RANG AND DALE'S Pharmacology Flashcards

Updated Edition

M.M. DALE • D.G. HAYLETT

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RANG & DALE'S

Pharmacology

Flash Cards Updated Edition

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ISBN: 9780702059575

Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

Commissioning Editor: Kate Dimock
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CONTENTS

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.

PREFACE

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

We wish to record our appreciation of the team at Elsevier who worked on this project: Kate Dimock (commissioning editor), Alexandra Mortimer (development editor), Kerrie-Anne McKinlay (project manager) and Stewart Larking (designer).

DRUG INDEX

ABBREVIATIONS

5-HT	5-hydroxytryptamine
ACE(I)	angiotensin converting enzyme (inhibitor)
ACh	Acetylcholine
AChE(I)	acetylcholinesterase (inhibitor)
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
ADHD	Attention Deficit Hyperactivity Disorder
ADP	adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ATP	adenosine triphosphate
AV	atrio-ventricular
BP	blood pressure
C	cholesterol
cAMP	cyclic adenosine monophosphate
CAT	cholineacetyltransferase
CE	cholesteryl esters
cGMP	cyclic guanosine monophosphate
CL	corpus luteum
CMV	cytomegalovirus
CNS	central nervous system
CoA	Coenzyme A
COMT	catechol-O-methyl transferase
COPD	Chronic obstructive pulmonary disease
COX	Cyclo-oxygenase
CSF	cerebrospinal fluid
CTZ	chemoreceptor trigger zone
CVS	cardiovascular system
DA	dopamine
DAG	diacylglycerol
DD	dopamine decarboxylase
DHFR	dihydrofolate reductase
DMARD	disease-modifying antirheumatoid drug
DNA	deoxyribonucleic acid
DOPA	dihydroxyphenylalanine
DOPAC	3,4 dihydroxyphenyl acetic acid
dTMP	thymidylate
dUMP	uridylate
EPS	extrapyramidal symptoms
FH2	dihydrofolate
FH4	tetrahydrofolate.
FSH	follicle stimulating hormone
G N-	acetylglucosamine
GABA	γ-aminobutyric acid
GC	glucocorticoid
GC	guanylate cyclase
GF	Graafian follicle
GIT	gastrointestinal tract
GnRH	gonadotropin-releasing hormone
GP	glycoprotein
GTP	guanosine triphosphate
Hb	haemoglobin
HBV	Hepatic B virus
HCV	Hepatic C virus

HDL	high density lipoprotein
HIV	human immunodeficiency virus
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
HV	herpes virus
i.m.	intramuscular
i.v.	intravenous
ICSH	interstitial cell stimulating hormone
IL	interleukin
IP_3	Inositol trisphosphate
LA	local anaesthetic
LDL	low density lipoprotein
LH	luteinizing hormone
LSD	lysergic acid diethylamide
LT	leukotriene
M	acetylmuramic acid
M	muscarinic
MA	monoamine
MAO(I)	monoamine oxidase (inhibitor)
MC	mineralocorticoid
MDMA	Methylenedioxymethamfetamine
MLCK	myosin light chain kinase
Mnp	mononuclear phagocytes
MOA	mechanism of action
MRSA	Methicillin-resistant Staphylococcus aureus
MTX	methotrexate
MVA	mevalonic acid
NA	noradrenaline
NMDA	N-methyl D-aspartate
NO	nitric oxide
NRM	nucleus raphe magnus
NSAID	non-steroidal anti-inflammatory drug
OB	osteoblast
OC	osteoclast
OTC	over the counter
P450	cytochrome p450
PABA	p-aminobutyric acid
PAF	platelet activating factor
PAG	periaqueductal gray
PDE(I)	phosphodiesterase (inhibitor)
PG	prostaglandin
PKA	Protein kinase A
PKG	protein kinase G
R	Receptor
RNA	ribonucleic acid
RSV	respiratory syncytial virus
s.c.	subcutaneous
SA	sino-atrial
SR	sarcoplasmic reticulum
SSRI	Selective serotonin reuptake inhibitors
TB	tuberculosis
TCA	Tricyclic antidepressant
TG	triglycerides
TNF	tumour necrosis factor
TX	Thromboxane
VLDL	very low density lipoprotein

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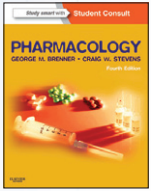

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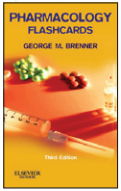

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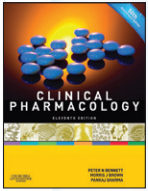

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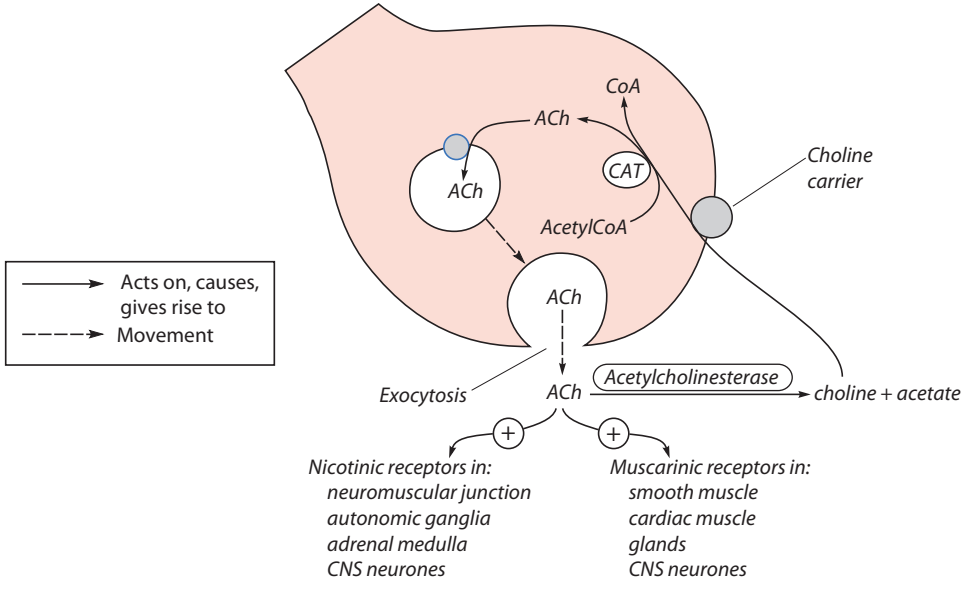
Simple figure of cholinergic transmission with potential sites of drug action



Pilocarpine

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 M_3 receptors which couple to G_q to increase cellular IP_3 and DAG concentrations. Constriction of pupil aids drainage of aqueous humour and lowers intraocular pressure.

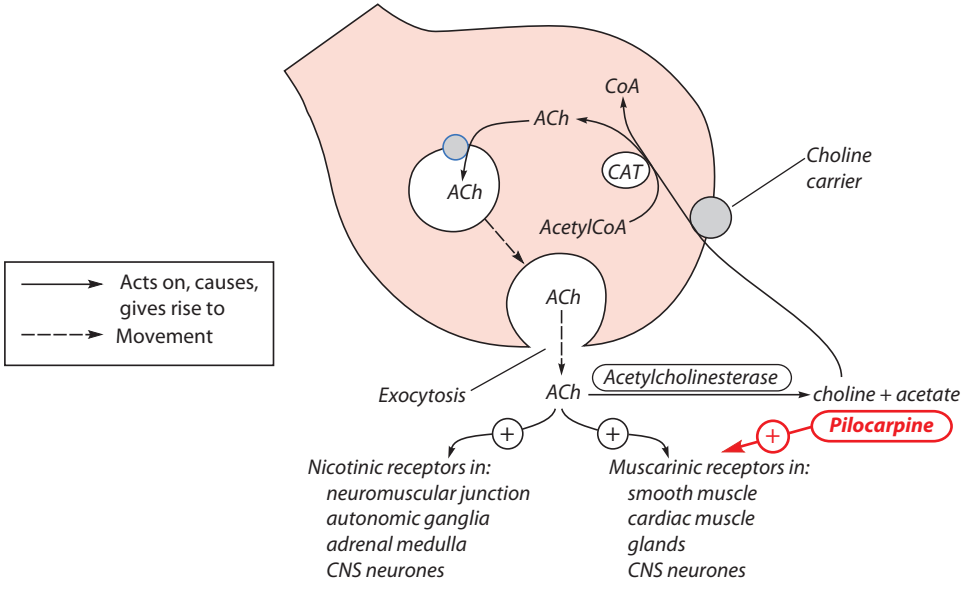
Abs/Distrb/Elim For glaucoma pilocarpine is given as eye drops and actions last for a day. A slow delivery system placed under the eyelid acts for several days.

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.

R&D 7e Ch 13, pp 157-158; D&H 2e Ch 10, pp 28-31

Simple figure of cholinergic transmission with potential sites of drug action



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.

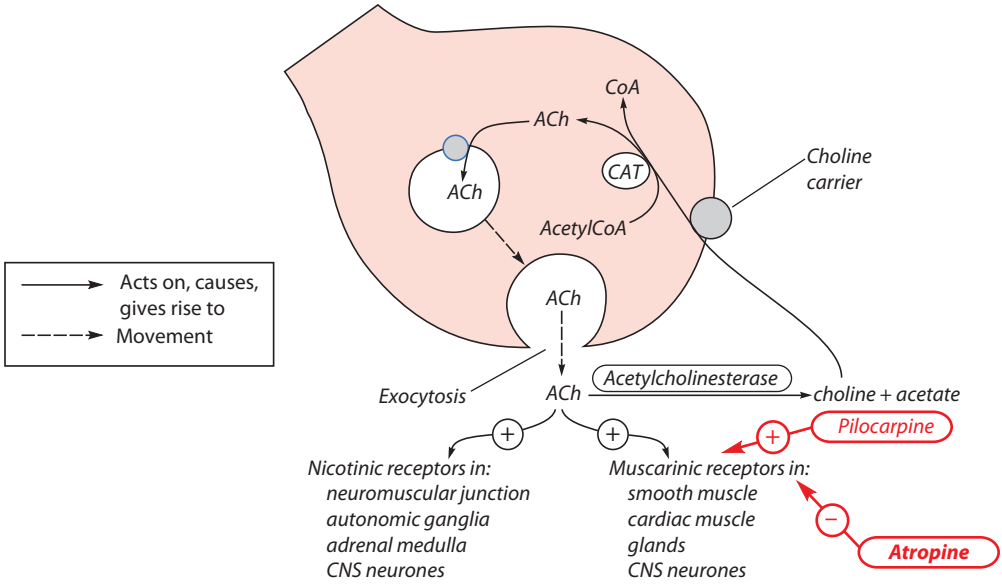
Abs/Distrb/Elim Given orally. Half-life 3h.

Clinical use Paralysis of accommodation and pupil dilation for eye examination (tropicamide). Urinary incontinence (oxybutinin). Irritable bowel syndrome (dicycloverine). Antidote for anticholinesterase poisoning. Treatment of cardiac slowing.

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

Simple figure of cholinergic transmission with potential sites of drug action



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.

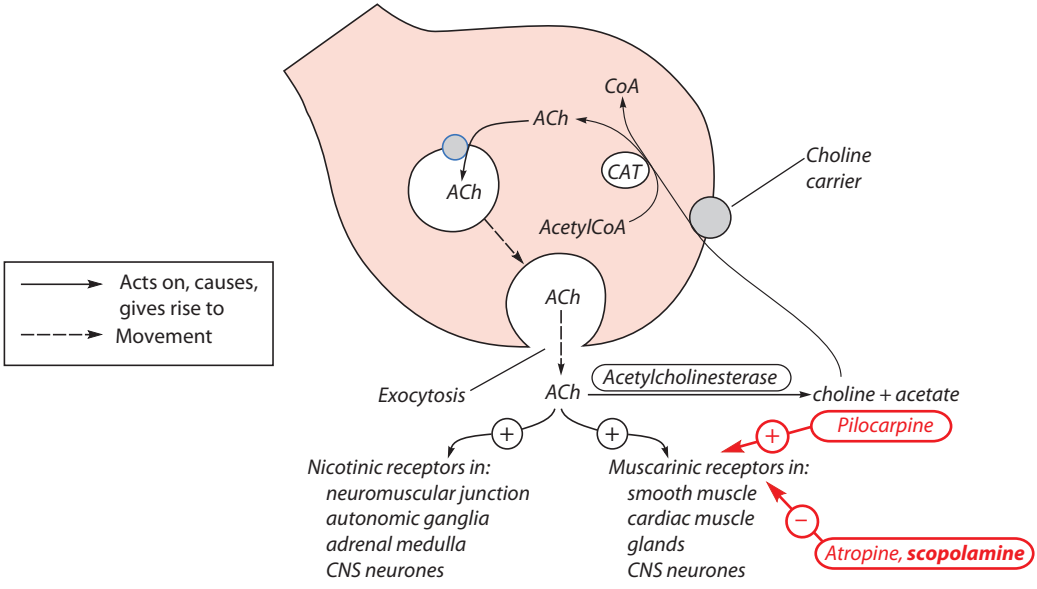
Abs/Distrb/Elim Oral admin. $T_{0.5}$ 4h. Also administered as transdermal patch for effects lasting 2–3 days.

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.

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

Simple figure of cholinergic transmission with potential sites of drug action



Succinylcholine

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.

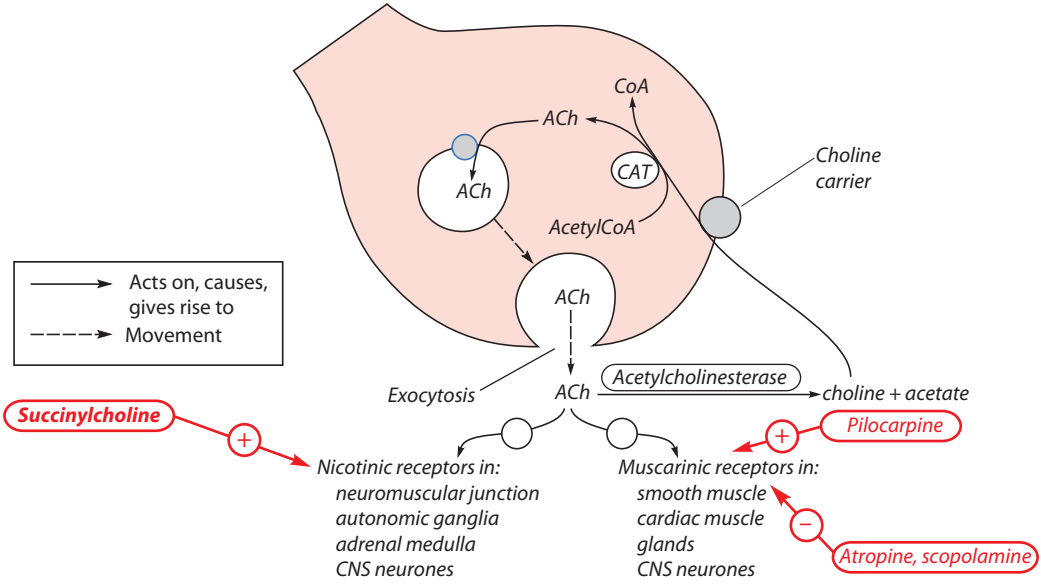
Abs/Distrb/Elim Given i.v. Hydrolysed by plasma cholinesterase within a few minutes. (A small percentage of people have an enzyme with much lower activity and action is prolonged.)

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).

R&D 7e Ch 13, pp 156-157; D&H 2e Ch 10, pp 28-31

Simple figure of cholinergic transmission with potential sites of drug action



Pancuronium

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).

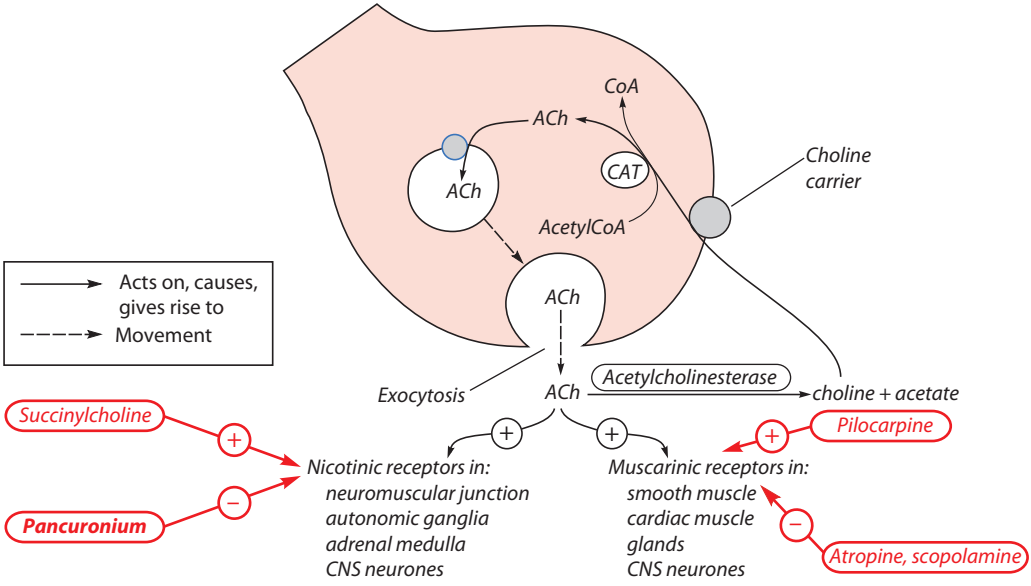
Clinical use In general anaesthesia – aids tracheal intubation, provides muscle relaxation for general surgery and aids mechanical ventilation.

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.

R&D 7e Ch 13, p 164; D&H 2e Ch 10, pp 28-31

Simple figure of cholinergic transmission with potential sites of drug action



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).

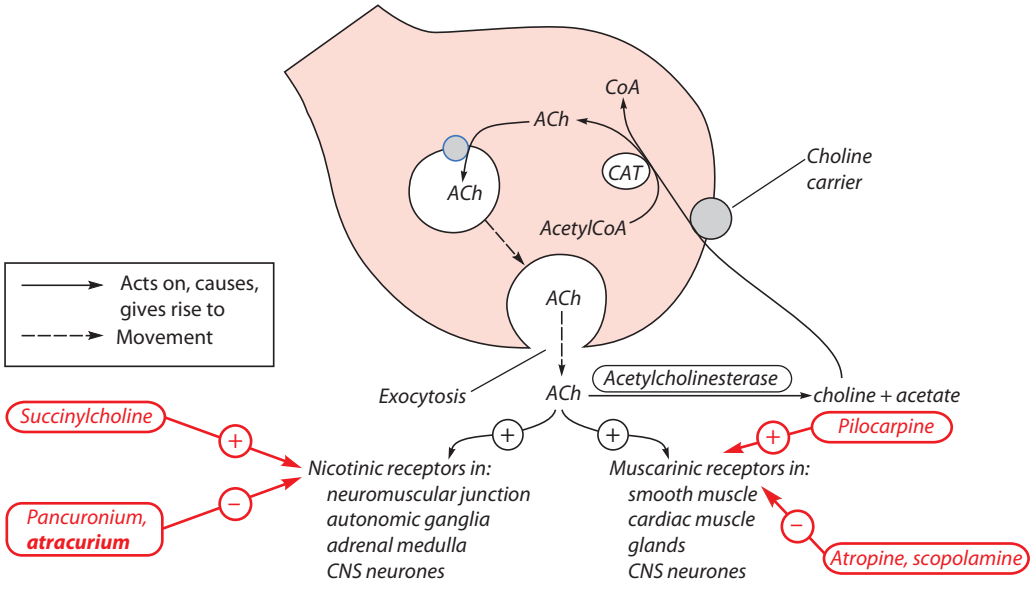
Abs/Distrb/Elim Given i.v. Half-life 30min. Eliminated mainly by a spontaneous chemical reaction (Hofmann elimination) in the plasma which makes duration of action relatively independent of renal function.

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.

R&D 7e Ch 13 p 164; D&H 2e Ch 10, pp 28-31

Simple figure of cholinergic transmission with 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. 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.

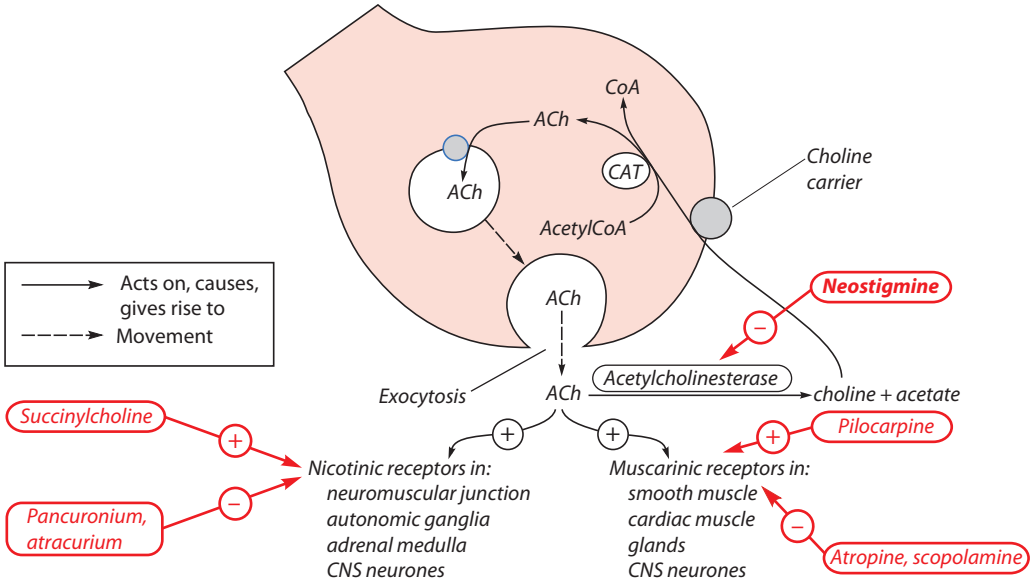
Abs/Distrb/Elim Given i.v. (to reverse neuromuscular block), by mouth (for myasthenia gravis). Mostly ionised, so low oral bioavailability and poor penetration of the blood–brain-barrier. Half-life 1h.

Clinical use Myasthenia gravis. Reversal of non-depolarising neuromuscular block. Post-operative urinary retention. Pyridostigmine – myasthenia gravis. Physostigmine – glaucoma.

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

R&D 7e Ch 13, p 169; D&H 2e Ch 10, pp 28-31

Simple figure of cholinergic transmission with potential sites of drug action



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.

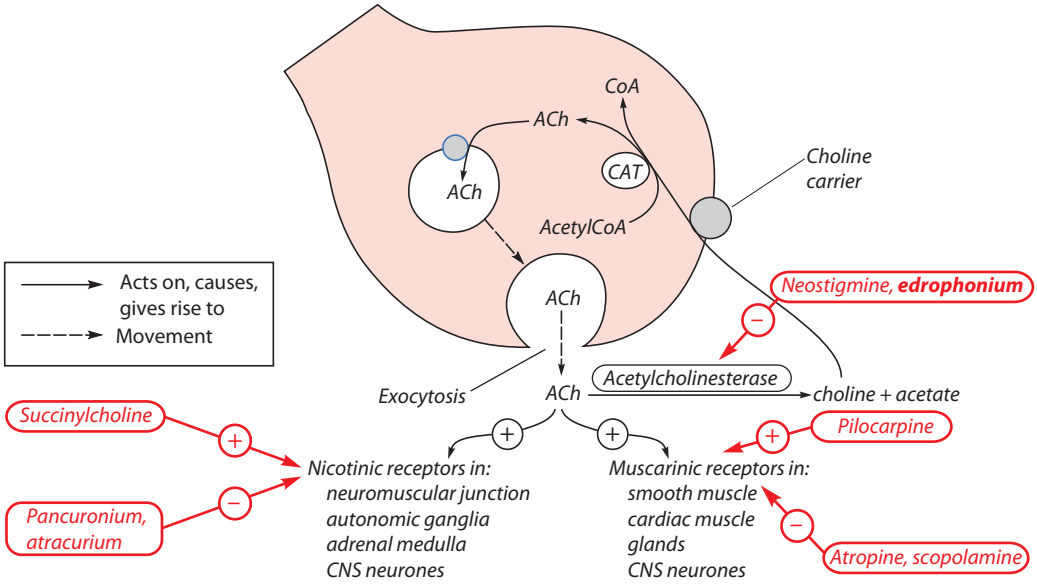
Abs/Distrb/Elim Given i.v. or i.m. Short duration of action (10min).

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 therapeutiic 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



Echothiophate

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.)

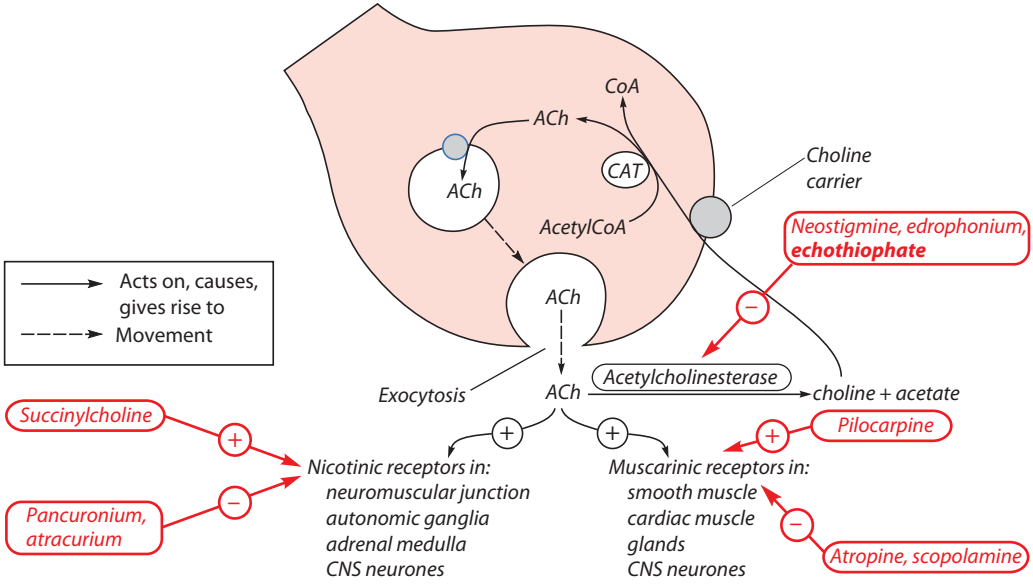
Abs/Distrb/Elim Most are readily absorbed through the skin, gut and lungs. (Protective clothing needed to avoid absorption of insecticides and nerve gases.) Long-acting.

