal stimulation.

**MOA**  Selective, reversible, competitive antagonism of histamine H$_2$ receptors on parietal cells.

**Abs/Distrib/Elim**  Oral administration. ($T_{0.5}$, 2h, ranitidine 3h).

**Clinical use**  Peptic and duodenal ulcers. Gastro-oesophageal reflux disease. NSAID-induced ulcers (with discontinuation of NSAID).


**Special points**  Cimetidine (but not the other H$_2$ antagonists) is a potent cytochrome P450 inhibitor. Many interactions due to increased plasma concentration of other drugs (e.g. propranolol, benzodiazepines, phenytoin, warfarin). Cimetidine and ranitidine also inhibit renal tubular secretion of other drugs.
Factors influencing gastric HCl secretion and the development of gastric ulcers

- **Helicobacter pylori** → Gastrin release
- Gastric lumen
- Parietal cell
- **PP** proton pump
- **C** K⁺–Cl⁻ symport carrier
- **G** gastrin receptor
- **H₂** histamine receptor
- **M** muscarinic receptor
- **PG** prostaglandin receptor
- **NSAIDs**
  - (NSAIDS are ulcerogenic)
- **Cimetidine, ranitidine**

Ulcer

- Gastric mucosa
- Mucosal damage

Vagus nerve

- Arachidonate
- **ACh**
- **PGE₂**
- **Histamine**
- ‘Mast cell’
**Actions**  Inhibition of gastric acid secretion.

**MOA**  Binds irreversibly to the H⁺/K⁺-ATPase (proton pump) in the gastric parietal cells to inhibit H⁺ transport. Omeprazole (like other PPIs) is a prodrug. The acidic conditions in the parietal cell canaliculi convert the drug to the active form.

**Abs/Distrib/Elim**  Mainly eliminated by rapid P450 metabolism in liver (T₀.₅, 1–2h), but duration of action is long (2–3 days) because of covalent binding. The production of new PP molecules determines the rate of recovery. Needs enteric coating to prevent action of acid before absorption.

**Clinical use**  Duodenal and peptic ulcer. Gastro-oesophageal reflux disease. Zollinger-Ellison syndrome. As part of the triple therapy for *Helicobacter pylori*-dependent ulcers. Treatment of NSAID-associated ulcers. PPIs are more effective than H₂ antagonists.

**Adverse effects**  Generally very safe. Occasionally, headache, abdominal pain, diarrhoea, flatulence and nausea. Long-term use can cause hypergastrinaemia which may increase risk of gastric carcinoid tumours.
Factors influencing gastric HCl secretion and the development of gastric ulcers

Helicobacter pylori → Gastrin release

Gastrin release

Mucosal damage

PP proton pump
C K⁺-Cl⁻ symport carrier
G gastrin receptor
H₂ histamine receptor
M muscarinic receptor
PG prostaglandin receptor

Gastric lumen

Parietal cell

K⁺

Cl⁻

H⁺

K⁺

PP

H₂

M

PG

NSAIDs

(NSAIDS are ulcerogenic)

Gastrin release

Histamine

‘Mast cell’

Cimetidine, ranitidine

Cimetidine, ranitidine

Cimetidine, ranitidine

PGE₂

Arachidonate

Vagus nerve
Macrolide antibiotic for eradication of *Helicobacter pylori*

**Actions**  Bactericidal.

**MOA**  Kills bacteria by binding to their ribosomes to inhibit protein synthesis.

**Abs/Distrib/Elim**  Active orally. Metabolised by liver (with significant first-pass metabolism). $t_{1/2}$ 3–4h.

**Clinical use**  Many peptic ulcers occur secondary to *H. pylori* infection. Triple therapy (a combination of two antibiotics with a proton pump inhibitor or H$_2$ antagonist) is an effective treatment. Amoxicillin may be replaced by metronidazole in patients allergic to penicillins.

**Adverse effects**  Gastrointestinal upsets – diarrhoea, nausea.
Bismuth chelate (tripotassium dicitratobismuthate, bismuth subsalicylate used in USA)

Factors influencing gastric HCl secretion and the development of gastric ulcers

- Helicobacter pylori
- Metronidazole, clarithromycin, amoxicillin
- Gastrin
- ‘Mast cell’
- Histamine
- Cimetidine, ranitidine
- Omeprazole, lansoprazole
- PPI proton pump
- C K⁺-Cl⁻ symport carrier
- Gastrin receptor
- H₂ histamine receptor
- Muscarinic receptor
- PG prostaglandin receptor
- NSAIDs

( NSAIDS are ulcerogenic)
**Actions**  Antidiarrhoea / antiulcer.

**MOA**  Antibacterial action against *H. pylori* plus a protective effect on the gastric mucosa. Coats ulcer/mucosa to reduce action of acid and pepsin and may increase mucus and bicarbonate secretion. May also enhance prostaglandin synthesis.

**Abs/Distrib/Elim**  Very little (1%) of oral dose is absorbed into the systemic circulation.

**Clinical use**  (I) Duodenal ulcers (in combination with metronidazole and tetracycline). Ranitidine bismuth citrate is used with antibiotics to eradicate *H. pylori* infection. (II) Diarrhoea (including travellers’, binds enterotoxins).

**Adverse effects**  Low frequency of side effects: nausea, vomiting, black stools.
Factors influencing gastric HCl secretion and the development of gastric ulcers

**Bismuth chelate**

**Helicobacter pylori**

**Mucosal damage**

**Gastric mucosa**

**Ulcer**

**Gastrointestinal lumen**

**Parietal cell**

**PP proton pump**

**C K⁺-Cl⁻ symport carrier**

**G gastrin receptor**

**H₂ histamine receptor**

**M muscarinic receptor**

**PG prostaglandin receptor**

**Gastrin release**

**Gastrin**

**Histamine**

**Mast cell**

**Cimetidine, ranitidine**

**Metronidazole, clarithromycin, amoxicillin**

**Omeprazole, lansoprazole**

**NSAIDs**

**Arachidonate**

**Vagus nerve**

**PGE₂**

**Helicobacter pylori**

**Mucosal damage**

**Gastric lumen**

**Parietal cell**

**NSAIDs are ulcerogenic**
**Actions**  Prevents damage to gut mucosa by HCl, pepsin and bile acids. Stimulates mucosal secretion of mucus, bicarbonate and prostaglandins.

**MOA**  Sucralfate is a complex of aluminium hydroxide and sulfated sucrose. This forms a viscous paste which adheres to ulcer bases to provide a protective barrier. Antacids and drugs reducing acid secretion will inhibit its action.

**Abs/Distrib/Elim**  Given orally. Local action, virtually no absorption.

**Clinical use**  Gastric and duodenal ulcer. Gastro-oesophageal reflux disease.

**Adverse effects**  Constipation. Formation of solid complexes (bezoars) within stomach. Aluminium toxicity in patients with renal impairment.

**Special points**  Sucralfate will reduce the absorption of many drugs and food substances. This can be minimised by taking them 2h before sucralfate.
Factors influencing gastric HCl secretion and the development of gastric ulcers

- **Bismuth chelate**
  - Mucosal damage

- **Helicobacter pylori**
  - Gastrin release

- **Metronidazole, clarithromycin, amoxicillin**

- **Sucralfate**
  - Mucosal damage

- **Omeprazole, lansoprazole**
  - PP proton pump
  - C K⁺-Cl⁻ symport carrier
  - G gastrin receptor
  - H₂ histamine receptor
  - M muscarinic receptor
  - PG prostaglandin receptor

- **Gastrin**
  - Gastrin release

- **Histamine**
  - ‘Mast cell’

- **Cimetidine, ranitidine**

- **Parietal cell**
  - K⁺, Cl⁻, H⁺, H₂, M, PG

- **Vagus nerve**
  - ACh

- **Arachidonate, PGE₂**

- **NSAIDs**
  - NSAIDS are ulcerogenic

- **Ulcer**
  - Ulceration of gastric mucosa

- **Gastric lumen**
**Antacid** (Similar drugs: magnesium hydroxide, sodium bicarbonate, calcium carbonate)

### Actions
Lowers pH in gut lumen.

### MOA
Antacids are weak bases that neutralise the HCl secreted in the stomach. The elevation of pH also usefully reduces the activity of pepsin. Stimulates prostaglandin synthesis.

### Abs/Distrib/Elim
Aluminium and magnesium hydroxides are poorly absorbed from the gut (no systemic actions). NaHCO₃ and CaCO₃ are absorbed and may have significant systemic actions.

### Clinical use

### Adverse effects
Al(OH)₃ causes constipation. Mg(OH)₂ has a strong laxative action (osmotic purgative). NaHCO₃ and CaCO₃ release CO₂ which causes belching and also metabolic alkalosis. CaCO₃ causes hypercalcaemia.

### Special point
Calcium and aluminium salts complex with orally administered tetracyclines to prevent their absorption.

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*R&D 7e Ch 29, p 364; D&H 2e Ch 27, p 66*
Factors influencing gastric HCl secretion and the development of gastric ulcers

- **Bismuth chelate**
- **Metronidazole, clarithromycin, amoxicillin**
- **Helicobacter pylori**
- **Gastrin release**
- **Cimetidine, ranitidine**
- **Sucralfate**
- **Antacids**
- **Omeprazole, lansoprazole**
- **Ulcer**
- **Gastric mucosa**

- **PP proton pump**
- **C K⁺-Cl⁻ symport carrier**
- **G gastrin receptor**
- **H₂ histamine receptor**
- **M muscarinic receptor**
- **PG prostaglandin receptor**

**(NSAIDS are ulcerogenic)**
**Actions**  Promotes gastric ulcer healing. Combats the ulcerogenic action of NSAIDs.

**MOA**  Activates prostaglandin receptors (EP₃ subtype) to inhibit acid secretion. Effects mediated by Gᵢ-mediated inhibition of adenylate cyclase. Additionally stimulates bicarbonate and mucus secretion.

**Abs/Distrib/Elim**  Well absorbed orally. Rapidly hydrolysed to free acid which is the active moiety. $T_{0.5}$ 30–40min.

**Clinical use**  Gastric ulcers – particularly those caused by NSAIDs and where the NSAIDs cannot be withdrawn. Abortifacient.

**Adverse effects**  Diarrhoea, abdominal cramps. Should be avoided in pregnancy because of contractile action on uterus.
The central control of vomiting and stimuli resulting in emesis

Disorienting motion

- Labyrinth

- Vestibular nuclei

Unpleasant/emotional sensations (repulsive experiences)

- Higher centres

- Vomiting centre in medulla

CTZ = chemoreceptor trigger zone

Stimuli to pharynx/stomach via vagus and nucleus of solitary tract

Toxins/drugs

Muscles involved in vomiting

CNS

Periphery
**Actions**  Antiemetic. Sedative. (Also prevents histamine’s actions in the periphery, e.g. Use in hay fever (see card 4.07).

**MOA**  Reversible competitive antagonist at $H_1$ receptors. Antiemetic action is due to blocking $H_1$ receptors in the vestibular nuclei and in the ‘vomiting centre’.

**Abs/Distrib/Elim**  $T_{0.5}$ 10h. Significant first-pass metabolism. Meclizine longer $T_{0.5}$.

**Clinical use**  Motion sickness and other emesis of vestibular origin (e.g. Meniere’s disease). Vomiting in early pregnancy. Emesis due to local stimuli in the gut acting via the vagus.

**Adverse effects**  Sedative action may not be desirable – contraindicated for driving etc. Confusion in elderly. Cyclizine and cinnarizine are less sedating. Dry mouth (anticholinergic action). Potentially fatal respiratory depression in infants under 2y.
The central control of vomiting and stimuli resulting in emesis

Disorienting motion

- Labyrinth
  - Vestibular nuclei

Unpleasant/emotional sensations (repulsive experiences)

- Higher centres
  - Vomiting centre in medulla

CTZ = chemoreceptor trigger zone

Promethazine, cyclizine, meclizine, cinnarizine

Periphery
- Stimuli to pharynx/stomach via vagus and nucleus of solitary tract

CTZ in area postrema
- Toxins/drugs
- Muscles involved in vomiting

Muscles involved in vomiting

CNS

Higher centres

Vomiting centre in medulla
**Actions**  
Antiemetic. Other actions consistent with antagonism of parasympathetic nervous system (see card 1.03).

**MOA**  
Reversible competitive antagonism of muscarinic receptors. Antiemetic effects due to blockade of receptors in vestibular nucleus and in the vomiting centre.

**Abs/Distrib/Elim**  
Active orally ($t_{1/2}$ 5h). A transdermal patch applied behind ear is particularly effective, lasting for up to 3 days.

**Clinical use**  
Particularly effective, when given prophylactically, against motion sickness. No efficacy against chemotherapy-induced emesis mediated via the CTZ. Effective against local gut stimuli.

**Adverse effects**  
Drowsiness. Amnesia. Actions attributable to muscarinic receptor block (dry mouth, tachycardia, blurred vision, urinary retention). Avoid in closed-angle glaucoma.
The central control of vomiting and stimuli resulting in emesis

Disorienting motion → Labyrinth → Vestibular nuclei

Unpleasant/emotional sensations (repulsive experiences) → Higher centres → Vomiting centre in medulla

CTZ in area postrema

CNS

Promethazine, cyclizine, meclizine, cinnarizine

Scopolamine

Periphery

Stimuli to pharynx/stomach via vagus and nucleus of solitary tract

CTZ = chemoreceptor trigger zone

Muscles involved in vomiting

Toxins/drugs
5-HT₃-receptor antagonist (Similar drugs: granisetron, dolasetron, tropisetron)

Ondansetron

**Actions**  Antiemetic.

**MOA**  Reversible competitive antagonism at 5-HT₃ receptors in the CTZ and at the sensory endings of vagal afferents in the GIT.

**Abs/Distrib/Elim**  Given orally or i.v. (if vomiting). T₀.₅ 4–6h. Metabolised by cytochrome P450 system in liver.

**Clinical use**  Main agents for nausea and vomiting due to cytotoxic, anticancer drugs. Often given a short time before starting chemotherapy. Nausea and vomiting arising postoperatively or after radiation treatment . Limited effectiveness in motion sickness.

**Adverse effects**  Well tolerated. Headache, GIT upsets.

R&D 7e Ch 29, pp 366-367; D&H 2e Ch 27, p 67
The central control of vomiting and stimuli resulting in emesis

Disorienting motion → Labyrinth

Unpleasant/emotional sensations (repulsive experiences) → Higher centres

CTZ in area postrema

Vomiting centre in medulla

CTZ = chemoreceptor trigger zone

Promethazine, cyclizine, meclizine, cinnarizine

Ondansetron, dolasetron, granisetron, tropisetron

Scopolamine

CNS

Periphery

Stimuli to pharynx/stomach via vagus and nucleus of solitary tract

Muscles involved in vomiting

Toxins/drugs
**Actions**  Antiemetic. Antipsychotic (see card 23.01).

**MOA**  Reversible competitive antagonism of dopamine D<sub>2</sub> receptors in CTZ. Some of the side effects are due to antagonism of other receptors (e.g. adrenoceptors and histamine receptors).

**Abs/Distrib/Elim**  Oral administration. T<sub>0.5</sub> 15–30h. (P450 metabolism in liver.)

**Clinical use**  Nausea and vomiting associated with cancer chemotherapy, radiation therapy and general anaesthesia.

**Adverse effects**  Extrapyramidal effects – Parkinsonian symptoms (avoid in patients with Parkinson’s disease). Prolactin release – galactorrhoea. Sedation. Hypotension. Antihistamine and antimuscarinic actions (e.g. dry mouth).
What other groups of drugs have useful antiemetic action?

GIT drugs

Antiemetics

CTZ = chemoreceptor trigger zone

The central control of vomiting and stimuli resulting in emesis

Disorienting motion

Unpleasant/emotional sensations (repulsive experiences)

Labyrinth

Higher centres

Vestibular nuclei

Vomiting centre in medulla

CTZ in area postrema

CNS

Periphery

Stimuli to pharynx/stomach via vagus and nucleus of solitary tract

Promethazine, cyclizine, meclizine, cinnarizine

Ondansetron, dolasetron, granisetron, tropisetron

Chlorpromazine, domperidone, prochlorperazine, metoclopramide

Scopolamine

Muscles involved in vomiting

Toxins/drugs
**Dexamethasone**  Mechanism of antiemetic action is not established. High doses used for nausea and vomiting of chemotherapy (esp. cisplatin). Generally used in combination with other antiemetics.

**Cannabinoids**  Action via CB$_1$ receptors. Used for nausea and vomiting associated with cancer chemotherapy. Dronabinol is the main active ingredient (tetrahydrocannabinol) of cannabis; nabilone is a synthetic analogue. May cause dependence. Nabilone is active by mouth; $T_{0.5}$ 2h.

**Neurokinin receptor antagonists**  E.g. aprepitant blocks substance P receptors in the vomiting centre. Adjunct for treatment of chemotherapy-induced and post-operative nausea and vomiting. Orally active. Metabolised by cytochrome P450 system in liver. $T_{0.5}$ 12h.
Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action

Viruses / bacteria (acute)

(Antibacterials)

Toxins e.g. Cholera toxin

Fluid secretion

Increased fluid volume

Diarrhoea

Reduced fluid / solids volume

Constipation

Increased peristalsis

Decreased peristalsis (stasis)

Parasympathetic / enteric nervous system

Osmotic load

Malabsorption

Drug side effects e.g. opioids, anticholinergics

Underlying disease, anxiety

Malabsorption
**Actions**  
Purgative.

**MOA**  
These agents are poorly absorbed and raise the osmotic load within the gut lumen. This causes ingested water to be retained and water also to be withdrawn from the blood stream. The increased fluid volume promotes movement along the gut. Purgation occurs within 2h.

**Abs/Distrib/Elim**  
Taken orally. Not absorbed.

**Clinical use**  
Bowel cleansing prior to surgery or examination (MgSO₄). Constipation (macrogols and lactulose). The effects of lactulose develop after 2–3 days.

**Adverse effects**  
Abdominal cramps. Few systemic actions because of low absorption.
Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action

Viruses / bacteria (acute) → (Antibacterials)

Osmotic load → Malabsorption

Toxins e.g. Cholera toxin → Fluid secretion → Increased fluid volume → Diarrhoea

Parasympathetic / enteric nervous system

Underlying disease, anxiety

Fluid secretion → Increased peristalsis → Diarrhoea

Reduced fluid / solids volume → Constipation

Drug side effects e.g. opioids, anticholinergics

Magnesium sulfate, lactulose, macrogols
**Actions**  Purgative.

**MOA**  These agents are poorly absorbed and, being hygroscopic, form a soft faecal mass which distends the gut to promote peristalsis.

**Abs/Distrib/Elim**  Taken orally. Not absorbed.

**Clinical use**  Constipation. Used if increasing dietary fibre is inadequate. Beneficial in various bowel disorders (e.g. haemorrhoids, irritable bowel syndrome). Maintain fluid intake to prevent intestinal obstruction.

**Adverse effects**  Flatulence. Few systemic actions because of low absorption. Obstruction.
Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action

- **Viruses / bacteria (acute)**
  - (Antibacterials)
  - Osmotic load
  - Malabsorption

- **Toxins e.g. Cholera toxin**
  - Fluid secretion
  - Increased fluid volume

- **Increased fluid / solids volume**
  - Diarrhoea

- **Increased peristalsis**
  - Parasympathetic / enteric nervous system

- **Decreased peristalsis (stasis)**
  - Underlying disease, anxiety
  - Drug side effects e.g. opioids, anticholinergics

- **Reduced fluid / solids volume**
  - Constipation

- **Magnesium sulfate, lactulose, macrogols**

- **Methylcellulose, dietary fibre (bran), ispaghula husk**

- **Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action**

- **Lubiprostone**
  - GIT drugs
  - Control of motility
**Actions**  
Increases fluid content of gut, thus aiding propulsive movements.

**MOA**  
Activates the CIC-2 chloride channel in the apical membrane of the gastrointestinal epithelium. The enhanced secretion of chloride ion is accompanied by water leading to an increase in intraluminal fluid.

**Abs/Distrib/Elim**  
Oral administration. Local action in the gut – little systemic absorption.

**Clinical use**  
Chronic constipation. Irritable bowel syndrome with constipation.

**Adverse effects**  
Nausea. Diarrhoea.
Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action

- Viruses / bacteria (acute)
  - (Antibacterials)
- Toxins e.g. Cholera toxin
- Fluid secretion
- Increased fluid volume
- Diarrhoea
- Increased peristalsis
- Parasympathetic / enteric nervous system
- Malabsorption
- Osmotic load
- Underlying disease, anxiety

- Reduced fluid / solids volume
- Constipation
- Decreased peristalsis (stasis)
- Drug side effects e.g. opioids, anticholinergics

- Magnesium sulfate, lactulose, macrogols
- Lubiprostone
- Methylcellulose, dietary fibre (bran), ispaghula husk
- Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action
**Actions**  Laxative.

**MOA**  Active metabolite of bisacodyl stimulates peristalsis by irritation of mucosa and/or an effect on the enteric nervous system. Also increases fluid volume by promoting net fluid secretion.

**Abs/Distrib/Elim**  Oral or rectal administration. $T_{0.5}$ 16h. Senna is activated in the colon by bacteria.

**Clinical use**  Chronic constipation. Bowel cleansing prior to surgery/investigation. Action of bisacodyl is more rapid rectally (30min) than orally (6h).

**Adverse effects**  Abdominal cramps. Tolerance to action with atony of the colon if used excessively.

R&D 7e Ch 29, p 368; D&H 2e Ch 27, p 67
Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action

- Viruses / bacteria (acute)
  - (Antibacterials)
- Osmotic load
  - Malabsorption
- Fluid secretion
  - Toxins e.g. Cholera toxin
- Increased fluid volume
- Increased peristalsis
- Diarrhoea
- Reduced fluid / solids volume
- Decreased peristalsis (stasis)
- Constipation

- Drug side effects e.g. opioids, anticholinergics
- Drug side effects e.g. opioids, anticholinergics

- Magnesium sulfate, lactulose, macrogols
- Lubiprostone
- Methylcellulose, dietary fibre (bran), ispaghula husk
- Bisacodyl, senna

- Parasympathetic / enteric nervous system
- Underlying disease, anxiety
**Actions**  Softens/lubricates the stool to allow easier passage along gut and defaecation.

**MOA**  Surfactant with emulsifying action.

**Abs/Distrib/Elim**  Docusate is given orally or rectally, arachis oil rectally.

**Clinical use**  Constipation. Haemorrhoids.

**Adverse effects**  Well-tolerated – possible abdominal cramping. Liquid paraffin may impair the absorption of fat-soluble vitamins.
Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action.

- Viruses / bacteria (acute)
  - (Antibacterials)
- Osmotic load
- Malabsorption
- Parasympathetic / enteric nervous system
- Underlying disease, anxiety

**Diarrhoea**
- Increased peristalsis
- Increased fluid volume
- Fluid secretion
- Toxins e.g. Cholera toxin

**Constipation**
- Decreased peristalsis (stasis)
- Reduced fluid / solids volume

### Drugs

- **Magnesium sulfate, lactulose, macrogols**
- **Lubiprostone**
- **Methylcellulose, dietary fibre (bran), ispaghula husk**
- **Bisacodyl, senna**
- **Docusate, liquid paraffin**

### Underlying causes
- Drug side effects e.g. opioids, anticholinergics
**Actions**  Reduces gut motility and secretions. The slower transit time allows for more fluid absorption and more solid stools.

**MOA**  Agonist action at μ opioid receptors in myenteric plexus of gut inhibits peristalsis. Effects can be reversed by naloxone. Loperamide and diphenoxylate, but not codeine, achieve low concentrations in CNS, so have few central effects (including analgesia and addiction).

**Abs/Distrib/Elim**  Oral administration. Metabolised by hepatic cytochrome P₄₅₀ system. $t_{1/2}$ 10h. Diphenoxylate is hydrolysed to an active metabolite.

**Clinical use**  Acute diarrhoea. Chronic diarrhoea associated with inflammatory bowel disease. Diphenoxylate is commonly administered in a combined preparation with atropine.

**Adverse effects**  Drowsiness and nausea. Constipation and abdominal cramps. CNS depression may occur in overdose.
Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action

Viruses / bacteria (acute)

(Antibacterials)

Toxins e.g. Cholera toxin

Fluid secretion

Increased fluid volume

Diarrhoea

Loperamide, codeine, diphenoxylate

Methylcellulose, dietary fibre (bran), ispaghula husk

Bisacodyl, senna

Drug side effects e.g. opioids, anticholinergics

Magnesium sulfate, lactulose, macrogols

Lubiprostone

Reduced fluid / solids volume

Constipation

Methylnedipropionate

Docusate, liquid paraffin

Parasympathetic / enteric nervous system

Underlying disease, anxiety

Osmotic load

Malabsorption
The main processes determining blood glucose concentrations

- **Absorption of glucose from GIT**
- **Glycogenolysis in muscle and liver**
- **Gluconeogenesis in liver**
- **Uptake and utilisation of glucose by tissues**
- **Glycogen synthesis in muscle and liver**
**Actions**

**MOA**
Binding to its receptor (tyrosine kinase type) causes autophosphorylation of the receptor. Subsequent tyrosine phosphorylation of ‘insulin receptor substrates’ leads to activation of SH2 domain proteins which regulate the action of various intracellular enzymes and cell membrane glucose transporters.

**Abs/Distrb/Elim**
Free insulin in the blood has a $T_{0.5}$ of only 10min so slow-release preparations are needed for regular use. Given s.c. or i.v. Short-acting (3–5h) – soluble (regular) insulin, insulin lispro, insulin aspart. Intermediate-acting (10–12h) – isophane insulin. Long-acting (24h) – insulin zinc suspension (crystalline), insulin glargine.

**Clinical use**
Life-long treatment of type 1 diabetes. Also for type 2 diabetes not controlled by oral hypoglycaemic agents. Soluble insulin also for emergency i.v. treatment of diabetic ketoacidosis.

**Adverse effects**
Hypoglycaemia – treated by glucose administration (by mouth, if conscious, otherwise i.v.) or glucagon (i.m.). Weight gain.

**Special points**
Recombinant human insulin is preferred to animal insulins which may cause antibody formation.

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R&D 7e Ch 30, pp 372-376; D&H 2e Ch 28, pp 68-69
The main processes determining blood glucose concentrations

- Absorption of glucose from GIT
- Glycogenolysis in muscle and liver
- Insulin
- Gluconeogenesis in liver
- Insulin release from B cells in pancreas
- Uptake and utilisation of glucose by tissues
- Glycogen synthesis in muscle and liver

Blood glucose regulation involves the interplay of these processes, influenced by insulin release from the pancreas.
**Glibenclamide**

**Oral hypoglycaemic agent (Similar drugs: tolbutamide, glipizide, glimepiride)**

**Actions**  Increases insulin release from functioning B cells, thus producing the effects of insulin indicated on card 15.01.

**MOA**  Interaction with the sulphonylurea receptor, which is a subunit of the $K_{ATP}$ channel in the cell membrane of B cells, causes the $K^+$ channel to close. This causes the cell to depolarise and activates voltage-dependent $Ca^{2+}$ channels. $Ca^{2+}$ entry stimulates exocytosis of insulin.

**Abs/Distrb/Elim**  Given orally they bind extensively to plasma proteins. Half-lives: glibenclamide 10h, tolbutamide 4h, glipizide 4h, glimepiride 5h. Actions prolonged in patients with renal disease.

**Clinical use**  Type 2 diabetes mellitus, effective in 30% of patients.

**Adverse effects**  Hypoglycaemia (more likely in elderly and with longer-acting sulphonylureas). Weight gain.
The main processes determining blood glucose concentrations

- Absorption of glucose from GIT
- Glycogenolysis in muscle and liver
- Gluconeogenesis in liver
- Insulin release from B cells in pancreas
- Insulin
- Glibenclamide, glipizide
- Uptake and utilisation of glucose by tissues
- Glycogen synthesis in muscle and liver
**Actions**  
Lowers blood glucose concentration.

**MOA**  
Inhibits gluconeogenesis in liver by activating AMP-activated protein kinase. May also enhance tissue sensitivity to insulin. Increases glucose uptake into tissues.

**Abs/Distrb/Elim**  
Given by mouth. Half-life 3h. Mostly excreted unchanged in urine (avoid in patients with renal insufficiency).

**Clinical use**  
Type 2 diabetes (alone or with other oral hypoglycaemic agents). Particularly useful in obese patients.

**Adverse effects**  
Anorexia and gastrointestinal upset including diarrhoea (leading to weight loss). May rarely cause potentially fatal lactic acidosis. (Unlike sulphonylureas does not cause hypoglycaemia.)
The main processes determining blood glucose concentrations

- Absorption of glucose from GIT
- Glycogenolysis in muscle and liver
- Gluconeogenesis in liver
- Insulin release from B cells in pancreas
- Metformin
- Uptake and utilisation of glucose by tissues
- Insulin
- Glibenclamide, glipizide

Insulin promotes uptake and utilisation of glucose by tissues, whereas Metformin inhibits this process.
**Actions**  
Lowers blood glucose concentration. Stimulates insulin release from B cells in pancreatic islets.

**MOA**  
Similar to sulphonylureas. Interaction with the sulphonylurea receptor, a subunit of the $K_{\text{ATP}}$ channel in the cell membrane of B cells, causes the $K^+$ channel to close. This depolarises the cell membrane and activates voltage-dependent $Ca^{2+}$ channels. $Ca^{2+}$ entry promotes exocytosis of insulin.

**Abs/Distrb/Elim**  
Quick onset and short duration of action. Half-life 1h. (Its actions can be reduced by drugs that induce hepatic P450 enzymes, e.g. carbamazepine.) Nateglinide half-life 1.5h.

**Clinical use**  
Type 2 diabetes mellitus. Rapid action allows good control of postprandial hyperglycaemia. May be combined with metformin or a glitazone. Mainly metabolised in liver, so useful in patients with renal insufficiency.

**Adverse effects**  
Hypoglycaemia (uncommon unless its metabolism is inhibited by other drugs, e.g. gemfibrozil).
The main processes determining blood glucose concentrations

- Absorption of glucose from GIT
- Glycogenolysis in muscle and liver
- Gluconeogenesis in liver
- Insulin release from B cells in pancreas
- Uptake and utilisation of glucose by tissues

Drugs:
- Glibenclamide, glipizide, repaglinide, nateglinide
- Metformin

Reactions:
- +: Increase
- -: Decrease

Insulin
**Actions**  
Lowers blood glucose concentration.

**MOA**  
Activates the peroxisomal proliferator – activated receptor – γ in adipose tissue, liver and skeletal muscle to promote transcription of genes coding for proteins important in insulin action. Important effects in control of blood glucose are: reduced glucose release from the liver, increased uptake into muscle and increased sensitivity (reduced resistance) to insulin. The effects develop over 2–3 months.

**Abs/Distrb/Elim**  
Rapid oral absorption, highly bound to plasma proteins. Eliminated mainly by P450 metabolism in liver. (Interactions may occur with drugs inhibiting or inducing cytochrome P450.) Short half-life (7h) but some activity of metabolites.

**Clinical use**  
Type 2 diabetes mellitus. Generally used with a sulphonylurea or metformin.

**Adverse effects**  
Weight gain, fluid retention (may precipitate heart failure). Risk of hypoglycaemia is low. Some glitazones are hepatotoxic so the group as a whole is avoided in patients with liver disease.

R&D 7e Ch 30, pp 381-382; D&H 2e Ch 28, p 69
The main processes determining blood glucose concentrations

- **Absorption of glucose from GIT**
- **Glycogenolysis in muscle and liver**
- **Gluconeogenesis in liver**
- **Insulin**
- **Metformin**
- **Rosiglitazone, pioglitazone**
- **Glibenclamide, glipizide, repaglinide, nateglinide**
- **Glycogen synthesis in muscle and liver**
- **Insulin release from B cells in pancreas**
- **Rosiglitazone, pioglitazone**
- **Insulin**
- **Uptake and utilisation of glucose by tissues**
**Actions**  Delays carbohydrate absorption from intestine.

**MOA**  Inhibits intestinal $\alpha$-glucosidase and pancreatic $\alpha$-amylase so reduces the rise in blood glucose which follows a meal. $\alpha$-glucosidase is the enzyme responsible for breaking down starches and oligosaccharides to yield the absorbable monosaccharides.

**Abs/Distrb/Elim**  Metabolised in GIT by bacteria and digestive enzymes. Half-life 2h.

**Clinical use**  Type 2 diabetes mellitus not controlled by other drugs.

**Adverse effects**  Gastrointestinal discomfort – flatulence, diarrhoea.
The main processes determining blood glucose concentrations

- **Glucose in intestine**
- **Absorption of glucose from GIT**
- **Glycogenolysis in muscle and liver**
- **Gluconeogenesis in liver**
- **Uptake and utilisation of glucose by tissues**
- **Glycogen synthesis in muscle and liver**
- **Insulin release from B cells in pancreas**

**Complex carbohydrates in food**
- **Acarbose**
- **Rosiglitazone, pioglitazone**
- **Glibenclamide, glipizide, repaglinide, nateglinide**
- **Metformin**
- **Rosiglitazone, pioglitazone**

**Blood glucose**

**Insulin**

**Uptake and utilisation of glucose by tissues**
**Actions**  Elevates blood glucose concentration. Increases rate and force of heart contraction.

**MOA**  Glucagon activates adenylate cyclase by acting on G-protein coupled receptors linked to $G_s$. Its actions thus mimic those of adrenaline activating $\beta$-adrenoceptors. It elevates blood glucose by stimulating hepatic gluconeogenesis and glycogenolysis and by inhibiting glycogen synthesis.

**Abs/Distrb/Elim**  Glucagon is a peptide hormone which must be given by injection. Plasma half-life 5min.

**Clinical use**  Emergency treatment of hypoglycaemic emergency (caused by insulin overdose), when oral or i.v. glucose administration is not possible. (Also used to treat heart failure precipitated by $\beta$-adrenoceptor antagonists.)

**Adverse effects**  Uncommon. Cardiac stimulation in patients taking $\beta$-blockers or with phaeochromocytoma.
The main processes determining blood glucose concentrations

- **Glucose in intestine**
  - Absorption of glucose from GIT
  - Complex carbohydrates in food
  - Acarbose
  - Rosiglitazone, pioglitazone

- **Glycogenolysis in muscle and liver**
  - Glucagon
  - Insulin
  - Gluconeogenesis in liver

- **Blood glucose**
  - Glibenclamide, glipizide, repaglinide, nateglinide
  - Insulin release from B cells in pancreas

- **Uptake and utilisation of glucose by tissues**
  - Insulin
  - Glycogen synthesis in muscle and liver
  - Glucagon

- **Secretion of hormones**
  - Metformin
  - Rosiglitazone, pioglitazone

- **Other processes**
  - Insulin release from B cells in pancreas
  - Glucagon
Notes
The figure outlines the synthesis and release of the endogenous corticosteroids.

- Hypothalamus
  - Corticotrophin-releasing factor
  - Corticotrophin (ACTH)
  - Adrenal cortex
    - Glucocorticoids
    - Mineralocorticoids
  - Neural factors
    - Short negative feedback loop
    - Renin-angiotensin system

- Long negative feedback loop
- Hypothalamus
- Anterior pituitary
  - Corticotrophin (ACTH)
  - Adrenal cortex
    - Glucocorticoids
    - Mineralocorticoids
  - Neural factors
    - Short negative feedback loop
    - Renin-angiotensin system
**Actions**  Reduction in chronic inflammation and in autoimmune and hypersensitivity reactions. Metabolic: ↓ uptake & utilisation of glucose; gluconeogenesis; ↑ catabolism and ↓ synthesis of protein; permissive effect on lipolytic hormones. Negative feedback action on ant. pituitary and hypothalamus.

**MOA**  GCs interact with intracellular receptors that control transcription of specific genes (see card 16.02).

**Abs/Distrb/Elim**  Short-acting. Given orally, by injection, topically. The main effects occur only after 2–8 h because protein synthesis of mediators and enzymes is required.

**Similar drugs**  Prednisolone (short-acting; oral, injectable). Triamcinolone (intermediate-acting; i.m. injection, topical). Dexamethasone (longer-acting; oral, injectable). Beclometasone (given by inhalation).

**Clinical use**  Inflammatory, hypersensitivity and autoimmune diseases (rheumatoid arthritis, asthma, anaphylactic shock etc.); to prevent graft rejection; in some cancers. Replacement therapy in adrenal failure.

**Adverse effects**  See card 16.03.
The ant. pituitary & the adrenal cortex

The figure outlines the synthesis and release of the endogenous corticosteroids.

Neural factors

- Hypothalamus
  - Corticotrophin-releasing factor
    - Anterior pituitary
      - Corticotrophin (ACTH)
        - Adrenal cortex
          - Glucocorticoids
          - Mineralocorticoids

Long negative feedback loop

- Hypothalamus
  - Corticotrophin-releasing factor
    - Anterior pituitary
      - Corticotrophin (ACTH)
        - Adrenal cortex
          - Glucocorticoids
          - Mineralocorticoids

Short negative feedback loop

Prednisolone, beclometasone

Peripheral actions:
- Metabolic
- Anti-inflammatory
- Immunosuppressive

Glucocorticoid — GC — Plasma

Cytoplasm

Nucleus

Acts on

Releases
(1) All GC (apart from synthetic compounds) are bound to corticosteroid-binding globulin (CBG) in the plasma.

(2) Released from CBG.

(3) Diffusion into cell and interaction with receptor.

(4) Receptor changes conformation.

(5) Complex interacts with DNA and alters gene expression.

(6a) Inhibition of transcription of some genes (e.g. for COX-2, some cytokines & interleukins etc).

(6b) Transcription of mediator proteins.

(7) Synthesis of mediator proteins.

Plasma

Cytoplasm

Nucleus

e.g. cAMP-dependent kinase, annexin-1 etc.

R&D 7e Ch 32, pp 402-405; D&H 2e Ch 29, pp 70-71
The figure outlines the synthesis and release of the endogenous corticosteroids.

**Neural factors**
- Corticotrophin-releasing factor
- Corticotrophin (ACTH)

**Long negative feedback loop**
- Hypothalamus
- Anterior pituitary

**Short negative feedback loop**
- Adrenal cortex

**Peripheral actions:**
- Metabolic
- Anti-inflammatory
- Immunosuppressive

**Before prolonged corticosteroid therapy**
- Prednisolone, beclometasone

**Acts on**
- Glucocorticoids
- Mineralocorticoids

**Renin-angiotensin system**
A. Used long-term in **inflammatory** or **hypersensitivity** or **autoimmune** conditions*:
   - suppression of response to infection
   - suppression of endogenous GC synthesis
   - osteoporosis
   - growth suppression in children
   - iatrogenic Cushing’s syndrome

* When used thus, the metabolic actions are unwanted

B. Used in corticosteroid **deficiency**
there are few adverse actions

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**Adverse effects of the corticosteroids**

- Euphoria (though sometimes depression, sometimes psychosis)
- Moon face
- Buffalo hump
- Abdominal fat
- Easy bruising
- Poor wound healing
- Thin arms and legs (muscle wasting)
- Iatrogenic Cushing’s syndrome (after prolonged glucocorticoid therapy)
The figure outlines the synthesis and release of the corticosteroids.

**Neural factors**

- Hypothalamus
- Corticotrophin-releasing factor
- Anterior pituitary
- Corticotrophin (ACTH)
- Adrenal cortex

**Renin-angiotensin system**

- Mineralocorticoids
- Glucocorticoids

**Long negative feedback loop**

Prednisolone, beclometasone

**Short negative feedback loop**

- Peripheral actions: Metabolic, anti-inflammatory, immunosuppressive
- Peripheral actions on salt and water metabolism

**ACTH**

**Prednisolone, beclometasone**
A mineralocorticoid (MC) regulating water and electrolyte balance

Fludrocortisone

**Actions**  Acts on the distal renal tubule to increase Na⁺ reabsorption and increase excretion of K⁺ and H⁺.

**MOA**  MCs interact with intracellular receptors in the kidney controlling transcription of specific genes (see card 16.02) that cause:
- ↑ number of Na⁺ channels
- ↑ number of Na⁺ pumps (P).

**Abs/Distrb/Elim**  Given orally.

**Clinical use**  Used (with a glucocorticoid) for replacement therapy in adrenal insufficiency.

**Adverse effects**  Few; hypokalaemia can occur and is increased by thiazides and loop diuretics.
Outline of the control and actions of thyroid hormone system

Hypothalamus

Thyrotrophin-releasing hormone (TRH)

Protirelin

Anterior pituitary

Thyrotrophin

Thyroid

T₄, T₃

Thyroid hormones

↑Metabolism of carbohydrates, proteins, fat; ↑basal metabolic rate
**Actions**  Gradually decreases thyroid hormone output and thus reduces signs & symptoms of thyrotoxicosis.

**MOA** Reduces the synthesis of thyroid hormones by inhibiting thyroperoxidase which normally iodinates tyrosyl residues in thyroglobulin to give the precursors of $T_3$ and $T_4$.

**Abs/Distrb/Elim** Given orally. Carbimazole is converted to methimazole, plasma half-life 6–15h.

**Clinical use** Hyperthyroidism; to control the disease before surgery.

**Adverse effects** Agranulocytosis (rare; incidence 0.1–1.2%); rashes (more common); joint pains.

**Special points** The clinical response may take several weeks because the thyroid stores of hormone need to be depleted and $T_4$ has a long half-life.

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R&D 7e Ch 33, pp 414–415; D&H 2e Ch30, p 73
Outline of the control and actions of thyroid hormone system

1. Hypothalamus
   - Releases Thyrotrophin-releasing hormone (TRH)

2. Anterior pituitary
   - Thyrotrophin

3. Thyroid
   - Secretes T4 and T3
   - Metabolism of carbohydrates, proteins, fat; ↑basal metabolic rate

Thyroid and antithyroid drugs

Levothyroxine

Carbimazole
**Actions**  Increased metabolism of carbohydrates, proteins and fats; increase in basal metabolic rate.

**MOA**  The drug enters cells and is converted to T₃ which enters the nucleus and binds to a thyroid hormone receptor. The complex activates transcription resulting in the generation of mRNA and the synthesis of proteins & enzymes responsible for the metabolic actions of T₄.

**Abs/Distrb/Elim**  Given orally. Has long half-life.

**Clinical use**  Hypothyroidism. Liothyronine is used for myxoedema coma.

**Adverse effects**  Nervousness, palpitations, insomnia, heat intolerance, weight loss.

**Special points**  Best given on an empty stomach since some foods can interfere with absorption.
Outline of the control and actions of thyroid hormone system

- Thyrotrophin-releasing hormone (TRH) released from Hypothalamus
- Protirelin
- Anterior pituitary
- Thyrotrophin
- Thyroid
- Levothyroxine
- Carbimazole

Metabolism of carbohydrates, proteins, fat; ↑basal metabolic rate
Radioactive iodine ($^{131}$I):

**MOA** Emits both X-rays (which do no damage) and $\beta$ radiation which has a very short range and is cytotoxic to local thyroid cells.

**Abs & Distrb** Given orally as a single dose, taken up by thyroid cells, incorporated into thyroglobulin. $^{131}$I half-life is 8 days.

**Clin. use** Thyrotoxicosis. Maximum effect takes ~ 4 months.

**Adverse effects** Hypothyroidism will eventually occur.

Radioactive iodine ($^{131}$I) acts on thyrotoxicosis to reduce thyroid hormone release and metabolism.
Schematic outline of bone formation

The bone remodelling cycle:

**Bone resorption**
1. The precursor cells differentiate to osteoclasts (OCs) or osteoblasts (OBs).
2. OCs digest bone.

**Bone formation**
3. OBs secrete osteoid (bone matrix).
4. Mineralisation of the osteoid occurs, i.e. complex calcium phosphate crystals (hydroxyapatite) are deposited.
**Actions**  It decreases bone resorption and increases bone density.

**MOA**  It prevents osteoclast-mediated bone resorption. Also it is incorporated into the bone matrix and ingested by osteoclasts, promoting osteoclast apoptosis.

**Abs/Distrb/Elim**  Given orally with a large amount of water 1 hour before eating, it localizes at sites of bone mineralisation. Being an analogue of pyrophosphate, it binds to the hydroxyapatite in bone matrix.


**Adverse effects**  GIT disturbances particularly oesophagitis; bone pain. Osteonecrosis of the jaw (rare).

**Special points**  Patient needs to remain upright for ~1 hour after administration to avoid reflux.
Schematic outline of bone formation

**The bone remodelling cycle:**

**Bone resorption**
1. The precursor cells differentiate to osteoclasts (OCs) or osteoblasts (OBs).
2. OCs digest bone.

**Bone formation**
3. OBs secrete osteoid (bone matrix).
4. Mineralisation of the osteoid occurs, i.e. complex calcium phosphate crystals (hydroxyapatite) are deposited.
**Teriparatide**

A recombinant form of parathyroid hormone (Similar drug: parathyroid hormone)

**Special points**
Should be given by experts in osteoporosis treatment.

**Actions**
It has anabolic effects on bone, increasing bone mass, structural integrity and strength.

**MOA**
It increases the number of osteoblasts in bone and activates the OBs already there.

**Abs/Distrb/Elim**
Given subcut. once daily.

**Clinical use**
Osteoporosis in postmenpausal women and in men.
Glucocorticoid-induced osteoporosis.

**Adverse effects**
GIT disturbances, dizziness, muscle cramps.

**Special points**
Should be given by experts in osteoporosis treatment.
Schematic outline of bone formation

The bone remodelling cycle:

**Bone resorption**
1. The precursor cells differentiate to osteoclasts (OCs) or osteoblasts (OBs).
2. OCs digest bone.

**Bone formation**
3. OBs secrete osteoid (bone matrix).
4. Mineralisation of the osteoid occurs, i.e. complex calcium phosphate crystals (hydroxyapatite) are deposited.
**Actions** It has agonist effects on bone and on the CVS but antagonist action on mammary glands and the uterus.

**MOA** Like the oestrogens, it inhibits the cytokines that recruit osteoclasts.

**Abs/Distrb/Elim** Given orally, undergoes first-pass metabolism. Bioavailability ~2%. Plasma half-life ~32h.

**Clinical use** Prophylaxis for postmenopausal osteoporosis and breast cancer.

**Adverse effects** Risk of thromboembolism.
What are the main hormones that affect bone metabolism and what is their clinical importance?

Schematic outline of bone formation

The bone remodelling cycle:

**Bone resorption**
1. The precursor cells differentiate to osteoclasts (OCs) or osteoblasts (OBs).
2. OCs digest bone.

**Bone formation**
3. OBs secrete osteoid (bone matrix).
4. Mineralisation of the osteoid occurs, i.e. complex calcium phosphate crystals (hydroxyapatite) are deposited.
**Oestrogens** are important in maintaining bone integrity in females and the decrease in their levels at menopause results in osteoporosis. Oestrogen preparations (see figure) are not the first choice for this condition because of the risk of breast cancer.

Large or long-continued doses of **glucocorticoids** can cause osteoporosis by inhibiting OB differentiation and activity and stimulating OC activity.

**Vitamin D** is converted into active metabolites which function as true hormones important in regulating plasma calcium and bone metabolism. Vit D preparations are used to treat bone diseases (see cards 18.05 & 18.06).
The vitamin D family, parathyroid and calcium metabolism

Cholesterol gives rise to 7-dehydrocholesterol
which gives rise to Vit D₃
then to the hormones:

- Calcifediol
- Calcitriol

Liver

Kidney

Parathyroid

Calcitriol in blood

Biological actions:

- Intracellular actions: cell growth and differentiation
- Calcium and phosphate homeostasis
**Actions**  A prehormone that gives rise to true hormones, calcifediol and calcitriol, needed in calcium and phosphate homeostasis and in bone metabolism.

**MOA**  Calcifediol and calcitriol act on receptors belonging to the steroid superfamily of receptors to increase serum calcium by increasing calcium and phosphate absorption from the intestine and decreasing their excretion by the kidney.

**Abs/Distrb/Elim**  Given orally it needs bile salts for absorption.

**Clinical use**  Rickets; the hypocalcaemia of hypoparathyroidism; the osteodystrophy of renal failure.

**Adverse effects**  Excessive intake can cause hypercalcaemia; if this persists renal calculi may result.

**Special points**  Serum calcium levels should be monitored.

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R&D 7e Ch 35, p 439; D&H 2e Ch 31, pp 74-75
The vitamin D family, parathyroid and calcium metabolism

Cholesterol gives rise to 7-dehydrocholesterol, which gives rise to Vit D₃, then to the hormones:

- 7-Dehydrocholesterol → UV
- Vit D₃ (cholecalciferol) → Liver
- 7-Dehydrocholesterol → Skin
- Vit D₃ (cholecalciferol) → Liver
- Ergocalciferol
- Calcifediol
- Calcitriol
- Parathormone
- Blood calcium
- Parathyroid

Biological actions:
- Intracellular actions: cell growth and differentiation
- Calcium and phosphate homeostasis

Blood calcium

Converted in the liver to calcifediol, actions are thus those of calcitriol
**Actions**  Increases serum calcium and phosphate levels.

**MOA**  Calcitriol acts on receptors belonging to the steroid superfamily of receptors to give mediator proteins that increase calcium and phosphate absorption from the intestine and decrease their excretion by the kidney.

**Abs/Distrib/Elim**  Given orally it needs bile salts for absorption. Can be given by i.v. injection.

**Clinical use**  The osteodystrophy of chronic renal failure which is due to decreased calcitriol; postmenopausal osteoporosis.

**Adverse effects**  Excessive intake can cause hypercalcaemia; if this persists renal calculi may result.

**Special points**  Serum calcium, phosphate and creatinine levels should be monitored.

R&D 7e, p 439; D&H 2e Ch 31, pp 74-75
Calcium homeostasis, parathyroid and bone

A fall in the plasma Ca\(^{2+}\) concentration causes:

- Secretion of parathormone from the parathyroid, which causes:
  - Conversion of calcifediol to calcitriol, which causes:
    - Decreased excretion of Ca\(^{2+}\) by the kidney which causes:
    - Increased Ca\(^{2+}\) absorption in the intestine which causes:
    - Mobilisation of Ca\(^{2+}\) from bone which causes:

A rise in the plasma Ca\(^{2+}\) concentration decreases:
**Actions**  Lower serum calcium levels and decreases bone resorption.

**MOA**  It decreases the reabsorption of both calcium and phosphate in the kidney; it inhibits bone resorption by binding to a specific receptor on osteoclasts, inhibiting their action.

**Abs/Distrb/Elim**  Given by subcut. or i.m. injection or by nasal spray. Plasma half-life is 4–12 min; action lasts several hours.

**Clinical use**  Hypercalcaemia; Paget’s disease; the prevention of postmenopausal osteoporosis.

**Adverse effects**  GIT disorders; facial flushing; taste disturbances; dizziness; muscle pain.
Calcium homeostasis, parathyroid and bone

A fall in the plasma Ca$^{2+}$ concentration causes:

- Secretion of parathormone from the parathyroid, which causes:
  - Conversion of calcifediol to calcitriol, which causes:
    - Decreased excretion of Ca$^{2+}$ by the kidney which causes:
    - Increased Ca$^{2+}$ absorption in the intestine which causes:
    - Mobilisation of Ca$^{2+}$ from bone which causes:

A rise in the plasma Ca$^{2+}$ concentration decreases:

- Calcitonin
  - Decreased excretion of Ca$^{2+}$ by the kidney which causes:
  - Increased Ca$^{2+}$ absorption in the intestine which causes:
  - Mobilisation of Ca$^{2+}$ from bone which causes:
**Actions**  Decreases the secretion of parathyroid hormone resulting in a rise in plasma calcium by:

- decreasing the conversion of calcifediol to calcitriol,
- decreasing the excretion of calcium by the kidney,
- increasing the absorption of calcium from the intestine,
- mobilising calcium from bone.

**MOA**  It activates the calcium-sensing receptor in parathyroid cells.

**Abs/Distrb/Elim**  Given orally it needs bile salts for absorption. Can be given by i.v. injection.

**Clinical use**  Hyperparathyroidism.

**Adverse effects**  Excessive intake can cause hypercalcaemia; if this persists renal calculi may result.

**Special points**  Serum calcium, phosphate and creatinine levels should be monitored.
A 69-year-old woman slips on her front steps, falls and breaks her arm. Probable diagnosis? Drug treatment? Which drugs and why?

A fall in the plasma $\text{Ca}^{2+}$ concentration causes:

- Secretion of parathormone from the parathyroid, which causes:
  - Conversion of calcifediol to calcitriol, which causes:
    - Decreased excretion of $\text{Ca}^{2+}$ by the kidney which causes:
    - Increased $\text{Ca}^{2+}$ absorption in the intestine which causes:
    - Mobilisation of $\text{Ca}^{2+}$ from bone which causes:

Cinacalcet decreases:

- Secretion of parathormone from the parathyroid,
- Conversion of calcifediol to calcitriol,
- Decreased excretion of $\text{Ca}^{2+}$ by the kidney,
- Increased $\text{Ca}^{2+}$ absorption in the intestine,
- Mobilisation of $\text{Ca}^{2+}$ from bone.
Probable diagnosis
Fracture due to established postmenopausal osteoporosis
(but whether or not the patient is on glucocorticoids needs to be checked).

Treatment
1. The primary treatment would be surgical, of course.
2. Drug treatment of the osteoporosis would also be needed.

Drugs to be considered:
A drug which decreases bone resorption and thus prevents further loss of bone density, e.g. a bisphosphonate (e.g. alendronate) which has primarily antiosteoclast action. Calcitonin also decreases bone resorption.

A drug which enhances bone formation. Both raloxifene and teriparatide do this. Raloxifene increases osteoblast action and decreases osteoclast activity; teriparatide has anabolic actions on bone increasing the number and activity of osteoblasts.
The figure shows the hormonal control of the menstrual cycle

1. The menstrual cycle starts with bleeding. When this ceases, the endometrium is regenerated during the rest of the cycle.

2. Gonadotrophin-releasing hormone (GnRH) is released from the hypothalamus...

3. In the first part of the cycle, FSH stimulates the development of the Graafian follicle, which contains the ovum.

4. FSH stimulates the granulosa cells surrounding the ovum to produce oestrogens whose level peaks at mid-cycle. The oestrogens control the proliferative phase of endometrium renewal (till mid cycle) and also act on the anterior pituitary to reduce gonadotrophin release.

5. At mid cycle, a surge of LH secretion stimulates ovulation.

6. Oestrogens promote progesterone receptor synthesis in peripheral target tissues, including the endometrium.

7. Progesterone, acting on oestrogen-induced receptors, stimulates the secretory phase of endometrium regeneration, preparing it for implantation of the ovum.

8. These sex steroids act on nuclear receptors in target tissues, activating transcription of some genes and inhibiting transcription of others.

9. The ruptured follicle, under LH action, develops into the corpus luteum, which secretes both oestrogen and progesterone.

10. Progesterone acts on the hypothalamus and anterior pituitary, reducing the secretion of GnRH and LH. It also raises body temperature by about 0.5 °C.

11. If the ovum does not implant, progesterone secretion ceases, triggering menstruation; in the absence of the negative feedback action the cycle begins again.

1. The menstrual cycle starts with bleeding. When this ceases, the endometrium is regenerated during the rest of the cycle.

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11. If the ovum does not implant, progesterone secretion ceases, triggering menstruation; in the absence of the negative feedback action the cycle begins again.
**Action and Use**  Prevention of pregnancy.

**MOA**  The ethinylestradiol suppresses the development of the ovarian follicle by inhibiting follicle-stimulating hormone (FSH) release from the anterior pituitary. The norethisterone prevents ovulation by inhibiting luteinizing hormone (LH) release. Together they make the endometrium unsuitable for implantation of the ovum.

**Abs/Distrb/Elim**  Given orally.

**Adverse effects**  Infrequent; but may cause weight gain, flushing, mood changes, dizziness and sometimes acne or skin pigmentation and a transient rise of blood pressure. Some risk of thromboembolism.

**Special points**  Other combinations: ethinylestradiol + desogestrel; ethinylestradiol + drospirenone.
The figure shows the hormonal control of the menstrual cycle
**Action & MOA**  Acts on the anterior pituitary to inhibit the negative feedback action of endogenous oestrogens thus increasing gonadotrophin release.

**Abs/Distrb/Elim**  Given orally.

**Clinical use**  Treatment of infertility.

**Adverse effects**  Menopausal-like hot flushes; ovarian enlargement. Sometimes visual symptoms (after images). GIT disturbances may occur.
The figure shows the hormonal control of the menstrual cycle.
**Action & MOA**  Inhibits gonadal function by suppressing the mid-cycle surge of gonadotrophins.

**Abs/Distr/Elim**  Given orally, $T_{0.5} > 15\text{h}$.

**Clinical use**  Treatment of endometriosis.

**Adverse effects**  Moderate effects are common: weight gain, acne, hot flushes, amenorrhoea, masculinisation (hirsutism, deepening of voice etc.).
The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries.
**Actions**  Contracts the uterus causing coordinated contractions that travel from fundus to cervix with complete relaxation between contractions. Has vasodilator action.

**MOA**  Acts on oxytocin receptors in the smooth muscle of the myometrium.

**Abs/Distrb/Elim**  Usually given by i.v. infusion; can be given i.m. Inactivated by liver and kidneys and by circulating oxytocinase.

**Clinical use**  To induce or augment labour when the uterine muscle is not functioning adequately. To prevent or treat post-partum bleeding due to uterine atony. To treat haemorrhage due to incomplete abortion.

**Adverse effects**  Dose-related hypotension due to vasodilatation. Can cause water retention due to an antidiuretic hormone-like effect.

**Special points**  Oxytocin contracts the myoepithelial cells in the post-partum mammary gland causing ‘milk let down’.

R&D 7e Ch 34, p 427; D&H 2e Ch 32, pp 76-77
The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries
**Actions**  Contracts the relaxed uterus. Has vasoconstrictor action.

**MOA**  Not understood; may act partly on α-adrenoceptors, partly on 5-HT receptors.

**Abs/Distrb/Elim**  Given orally, i.m. or i.v. Rapid onset of action. Duration: 3–6h.

**Clinical use**  To treat post-partum haemorrhage.

**Adverse effects**  GIT disturbances; increase in BP and in some cases angina (due to vasoconstriction); headache, dizziness; dysrhythmias.
The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries.
**Actions**  Causes coordinated contractions of the pregnant uterus; relaxes the cervix.

**MOA**  Activates PGF$_{2\alpha}$ (FP) receptors on uterine smooth muscle.

**Abs/Distrb/Elim**  Given by deep intramuscular injection.

**Clinical use**  To treat post-partum haemorrhage unresponsive to oxytocin or ergometrine.

**Adverse effects**  GIT disturbances, bronchospasm, fever. Sometimes headache, dizziness, hypertension.

**Similar drugs**  Dinoprostone (PGE$_2$); used intravaginally to augment or induce labour. Gemeprost (a PGE$_1$ analogue), used in pessary form for medical induction of abortion.
The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries.

**Uterine stimulants**
- Oxytocin
- Ergometrine
- Carboprost

**Uterine relaxants**
- Carboprost
**Actions**  Inhibits spontaneous and oxytocin-induced contractions of the pregnant uterus.

**MOA**  Activates $\beta$-adrenoceptors on uterine smooth muscle causing relaxation.

**Abs/Distrb/Elim**  Given by i.v. infusion.

**Clinical use**  To delay pre-term labour.

**Adverse effects**  GIT disturbances; headache, dysrhythmias, vasodilatation, hypersensitivity reactions.
The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries.
**Actions**  Inhibits oxytocin-induced contractions of the pregnant uterus.

**MOA**  Antagonises oxytocin action on oxytocin receptors on uterine smooth muscle causing relaxation.

**Abs/Distrb/Elim**  Given by i.v. injection.

**Clinical use**  To delay pre-term labour.

**Adverse effects**  GIT disturbances, tachycardia, hypotension, dizziness, headache.
Hormonal control of the male reproductive system

- **Hypothalamus**
  - GnRH
  - Anterior pituitary
    - FSH
    - ICSH
    - Testosterone
- Testis
  - Sertoli cell
  - Spermatozoa
  - Gametogenesis in the seminiferous tubules
  - **Testosterone**
    - 5α-Reductase
      - Dihydrotestosterone
      - Peripheral effects secondary sex organs
- **Interstitial cells**
**Actions**  Has the same actions as endogenous testosterone; the effects will depend on the age of the patient.

**MOA**  Converted to dihydrotestosterone which enters cells and interacts with nuclear receptors to initiate transcription of some genes (resulting in DNA-directed RNA and protein synthesis) and repression of others.

**Abs/Distrb/Elim**  Administration can be oral, buccal, by i.m. injection or transdermally.

**Clinical use**  Replacement therapy in hypogonadism.

**Adverse effects**  Eventual decrease of gonadotrophin release resulting in infertility; oedema due to salt and water retention.
Hormonal control of the male reproductive system

- **Hypothalamus**
  - GnRH
  - Anterior pituitary
    - FSH
    - ICSH
    - Testis
      - Sertoli cell
      - Spermatozoa
      - Gametogenesis in the seminiferous tubules
      - Interstitial cells
      - Testosterone
      - 5α-Reductase
      - Dihydrotestosterone
      - Peripheral effects secondary sex organs
**Action & MOA**  
Finasteride inhibits the $5\alpha$-reductase that converts testosterone to dihydrotestosterone which has greater affinity for the androgen receptor than the parent molecule. (Flutamide is an androgen-receptor antagonist.)

**Abs/Distrb/Elim**  
Given orally; $T_{0.5} \sim 7h$

**Clinical use**  
Benign prostatic hyperplasia (but note that $\alpha$-adrenoceptor blockers are more effective). Flutamide is used to treat prostate cancer.

**Adverse effects**  
Erectile dysfunction; libido loss.
The mechanisms controlling the contraction and relaxation of the smooth muscle of the corpora cavernosa

1. Nitrergic nerves release nitric oxide

2. NO activates GC

3. GC activates cGMP which activates PKG which inhibits MYOSINP and thus results in: RELAXATION and DILATATION

4. MLCK

5. Ca²⁺ + calmodulin activate Phosphodiesterase V

Ca²⁺

SR

Phosphodiesterase V

GTP cGMP

Activates PKG which inhibits

MyosinP + actin

CONTRACTION

Smooth muscle cell

NO = nitric oxide

GC = guanylate cyclase

MLCK = myosin light chain kinase

PKG = protein kinase G

SR = sarcoplasmic reticulum
**Actions**  Relaxes the non-vascular smooth muscle of the copora cavernosa. Blood at virtually arterial pressure then flows into the cavenosa sinuses resulting in swelling and erection of the penis.

**MOA**  It inhibits phosphodiesterase type V – an enzyme that normally converts cGMP to 5’-GMP. This increases the concentration of cGMP which inhibits the contractile mechanisms of the muscle allowing relaxation (see front of card).

**Abs/Distrb/Elim**  Given orally, peak action occurs in 30–120min.

**Clinical use**  For erectile dysfunction.

**Adverse effects**  These are due to the action of the drug on other vascular beds and include fall in blood pressure, headache and flushing.

**Special points**  The drugs increase the action of the organic nitrates which also work by increasing cGMP.

R&D 7e Ch 34, pp 429-430; D&H 2e Ch 32, p 78
The mechanisms controlling the contraction and relaxation of the smooth muscle of the corpora cavernosa

1. Nitrergic nerves release nitric oxide

2. NO activates GC

3. GTP activates PKG which inhibits MLCK and thus results in:
   - RELAXATION
   - DILATATION

4. MLCK

5. Phosphodiesterase V

Ca\(^{2+}\) + calmodulin activate

NO = nitric oxide
GC = guanylate cyclase
MLCK = myosin light chain kinase
PKG = protein kinase G
SR = sarcoplasmic reticulum

The mechanisms involve the following steps:

1. Nitric oxide (NO) is released from nitrergic nerves.
2. NO activates guanylate cyclase (GC), which converts GTP to cGMP.
3. cGMP activates protein kinase G (PKG), which inhibits myosin light chain kinase (MLCK).
4. MLCK inhibits the contraction of the smooth muscle cell.
5. Phosphodiesterase V breaks down cGMP to 5′GMP, allowing calcium ions (Ca\(^{2+}\)) and calmodulin to activate MLCK.

Sildenafil blocks the action of MLCK, leading to smooth muscle relaxation and dilatation.
Notes on the female and male reproductive systems
Transmitter systems in the striatum providing targets for antiparkinsonian drugs

COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Cholinergic nerve in striatum

L-dopa
Nigrostriatal dopaminergic neuron

DD
Dopamine
DOPAC
Aldehyde intermediate

DD = DOPA decarboxylase

MAO = monoamine oxidase

ACh

Postsynaptic neuron in striatum
**Levodopa** — precursor of dopamine  
**Carbidopa** — peripheral DOPA decarboxylase inhibitor (Similar drug: benserazide)

### Actions
Antiparkinsonian.

### MOA
Decarboxylation of levodopa to dopamine restores some activity in nigrostriatal pathway. Carbidopa inhibits levodopa decarboxylation outside the brain, allowing the use of smaller doses and reducing peripheral side effects of dopamine (e.g. postural hypotension).

### Abs/Distrib/Elim
Oral admin. Levodopa $T_{0.5}$ 1–2h when co-administered with carbidopa.

### Clinical use
Cornerstone of therapy in Parkinson’s disease. Levodopa is usually given with a peripheral DOPA decarboxylase inhibitor. More effective against akinesia and rigidity than against tremor. Effectiveness diminishes over some months to a few years.

### Adverse effects
Anorexia, nausea and vomiting. Postural hypotension. Acute schizophrenia-like syndrome. Confusion, anxiety, disorientation and insomnia or nightmares. More slowly developing effects: dyskinesia (in most patients after 2 years) and 'on-off' effects (rapid fluctuations between dyskinesia and hypokinesia/rigidity).

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R&D 7e Ch 39, pp 487-488; D&H 2e Ch 36, p 85
Transmitter systems in the striatum providing targets for antiparkinsonian drugs

L-dopa

DD in periphery

Carbidopa

Dopamine

Nigrostriatal dopaminergic neuron

DD

MAO

Aldehyde intermediate

DOPAC

Dopamine

COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Cholinergic nerve in striatum

ACh

Postsynaptic neuron in striatum
**Actions** Synergises with the antiparkinsonian effects of levodopa/carbidopa. Potentiates actions of catecholamines.

**MOA** Reversible inhibition of COMT in the periphery reduces levodopa breakdown (like peripheral dopa decarboxylase inhibitors) allowing more of levodopa dose to penetrate brain.

**Abs/Distrib/Elim** Oral admin. Short $T_{0.5}$ (1h) necessitates dosing several times/day.

**Clinical use** Adjunct to levodopa/carbidopa therapy – especially for patients showing ‘end of dose’ symptoms. (No antiparkinsonian effect by itself.)