Clinical use Glaucoma.

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

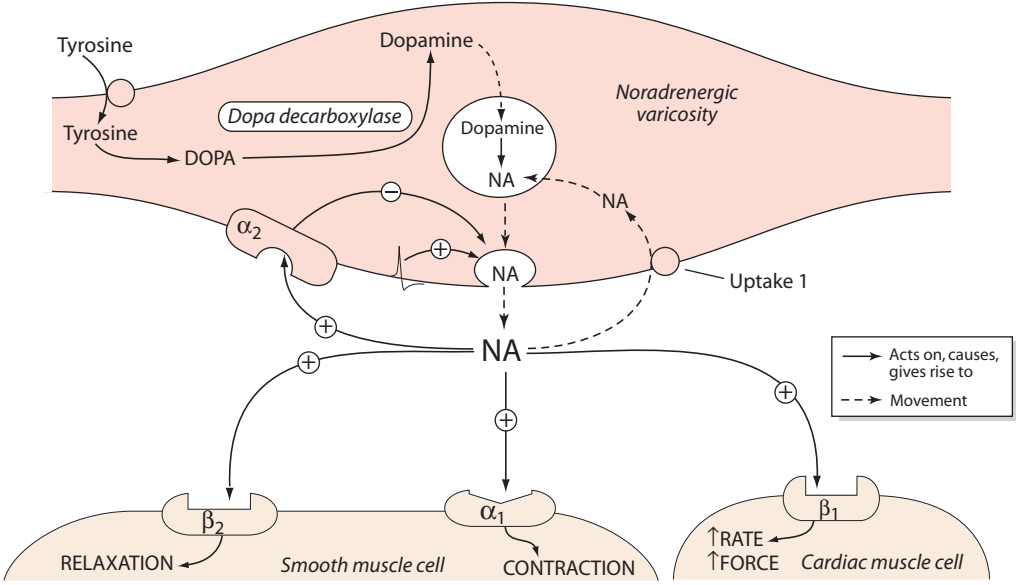
R&D 7e Ch 13, pp 168-170; D&H 2e Ch 10, pp 28-31

Simple figure of cholinergic transmission with potential sites of drug action



Notes

The figure gives a simple outline of noradrenergic transmission



Salbutamol

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/Distrb/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.

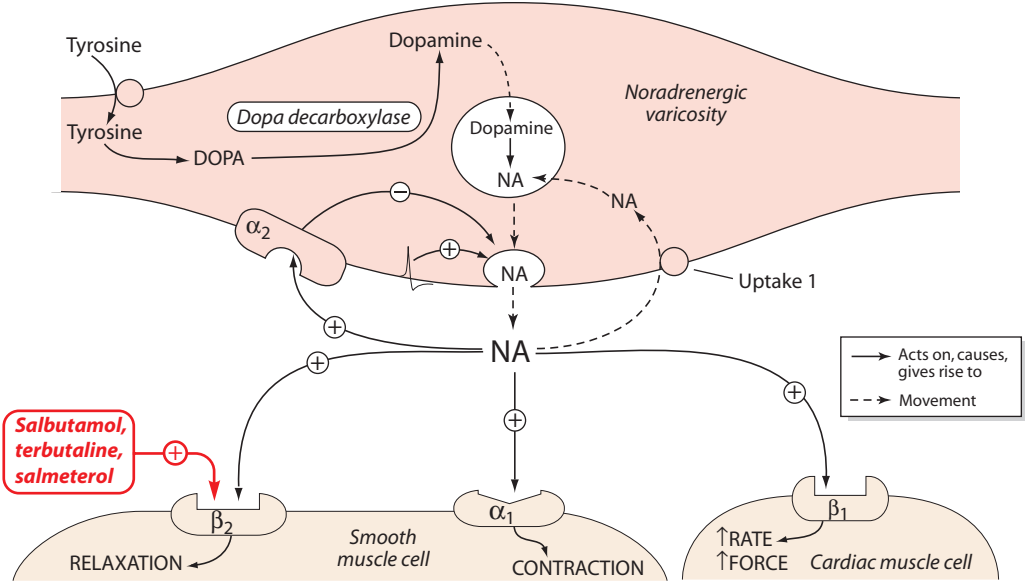
Clinical use Asthma (main use). Salbutamol and terbutaline for the acute attack; salmeterol for nocturnal asthma, exercise-induced asthma and for long-term therapy. Chronic obstructive pulmonary disease (COPD): salbutamol, terbutaline or salmeterol (with ipratropium; card 12.05).

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.

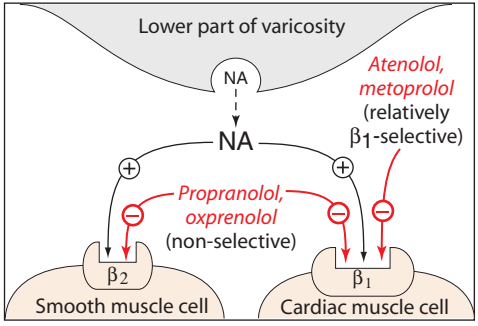
R&D 7e Ch 34, p 428; D&H 2e Ch 11, pp 32-35

The figure gives a simple outline of noradrenergic transmission



Atenolol

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 β_1-receptors.

Abs/Distrb/Elim Absorbed orally; plasma $t_{½}$ 4h; metabolised by liver.

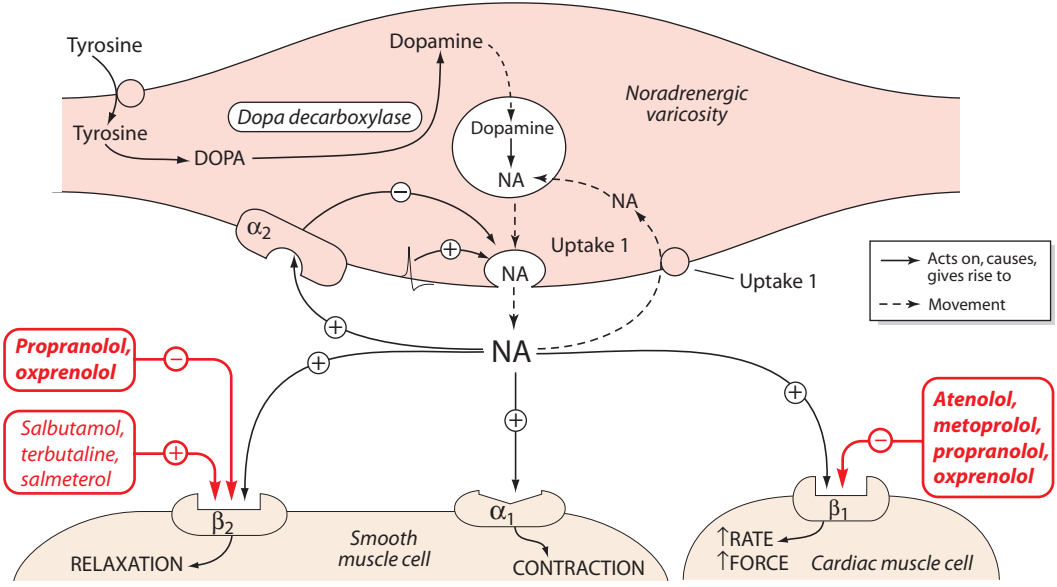
Clinical use Hypertension. Angina. Prevention of dysrhythmia in myocardial infarction.

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.

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



Epinephrine

Actions α_1: vasoconstriction (thus ↑BP); contraction of uterus, GIT sphincters, bladder sphincter, radial iris muscle.
α_2: inhibition of lipolysis, inhibition of NA release.
β_1: increased heart rate; β_2: bronchodilation, vasodilation with decrease in diastolic blood pressure.

MOA At α_1-receptors: Activation of phospholipase C with generation of IP_3 (which increases intracellular calcium and thus force of contraction).
At β_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 $t_{½}$ 2min. Metabolised by monoamine oxidase and catechol-O-methyl transferase.

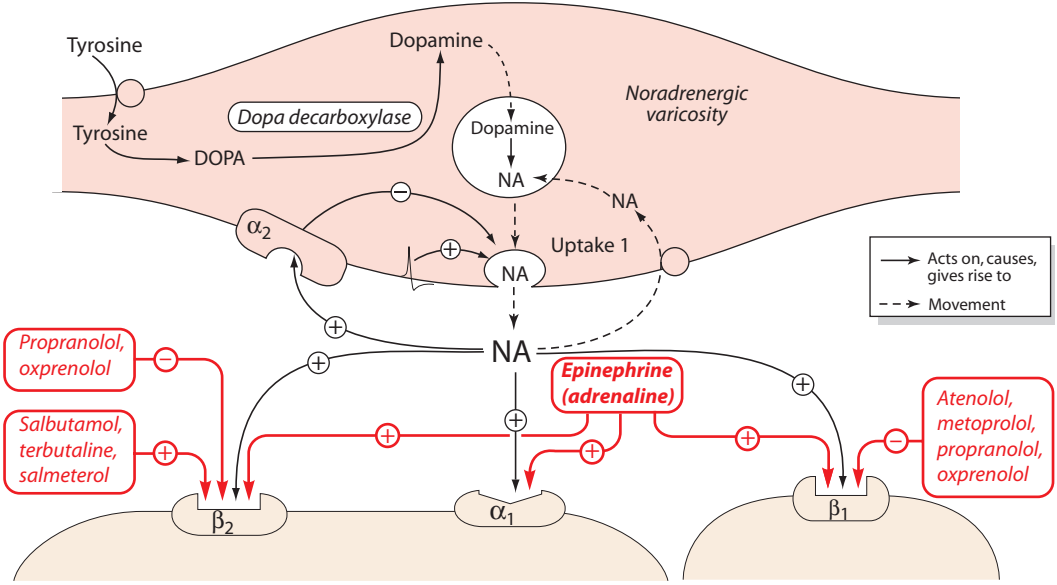
Clinical use Asthma, anaphylactic shock, cardiac arrest. Also added to local anaesthetic solutions.

Adverse effects Tachycardia, raised BP, anxiety.

Special points Phenylephrine and oxymetazoline are similar drugs except that they are α_1-selective

R&D 7e Ch 14, p 174; D&H 2e Ch 11, pp 32-35

The figure gives a simple outline of noradrenergic transmission



Prazosin

Actions Vasodilatation and thus ↓blood pressure
↑Heart rate (a reflex β_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 α_1-receptors. Tamsulosin is an α_{1A}-receptor antagonist.

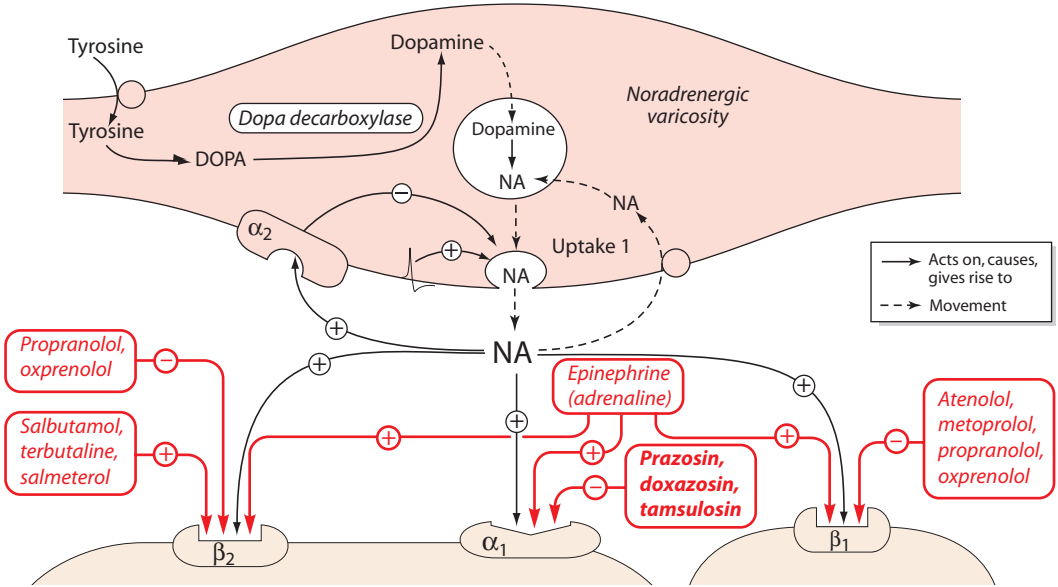
Abs/Distrb/Elim *Prazosin:* absorbed orally; plasma half-life 3–4h; metabolised by liver, extensive first-pass metabolism. *Tamsulosin:* absorbed orally; plasma half-life 10–15h; metabolised by liver. *Doxazosin* half-life 22h.

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

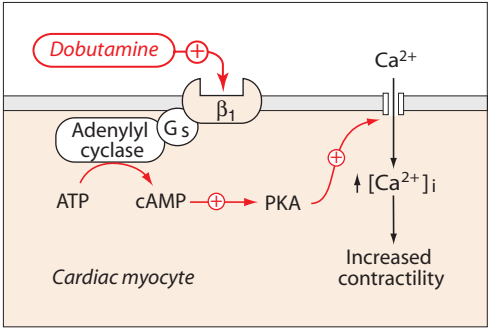
The figure gives a simple outline of noradrenergic transmission



Dobutamine

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 β_1-receptors causing G-protein-mediated increase of cAMP which increases calcium influx in the cardiac myocytes.
Minimal effect on β_2-receptors.

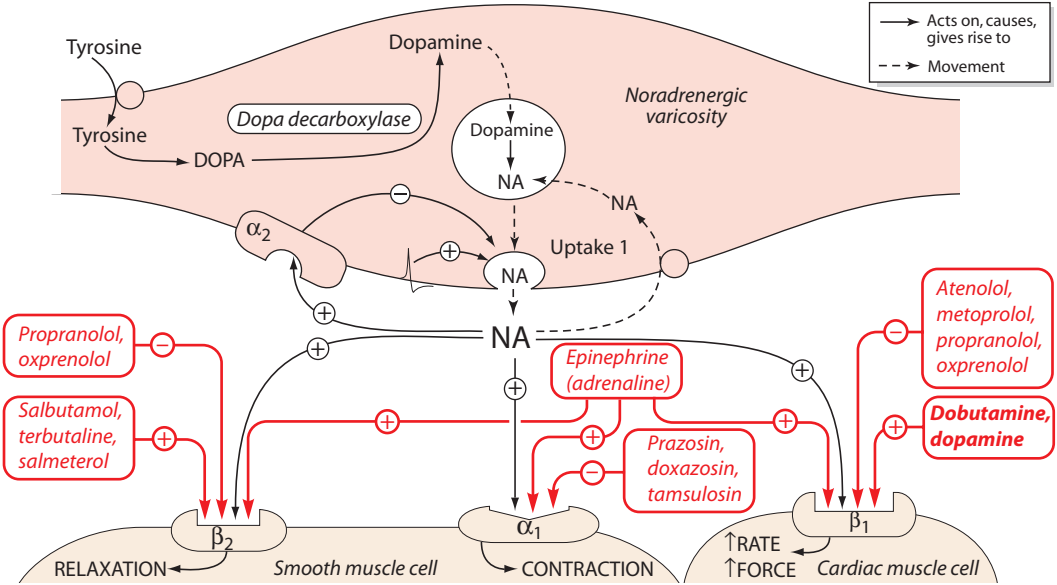


Abs/Distrb/Elim Given i.v.; plasma $t_{½}$ 2min
Inactivated by MAO and COMT.

Clinical use Cardiogenic shock. Decompensated congestive cardiac failure.

Adverse effects Dysrhythmias.

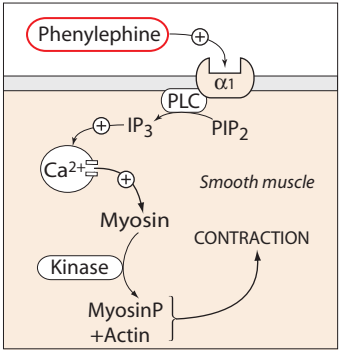
The figure gives a simple outline of noradrenergic transmission



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.



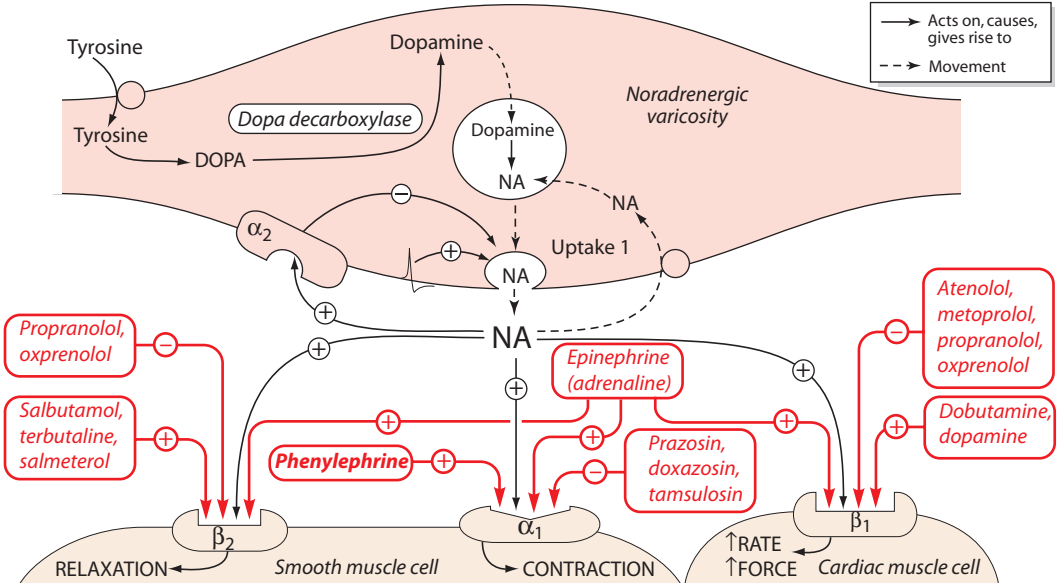
Abs/Distrb/Elim Given intranasally or topically in the eye, plasma half-life 3h, (longer in the elderly).

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



A non-selective α-adrenoceptor antagonist (Similar drug: phentolamine)

Phenoxybenzamine

Actions Block of α_1-receptor effects: vasodilatation and postural hypotension.
Block of α_2 effects: reduced NA action on α_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 α receptors and blocks NA action, but phentolamine's action is reversible.

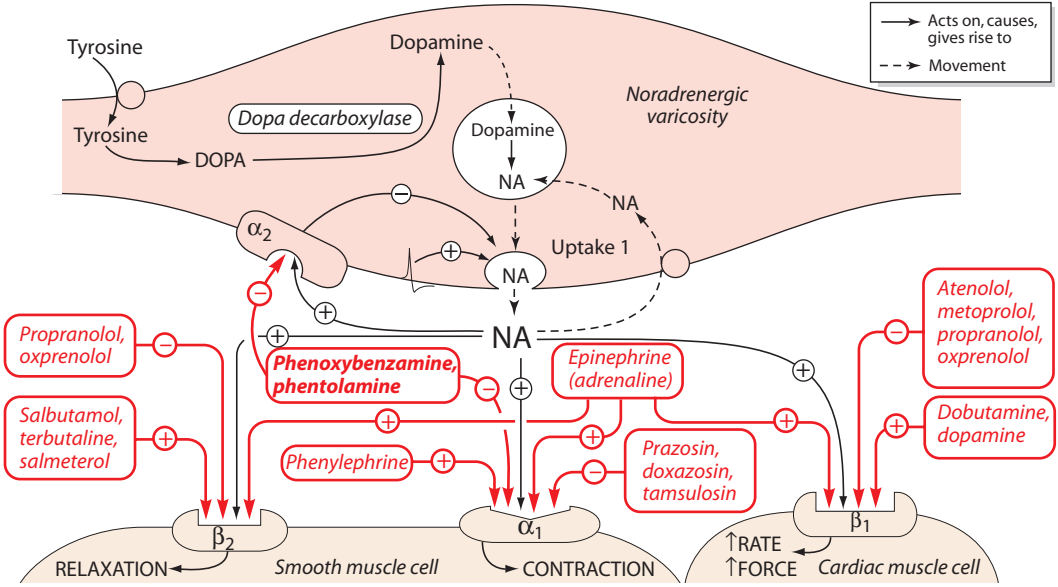
Abs/Distrb/Elim Plasma half-life 3h, (longer in the elderly). Given orally; plasma half-life ~12h; action lasts longer (up to several days) because of irreversible binding to receptor.

Clinical use Used in the treatment of phaeochromocytoma.

Adverse effects Postural hypotension and tachycardia.

R&D 7e Ch 14, pp 186-187; D&H 2e Ch 11, pp 32-35

The figure gives a simple outline of noradrenergic transmission



Amfetamine

Actions Releases NA from the varicosity therefore has similar actions to NA and epinephrine, but weaker:
α_1 receptor stimulation: →vasoconstriction →increased BP.
β_2 receptor stimulation: →bronchodilatation.
β_1 stimulation: →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.

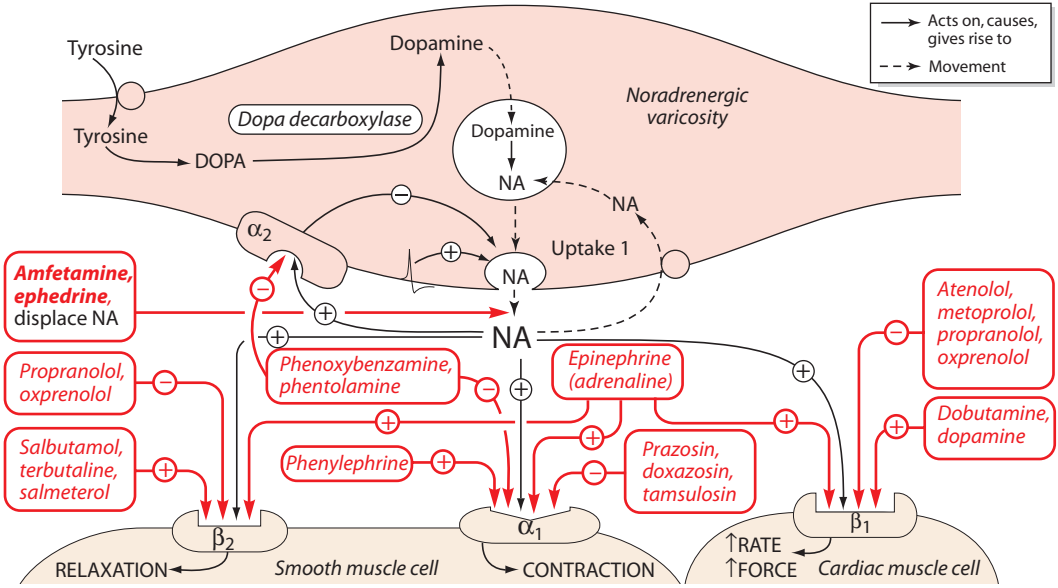
Clinical use Narcolepsy, hyperactivity in children.

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



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.

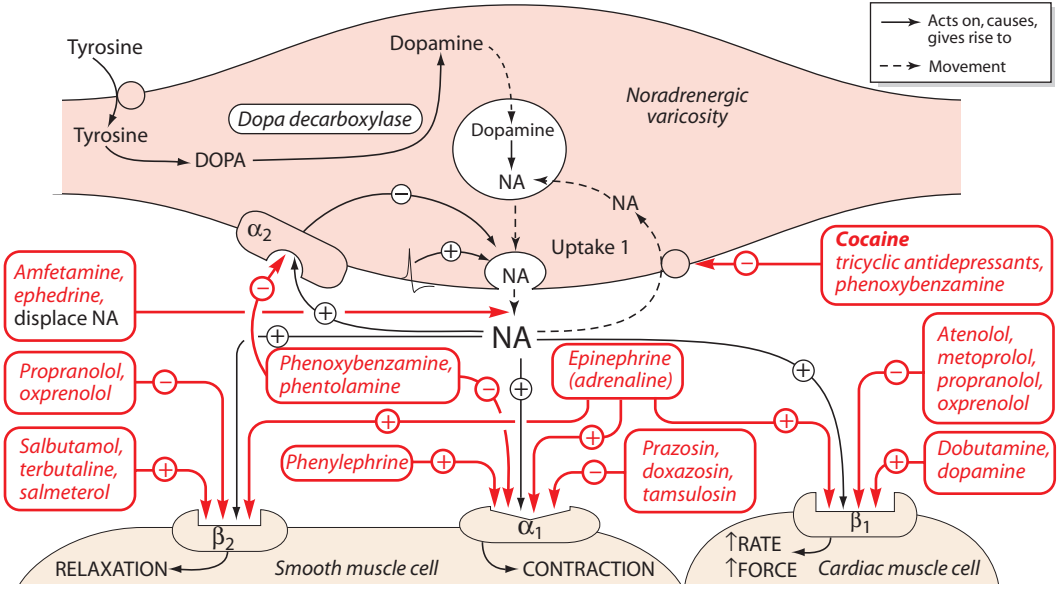
Clinical use Local anaesthetic.