**Adverse effects** Exacerbates adverse effects of levodopa/carbidopa taken at the same time. Dyskinesia, nausea, diarrhoea. Postural hypotension. Hallucinations. Anxiety and sleepiness.
Transmitter systems in the striatum providing targets for antiparkinsonian drugs

L-dopa → Nigrostriatal dopaminergic neuron → Dopamine → Aldehyde intermediate → DOPAC → Postsynaptic neuron in striatum

- COMT in periphery
- Entacapone
- Carbidopa
- DD in periphery

DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
COMT = catechol-O-methyl transferase
MAO = monoamine oxidase

Cholinergic nerve in striatum

ACh → Postsynaptic neuron in striatum

3-methoxy-4-hydroxy-L-phenylalanine
Actions  Antiparkinsonian.

MOA  Selective irreversible inhibition of MAO_B, the isozyme which has dopamine as a preferred substrate. Potentiates action of endogenous dopamine and dopamine formed from administered levodopa.

Abs/Distrib/Elim  Oral admin. (but low bioavailability), t₁/₂ 2h. Rasagiline T₀.₅ 3h.

Clinical use  Adjunct to levodopa/carbidopa, as their effect wanes, in Parkinson’s disease. Irreversible nature of MAO inhibition prolongs effects of drug for some days. Also approved for major depression.

Adverse effects  Adverse effects mainly due to increased action of levodopa taken concurrently: nausea, dyskinesia, depression, insomnia, postural hypotension, hallucinations, confusion. At clinical doses, spares MAO_A so less likely to provoke the ‘cheese reaction’ than non-selective MAO inhibitors. Severe interactions may occur with tricyclic and SSRI antidepressants.

R&D 7e Ch 39, p 488; D&H 2e Ch 36, p 85
Transmitter systems in the striatum providing targets for antiparkinsonian drugs

- **L-dopa**
  - Nigrostriatal dopaminergic neuron
  - **DD in periphery**
  - **COMT in periphery**
  - **Entacapone**
  - **Carbidopa**
  - **Selegiline**
  - **DD in periphery**
  - **3-methoxy-4-hydroxy-L-phenylalanine**
  - **Dopamine**

**Enzymes and Acids**
- **COMT** = catechol-O-methyl transferase
- **DD** = DOPA decarboxylase
- **DOPAC** = 3,4-dihydroxyphenyl acetic acid
- **MAO** = monoamine oxidase

**Other Compounds**
- **ACh**
- **D**
- **M**

**Terms**
- **Postsynaptic neuron in striatum**
- **Cholinergic nerve in striatum**

**Legend**
- **+** indicates an activation
- **-** indicates an inhibition
**Actions**  Antiparkinsonian. Inhibits prolactin secretion from pituitary.

**MOA**  Activation of $D_2$ receptors on striatal neurones counters impairment of dopaminergic transmission. Actions on $D_1$ receptors may be important in ameliorating the non-Parkinsonian symptoms associated with disease.

**Abs/Distrib/Elim**  Dopamine agonists have longer $T_{0.5}$s than levodopa and provide a more continuous control of symptoms. $T_{0.5}$: bromocriptine 12h, pramipexole 12h, ropinirole 6h.

**Clinical use**  Used alone or as adjuvants to levodopa therapy in Parkinson’s. Often used in early stages before use of levodopa. Bromocriptine’s effect on prolactin secretion is used for amenorrhoea and acromegaly.

**Adverse effects**  Hallucinations and sleepiness (more than with levodopa). Postural hypotension. Dyskinesias – but less than with levodopa. Bromocriptine (and other ergot derivatives) rarely cause fibrotic reactions.
Transmitter systems in the striatum providing targets for antiparkinsonian drugs

**L-dopa**

Nigrostriatal dopaminergic neuron

COMT in periphery

DD in periphery

Carbidopa

Selegiline

DD = DOPA decarboxylase

DOPAC = 3,4-dihydroxyphenyl acetic acid

MAO = monoamine oxidase

Aldehyde intermediate

Dopamine

Bromocriptine

Entacapone

3-methoxy-4-hydroxy-L-phenylalanine

Dopamine

Postsynaptic neuron in striatum

ACh

COMT = catechol-O-methyl transferase

DD = DOPA decarboxylase

DOPAC = 3,4-dihydroxyphenyl acetic acid

MAO = monoamine oxidase
**Actions**  Antiparkinsonian. Antiviral.

**MOA**  Thought to act by increasing dopamine release from nerve endings in striatum. Antimuscarinic actions, like those of benztropine, may also contribute.

**Abs/Distrib/Elim**  Oral admin. Most excreted unchanged in urine. T<sub>0.5</sub> 17h.

**Clinical use**  Parkinson’s disease. Generally less effective than levodopa, dopamine agonists or MAO<sub>B</sub> inhibitors. Also effective against the dyskinesia associated with levodopa therapy. (Antiviral action used for influenza infection.)

**Adverse effects**  Nausea, dizziness, insomnia. Postural hypotension. Anxiety, confusion, hallucinations. Antimuscarinic action is important contributor to death from overdose.
Transmitter systems in the striatum providing targets for antiparkinsonian drugs

- **L-dopa**
  - **DD in periphery**
  - **Entacapone**
  - **3-methoxy-4-hydroxy-L-phenylalanine**
  - **Dopamine**

- **Nigrostriatal dopaminergic neuron**
  - **DD**
  - **MAO**
  - **Selegiline**
  - **DOPAC**

- **Cholinergic nerve in striatum**
  - **ACh**

**Key Enzymes and Compounds**

- **COMT** = catechol-O-methyl transferase
- **DD** = DOPA decarboxylase
- **DOPAC** = 3,4-dihydroxyphenyl acetic acid
- **MAO** = monoamine oxidase

**Notes**

- **COMT in periphery**
- **DD in periphery**
- **Bromocriptine**
- **Entacapone**
- **Carbidopa**
- **Selegiline**
- **Amantadine**
**Actions**  Antiparkinsonian.

**MOA**  Reduces muscarinic actions of ACh in striatum. (Restores ‘balance’ between dopaminergic and cholinergic activities.) Action is probably on M₁ receptors

**Abs/Distrib/Elim**  Orally active. Long $T_{0.5}$ – 36h. Trihexyphenidyl $T_{0.5}$ 3–4h.

**Clinical use**  Second-line drug for Parkinson’s disease. Much less effective than those drugs increasing dopaminergic transmission but has value in treating tremor. Used as adjunct with other agents and in drug (antipsychotic)-induced Parkinsonism.

**Adverse effects**  Effects due to parasympathetic block – dry mouth, inhibition of peristalsis, raised intraocular pressure (avoid in narrow-angle glaucoma), blurred vision, urinary retention, tachycardia, etc. Confusion, hallucinations.
Transmitter systems in the striatum providing targets for antiparkinsonian drugs

L-dopa → Nigrostriatal dopaminergic neuron → Dopamine

- Carbidopa
- Selegiline
- Entacapone

DD in periphery

DD → 3-methoxy-4-hydroxy-L-phenylalanine → Dopamine

MAO

DOPAC → Postsynaptic neuron in striatum → Dopamine

COMT in periphery

DD in periphery

Selegiline + Amantadine + Benztropine

COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase
Cholinergic and glutamatergic transmission are targets for drug action in Alzheimer’s disease.

Alzheimer’s disease is associated with a loss of neurons and shrinkage of brain tissue, particularly in the hippocampus and basal forebrain. The loss of cholinergic neurons in particular is believed to be associated with the impairment of learning and memory. Excitotoxicity, mediated by NMDA receptors, may also be important in neuronal death.

AChE = acetylcholinesterase
NMDA = N-methyl D-aspartate
Actions  Ameliorates symptoms of Alzheimer’s disease.

MOA  Reversible inhibition of acetylcholinesterase. Enhances cholinergic transmission in the cerebral cortex and hippocampus.

Abs/Distrib/Elim  Orally active. Donepezil has long $T_{0.5}$ of 70h. Galantamine $T_{0.5}$ 7h. Rivastigmine has a short half-life 1.5h.

Clinical use  Mild to moderate Alzheimer’s disease, providing limited relief from the symptoms but having no effect on the progression of the disease.

Adverse effects  Predictable parasympathomimetic side effects: nausea, diarrhoea, vomiting, bradycardia, increased gastric acid secretion. Anorexia with weight loss and insomnia also occur.
Alzheimer’s disease is associated with a loss of neurons and shrinkage of brain tissue, particularly in the hippocampus and basal forebrain. The loss of cholinergic neurons in particular is believed to be associated with the impairment of learning and memory. Excitotoxicity, mediated by NMDA receptors, may also be important in neuronal death.

**AChE** = acetylcholinesterase  
**NMDA** = N-methyl D-aspartate
**Actions**  Ameliorates symptoms of Alzheimer’s disease.

**MOA**  Open channel block of NMDA receptors. Prevents Na⁺ and, more importantly, Ca²⁺ entry into the neurone, so reducing glutamate excitotoxicity. Normal glutamatergic transmission continues.

**Abs/Distrib/Elim**  Oral admin. T₀.₅ 60–80h.

**Clinical use**  Moderate to severe Alzheimer’s disease. Provides only symptomatic relief of the cognitive and memory impairment of the disease. No effect on the degenerative process. Can be used in combination with centrally acting anticholinesterases.

**Adverse effects**  Usually well tolerated. Confusion, dizziness, drowsiness, headache, insomnia, agitation, hallucinations.
Alzheimer’s disease is associated with a loss of neurons and shrinkage of brain tissue, particularly in the hippocampus and basal forebrain. The loss of cholinergic neurons in particular is believed to be associated with the impairment of learning and memory. Excitotoxicity, mediated by NMDA receptors, may also be important in neuronal death.

AChE = acetylcholinesterase
NMDA = N-methyl D-aspartate
Established/possible targets for anaesthetic agents are indicated in the diagram.

<table>
<thead>
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<th>Target in brain</th>
<th>Effect on target</th>
</tr>
</thead>
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<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
<td>Increased response to GABA</td>
</tr>
<tr>
<td>Two-pore domain (TREK) potassium channel</td>
<td>Increased channel opening</td>
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<tr>
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</tr>
<tr>
<td>Glycine and nicotinic receptors are also potential sites of anaesthetic action.</td>
<td></td>
</tr>
</tbody>
</table>

Inhalation anaesthetic agents in general act at high (mM) concentrations and have less well-defined targets than the more potent intravenous agents.
**Actions**  CNS depressant. Causes unconsciousness. Only weakly analgesic.

**MOA**  Potentiates GABA action on GABA<sub>A</sub> receptors and opens K<sup>+</sup> channels (TREK type) to reduce neuronal activity, especially in cerebral cortex, thalamus and hippocampus. Lipid solubility important for action.

**Abs/Distrib/Elim**  Given by inhalation with oxygen. Rate of equilibration with body and onset of anaesthesia depends on the ‘blood/gas solubility’. Halothane has a medium onset of action – desflurane and sevoflurane (with lower blood/gas solubilities) a fast onset. Mostly eliminated unchanged by the lungs.

**Clinical use**  Maintenance, and less frequently induction, of general anaesthesia.

**Adverse effects**  Cardiac and respiratory depression. Cardiac dysrhythmias. Post-operative nausea and vomiting. Rarely malignant hyperthermia and liver damage (due to metabolites). Sevoflurane may produce kidney damage.
Established/possible targets for anaesthetic agents are indicated in the diagram.

**Target in brain**

- **GABA$_A$ receptors**
  - Increased response to GABA

- **Two-pore domain (TREK) potassium channel**
  - Increased channel opening

- **NMDA receptors**
  - Reduced response to glutamate

Glycine and nicotinic receptors are also potential sites of anaesthetic action.

**Effect on target**

- **Halothane**
  - Reduced neuronal excitability / depression of CNS activity / unconsciousness / anaesthesia

Inhalation anaesthetic agents in general act at high (mM) concentrations and have less well-defined targets than the more potent intravenous agents.
**Actions**  CNS depression, unconsciousness (in combination with other anaesthetics). Analgesia. Euphoria.

**MOA**  Reduces opening of NMDA receptor channels. Increases opening of TREK-1 potassium channels. (No action on GABA_A receptors.) Analgesic action inhibited by opioid antagonists, suggesting release of endogenous opioids.

**Abs/Distrib/Elim**  Administered by inhalation. Low blood/gas partition coefficient results in rapid onset and offset of action. Eliminated unchanged via lungs. No metabolism.

**Clinical use**  General anaesthesia. Because of low potency will not produce full surgical anaesthesia by itself; must be combined with more potent agents. In subanaesthetic doses used as analgesic for childbirth and emergency pain relief (e.g. by paramedics).

**Adverse effects**  Few side effects. Oxygen may be required during recovery due to possibility of ‘diffusion anoxia’.

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R&D 7e Ch 40, pp 500-501; D&H 2e Ch 37, pp 86-87
Established/possible targets for anaesthetic agents are indicated in the diagram.

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Glycine and nicotinic receptors are also potential sites of anaesthetic action.

Inhalation anaesthetic agents in general act at high (mM) concentrations and have less well-defined targets than the more potent intravenous agents.

Halothane
Reduced neuronal excitability / depression of CNS activity / unconsciousness / anaesthesia

Nitrous oxide
**Actions**  Ultrashort-acting anaesthetics. All have only weak analgesic action.

**MOA**  Binds to particular site (different to benzodiazepine binding site) on $\text{GABA}_A$ receptor to enhance opening of intrinsic $\text{Cl}^-$ channel by GABA. Higher concentrations directly activate receptor.

**Abs/Distrib/Elim**  I.v. injection. Very lipid soluble allowing rapid CNS penetration. Rapid onset (20s) and short acting (5–10min). Short duration due to rapid redistribution in body, particularly to muscle. Thiopental is slowly metabolised ($T_{0.5}$ 8–10h) and may produce a ‘hangover’. Propofol is rapidly metabolised and lack of hangover makes it suitable for day case surgery. Etomidate $T_{0.5}$ 2h.

**Clinical use**  Anaesthesia for short procedures and to induce anaesthesia for subsequent maintenance with volatile agents.

**Adverse effects**  Cardiorespiratory depression: less with etomidate. Post-operative vomiting and adrenocortical suppression with etomidate.

R&D 7e Ch 40, pp 495-496; D&H 2e Ch 37, pp 86-87
Established/possible targets for anaesthetic agents are indicated in the diagram.

**Target in brain**
- GABA<sub>A</sub> receptors
- Two-pore domain (TREK) potassium channel
- NMDA receptors

**Effect on target**
- Thiopentone
  - Increased response to GABA
  - Increased channel opening
- Halothane
  - Reduced response to glutamate
  - Reduced neuronal excitability / depression of CNS activity / unconsciousness / anaesthesia
- Nitrous oxide

Glycine and nicotinic receptors are also potential sites of anaesthetic action.

Inhalation anaesthetic agents in general act at high (mM) concentrations and have less well-defined targets than the more potent intravenous agents.
**Actions**  Dissociative anaesthesia, in which the patient may remain conscious but have good pain relief and short-term amnesia. Analgesia at subanaesthetic doses.

**MOA**  Blocks NMDA type glutamate receptor ion channel.

**Abs/Distrib/Elim**  I.v. or i.m. admin. Rapid onset and short duration of action following i.v. dosing. Metabolised in liver; \( T_{0.5} \) 2.5h.

**Clinical use**  Induction and maintenance of anaesthesia for brief surgical/diagnostic procedures. Mainly used for minor procedures in children, who exhibit fewer untoward psychotic side effects.

**Adverse effects**  Increased heart rate and blood pressure (by activation of sympathetic system). Involuntary muscle movement. Hallucinations, delerium and dysphoria during recovery. Respiratory depression in overdose.
Established/possible targets for anaesthetic agents are indicated in the diagram.

Inhalation anaesthetic agents in general act at high (mM) concentrations and have less well-defined targets than the more potent intravenous agents.
Notes
The important anxiolytic and hypnotic drugs act on GABA_A or 5HT_1A receptors.
**Actions**  Anxiolytic, hypnotic, amnestic, anticonvulsant and reduction in muscle tone.

**MOA**  Binds to benzodiazepine binding site on GABA$_A$ receptor to enhance channel opening by GABA. The increased Cl$^-$ conductance reduces neuronal excitability.

**Abs/Distrb/Elim**  Given orally. Diazepam is long acting due to active metabolite with long $T_{0.5}$. Nitrazepam and temazepam have a medium duration. Oxazepam is short acting.

**Clinical use**  Anxiety and insomnia. Temazepam & nitrazepam are used as hypnotics. Diazepam is also used for premedication and status epilepticus (see card 25.04).

**Adverse effects**  Drowsiness and confusion. Tolerance and dependence (with withdrawal symptoms) can occur as can severe respiratory depression in combination with other CNS depressants (e.g. alcohol).
The important anxiolytic and hypnotic drugs act on GABA\(_A\) or 5HT\(_{1A}\) receptors.
Non-benzodiazepine agonist at benzodiazepine receptor (Similar drugs: zopiclone, zaleplon)

**Actions**  Hypnotic (less anxiolytic, amnestic and muscle relaxant activity than benzodiazepines).

**MOA**  Binds to benzodiazepine binding site on GABA$_A$ receptor (the more limited actions are due to selective action on BZ$_1$ receptors) to enhance the channel opening activity of GABA. Reduces electrical excitability of neuronal cell membrane.

**Abs/Distrb/Elim**  Oral admin. Zolpidem and zopiclone are short acting ($t_{1/2}$ 2–3 and 6h respectively): zaleplon very short acting.

**Clinical use**  Insomnia.

**Adverse effects**  Well tolerated. Some drowsiness, confusion and dizziness. Tolerance and dependence (with withdrawal symptoms) may develop. Allergic reactions. Enhances CNS depression caused by other drugs (e.g. ethanol).

R&D 7e Ch 43, pp 532-533; D&H 2e Ch 38, p 88
The important anxiolytic and hypnotic drugs act on GABA<sub>A</sub> or 5HT<sub>1A</sub> receptors.
**Actions**  Antagonises actions of benzodiazepines and zolpidem-like drugs.

**MOA**  Competitive binding to the benzodiazepine binding site on GABA$_A$ receptor.

**Abs/Distrb/Elim**  Given intravenously. Short $T_{0.5}$ 1–2h, so will need repeat doses to antagonise the longer-acting benzodiazepines.

**Clinical use**  Treatment of overdose of benzodiazepines or zolpidem.

**Adverse effects**  Anxiety, palpitations, insomnia. Convulsions.
The important anxiolytic and hypnotic drugs act on GABA$_A$ or 5HT$_{1A}$ receptors.
**Actions**  CNS depressant. Hypnotic, anxiolytic.

**MOA**  Binds to barbiturate binding site on GABA\(_A\) receptor to increase action of GABA. At higher concentration can increase channel opening in absence of GABA.

**Abs/Distrb/Elim**  Orally active. Metabolised by hepatic P450 system. \(T_{0.5}\) 24–36h.

**Clinical use**  Severe insomnia unresponsive to other, safer drugs. Much less used nowadays. (Barbiturates also find use as general anaesthetics and antiepileptic agents.)

**Adverse effects**  Cardiorespiratory depression. Daytime sedation, impaired motor function. Dependence with severe withdrawal symptoms. Potent inducer of hepatic P450 system, leading to many drug interactions.
The important anxiolytic and hypnotic drugs act on GABA_A or 5HT_1A receptors.
**Actions**  Anxiolytic.

**MOA**  Partial agonist at 5-HT$_{1A}$ receptors. Acts presynaptically to inhibit firing of serotonergic neurons, particularly in the dorsal raphe nucleus. (Actions on postsynaptic 5-HT$_{1A}$ receptors in amygdala also likely.) Clinical response is not seen for 1–2 weeks, suggesting effects may require more complex, plastic changes.

**Abs/Distrb/Elim**  Given orally, but significant first-pass metabolism. $T_{0.5}$ 2–3h, but effects are longer lasting, possibly due to metabolite with similar action.

**Clinical use**  Generalised anxiety disorder.

**Adverse effects**  Nausea, dizziness, nervousness, headache. Blurred vision. (Does not cause dependence, nor cause the sedation and motor incoordination seen with benzodiazepines.)
The important anxiolytic and hypnotic drugs act on GABA\(_A\) or 5HT\(_{1A}\) receptors.
Diagram illustrating the effects of first- and second-generation antipsychotics

First-generation agents
('Typical' neuroleptics)

- D₂ receptor antagonism
- Extrapyramidal symptoms (EPS)
  (dystonias, akathisia, bradykinesia, dyskinesias)
- ↑ Prolactin secretion from pituitary
  (galactorrhoea, amenorrhoea, gynaecomastia)

Unwanted side effects

Second-generation agents
('Atypical' neuroleptics)

- D₂ receptor antagonism
  + effects on other receptors
  e.g. 5-HT₂A
- ↓ +ve symptoms of schizophrenia
  (delusions, hallucinations, aggression)
- ↓ -ve symptoms of schizophrenia
  (withdrawal, apathy, demotivation)

Wanted effects
**Actions**  Antipsychotic. Apathy and inertia. Reduced aggression. Antiemetic.

**MOA**  Competitive antagonism of dopamine D₂ receptors in the mesolimbic/mesocortical pathways. Clinical benefits are delayed although receptor block is immediate, suggesting that slower changes in neurotransmission occur.

**Abs/Distrib/Elim**  Given orally or by i.m. injection. $t_{1/2}$ 16–32h. Fluphenazine decanoate available as i.m. depot formulation.


**Adverse effects**  Marked sedation. EPS (dystonias and Parkinsonian symptoms) reduced by antimuscarinic action. Endocrine effects (e.g. galactorrhoea, gynaecomastia, weight gain). Antimuscarinic effects (e.g. constipation, dry mouth). Hypotension ($\alpha$-adrenoceptor antagonism). Rare, but serious, neuroleptic malignant syndrome. Hypersensitivity reactions. Agranulocytosis. Hepatotoxicity.
Diagram illustrating the effects of first- and second-generation antipsychotics

Chlorpromazine

First-generation agents ('Typical' neuroleptics)
- D₂ receptor antagonism
  - Extrapyramidal symptoms (EPS)
    (dystonias, akathisia, bradykinesia, dyskinesias)
  - Prolactin secretion from pituitary
    (galactorrhoea, amenorrhoea, gynaecomastia)

Second-generation agents ('Atypical' neuroleptics)
- D₂ receptor antagonism
  + effects on other receptors e.g. 5-HT₂A
  - +ve symptoms of schizophrenia
    (delusions, hallucinations, aggression)
  - -ve symptoms of schizophrenia
    (withdrawal, apathy, demotivation)

Unwanted side effects
Wanted effects
**Actions**  Antipsychotic. Apathy. Reduced aggression. Antiemetic

**MOA**  Competitive antagonism of dopamine D₂ receptors in the mesolimbic/mesocortical pathways. Clinical benefits are delayed although receptor block is immediate, suggesting that more complex changes in neurotransmission occur. Higher potency compared to chlorpromazine.

**Abs/Distrib/Elim**  Oral or i.m. admin. (Also i.m. depot.) t½ 12–36h.

**Clinical use**  Schizophrenia (less effective against negative symptoms) and other psychotic states. Mania. Aggressive behaviour. Tourette’s syndrome. Nausea & vomiting. Persistent hiccups.

**Adverse effects**  Marked EPS. Hyperprolactinaemia. Little sedative, hypotensive or antimuscarinic actions. Neuroleptic malignant syndrome.
Antipsychotics

First-generation agents ('Typical' neuroleptics)

Second-generation agents ('Atypical' neuroleptics)

Diagram illustrating the effects of first- and second-generation antipsychotics

**Haloperidol**

- First-generation agents ('Typical' neuroleptics)
- D₂ receptor antagonism
- Extrapyramidal symptoms (EPS) (dystonias, akathisia, bradykinesia, dyskinesias)
  - D₂ receptor antagonism + effects on other receptors (e.g. 5-HT₂A)
- Prolactin secretion from pituitary (galactorrhoea, amenorrhoea, gynaecomastia)

**Chlorpromazine**

- Second-generation agents ('Atypical' neuroleptics)
- D₂ receptor antagonism
- -ve symptoms of schizophrenia (withdrawal, apathy, demotivation)
- +ve symptoms of schizophrenia (delusions, hallucinations, aggression)

Unwanted side effects

Wanted effects
**Actions**  Antipsychotic. Antidepressant (tricyclic-like) activity.

**MOA**  Competitive antagonism of dopamine D₂ receptors in the mesolimbic/mesocortical pathways. Clinical benefits are delayed although receptor block is immediate, suggesting that more complex changes in neurotransmission occur.

**Abs/Distrib/Elim**  Effective orally but most often used as i.m. depot formulation. $T_{0.5}$ 19–39h.

**Clinical use**  Schizophrenia and other psychotic states. Bipolar disorder. Depression.

**Adverse effects**  EPS. Hyperprolactinaemia. Neuroleptic malignant syndrome.
Diagram illustrating the effects of first- and second-generation antipsychotics

First-generation agents
(‘Typical’ neuroleptics)

Second-generation agents
(‘Atypical’ neuroleptics)

Haloperidol

Chlorpromazine

Flupentixol

D₂ receptor antagonism

Extrapyramidal symptoms (EPS)
(dystonias, akathisia, bradykinesia, dyskinesias)

Prolactin secretion from pituitary
(galactorrhoea, amenorrhoea, gynaecomastia)

Prolactin secretion from pituitary
(e.g. 5-HT₂A)

+ve symptoms of schizophrenia
(delusions, hallucinations, aggression)

↓ -ve symptoms of schizophrenia
(withdrawal, apathy, demotivation)

Unwanted side effects

Wanted effects
**Actions** Antipsychotic – effective against +ve and -ve symptoms.

**MOA** MOA less well established than for typical agents. Action on 5HT\(_{2A}\) receptors may be important. Antagonist action at muscarinic, 5HT\(_2\), \(\alpha_1\) adrenoceptors, and H\(_1\) histamine receptors. Higher affinity for D\(_4\) than other dopamine receptors.

**Abs/Distrib/Elim** Orally active. \(t_\frac{1}{2}\) 12h.

**Clinical use** Schizophrenia. Because of toxicity, used mainly in patients resistant to other drugs, for whom it is very effective.

**Adverse effects** Little EPS (reduced D\(_2\) antagonism coupled with antimuscarinic action). Antimuscarinic actions (e.g. constipation). Agranulocytosis (not with olanzapine) – blood testing needed. Sedation. Epileptic seizures. Weight gain (more than with other antipsychotics). Hyperglycaemia.
Diagram illustrating the effects of first- and second-generation antipsychotics

First-generation agents ('Typical' neuroleptics)

- Haloperidol
- Chlorpromazine
- Flupentixol

D₂ receptor antagonism

- Extrapyramidal symptoms (EPS)
  (dystonias, akathisia, bradykinesia, dyskinesias)
- Prolactin secretion from pituitary
  (galactorrhoea, amenorrhoea, gynaecomastia)

Second-generation agents ('Atypical' neuroleptics)

- Clozapine

D₂ receptor antagonism + effects on other receptors
  e.g. 5-HT₂A

- ↓ +ve symptoms of schizophrenia
  (delusions, hallucinations, aggression)
- ↓ -ve symptoms of schizophrenia
  (withdrawal, apathy, demotivation)

Unwanted side effects

Wanted effects
**Actions** Antipsychotic. Effective against +ve and -ve symptoms of schizophrenia.

**MOA** Potent antagonist of D₂ and 5HT₂A receptors and α₁ adrenoceptors. As for other atypical agents, a combination of D₂ and 5HT₂A antagonism may be important in modifying activity in the mesolimbic and mesocortical pathways.

**Abs/Distrib/Elim** Oral and i.m. depot admin. Hepatic P450 metabolism. $t_{1/2}$ 3–20h. Active metabolite is longer acting.

**Clinical use** Schizophrenia and other psychotic states. Manic phase of bipolar disorder.

**Adverse effects** EPS (more than with other atypicals). Insomnia and sedation. Anxiety. Hyperprolactinaemia. Weight gain. Hypotension.
Antipsychotics

First-generation agents
('Typical' neuroleptics)

Second-generation agents
('Atypical' neuroleptics)

Diagram illustrating the effects of first- and second-generation antipsychotics

- Haloperidol
- Chlorpromazine
- Clozapine
- Risperidone
- Flupentixol

**D2 receptor antagonism**

- Extrapyramidal symptoms (EPS)
  (dystonias, akathisia, bradykinesia, dyskinesias)
- Prolactin secretion from pituitary
  (galactorrhoea, amenorrhoea, gynaecomastia)

**Unwanted side effects**

- +ve symptoms of schizophrenia
  (delusions, hallucinations, aggression)

**Wanted effects**

- -ve symptoms of schizophrenia
  (withdrawal, apathy, demotivation)
**Actions**  Antipsychotic. Effective against +ve and -ve symptoms.

**MOA**  Competitive antagonism of dopamine D$_2$ and 5HT$_{2A}$ receptors in the mesolimbic/mesocortical pathways is likely to be important. Antagonism of histamine H$_1$ receptors may underlie sedative action.

**Abs/Distrib/Elim**  Oral admin. Short (6h) half-life.

**Clinical use**  Schizophrenia and other psychotic states. Bipolar disorder.

Antipsychotics

Aripiprazole

First-generation agents ('Typical' neuroleptics)

Second-generation agents ('Atypical' neuroleptics)

Diagram illustrating the effects of first- and second-generation antipsychotics

Haloperidol

Chlorpromazine

Clozapine

Risperidone

Flupentixol

D₂ receptor antagonism

Prolactin secretion from pituitary (galactorrhoea, amenorrhoea, gynaecomastia)

Extrapyramidal symptoms (EPS) (dystonias, akathisia, bradykinesia, dyskinesias)

Unwanted side effects

Wanted effects

↑ D₂ receptor antagonism + effects on other receptors e.g. 5-HT₂A

↓ +ve symptoms of schizophrenia (delusions, hallucinations, aggression)

↓ -ve symptoms of schizophrenia (withdrawal, apathy, demotivation)

↑ Prolactin secretion from pituitary (galactorrhoea, amenorrhoea, gynaecomastia)

↓ Extrapyramidal symptoms (EPS) (dystonias, akathisia, bradykinesia, dyskinesias)
**Actions**  Antipsychotic. Effective against +ve and -ve symptoms.

**MOA**  Modification of dopaminergic transmission in the mesolimbic/mesocortical pathways. Aripiprazole binds strongly to dopamine D<sub>2</sub> receptors but has partial agonist activity which may explain its low incidence of EPS. 5HT<sub>2A</sub> antagonism is probably important.

**Abs/Distrib/Elim**  Oral admin. Long (75h) half-life.

**Clinical use**  Schizophrenia and other psychotic states. Manic phase of bipolar disorder.

**Adverse effects**  Fewer side effects than many other antipsychotics (e.g. minor EPS (some akathisia), less weight gain, less antimuscarinic, less prolactin secretion). Some hypotension and nausea & vomiting.
Antipsychotics

Amisulpride

First-generation agents ('Typical' neuroleptics)

Second-generation agents ('Atypical' neuroleptics)

Diagram illustrating the effects of first- and second-generation antipsychotics

Haloperidol

Chlorpromazine

Flupentixol

Clozapine

Risperidone

Quetiapine

Aripiprazole

D$_2$ receptor antagonism

→ Prolactin secretion from pituitary
  (galactorrhoea, amenorrhoea, gynaecomastia)

↑ Extrapyramidal symptoms (EPS)
  (dystonias, akathisia, bradykinesia, dyskinesias)

D$_2$ receptor antagonism
  + effects on other receptors
  e.g. 5-HT$_{2A}$

↓ +ve symptoms of schizophrenia
  (delusions, hallucinations, aggression)

↓ -ve symptoms of schizophrenia
  (withdrawal, apathy, demotivation)

Unwanted side effects

Wanted effects
Second-generation ('atypical') antipsychotic drug (Similar drug: sulpiride)

**Amisulpride**

**Actions**  Antipsychotic. Effective against +ve and -ve symptoms of schizophrenia.

**MOA**  Dopamine D$_2$ and D$_3$ receptor antagonist. Preferential action on dopamine autoreceptors may explain lower incidence of EPS and effectiveness against -ve symptoms. Low affinity for 5HT, histamine, muscarinic and $\alpha_1$ adrenergic receptors.

**Abs/Distrib/Elim**  Mostly excreted unchanged in kidney. $t_{1/2}$ 12h.

**Clinical use**  Schizophrenia.

**Adverse effects**  Hyperprolactinaemia. Insomnia. Anxiety. Weight gain. Constipation and dry mouth.
23.09 Summary
Antipsychotics

Diagram illustrating the effects of first- and second-generation antipsychotics

First-generation agents
('Typical' neuroleptics)
- Haloperidol
- Chlorpromazine
- Flupentixol

D₂ receptor antagonism

Extrapyramidal symptoms (EPS)
(dystonias, akathisia, bradykinesia, dyskinesias)

Prolactin secretion from pituitary
(galactorrhoea, amenorrhoea, gynaecomastia)

Second-generation agents
('Atypical' neuroleptics)
- Clozapine
- Risperidone
- Quetiapine
- Aripiprazole
- Amisulpride

D₂ receptor antagonism
+ effects on other receptors
e.g. 5-HT₂A

+ve symptoms of schizophrenia
(delusions, hallucinations, aggression)

-ve symptoms of schizophrenia
(withdrawal, apathy, demotivation)

Unwanted side effects

Wanted effects
Comparison of pharmacological activity of antipsychotic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>↓+ve symptoms</th>
<th>↓-ve symptoms</th>
<th>EPS</th>
<th>Prolactin secretion</th>
<th>Anti-muscarinic</th>
<th>Anti-histamine</th>
<th>α-block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
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R&D 7e Ch 45, pp 555-563; D&H 2e Ch 39, pp 90-91
Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS

Noradrenergic neuron

- NA transporter
- NA aldehyde
- MAO-A

Serotonergic neuron

- 5-HT transporter
- 5-HT aldehyde
- MAO-A

- NA, noradrenaline
- 5-HT, 5-hydroxytryptamine
- MAO-A, monoamineoxidase-A

Noradrenalinne

Adrenoceptor on forebrain neuron

5-HT receptor on forebrain neuron

α₂-adrenoceptor
**Tricyclic antidepressant (TCA) (Similar drugs: nortriptyline, desipramine, clomipramine)**

**Amitriptyline**

**Actions**  Antidepressant.

**MOA**  Inhibits reuptake of noradrenaline into noradrenergic neurons and 5-HT into serotonergic neurons, so potentiating transmitter action. The clinical effects are not seen for a few weeks, meaning that longer-term changes (e.g. down-regulation of receptors) are required.

**Abs/Distrib/Elim**  Oral administration. Metabolised in liver by cytochrome P450 system with subsequent conjugation reactions. Plasma half-life 12–24h (influenced by P450 inhibitors or inducers). Strong protein binding.

**Clinical use**  Depression. Panic disorder. Neuropathic pain (see set 26). Enuresis.

**Adverse effects**  Sedation (antihistamine action, less with nortriptyline and desipramine). Blurred vision, dry mouth, constipation, urinary retention (antimuscarinic action). Postural hypotension (α₁-adrenoceptor antagonism). Overdose potentially fatal due to cardiac dysrhythmia, severe hypotension, seizure and CNS depression. Not given with MAOIs. Increased risk of suicide in young patients.

R&D 7e Ch 46, pp 574-576; D&H 2e Ch 40, pp 92-93
Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS

Noradrenergic neuron

Serotonergic neuron

NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamine oxidase-A

Amitriptyline, nortriptyline, desipramine, clomipramine

Arrow thickness indicates strength of action
**Actions**  Antidepressant.

**MOA**  Inhibits the reuptake 5-HT into serotonergic neurons, so potentiating transmitter action. The antidepressant action is not seen for a few weeks, because longer-term changes (e.g. down-regulation of receptors) are required for this. (Less marked antimuscarinic and antihistaminergic actions than the TCAs.)

**Abs/Distrib/Elim**  Oral administration. Brain concentration rises over a few days. Hepatic P450 metabolism followed by conjugation reactions. T\textsubscript{0.5} 1–3 days. Longer-lasting active metabolite. (Half-lives of other SSRIs: paroxetine, 18–24h, fluvoxamine, 18–24h, escitalopram, 24–36h, sertraline, 24–36h.) Strongly bound.


**Adverse effects**  Anxiety and insomnia; can cause nausea, diarrhoea and headache. Sexual dysfunction. Increased risk of suicide in young patients. Not prescribed with MAOIs (risk of serotonin syndrome). Hyponatraemia in elderly. Overdose toxicity much less than for TCAs.

**Special points**  Escitalopram is the active enantiomer of citalopram. Sertraline and escitalopram are the SSRIs which are most selective for 5-HT uptake inhibition.
Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS

Noradrenergic neuron

Serotonergic neuron

NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

Amitriptyline, nortriptyline, desipramine, clomipramine

Fluoxetine, paroxetine, citalopram, sertraline

Adrenoceptor on forebrain neuron

5-HT receptor on forebrain neuron

Noradrenaline
**Actions**  Antidepressant.

**MOA**  Inhibits the reuptake of noradrenaline into noradrenergic neurons and 5-HT into serotonergic neurons, so potentiating transmitter action. The antidepressant action is not seen until a few weeks later. No important effects on histamine, muscarinic or adrenergic receptors.

**Abs/Distrib/Elim**  Oral administration. Half-life 5h (active metabolite – desmethylvenlafaxine. T_{0.5} 11h) Metabolised in liver by cytochrome P450 system. T_{0.5} of duloxetine 12–24h.

**Clinical use**  Depression (reported to be effective in cases resistant to SSRIs). Panic disorder. Generalised anxiety disorder. Social phobia.

**Adverse effects**  Nausea, headache, sleep problems and sexual dysfunction. Not given with MAOIs (induces serotonin syndrome). Increased risk of suicide in young patients. Overdose causes CNS depression, seizures, cardiac dysrhythmias.

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R&D 7e Ch, pp 576-577; D&H 2e Ch 40, pp 92-93
Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS

- **Noradrenergic neuron**
  - NA transporter
  - NA aldehyde
  - MAO-A

- **Serotonergic neuron**
  - 5-HT transporter
  - 5-HT aldehyde
  - MAO-A

**Reboxetine**

- Adrenoceptor on forebrain neuron
- 5-HT receptor on forebrain neuron

**Drugs**

- **Amitriptyline, nortriptyline, desipramine, clomipramine**
- **Venlafaxine, duloxetine**
- **Fluoxetine, paroxetine, citalopram, sertraline**

**Chemicals**

- NA, noradrenaline
- 5-HT, 5-hydroxytryptamine
- MAO-A, monoamineoxidase-A

**Sites of Action**

- Noradrenergic neuron
  - NA transporter
  - NA aldehyde
  - MAO-A

- Serotonergic neuron
  - 5-HT transporter
  - 5-HT aldehyde
  - MAO-A

**Reboxetine** action points:

- Blocks NA reuptake
- Blocks 5-HT reuptake

**Drug Action**

- **Amitriptyline, nortriptyline, desipramine, clomipramine**
- **Venlafaxine, duloxetine**
- **Fluoxetine, paroxetine, citalopram, sertraline**

**Adrenoceptor**

- Noradrenaline
- α₂-adrenoceptor on forebrain neuron
**Actions**  Antidepressant.

**MOA**  Inhibits selectively the reuptake of noradrenaline into noradrenergic neurons. (No effect on 5-HT and dopamine transmission.) The antidepressant action is not seen for a few weeks, indicating that other changes (e.g. down-regulation of receptors) are required for the clinical effects.

**Abs/Distrib/Elim**  Oral administration. Metabolised in liver by cytochrome P450 system. Plasma half-life 15h (influenced by P450 inhibitors or inducers).

**Clinical use**  Depression. Panic disorder. Proposed for ADHD.

**Adverse effects**  Insomnia, headache, effects due to antagonism of muscarinic and histamine receptors, e.g. sweating, dry mouth, constipation. Unlike SSRIs does not increase risk of suicide in young patients. Maprotiline has similar side effects, consistent with block of receptors, to the TCAs. Not given with MAOIs.
Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS

Noradrenergic neuron

Serotonergic neuron

Affective disorders – Major Depressive Disorder

Phenelzine

NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

Adrenoceptor on forebrain neuron
5-HT receptor on forebrain neuron

Amitriptyline, nortriptyline, desipramine, clomipramine
Venlafaxine, duloxetine
Fluoxetine, paroxetine, citalopram, sertraline

Noradrenaline

5-HT

MAO-A

α₂-adrenoceptor

Noradrenaline

NA aldehyde

5-HT aldehyde

NA transporter

5-HT transporter

NA aldehyde

5-HT aldehyde

Adrenoceptor on forebrain neuron

5-HT receptor on forebrain neuron

Noradrenaline
Phenelzine

**Actions**  
Antidepressant.

**MOA**  
Phenelzine and isocarboxazid irreversibly inhibit both the A & B forms of monoamine oxidase. MAO is found in nerve endings, MAO-A acting preferentially on noradrenaline and 5-HT and MAO-B acting mainly on dopamine. MAO inhibition increases the amount of transmitter in the nerve-ending. Antidepressant action is due to MAO-A inhibition. Moclobemide is a selective, reversible inhibitor of MAO-A. (MAO-B inhibitors are used for Parkinson’s disease (see card 20.03).)

**Abs/Distrib/Elim**  
Oral administration. Plasma half-life 1–2h, but action lasts much longer because of irreversible inhibition of MAO. Moclobemide $T_{0.5}$ 1–2h.

**Clinical use**  
Depression; may have particular value for atypical depression. Social phobia. Clinical effect takes some days to develop.

**Adverse effects**  

**Special points**  
Adverse effects are more frequent than with the TCAs or SSRIs so MAOIs are second-line treatment for depression.

R&D 7e Ch 46, pp 577-578; D&H 2e Ch 40, pp 92-93
Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS

- **Noradrenergic neuron**
  - NA transporter
  - NA, noradrenaline
  - NA aldehyde
  - MAO-A, monoamine oxidase-A
  - α₂-adrenoceptor

- **Serotonergic neuron**
  - 5-HT transporter
  - 5-HT, 5-hydroxytryptamine
  - 5-HT aldehyde
  - MAO-A
  - 5-HT receptor on forebrain neuron
  - Adrenoceptor on forebrain neuron

**Drugs**

- **Noradrenergic drugs**
  - Amitriptyline, nortriptyline, desipramine, clomipramine
  - Venlafaxine, duloxetine

- **Serotonergic drugs**
  - Fluoxetine, paroxetine, citalopram, sertraline
  - Reboxetine
  - Venlafaxine, duloxetine
  - Phenelzine, isocarboxazid moclobamide

NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamine oxidase-A
**Actions**  
Antidepressant.

**MOA**  
Antagonist at presynaptic $\alpha_2$-adrenoceptors so preventing the inhibitory effect of noradrenaline on 5-HT and perhaps also on noradrenaline release from CNS neurons, thus enhancing monoaminergic transmission. Antagonism of 5-HT$_2$ and 5-HT$_3$ receptors may be beneficial in reducing side effects due to potentiation of serotonergic transmission (e.g. the sexual dysfunction and nausea produced by uptake inhibitors).

**Abs/Distrib/Elim**  
Oral admin. Subject to hepatic cytochrome P450 metabolism. $t_\frac{1}{2}$ 30h. Longer in elderly and those with liver/renal impairment.

**Clinical use**  
Major depression. Post-traumatic stress disorder.

**Adverse effects**  
Devoid of many side effects associated with muscarinic or adrenoceptor block, but does have antihistamine actions, e.g. sedation (useful if insomnia accompanies depression). Increased appetite and weight gain. Agranulocytosis is rare but serious.
Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS

Noradrenergic neuron

- NA transporter
- NA aldehyde
- α₂-adrenoceptor
- MAO-A

NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamine oxidase-A

Serotonergic neuron

- 5-HT transporter
- 5-HT aldehyde
- MAO-A

Amitriptyline, nortriptyline, desipramine, clomipramine
Venlafaxine, duloxetine
Fluoxetine, paroxetine, citalopram, sertraline

Phenelzine, isocarboxazid moclobamide
Reboxetine

Mirtazapine
**Actions**  ‘Atypical’ antidepressant. Elevates mood.

**MOA**  Relatively selective inhibitor of neuronal dopamine reuptake with a lesser effect on noradrenaline and little effect on 5-HT uptake. Also antagonist at neuronal nicotinic receptors.

**Abs/Distrib/Elim**  Oral admin. Extensive hepatic metabolism by Cyt P450 yields active metabolites which contribute to antidepressant action. $T_{0.5}$ 20h.

**Clinical use**  Alone or in combination with SSRIs for major depression. Also used to help people give up tobacco smoking. Clinical effects take some weeks to develop.

**Adverse effects**  Side effects include: agitation, tremor, dry mouth, nausea, insomnia and skin rashes. It does not cause the weight gain or sexual dysfunction common with other antidepressants. Seizures may be induced with larger doses.
Bipolar disorder (manic-depressive illness) is characterised by mood changes which swing between mania and depression.

Each phase may last for some weeks or months.
A group 1 metallic element

Lithium

**Actions**  Mood ‘stabiliser’.

**MOA**  Not well established. Being a group 1 element like Na\(^+\) and K\(^+\), one proposal is that Li\(^+\) interferes with membrane ion transport, perhaps including neurotransmitter reuptake. Actions on phosphatidyl inositol metabolism and on glycogen synthase kinase are other possible mechanisms.

**Abs/Distrib/Elim**  Oral admin. Uptake of lithium into cells leads to accumulation in the body over a period of 2 weeks.

**Clinical use**  Bipolar (manic-depressive) disorder, mania and as adjunct to other agents in unipolar depression. Clinical effect develops over 3–4 weeks.

**Adverse effects**  Diarrhoea, tremor, confusion. Renal toxicity, including nephrogenic diabetes insipidus – dehydration. Depresses thyroid function. Overdose results in convulsions, coma and death. Many drug interactions (e.g. with diuretics).

**Special points**  Because of a low therapeutic index, it is essential to measure the serum Li\(^+\) concentration to ensure an effective therapeutic concentration with minimal toxicity. Other treatments: antipsychotics (olanzapine) and some antiepileptics (lamotrigine, valproate).

R&D 7e Ch 46, pp 581-582; D&H 2e Ch 40, p 93
Potential sites of action of antiepileptic drugs

- Glutamatergic nerve
  - Ca\(^{2+}\) channel
  - Na\(^{+}\) channel

- GABAergic nerve
  - GABA transporter
  - Succinic semialdehyde
  - GABA-T

- Glutamate
  - Glutamate sites
  - AMPA receptor
  - NMDA receptor
  - T-type Ca\(^{2+}\) channel

- GABA
  - GABA binding site

- Glycine site
- NMDA receptor
- Benzodiazepine site
- Barbiturate site

- Ca\(^{2+}\) channel
- Na\(^{+}\) channel
- Cl\(^{-}\)

- Depolarisation
- Hyperpolarisation
- Excitation
- Inhibition
**Actions**  Anticonvulsant. Relieves neuropathic pain.

**MOA**  Blocks Na$^+$ channels to inhibit action potential initiation and propagation. Use-dependence of block means that action is preferentially on rapidly firing neurons in the epileptic focus.

**Abs/Distrib/Elim**  Oral admin. Metabolised by P450 system in liver to give an active metabolite. T$_{0.5}$ 30h. Phenytoin T$_{0.5}$ 20h but increases with dose due to saturation kinetics.

**Clinical use**  Partial and generalised seizures (tonic-clonic), but not absence seizures. Also neuropathic pain and bipolar disorder. Phenytoin also used for status epilepticus. Saturable elimination of phenytoin makes it useful to monitor its plasma concentration.

**Adverse effects**  Drowsiness, headache, mental disorientation, motor disturbances. Rare, but serious: liver damage, agranulocytosis, aplastic anaemia, skin reaction. Teratogenic effects (e.g. cleft palate with phenytoin). Phenytoin may cause thickening of the gums and hirsutism.

**Special points**  Induction of cytochrome P450 enzymes causes many drug interactions (e.g. ineffectiveness of oestrogenic contraceptives). Oxcarbazepine much weaker P450 inducer.

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R&D 7e Ch 44, p 546; D&H 2e Ch 41, pp 94-95
Potential sites of action of antiepileptic drugs

- Carbamazepine
- GABAergic nerve
- Glutamatergic nerve
- Succinic semialdehyde
- GABA-T
- GABA binding site
- GABA transporter
- T-type Ca\(^{2+}\) channel
- Na\(^{+}\) channel
- Ca\(^{2+}\) channel
- Glutamate
- Glutamate sites
- GABA
- GABA receptor
- AMPA receptor
- NMDA receptor
- T-type Ca\(^{2+}\) channel
- Na\(^{+}\) channel
- Na\(^{+}\) channel
- Cl\(^{-}\)
- Excitation
- Inhibition
- Hyperpolarisation
- Depolarisation
- Benzodiazepine site
- Glycine site
- Barbiturate site
- Na\(^{+}\) channel
**Actions**  Anticonvulsant with specific action on absence seizures.

**MOA**  Blocks T-type Ca\(^{2+}\) channels in thalamic neurons to counteract the slow (3Hz), spike and wave, firing pattern thought to be important in absence epilepsy.

**Abs/Distrib/Elim**  Oral admin. Oxidised by cytochrome P450 system. T\(_{0.5}\) 50h.

**Clinical use**  Drug of choice for absence seizures (not effective against partial or tonic-clonic seizures).

**Adverse effects**  Anorexia, GIT upset, pancytopaenia. Rash, drowsiness, fatigue. Overdose can cause coma and respiratory depression.
Potential sites of action of antiepileptic drugs

- GABAergic nerve
- Glutamatergic nerve
- GABA
- GABA-T
- Succinic semialdehyde
- GABA binding site
- GABA transporter
- Benzodiazepine site
- Glycine site
- Barbiturate site
- AMPA receptor
- NMDA receptor
- T-type Ca$^{2+}$ channel
- Na$^{+}$ channel
- Ca$^{2+}$ channel

Drugs:
- Carbamazepine
- Ethosuximide

Sites of action:
- Excitation
- Inhibition
- Depolarisation
- Hyperpolarisation
**Actions**  Anticonvulsant. Mood stabiliser.

**MOA**  Several actions may contribute to the antiepileptic action: block of voltage-gated Na⁺ channels to inhibit action potential initiation and propagation; inhibition of GABA transaminase to reduce GABA breakdown; various effects on second messenger pathways.

**Abs/Distrib/Elim**  Oral admin. Subject to glucuronidation and mitochondrial oxidation. T$_{0.5}$ 9–16h.

**Clinical use**  Most forms of epilepsy (esp. useful in myoclonic seizures). Manic phase of bipolar disorder. Migraine.

**Adverse effects**  Nausea & vomiting. Tremor. Weight gain. Reproductive dysfunction. Hepatic (especially in infants) and pancreatic toxicity. Teratogenic effects (e.g. neural tube defects including spina bifida).

R&D 7e Ch 44, pp 547-548; D&H 2e Ch 41, pp 94-95
Potential sites of action of antiepileptic drugs

- **GABA**
- **Glutamate**
- **GABA receptor**
- **AMPA receptor**
- **NMDA receptor**

- **Depolarisation**
- **Hyperpolarisation**
- **Excitation**
- **Inhibition**

- **Na⁺ channel**
- **Ca²⁺ channel**

- **Carbamazepine**
- **Valproate**
- **Ethosuximide**
- **Succinic semialdehyde**
- **GABA transporter**
- **GABA binding site**
- **Glutamate binding site**
- **GABAergic nerve**
- **Glutamatergic nerve**
- **Benzodiazepine site**
- **Glycine site**
- **Barbiturate site**
- **T-type Ca²⁺ channel**
**Actions**  Anticonvulsant. Also hypnotic and anxiolytic (see set 22).

**MOA**  Interacts with benzodiazepine binding site on GABAₐ receptor to enhance channel opening by GABA. Increased Cl⁻ permeability reduces electrical excitability. Clonazepam and clobazam said to be more selective anticonvulsants with less sedation.

**Abs/Distrib/Elim**  Given orally (i.v. for status epilepticus). Active metabolite of diazepam has a longer half-life (60h) and contributes significantly to actions. Metabolised by P450 system and glucuronide conjugation.

**Clinical use**  Diazepam given i.v. for status epilepticus. Clonazepam used for tonic-clonic and absence seizures. Clobazam as an adjunctive anticonvulsant. Tolerance to anticonvulsant activity develops.

**Adverse effects**  Benzodiazepines are safe drugs. Unwanted effect in treating epilepsy is sedation. Severe respiratory depression in combination with other CNS depressants (e.g. alcohol).
Potential sites of action of antiepileptic drugs

- **Glutamatergic nerve**
- **Glycine site**
- **NMDA receptor**
- **Ca\(^{2+}\) channel**
- **Na\(^{+}\) channel**

- **GABAergic nerve**
- **GABA transporter**
- **Succinic semialdehyde**
- **GABA**
- **GABA binding site**

Drugs and their effects:
- **Carbamazepine, valproate**
  - Depolarisation
  - Hyperpolarisation
- **Diazepam**
  - Excitation
  - Inhibition
- **Valproate**
  - Depolarisation
  - Hyperpolarisation
- **Ethosuximide**
  - Excitation
  - Inhibition
**Actions**  Anticonvulsant. Hypnotic (at higher doses).

**MOA**  Binds to the barbiturate site on the GABA$_A$ receptor to enhance the activity of GABA in opening the Cl$^-$ channel. This reduces neuronal excitability and action potential frequency at the epileptic focus. Effects on Na$^+$ and Ca$^{2+}$ channels may contribute to the anticonvulsant activity.

**Abs/Distrib/Elim**  Oral admin. Some drug is excreted unchanged, but majority of drug is oxidised in liver. $T_{0.5}$ 50–100h.

**Clinical use**  Tonic-clonic and simple partial seizures, particularly in children.

**Adverse effects**  Highly sedative. Megaloblastic anaemia, hypersensitivity reactions. In overdose coma and respiratory and circulatory failure. Induces dependence. Drug interactions due to hepatic enzyme induction.
Potential sites of action of antiepileptic drugs

- **GABA** (Glutamate and GABA receptor)
- **AMPA receptor**
- **NMDA receptor**
- **Depolarisation**
- **Hyperpolarisation**
- **Excitation**
- **Inhibition**
- **Na⁺ channel**
- **Ca²⁺ channel**
- **GABA transporter**
- **Succinic semialdehyde**
- **GABAergic nerve**
- **Glutamatergic nerve**
- **Carbamazepine, valproate**
- **Diazepam**
- **Phenobarbital**
- **Valproate**
- **Ethosuximide**
- **T-type Ca²⁺ channel**
- **GABA binding site**
- **GABA receptor**
- **Glutamate sites**
- **Glycine site**
- **NMDA receptor**
- **Na⁺ channel**
- **Barbiturate site**
- **Benzodiazepine site**
- **Glycine site**

**Actions**  Anticonvulsant.

**MOA** Irreversible inhibition of GABA transaminase in GABAergic nerves increases the GABA concentration in the nerve terminal. Synaptic GABA concentration probably rises as a consequence of reverse operation of the GABA transporter. Action potential mediated release is also increased.

**Abs/Distrib/Elim** Oral admin. Mostly excreted unchanged. $T_{0.5}$ 10h, though irreversible enzyme inhibition prolongs drug action.

**Clinical use** As an adjunct to other anticonvulsants.

**Adverse effects** Sedation. Fatigue. Hyperactivity in children. Long-term use may produce visual field defects in a high percentage of patients.
Potential sites of action of antiepileptic drugs

- **Glutamatergic nerve**
  - Ca²⁺ channel
  - Na⁺ channel

- **GABAergic nerve**
  - GABA transporter
  - Succinic semialdehyde
  - GABA-T

- **GABAergic nerve**
  - GABA binding site
  - GABA receptor
  - Glutamate sites
  - Glutamate binding site

- **Excitatory neurotransmitters**
  - Glutamate
  - NMDA receptor
  - AMPA receptor

- **Inhibitory neurotransmitters**
  - GABA
  - GABA receptor
  - GABA-T

Drugs and their actions:
- **Carbamazepine, valproate**
  - Depolarisation
  - Excitation

- **Diazepam**
  - Hyperpolarisation
  - Inhibition

- **Phenobarbital**
  - Hyperpolarisation
  - Inhibition

- **Valproate, vigabatrin**
  - Depolarisation
  - Excitation

- **Succinic semialdehyde**

- **T-type Ca²⁺ channel**
  - Excitation
  - Inhibition

- **Glycine site**

- **NMDA receptor**

- **Benzodiazepine site**

- **Benzodiazepine site**

- **GABA receptor**
**Actions**  Anticonvulsant. Reduces frequency of mood episodes in bipolar disorder.

**MOA**  Inhibition of glutamate release decreases postsynaptic neuronal excitation. This may be due to Na$^+$ (and perhaps Ca$^{2+}$) channel inhibition in the nerve ending.

**Abs/Distrib/Elim**  Oral admin. Subject to hepatic glucuronidation. $T_{0.5}$ 24–36h.

**Clinical use**  Partial and generalised seizures, including absence. Bipolar disorder.

**Adverse effects**  Dizziness, headache, double vision and sedation. Serious skin rashes may occur in a small percentage of patients, particularly children.
Potential sites of action of antiepileptic drugs

Glutamatergic nerve

- Ca\(^{2+}\) channel
- Na\(^{+}\) channel

GABAergic nerve

- GABA transporter
- Succinic semialdehyde

GABA

- GABA-T
- GABA binding site
- GABA-A receptor
- GABA-B receptor
- Glutamate

Glutamate sites

- Excitation
- Inhibition

Na\(^{+}\) channel

T-type Ca\(^{2+}\) channel

Barbiturate site

Benzodiazepine site

Glutamate

NMDA receptor

AMPA receptor

Glycine site

Na\(^{+}\) channel

Depolarisation

Hyperpolarisation

Excitation

Inhibition

Carbamazepine, valproate

Diazepam

Lamotrigine

Phenobarbital

Valproate, vigabatrin

Ethosuximide
**Actions**  Anticonvulsant.

**MOA**  Inhibits the reuptake of GABA (by GAT-1) into GABAergic nerve endings and glia, thus raising synaptic GABA concentration and inhibiting neuronal activity.

**Abs/Distrib/Elim**  Orally active. P450 metabolism in liver. $T_{0.5}$ 7h.

**Clinical use**  Adjunct to other agents in treatment of partial seizures.

**Adverse effects**  Dizziness, sedation, confusion, fatigue. Nausea.

R&D 7e Ch 44, p 549; D&H 2e Ch 41, pp 94-95
Potential sites of action of antiepileptic drugs

**GABA**
- GABA receptor
- GABA-T
- GABA binding site

**Glutamate**
- Glutamate sites
- AMPA receptor
- NMDA receptor
- Ca\(^{2+}\) channel
- Na\(^{+}\) channel
- T-type Ca\(^{2+}\) channel

**Excitation**
- Depolarisation
- Excitation
- Na\(^{+}\) channel

**Inhibition**
- Hyperpolarisation
- Inhibition
- GABA receptor
- GABA binding site
- GABA transporter

**Antiepileptic Drugs**
- Topiramate
- Carbamazepine, valproate
- Phenobarbital
- Lamotrigine
- Tiagabine
- Valproate, vigabatrin
- Ethosuximide
**Actions**  Anticonvulsant.

**MOA**  Most likely channel block of AMPA/kainate receptors for glutamate but topiramate also blocks voltage-dependent Na\(^+\) channels and potentiates GABA action on GABA\(_A\) receptors.

**Abs/Distrib/Elim**  Oral admin. Mostly excreted unchanged in urine with some hepatic metabolism. T\(_{0.5}\) 21h.

**Clinical use**  Generalised tonic-clonic and partial seizures. Used as frequently for migraine.

**Adverse effects**  Psychomotor slowing, motor incoordination, memory impairment, paraesthesia, sedation, fatigue, confusion. Loss of appetite and weight loss. Rarely serious vision loss. Metabolic acidosis.
Potential sites of action of antiepileptic drugs

Antiepileptic drugs

Levetiracetam

Potential sites of action of antiepileptic drugs

- GABAergic nerve
- GABA receptor
- AMPA receptor
- NMDA receptor
- Depolarisation
- Hyperpolarisation
- Excitation
- Inhibition

- Ca\(^{2+}\) channel
- Na\(^+\) channel
- NMDA receptor
- GABA-T
- Succinic semialdehyde
- GABA binding site
- GABA transporter
- Valproate, vigabatrin
- Carbamazepine, valproate
- Lamotrigine
- Phenobarbital
- Tiagabine
- Topiramate
- Ethosuximide
- Benzodiazepine site
- Glycine site
- Barbiturate site
- T-type Ca\(^{2+}\) channel
- AMPA receptor
- Na\(^+\) channel
- Cl\(^-\) channel
- Depolarisation
- Hyperpolarisation
- Excitation
- Inhibition
**Actions**  Anticonvulsant.

**MOA**  Activity is thought to be due to binding to synaptic vesicle protein SV2A – how this modifies the release of neurotransmitter (e.g. glutamate) is not established.

**Abs/Distrib/Elim**  Oral admin. Mostly excreted unchanged. $T_{0.5} \approx 7h$.

**Clinical use**  As an adjunct to other anticonvulsants in the treatment of partial seizures.

**Adverse effects**  Sedation, dizziness, paraesthesia. Few drug interactions.
Potential sites of action of antiepileptic drugs

- **GABAergic nerve**
- **GABA binding site**
- **Glutamatergic nerve**
- **Glutamate sites**
- **Benzodiazepine site**
- **Glycine site**
- **Barbiturate site**
- **T-type Ca$^{2+}$ channel**
- **Na$^+$ channel**
- **Ca$^{2+}$ channel**

**Drugs and Actions**

- **Levetiracetam**
- **Tiagabine**
- **Phenobarbital**
- **Topiramate**
- **Valproate, vigabatrin**
- **Carbamazepine, valproate**
- **Lamotrigine**
- **Diazepam**
- **Ethosuximide**

**Sites of Action**

- **GABA transporter**
- **Succinic semialdehyde**
- **GABA-T**
- **GABA receptor**
- **AMPA receptor**
- **NMDA receptor**

**Mechanisms**

- **Depolarisation**
- **Hyperpolarisation**
- **Excitation**
- **Inhibition**
**Actions**  Anticonvulsant. Analgesic.

**MOA**  Action is attributed to binding to the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits of voltage-activated Ca$^{2+}$ channels (P/Q or N-type) to block Ca$^{2+}$ entry and exocytosis of transmitter (glutamate) from nerve endings. (Enhanced release of GABA has also been suggested.)

**Abs/Distrib/Elim**  Oral admin. Excreted unchanged. $T_{0.5}$ 6h (longer with renal impairment).

**Clinical use**  Adjunctive treatment for partial seizures. Widely used to treat neuropathic pain (see set 26).

**Adverse effects**  Sedation, dizziness and unsteadiness.
Potential sites of action of antiepileptic drugs

- **GABAergic nerve**
- **GABA transporter**
- **GABA binding site**
- **GABA receptor**
- **AMPA receptor**
- **NMDA receptor**

**Excitation**
- **Depolarisation**
- **Na⁺ channel**
- **Ca²⁺ channel**
- **Carbamazepine, valproate**
- **Lamotrigine**
- **Topiramate**
- **Phenobarbital**
- **Levetiracetam**

**Inhibition**
- **Hyperpolarisation**
- **Cl⁻**
- **Na⁺ channel**
- **Barbiturate site**
- **Glycine site**
- **GABA binding site**
- **Succinic semialdehyde**
- **T-type Ca²⁺ channel**

**Drugs**
- Carbamazepine, valproate
- Lamotrigine
- Gabapentin
- Topiramate
- Ethosuximide
- Levetiracetam
- Tiagabine
- Valproate, vigabatrin
- Phenobarbital
- Diazepam
- Phenobarbital
Simplified diagram of pain pathway from periphery to brain

- **Tissue damage**
  - Bradykinin, ATP, H⁺
  - Prostaglandins

- **Nociceptive C or Aδ pain afferent**

- **Spinothalamic tract neuron**
  - Glutamate/substance P

- **Interneuron in dorsal horn**
  - GABA/enkephalin

- **Descending noradrenergic inhibition**
  - Descending serotonergic/enkephalinergic inhibition

- **Brain**
  - Locus ceruleus
  - NRM

- **Sensory cortex**

- **Periphery**

- **Nerve inflammation/chemokines**
  - Neuropathic pain
Morphine


**MOA**  Activates \( \mu \) opioid receptors in the brain and spinal cord to inhibit pain transmission and modify the central perception of pain. Activation of \( \kappa \) receptors may exert an additional effect on pain transmission in the spinal cord. May inhibit the activation of sensory nerve endings. Opioid receptors are G-protein coupled receptors which inhibit adenylate cyclase activity, open \( K^+ \) channels and inhibit the opening of \( Ca^{2+} \) channels in nerve endings.

**Abs/Distrb/Elim**  Oral or s.c., i.m. injection. Glucuronic acid conjugation in liver: \( t_{0.5} \) 3–4h. The actions of diamorphine and codeine are due, at least in part, to metabolism to morphine. Buprenorphine \( T_{0.5} \) 12h.


**Adverse effects**  Hypotension. Constipation, nausea, vomiting, drowsiness, dizziness. Tolerance, dependence and withdrawal effects (much less with codeine). Larger doses – coma with respiratory depression.
**Analgesic drugs and the control of pain**

**Pethidine (Meperidine)**

- **Simplified diagram of pain pathway from periphery to brain**

  - **Periphery**
    - Tissue damage
    - Bradykinin, ATP, H⁺
    - Nociceptive C or A δ pain afferent
  
  - **Spinal cord**
    - Prostaglandins
    - Spinothalamic tract neuron
    - Glutamate/ substance P
    - Interneuron in dorsal horn
      - GABA/ enkephalin
  
  - **Brain**
    - Locus ceruleus
    - PAG
    - Sensory cortex
    - Thalamus
  
  - **Descending inhibition**
    - Noradrenergic
    - Serotonergic/enkephalinergic
  
  - **Morphine, diamorphine, buprenorphine, codeine**

- **Neuropathic pain**
  - Nerve inflammation / chemokines

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**Notes:**

- Morphine, diamorphine, buprenorphine, codeine inhibit pain transmission by modulating the neurotransmission pathways.
**Actions**

**MOA**
Activates μ opioid receptors in the brain and spinal cord to inhibit pain transmission. Activation of κ receptors may exert an additional effect on pain transmission in the spinal cord. May inhibit activation of the sensory nerve endings. (See also ‘Morphine’ – card 26.01).

**Abs/Distrb/Elim**
Oral/ i.m. admin. Subject to hydrolysis and P450 oxidation – T$_{0.5}$ 3–5h. Fentanyl is also available as a patch for transdermal admin. for long-term effects. Remifentanil has a very short half-life (0.1h).

**Clinical use**
Moderate to severe pain. Does not reduce uterine contractions so favoured for labour pain. Remifentanil and sufentanil are given i.v. for surgical analgesia.

**Adverse effects**
Constipation (less than morphine), nausea, vomiting, drowsiness, dizziness. Tolerance, dependence and withdrawal effects. Larger doses – coma with respiratory depression.
Analgesic drugs and the control of pain

Methadone

Simplified diagram of pain pathway from periphery to brain

**Tissue damage**
- Bradykinin, ATP, H^+ 
- Prostaglandins 

**Periphery**
- Nociceptive C or A δ pain afferent

**Spinal cord**
- Spinothalamic tract neuron
  - Glutamate/ substance P

**Interneuron in dorsal horn**
- GABA/ enkephalin

**Brain**
- Locus ceruleus
- NRM
- PAG
- Sensory cortex

**Descending noradrenergic inhibition**

**Descending serotonergic/enkephalinergic inhibition**

**Morphine, diamorphine, buprenorphine, codeine**

**Pethidine, fentanyl**

**Neuropathic pain**

**Nerve inflammation/ chemokines**
**Actions**  Analgesia (methadone strong, propoxyphene weak). Euphoria. Physical/psychological dependence. Respiratory depression. Inhibition of gut motility.