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.

The figure gives a simple outline of noradrenergic transmission



Methyldopa

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.

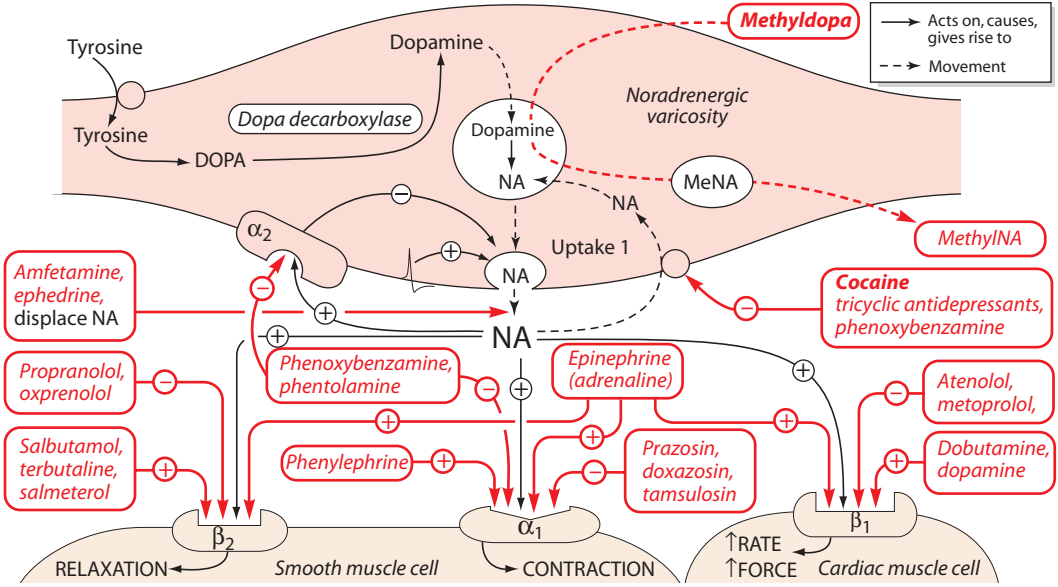
Abs/Distrb/Elim Given orally, actively transported into CNS neurones. Plasma half-life ~ 2h; duration of action ~ 24h.

Clinical use Hypertension in pregnancy.

Adverse effects Hypotension, transient sedation, dry mouth, diarrhoea, hypersensitivity reactions.

R&D 7e Ch 14, p 190; D&H 2e Ch 11, p 35

The figure gives a simple outline of noradrenergic transmission



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.

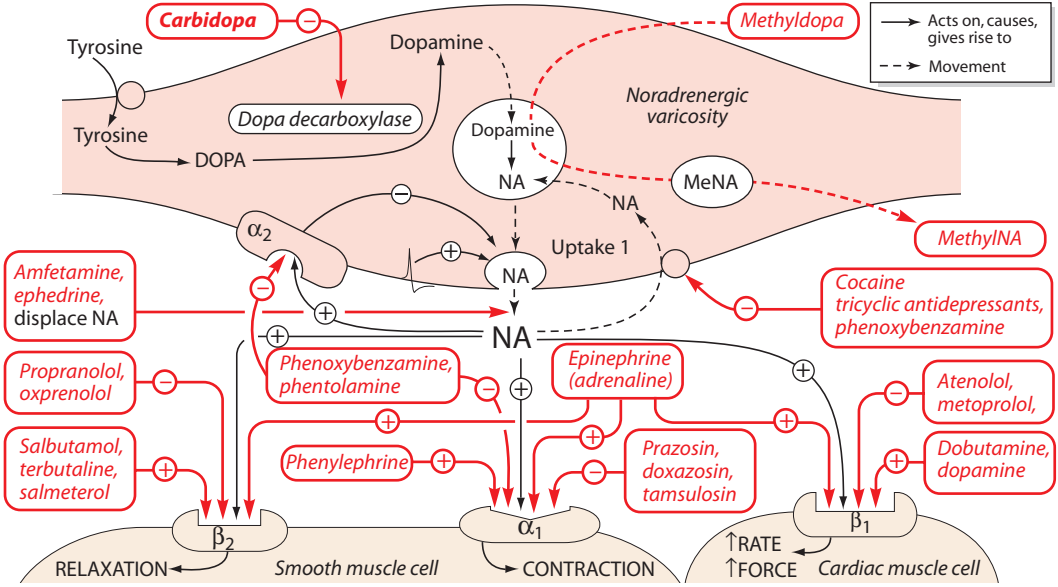
Carbidopa inhibits DOPA decarboxylase increasing the availabilty of levodopa to the CNS and reducing the its dopamine-mediated side effects. See CNS card 20.01.

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.

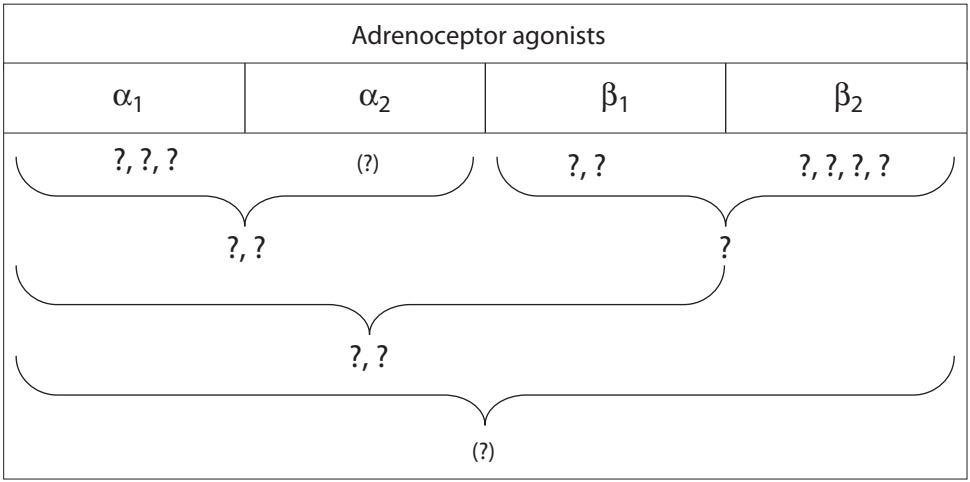
Adverse effects Hypotension, transient sedation, dry mouth, diarrhoea, hypersensitivity reactions.

The figure gives a simple outline of noradrenergic transmission

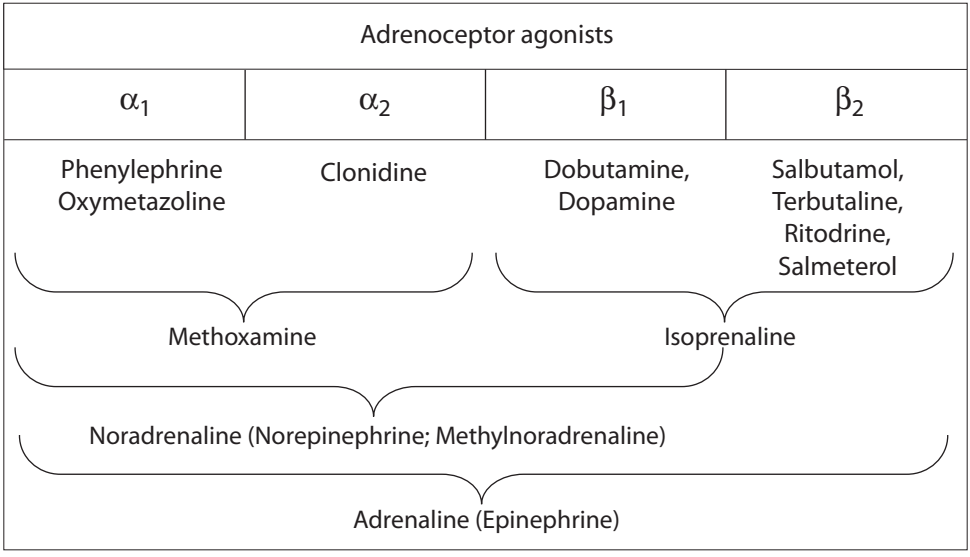


Notes

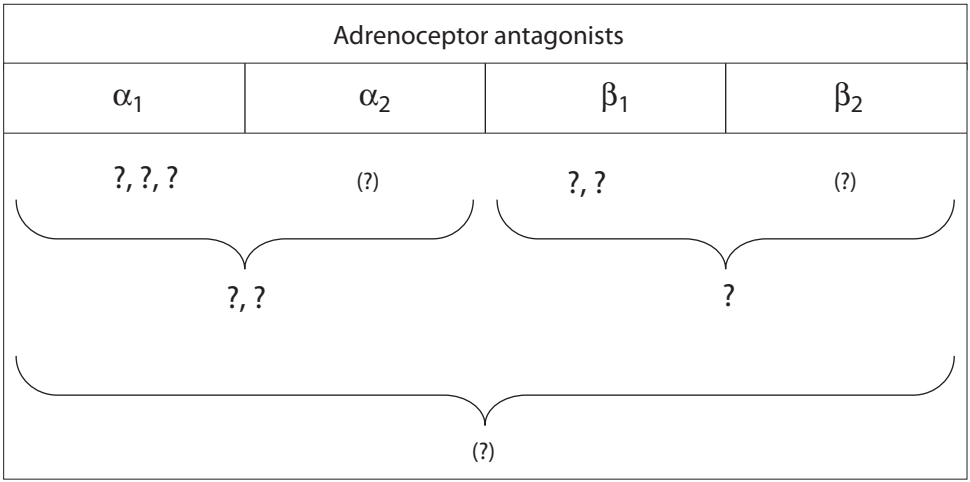
Add the drugs dealt with in the NA cards in the relevant places



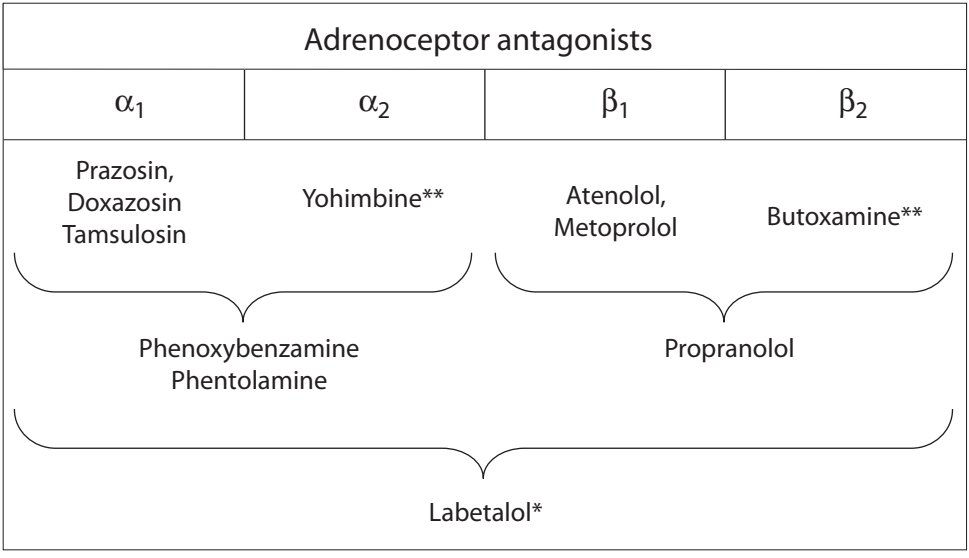
Note that (?) indicates a drug not dealt with in the cards; have a go at giving the names.


Adrenoceptor agonists
α1
α2
β1
β2
Phenylephrine
Oxymetazoline
Clonidine
Dobutamine,
Dopamine
Salbutamol,
Terbutaline,
Ritodrine,
Salmeterol
Methoxamine
Isoprenaline
Noradrenaline (Norepinephrine; Methylnoradrenaline)
Adrenaline (Epinephrine)

Add the drugs dealt with in the NA cards in the relevant places

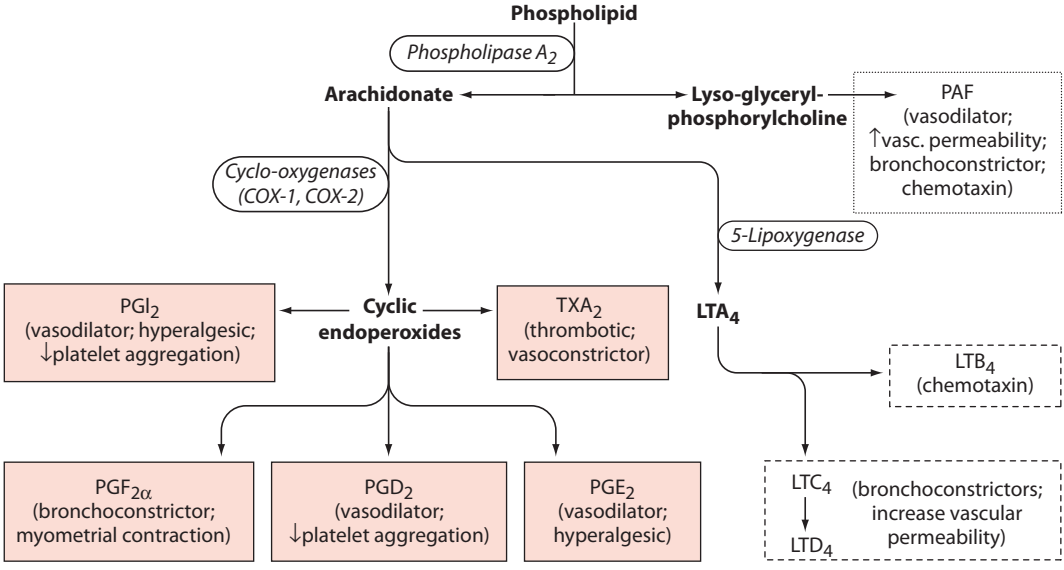


Note that (?) indicates a drug not dealt with in the cards; have a go at giving the names.



* 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)



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

MOA Reversible inhibition of COX-1, weak inhibition of COX-2.

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

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

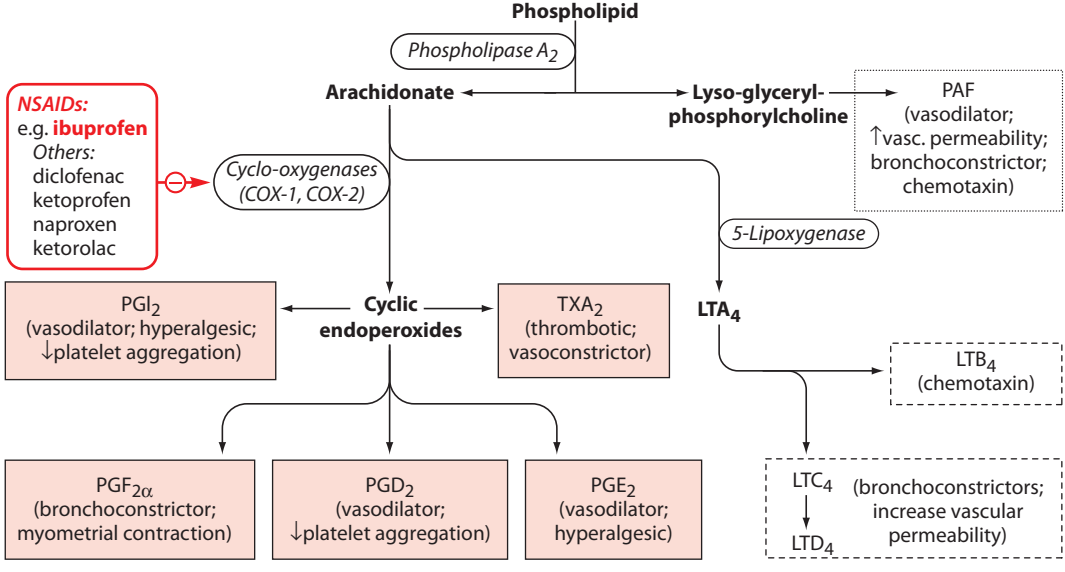
Adverse effects Gastrointestinal disturbances including gastric bleeding; headache, dizziness less commonly, allergic reactions occasionally; renal toxicity rarely.

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).

R&D 7e Ch 26, p 319t; D&H 2e Ch 16, pp 42-43

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



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.

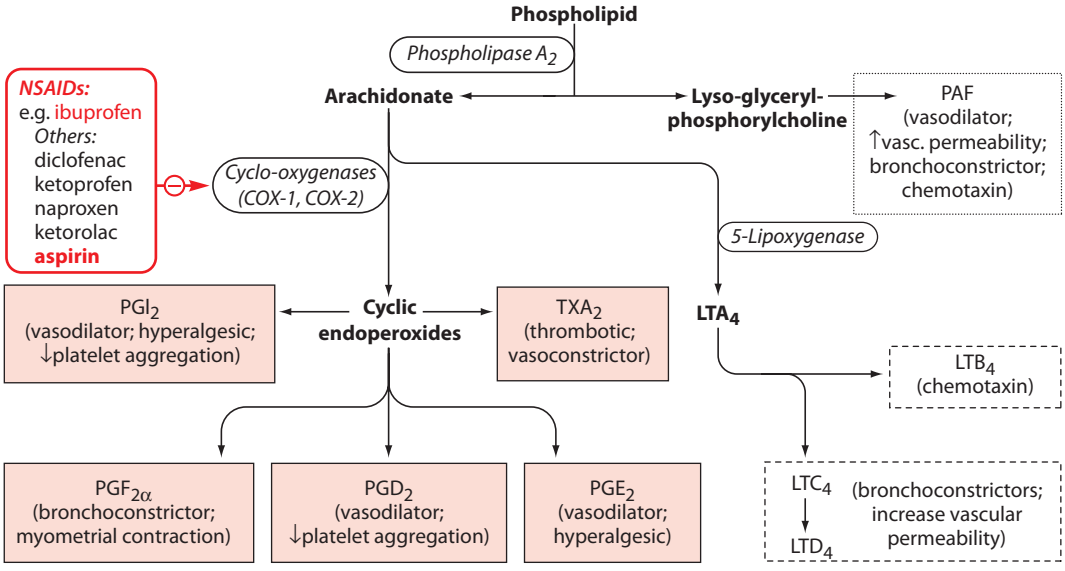
Clinical use ***Main use: as antithrombotic in myocardial infarction*** (see card set 7). Other NSAIDs are preferred for anti-inflammatory action and analgesia in musculo-skeletal conditions.

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.

R&D 7e Ch 26, pp323-325; D&H 2e Ch 16, pp 42-43

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



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*.

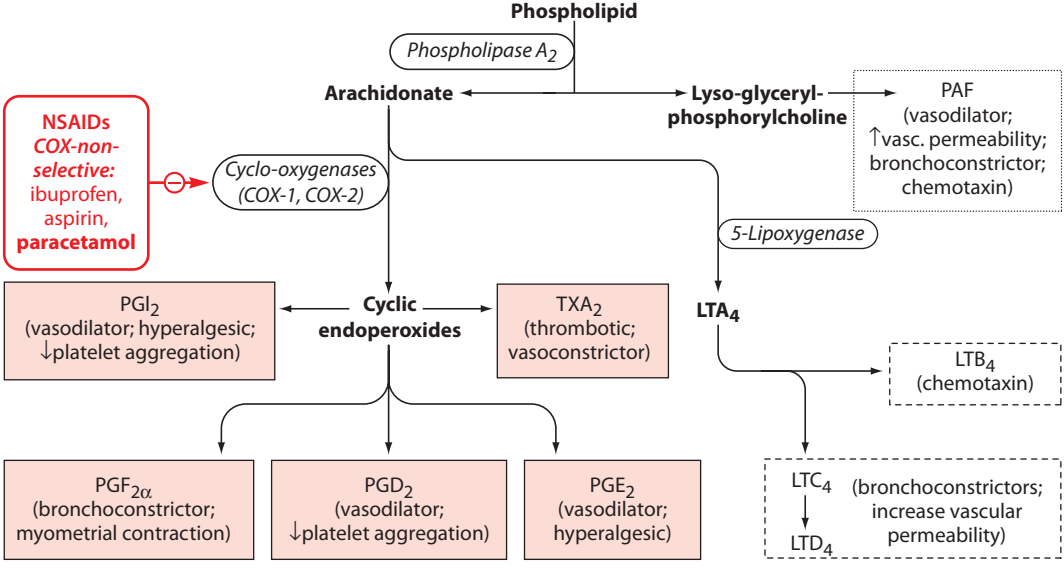
Abs/Distrb/Elim Given orally, half-life 2–4h, inactivated in the liver.

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.

R&D 7e Ch 26, p 325; D&H 2e Ch 16, pp 42-43

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



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.

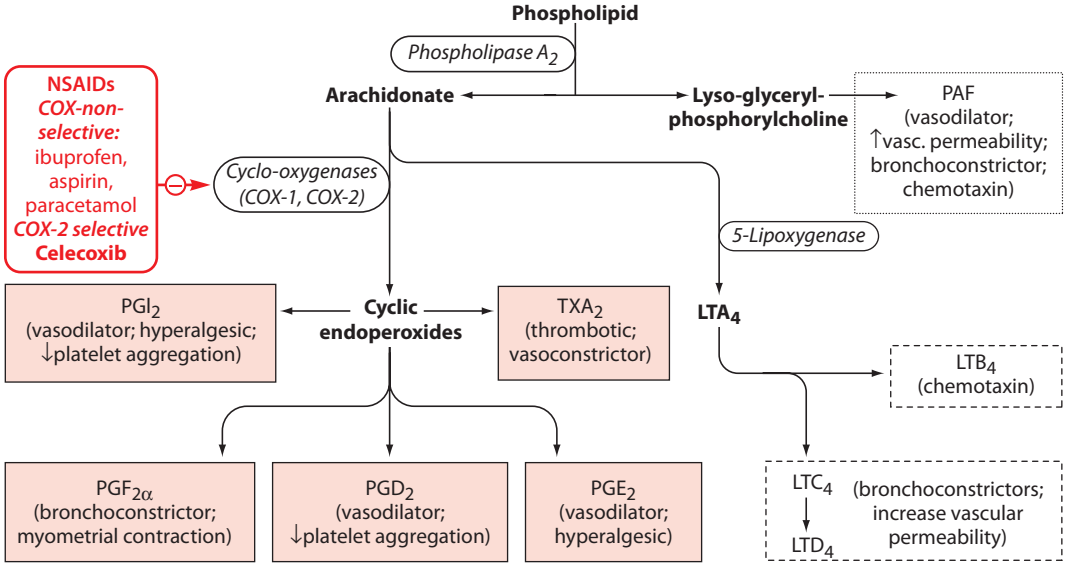
Clinical use Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis. (No cardioprotective effect because no antiplatelet action.)

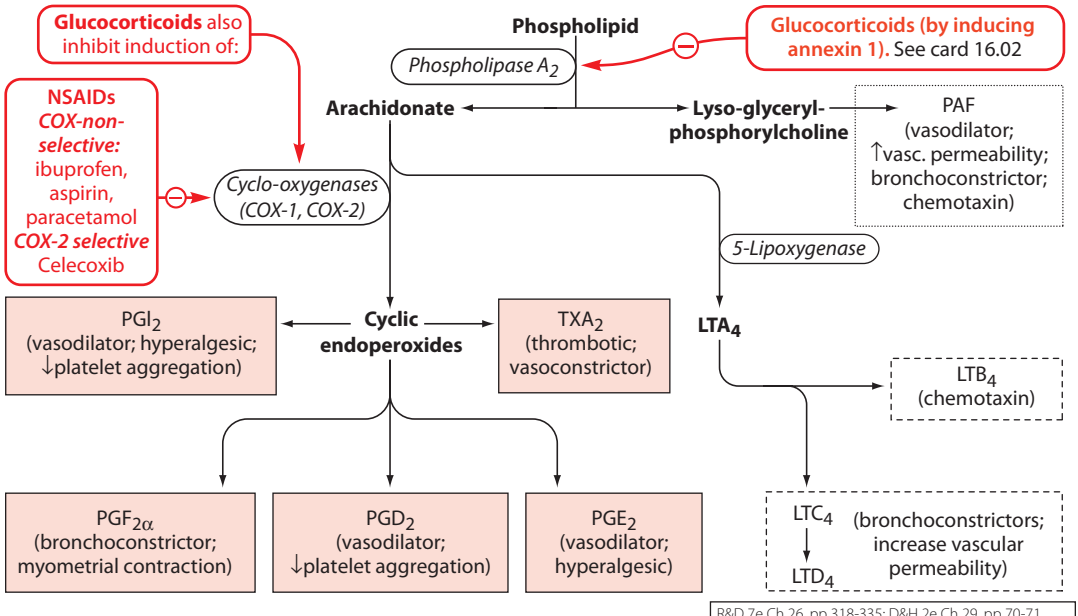
Adverse effects Fewer adverse gastrointestinal effects than the traditional NSAIDs. Some renal toxicity because COX-2 occurs constitutively in the kidney.