**MOA**  Activation of μ opioid receptors in the brain and spinal cord to inhibit pain transmission. Also modifies the central perception of pain. Opioids may also inhibit the activation of sensory nerve endings. (See also ‘Morphine’ – card 26.01.)

**Abs/Distrb/Elim**  Oral absorption. Long duration of action. P450 metabolism in liver $T_{0.5}$ 15–40h. Propoxyphene $T_{0.5}$ 6h.

**Clinical use**  Analgesia (propoxyphene only copes with mild to moderate pain). Maintenance of opioid addicts and assistance in withdrawal program. Cough suppression. Propoxyphene is often combined with paracetamol.

**Adverse effects**  Constipation, nausea, vomiting, drowsiness, dizziness. Tolerance, dependence and withdrawal effects. Larger doses – coma with respiratory depression and possible cardiac dysrhythmia.
Simplified diagram of pain pathway from periphery to brain

- **Tissue damage**
  - Bradykinin, ATP, H⁺
- **Periphery**
  - Nociceptive C or A δ pain afferent
- **Prostaglandins**
- **Spinal cord**
  - Spinothalamic tract neuron
  - Glutamate/substance P
- **Brain**
  - Locus ceruleus
  - NRM
  - PAG
  - Sensory cortex
- **Thalamus**
- **Sensory cortex**
- **Descending noradrenergic inhibition**
- **Descending serotonergic/enkephalinergic inhibition**

- **Morphine, diamorphine, buprenorphine, codeine**
- **Pethidine, fentanyl**
- **Methadone, propoxyphene**

- **Neuropathic pain**
- **Nerve inflammation/chemokines**
**Actions**  Analgesia.

**MOA**  Weak agonist action at µ opioid receptors but main action is attributed to enhancement of monoamine neurotransmission by inhibition of 5-HT and noradrenaline reuptake into nerve endings. Analgesic action is reported to be inhibited by 5-HT₃ receptor antagonists.

**Abs/Distrb/Elim**  Oral admin. Subject to hepatic demethylation and conjugation, T₀.₅ 6h.

**Clinical use**  Moderate/moderately severe pain. Used post-operatively. Neuropathic pain.

**Adverse effects**  Dizziness, nausea and vomiting. Respiratory depression, constipation and addiction (but less than with morphine). Convulsions.
Simplified diagram of pain pathway from periphery to brain

- **Tissue damage**
  - Bradykinin, ATP, H⁺
  - Nociceptive C or Aδ pain afferent
  - Periphery

- **Prostaglandins**
  - Spinothalamic tract neuron
  - Spinal cord

- **Nociceptive C or Aδ pain afferent**
  - Morphine, diamorphine, buprenorphine, codeine
  - Pethidine, fentanyl
  - Methadone, propoxyphene
  - Tramadol

- **Interneuron in dorsal horn**
  - Glutamate/substance P
  - GABA/enkephalin

- **Spinothalamic tract neuron**
  - Locus ceruleus
  - NRM
  - Thalamus
  - Sensory cortex

- **Descending inhibition**
  - Noradrenergic
  - Serotonergic/enkephalinergic

- **Neuropathic pain**
  - Nerve inflammation/chemokines
**Actions**  Antagonises the actions of opioid drugs. May cause hyperalgesia under conditions, such as stress, where endogenous opioids may be operative.

**MOA**  Competitive antagonist of opioids at μ, δ and κ-receptors.

**Abs/Distrb/Elim**  Given by injection (i.v., i.m. or s.c.) (very low oral bioavailability). Conjugated with glucuronic acid in liver, short $t_{1/2}$: 1–2h. Naltrexone is orally active and has a $t_{1/2}$ of 4h though action is extended by an active metabolite with $t_{1/2}$ of 13h.

**Clinical use**  Treatment of respiratory depression and coma caused by opioid overdose. The longer-acting naltrexone is used to aid in treating opioid and alcohol addiction.

**Adverse effects**  Free of important side effects. May cause withdrawal symptoms in opiate addicts.
Analgesic drugs and the control of pain

Ibuprofen

Simplified diagram of pain pathway from periphery to brain

- **Tissue damage**
  - Bradykinin, ATP, H⁺
  - Prostaglandins
  - Bradykinin, ATP, H⁺
  - Nociceptive C or Aδ pain afferent

- **Periphery**
  - Nociceptive C or Aδ pain afferent
  - Prostaglandins
  - Bradykinin, ATP, H⁺

- **Spinal cord**
  - Spinothalamic tract neuron
  - Glutamate/substance P

- **Brain**
  - Locus ceruleus
  - NRM
  - PAG
  - Sensory cortex

- **Descending inhibition**
  - noradrenergic
  - serotoninergic/enkephalinergic

- **Neuropathic pain**
  - Glutamate/substance P
  - Prostaglandins

- **Nerve inflammation/chemokines**

- **Morphine, diamorphine, buprenorphine, codeine**
- **Pethidine, fentanyl**
- **Methadone, propoxyphene**
- **Tramadol**

- **Naloxone**

- **Descending serotoninergic/enkephalinergic inhibition**
- **Descending noradrenergic inhibition**

- **Thalamus**

- **Sensory cortex**

- **Locus ceruleus**

- **NRM**

- **PAG**
**Actions**  Anti-inflammatory (except paracetamol) (see card 3.01). Analgesic. Antipyretic.

**MOA**  Inhibit cyclo-oxygenase iso-enzymes. Ibuprofen, naproxen and aspirin are non-selective inhibitors, celecoxib is COX-2 selective and paracetamol is COX-3 selective. (See cards 3.01–3.04.) Inhibit production of prostaglandins at the site of inflammation; this prevents an increase in sensitivity of pain receptors. Also act within the CNS. Paracetamol may utilise additional mechanisms.

**Abs/Distrb/Elim**  Oral admin. Metabolised by P450 system, $T_{0.5} 2h$. Aspirin is rapidly hydrolysed to yield salicylate which is also a COX inhibitor. Naproxen $T_{0.5} 14h$. Paracetamol $T_{0.5} 2–3h$.

**Clinical use**  Mild to moderate pain due to inflammatory disease, surgery, dysmenorrhoea and headache (including migraine). Naproxen is used for chronic pain. Paracetamol is ineffective in rheumatic pain.

**Adverse effects**  GIT bleeding and ulceration (less with COX-2 selective agents). Tinnitus. Skin rashes. Celecoxib (and other selective COX-2 inhibitors) may provoke myocardial infarction or stroke and should be avoided in patients with heart disease. Paracetamol is hepatotoxic in overdose.
Simplified diagram of pain pathway from periphery to brain

**Tissue damage**
- Bradykinin, ATP, H^+  
- Prostaglandins

**Periphery**
- Nociceptive C or A δ pain afferent

**Interneuron in dorsal horn**
- Glutamate/substance P

**Spinothalamic tract neuron**
- GABA/enkephalin

**Brain**
- Locus ceruleus
- NRM

**Sensory cortex**
- Sensory cortex

**Descending noradrenergic inhibition**
- Morphine, diamorphine, buprenorphine, codeine
- Pethidine, fentanyl
- Methadone, propoxyphene
- Tramadol

**Descending serotonergic/enkephalinergic inhibition**
- Ibuprofen

**Neuropathic pain**
- Naloxone

**Nerve inflammation /chemokines**
- Morphone, diamorphine, buprenorphine, codeine
- Methadone, propoxyphene
- Pethidine, fentanyl
- Tramadol
- Ibuprofen
**Actions**  Reduction of neuropathic pain. (For antiepileptic action see cards 25.01 & 25.07.)

**MOA**  Inhibits the opening of neuronal voltage-gated Na\(^+\) channels to reduce nociceptive transmission from site of nerve injury.

**Abs/Distrb/Elim**  Oral administration. Active P450 metabolite.

**Clinical use**  Second- or third-line treatment of neuropathic pain. Main use in trigeminal neuralgia and diabetic neuropathy.

**Adverse effects**  Drowsiness, headache, mental disorientation, motor disturbances. Rare, but serious, adverse effects are liver damage, agranulocytosis and aplastic anaemia. Serious dermatological reaction in genetically susceptible patients. Strong inducer of cytochrome P450 enzymes leading to many drug interactions. Lamotrigine may cause a skin rash, particularly in children.
Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain

- **Tissue damage**
  - Bradykinin, ATP, H⁺

- **Nociceptive C or Aδ pain afferent**
  - Prostaglandins

- **Spinothalamic tract neuron**
  - Glutamate/substance P
  - GABA/enkephalin

- **Brain**
  - Locus ceruleus
  - NRM
  - PAG
  - Sensory cortex

- **Interneuron in dorsal horn**
  - Descending noradrenergic inhibition
  - Descending serotonergic/enkephalinergic inhibition

- **Periphery**
  - Carbamazepine
  - Ibuprofen
  - Morphine, diamorphine, buprenorphine, codeine
  - Pethidine, fentanyl
  - Methadone, propoxyphene
  - Tramadol

- **Neuropathic pain**
  - Naloxone
**Actions**  Reduction of neuropathic pain. (For antidepressant action see set 24).

**MOA**  Analgesic action of antidepressants is mainly due to inhibition of the opening of neuronal voltage-gated Na\(^+\) channels (Na\(_v\) 1.7 subtype) rather than to inhibition of monoamine reuptake. Na\(^+\) channel block reduces pain transmission from site of nerve injury.

**Abs/Distrb/Elim**  Oral administration. Hepatic P450 metabolism (nortriptyline is a metabolite of amitriptyline). T\(_{0.5}\) 12–24h.

**Clinical use**  Postherpetic neuralgia, diabetic peripheral neuropathy, neuropathic cancer pain.

**Adverse effects**  Sedation (antihistamine action, less with nortriptyline). Blurred vision, dry mouth, constipation, urinary retention (antimuscarinic action). Postural hypotension (\(\alpha_1\)-adrenoceptor antagonism). Overdose potentially fatal due to cardiac dysrhythmia, severe hypotension, seizure and CNS depression. Increased risk of suicide in young patients.
**Simplified diagram of pain pathway from periphery to brain**

**Periphery**
- Tissue damage
- Bradykinin, ATP, H^+
- Prostaglandins
  - Nociceptive C or A δ pain afferent

**Spinal cord**
- Spinothalamic tract neuron
  - Glutamate/substance P
  - GABA/enkephalin

**Brain**
- Locus ceruleus
- NRM
- PAG
- Sensory cortex
  - Descending noradrenergic inhibition
  - Descending serotonergic/enkephalinergic inhibition

**Nerve inflammation /chemokines**
- Bradykinin, ATP, H^+
- Nerve inflammation /chemokines

**Analgesic drugs**
- Gabapentin
- Morphine, diamorphine, buprenorphine, codeine
- Pethidine, fentanyl
- Methadone, propoxyphene
- Tramadol
- Ibuprofen
- Amitriptyline
- Carbamazepine
- Naloxone
**Actions**  Reduction of neuropathic pain. (For antiepileptic action see set 25).

**MOA**  Effectiveness in neuropathic pain is due to binding to the $\alpha_2-\delta-1$ and $\alpha_2-\delta-2$ subunits of voltage-activated Ca$^{2+}$ channels (P/Q or N-type) to block Ca$^{2+}$ entry and exocytosis of transmitter (glutamate) from pain nerve endings.

**Abs/Distrb/Elim**  Oral admin. Excreted unchanged. $t_{1/2}$ 6h.

**Clinical use**  Postherpetic and trigeminal neuralgia. Pregabalin is also used for painful diabetic peripheral neuropathy.

**Adverse effects**  Sedation, dizziness and unsteadiness.
Sumatriptan and the treatment of migraine

Simplified diagram of pain pathway from periphery to brain

**Tissue damage**
- Bradykinin, ATP, H^+ → Nociceptive C or A δ pain afferent

**Periphery**
- Prostaglandins
- Bradykinin, ATP, H^+ → Nociceptive C or A δ pain afferent

**Spinal cord**
- Spinothalamic tract neuron
  - Glutamate/substance P
  - GABA/enkephalin

**Brain**
- Locus ceruleus
  - Descending noradrenergic inhibition
  - Descending serotonergic/enkephalinergic inhibition

**Sensory cortex**
- Sensory cortex

**Thalamus**
- Thalamus

**PAG**
- PAG

**NRM**
- NRM

**Periphery**
- Pethidine, fentanyl
- Methadone, propoxyphene
- Tramadol
- Gabapentin
- Amitriptyline
- Carbamazepine
- Ibuprofen

**Brain**
- Locus ceruleus
  - Descending serotonergic/enkephalinergic inhibition

**Nerve inflammation/chemokines**
- Nerve inflammation/chemokines

**Neuropathic pain**
- Naloxone

**Morphine, diamorphine, buprenorphine, codeine**
- Morphine, diamorphine, buprenorphine, codeine

**Pethidine, fentanyl**
- Pethidine, fentanyl

**Methadone, propoxyphene**
- Methadone, propoxyphene

**Tramadol**
- Tramadol

**Carbamazepine**
- Carbamazepine

**Gabapentin**
- Gabapentin

**Amitriptyline**
- Amitriptyline
The pathophysiology of migraine is likely to involve inflammatory vasodilatation in extracerebral cranial blood vessels and stimulation of trigeminal nerve terminals (which might induce further inflammation by the release of neuropeptides).

*Treatment of acute attack* is with **NSAIDS** (aspirin, ibuprofen, tolfenamic acid, etc.) or **paracetamol**. If this is inadequate, ‘triptans’ are used.

**Sumatriptan** is the standard triptan.

**MOA** Triptans are agonists at 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors. Activation of 5-HT\textsubscript{1D} receptors causes vasoconstriction of cranial blood vessels (with little effect on peripheral vessels). They also inhibit trigeminal nerve stimulation and peptide release.

**Abs/Distrb/Elim** Orally active, but low bioavailability. T\textsubscript{0.5} 1.5h. May be given s.c. if migraine is accompanied by vomiting.

**Clinical use** Acute migraine attack. Sumatriptan is also effective in cluster headache.

**Adverse effects** Sumatriptan has adverse cardiac effects and is contraindicated in heart disease.

**Prophylaxis** employs other drugs: β-adrenoceptor antagonists (e.g. propranolol), tricyclic antidepressants (e.g. amitriptyline), some antiepileptics (topiramate, valproate), pizotifen (5-HT\textsubscript{2} receptor antagonist).
Dopaminergic, noradrenergic and serotonergic transmission as targets for CNS stimulants and psychotomimetics

- Dopaminergic neuron in ventral tegmental area
- Serotonergic neuron in dorsal raphe nuclei
- Noradrenergic neuron in locus ceruleus

MA, monoamine
DA, dopamine
NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamine oxidase-A

5-HT receptors and adrenoceptors in reticular formation, prefrontal cortex and hypothalamus
Arousal, effects on mood

Dopamine receptors in nucleus accumbens/prefrontal cortex
Reward, pleasure
**Actions**  
CNS stimulation: arousal, alertness, concentration. Euphoria/excitement. Stereotyped behaviour. Anxiety. Reduced appetite. Sympathomimetic actions: tachycardia, pupillary dilation, etc.

**MOA**  
Inhibition of neuronal reuptake of MA, inhibition of MAO, inhibition of the vesicular monoamine transporter. Raised cytosolic levels of MAs and release from nerve terminals, mainly by reverse operation of the MA transporter. Increased MA levels in synapse. Sympathomimetic actions due to release of NA in the periphery.

**Abs/Distrib/Elim**  
Orally active. $T_{0.5}$ 10h. Renal excretion enhanced by urine acidification. Methylphenidate also administered by patch.

**Clinical use**  
Attention deficit hyperactivity disorder (ADHD), narcolepsy.

**Adverse effects**  

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R&D 7e Ch 47, pp 584-586; D&H 2e Ch 43, p 99
CNS stimulants and psychotomimetics

- Dopaminergic neuron in ventral tegmental area
- Serotonergic neuron in dorsal raphe nuclei
- Noradrenergic neuron in locus ceruleus

Release by reversed action of monoamine transporter

Dopamine receptors in nucleus accumbens/prefrontal cortex

Reward, pleasure

Arousal, effects on mood

5-HT receptors and adrenoceptors in reticular formation, prefrontal cortex and hypothalamus

MA, monoamine
DA, dopamine
NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamine oxidase-A
**Actions**  Euphoria, alertness and other effects like amphetamine. Sympathomimetic actions: tachycardia, vasoconstriction with increased blood pressure etc. Local anaesthesia.

**MOA**  Inhibits action of monoamine transporters (but unlike amphetamine-like drugs is not transported and does not provoke monoamine release). Local anaesthetic action due to Na⁺ channel block (see card 28.03).

**Abs/Distrib/Elim**  Abusers favour i.v. or nasal admin. (The free base ‘crack cocaine’ is volatile and is smoked.) \( T_{0.5} \ 1h \).

**Clinical use**  Important as drug of abuse. Limited use as surface anaesthetic.

**Adverse effects**  Cardiac toxicity. Hypertension. Hyperthermia. Addiction. Taken intranasally, vasoconstriction may cause necrosis of nasal tissue.
Dopaminergic, noradrenergic and serotonergic transmission as targets for CNS stimulants and psychotomimetics

- Dopaminergic neuron in ventral tegmental area
- Serotonergic neuron in dorsal raphe nuclei
- Noradrenergic neuron in locus ceruleus

5-HT receptors and adrenoceptors in reticular formation, prefrontal cortex and hypothalamus
Arousal, effects on mood

Monoamine transporter
Release by reversed action of monoamine transporter

MA, monoamine
DA, dopamine
NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamine oxidase-A

Dopamine receptors in nucleus accumbens/prefrontal cortex
Reward, pleasure
**Actions** Mood alteration, perceptual changes (psychedelic effects), cognitive impairment. Paranoid delusions (‘bad trips’). Hallucinations at higher doses.

**MOA** Agonist at several 5-HT receptors but psychotomimetic action is attributed to 5-HT$_{2A}$ receptors enhancing glutamatergic transmission in cerebral cortex. Additional actions may be inhibition of 5-HT release in the Raphe nuclei by 5-HT$_{1A}$ receptors and modulation of dopaminergic activity in the mesolimbic pathway. Mescaline acts partly by inhibiting MA reuptake.

**Abs/Distrib/Elim** Effective orally. LSD $T_{0.5}$ 3h. DMT has a low oral bioavailability so may be smoked.

**Clinical use** No clinical use. Important only as a drug of abuse.

**Adverse effects** Some sympathomimetic actions (e.g. pupil dilatation, tachycardia). Unlike other drugs of abuse they produce little dependence or withdrawal effects. LSD is non-fatal in overdose.
CNS stimulants and psychotomimetics

**Phencyclidine**

**Dopaminergic, noradrenergic and serotonergic transmission as targets for CNS stimulants and psychotomimetics**

- Dopaminergic neuron in ventral tegmental area
- Serotonergic neuron in dorsal raphe nuclei
- Noradrenergic neuron in locus ceruleus

**Key Receptors:**
- 5-HT receptors and adrenoceptors in reticular formation, prefrontal cortex and hypothalamus
- Dopamine receptors in nucleus accumbens/prefrontal cortex
- Reward, pleasure

**Key Compounds:**
- MA, monoamine
- DA, dopamine
- NA, noradrenaline
- 5-HT, 5-hydroxytryptamine
- MAO-A, monoamine oxidase A

**Aldehyde**

**Monoamine Transporter**

**Release by reversed action of monoamine transporter**

**Amphetamine**

**LSD**
**Actions**  Euphoria, sensory distortion, hallucinations. Schizophrenia-like psychosis. Like ketamine, it produces analgesia and amnesia which confers action as a dissociative anaesthetic.

**MOA**  Blocks the ion channel of NMDA-type glutamate receptor. How this leads to the behavioural effects is not fully established, but effects on dopaminergic transmission are likely. Phencyclidine also blocks σ receptors.

**Abs/Distrib/Elim**  Most commonly absorbed by inhalation of smoke but also orally active. $T_{0.5}$ 10–90h.

**Clinical use**  Use of phencyclidine as anaesthetic now stopped, though ketamine is still used for this purpose (see card 21.04). Dangerous drug of abuse.

**Adverse effects**  In overdose: hypertension and seizures.
Local anaesthetics may be administered in a variety of ways to reduce the transmission of pain to the CNS.
**Actions**  Prevents the propagation of nerve action potentials. Blocks small-diameter pain fibres at lower concentration than large fibres.

**MOA**  Use-dependent block of voltage-gated Na⁺ channels from inside of cell membrane. Penetrates cell membrane in its lipid-soluble, uncharged form. (See fig.) Less active in inflamed tissue, where the lower pH increases ionisation of the weakly basic local anaesthetic (LA).

**Abs/Distrb/Elim**  Topical application (gel, solution, patch) or injection. Penetrates membranes readily. Lidocaine, like other amide LAs, is metabolised mainly in the liver by P450 system. $t_{1/2}$ 2h.

**Clinical use**  Surface and infiltration anaesthesia, nerve block (e.g. dentistry) and epidural and spinal anaesthesia (sometimes combined with an opioid). Adrenaline may be added to reduce loss to blood stream. EMLA (eutectic mixture of LA) is a widely used topical combination of lidocaine with prilocaine. Ventricular dysrhythmia (see card 5.02).

**Adverse effects**  Few adverse effects. High plasma concentration may cause seizures and cardiac depression. Transient neurologic symptoms are more prevalent with lidocaine than bupivacaine following epidural use.

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R&D 7e Ch 42, pp 526-529; D&H 2e Ch 44, p 100
Local anaesthetics may be administered in a variety of ways to reduce the transmission of pain to the CNS.
**Actions** Prevents the propagation of nerve action potentials. Blocks small-diameter pain fibres at lower concentration than large fibres.

**MOA** Use-dependent block of voltage-gated Na⁺ channels from inside of cell membrane. Penetrates cell membrane in its lipid-soluble, uncharged form. (See fig.) Less active in inflamed tissue, where the lower pH increases ionisation of the weakly basic local anaesthetic (LA).

**Abs/Distrb/Elim** These drugs are amides metabolised by P450 system in liver, eventually yielding glucuronides. They are longer acting than other LAs. Bupivacaine $T_{0.5}$ 2–3h.

**Clinical use** Infiltration, nerve block, epidural, and spinal anaesthesia. Used when longer action is required. May be combined with adrenaline to prolong action and fentanyl for epidural use.

**Adverse effects** At normal doses few adverse effects. More cardiotoxic than other LAs. (Levobupivacaine and ropivacaine less cardiotoxic.)
Local anaesthetics may be administered in a variety of ways to reduce the transmission of pain to the CNS.
Ester-type local anaesthetic (Similar drugs: cocaine, tetracaine)

**Procaine**

*Actions* Prevents the propagation of nerve action potentials. Blocks small-diameter pain fibres at lower concentration than large fibres.

*MOA* Use-dependent block of voltage-gated Na⁺ channels from inside of cell membrane. Penetrates cell membrane in its lipid-soluble, uncharged form. (See fig.) Less active in inflamed tissue, where the lower pH increases ionisation of the weakly basic local anaesthetic (LA).

*Abs/Distrb/Elim* Ester-type LAs are in general shorter acting than lidocaine or bupivacaine, being mainly hydrolysed by plasma esterases. (Plasma T₀.₅ is only a few minutes, but duration of action is increased due to slower removal from site of injection, especially so for the very lipid-soluble tetracaine.)

*Clinical use* Cocaine’s vasoconstrictor action is useful when applied topically for nose and throat surgery. Tetracaine is used mainly for surface (skin, cornea – sometimes combined with lidocaine) and spinal anaesthesia.

*Adverse effects* Cardiac depression. Procaine has more central effects than other LAs and is rarely used. Ester LAs are more likely than amides to cause an allergic reaction. Cocaine is a CNS stimulant (see card 27.02).

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R&D 7e Ch 42, pp 526-529; D&H 2e Ch 44, p 100
Local anaesthetics may be administered in a variety of ways to reduce the transmission of pain to the CNS.

- **Surface anaesthesia**
  - Lidocaine, EMLA, tetracaine, cocaine,

- **Infiltration anaesthesia**
  - Lidocaine, bupivacaine, ropivacaine

- **Nerve block**
  - Lidocaine, bupivacaine, ropivacaine

- **Epidural anaesthesia**
  - Lidocaine, bupivacaine, ropivacaine

- **Spinal anaesthesia**
  - Lidocaine, bupivacaine, tetracaine
**Actions** Prevents the propagation of nerve action potentials. Blocks small-diameter pain fibres at lower concentration than large fibres.

**MOA** Benzocaine (pKa = 2.5) is a much weaker base than most LAs and is mainly unionised in the body. It is not use-dependent and can gain access to the Na⁺ channel via the membrane lipid (See fig.).

**Abs/Distrb/Elim** Topical application as gel, ointment or powder (low aqueous solubility). High lipid solubility allows rapid penetration of mucous membranes.

**Clinical use** Used only for surface anaesthesia (e.g. for placement of nasogastric tubes, pain relief for wounds and burns). Also in throat lozenges.

**Adverse effects** Allergic reactions, but generally safe and available in many OTC preparations.
Local anaesthetics may be administered in a variety of ways to reduce the transmission of pain to the CNS.
**Actions**  Prevents the propagation of nerve action potentials. Blocks small-diameter pain fibres at lower concentration than large fibres.

**MOA**  Use-dependent block of voltage-gated Na⁺ channels from inside of cell membrane. Penetrates cell membrane in its lipid-soluble, uncharged form. (See fig.) Less active in inflamed tissue, where the lower pH increases ionisation of the weakly basic local anaesthetic (LA).

**Abs/Distrb/Elim**  Articaine is an amide-type LA (like lidocaine) but has an additional ester group which can be rapidly hydrolysed to give a short plasma half-life (30min).

**Clinical use**  Articaine, usually combined with epinephrine, is the favoured LA for dentistry in many countries.

**Adverse effects**  Low toxicity due to rapid breakdown in blood. Potential paresthesia if used for mandibular nerve block.
Antibacterial agents

Benzylpenicillin (Penicillin G)

Peptidoglycan synthesis and the site of action of drugs

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane.

N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. Beta-lactams inhibit this cross-linking.
**Actions**  Bactericidal; interferes with cell wall synthesis in dividing bacteria.

**MOA**  Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed ‘building block’ to the peptidoglycan cell wall backbone.

**Special points**  Inactivated by bacterial beta-lactamases.

**Abs/Distrb/Elim**  Given i.m. or i.v. Passes into all body fluids; crosses the placenta but not the blood-brain barrier unless the meninges are inflamed. Excreted in the urine (blocked by probenecid). The less active phenoxyethyl penicillin can be given orally.

**Clinical use**  Streptococcal, gonococcal, meningococcal infections; also anthrax, diphtheria, gas gangrene.

**Resistance**  Staphylococci are generally resistant (mainly because they produce beta-lactamase); some pneumococci, meningococci and gonococci have decreased sensitivity.

**Adverse effects**  Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis).
Peptidoglycan synthesis and the site of action of drugs

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane.

N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. Beta-lactams inhibit this cross-linking.

Beta-lactams e.g Penicillin G inhibit the formation of this link.
Actions Bactericidal; interferes with cell wall synthesis in dividing bacteria.

MOA Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed ‘building block’ to the peptidoglycan cell wall backbone.

Abs/Distrb/Elim Given orally, i.m. or i.v. or by slow i.v. infusion. Passes into all body fluids; excreted in the urine (blocked by probenecid).

Clinical use Penicillin-resistant staphylococci infections.

Resistance Some pneumococci, meningococci and gonococci have decreased sensitivity.

Adverse effects Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis); GIT disturbances. Rarely: hepatitis and cholestatic jaundice.
Peptidoglycan synthesis and the site of action of drugs

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane.

N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. Beta-lactams inhibit this cross-linking.

Beta-lactams e.g. Penicillin G, flucloxacillin inhibit the formation of this link.
A broad-spectrum penicillin antibacterial agent (Similar drug: ampicillin)

**Amoxicillin**

**Actions**  Bactericidal; interferes with cell wall synthesis in dividing bacteria.

**MOA**  Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed ‘building blocks’ to the peptidoglycan cell wall backbone.

**Special points**  Inactivated by bacterial β-lactamases; usually given with clavulanic acid which inhibits β-lactamases.

**Abs/Distrb/Elim**  Given i.m. or i.v. or by slow i.v. infusion. Passes into all body fluids; excreted in the urine (blocked by probenecid). Ampicillin is given i.v.

**Clinical use**  Gram-negative bacteria as well as streptococcal, gonococcal, meningococcal infections, anthrax, diphtheria, gas gangrene.

**Resistance**  Not effective against staphylococci (due to β-lactamase) and to streptococci which have impaired β-lactam binding due to mutation of the transpeptidase enzyme.

**Adverse effects**  Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis); GIT disturbances; rarely colitis.
**Peptidoglycan synthesis and the site of action of drugs**

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane. N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. Beta-lactams inhibit this cross-linking.

*Beta-lactams* e.g. Penicillin G, flucloxacillin, **amoxicillin** inhibit the formation of this link.
**Actions**  Bactericidal; interferes with cell wall synthesis in dividing bacteria.

**MOA**  Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed ‘building blocks’ to the peptidoglycan cell wall backbone.

**Special points**  Inactivated by bacterial β-lactamases; usually given with tazobactam which inhibits β-lactamases.

**Abs/Distrb/Elim**  Given by i.v. injection or infusion. Passes into all body fluids; excreted in the urine (blocked by probenecid).

**Clinical use**  Gram-negative bacterial and *Pseudomonas aeruginosa* infections.

**Resistance**  Ineffective against staphylococci due to β-lactamase (unless given with the β-lactamase inhibitor tazobactam) and to streptococci which have impaired β-lactam binding due to mutation of the transpeptidase enzyme.

**Adverse effects**  Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis); GIT disturbances, pseudomembranous colitis.

R&D 7e Ch 50, p 627; D&H 2e Ch 47, pp 107-108
Peptidoglycan synthesis and the site of action of drugs

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane.

N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. Beta-lactams inhibit this cross-linking.

Beta-lactams e.g. Penicillin G, flucloxacillin, amoxicillin, piperacillin inhibit the formation of this link.
**Actions**  Bactericidal; interferes with cell wall synthesis in dividing bacteria.

**MOA**  Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed ‘building blocks’ to the peptidoglycan cell wall backbone.

**Abs/Distrb/Elim**  Given orally. i.m. or i.v. Passes into all body fluids; excreted in the urine (blocked by probenecid).

**Clinical use**  Active against β-lactamase-producing *H. influenzae* & *N. gonorrhoea*. Used to treat sinusitis, ear infections, lower respiratory tract infections, urinary infections.

**Adverse effects**  Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis); GIT disturbances, pseudomembranous colitis; superinfection.
Peptidoglycan synthesis and the site of action of drugs

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane.

N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. Beta-lactams inhibit this cross-linking.

- Beta-lactams e.g. Penicillin G, flucloxacillin, amoxicillin, piperacillin, cefuroxime inhibit the formation of this link.

Antibacterial agents

Ceftazidime
**Actions**  Bactericidal; interferes with cell wall synthesis in dividing bacteria.

**MOA**  Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed ‘building blocks’ to the peptidoglycan cell wall backbone.

**Resistance**  Susceptible to bacterial β-lactamases.

**Abs/Distrb/Elim**  Given by deep i.m. or by i.v. injection or by i.v. infusion. Passes into all body fluids; excreted in the urine (blocked by probenecid). Half-life 1–1.5h.

**Clinical use**  Gram-positive & Gram-negative bacterial and *Pseudomonas aeruginosa* infections.

**Adverse effects**  Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis); GIT disturbances, pseudomembranous colitis; superinfection.

**Similar drugs**  Ceftriaxone (half-life 7–8h), cefoperazone (half-life 2h).
Antibacterial agents

Peptidoglycan synthesis and the site of action of drugs

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane.

N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. Beta-lactams inhibit this cross-linking.

Beta-lactams e.g. Penicillin G, flucloxacillin, amoxicillin, piperacillin, cefuroxime, ceftazidime inhibit the formation of this link.
**Actions**  Bactericidal; interferes with cell wall synthesis in dividing bacteria.

**MOA**  Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed ‘building blocks’ to the peptidoglycan cell wall backbone.

**Abs/Distrb/Elim**  Given by i.v. infusion. Passes into all body fluids including the CSF. Inactivated by renal enzymes so must be given with cilastatin which inhibits the relevant enzymes.

**Clinical use**  Broad spectrum: active against Gram-positive, Gram-negative and anaerobic bacteria. Not active against MRSA. Used to treat severe polymicrobial hospital-acquired infections, e.g. septicaemia, pneumonia, complicated urinary infections.

**Adverse effects**  GIT disturbances, rashes, injection site reactions.

**Similar drugs**  Meropenem.
Peptidoglycan synthesis and the site of action of drugs

Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (\(-P-P\)-) and towed across the membrane.

N-Acetylglucosamine (G) is attached as are five glycine residues. This is the basic building block of the peptidoglycan.

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (\(\circ\)) providing the energy. Beta-lactams inhibit this cross-linking.

Beta-lactams: e.g. Penicillin G, flucloxacillin, amoxicillin, cefuroxime, ceftazidime, imipenem inhibit the formation of this link.
Acetylmuramic acid (M), with a side-chain of 5 amino acids, is attached to a large carrier lipid by a pyrophosphate bridge (-P-P-) and towed across the membrane.

**Action & MOA**
- **Bactericidal; interferes with cell wall synthesis in dividing bacteria.**

**Abs/Distrb/Elim**
- Given orally for local effect in the mouth, otherwise i.v.; renal excretion

**Clinical use**
- MRSA infections, pseudomembranous colitis

**Advers effects**
- Reversible hearing loss; rarely: renal failure

On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (o) providing the energy. **Vancomycin inhibits this removal and thus the attachment of the building block.**

**Beta-lactams**
- e.g. Penicillin G, flucloxacillin, amoxicillin, cefuroxime, ceftazidime, imipenem inhibit the formation of this link
Bacterial protein synthesis and the antibiotics that act thereon

The ribosome moves along the messenger RNA (mRNA) which has been transcribed from DNA. Codons pass along the ribosome from the A site to the P site. A transfer RNA (tRNA) with growing peptide chain is in the P site. The incoming tRNA carries valine (V).
**Actions & MOA**  Interferes with bacterial protein synthesis by competing with tRNA for the A site of the ribosome and reversibly inhibiting its binding to the mRNA codons in the 30s subunit.

**Abs/Distr/Elim**  Given orally, absorption impaired by milk and by calcium, magnesium and iron preparations.

**Clinical use**  A drug of choice for chlamydial, rickettsial and brucella infections. Effective in infections with mycoplasma and *Haemophilus influenzae*. Used in sinusitis, prostatitis, syphilis, Lyme disease and in treatment/prevention of malaria (see card 31.02).

**Adverse effects**  Staining of the teeth, GIT disturbances, anorexia, flushing, tinnitus. Rare: hepatotoxicity pancreatitis, hypersensitivity reactions.

**Similar drug:**  Minocycline (has broader spectrum), demeclocycline.
Bacterial protein synthesis and the antibiotics that act thereon

Tetracyclines (e.g. doxycycline) compete with tRNA for the A site and prevent binding to the mRNA/ribosome complex.

The ribosome moves along the messenger RNA (mRNA) which has been transcribed from DNA. Codons pass along the ribosome from the A site to the P site. A transfer RNA (tRNA) with growing peptide chain is in the P site. The incoming tRNA carries valine (V).
**Actions**  Inhibits bacterial protein synthesis.

**MOA**  Causes misreading of the mRNA message due to abnormal codon:anticodon recognition with the production of abnormal proteins.

**Abs/Distrb/Elim**  Given i.m. or by slow i.v. injection or infusion. Can be given intrathecally. Renal excretion.

**Clinical use**  Infections with staphylococci (with a β-lactam antibiotic), streptococci, enterococci, Gram-negative bacilli (including *P. aeruginosa*). Used for septicaemia, meningitis, pyelonephritis, endocarditis, pneumonia.

**Adverse effects**  Dose-related ototoxicity and nephrotoxicity. GIT disturbances, rash, blood disorders can occur; ↑ ototoxicity with loop diuretics; ↑ effect of neuromuscular blockers.

**Special points**  Serum levels should be monitored.

**Similar drugs:**  Amikacin, tobramycin.

R&D 7e Ch 50, p 630; D&H 2e Ch 47, pp 108-110
Bacterial protein synthesis and the antibiotics that act thereon

**Tetracyclines (e.g. doxycycline)** compete with tRNA for the A site and prevent binding to the mRNA/ribosome complex.

**Aminoglycosides (e.g. gentamicin)** cause misreading of mRNA message due to abnormal codon: anticodon recognition.

The ribosome moves along the messenger RNA (mRNA) which has been transcribed from DNA. Codons pass along the ribosome from the A site to the P site. A transfer RNA (tRNA) with growing peptide chain is in the P site. The incoming tRNA carries valine (V).
**Actions**  Inhibits bacterial protein synthesis.

**MOA**  Inhibits transpeptidation.

**Abs/Distrb/Elim**  Given orally or by i.v. injection or infusion; enters CSF and CNS; inactivated in the liver; excreted in the urine.

**Clinical use**  Used mainly for life-threatening *H. influenzae* infections, for meningitis resistant to penicillin and for typhoid. Used topically for bacterial eye infections.

**Adverse effects**  Dose-related bone marrow depression. ‘Grey baby’ syndrome in neonates who lack the relevant inactivating enzyme: circulatory collapse, flaccidity, vomiting. Aplastic anaemia in a few genetically predisposed individuals.
Bacterial protein synthesis and the antibiotics that act thereon

**Erythromycin**

- **Aminoglycosides (e.g. gentamicin)** cause misreading of message due to abnormal codon: anticodon recognition

- **Tetracyclines (e.g. doxycycline)** compete with tRNA for the A site and prevent binding to the mRNA/ribosome complex

- **Chloramphenicol** inhibits transpeptidation

- A transfer RNA with growing peptide chain is in the P site. The Incoming tRNA carries valine (V).
**Actions**  Inhibits bacterial protein synthesis.

**MOA**  Inhibits the translocation of the transfer RNA (with its attached peptide) from the A site to the P site.

**Abs/Distrb/Elim**  Given orally or by i.v. infusion. Half-life 1.5h. Distributed widely but doesn’t enter brain or CSF.

**Clinical use**  For pneumococcal & streptococcal infections in patients allergic to penicillin. For chlamydial and mycoplasma infections. For infections of the skin and the respiratory tract; for syphilis, diphtheria, prostatitis, whooping cough, campylobacter enteritis.

**Adverse effects**  GIT disturbances. Less frequent: allergic reactions, cholestatic jaundice.

**Similar drugs**  Clarithromycin and azithromycin.
Bacterial protein synthesis and the antibiotics that act thereon

**Tetracyclines** (e.g., doxycycline) compete with tRNA for the A site and prevent binding to the mRNA/ribosome complex.

A transfer RNA with growing peptide chain is in the P site. The incoming tRNA carries valine (V).

**Aminoglycosides** (e.g., gentamicin) cause misreading of message due to abnormal codon: anticodon recognition.

Transpeptidation occurs, linking the peptide chain on the tRNA at the P site to the amino acid on the incoming tRNA at the A site.

**Chloramphenicol** inhibits transpeptidation.

The tRNA denuded of its peptide chain is ejected and the tRNA (with peptide attached) in the A site is translocated to the P site. The ribosome then moves on one codon on the mRNA.

**Macrolides** (e.g., erythromycin) inhibit translocation.

A new tRNA with attached amino acid can now move into the A site.
**Actions**  Inhibits bacterial protein synthesis.

**MOA**  Inhibits the translocation of the transfer RNA (with its attached peptide) from the A site to the P site.

**Abs/Distrb/Elim**  Given orally or by deep i.m. injection or by i.v. infusion. Half-life 2.5h. Distributed widely, entering abscesses but doesn’t penetrate brain or CSF. Is concentrated in bone. Metabolised in liver to give active metabolite, excreted in urine.

**Clinical use**  Effective against streptococci, penicillin-resistant staphylococci and many anaerobes (except *Clostridium difficile*). Used for lung abscesses, and for bone, joint, skin and soft tissue infections.

**Adverse effects**  GIT disturbances, skin rashes, jaundice, pseudomembranous colitis.
**Bacterial protein synthesis and the antibiotics that act thereon**

*Tetracyclines* (e.g. doxycycline) compete with tRNA for the A site and prevent binding to the mRNA/ribosome complex.

A transfer RNA with growing peptide chain is in the P site. The Incoming tRNA carries valine (V).

*Aminoglycosides* (e.g. gentamicin) cause misreading of message due to abnormal codon: anticodon recognition.

Transpeptidation occurs, linking the peptide chain on the tRNA at the P site to the amino acid on the incoming tRNA at the A site.

Chloramphenicol inhibits transpeptidation.

The tRNA denuded of its peptide chain is ejected and the tRNA (with peptide attached) in the A site is translocated to the P site. The ribosome then moves on one codon on the mRNA.

A new tRNA with attached amino acid can now move into the A site.

Clindamycin and erythromycin inhibit translocation.
**Actions**
Inhibit bacterial protein synthesis by disrupting the translation of mRNA into protein.

**MOA**
Dalfopristin inhibits the binding of the aa-tRNA to the ribosome and the formation of the peptide bonds; quinupristin causes dissociation of the peptidyl-tRNA.

**Abs/Distrib/Elim**
Given by i.v. infusion, metabolised in the liver; $T_{0.5} 1–3$ h.

**Clinical use**
Serious Gram-positive infections unresponsive to other antibacterials, e.g. MRSA, infections of the skin & soft tissues, hospital-acquired pneumonia, vancomycin-resistant *Enterococcus faecium*.

**Adverse effects**
GIT disturbances, headache, joint and muscle pain, rash, pruritis, infusion site reactions, anaemia, leucopenia.

**Special points**
Inhibits the metabolism and thus increases action of ciclosporin, midazolam, nifedipine, antidysrhythmics (lidocaine, disopyramide).
**Antibacterial agents**

**Ciprofloxacin**

**The bacterial chromosome**
- Cell wall
- Chromosome
  - Portion of the chromosomal double helix
  - Portion of the double helix in supercoiled form
- Chromosome folded round RNA core
- RNA core
- DNA gyrase

**Folate metabolism**
- PABA
- Dihydropteroate synthetase
- Folate
- Dihydrofolate reductase
- Tetrahydrofolate
- Synthesis of thymidylate etc.
- DNA
**Actions**  Interferes with bacterial DNA function.

**MOA**  Inhibits DNA gyrase (aka topoisomerase II) – the enzyme that produces the supercoil in the chromosome that is essential for transcription and replication.

**Abs/Distrb/Elim**  Given orally or by i.v. infusion. Not absorbed from GIT in the presence of magnesium or aluminium salts. Accumulates in the kidney, prostate and lung and concentrates in phagocytes. Partly metabolised in the liver and partly excreted in urine.

**Clinical use**  Active against Gram-positive organisms; particularly effective against Gram-negative bacteria. Used for infections of the urinary tract, the GIT and bones & joints; for respiratory tract infections not caused by pneumococci; for gonorrhoea and septicaemia caused by sensitive organisms.

**Adverse effects**  GIT upsets, headache, dizziness, rashes. Rare: tendon damage, CNS effects (seizures, insomnia) due to competition with GABA binding to its receptors.

**Similar drugs:**  Norfloxacin, levofloxacin.
**Antibacterial agents**

**Co-trimoxazole**

**The bacterial chromosome**

- Cell wall
- Chromosome
- Portion of the chromosomal double helix
- Portion of the double helix in supercoiled form
- DNA gyrase
- RNA core
- Folded round RNA core

**Folate metabolism**

1. PABA
2. Dihydropteroate synthetase
3. Folate
4. Dihydrofolate reductase
5. Tetrahydrofolate
6. Synthesis of thymidylate etc.
7. DNA
**Actions**  Both sulfamethoxazole and trimethoprim interfere with bacterial folate metabolism and thus with DNA synthesis.

**MOA**  Sulfamethoxazole competitively inhibits the enzyme dihydropteroate synthetase. Trimethoprim inhibits dihydrofolate reductase and thus the conversion of folate to tetrahydrofolate.

**Abs/Distrb/Elim**  Given orally or by i.v. infusion. Sulfa drugs pass into inflammatory exudates, but are inactive in the presence of pus.

**Clinical use**  Pneumocystis pneumonia, toxoplasmosis and nocardiasis, urinary infections, acute exacerbations of chronic bronchitis. Trimethoprim alone used for prostatitis, and for urinary and respiratory infections.

**Adverse effects**  GIT upsets, rashes. Very rare but serious: Stevens-Johnson syndrome, blood dyscrasias, toxic epidermal necrolysis, photosensitivity.

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R&D 7e Ch 50, pp 625-626; D&H 2e Ch 47, p 111
Regimen of directly observed treatment (DOT) for tuberculosis

Drug 1 given for 2-month initial and 4-month continuation therapy.

Drug 2 given for 2-month initial and 4-month continuation therapy.

Drug 3 given for 2-month initial phase only.

Drug 4 given for 2-month initial phase only.

Different countries may have different regimens.
Actions  Bacteriostatic for resting mycobacteria, bactericidal for proliferating mycobacteria.

MOA Disrupts the synthesis of mycolic acids – major components of mycobacterial cell walls.

Abs/Distrb/Elim  Given orally, well absorbed. Passes into CSF and tuberculous lesions. Enters cells and is taken up by tubercle bacilli. Acetylated in liver – slowly by some individuals (genetically 'slow metabolisers’), fast by others who thus respond less efficiently to the drug.

Clinical use  Tuberculosis.

Adverse effects  GIT disturbances, hypersensitivity reactions, peripheral neuritis (with high doses, pyridoxine prophylaxis required).
Regimen of directly observed treatment (DOT) for tuberculosis

Drug 1 given for 2-month initial and 4-month continuation therapy.

Isoniazid

Drug 2 given for 2-month initial and 4-month continuation therapy.

Drug 3 given for 2-month initial phase only.

Drug 4 given for 2-month initial phase only.

Different countries may have different regimens.
**Actions**  Bactericidal for mycobacteria; also effective against most Gram-positive and many Gram-negative bacteria.

**MOA**  Inhibits bacterial but not human DNA-dependent RNA polymerase leading to reduced RNA synthesis in the bacterial cell.

**Abs/Distrb/Elim**  Given orally, widely distributed excreted in urine and bile.

**Clinical use**  Tuberculosis (in combination with other drugs). Leprosy. Prophylaxis for meningococcal meningitis, and *Haemophilus influenzae*. Also used (combined with other drugs) for brucellosis, endocarditis, legionnaires’ disease, serious staphylococcal infections.

**Adverse effects**  GIT disturbances, hepatitis, rash, harmless orange tint to saliva, sweat & tears. If treatment is intermittent patients can develop influenza-like and respiratory symptoms, shock, renal problems and thrombocytopenic purpura.

**Special points**  Induction of metabolising enzymes results in decreased action of anticoagulants, narcotic analgesics, phenytoin, glucocorticoids, oral contraceptives.

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R&D 7e Ch 50, p 634; D&H 2e Ch 47, p 112
Regimen of directly observed treatment (DOT) for tuberculosis

Drug 1 given for 2-month initial and 4-month continuation therapy.

Isoniazid

Drug 2 given for 2-month initial and 4-month continuation therapy.

Rifampicin

Drug 3 given for 2-month initial phase only.

Drug 4 given for 2-month initial phase only.

Different countries may have different regimens.
**Actions**  Bactericidal for actively dividing intracellular mycobacteria. Main effects occur in first few months.

**MOA**  Is converted to pyrazinoic acid which disrupts membrane energetics and inhibits membrane transport function in *Mycobacterium tuberculosis*.

**Abs/Distrb/Elim**  Given orally, widely distributed, crosses into the CSF, excreted in urine.

**Clinical use**  Tuberculosis (in combination with other drugs). Tuberculous meningitis.

**Adverse effects**  Joint pains, GIT disturbances, sideroblastic anemia, rash; sometimes serious hepatotoxicity.

**Special points**  Induction of metabolising enzymes results in decreased action of anticoagulants, narcotic analgesics, phenytoin, glucocorticoids, oral contraceptives.
Regimen of directly observed treatment (DOT) for tuberculosis

Drug 1 given for 2-month initial and 4-month continuation therapy.

*Isoniazid*

Drug 2 given for 2-month initial and 4-month continuation therapy.

*Rifampicin*

Drug 3 given for 2-month initial phase only.

*Pyrazinamide*

Drug 4 given for 2-month initial phase only.

Different countries may have different regimens.
**Actions**  Bacteriostatic for rapidly growing TB bacilli.

**MOA**  It obstructs the formation of the cell wall in dividing TB bacilli.

**Abs/Distrb/Elim**  Given orally; can cross into the CSF; some is metabolised, some is excreted in the urine.

**Clinical use**  Tuberculosis (in combination with other drugs).

**Adverse effects**  Visual disturbances (e.g. colour blindness, loss of acuity), peripheral neuritis, rash, fever.

Regimen of directly observed treatment (DOT) for tuberculosis

- Drug 1 given for 2-month initial and 4-month continuation therapy: **Isoniazid**
- Drug 2 given for 2-month initial and 4-month continuation therapy: **Rifampicin**
- Drug 3 given for 2-month initial phase only: **Pyrazinamide**
- Drug 4 given for 2-month initial phase only: **Ethambutol**

R&D 7e Ch 50, p 635; D&H 2e Ch 47, pp 111-112
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
5. Assembly and budding
5. Protein synthesis

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HV = Herpes viruses
RSV = Respiratory syncytial virus
A nucleoside antiretroviral agent (Similar drug: didanosine)

**Actions**
Inhibits the action of the viral reverse transcriptase of HIV viruses.

**MOA**
Phosphorylated by host cell enzymes to give zidovudine trisphosphate which interferes with viral DNA synthesis.

**Abs/Distrb/Elim**
Given orally but can be given by i.v. infusion; the concentration in the CSF is 65% of the blood level. The $T_{0.5}$ of the false trisphosphate is 3h.

**Clinical use**
Human immunodeficiency virus infection in combination with other agents. Slows progress of the disease without curing the infection.

**Adverse effects**
With long-term use: blood dyscrasias, GIT disturbances, myopathy, rashes, fever and a flulike syndrome.

**Special points**
Resistance is likely to occur. To reduce this possibility, the drug is used in combination with other antiretrovirals.

R&D 7e Ch 51, pp 641-643; D&H 2e Ch 48, pp 113-114
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
5. Assembly and budding
5. Protein synthesis

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HV = Herpes viruses
RSV = Respiratory syncytial virus

Zidovudine (HIV)
Nevirapine

**Actions**  Inhibits the action of the viral reverse transcriptase of the immunodeficiency virus. Active against HIV-1 but not HIV-2.

**MOA**  Binds to and denatures the viral reverse transcriptase enzyme.

**Abs/Distrb/Elim**  Given orally; the concentration in the CSF is 45% of the plasma level.

**Clinical use**  HIV-1 infection in combination with other antiretrovirals. Can reduce mother-to-foetus transmission of the virus by ~50%.

**Adverse effects**  Hepatotoxicity. Rash, Stevens-Johnson syndrome. Less common: GIT disturbances, myalgia. Efavirenz can cause disturbances of sleep and dreaming.

R&D 7e Ch 51, p 643; D&H 2e Ch 48, pp 113-114
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
5. Assembly and budding

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HV = Herpes viruses
RSV = Respiratory syncytial virus

Zidovudine (HIV)
nevirapine (HIV)
**Action & MOA**  
Reversibly inhibits the viral-specific protease that, during assembly & budding, cleaves precursor viral proteins to give the structural and functional proteins of the new virions.

**Abs/Distrb/Elim**  
Given orally, extensive first-pass metabolism. Elimination $t_{1/2}$ 12h.

**Clinical use**  
HIV-1 infection in combination with other antiretrovirals. Can reduce mother-to-foetus transmission of the virus by ~50%.

**Adverse effects**  
GIT disturbances, rhinitis, insulin resistance, lipodystrophy.
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
5. Protein synthesis
5. Assembly and budding

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HV = Herpes viruses
RSV = Respiratory syncytial virus
HIV = Human immunodeficiency virus

Zidovudine (HIV)
Nevirapine (HIV)
Saquinavir (HIV)
**Action**
Inhibits HIV entry into host cells.

**MOA**
Binds to a subunit on the HIV envelope preventing fusion of the virus with the target cell membrane, thus inhibiting infection of the mammalian cell.

**Abs/Distrb/Elim**
Given by subcut. injection. Elimination $t_{1/2} \sim 4\text{h}$.

**Clinical use**
HIV-1 infection in combination with other antiretrovirals.

**Adverse effects**
Hypersensitivity reactions.
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
5. Assembly and budding
5. Protein synthesis

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HV = Herpes viruses
RSV = Respiratory syncytial virus
HIV = Human immunodeficiency virus

Enfuvirtide (HIV)
Zidovudine (HIV)
nevirapine (HIV)
Saquinavir (HIV)
**Actions**  Interferes with viral nucleic acid synthesis.

**MOA**  Converted by viral and host cell kinases to aciclovir triphosphate which selectively inhibits viral DNA polymerase.

**Abs/Distrb/Elim**  Given orally, i.v. (slowly) or topically; is degraded fairly rapidly within the host cell. CSF concentration is ~50% of plasma level.

**Clinical use**  Herpes simplex infections (cold sores, mouth ulcers, conjunctivitis, genital infections and, more seriously, encephalitis). Herpes zoster infections (shingles, chickenpox).

**Adverse effects**  Usually minimal; sometimes nausea, headache; rarely encephalitis.
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
5. Assembly and budding

**Aciclovir (HV)**

**Enfuvirtide (HIV)**

**Zidovudine (HIV)**

**Nevirapine (HIV)**

**Saquinavir (HIV)**

New virions

CMV = Cytomegalovirus  
HBV = Hepatitis B virus  
HCV = Hepatitis C virus  
HIV = Human immunodeficiency virus  
HV = Herpes viruses  
RSV = Respiratory syncytial virus

Ganciclovir

Antiviral agents
**Actions**  Interferes with viral nucleic acid synthesis.

**MOA**  Converted by viral and host cell kinases to ganciclovir triphosphate which competes with guanosine triphosphate for incorporation into viral DNA, and suppresses viral DNA replication.

**Abs/Distr/Elim**  Given intravenously; $t_\frac{1}{2}$ 4h but persists in host cells for 18-20h.

**Clinical use**  Cytomegalovirus infection (common in AIDS & immunocompromised patients).

**Adverse effects**  Bone marrow depression; therefore used only for life-threatening infections.
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and ...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
6. Protein synthesis
7. Assembly and budding

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HV = Herpes viruses
RSV = Respiratory syncytial virus

Acyclovir (HV)
Ganciclovir
Zidovudine (HIV)
nevirapine (HIV)
Saquinavir (HIV)
Enfuvirtide (HIV)
**Actions**  Reduces viral replication.

**MOA**  Inhibits neuraminidase which is necessary for virion release.

**Abs/Distrb/Elim**  Given orally – within 48h of onset of symptoms for post-exposure prophylaxis. Zanamivir is given intranasally.

**Clinical use**  Prevention and treatment of infections with influenza viruses A and B.

**Adverse effects**  GIT disturbances, headache, dizziness, rashes; very rarely hepatitis.
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
5. Protein synthesis
5. Assembly and budding

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HV = Herpes viruses
RSV = Respiratory syncytial virus

Enfuvirtide (HIV)
Oseltamivir & zanamivir (flu virus)
Acyclovir (HV)
Ganciclovir
Zidovudine (HIV)
Nevirapine (HIV)
Saquinavir (HIV)
**Actions** Inhibits viral entry into host cells.

**MOA** It is a humanized monoclonal antibody against a protein on the surface of the respiratory syncytial virus.

**Abs/Distrb/Elim** Given by intramuscular injection.

**Clinical use** For respiratory syncytial virus infection in children. (Needs specialist prescription and administration.)

**Adverse effects** Hypersensitivity reactions against the monoclonal antibody are possible.
A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
6. Protein synthesis
7. Assembly and budding
8. Budding

New virions

Enfuvirtide (HIV)
opalivizumab (RSV)
Aciclovir (HV)
Ganciclovir
Zidovudine (HIV)
Nevirapine (HIV)
Oseltamivir & zanamivir (flu virus)
Saquinavir (HIV)

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HV = Herpes viruses
RSV = Respiratory syncytial virus
**Actions**  Kills viruses and virus-infected cells.

**MOA**  It stimulates the production of host enzymes that degrade both viral mRNA (thus inhibiting viral protein synthesis and halting replication) and host cell mRNA in the infected cell, thus killing it.

**Abs/Distrb/Elim**  Given i.v.; $T_{0.5}$ 2–4h. Peginterferon-alfa2a has a longer $t_{1/2}$.

**Clinical use**  For viral hepatitis B; with ribavirin for chronic viral hepatitis C.

**Adverse effects**  Fever, headache and myalgia are common. CVS and liver dysfunction and bone marrow depression can also occur.
Why are combinations of drugs used to treat HIV infection? What combinations are used?

A schematic diagram of virus infection of a mammalian cell

1. Attachment
2. Entry and...
3. Uncoating
4. Transfer of viral DNA to nucleus
5. Viral nucleic acid synthesis
6. Protein synthesis
7. Assembly and budding
8. Budding

New virions

CMV = Cytomegalovirus
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HV = Herpes viruses
RSV = Respiratory syncytial virus

Enfuvirtide (HIV)
palivizumab (RSV)

Aciclovir (HV)
Ganciclovir

Zidovudine (HIV)
nevirapine (HIV)

Oseltamivir & zanamivir (flu virus)

Interferon-α (HBV, HCV)

Saquinavir (HIV)
Combinations of anti-HIV drugs* are used to reduce the development of resistance.

The drugs combined should have additive antiviral action but not additive adverse reactions.

A frequently used combination is:

Two nucleoside reverse transcriptase inhibitors e.g. zidovudine, didanosine, lamivudine

PLUS

Either a non-nucleoside reverse transcriptase inhibitor, e.g. nevirapine, enfuvirtide

OR a protease inhibitor, e.g. saquinavir, atazanavir.

*referred to as highly active antiretroviral therapy (HAART).
The malarial cycle and the sites at which drugs can affect it

**HUMAN**

1. Sporozoites injected by bite and enter liver (**Pre-erythrocytic stage**)
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont...
6. ...then forms motile trophozoite and starts to divide
7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

**MOSQUITO**

Sporozoites ← Oocyst ← Zygote

**Erythrocytic stage**

**A. Blood schizonticides treat the acute attack**

**B. Drugs of radical cure**

- Inhibit hypnozoites

**C. Chemoprophylactic drugs** (prevent clinical attack)

**D. Drugs preventing transmission destroy gametocytes**
**Actions**  A schizonticidal drug that kills malarial parasites in red blood cells.

**MOA**  It inhibits haem polymerase which would normally degrade haem, rendering it harmless to the parasite. The toxic haem molecules accumulate and kill the parasite.

**Abs/Distrb/Elim**  Given orally (or in severe falciparum malaria subcut. or i.v.) it concentrates in parasitised erythrocytes. Slowly eliminated; T_{0.5} 50h, but a residue persists for longer.

**Clinical use**  To treat acute attacks of benign malaria (*Plasmodium vivax, P. ovale, P. malariae*). For chemoprophylaxis of benign malaria and of chloroquine-sensitive falciparum malaria. To treat rheumatoid arthritis and lupus erythematosus (see card 3.10).

**Adverse effects**  Few when used for chemoprophylaxis. The larger doses used to treat the acute attack can cause GIT disturbances, dizziness, urticaria. Bolus i.v. injections can cause dysrhythmias.

**Special points**  Chloroquine resistance is spreading.
The malarial cycle and the sites at which drugs can affect it

**HUMAN**

1. Sporozoites injected by bite and enter liver (Pre-erythrocytic stage)
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont ...
6. ... then forms motile trophozoite and starts to divide
7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

**MOSQUITO**

Sporozoites ← Oocyst ← Zygote

**A. Blood schizonticides treat the acute attack:** chloroquine

**B. Drugs of radical cure inhibit hypnozoites**

**C. Chemoprophylactic drugs (prevent clinical attack): chloroquine**

**D. Drugs preventing transmission destroy gametocytes**
**Actions**  A schizonticidal drug that kills malarial parasites in red blood cells.

**MOA**  It is thought to inhibit haem polymerase which would normally degrade haem, rendering it harmless to the parasite. The toxic haem molecules accumulate and kill the parasite.

**Abs/Distrb/Elim**  Given orally, $t_{1/2}$ 10h but can be given by i.v. infusion. It partially concentrates in parasitised red blood cells. Metabolised in liver; $t_{1/2}$ 10h.

**Clinical use**  To treat acute attacks of malignant malaria (*P. falciparum*). Often given in combination with (or followed by) doxycycline or clindamycin or pyrimethamine + sulfadoxine (see cards 29.09 & 31.06).

**Adverse effects**  GIT disturbances, tinnitus, blurred vision. With large doses: hypotension, dysrhythmias and CNS disturbances. Black water fever (intravascular haemolysis, haemoglobinuria, kidney failure) can be associated with quinine.

**Special points**  Not suitable for chemoprophylaxis.

R&D 7e Ch 53, pp 660-661; D&H 2e Ch 49, pp 115-116
The malarial cycle and the sites at which drugs can affect it

**HUMAN**

1. **Sporozoites** injected by bite and enter liver (**Pre-erythrocytic stage**)
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont ...
6. ... then forms motile trophozoite and starts to divide

**Liver**

2a. Hypnozoites of *P. vivax* & *P. ovale* lie dormant (**Exo-erythrocytic stage**)

**Erythrocytic stage**

7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

**MOSQUITO**

Sporozoites → Oocyst → Zygote

**A. Blood schizonticides treat the acute attack:**
- chloroquine (benign malaria)
- **quinine + doxycycline** (falciparum malaria)

**B. Drugs of radical cure**
- inhibit hypnozoites

**C. Chemoprophylactic drugs** (prevent clinical attack): chloroquine

**D. Drugs preventing transmission destroy gametocytes**
**Actions**  A schizonticidal drug that kills malarial parasites in red blood cells.

**MOA**  It is thought to inhibit haem polymerase which would normally degrade haem, rendering it harmless to the parasite. The toxic haem molecules accumulate and kill the parasite.

**Abs/Distrb/Elim**  Given orally, onset of action is slow, $T_{0.5} 16h$.

**Clinical use**  For chemoprophylaxis of falciparum malaria in areas where it is chloroquine resistant.

**Adverse effects**  GIT disturbances, neuropsychiatric reactions (e.g. ataxia, confusion, hallucinations, convulsions), CVS disorders, rash, fever, leucopenia.

**Special points**  Not used for treatment of falciparum malaria because of resistance; not used for the benign malarias because less toxic drugs are available.
The malarial cycle and the sites at which drugs can affect it

HUMAN

1. Sporozoites injected by bite and enter liver **(Pre-erythrocytic stage)**
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont ...
6. ... then forms motile trophozoite and starts to divide
7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

MOSQUITO

Sporozoites ➔ Oocyst ➔ Zygote

A. Blood schizonticides treat the acute attack: chloroquine (benign malaria), quinine + doxycycline (falciparum malaria)

B. Drugs of radical cure inhibit hypnozoites
C. Chemoprophylactic drugs (prevent clinical attack): chloroquine, mefloquine

**Liver**

2a. Hypnozoites of *P. vivax* & *P. ovale* lie dormant **(Exo-erythrocytic stage)**

D. Drugs preventing transmission destroy gametocytes
**Actions**  
Kills hypnozoites in the liver. Kills gametocytes.

**MOA**  
Not really known.

**Abs/Distrb/Elim**  
Given orally, rapidly metabolised; $t_{1/2}$ 3–6h.

**Clinical use**  
For radical cure of *P. vivax* and *P. ovale* by eliminating the exo-erythrocytic stage. Given as adjunct to chloroquine treatment of the acute attack.

**Adverse effects**  
Dose-related GIT disturbances and methaemoglobinaemia. Causes haemolytic anaemia in patients with genetic glucose 6-phosphate dehydrogenase deficiency (G6PD).

**Special points**  
Test for G6PD.
The malarial cycle and the sites at which drugs can affect it

**HUMAN**

1. Sporozoites injected by bite and enter liver (**Pre-erythrocytic stage**)
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont ...
6. ... then forms motile trophozoite and starts to divide

**Liver**

2a. Hypnozoites of *P. vivax* & *P. ovale* lie dormant (**Exo-erythrocytic stage**)

**Erythrocytic stage**

7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

**MOSQUITO**

Sporozoites → Oocyst → Zygote

**A. Blood schizonticides treat the acute attack:** chloroquine (benign malaria), quinine + doxycycline (falciparum malaria)

**B. Drugs of radical cure inhibit hypnozoites:** primaquine

**C. Chemoprophylactic drugs (prevent clinical attack):** chloroquine, mefloquine

**D. Drugs preventing transmission destroy gametocytes:** primaquine
**Actions**  A slow blood schizonticide.

**MOA**  Inhibits the malaria parasite’s dihydrofolate reductase (DHFR) and thus interferes with its thymidylate synthesis.

**Abs/Distrb/Elim**  Given orally, T$_{0.5}$ 16h.

**Clinical use**  For chemoprophylaxis of malaria usually in combination with chloroquine. Proguanil + atovaquone is used for both chemoprophylaxis and treatment of falciparum malaria in some regions.

**Adverse effects**  Few since the drug does not inhibit host DHFR. Rare: GIT disturbances, rash, mouth ulcers, hair loss.
The malarial cycle and the sites at which drugs can affect it

**HUMAN**

1. Sporozoites injected by bite and enter liver *(Pre-erythrocytic stage)*
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont...
6. ...then forms motile trophozoite and starts to divide
7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

**MOSQUITO**

Sporozoites → Oocyst → Zygote → 10. Taken up in insect bite

**C. Chemoprophylactic drugs (prevent clinical attack):** chloroquine, mefloquine, proguanil

**B. Drugs of radical cure inhibit hypnozoites:** primaquine

**A. Blood schizonticides treat the acute attack:** chloroquine (benign malaria), quinine + doxycycline (falciparum malaria)

**D. Drugs preventing transmission destroy gametocytes:** primaquine

**2a. Hypnozoites of *P. vivax* & *P. ovale* lie dormant (Exo-erythrocytic stage)**
**Actions**  A slow blood schizonticide.

**MOA** Pyrimethamine inhibits the malaria parasite’s dihydrofolate reductase (DHFR) and thus interferes with its thymidylate synthesis. Sulfadoxine inhibits dihydropteroate synthetase – an earlier step in thymidylate synthesis.