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)

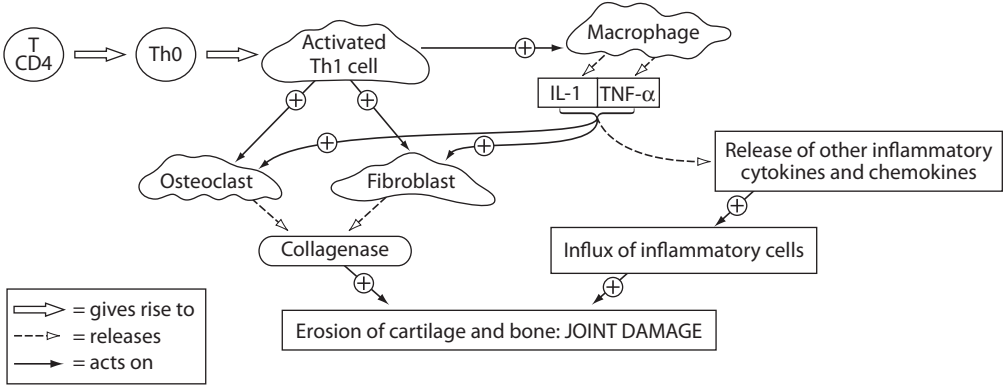




R&D 7e Ch 26, pp 318-335; D&H 2e Ch 29, pp 70-71

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)

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).

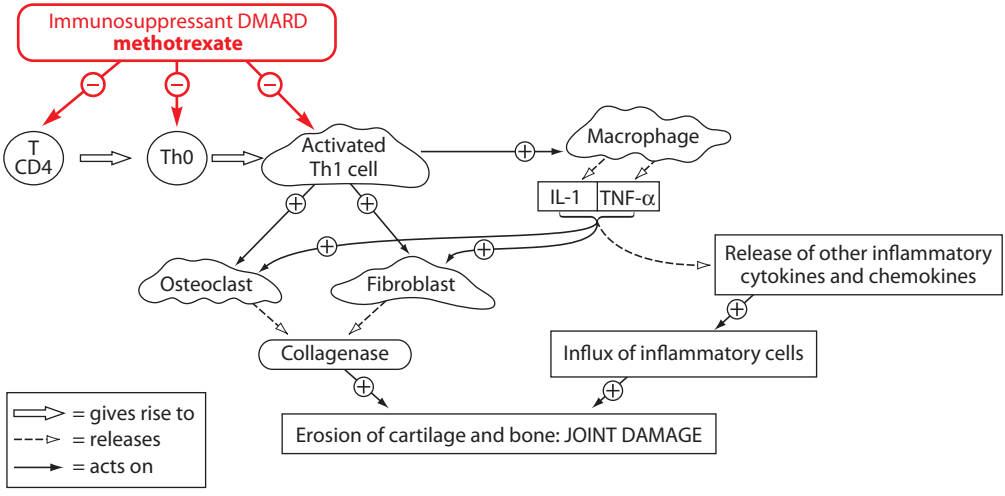
Abs/Distrb/Elim Given orally; has active metabolite; both MTX and metabolite are poly-glutamated (PgMTX). Half-life 6–9h.

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



Sulfasalazine

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.

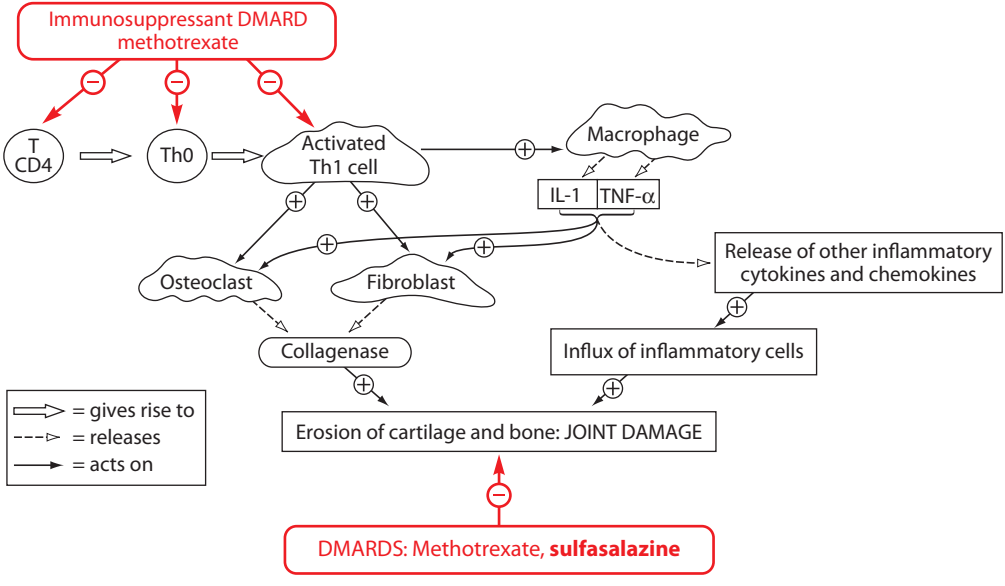
Abs/Distrb/Elim Given orally; only ~15% is absorbed in the GIT. Half-life 6–16h.

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.

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

The figure shows the pathophysiology of rheumatoid joint damage



Leflunomide

Actions Modifies the immune reaction underlying rheumatoid arthritis through an inhibitory action on activated T cells.

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

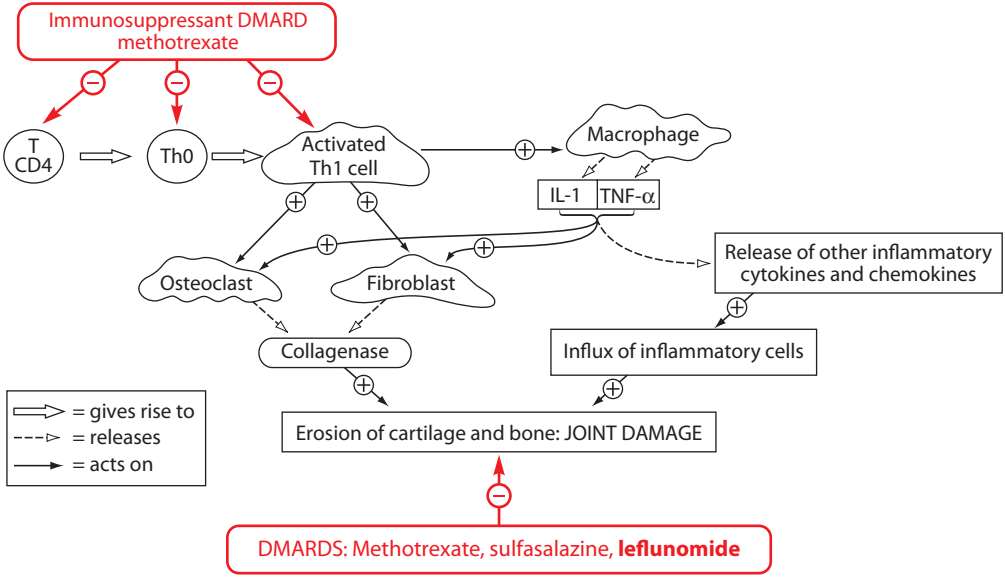
Abs/Distrb/Elim Absorbed orally. The metabolite undergoes enterohepatic cycling, half-life thus ~18 days.

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.

R&D 7e Ch 26, p 330

The figure shows the pathophysiology of rheumatoid joint damage



Infliximab

Actions Reduces joint inflammation and symptoms of rheumatoid arthritis. Reduces symptoms of Crohn's disease.

MOA It is a monoclonal antibody against TNF-α that binds with the TNF-α 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.

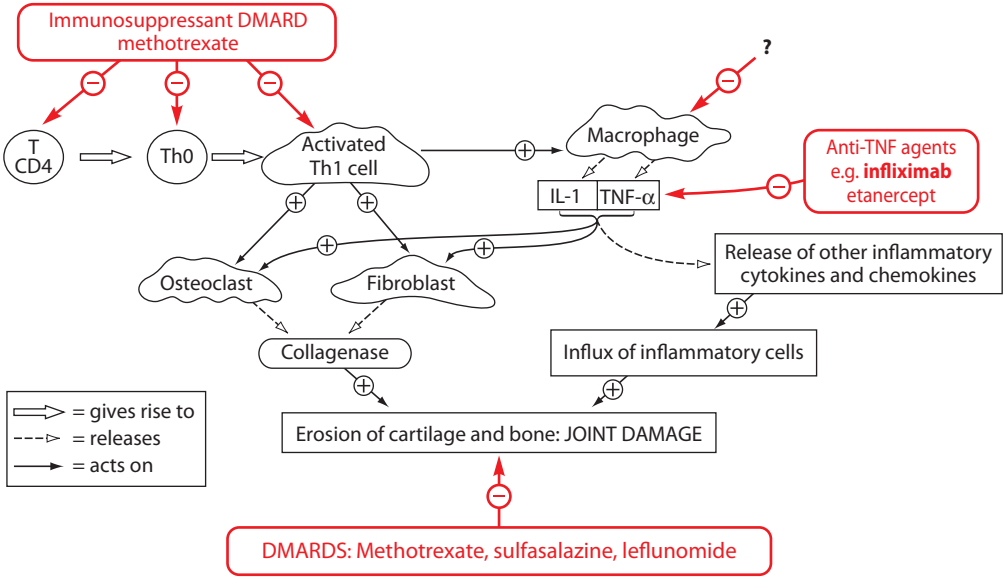
Adverse effects Nausea, vomiting, headache, upper respiratory tract infections with cough. Because of inactivation of macrophages latent TB and other conditions (e.g. hepatitis B) could be reactivated. Blood dyscrasias can occur. Antibodies against infliximab may be produced.

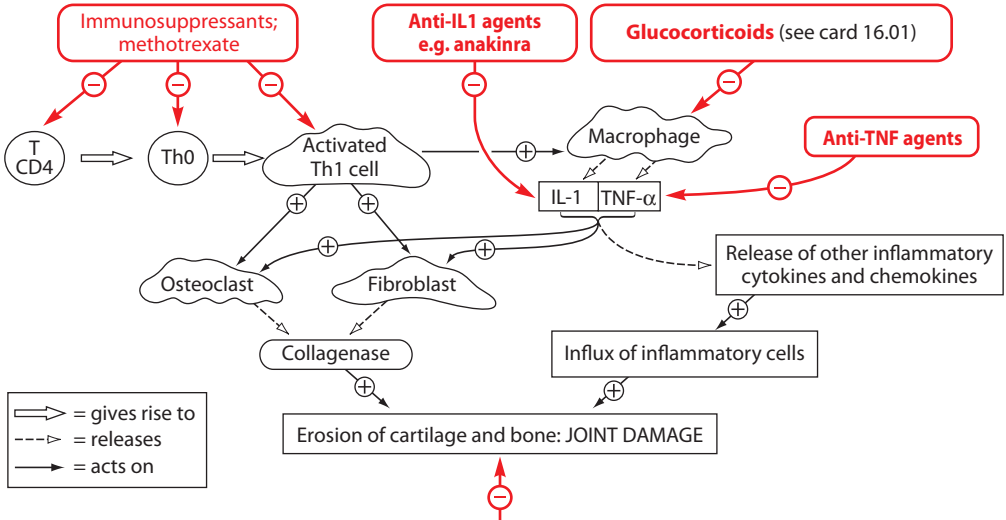
Similar drugs *Adalimumab* is also an anti-TNF-α antibody (half-life 10–20 days, MTX reduces clearance). *Etanercept* another anti-TNF-α antibody (given subcut. twice a week; half-life ~5 days).

R&D 7e Ch 26, p 330

What group of drugs inhibits mediator release from the macrophage?

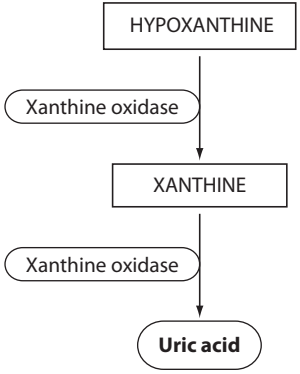
The figure shows the pathophysiology of rheumatoid joint damage




Immunosuppressants; methotrexate
Anti-IL1 agents e.g. anakinra
Glucocorticoids (see card 16.01)
T CD4
Th0
Activated Th1 cell
Macrophage
Anti-TNF agents
IL-1
TNF-α
Osteoclast
Fibroblast
Release of other inflammatory cytokines and chemokines
Collagenase
Influx of inflammatory cells
= gives rise to
= releases
= acts on
Erosion of cartilage and bone: JOINT DAMAGE
DMARDS: Methotrexate, sulfasalazine, leflunomide, anticytokine agents, gold compounds (auranofin, aurothiomalate), hydroxychloroquine, penicillamine

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.

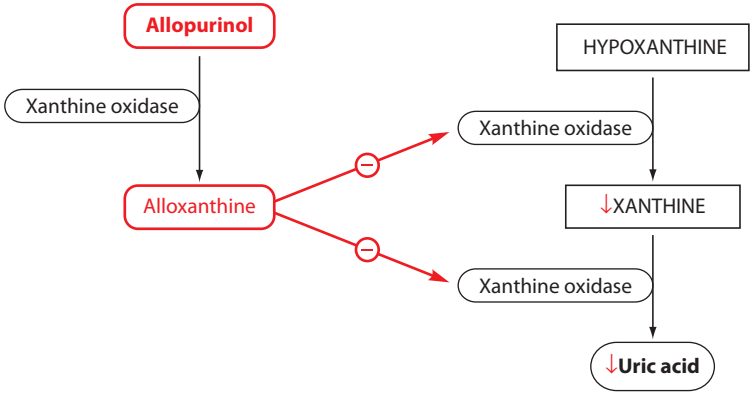
Special points Allopurinol is not used to treat acute attacks of gout – these are treated with NSAIDs. Allopurinol interferes with the metabolism of oral anticoagulants and can increase the effect of azathioprine and cyclophosphamide.

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.

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 B_4.

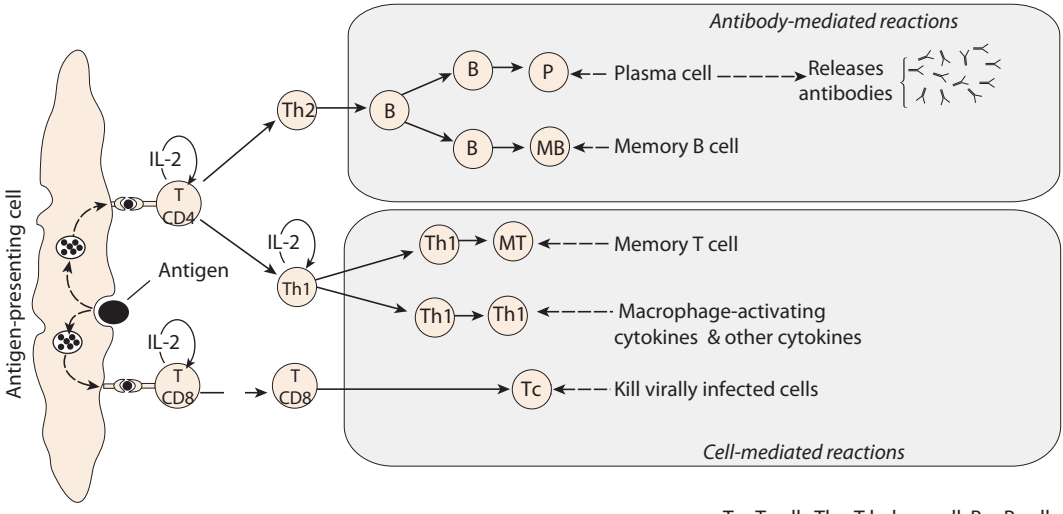
Abs/Distrb/Elim Given orally, well-absorbed; half-life 9h.

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.

R&D 7e Ch 26, p 332; D&H 2e Ch 16, p 43



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 × that in the plasma. Metabolised in the liver by the P450 3A enzyme system.

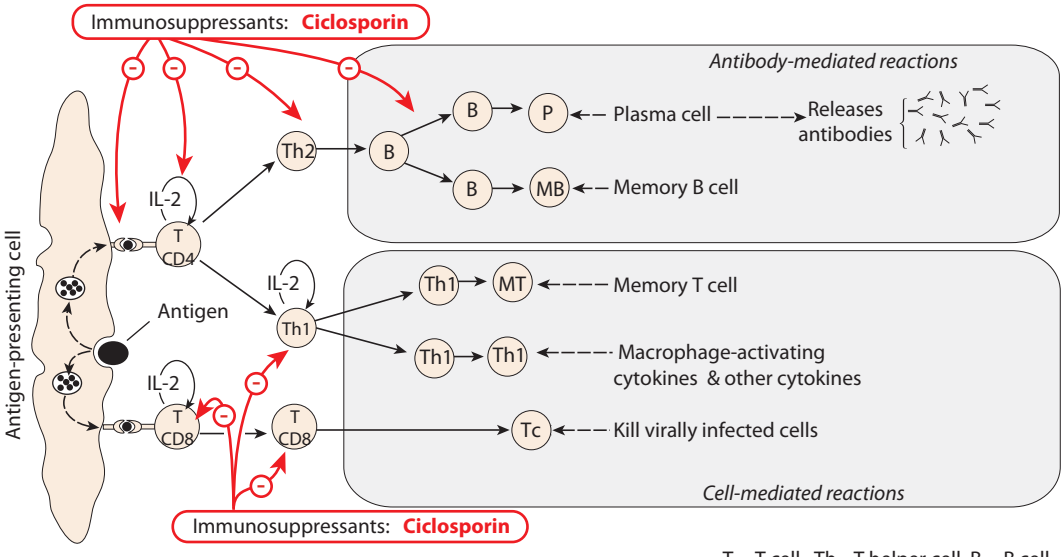
Clinical use Used to prevent rejection of organ and tissue transplants & for prevention of graft v host disease. Can be useful in autoimmune diseases. Often used in combination with glucocorticoids or methotrexate.

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



T = T cell, Th =T helper cell, B = B cell

Azathioprine

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.

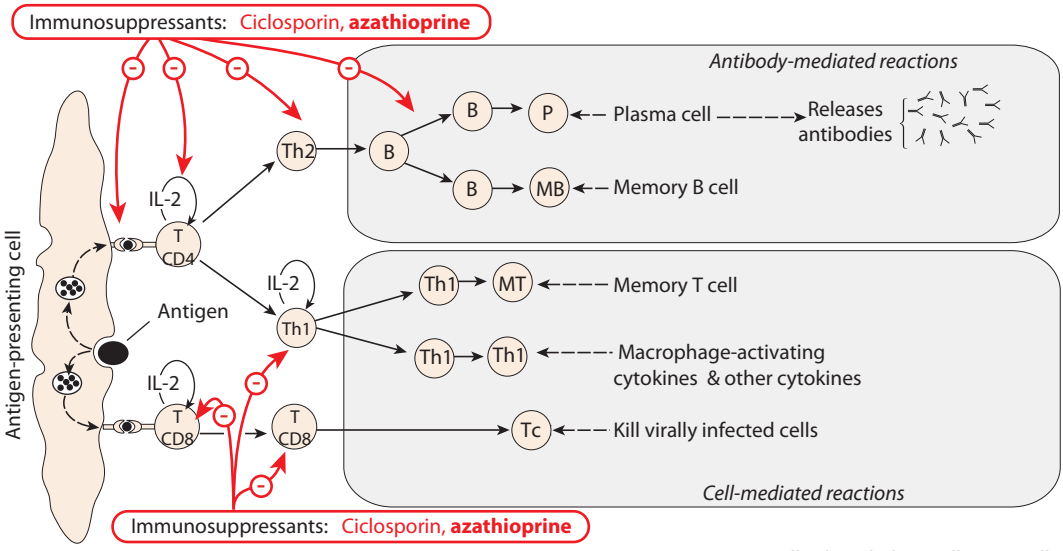
Abs/Distrb/Elim Given orally or by i.v. infusion. Metabolised to mercaptopurine (mcp) which is the cytotoxic moiety acting by interfering with purine nucleotide metabolism. Mcp is inactivated by xanthine oxidase.

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.

R&D 7e Ch 26, p 330; D&H 2e Ch 17, pp 44-45



T = T cell, Th =T helper cell, B = B cell

Mycophenolate mofetil

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).

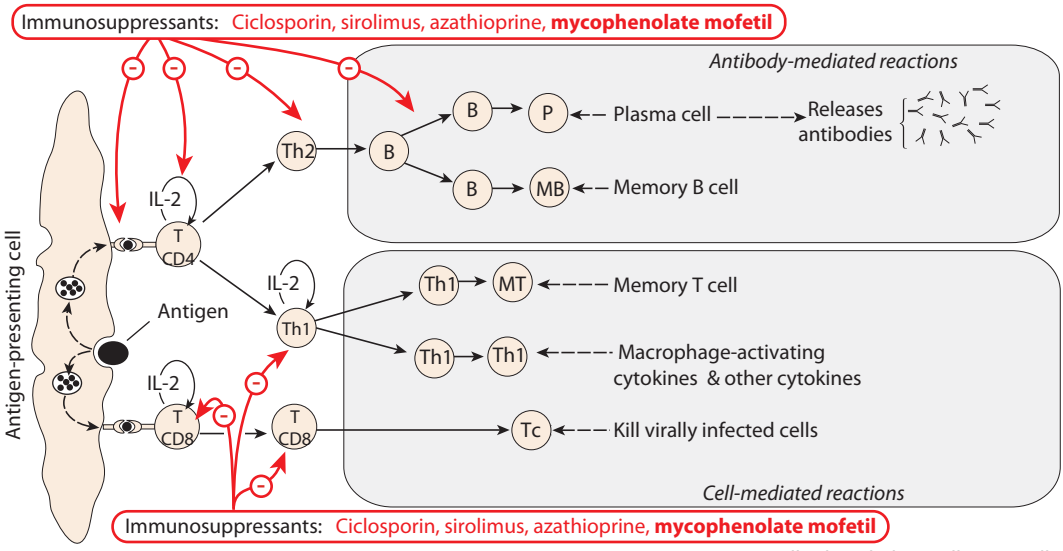
Abs/Distrb/Elim Given orally or by i.v. infusion. Metabolised to mycophenolic acid which is the active moiety which interferes with purine nucleotide metabolism.

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



T = T cell, Th =T helper cell, B = B cell

Sirolimus

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.

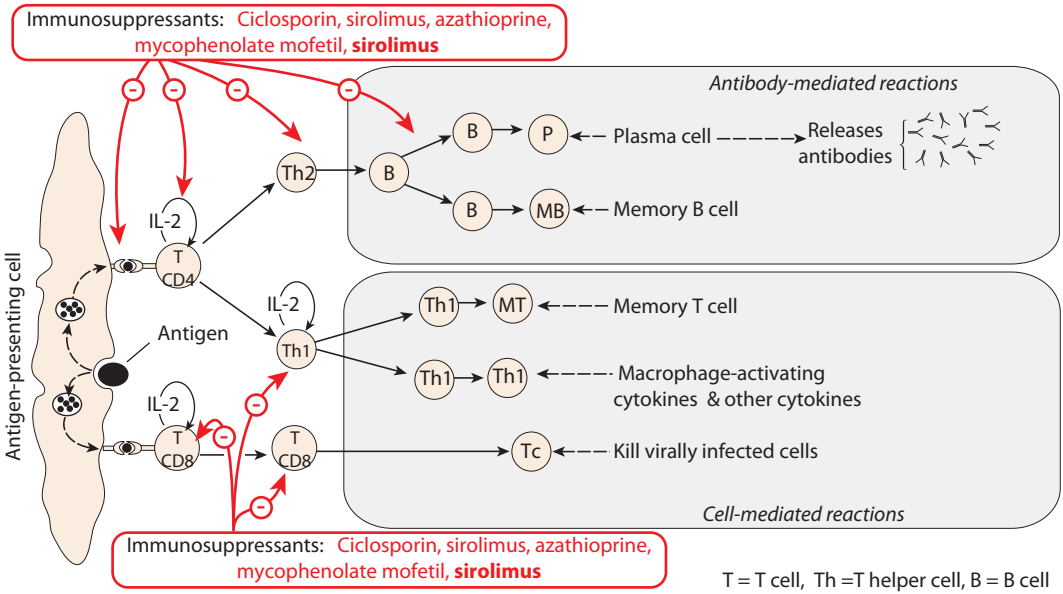
Abs/Distrb/Elim Given orally; metabolised by P450 3A in the liver – therefore many drug interactions.

Clinical use Used to prevent rejection of organ transplants (particulary 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.

R&D 7e Ch 26, p 329; D&H 2e Ch 17, pp 44-45



T = T cell, Th =T helper cell, B = B cell

Prednisolone

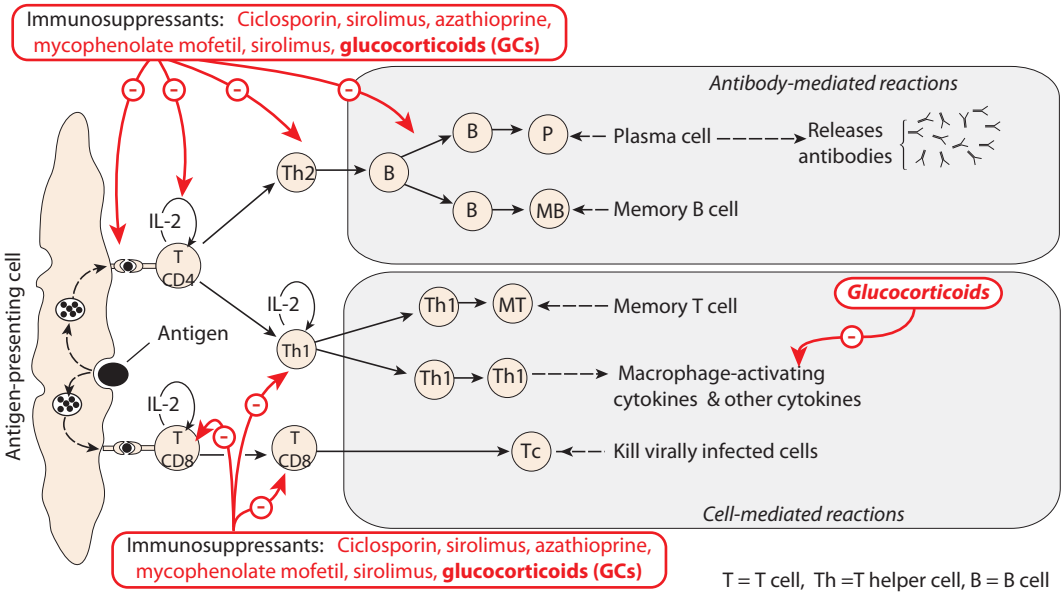
Actions Inhibits clonal proliferation of T & B cells and macrophage activation.
(Other actions : reduction in chronic inflammation, autoimmune and hypersensitivity reactions; various metabolic effects; negative feedback action on ant. pituitary and hypothalamus. (see card 16.01)

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 syndome (see card 16.03 for pictorial expression of Cushing's syndrome).