**Abs/Distrb/Elim**  Given orally.

**Clinical use**  Used in combination tablet with sulfadoxine for the treatment of falciparum malaria.

**Adverse effects**  GIT disturbances, moderate depression of haemopoiesis, rashes, allergic alveolitis.
The malarial cycle and the sites at which drugs can affect it

**HUMAN**

1. Sporozoites injected by bite and enter liver (*Pre-erythrocytic stage*)
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont ...
6. ... then forms motile trophozoite and starts to divide
7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

**MOSQUITO**

Sporozoites → Oocyst → Zygote → 10. Taken up in insect bite

**A. Blood schizonticides treat the acute attack:** chloroquine (benign malaria), quinine + doxycycline; or **pyrimethamine + sulfadoxine** (falciparum malaria)

**B. Drugs of radical cure inhibit hypnozoites:** primaquine

**C. Chemoprophylactic drugs (prevent clinical attack):** chloroquine, mefloquine, proguanil

**D. Drugs preventing transmission destroy gametocytes:** primaquine

2a. Hypnozoites of *P. vivax* & *P. ovale* lie dormant (*Exo-erythrocytic stage*)

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**Antiprotozoal drugs – Malaria**

- **Artemether + lumefantrine**

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**The malarial cycle and the sites at which drugs can affect it**

- **Liver**
- **Erythrocytic stage**
**Actions**  A blood schizonticide combination.

**MOA**  Artemether inhibits falciparum sarcoplasmic-endoplasmic reticulum calcium ATPase. Lumefantrine inhibits the metabolism of haem within the parasite food vacuole.

**Abs/Distrb/Elim**  Given orally. Artemether: T<sub>0.5</sub> 3–7h. Lumefantrine: T<sub>0.5</sub> 4–7 days.

**Clinical use**  To treat acute uncomplicated falciparum malaria.

**Adverse effects**  GIT disturbances, headache, dizziness, paraesthesia, myalgia, rash.
A patient is due to go to an area with a high risk of falciparum malaria. What drugs could be used for chemoprophylaxis?

**The malarial cycle and the sites at which drugs can affect it**

**HUMAN**

1. Sporozoites injected by bite and enter liver (Pre-erythrocytic stage)
2. Schizonts in liver cells
3. Schizonts divide to form merozoites
4. Merozoites released
5. Merozoite enters erythrocyte and forms schizont...
6. ... then forms motile trophozoite and starts to divide
7. Merozoites
8. Release of merozoites causes fever
9. Some merozoites form gametocytes
10. Taken up in insect bite

**MOSQUITO**

Sporozoites → Oocyst → Zygote

**C. Chemoprophylactic drugs (prevent clinical attack):**
- chloroquine, mefloquine, proguanil

**B. Drugs of radical cure inhibit hypnozoites:**
- primaquine

**D. Drugs preventing transmission destroy gametocytes:**
- primaquine

**A. Blood schizonticides treat the acute attack:**
- chloroquine (benign malaria), quinine + doxycycline; or pyrimethamine + sulfadoxine or artemether with lumefantrine (falciparum malaria)

**Notes:**
- 2a. Hypnozoites of *P. vivax* & *P. ovale* lie dormant (Exo-erythrocytic stage)
- 31.08
A patient is due to go to an area with a high risk of falciparum malaria. What drugs could be used for chemoprophylaxis?

If falciparum malaria in the region is chloroquine resistant, the drugs to be used could be:

Mefloquine or doxycycline or proguanil + atovaquone

If it is known that the falciparum malaria in the relevant region is sensitive to chloroquine, the drugs used could be:

Chloroquine + proguanil

R&D 7e Ch 53, pp 659-663; D&H 2e Ch 49, pp 115-116
Amoebiasis is caused by the ingestion of the cysts of *Entamoeba histolytica*.

1. Ingestion of cysts

2. In the GI tract, the cysts develop into motile trophozoites, which invade the intestinal wall causing **amoebic dysentery**

3. Rarely, the trophozoites migrate to the liver causing **amoebic liver abscess**

4. Some trophozoites become encysted and are excreted

5. Cysts in faeces

6. Cysts in contaminated food or water

Some individuals remain symptom-free ‘carriers’ who excrete cysts that can infect others.
**Actions**  Kills the motile forms of *Entamoeba histolytica*.

**MOA**  The trophozoite generates, from the drug, free radicals that damage the trophozoite's DNA.

**Abs/Distrb/Elim**  Given orally, can be given i.v. and rectally; $t_{1/2}$ 7h. Tinidazole has longer action.

**Clinical use**  To treat amoebic dysentry (followed by treatment with diloxanide); to treat amoebic liver abscess. Also used for trichomoniasis, and giardiasis.

**Adverse effects**  GIT disturbances; anorexia. *Occasionally* dizziness, ataxia, myalgia, hepatitis, blood dyscrasias, Can cause disulfiram reactions after alcohol.

R&D 7e Ch 53, p 664; D&H 2e Ch 49, p 116
Amoebiasis is caused by the ingestion of the cysts of *Entamoeba histolytica*.

1. Ingestion of cysts

2. In the GI tract, the cysts develop into motile trophozoites, which invade the intestinal wall causing amoebic dysentery.

3. Rarely, the trophozoites migrate to the liver causing amoebic liver abscess.

4. Some trophozoites become encysted and are excreted.

5. Cysts in faeces

6. Cysts in contaminated food or water

Some individuals remain symptom-free 'carriers' who excrete cysts that can infect others.

Metronidazole, tinidazole
**Actions**  Acts against the non-motile forms of *Entamoeba histolytica*.

**MOA**  Not clearly known.

**Abs/Distrb/Elim**  Given orally, can be given i.v. and rectally; $t_{1/2}$ 7h.

**Clinical use**  To treat amoebic dysentery (*after* treatment with metronidazole); to treat asymptomatic cyst carriers.

**Adverse effects**  GIT disturbances; anorexia. *Occasionally* dizziness, ataxia, myalgia, hepatitis, blood dyscrasias, Can cause disulfiram reactions after alcohol.
Leishmaniasis is a disease of the skin and viscera caused by leishmania protozoa transmitted by the bite of a sandfly.

1. Sandfly bite transfers the flagellated form of the protozoa to host
2. Macrophages phagocytose them
3. The parasites multiply and transform into non-flagellated amastigotes in the macrophages which rupture releasing the protozoa ...
4. ... which cause chronic inflammatory lesions of the skin, and sometimes the viscera (spleen, liver) ...
5. ... and also parasitise other macrophages
6. Sandfly sucks blood containing parasitised macrophages
7. Flagellated forms (promastigotes) develop in the sandfly
**Actions & MOA**  Inactivates the protozoa within the macrophage, possibly by triggering toxic oxygen radicals.

**Abs/Distrb/Elim**  Given i.m. (painful) or by slow i.v. injection daily for 10–20 days.

**Clinical use**  To treat visceral leishmaniasis (kala-azar) and, if necessary, cutaneous leishmaniasis. Specialist supervision needed.

**Adverse effects**  GIT disturbances, ECG changes, headache, coughing, arthralgia, myalgia.
Simplified diagram of a fungal cell

Antifungal agents

Amphotericin

Fungal cell wall
Ergosterol-rich fungal cell membrane
Microtubule system
Nucleus
Ergosterol
Lanosterol
Squalene
14α-demethylase
Squalene epoxidase
Squalene
DNA

Fungal cell wall
Ergosterol-rich fungal cell membrane
A broad-spectrum antifungal agent

**Amphotericin**

*Candidiasis; cryptococcal meningitis; histoplasmosis; apergillosis; blastomycosis; coccidio-mycosis; mucormycosis.*

**Clinical use**
Candidiasis; cryptococcal meningitis; histoplasmosis; apergillosis; blastomycosis; coccidiomycosis; mucormycosis.

**Actions & MOA**
Kills fungi by binding to the ergosterol in the fungal cell membrane (missing in mammalian cells) and increasing membrane permeability.

**Abs/Distrb/Elim**
Not absorbed in the GIT. Given by i.v. infusion in a lipid formulation; can cross the blood–brain barrier in meningitis; given topically by lozenge for oral fungal infections.

**Adverse effects**
When given i.v.: renal toxicity; CVS toxicity; GIT disturbances; neurological disturbances; anaphylactoid reactions; infusion reactions (fever, headache, chills); myalgia, arthralgia.

**Drug with similar action**
Nystatin. Given orally for GIT candidiasis.
Simplified diagram of a fungal cell

- **Fungal cell wall**
- **Ergosterol-rich fungal cell membrane**
- **Microtubule system**
- **Nucleus**
  - DNA
- **Ergosterol**
- **Lanosterol**
- **14α demethylase**
- **Squalene epoxidase**
- **Squalene**
- **Ergosterol-rich fungal cell membrane**
- **Amphotericin**
  - Orange circle
**Action**  Fungistatic by inhibiting the synthesis of ergosterol – a crucial component of fungal cell membranes (missing in mammalian cells).

**MOA**  Inhibits 14α demethylase – a p450-dependent enzyme important in the conversion of lanosterol to ergosterol.

**Abs/Distrb/Elim**  Given orally or i.v., widely distributed, passing into CSF, ocular fluids, vaginal tissue, nails, saliva, skin. Half-life ~25h.

**Clinical use**  Candidiasis: local (dermal, mucosal) and invasive; tinea corporis, tinea cruris & tinea pedis; cryptococcal meningitis; histoplasmosis; blastomycosis; coccidiomycosis.

**Adverse effects**  GIT disturbances; headache, rash. Less frequently liver disorders, hypersensitivity reactions.

**Drug with similar action**  Itraconazole (used for fungal skin infections); hepatotoxicity. Voriconazole: broad spectrum; used for life-threatening fungal infections.
Simplified diagram of a fungal cell

- **Fungal cell wall**
- **Ergosterol-rich fungal cell membrane**
- **Microtubule system**
- **Nucleus**
- **DNA**

- **Squalene**
- **Lanosterol**
- **Ergosterol**
- **14α-demethylase**
- **Squalene epoxidase**

**Antifungal agents**

- **Terbinafine**
- **Fluconazole, itraconazole**
- **Amphotericin**
**Action**  Fungicidal by inhibiting the synthesis of ergosterol – a crucial component of fungal cell membranes (missing in mammalian cells).

**MOA**  Inhibits squalene epoxidase which is responsible for the conversion of squalene to lanostreol.

**Abs/Distrb/Elim**  Given orally it is taken up into skin, nails and fatty tissue. Can be given topically.

**Clinical use**  Fungal infections of the nails & skin (tinea corporis, tinea cruris & tinea pedis, aka ‘ringworm’)

**Adverse effects**  GIT disturbances; headache, dizziness, rash.

**Drug with similar action**  Amorolfine; used topically on the nails.
Simplified diagram of a fungal cell

- **Antifungal agents**
  - Caspofungin

**Fungal cell wall**
- **Ergosterol-rich fungal cell membrane**
- **Microtubule system**
- **Nucleus**
- **Squalene epoxidase**
- **14α-demethylase**
- **Squalene**
- **Lanosterol**
- **Ergosterol**

**Pathways**
- **Amphotericin**: Acts on the fungal cell wall.
- **Fluconazole, itraconazole**: Inhibits 14α-demethylase.
- **Terbinafine**: Inhibits squalene epoxidase.

**Other**
- **DNA**
- **Fungal cell wall**
**Action**  Fungicidal by weakening the fungal cell wall.

**MOA**  Inhibits the synthesis of 1,3-β-D-glucan, a crucial component of the fungal cell wall that is missing from mammalian cells.

**Abs/Distrb/Elim**  Given i.v. Half-life ~9h.

**Clinical use**  Candidiasis; aspergillosis.

**Adverse effects**  GIT disturbances; headache, dizziness, rash.

**Drug with similar action**  Micafungin. Used for invasive candidiasis.
Simplified diagram of a fungal cell

- **Ergosterol-rich fungal cell membrane**
- **Microtubule system**
- **Fungal cell wall**

- **Amphotericin**
- **Caspofungin**
- **Fluconazole, itraconazole**
- **Terbinafine**

- **Ergosterol**
- **14α demethylase**
- **Lanosterol**
- **Squalene epoxidase**
- **Squalene**

- **DNA**

- **Nucleus**

- **Ergosterol-rich fungal cell membrane**
**Action**  Fungistatic by interfering with mitosis of fungal cells.

**MOA** Interacts with polymerized microtubules inhibiting spindle formation.

**Abs/Distrb/Elim** Given orally; taken up by proliferating skin cells, binds to the keratin. Half-life ~24h.

**Clinical use**  Fungal infections of skin, hair and scalp; trichophyton infections in children.

**Adverse effects**  Infrequent: GIT disturbances; headache.
Simplified diagram of a fungal cell

- **Antifungal agents**
- **Flucytosine**

- **Simplified diagram of a fungal cell**

  - **Amphotericin**
  - **Caspofungin**
  - **Fluconazole, itraconazole**
  - **Terbinafine**
  - **Griseofulvin**

- **Ergosterol-rich fungal cell membrane**
- **Fungal cell wall**
- **Microtubule system**

**Key Components:**
- **DNA**
- **Nucleus**
- **Lanosterol**
- **14α demethylase**
- **Squalene epoxidase**
- **Squalene**
- **Ergosterol**

**Action & MOA**  
Is converted in fungal cells (but not mammalian cells) into the antimetabolite, 5-fluorouracil, which interrupts DNA synthesis by inhibiting thymidylate synthetase.

**Abs/Distrb/Elim**  
Given by i.v. infusion, but can be given orally. Plasma half-life ~4h.

**Clinical use**  
Systemic fungal & yeast infections: systemic candidiasis, cryptococcal meningitis.

**Adverse effects**  
GIT disturbances; rashes. Less commonly: blood dyscrasias, headaches, confusion, cardiotoxicity.

**Special points**  
Resistance can occur, therefore usually given with amphotericin.
Simplified diagram of a fungal cell

- **Antifungal agents**
- **Notes on antifungal drugs**

**Ergosterol-rich fungal cell membrane**

- **Microtubule system**
- **Griseofulvin**
- **Flucytosine**

**Nucleus**

- **DNA**

**Fungal cell wall**

- **Ergosterol**
- **Lanosterol**
- **Squalene**
- **Squalene epoxidase**
- **14β demethylase**

**Antifungal drugs**

- **Amphotericin**
- **Caspofungin**
- **Fluconazole, itraconazole**
- **Terbinafine**
- **Amphotericin**
- **Griseofulvin**
- **Flucytosine**
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Mebendazole

A broad-spectrum anthelminthic agent

**Actions & MOA**  Inhibits microtubule synthesis, impairing microtubule functions such as glucose uptake.

**Abs/Distrb/Elim**  Given orally; poor uptake is improved by fatty foods.

**Clinical use**  Thread worm, round worm, whip worm and hookworm infections.

**Adverse effects**  GIT disturbances, rash. Rarely convulsions in infants.

**Drugs with similar action**  Albendazole: also used for cutaneous larva migrans, cystercercosis, strongyloidiasis.

**Special points**  Albendazole is only available in the UK from the pharmaceutical company on a ‘named patient’ basis.

R&D 7e Ch 54, p 670; D&H 2e Ch 50, p 117
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Levamisole

A narrow-spectrum anthelminthic agent

**Actions & MOA**  Causes tonic paralysis of the worm by stimulating nicotinic receptors at the neuromuscular junction. The paralysed worms (but not the ova) are expelled in the faeces.

**Abs/Distrb/Elim**  Given orally; plasma half-life is 4h.

**Clinical use**  Common round worm infection.

**Adverse effects**  Mild GIT disturbances.

**Special points**  Only available in the UK from the relevant pharmaceutical company on a ‘named patient’ basis.

R&D 7e Ch 54, p 671; D&H 2e Ch 50, p 117
## Anthelmintic drugs

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**A narrow-spectrum anthelminthic agent**

**Piperazine**

**Actions & MOA** It reverses neuromuscular transmission in the worm. The paralysed worms are expelled alive in the faeces.

**Abs/Distrb/Elim** Given orally.

**Clinical use** Common round worm infection.

**Adverse effects** GIT disturbances. Rash, bronchospasm. Some patients experience CNS symptoms, e.g. dizziness, paraesthesias.

**Special points** Only available in the UK from the relevant pharmaceutical company on a ‘named patient’ basis.

R&D 7e Ch 54, p 670; D&H 2e Ch 50, p 117
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**Actions & MOA**  It causes an increase in the calcium permeability of the cell membranes, promoting calcium influx, resulting in prolonged contraction of muscle with eventual paralysis and death.

**Abs/Distrb/Elim**  Given orally, well absorbed, metabolised to inactive products. Plasma half-life 60–90 min.

**Clinical use**  Schistosomiasis, cysticercosis.

**Adverse effects**  Few and minor: sometimes GIT disturbances.

**Special points**  Available in the UK from special-order manufacturers.
## Anthelmintic drugs

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A broad-spectrum anthelminthic agent

**Ivermectin**

**Actions & MOA** Acts at the worm’s neuromuscular junction, causing paralysis either by intensifying GABA-mediated inhibition or by activating an invertebrate-specific glutamate-gated chloride channel.

**Abs/Distr/Elim** Given orally.

**Clinical use** Onchocerciasis (drug of choice); strongyloidiasis.

**Adverse effects** Infrequent: itching, rash, GIT disturbances, dizziness, fatigue.

**Special points** Available in the UK from special-order manufacturers.

R&D 7e Ch 54, p 671; D&H 2e Ch 50, p 117
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Diagram of the main targets for anticancer drug therapy

- Purine synthesis
- Pyrimidine synthesis
- Ribonucleotides
- Deoxyribonucleotides
- DNA
- RNA (transfer, messenger, ribosomal)
- Proteins
- Receptors
- Enzymes
- Microtubules
**Actions**  Interferes with purine synthesis and the synthesis of thymidylate and thus with DNA synthesis.

**MOA**  Competitively inhibits dihydrofolate reductase (DHFR).

**Abs/Distrb/Elim**  Given orally, i.v., i.m., or intrathecally; taken up into cells by the folate transport system.

**Clinical use**  Acute lymphoblastic leukemia in children; choriocarcinoma; tumours of head, neck breast & lung.

**Adverse effects**  Myelosupression, GIT disturbances, mucositis and sometimes pneumonitis.

**Special points**  High-dose regimens should be followed by ‘rescue’ with folinic acid – a form of tetrahydrofolate – to minimise toxic effects on the bone marrow and GIT mucosa.

FH₂ = dihydrofolate
FH₄ = tetrahydrofolate
dTMP = thymidylate
dUMP = uridylate
Anticancer drugs

Fluorouracil

Diagram of the main targets for anticancer drug therapy

- Purine synthesis
- Pyrimidine synthesis
- Ribonucleotides
- Deoxyribonucleotides
- DNA
- RNA (transfer, messenger, ribosomal)
- Proteins
- Receptors
- Enzymes
- Microtubules

Methotrexate inhibits purine synthesis and dTMP synthesis.
**Actions**
Interferes with the synthesis of dTMP and thus with DNA synthesis.

**MOA**
Gives rise to a fraudulent nucleotide and Inhibits thymidylate synthetase.

**Abs/Distrb/Elim**
Given i.v.

**Clinical use**
Cancers of GIT (gastric, colorectal), pancreas, breast; malignant skin conditions.

**Adverse effects**

**Special points**
High-dose regimens should be followed by ‘rescue’ with folinic acid – a form of tetrahydrofolate – to minimise toxic effects on the bone marrow and GIT mucosa.

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**R&D 7e Ch 55, p 681; D&H 2e Ch 46, p 105**
Diagram of the main targets for anticancer drug therapy

Purine synthesis

Pyrimidine synthesis

Ribonucleotides

Deoxyribonucleotides

DNA

RNA (transfer, messenger, ribosomal)

Proteins

Receptors

Enzymes

Microtubules

Methotrexate inhibits purine synthesis and dTMP synthesis

Fluorouracil inhibits dTMP synthesis
**Actions & MOA**  Purine analogue that inhibits purine synthesis and gives rise to a fraudulent nucleotide.

**Abs/Distr/Elim**  Given orally.

**Clinical use**  Acute leukemias and chronic myeloid leukemia.

**Adverse effects**  Myelosuppression, hepatotoxicity, immunosuppression. Rare: pancreatitis, GIT ulceration.

**Special points**  Note that azathioprine, an immunosuppressant agent, is metabolised to mercaptopurine.

**Similar drug**  Pentostatin, also a purine analogue, inhibits adenosine deaminase – important in generation of inosine, an early stage of ribonucleic acid synthesis.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine**: inhibit purine & ribonucleotide synthesis
- **Methotrexate**: inhibits purine synthesis and dTMP synthesis
- **Fluorouracil**: inhibits dTMP synthesis

- **Purine synthesis**
- **Pyrimidine synthesis**
- **Ribonucleotides**
- **Deoxyribonucleotides**
- **DNA**
- **RNA**: (transfer, messenger, ribosomal)
- **Proteins**
- **Receptors**
- **Enzymes**
- **Microtubules**
**Actions & MOA**  Pyrimidine analogue that is converted in the cell to the trisphosphate which inhibits DNA polymerase.

**Abs/Distrb/Elim**  Given i.v., subcut. or intrathecally.

**Clinical use**  Acute myeloblastic leukemia.

**Adverse effects**  Marked myelosuppression. GIT disturbances; cerebellar ataxia.

**Special points**  Careful haematological monitoring necessary.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis

- **Fluorouracil** inhibits dTMP synthesis

**Pyrimidine synthesis**
- Ribonucleotides
- Deoxyribonucleotides
- DNA
- RNA (transfer, messenger, ribosomal)
- Proteins
- Enzymes
- Receptors
- Microtubules

**Purine synthesis**
- Ribonucleotides
- Deoxyribonucleotides
- DNA
- RNA (transfer, messenger, ribosomal)
- Proteins
- Enzymes
- Microtubules
**Actions & MOA**  Causes DNA fragmentation.

**Abs/Distrb/Elim**  Given i.v. or i.m.

**Clinical use**  Squamous cell cancer, metastatic germ cell cancer. Non-Hodgkin’s lymphoma.

**Adverse effects**  Dose-related pulmonary fibrosis; skin toxicity (pigmentation, subcutaneous sclerotic plaques); mucositis; transient hypersensitivity reactions. Minimal myelosuppression.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis
- **Fluorouracil** inhibits dTMP synthesis
- **Bleomycin** damages DNA

**Anticancer drugs**

- **Cisplatin**
- **Pentostatin**, **mercaptopyrurine** inhibit purine & ribonucleotide synthesis

**Diagram components:**
- **Pyrimidine synthesis**
- **Ribonucleotides**
- **Deoxyribonucleotides**
- **DNA**
- **RNA** (transfer, messenger, ribosomal)
- **Proteins**
- **Receptors**
- **Enzymes**
- **Microtubules**

**Chemical interactions:**
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis
- **Fluorouracil** inhibits dTMP synthesis
- **Bleomycin** damages DNA
**Actions & MOA**  Forms a reactive complex that causes intrastrand cross-linking and denaturation of the DNA.

**Abs/Distrb/Elim**  Given by i.v. infusion. Can be given to outpatients.

**Clinical use**  Cancers of testes, ovaries, cervix, bladder, lung and head & neck.

**Adverse effects**  Nephrotoxicity, ototoxicity, severe nausea & vomiting, myelosuppression, peripheral neuropathy, hypomagnesaemia.

**Drug with similar action**  Carboplatin: more myelosuppressive but other adverse effects less marked so better tolerated; preferred for ovarian cancer.
Diagram of the main targets for anticancer drug therapy

- Pentostatin, mercaptopurine inhibit purine & ribonucleotide synthesis
- Methotrexate inhibits purine synthesis and dTMP synthesis
- Cytarabine inhibits DNA synthesis
- Fluorouracil inhibits dTMP synthesis
- Bleomycin damages DNA
- Cisplatin cross-links DNA strands

Purine synthesis
Pyrimidine synthesis
Ribonucleotides
Deoxyribonucleotides
DNA
RNA (transfer, messenger, ribosomal)
Proteins
Receptors
Enzymes
Microtubules
**Actions & MOA**  Cross-links DNA by forming covalent bonds with guanine residues on each strand, interfering with cell division and triggering apoptosis.

**Abs/Distrb/Elim**  Given orally or i.v. Metabolised in the liver to phosphoramid mustard (the active moiety) and acrolein.

**Clinical use**  Chronic lymphocytic leukemia, soft tissue sarcoma, osteogenic sarcoma, ovarian & breast cancers.

**Adverse effects**  Nausea & vomiting; myelosuppression; acrolein-mediated haemorrhagic cystitis; alopecia. Gametogenesis can be affected. Prolonged use can result in acute non-lymphocytic leukemia.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis

**Ribonucleotides**

**Pyrimidine synthesis**

**Deoxyribonucleotides**

**DNA**

**RNA** (transfer, messenger, ribosomal)

**Proteins**

**Receptors**

**Enzymes**

**Microtubules**

**Cisplatin** cross-links DNA strands

**Cyclophosphamide** intercalates & cross-links

**Bleomycin** damages DNA

**Fluorouracil** inhibits dTMP synthesis
**Actions & MOA**  Inhibits DNA and RNA synthesis through an effect on topoisomerase II.

**Abs/Distrb/Elim**  Given by infusion (extravasation can cause tissue damage); by bladder instillation for bladder cancers.

**Clinical use**  Acute leukemias; Hodgkin & non-Hodgkin lymphomas; tumours of breast, ovary, bladder, bronchi.

**Adverse effects**  Dose-related cardiac damage; nausea & vomiting; myelosuppression; hair loss.
Diagram of the main targets for anticancer drug therapy

- Pentostatin, mercaptopurine inhibit purine & ribonucleotide synthesis
- Methotrexate inhibits purine synthesis and dTMP synthesis
- Cytarabine inhibits DNA synthesis

- Purine synthesis
- Pyrimidine synthesis

- Ribonucleotides

- Deoxyribonucleotides

- DNA

- RNA (transfer, messenger, ribosomal)

- Proteins
- Receptors

- Enzymes
- Microtubules

- Fluorouracil inhibits dTMP synthesis
- Bleomycin damages DNA
- Cisplatin cross-links DNA strands
- Cyclophosphamide intercalates & cross-links
- Doxorubicin intercalates & inhibits topoisomerase II

- Cytarabine inhibits DNA synthesis
**Actions & MOA**  Binds to and inhibits topoisomerase I, thus interfering with cell proliferation.

**Abs/Distrib/Elim**  Given by i.v. infusion

**Clinical use**  Metastatic tumours of colon and rectum (in combination with other agents).

**Adverse effects**  GIT disturbances, interstitial pulmonary disease.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis

For DNA:
- **Bleomycin** damages DNA
- **Cisplatin** cross-links DNA strands
- **Cyclophosphamide** intercalates & cross-links
- **Doxorubicin** intercalates & inhibits topoisomerase II
- **Irinotecan** inhibits topoisomerase I

For RNA (transfer, messenger, ribosomal):
- **Fluorouracil** inhibits dTMP synthesis

For Proteins and Receptors:
- **Enzymes**
- **Microtubules**

Simplified Pathways:
- **Purine synthesis**
- **Pyrimidine synthesis**
- **Ribonucleotides**
- **Deoxyribonucleotides**
- **DNA**
- **RNA**
**Actions & MOA**  Intercalates in the DNA and inhibits RNA polymerase and topoisomerase II.

**Abs/Distr/Elim**  Given by i.v. injection.

**Clinical use**  Paediatric cancers.

**Adverse effects**  Nausea & vomiting; myelosuppression; hair loss.
Diagram of the main targets for anticancer drug therapy

**Anticancer drugs**

- **Vincristine**

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis
- **Dactinomycin** inhibits topoisomerase II and RNA polymerase

**Ribonucleotides**

- **Purine synthesis**
- **Pyrimidine synthesis**

**Deoxyribonucleotides**

- **DNA**

**RNA** (transfer, messenger, ribosomal)

- **Proteins**
- **Receptors**

- **Enzymes**
- **Microtubules**

**Fluorouracil** inhibits dTMP synthesis
**Bleomycin** damages DNA
**Cisplatin** cross-links DNA strands
**Cyclophosphamide** intercalates & cross-links
**Doxorubicin** intercalates & inhibits topoisomerase II
**Irinotecan** inhibits topoisomerase I
**Actions & MOA**  Binds to tubulin, preventing spindle formation in dividing cells stopping them in mitosis.

**Abs/Distrb/Elim**  Given by i.v. injection.

**Clinical use**  Leukemias, lymphomas, breast and lung cancers.

**Adverse effects**  Nausea & vomiting; hair loss; **neurotoxicity** (peripheral & autonomic); negligible myelosuppression.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis
- **Dactinomycin** inhibits topoisomerase II and RNA polymerase

- **Fluorouracil** inhibits dTMP synthesis
- **Bleomycin** damages DNA
- **Cisplatin** cross-links DNA strands
- **Cyclophosphamide** intercalates & cross-links
- **Doxorubicin** intercalates & inhibits topoisomerase II
- **Irinotecan** inhibits topoisomerase I

- **Vincristine** inhibits microtubule function

**Anticancer drugs**

- **Paclitaxel**

**Main Targets:**
- Pyrimidine synthesis
- Ribonucleotides
- Deoxyribonucleotides
- DNA
- RNA (transfer, messenger, ribosomal)
- Proteins
- Receptors
- Enzymes
- Microtubules
**Actions & MOA**  Binds to tubulin, keeping microtubules polymerised (‘frozen’), preventing spindle formation in dividing cells and stopping them in mitosis.

**Abs/Distrb/Elim**  Given by i.v. infusion.

**Clinical use**  Cancers of ovary and breast, non-small-cell lung cancer.

**Adverse effects**  Hypersensitivity reactions, myelosuppression, peripheral neuropathy, bradycardia, muscle & joint pain, hair loss. GIT disturbance: moderate.
Anticancer drugs

Diagram of the main targets for anticancer drug therapy

- Pentostatin, mercaptopurine inhibit purine & ribonucleotide synthesis
- Methotrexate inhibits purine synthesis and dTMP synthesis
- Cytarabine inhibits DNA synthesis
- Dactinomycin inhibits topoisomerase II and RNA polymerase

- Fluorouracil inhibits dTMP synthesis
- Bleomycin damages DNA
- Cisplatin cross-links DNA strands
- Cyclophosphamide intercalates & cross-links
- Doxorubicin intercalates & inhibits topoisomerase II
- Irinotecan inhibits topoisomerase I
- Vincristine, paclitaxel inhibit microtubule function

Purine synthesis

Pyrimidine synthesis

Ribonucleotides

Deoxyribonucleotides

DNA

RNA (transfer, messenger, ribosomal)

Proteins

Receptors

Enzymes

Microtubules
**Actions & MOA**  Inhibits protein kinases important in chronic myeloid leukemia and other malignancies.

**Abs/Distrb/Elim**  Given orally, well absorbed.

**Clinical use**  Chronic myeloid leukemia, acute lymphoblastic leukemia, GIT stromal tumours, chronic eosinophilic leukemia, myeloproliferative diseases.

**Adverse effects**  GIT disturbances, abdominal pain, oedema, haemorrhage, cough, dyspnoea, paraesthesia, arthralgia, conjunctivitis, photosensitivity, headache, dizziness, sweating, rash.

R&D 7e Ch 55, p 684; D&H 2e Ch 46, pp 104-105
Diagram of the main targets for anticancer drug therapy

- Anticancer drugs
  - Trastuzumab

Purine synthesis
- Pentostatin, mercaptopurine inhibit purine & ribonucleotide synthesis
- Methotrexate inhibits purine synthesis and dTMP synthesis
- Cytarabine inhibits DNA synthesis
- Dactinomycin inhibits topoisomerase II and RNA polymerase

Pyrimidine synthesis
- Fluorouracil inhibits dTMP synthesis
- Bleomycin damages DNA
- Cisplatin cross-links DNA strands
- Cyclophosphamide intercalates & cross-links
- Doxorubicin intercalates & inhibits topoisomerase II
- Irinotecan inhibits topoisomerase I

Ribonucleotides
- Dactinomycin inhibits topoisomerase II and RNA polymerase

Deoxyribonucleotides
- Dactinomycin inhibits topoisomerase II and RNA polymerase

DNA
- Cytarabine inhibits DNA synthesis
- Dactinomycin inhibits topoisomerase II and RNA polymerase

RNA (transfer, messenger, ribosomal)
- Cytarabine inhibits DNA synthesis
- Dactinomycin inhibits topoisomerase II and RNA polymerase

Proteins
- Imatinib protein kinase inhibitor

Receptors
- Imatinib protein kinase inhibitor

Enzymes
- Imatinib protein kinase inhibitor

Microtubules
- Imatinib protein kinase inhibitor

Vincristine, paclitaxel inhibit microtubule function
**Actions & MOA**  Binds to and inhibits the epidermal growth factor receptor (a tyrosine kinase receptor), preventing its activation and inhibiting cell proliferation.

**Abs/Distrb/Elim**  Given by i.v. infusion.

**Clinical use**  Breast cancers.

**Adverse effects**  GIT disturbances, abdominal pain, hypersensitivity reactions, cardiac toxicity, paraesthesia, headache, dizziness, anxiety, depression, oedema, arthralgia, bruising, bone pain, leg cramps, rash, alopecia.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis
- **Dactinomycin** inhibits topoisomerase II and RNA polymerase
- **Fluorouracil** inhibits dTMP synthesis
- **Bleomycin** damages DNA
- **Cisplatin** cross-links DNA strands
- **Cyclophosphamide** intercalates & cross-links
- **Doxorubicin** intercalates & inhibits topoisomerase II
- **Irinotecan** inhibits topoisomerase I
- **Trastuzumab** antibody v EGRF 2 (epidermal growth factor receptor 2)
- **Vincristine, paclitaxel** inhibit microtubule function

**Purine synthesis**

- **Pyrimidine synthesis**

**Ribonucleotides**

- **Deoxyribonucleotides**

**DNA**

**RNA** (transfer, messenger, ribosomal)

**Proteins**

**Receptors**

**Enzymes**

**Microtubules**

**Imatinib** protein kinase inhibitor
**Actions & MOA** Competes with endogenous oestrogen for the oestrogen receptor, preventing cell activation and proliferation.