T = T cell, Th =T helper cell, B = B cell

Cetirizine

Actions Inhibits H_1-receptor actions and thus reduces immediate hypersensivity reactions.

MOA Competitive inhibitor of histamine at H_1-receptors on smooth muscle.

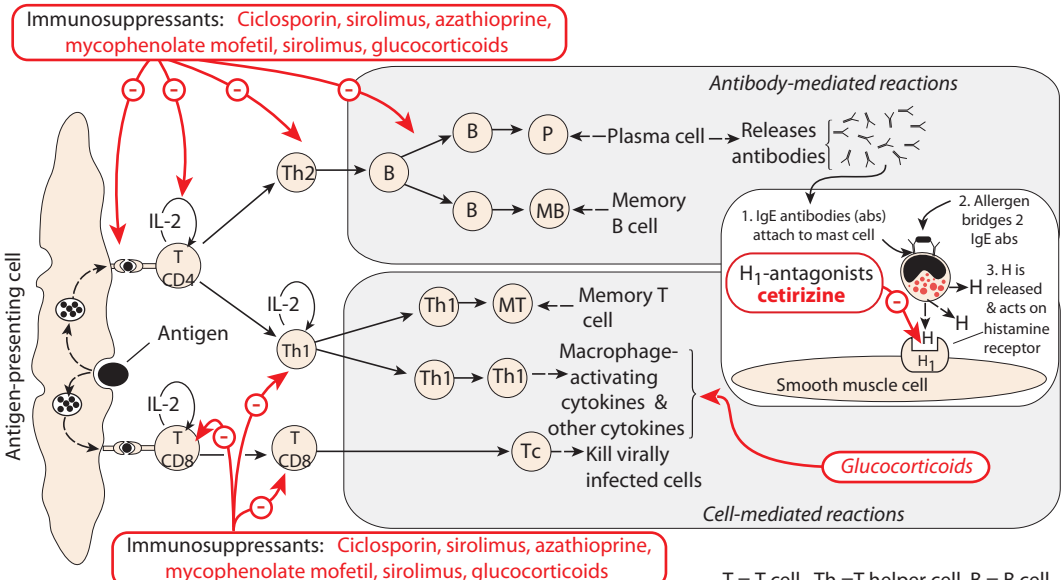
Abs/Distrb/Elim Given orally well absorbed, doesn't cross the blood–brain barrier, metabolised in the liver , excreted in the urine.

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.

R&D 7e Ch 26, p 333t; D&H 2e Ch 17, pp 44-45



T = T cell, Th =T helper cell, B = B cell

Promethazine

Actions Inhibits H_1-receptor actions and thus reduces immediate hypersensitivity reactions; has anticholinergic action, some local anaesthetic action, weak α-adrenoceptor antagonism and fairly marked sedative effect.

MOA Competitive inhibitor of histamine at H_1-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.

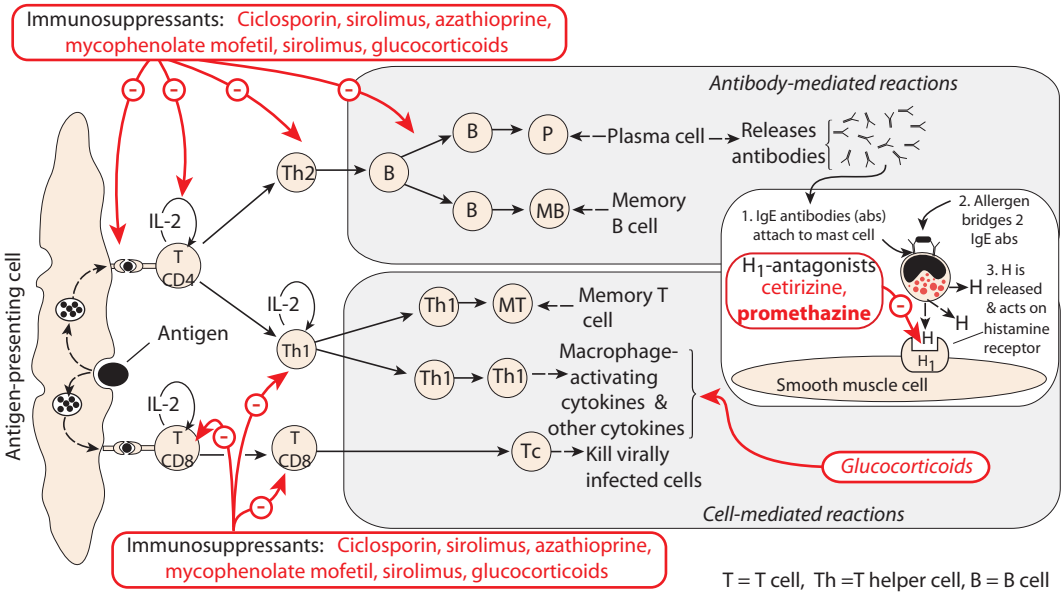
Clinical use Hypersensitivity reactions – hay fever, urticaria; premedication; sedation; emergency treatment of anaphylaxis; motion sickness.

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

Special points Injection can be painful.

R&D 7e Ch 26, p 333t; D&H 2e Ch 17, pp 44-45

What antihistamines are used for motion sickness?



T = T cell, Th =T helper cell, B = B cell

Antihistamines

Promethazine (as specified on cards 4.07 & 14.08)

Cyclizine

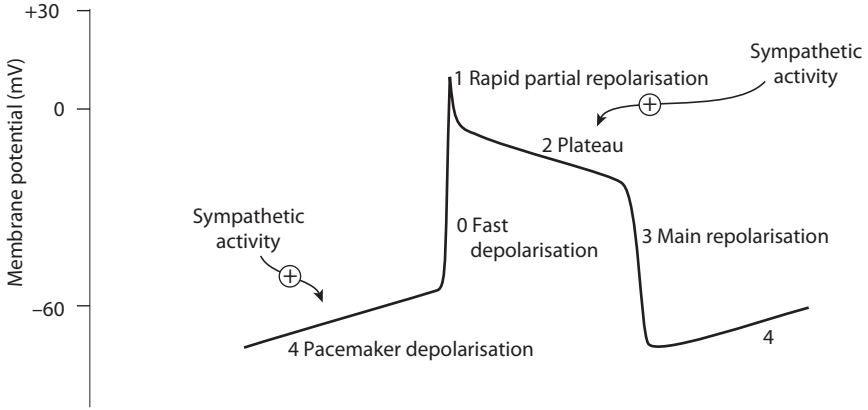
Cinnarizine

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.



Disopyramide

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).

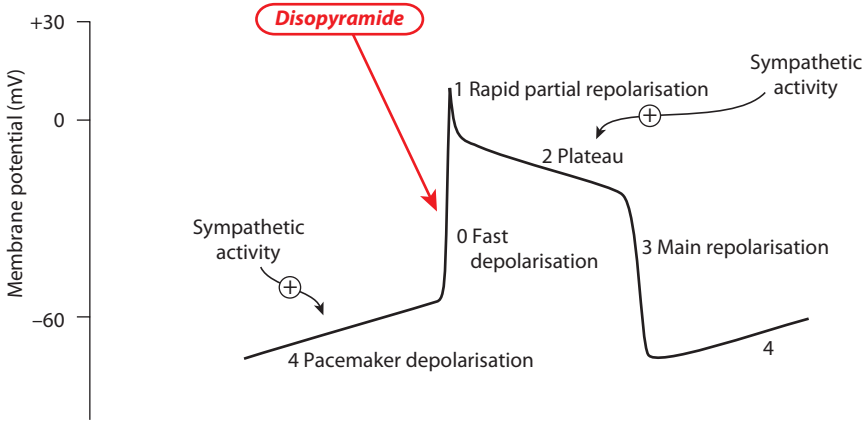
Abs/Distrib/Elim Oral and i.v. admin. $T_{0.5}$ 5–10h. Half is excreted unchanged by kidney; half is metabolised in liver.

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.

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.

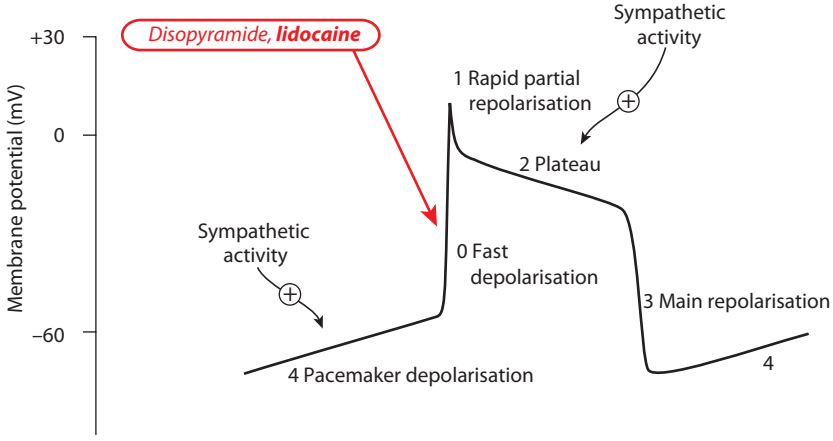
Abs/Distrib/Elim Given i.v. (Very high first-pass metabolism precludes oral admin.).
Short $T_{0.5}$ – 2h. Subject to cytochrome P450 metabolism. Mexiletine and tocainide are orally active.

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.



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 Ia or Ib agents.

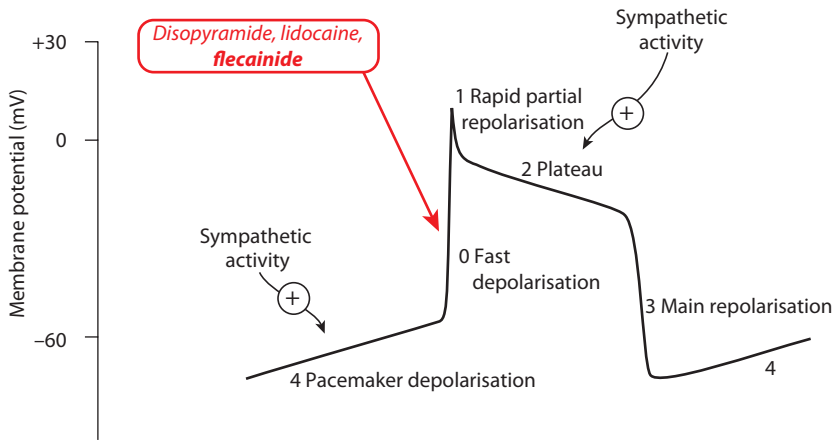
Abs/Distrib/Elim Oral admin. $T_{0.5}$ 20h. Mostly excreted unchanged in urine. Propafenone is metabolised more rapidly by the liver and has a shorter $T_{0.5}$ (5–10h).

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

Adverse effects Increases likelihood of dysrhythmia. May **increase mortality** due to ventricular fibrillation post infarction. Needs careful use. Avoid in patients with structural heart disease. Negative inotropic action.

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.

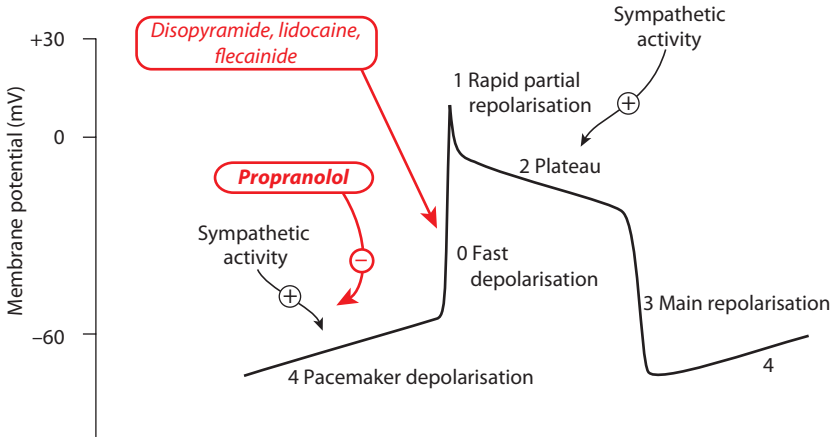
Abs/Distrib/Elim Oral admin. $T_{0.5}$ s: propranolol – 4h, atenolol – 6h, esmolol – 10min.

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 β-adrenoceptors so has class I and class II actions. Sotalol also has class II actions.

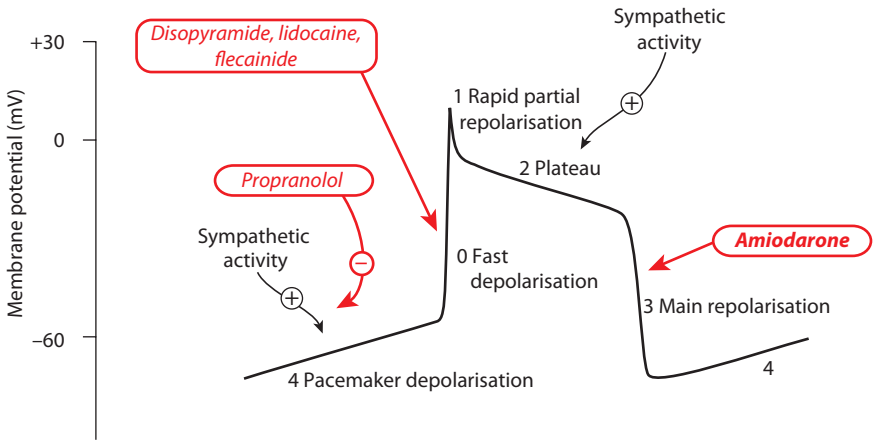
Abs/Distrib/Elim Long acting; extensive tissue binding, $t_{½}$ several weeks. Sotalol and ibutilide have half-lives of 5–10h.

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.

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.



Verapamil

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 tachyarrythmias. Decreases automaticity and slows AV conduction.

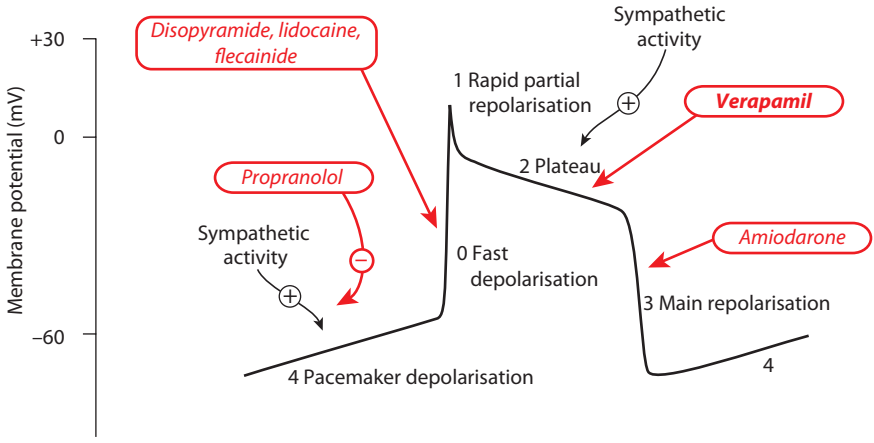
Abs/Distrib/Elim Oral (less commonly i.v.) admin. $t_{½}$ 6–8h.

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.



Adenosine

Actions Antidysrhythmic.

MOA Activates G-protein-coupled adenosine receptors. Action (on A_1 receptors) is due to inhibition of Ca^{2+} 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.

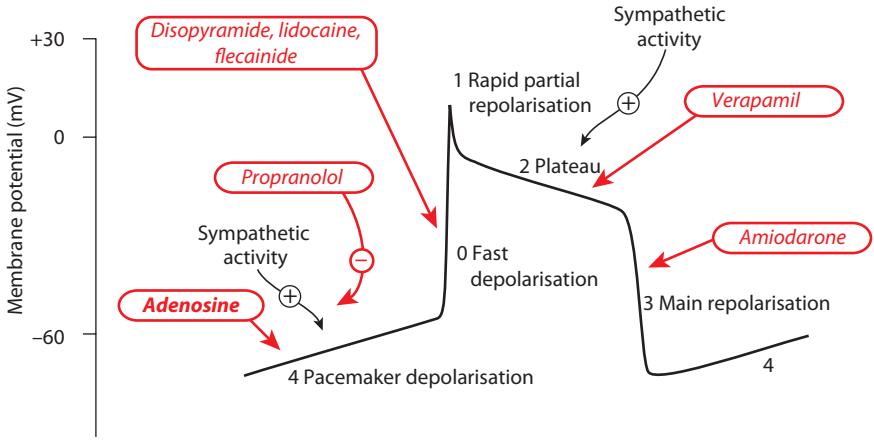
Abs/Distrib/Elim Given i.v. Short duration of action. $T_{0.5}$ 10secs.

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.

R&D 7e Ch 21, p 258; D&H 2e Ch 18, pp 46-47

Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.



Magnesium sulfate

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.

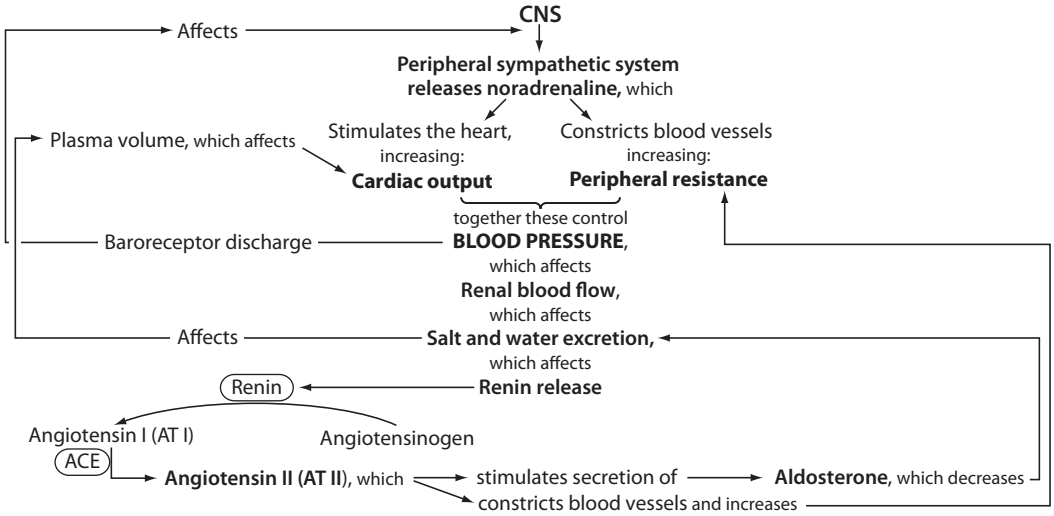
Abs/Distrib/Elim Given i.v.

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.



Captopril

Actions Lowers blood pressure by decreasing vasoconstrictor tone, also by reducing cardias 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.

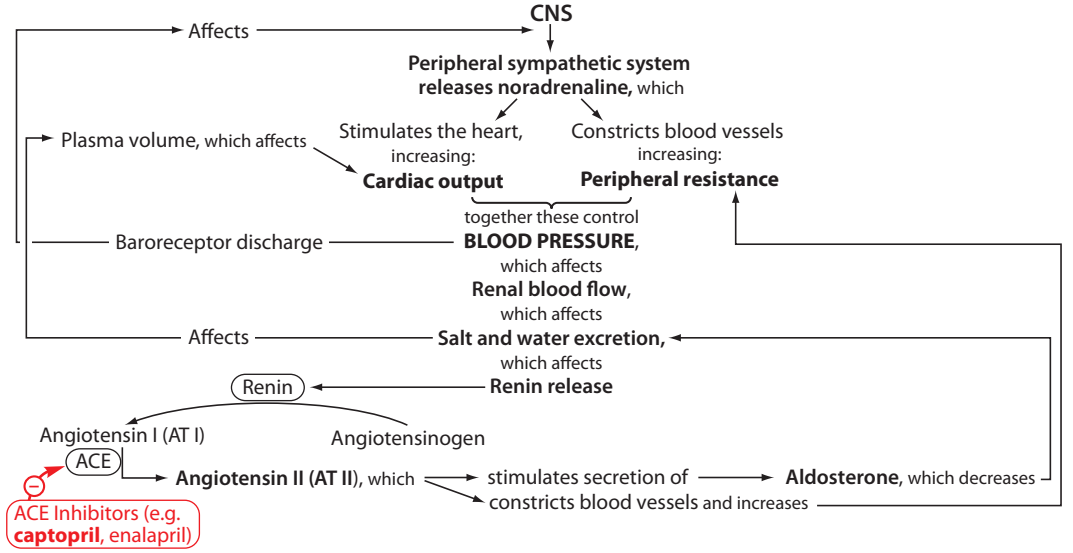
Clinical use Hypertension; heart failure; ventricular dysfunction following myocardial infarction; diabetic nephropathy.

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 angiooedema 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.



Losartan

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.

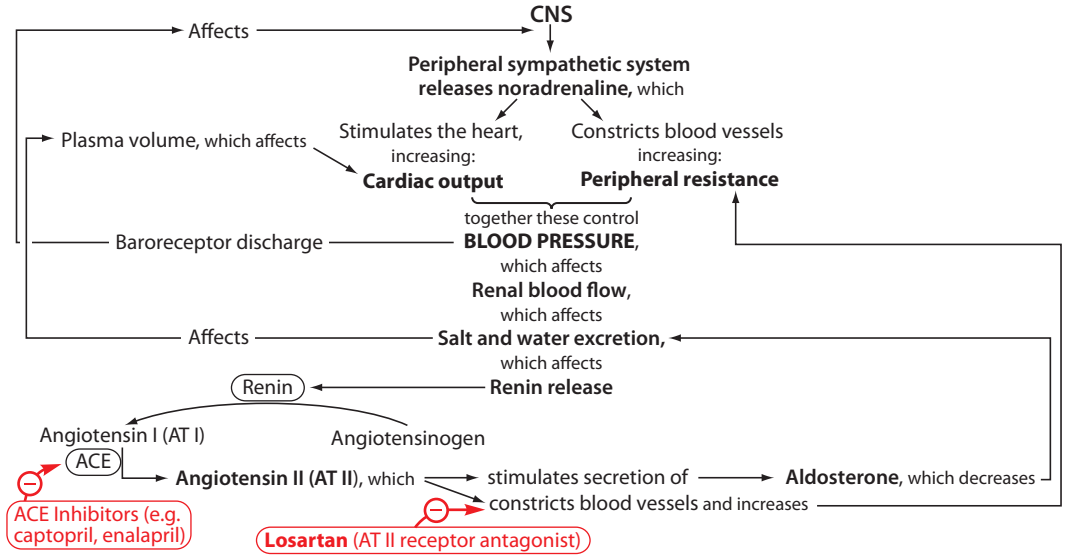
Clinical use Hypertension; congestive heart failure; nephropathy.

Adverse effects Hypotension, dizziness. Hyperkalaemia can occur.

Special points Doesn't cause the dry cough or angioedma seen with the ACE inhibitors.

R&D 7e Ch 22, pp 275-276; D&H 2e Ch 19, pp 48-49

The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension.



Amlodipine

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).

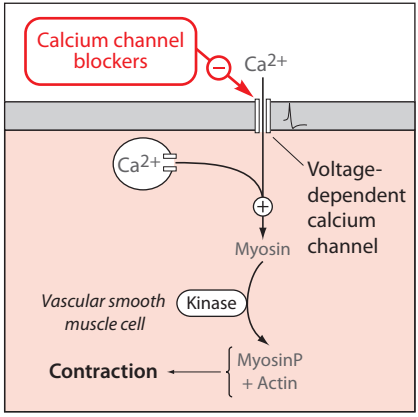
MOA Block voltage-gated calcium channels in vascular smooth muscle inhibiting calcium influx and thus contraction.

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.

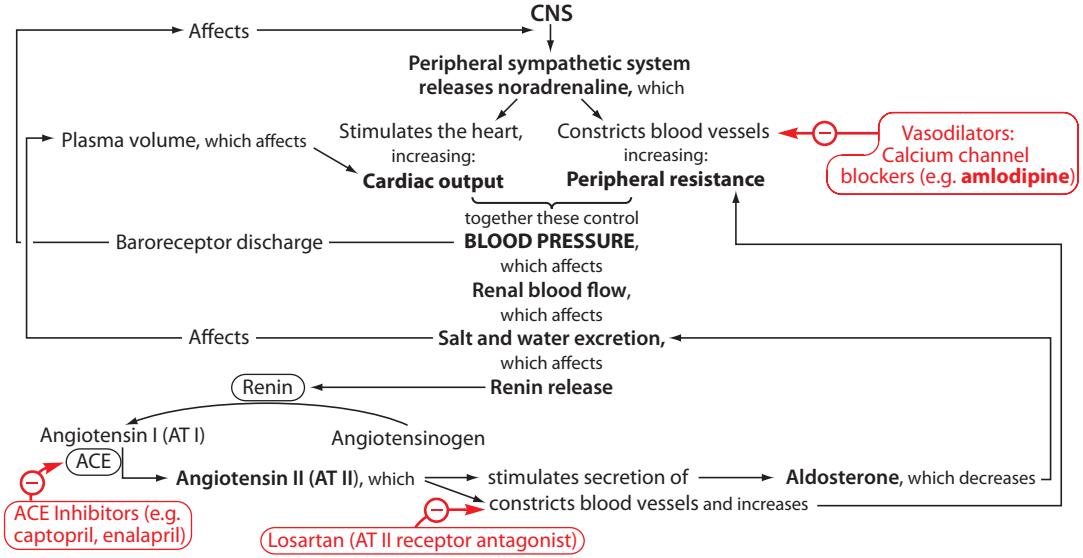
Adverse effects Nifedipine & amlodipine: reflex tachycardia, hypotension and headache due to vasodilatation.

Special points Grapefruit juice increases the effects.



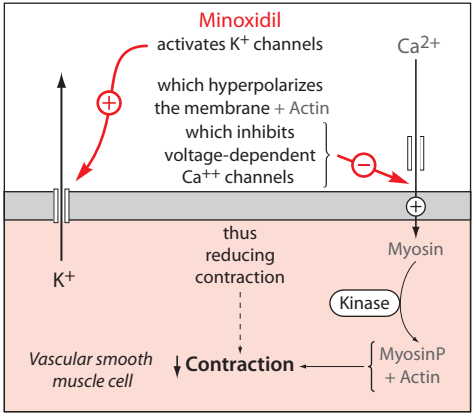
R&D 7e Ch 21, pp 262-263; D&H 2e Ch 19, pp 48-49

The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension.



Actions Marked long-lasting vascular dilatation; lowers blood pressure.

MOA ----------→



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

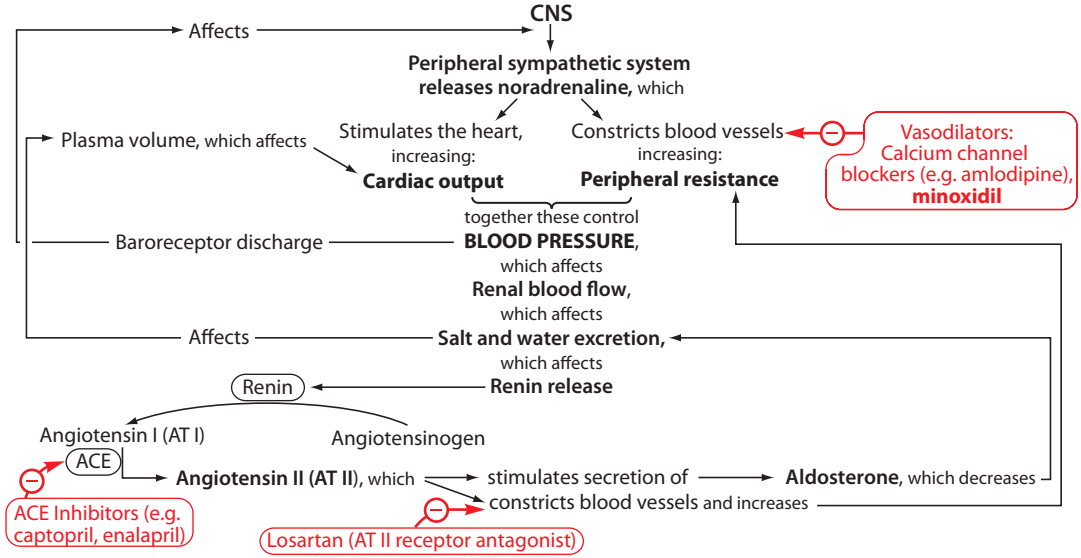
Clinical use Very severe hypertension.

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.

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.



Actions Relaxes arterial smooth muscle lowering blood pressure.

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

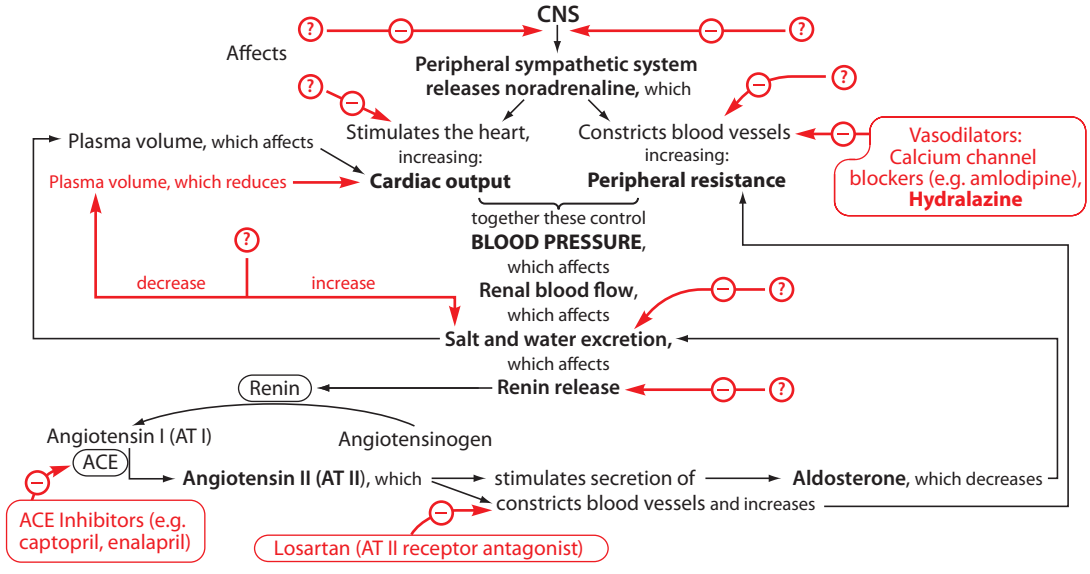
Abs/Distrb/Elim Given orally. Half-life ~ 1-3h.

Clinical use Very severe hypertension – particularly in pregnancy.

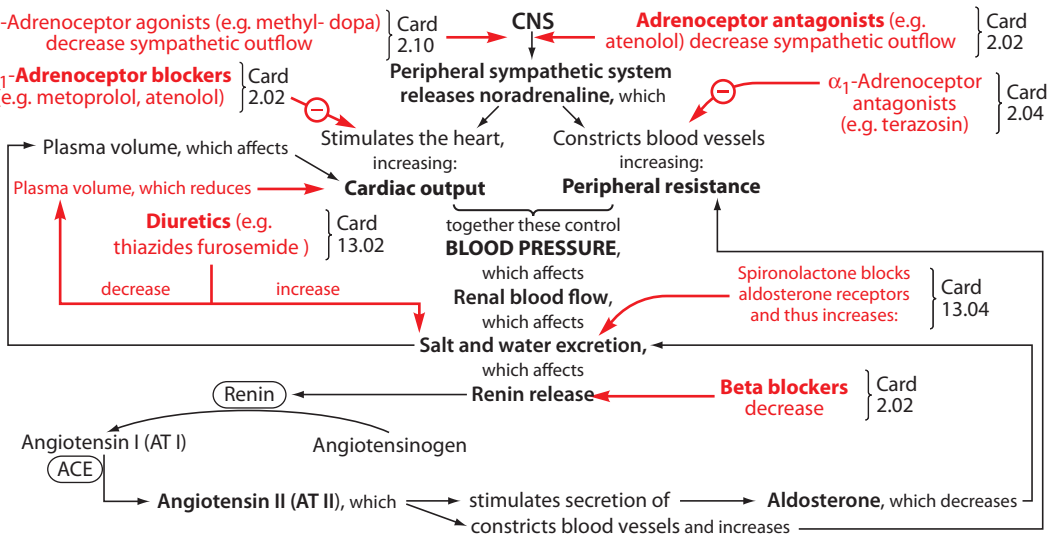
Adverse effects Palpitations, hypotension, GIT disturbances, dizziness, allergic reactions (which can be severe with long-term use)

R&D 7e Ch 22, p 273; D&H 2e Ch 21, p 55

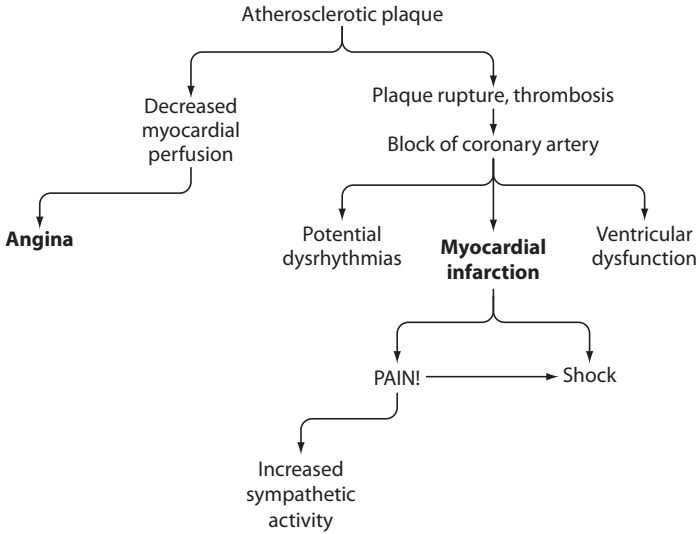
The figure shows the homeostatic mechanisms controlling blood pressure. Various pathological factors can disturb the homeostasis and cause hypertension. Important drugs in bold.



Important drugs in bold. For details see the cards specified



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.

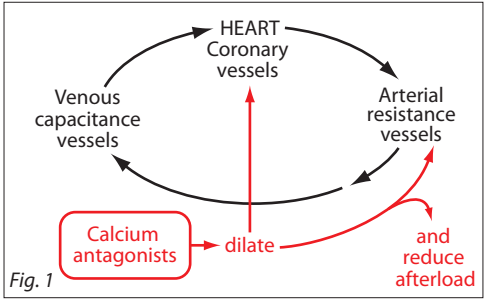


Fig. 1

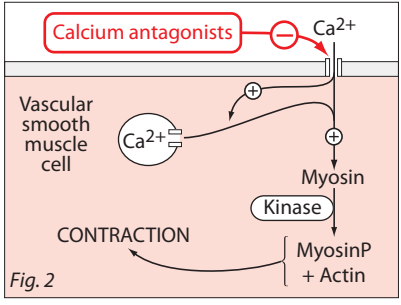


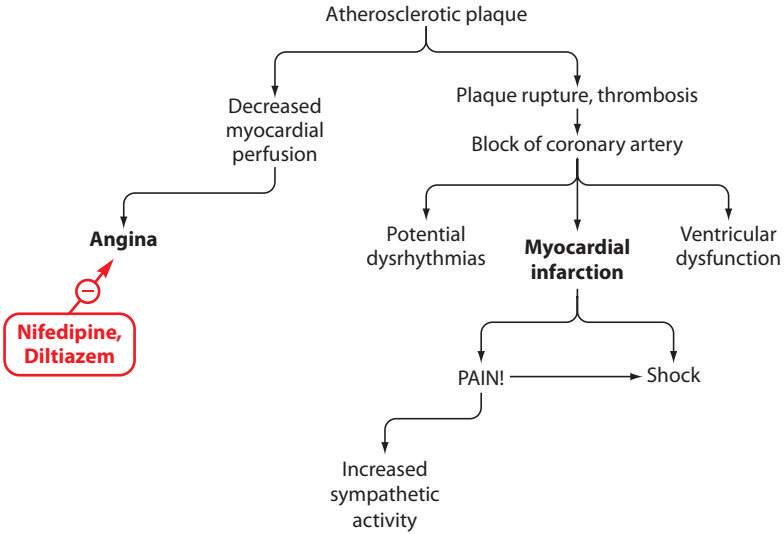
Fig. 2

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.

The figure below outlines the pathophysiology of angina and myocardial infarction



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.

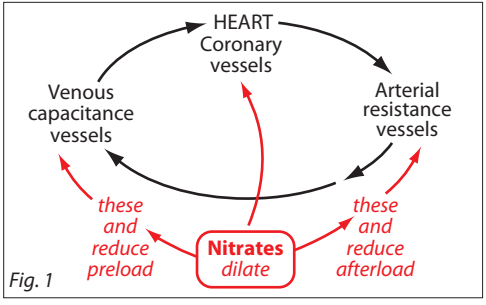


Fig. 1

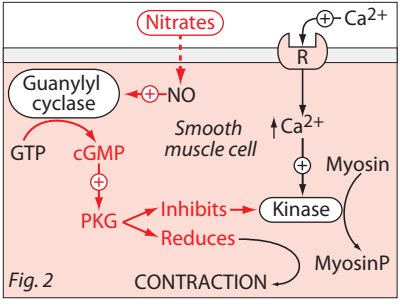


Fig. 2

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).

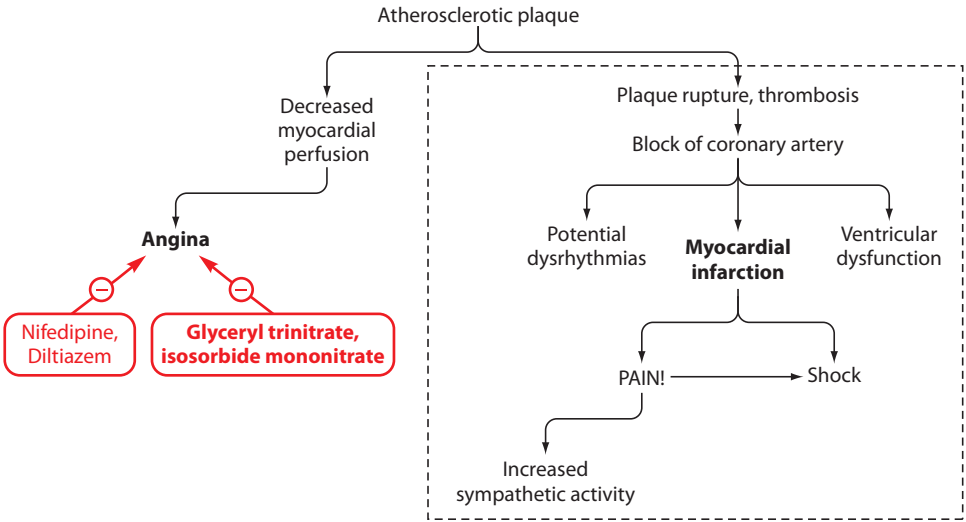
Adverse effects Headache due to vasodilatation; postural hypotension due to ↓vasomotor tone; prolonged usage leads to tolerance; methaemoglobinaemia (rare) with continued high doses.

R&D 7e Ch 21, pp 260-261; D&H 2e Ch 20, pp 50-52

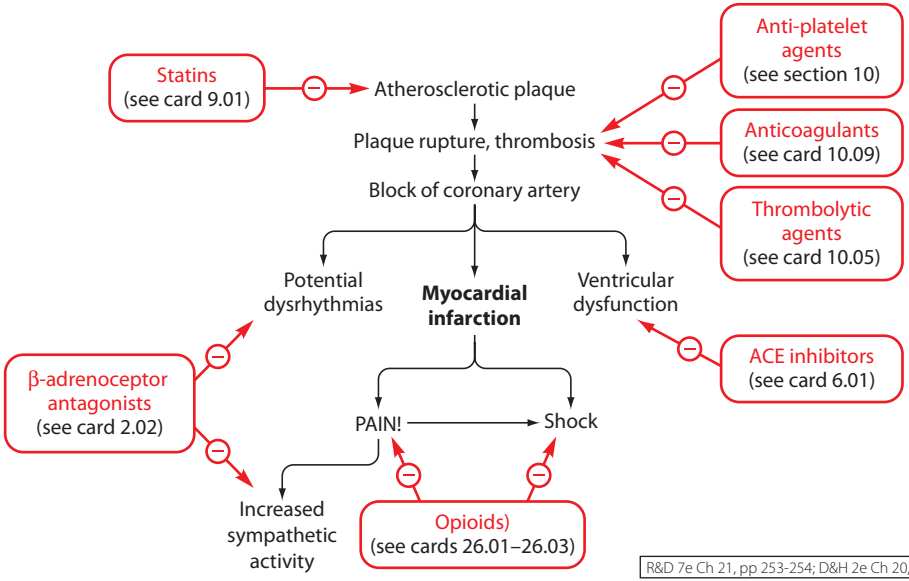
Angina and myocardial infarction

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

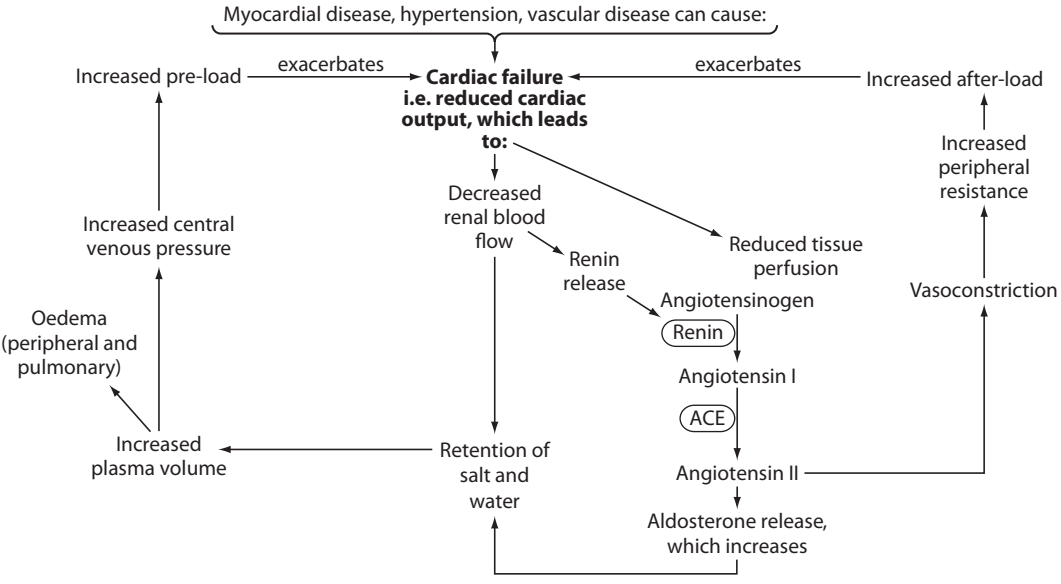


Myocardial infarction is a medical emergency requiring hospitalisation.



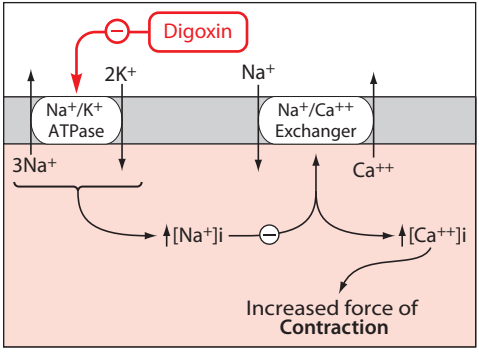
R&D 7e Ch 21, pp 253-254; D&H 2e Ch 20, p 52

The pathophysiology of heart failure – showing the autocatalytic (positive feedback) mechanisms



Actions Slows heart. Slows AV conduction. Prolongs AV node refractory period. Increases force of contraction in failing heart.

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



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

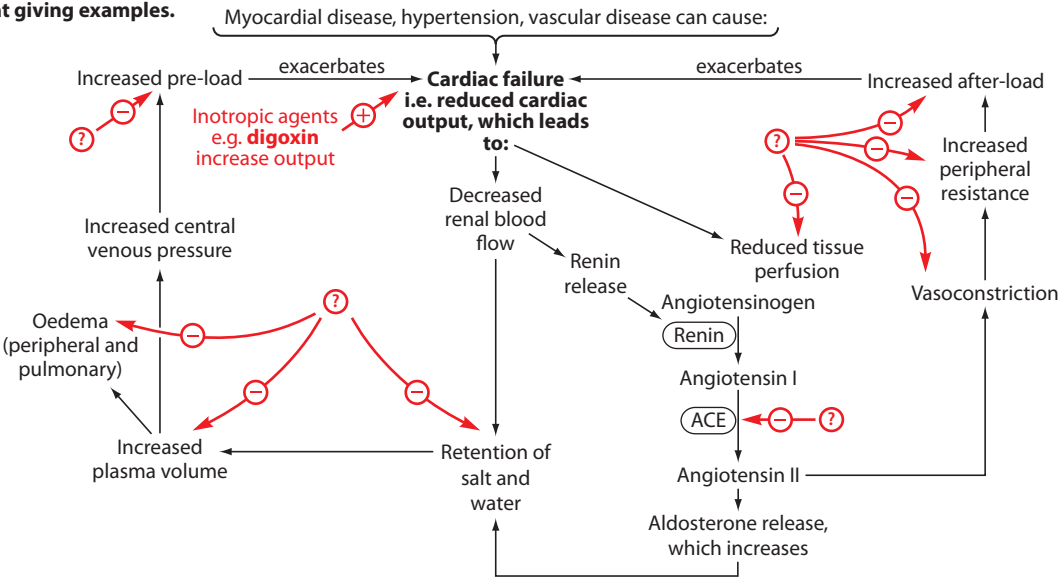
Clinical use Atrial fibrillation. Heart failure (if diuretics and ACE inhibitors haven't worked).

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

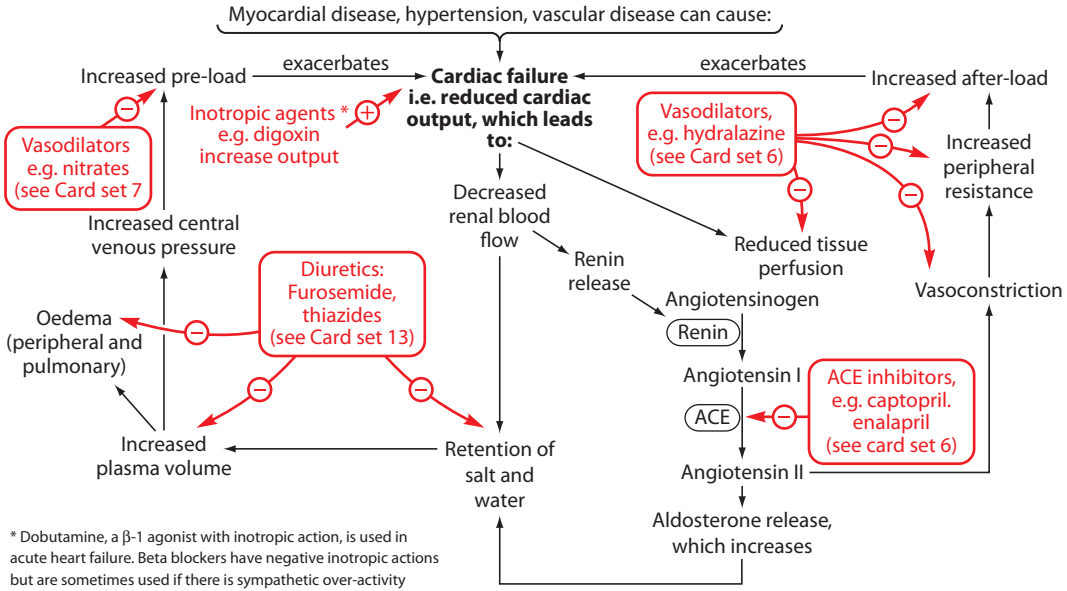
Special points Narrow margin between effective dose and toxic dose. Decreased plasma K^+ increases toxicity due to competition between K^+ and digoxin for the Na^+/K^+ ATPase.

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.



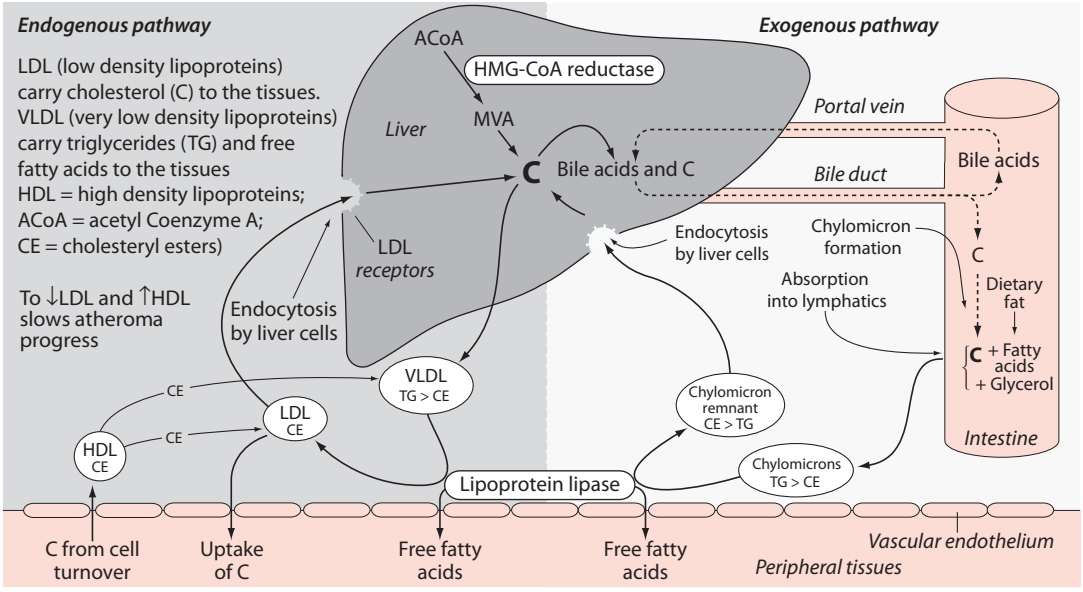
Drugs used in the treatment of heart failure



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

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

Cholesterol and lipoprotein metabolism



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.