**Abs/Distr/Elim** Given orally.

**Clinical use** Breast cancer.

**Adverse effects** Hot flushes, GIT disturbances, headache, menstrual irregularities.
Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis
- **Dactinomycin** inhibits topoisomerase II and RNA polymerase
- **Imatinib** protein kinase inhibitor

- **Ribonucleotides**
- **Deoxyribonucleotides**
- **DNA**
- **RNA** (transfer, messenger, ribosomal)
- **Proteins**
- **Enzymes**
- **Receptors**
- **Microtubules**

**Anticancer Drugs**

- **Fluorouracil** inhibits dTMP synthesis
- **Bleomycin** damages DNA
- **Cisplatin** cross-links DNA strands
- **Cyclophosphamide** intercalates & cross-links
- **Doxorubicin** intercalates & inhibits topoisomerase II
- **Irinotecan** inhibits topoisomerase I
- **Trastuzumab antibody** v EGRF 2 (epidermal growth factor receptor 2)
- **Tamoxifen**, an antioestrogen
- **Vincristine, paclitaxel** inhibit microtubule function
A preparation of the enzyme asparaginase used as an anticancer agent

Crisantaspase

**Actions & MOA**  Breaks down asparagine and is active in tumours (e.g. acute lymphoblastic leukemia) that have lost the ability to synthesise asparagine and require an external source.

**Abs/Distrb/Elim**  Given i.v., i.m. or subcut.

**Clinical use**  Acute lymphoblastic leukemia.

**Adverse effects**  Nausea & vomiting, CNS depression, liver disorder, anaphylactic reactions, risk of hyperglycaemia.
Anticancer drugs

What are the main adverse effects of anticancer drugs?

Diagram of the main targets for anticancer drug therapy

- **Pentostatin, mercaptopurine** inhibit purine & ribonucleotide synthesis
- **Methotrexate** inhibits purine synthesis and dTMP synthesis
- **Cytarabine** inhibits DNA synthesis
- **Dactinomycin** inhibits topoisomerase II and RNA polymerase
- **Crisantaspase** deaminates asparagine, inhibits protein synthesis
- **Imatinib** protein kinase inhibitor

**Pyrimidine synthesis**

- **Ribonucleotides**
- **Deoxyribonucleotides**

**Purine synthesis**

**DNA**

*Enzymes*

**Proteins**

**Receptors**

**Microtubules**

**Enzymes**

**Proteins**

**Receptors**

**DNA**

**RNA** (transfer, messenger, ribosomal)

**Ribonucleotides**

**Deoxyribonucleotides**

**Pyrimidine synthesis**

**Fluorouracil** inhibits dTMP synthesis

**Bleomycin** damages DNA

**Cisplatin** cross-links DNA strands

**Cyclophosphamide** intercalates & cross-links

**Doxorubicin** intercalates & inhibits topoisomerase II

**Irinotecan** inhibits topoisomerase I

**Trastuzumab** antibody v EGRF 2 (epidermal growth factor receptor 2)

**Tamoxifen**, an antioestrogen

**Vincristine, paclitaxel** inhibit microtubule function
Most anticancer drugs are **cytotoxic** (they damage or kill cells) and they are **antiproliferative** (they stop cells from dividing – both cancer cells and rapidly dividing normal cells). Thus they can:

- depress the bone marrow
- impair healing
- interfere with normal growth (in children)
- cause sterility
- result in hair loss
- be teratogenic

Most also cause nausea and vomiting.

Different cytotoxic drugs manifest the above adverse effects to different degrees. **Examples are the drugs that affect DNA & RNA synthesis and actions (see figure on the face of this card)**

Newer, non-proliferative agents target the underlying pathogenic mechanisms such as changes in:

- the relevant growth factors and/or their receptors
- cell cycle control mechanisms
- apoptotic pathways
- telomerase expression
- tumour-related angiogenesis

These agents are less likely to have the above cytotoxic actions but have their own adverse effects. **Examples are the drugs that don’t affect DNA & RNA synthesis (see the face of this card)**
Panel A shows the response of a tissue to drugs A, B and C. Panels B and C show the effects that drugs D and E have on the log.dose/response curves to drug A. Which drugs are agonists and which antagonists?
An **agonist** binds to a receptor to elicit a response (e.g. increase in heart rate; contraction of smooth muscle). The log.dose/response curves to three different agonists, which work through the same receptor, are shown in panel A.

An **antagonist** prevents the action of an agonist. In panels B and C drugs D and E, both antagonists, reduce responses to the agonist A. They move the log.dose/response curve for the agonist to the right.

There are several ways in which antagonism can occur:

*Competitive receptor antagonism* – the antagonist binds to the receptor to prevent the agonist binding (see card 35.04).

*Non-competitive antagonism* – the antagonist interferes with the transduction process between agonist binding and response.

*Physiological antagonism* – the antagonist (in fact an agonist) produces a response which opposes the action of the agonist.

*Pharmacokinetic antagonism* – the antagonist reduces the concentration of the agonist at its site of action. This might be due to reduced drug absorption or an enhanced rate of elimination.

*Chemical antagonism* – the antagonist combines with the agonist. Very uncommon.
Panel A shows the response of a tissue to drugs A, B and C. Panels B and C show the effects that drugs D and E have on the log.dose/response curves to drug A.

How does the affinity of a drug for its receptor influence its log.dose/response curve?

A, B and C are agonists

D and E are antagonists
The affinity of a drug, D (agonist or antagonist), for its receptor, R, determines the proportion of receptors which are occupied by the drug, DR. The interaction follows the law of mass action:

\[ D + R \underset{K_D}{\overset{\text{DR}}{\rightleftharpoons}} \]

where \([D]\), \([R]\) and \([\text{DR}]\) are the concentrations of D, R and DR respectively and \(K_D\) is the equilibrium dissociation constant. Occupancy of receptors by D is given by the equation:

\[
\% \text{ occupancy} = 100 \times \frac{[D]}{[D] + K_D}
\]

This equation predicts the relationship between occupancy and drug concentration will be a rectangular hyperbola, which will appear as a sigmoid curve if the drug concentration is plotted on a log scale:

The tissue log.dose/response curve is also invariably sigmoidal. A low \(K_D\) value represents a high affinity and the curve will rise at low drug concentrations. If \(K_D\) is higher (lower affinity) the curve will appear at higher drug concentrations. Thus in panel A overleaf, drug A would have a higher affinity for the receptor than drug B – assuming they have the same efficacy (see card 35.03)
Panel A shows the response of a tissue to drugs A, B and C. Panels B and C show the effects that drugs D and E have on the log.dose/response curves to drug A.

How does the efficacy of a drug influence its log.dose/response curve?

Assuming equal efficacy agonist A has a higher affinity for receptor than agonist B.
Efficacy describes the ability of an agonist, once bound to its receptor, to elicit a response. A full agonist produces the maximum response which a tissue is capable of.

A partial agonist cannot produce such a large response, even when occupying all the receptors.

In panel A overleaf drugs A and B are full agonists whereas drug C is a partial agonist.

The distinction between full and partial agonists is best illustrated in the context of agonists acting on ligand-gated ion channels (e.g. the NMDA receptor). The following reaction scheme indicates an agonist, A, binding to a receptor, R, to give AR;

\[
A + R \xleftrightarrow{k_{-1}} AR \xleftrightarrow{k_{+1}} AR^* \]

\(k_{+1}\) and \(k_{-1}\) are the forward and reverse rate constants for agonist binding.

The agonist–receptor complex isomerises to \(AR^*\) which is the active, open channel form of the receptor, \(\beta\) and \(\alpha\) are the forward and reverse rate constants for the isomerisation reaction. It is now easy, for this receptor mechanism, to understand full and partial agonism. For a full agonist \(\beta\) is much greater than \(\alpha\) so that many of the channels open. For a partial agonist, with low efficacy, \(\alpha\) is greater than \(\beta\) so that few of the receptors isomerise to \(AR^*\).
Panel A shows the response of a tissue to drugs A, B and C. Panels B and C show the effects that drugs D and E have on the log.dose/response curves to drug A.

How does a competitive antagonist influence the dose/response curve for an agonist?

**Partial agonists** have a low efficacy.
A competitive antagonist binds to the receptor and in so doing prevents the binding of an agonist molecule. If the antagonist binds reversibly, the effect of the antagonist can be overcome by increasing the concentration of the agonist.

Reversible competitive antagonism shifts the log.dose/response curve to the right in a parallel fashion (drug D in panel B overleaf). The shift is expressed as a ‘dose ratio’, \( r \), – the factor by which the concentration of agonist must be increased to make any response in the presence of the antagonist the same as that in its absence. The Schild equation then allows the affinity of the antagonist for the receptor to be determined:

\[
\begin{align*}
\text{r-1} = \frac{[B]}{K_B} \\
\end{align*}
\]

Where \([B]\) is the antagonist concentration and \(K_B\) is the dissociation equilibrium constant for antagonist binding.

If the competitive antagonist binds irreversibly then raising the agonist concentration may not allow sufficient agonist occupancy for a maximum response. Irreversible competitive antagonism is shown by drug E in Panel C overleaf, where, with the higher concentration of antagonist, no amount of increase in \([A]\) allows the maximum response to be regained. Often a maximum response does not need the agonist to occupy all of the receptors. There are said to be ‘spare receptors’. A low dose of irreversible competitive antagonist may then appear to produce a parallel shift of the log.dose/response curve (suggested by the change in the log.dose/response curve with the lower concentration of E).
Panel A shows the response of a tissue to drugs A, B and C. Panels B and C show the effects that drugs D and E have on the log.dose/response curves to drug A.
Key stages in the development and introduction of a new drug

Identification of novel chemical with therapeutic potential

- Preclinical studies in animals
  - Pharmacological actions
  - Pharmacokinetics
  - Toxicology

Clinical studies

- Phase I – Studies in healthy volunteers
  - Pharmacological actions
  - Pharmacokinetics
  - Tolerability/side effects

- Phase II – Small-scale trials in patients
  - Efficacy in target condition(s)
  - Dosage regimen
  - Toxicity

- Phase III – Large-scale, formal clinical trial
  - Comparison with established treatments

- Phase IV – Postmarketing surveillance
  - Discovery of rare or long-term/delayed adverse effects
  - Identification of sensitive/insensitive populations

NEW DRUG!!
**Human studies**  Trials must ask a particular, relevant question and be designed so that an unambiguous answer can be provided. Independent ethical committees must approve the study.

A new drug can only be compared to the best treatment currently available (i.e. the use of a placebo may be unethical).

A comparative trial should be terminated early if data indicate one treatment is clearly better (so that all may benefit).

All patients (or guardian) should provide informed consent for participation.

Drugs known to be toxic (e.g. from animal studies) should not be tested in healthy volunteers.

**Animal studies**  The minimum number of animals, consistent with achieving a statistically valid assessment of the drug action under study, should be used. Suffering must also be minimised.
Key stages in the development and introduction of a new drug

- Identification of novel chemical with therapeutic potential
- Preclinical studies in animals
  - Pharmacological actions
  - Pharmacokinetics
  - Toxicology
- Phase I – Studies in healthy volunteers
  - Tolerability/side effects
- Phase II – Small-scale trials in patients
  - Efficacy in target condition(s)
  - Dosage regimen
  - Toxicity
- Phase III – Large-scale, formal clinical trial
  - Comparison with established treatments
- Phase IV – Postmarketing surveillance
  - Discovery of rare or long-term/delayed adverse effects
  - Identification of sensitive/insensitive populations

NEW DRUG!!
Random allocation to treatment groups

The main aim is to avoid bias in selecting patients for particular treatments yet to ensure the groups are essentially similar in composition. In a large trial, with many participants, simple, random allocation will generally ensure the treatment groups are similar.

Stratified randomisation
In a small trial, randomisation may not ensure similarity. It may be desirable to make sure that each group has broadly the same numbers of each sex, a similar age spread and that disease severity is comparable. Stratification may also allow groups of individuals who respond more favourably to a particular treatment to be identified.

Cross-over design
With stable, chronic conditions it is possible that all subjects may be able take both treatments at different times. Each patient effectively serves as their own control and the outcome may be recorded as a preference.
Key stages in the development and introduction of a new drug

Identification of novel chemical with therapeutic potential

Preclinical studies in animals

Ethics

Clinical studies

Phase I – Studies in healthy volunteers

Phase II – Small-scale trials in patients

Phase III – Large-scale, formal clinical trial

Phase IV – Postmarketing surveillance

Randomisation

Pharmacological actions
Pharmacokinetics
Toxicology
Pharmacological actions
Pharmacokinetics
Tolerability/side effects
Efficacy in target condition(s)
Dosage regimen
Toxicity
Comparison with established treatments
Discovery of rare or long-term/delayed adverse effects
Identification of sensitive/insensitive populations

NEW DRUG !!
**Single blind**  In single-blind trials patients are not told which treatment they are to receive. The aim is to ensure that any expectations that the patient has does not generate or modify a placebo effect or otherwise influence their assessment of the treatment.

**Double blind**  ‘Double blind’ is where neither patient nor doctor knows which treatment is being administered. Bias in allocating patients to a treatment can be avoided if the trial organiser does not know which treatment a patient is to receive. This ensures that, for example, the more seriously ill patients are not given the new treatment, perhaps in the expectation that ‘new is better’. It should also prevent bias affecting the clinician’s assessment of the comparative effectiveness of the treatments.
The introduction of new drugs

Key stages in the development and introduction of a new drug

1. Identification of novel chemical with therapeutic potential
   - Preclinical studies in animals
     - Pharmacological actions
     - Pharmacokinetics
     - Toxicology

2. Clinical studies
   - Phase I – Studies in healthy volunteers
     - Pharmacological actions
     - Pharmacokinetics
     - Tolerability/side effects

   - Phase II – Small-scale trials in patients
     - Efficacy in target condition(s)
     - Dosage regimen
     - Toxicity

   - Phase III – Large-scale, formal clinical trial
     - Comparison with established treatments

   - Phase IV – Postmarketing surveillance
     - Discovery of rare or long-term/delayed adverse effects
     - Identification of sensitive/insensitive populations

- Ethics
- Randomisation
- Blinding
The therapeutic index (TI) is a simple attempt to quantify the benefit versus risk ratio of a drug.

\[ TI = \frac{TD_{50}}{ED_{50}} \quad \text{or} \quad \frac{LD_{50}}{ED_{50}} \]

The TD$_{50}$ is the dose required to produce a toxic effect in 50% of the subjects (the median toxic dose) and the ED$_{50}$ is the median effective dose. In animal studies, toxicity may be measured by death, in which case the median lethal dose (LD$_{50}$) replaces the TD$_{50}$. Clearly, if the TD$_{50}$ or LD$_{50}$ is much greater than the ED$_{50}$ then the TI will be large and the drug might be considered to have a large safety margin. The LD$_{50}$, necessarily measured in animals, is a poor measure of human toxicity.

The risk which is accepted in taking a drug will obviously be affected by the severity of the condition being treated. Many quite toxic drugs are used for life-threatening illnesses.
Simple diagram of absorption and distribution of a drug
How do lipid solubility and ionisation influence the passage of drugs through cell membranes?
- Passive diffusion of drug through a cell membrane depends on its concentration gradient across the membrane and its diffusion coefficient.

- Concentration gradient established within the cell membrane depends on the drug's lipid/water partition coefficient.

- Most drugs ionise to some extent in aqueous solution.

- The ionised form is *lipophobic*, so that ionisation impedes passive membrane permeation.

- The fractional ionisation can be determined from the Henderson-Hasselbalch equation:

  for a weak acid: \( \log_{10} \frac{c_i}{c_u} = \text{pH} - \text{pK}_a \)
  for a weak base: \( \log_{10} \frac{c_i}{c_u} = \text{pK}_a - \text{pH} \)

[Where \(c_i\) is the concentration of drug in ionised form, \(c_u\) is that in unionised form, \(\text{pK}_a\) is -log\(_{10}\) of the acid dissociation constant for the drug and \(\text{pH}\) is -log\(_{10}\) of the hydrogen ion concentration.]

- Ionisation thus depends on the pH of the aqueous environment and the drug's acid dissociation constant (a strong acid has a low \(\text{pK}_a\) and a strong base has a high \(\text{pK}_a\)).
Simple diagram of absorption and distribution of a drug

What are the features, advantages and disadvantages of the different routes of drug administration?

- Passage across the blood–brain barrier
- Absorption across the mucosa of the intestine
- Passive reabsorption from the renal tubules
- Penetration into cells

Lipid solubility and ionisation

Drug administration → Drug in plasma

Drug in plasma → Drug in brain

Drug in brain → Drug in peripheral tissues

Drug in peripheral tissues → Drug elimination
**Enteral, i.e. oral, rectal, sublingual**

Easy, requires no skill, and little need for sterility. Many drugs, however, are poorly absorbed from the gut and bioavailability (see card 37.03) may be low. Rectal and sublingual admin. largely avoid first-pass metabolism. Rectal route useful for irritant medicines or if the patient is vomiting or comatose.

**Intravenous, i.v.**

100% of dose is immediately available within the circulation (though injection is often made slowly to avoid an excessive, transient concentration in the blood.) Skill and sterility required.

**Intramuscular, i.m.**

Requires less skill and all the drug enters the circulation. Depot preparations can be used for drug action over periods of days to weeks.

**Subcutaneous, s.c.**

Requires little skill. Depots can be used.

**Percutaneous**

Very lipid-soluble substances can be usefully administered this way, e.g. nicotine/fentanyl/glyceryl trinitrate as patches.

**Inhalation**

Rapid absorption – large surface area, rich blood supply, thin membranes. Used for systemic action, esp. gaseous anaesthetics, or local action, e.g. bronchodilators and antiasthmatic glucocorticoids.

**Intrathecal**

For drugs which do not readily cross the blood–brain barrier.

**Local/topical**

To provide local treatment (eye, joint etc.) and minimise effects elsewhere in body.
Simple diagram of absorption and distribution of a drug

What is meant by the term ‘bioavailability’?

Lipid solubility and ionisation

Passage across the blood–brain barrier

Absorption across the mucosa of the intestine

Drug administration

Routes of administration

Drug in brain

Drug in plasma

Drug in peripheral tissues

Drug elimination

Passive reabsorption from the renal tubules

Penetration into cells

Lipid solubility and ionisation
The most useful definition is ‘the proportion of the administered dose that reaches the systemic circulation’. Incomplete release from the dosage form, destruction within the gut, poor absorption and first-pass elimination are important causes of low bioavailability. For drugs with a low therapeutic index it is important that repeat prescriptions provide medicines of equivalent bioavailability (bioequivalence).

**Diagram showing factors influencing bioavailability**

- Drug in solution in the gut
- Disintegration and dissolution of tablet
- **Destruction in gut.** Peptides and proteins subject to proteolytic enzymes. Some drugs acid labile.
- **Partial absorption**
  - Low lipid solubility.
  - Ionisation.
  - Complexation with gut contents (e.g. tetracycline/Ca\(^{2+}\) salts)
  - Rapid loss from gut (diarrhoea).
- **Metabolism by gut mucosa or liver in ‘first pass’;**
  - 90% or more of a drug dose may be metabolised during its first passage through the liver.

**Drug formulation:** the main factor determining differences between preparations.
Simple diagram of absorption and distribution of a drug

How can the bioavailability of a drug preparation be established?
Bioavailability may be quantified by measuring the area under the curve of plasma concentration versus time. For intravenous administration, bioavailability is 100%. If the same dose is given by another route, the area under the curve, expressed as a percentage of the area for i.v. administration, gives the bioavailability. In the illustration below the relative areas would suggest a bioavailability of approximately 50% for the oral dosage form.
Simple diagram of absorption and distribution of a drug
What are the features and consequences of drug binding to plasma proteins and other tissue components?

Drug administration

Lipid solubility and ionisation

Absorption across the mucosa of the intestine

Passage across the blood–brain barrier

Drug in brain

Drug in plasma

Drug in peripheral tissues

Drug elimination

Passive reabsorption from the renal tubules

Penetration into cells

Lipid solubility and ionisation

Bioavailability

Routes of administration

Bioavailability
Many drugs bind to plasma proteins, albumin in general being the most important. $\alpha$-Acid glycoprotein is more important for some basic drugs (e.g. propranolol). Binding to plasma proteins is usually reversible, of finite capacity and of low specificity and has several consequences:

- Bound drug is usually inactive.

- The reduction in free drug concentration may reduce elimination (by reducing glomerular filtration) or, conversely, protein binding may act to deliver drug to the kidney and liver, and so enhance elimination.

- One drug may prevent the binding of another, and so enhance drug action (significant only for highly bound drugs such as warfarin, whose displacement and resulting increased activity can cause bleeding).

Tetracyclines bind to calcium in bones and teeth (which can produce abnormalities in tooth development in children).
Simple diagram of absorption and distribution of a drug

How can the same dose of different drugs result in different concentrations in the body?
After absorption, drugs do not spread rapidly throughout the whole of body water to achieve a uniform concentration. Large molecules (heparin, insulin) cannot easily enter interstitial and intracellular spaces, whereas smaller and lipid-soluble molecules can. A drug's penetration into these compartments is indicated by its *apparent volume of distribution* $V_d$: the volume of fluid that would be required to hold the amount of drug in the body at the measured plasma concentration. It can be estimated by the equation:

$$V_d = \frac{\text{Dose}}{c_p}$$

Where $c_p$ is the concentration of drug in the plasma after it has equilibrated in its distribution volume but before a significant fraction has been eliminated. Examples of $V_d$ values (l/kg) are:

- Heparin: 0.05–0.1
- Tubocurarine: 0.2–0.4
- Ethanol: 1.0
- Propranolol: 2–5
- Nortriptyline: >20

A drug with a large $V_d$ will clearly require a larger dose to achieve a given plasma concentration than one with a small $V_d$ (given the same degree of binding to plasma protein).
The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.
Drug metabolism often occurs in two steps; **phase I** generally adds a reactive group to the molecule which provides a point of attack for the group added by a **phase II**, conjugation, reaction. Drug conjugates are nearly always biologically inactive (an exception is morphine 6-glucuronide) whereas phase I products may retain the therapeutic action or be toxic.

**Phase I Reactions**

- Oxidation: Mainly carried out by the P450 system (see card 38.02) in the liver. Examples:
  - propranolol → 4-hydroxypropranolol (retains β-blocking activity)
  - paracetamol → N-acetyl-p-benzoquinone imine (responsible for hepatotoxicity)

- Reduction: Nitrazepam → 7-amino-nitrazepam (nitro reduction)
  - prednisone → prednisolone

- Hydrolysis: Often carried out by esterases in liver or blood. Examples:
  - procaine
  - succinylcholine

**Phase II Reactions**

These are the (mostly hepatic) conjugation reactions.

- Glucuronidation: E.g. morphine, valproate
- Sulfation: E.g. paracetamol, salbutamol
- Methylation: E.g. o-methylation of catecholamines
- Acetylation: E.g. sulphonamides, isoniazid
- Amino acid: Especially with glycine. E.g. aspirin
- Glutathione: E.g. busulfan and toxic metabolite of paracetamol
The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.
Drug oxidation, usually carried out by the P450 monooxygenase system, is a major route of drug metabolism. The P450 haem proteins are found particularly in the smooth endoplasmic reticulum of the liver. NADPH/cytochrome P450 reductase is generally an essential component of the system.

There is a large family of P450 enzymes, only some of which are important for drug metabolism. These demonstrate selectivity in the drugs which act as substrates:

- **CYP1A2** caffeine, paracetamol
- **CYP2B6** cyclophosphamide, methadone
- **CYP2C8** paclitaxel, repaglinide
- **CYP2C19** omeprazole, phenytoin
- **CYP2C9** ibuprofen, tolbutamide
- **CYP2D6** codeine, propranolol
- **CYP2E1** alcohol, paracetamol
- **CYP3A4,5,7** ciclosporin, nifedipine

Reactions catalysed by P450 include: O-dealkylation (codeine), aliphatic hydroxylation (ciclosporin), deamination (amfetamine), N-dealkylation (morphine), N-oxidation (dapsone), s-oxidation (cimetidine) and aromatic hydroxylation (propranolol).
The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.
The activity of the P450 system can be increased (induced) or inhibited by drugs or by dietary constituents. This is an important cause of drug interactions. The induction or inhibition of particular P450 isoenzymes will either reduce or enhance the activity of drugs metabolised by the enzyme. Just a few examples are:

<table>
<thead>
<tr>
<th>Drug metabolising P450s</th>
<th>Inducers</th>
<th>Inhibitors</th>
<th>Substrates affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP1A2</strong></td>
<td>Omeprazole, modafinil</td>
<td>Fluvoxamine, ciprofloxacin, cimetidine, amiodarone</td>
<td>Clomipramine, clozapine, paracetamol</td>
</tr>
<tr>
<td><strong>CYP2B6</strong></td>
<td>Phenobarbital, rifampin</td>
<td>Ticlopidine</td>
<td>Bupropion, cyclophosphamide, methadone</td>
</tr>
<tr>
<td><strong>CYP2C8</strong></td>
<td>Rifampin</td>
<td>Gemfibrozil, trimethoprim</td>
<td>Paclitaxel, repaglinide</td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
<td>Carbamazepine, prednisone rifampin</td>
<td>Omeprazole, fluoxetine, topiramate</td>
<td>Omeprazole, diazepam, phenytoin</td>
</tr>
<tr>
<td><strong>CYP2C19</strong></td>
<td>Rifampin, secobarbital</td>
<td>Fluconazole, amiodarone</td>
<td>Ibuprofen, tolbutamide, losartan, tamoxifen</td>
</tr>
<tr>
<td><strong>CYP2D6</strong></td>
<td>Dexamethasone, rifampin</td>
<td>Fluoxetine, quinidine, terbinafine</td>
<td>Codeine, lidocaine, propranolol</td>
</tr>
<tr>
<td><strong>CYP2E1</strong></td>
<td>Ethanol, isoniazid</td>
<td>Disulfiram</td>
<td>Ethanol, paracetamol, halothane</td>
</tr>
<tr>
<td><strong>CYP3A4,5,7</strong></td>
<td>Nevirapine, barbiturates, carbamazepine, rifampin</td>
<td>Indinavir, clarithromycin, itraconazole, grapefruit juice</td>
<td>Ciclosporin, terfenadine, simvastatin, buspirone</td>
</tr>
</tbody>
</table>
The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.
Most are excreted into the urine, either in an unchanged form or as a metabolite.
Three renal processes are involved:

**Glomerular filtration** Small drug molecules are forced across the glomerular membrane by the pressure in the renal arteries, entering the renal tubule at a concentration equal to that in the plasma. Drug bound to plasma proteins will not be filtered.

**Tubular secretion** Drug molecules which are not filtered pass to capillaries surrounding the proximal convoluted tubule. Here separate anion and cation transporters secrete drugs into the urine. This process can be very effective, possibly removing most of a drug (e.g. benzylpenicillin) from the blood in a single passage. The process is saturable and subject to competition. Thus probenecid inhibits the transport of the weak acid penicillin.

**Tubular reabsorption** As water is reabsorbed from the filtrate, the concentration of drug in the urine rises and unionised, lipid-soluble drug is also reabsorbed. Excretion of suitable drugs can be modified by manipulating urinary pH to change the fraction of drug ionised. In **forced alkaline diuresis** the ionisation of acidic drugs, e.g. salicylate, is increased, so reducing reabsorption and increasing clearance. (May be useful in drug overdose.)
The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.
**Biliary excretion**  For some drugs (e.g. cromoglicate, vecuronium) biliary excretion of drug or metabolite is more important than renal excretion. Biliary excretion is by active transport, which is saturable and subject to competition. Drug excreted in bile may be reabsorbed from the intestine and enter an ‘enterohepatic circulation’. Drug tied up in this ‘enteric pool’ acts as a reservoir which may increase the drug’s half-life.

**Excretion via lungs**  Volatile/gaseous agents can be readily excreted via the lungs, which receive the whole of the cardiac output and which have thin membranes which are very permeable to small gas molecules. The main agents lost via the lungs are the gaseous/volatile anaesthetics.
The time-course of drug concentrations in the plasma

A1 and A2 illustrate an exponential fall in plasma concentration after i.v. administration (A1 uses a linear concentration scale, A2 a logarithmic scale). B shows a drug whose concentration falls in a linear fashion.
Where passive diffusion is responsible for absorption or excretion, drug transport is often first order, i.e. the rate is proportional to the concentration gradient. First-order kinetics is exemplified by the exponentially declining plasma concentration of the drug, $c_p$, which follows first-order elimination after i.v. administration (Fig. A1 overleaf)*. The equation describing this decline is:

$$c_p = c_p(0)e^{-k_el t}$$

Where $c_p$ is the drug concentration in the plasma, $c_p(0)$ is the initial drug concentration at time $t = 0$ and $k_{el}$ is the elimination rate constant.

The relationship can be linearised by taking logarithms (Fig. A2 overleaf). For natural logarithms ($\ln$):

$$\ln c_p = \ln c_p(0) - k_{el} t$$

A plot of $\ln c_p$ against time gives a straight line of slope $-k_{el}$.

*Note: A simple exponential decline will only be observed where the body behaves as one compartment – see D&H ref.
The time-course of drug concentrations in the plasma

A1 and A2 illustrate an exponential fall in plasma concentration after i.v. administration (A1 uses a linear concentration scale, A2 a logarithmic scale). B shows a drug whose concentration falls in a linear fashion.
Zero-order kinetics applies when the rate of a process (e.g. drug metabolism) is independent of the drug’s concentration (Fig. B overleaf). Zero-order kinetics will be found where an enzyme reaction or membrane transport process has been saturated. These processes follow Michaelis-Menten kinetics.

Where the process lowers the drug concentration in the plasma ($c_p$):

$$- \frac{dc_p}{dt} = \frac{V_{\text{max}} \cdot c_p}{c_p + K_M}$$

Where $V_{\text{max}}$ is the maximum rate of transport or biotransformation and $K_M$ is the Michaelis constant.

When the drug concentration is high (relative to $K_M$), and the process effectively saturated, the equation reduces to:

$$- \frac{dc_p}{dt} \approx V_{\text{max}}$$

The rate of change of concentration has reached a maximum and is now unaffected by the drug concentration. ($C_p$ declines at a fixed rate (Fig. B overleaf)).

Ethanol is a well-known example of a substance subject to first-order elimination.
The time-course of drug concentrations in the plasma

A1 and A2 illustrate an exponential fall in plasma concentration after i.v. administration (A1 uses a linear concentration scale, A2 a logarithmic scale). B shows a drug whose concentration falls in a linear fashion.

A1

First-order elimination

Elimination rate constant = 0.03 min⁻¹

Exponential decline

A2

B

Linear decline

Zero-order elimination

Constant elimination rate of 0.006 units min⁻¹
A feature of exponential decline in $c_p$ according to first-order elimination is that in a given period of time the concentration will reduce by the same proportion. (One-compartment system is assumed.) In particular, the plasma half-life, $T_{0.5}$, is the time taken for any given plasma concentration to fall by 50%.

It is relatively easy to show that in the equation (from card 39.01):

$$c_p = c_p(0)e^{-k_{el}t}$$

When $t$ is made equal to $t_{1/2}$ and $c_p$ is made equal to a half of $c_p(0)$ then:

$$t_{1/2} = \frac{0.693}{k_{el}}$$

Thus in the example given here $T_{0.5} = \frac{0.693}{0.03}$, i.e. 23 min.

<table>
<thead>
<tr>
<th>Representative plasma half-lives of drugs, h</th>
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</thead>
<tbody>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Penicillin G</td>
</tr>
<tr>
<td>Lidocaine</td>
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<tr>
<td>Salicylate</td>
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<tr>
<td>Sulfadiazine</td>
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<tr>
<td>Atropine</td>
</tr>
<tr>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Phenobarbitone</td>
</tr>
<tr>
<td>Digitoxin</td>
</tr>
</tbody>
</table>
The time-course of drug concentrations in the plasma

A1 and A2 illustrate an exponential fall in plasma concentration after i.v. administration (A1 uses a linear concentration scale, A2 a logarithmic scale). B shows a drug whose concentration falls in a linear fashion.

In this example, the plasma concentration of drug reduces from 1 to 0.5 to 0.25 to 0.125 units in successive half-lives.
Another useful way of quantifying drug elimination is by its clearance. Drug clearance (Cl) is defined as the volume of plasma cleared of drug per unit time. Thus (assuming first-order, one-compartment behaviour):

\[
\text{Clearance} = \frac{\text{elimination rate}}{\text{plasma concentration}}
\]

The elimination rate is also given by the amount of drug in body \(c_pV_d\) multiplied by \(k_{el}\). \(V_d = \) volume of distribution. Therefore:

\[
\text{Cl} = \frac{k_{el}c_pV_d}{c_p} = k_{el}V_d
\]

As \(k_{el} = 0.693/t_{1/2}\), clearance = 0.693\(V_d/t_{1/2}\)

Total body clearance is the sum of the clearances occurring by whatever routes are applicable to the drug in question; often only renal and hepatic clearances are important.

A drug’s clearance can be used to determine the expected steady-state concentration in the plasma, \(c_{ss}\), during infusion or regular intermittent dosing. In the steady state, the rate of drug administration (e.g. 500mg/day) will equal the rate of loss (elimination rate, i.e. Cl x \(c_{ss}\)). Therefore, \(c_{ss}\) is given by the dose rate divided by the clearance. Alternatively, by knowing the clearance of a drug and the desired target plasma concentration, it is possible to calculate the required dose rate (Cl x \(c_{ss}\)).