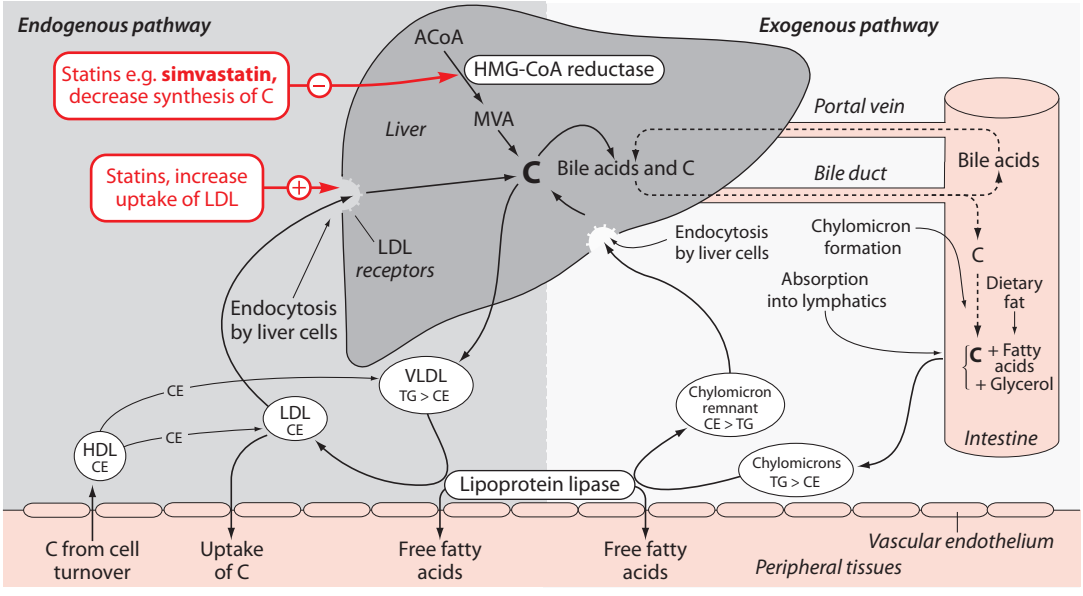
Clinical use Hypercholesterolaemia. Used to prevent atherosclerosis in patients with high C serum levels and to prevent cardiac infarction in patients who already have atherosclerosis.

Adverse effects Usually mild: muscle pain, GIT distubances, 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



Gemfibrozil

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.

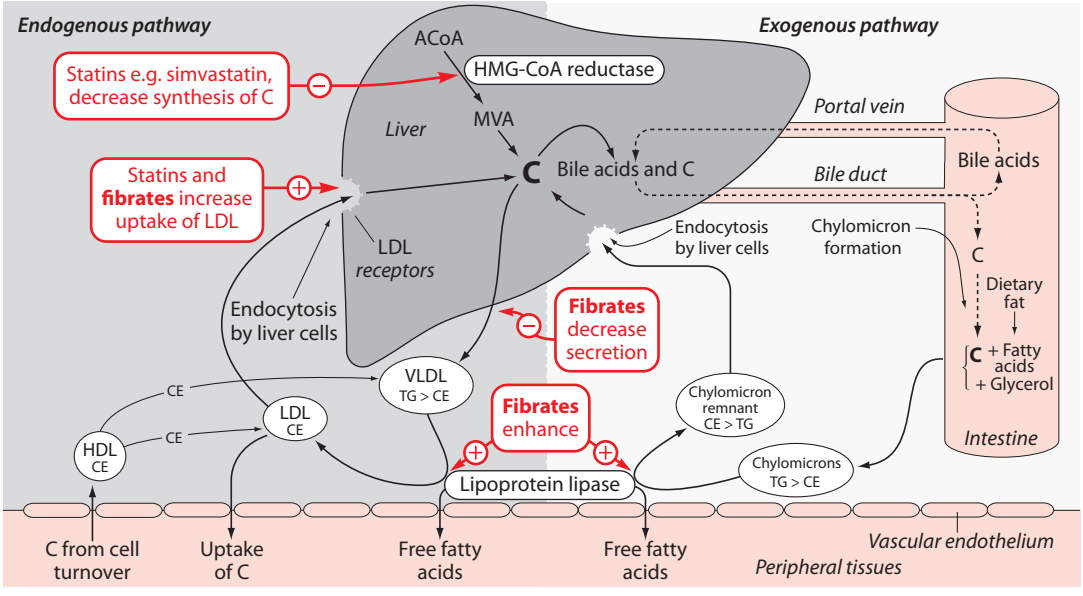
Clinical use Used for mixed dyslipidemia (i.e. ↑in both plasma TGs and C); also in cases with low HDL and thus ↑risk of atheroma.

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

Special points Avoid use of statins with fibrates.

R&D 7e Ch 23, p 290; D&H 2e Ch 22, pp 56-57

Cholesterol and lipoprotein metabolism



Ezetimibe

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.

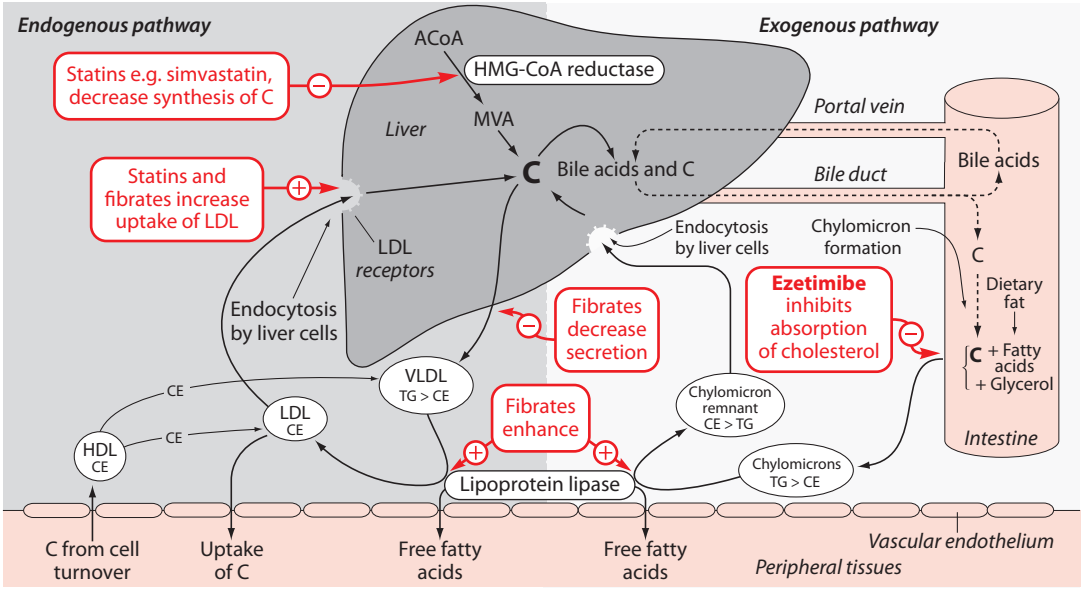
Clinical use Hypercholesterolaemia, usually as adjunct to a statin.

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.

R&D 7e Ch 23, p 291; D&H 2e Ch 22, pp 56-57

Cholesterol and lipoprotein metabolism



Colestyramine

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.

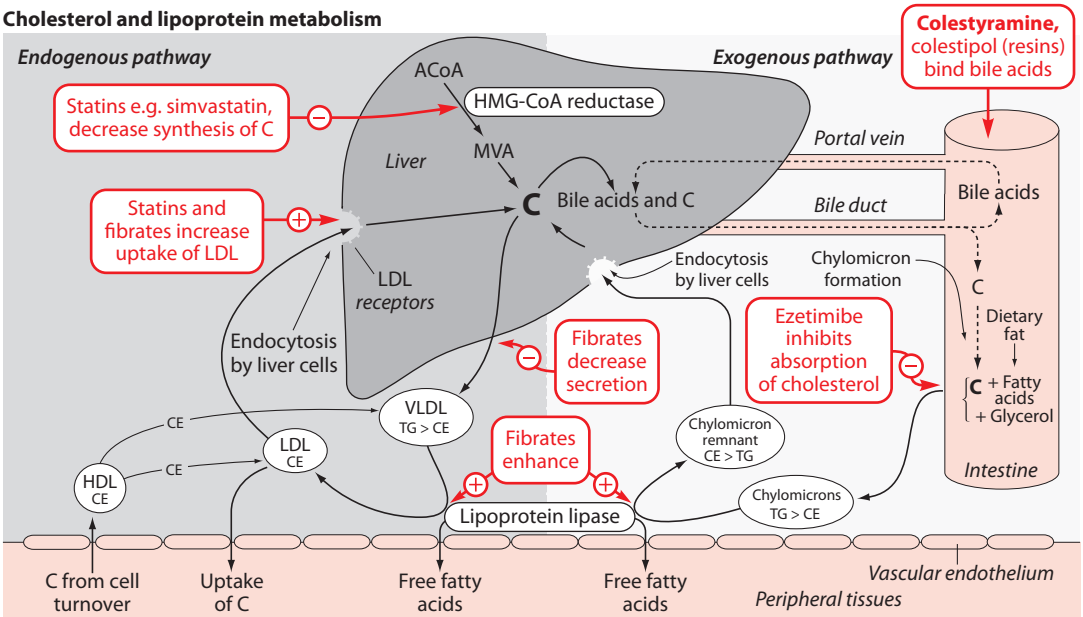
Clinical use Hypercholesterolaemia, often used with a statin.

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).

R&D 7e Ch 23, p 290-291; D&H 2e Ch 22, pp 56-57

Cholesterol and lipoprotein metabolism



A vitamin (B_3) 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.

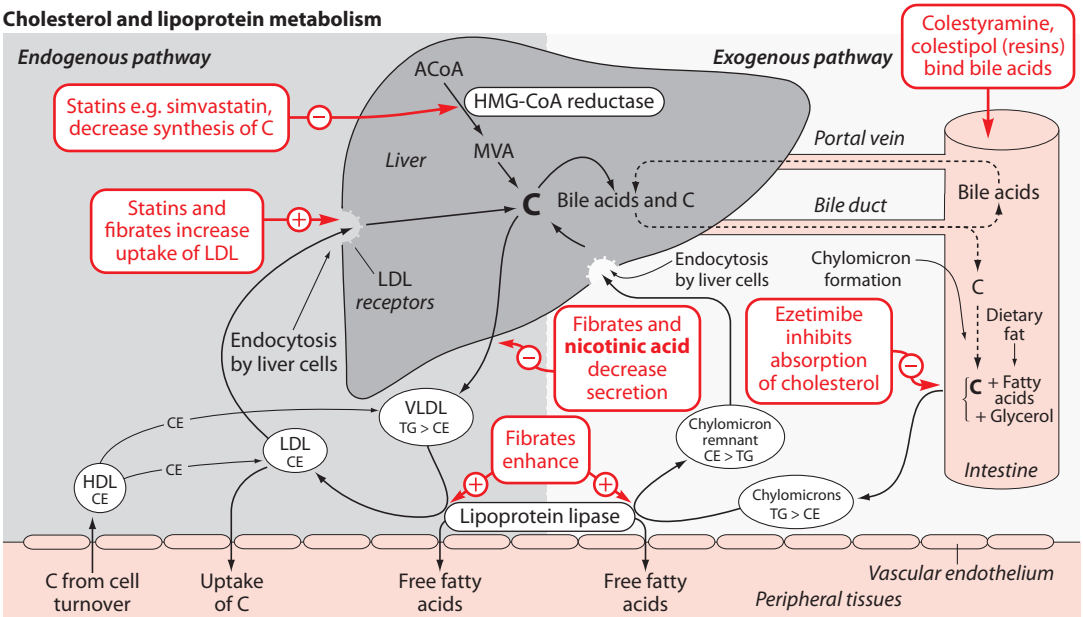
Clinical use As an adjunct to a statin in dyslipidaemia, or when a statin is contraindicated.

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.

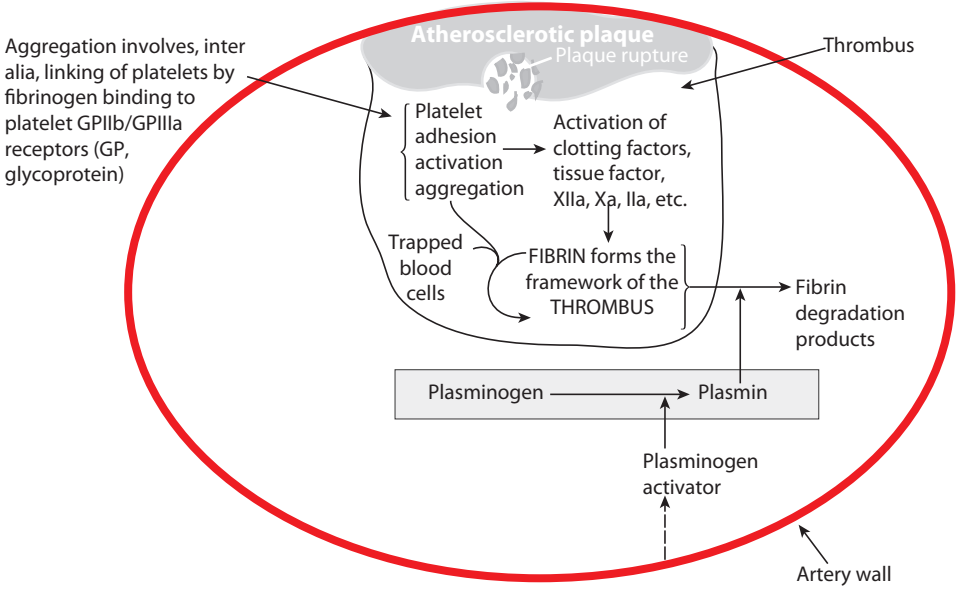
R&D 7e Ch 23, pp 291-292

Cholesterol and lipoprotein metabolism



Notes

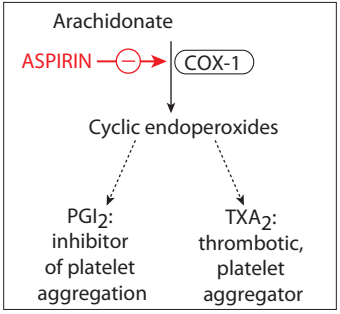
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



Aspirin

Actions Antiplatelet (also analgesic and anti-inflammatory).

MOA Irreversibly inactivates (COX-1); alters balance between TXA_2 and PGI_2 in the platelet/vascular endothelium axis.



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

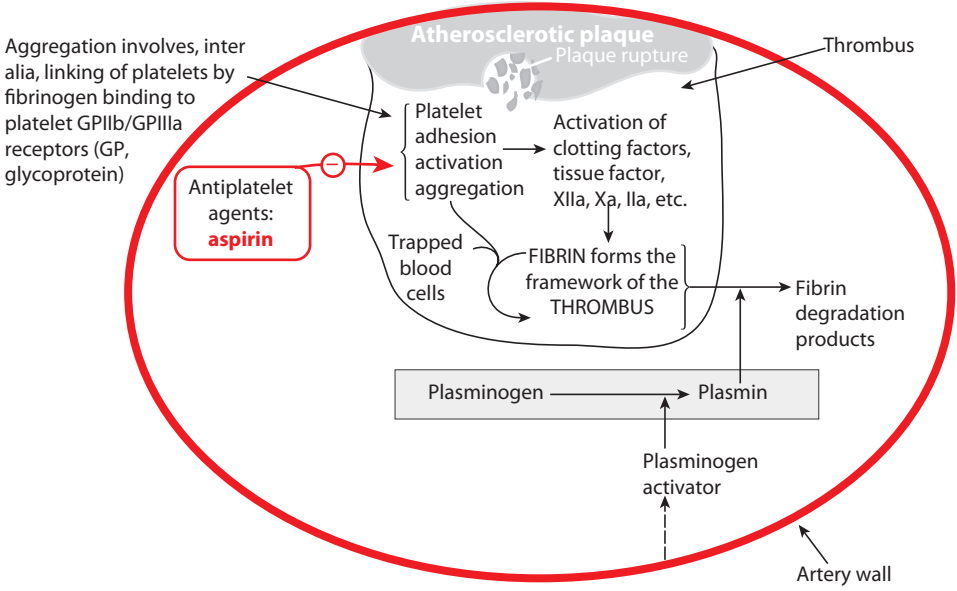
Clinical use in the context of thrombosis To reduce risk of myocardial infarction or transient ischaemic attacks; intermittent small doses given orally decrease platelet TXA_2 without significantly reducing endothelial PGI_2. Also used to treat acute stroke.

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.

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



Actions It prevents platelet activation.

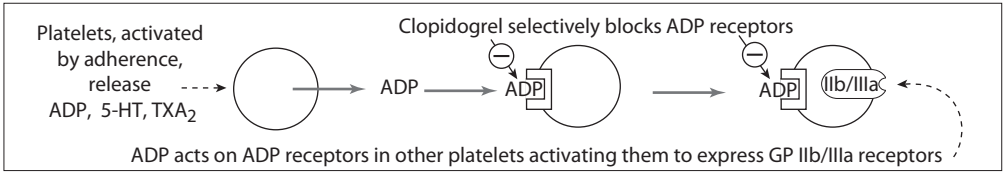
MOA It irreversibly inhibits the binding of ADP to the purine receptor on platelets thus inhibiting ADP-mediated platelet activation and interfering with GpIIb/IIIa-mediated platelet aggregation.

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.

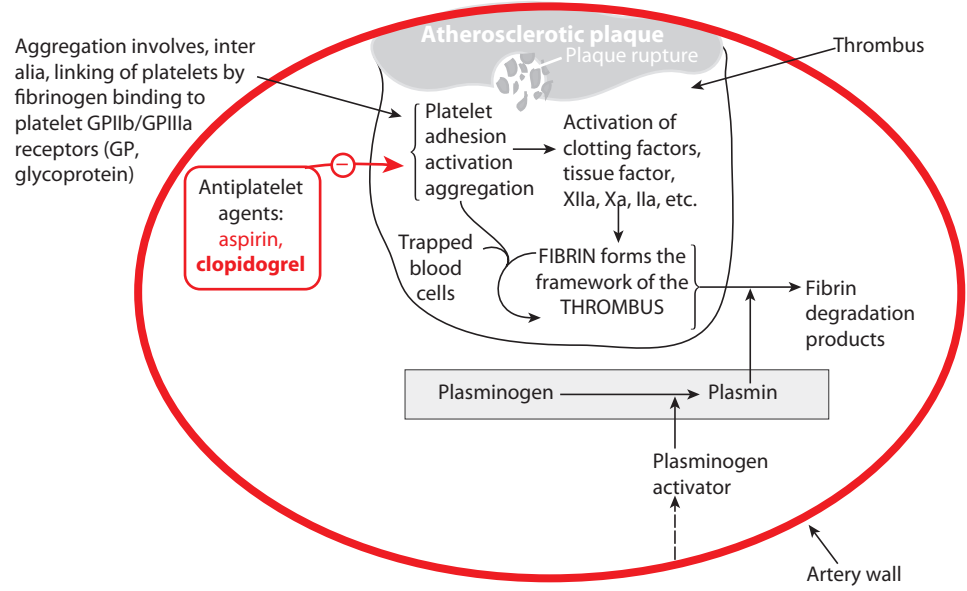
Adverse effects Unwanted effects: bleeding; GIT discomfort; rashes. Rarely neutropaenia.

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



R&D 7e Ch 24, pp 304-305; D&H 2e Ch 23, pp 58-59

The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



Abciximab

Actions It inhibits platelet activation.

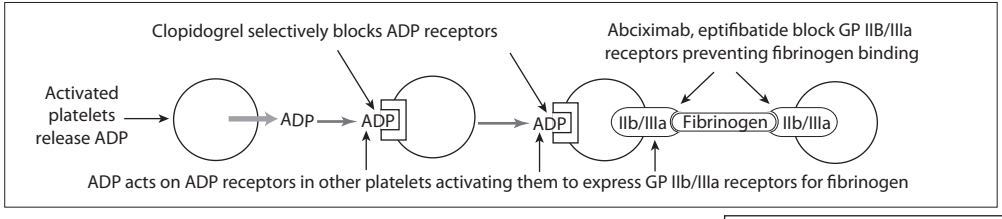
MOA Abciximab is a monoclonal antibody Fab fragment against the platelet GP IIb/IIIa receptor. It binds and inactivates the receptor preventing the binding of fibrinogen thus inhibiting platelet aggregation.

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.

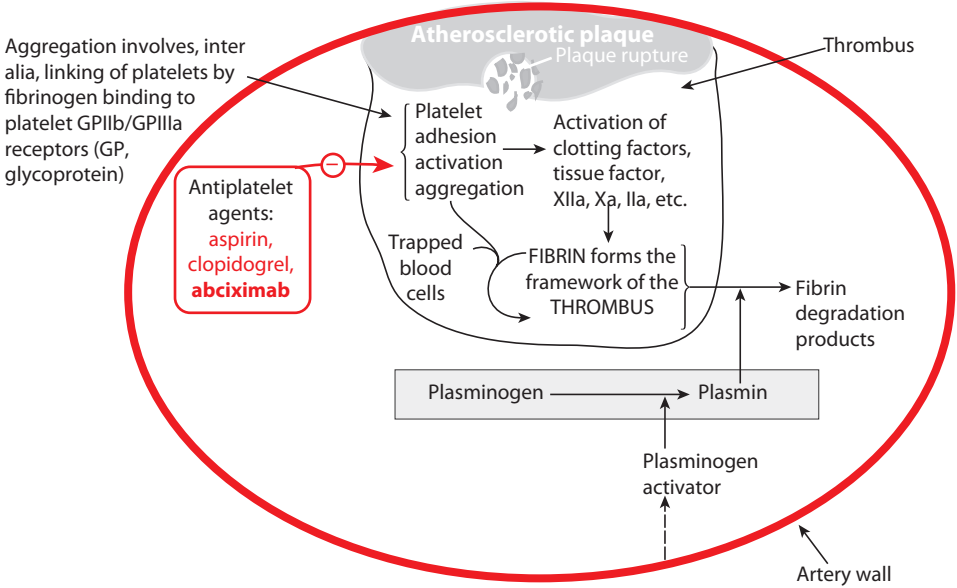
Adverse effects Bleeding; thrombocytopaenia.

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.



R&D 7e Ch 24, p 305; D&H 2e Ch 23, pp 58-59

The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



Dipyridamole

Actions It inhibits platelet aggregation.

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

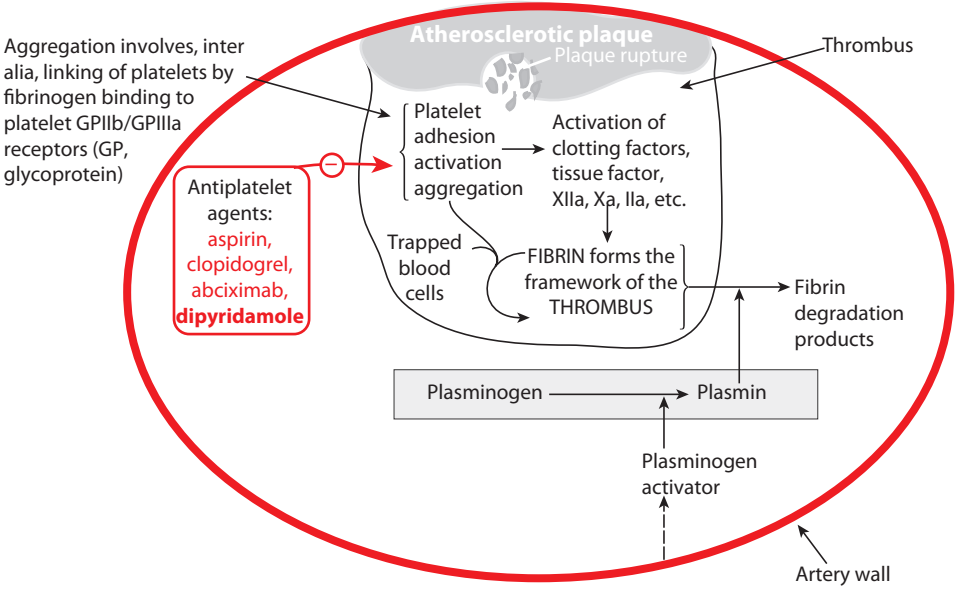
Abs/Distrib/Elim Given orally, usually as a modified release preparation.

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

Adverse effects Headache (common); GIT disturbances; hypotension, hypersensitivity reactions.

R&D 7e Ch 24, p 304; D&H 2e Ch 23, pp 58-59

The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



Alteplase

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.

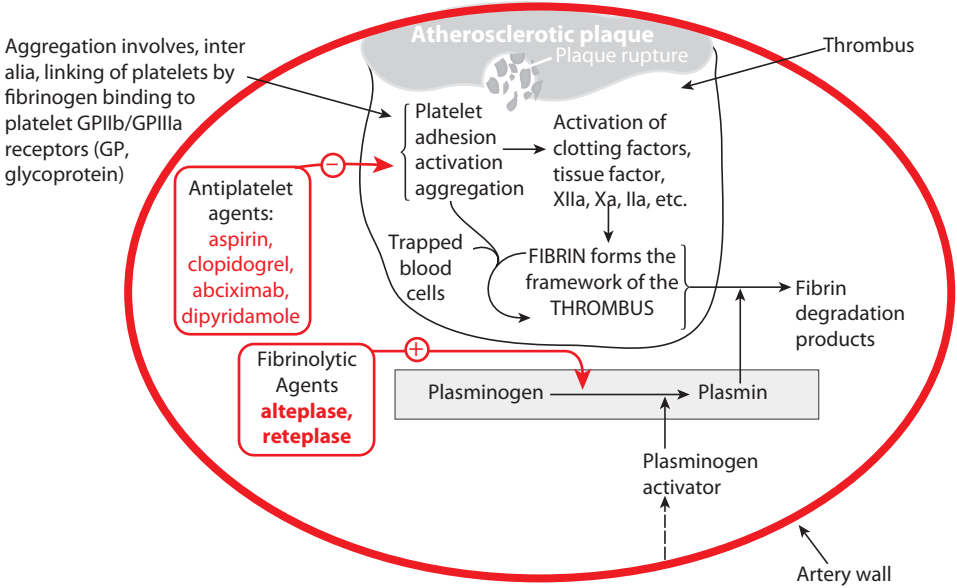
Adverse effects Bleeding (most important), reperfusion dysrhythmias, nausea & vomiting, hypersensitivity reactions.

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

Similar drug Reteplase (long half-life).

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



Tranexamic acid

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

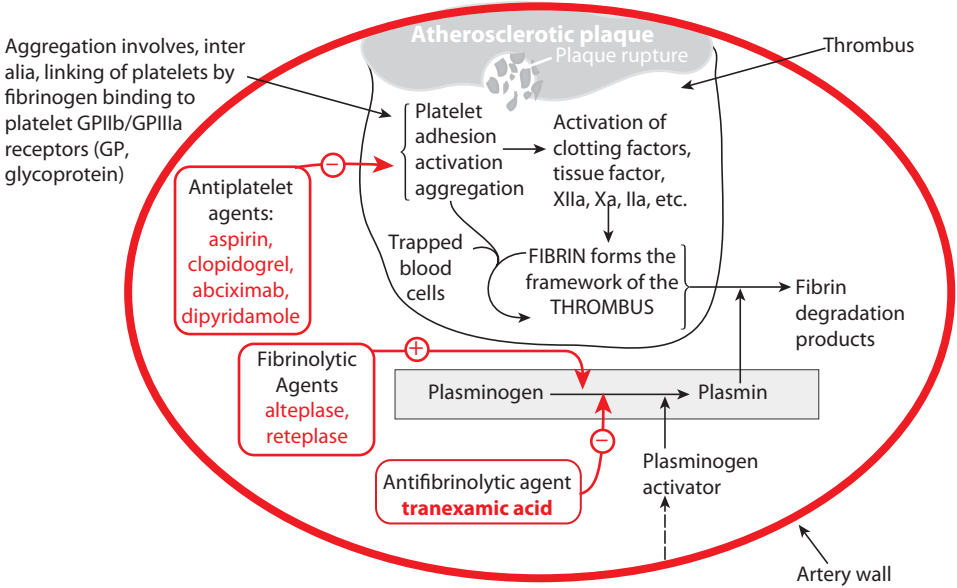
Abs/Distrib/Elim Given orally and by i.v. injection or infusion.

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

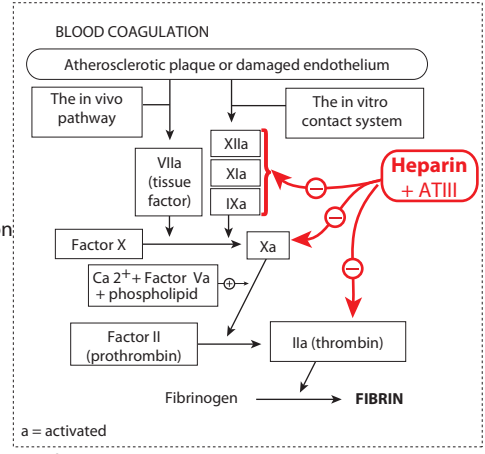


Action It inhibits blood coagulation.

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.



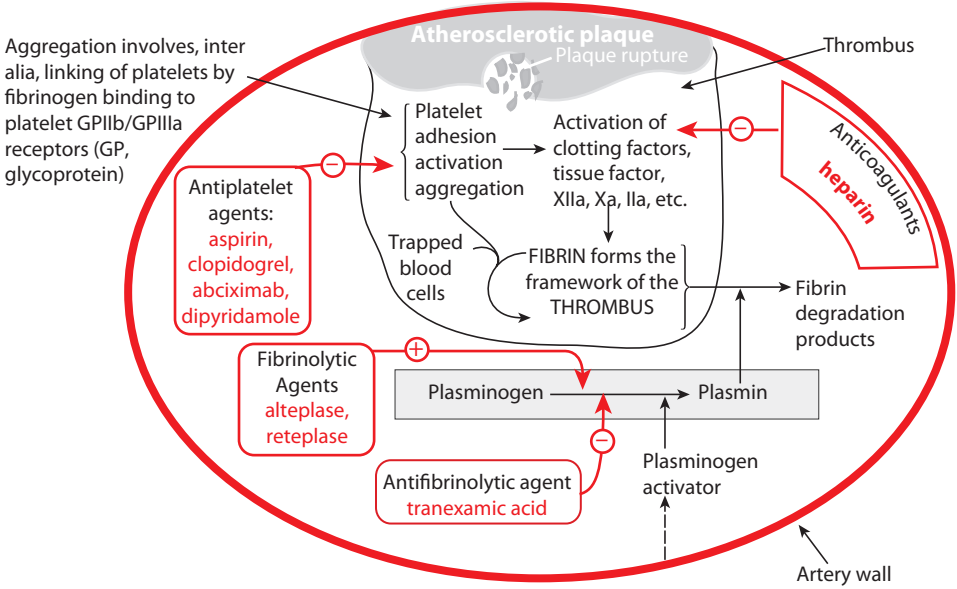
Adverse effects Main adverse effect: bleeding. Thrombocytopaenia, hypersensitivity reactions, osteoporosis.

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

Similar drugs Low molecular weight heparins.

R&D 7e Ch 24, pp 298-300; D&H 2e Ch 23, pp 58-59

The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



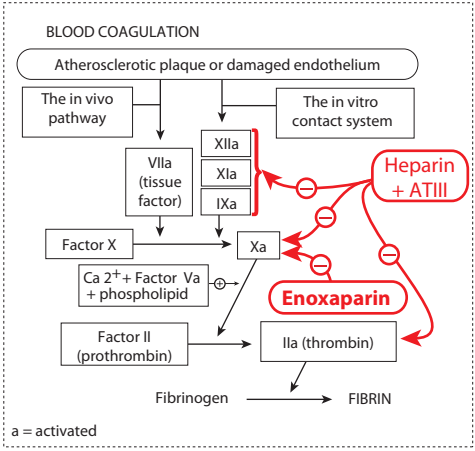
Enoxaparin

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.



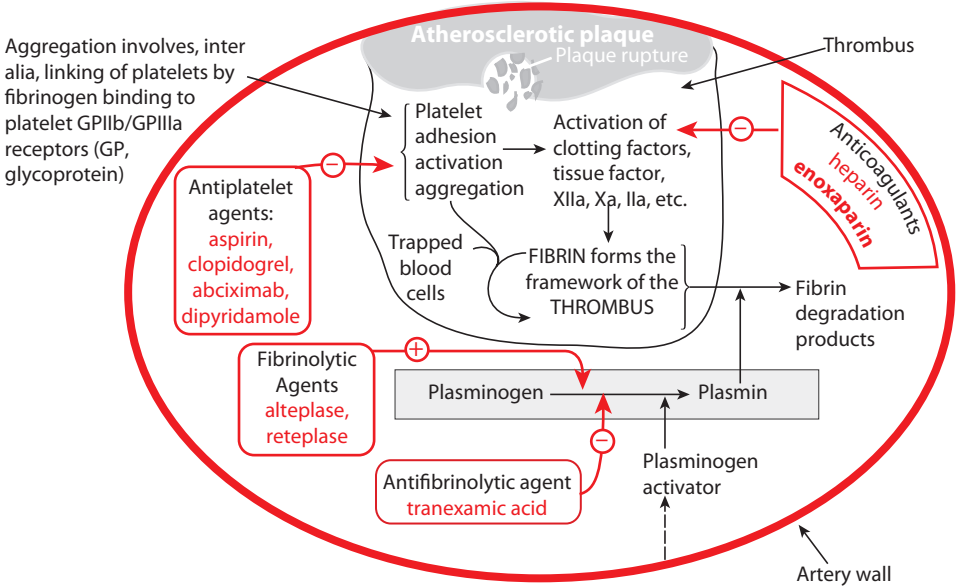
Adverse effects Main adverse effect: bleeding. Less likely than heparin to cause thrombocytopaenia, hypersensitivity reactions, osteoporosis.

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.

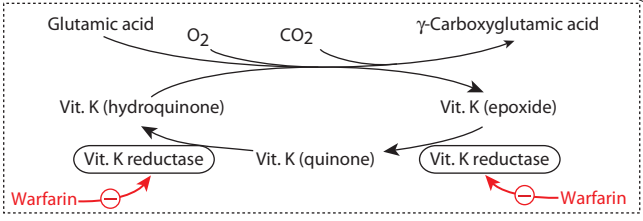
R&D 7e Ch 24, p 299; D&H 2e Ch 23, pp 58-59

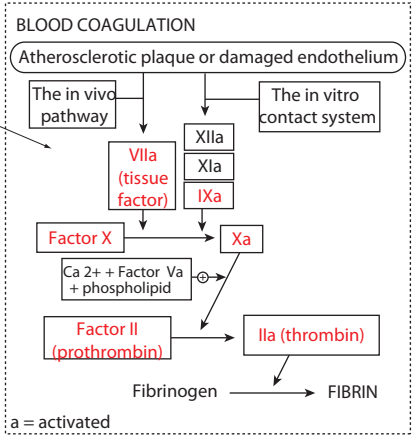
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



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.

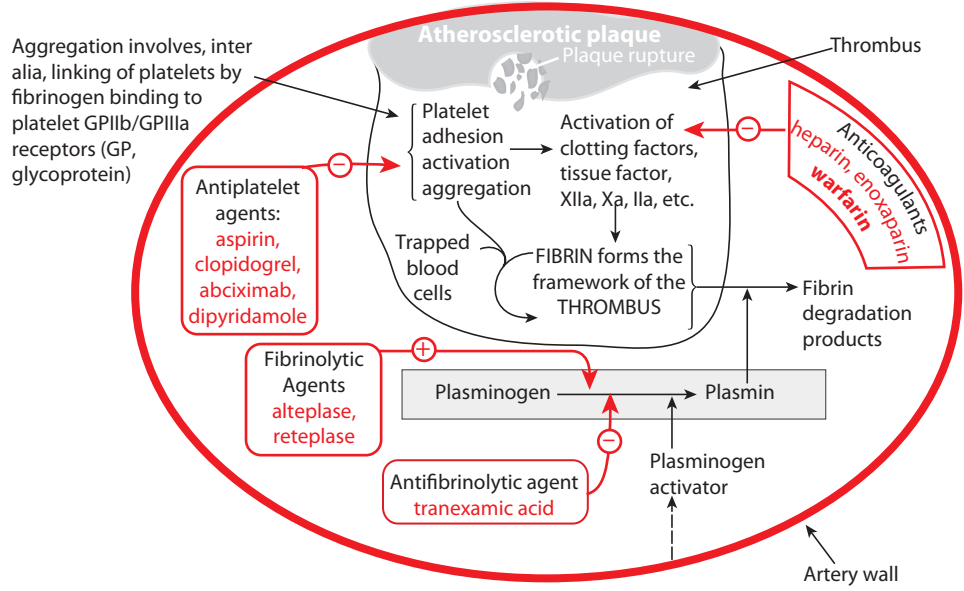
Adverse effects Bleeding; treated by giving natural Vit K or fresh plasma or coagulation factor concentrates.

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.

R&D 7e Ch 24, pp 300-301; D&H 2e Ch 23, pp 58-59

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

The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



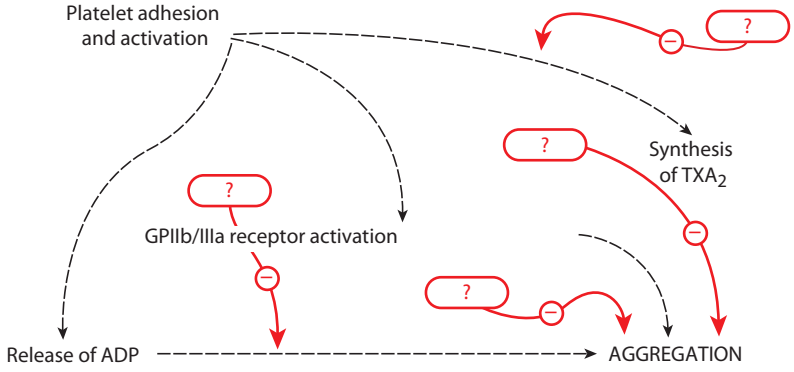
The diagram used on the front faces of this set of cards was a schematic diagram of an arterial thrombus showing – for simplicity – both platelet aggregation/activation and blood coagulation contributing to the thrombus.

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.

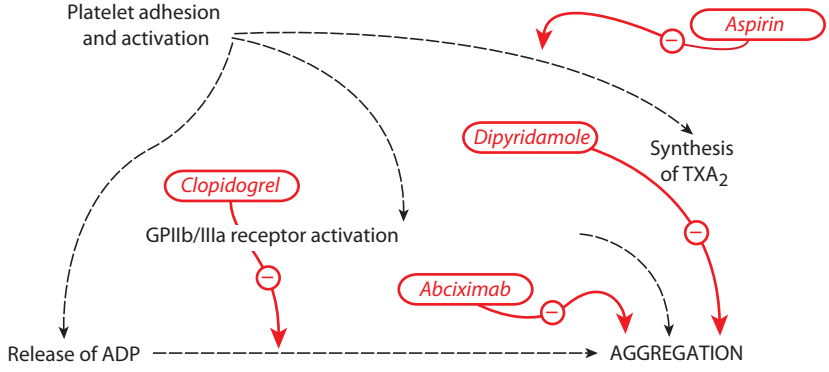
Antiplatelet drugs (e.g. aspirin, clopidogrel which modify platelet aggregation and activation) are used mainly for thromboembolism in arteries because arterial thrombi have a large platelet component with not much contribution from blood coagulation. Anticoagulants have little effect on arterial thrombi.

R&D 7e Ch 24, pp 298-302; D&H 2e Ch 23, pp 58-59

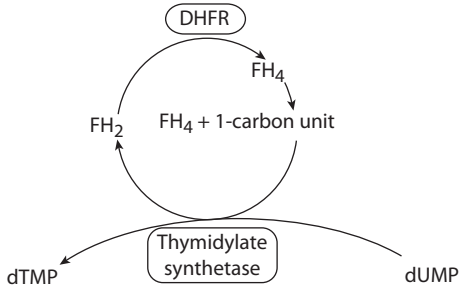
The diagram shows the events leading up to platelet aggregation.



The main examples of drugs that affect platelet aggregation at the site indicated.
There are, of course, others.



Synthesis of nucleotide thymidylate (dTMP)



dTMP (aka TMP) = thymidylate
DHFR = dihydrofolate reductase
FH_2 = dihydrofolate
FH_4 = tetrahydrofolate
dUMP (aka UMP)= uridylate

Folic acid

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).

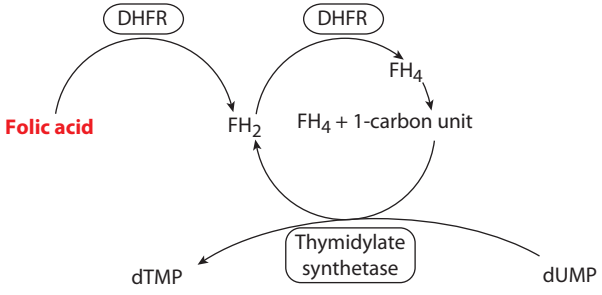
Clinical use To treat megaloblastic anaemias caused by folate deficiency. To prevent the development of folate deficiency in susceptible individuals (e.g. pregnant women, premature infants, patients with severe chronic haemolytic anaemias). To treat toxicity caused by methotrexate (a folate antagonist).

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.

R&D 7e Ch 25, pp 311-314; D&H 2e Ch 24, pp 60-61

Synthesis of nucleotide thymidylate (dTMP)



dTMP (aka TMP) = thymidylate
DHFR = dihydrofolate reductase
FH_2 = dihydrofolate
FH_4 = tetrahydrofolate
dUMP (aka UMP)= uridylate

Hydroxocobalamin

Actions 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).

MOA 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.

Abs/Distrib/Elim Given by i.m. injection.

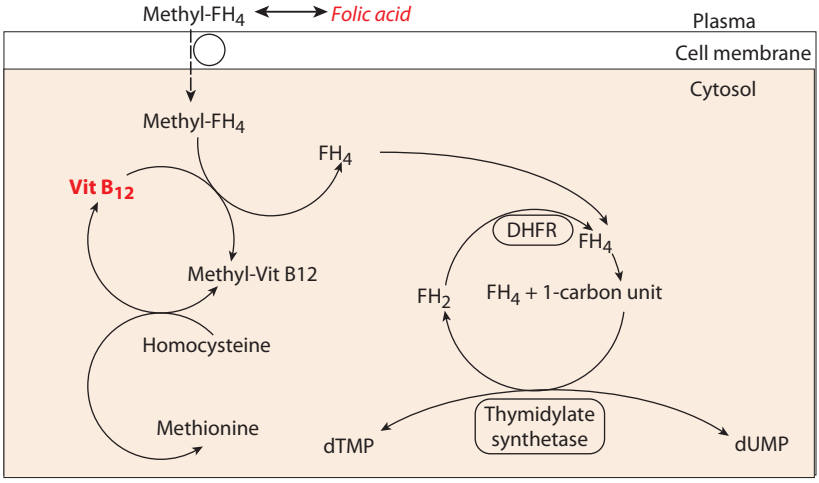
Clinical use To treat pernicious anaemia and other causes of vitamin B_{12} deficiency.

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

Drug with similar action Cyanocobalamin.

R&D 7e Ch 25, pp 311-314; D&H 2e Ch 24, pp 60-61

Role of Vit B_{12} (hydroxocobalamin) in reactions necessary for synthesis of thymidylate (dTMP)



DHFR = dehydrofolate reductase, FH_2 = dihydrofolate, FH_4 = tetrahydrofolate. dUMP = uridylate, dTMP= thymidylate

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.

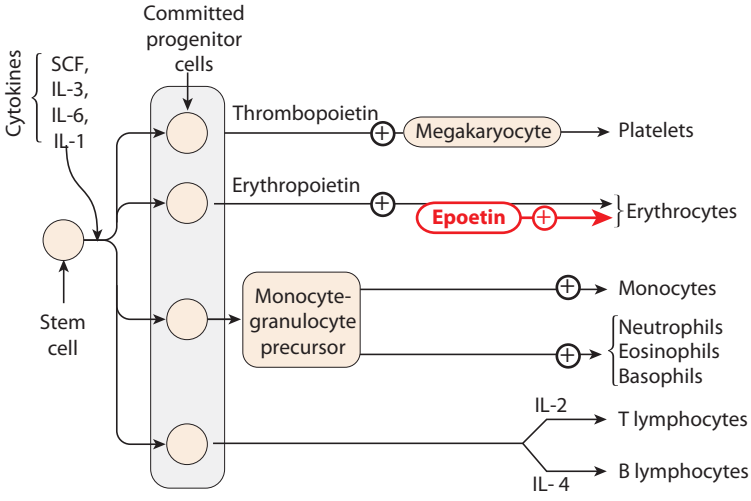
Clinical use To treat the anaemia of chronc renal failure and of AIDS; to alleviate anaemia caused by cytotoxic anticancer drugs; to prevent anaemia in premature infants.

Adverse effects GIT disturbances; hypertension.

R&D 7e Ch 25, p 314; D&H 2e Ch 24, p 61

Growth factors controlling haemopoiesis

IL = interleukin
SCF = stem cell 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.

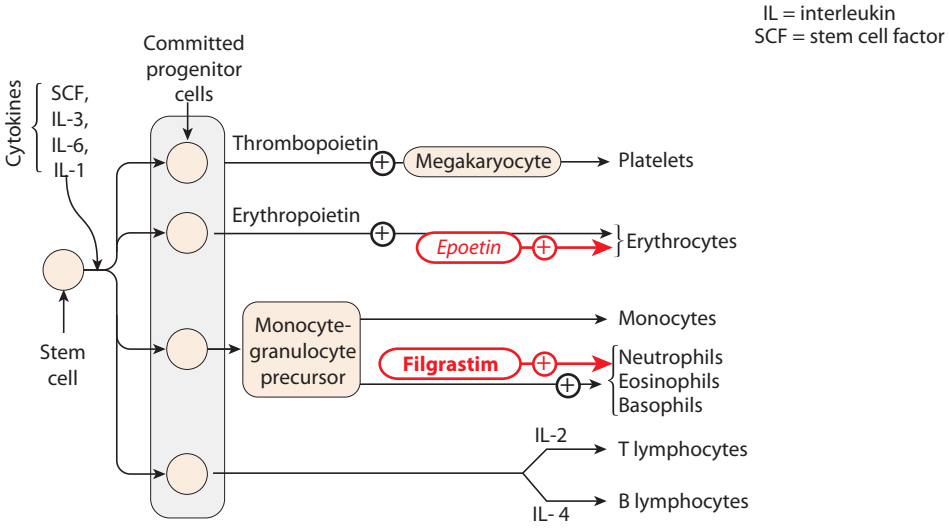
Adverse effects GIT disturbances, bone pain, muscle pain, fever, rash, alopecia.

Similar drug Lenograstim.

Special points For use only by experienced clinicians.

R&D 7e Ch 25, pp 314-315; D&H 2e Ch 24, p 61

Growth factors controlling haemopoiesis



Ferrous sulfate

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

Abs/Distrib/Elim Given orally.

Clinical use Iron-deficiency anaemia.

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

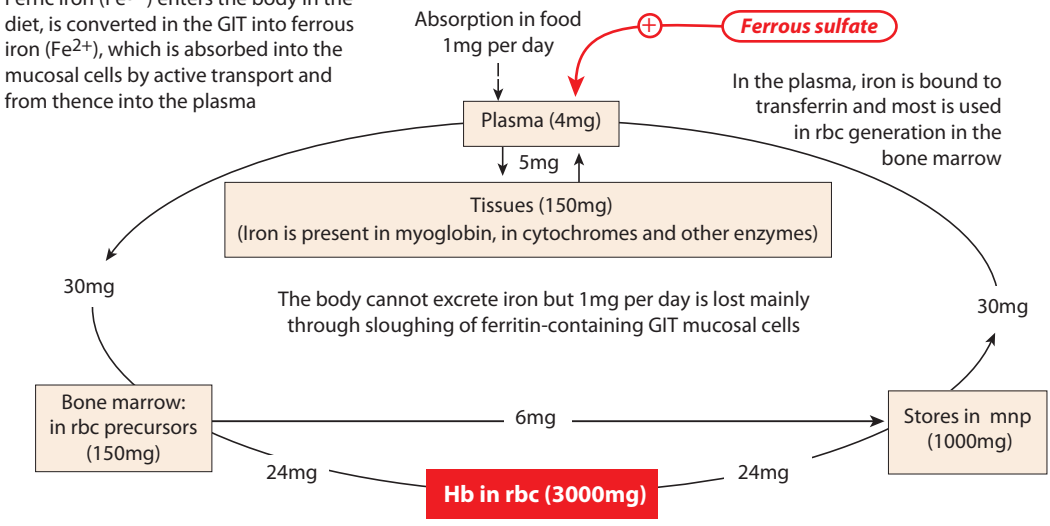
Drugs with similar action Ferrous fumarate, ferrous gluconate – given orally. Iron dextran given by deep i.m. injection or slow i.v. infusion.

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

Which haematinic agent(s) should be given as supplement(s) to pregnant women and why?

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



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

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.

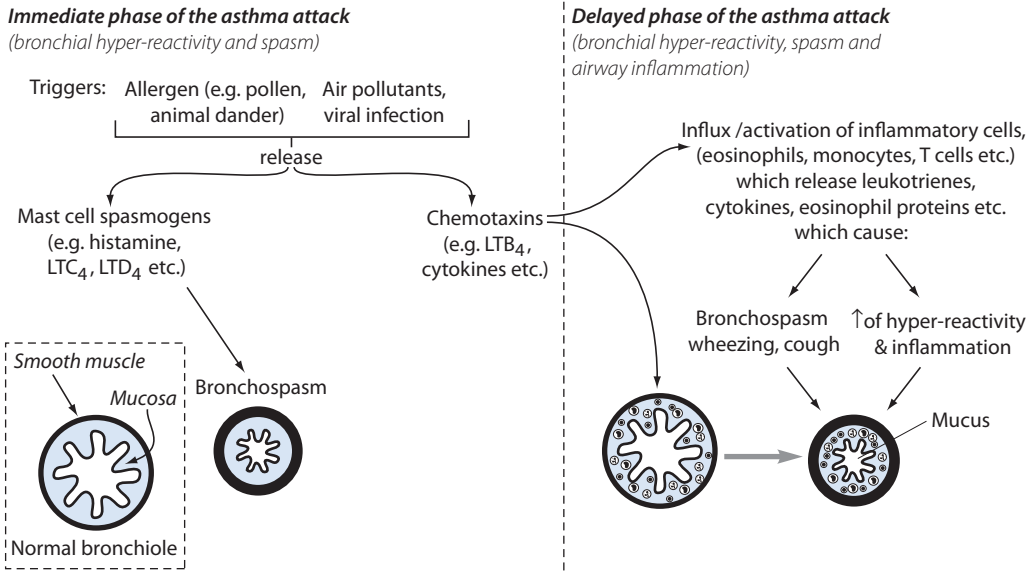
Iron is also important in pregnant women but whether it should be given as a supplement is controversial; there are two schools of thought:

- Some authorities believe that a good diet contaning 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.

R&D 7e Ch 25, p 309; D&H 2e Ch 24, p 60

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



A selective β_2-agonist (Similar drug: terbutaline. See also card 2.01)

Salbutamol

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.

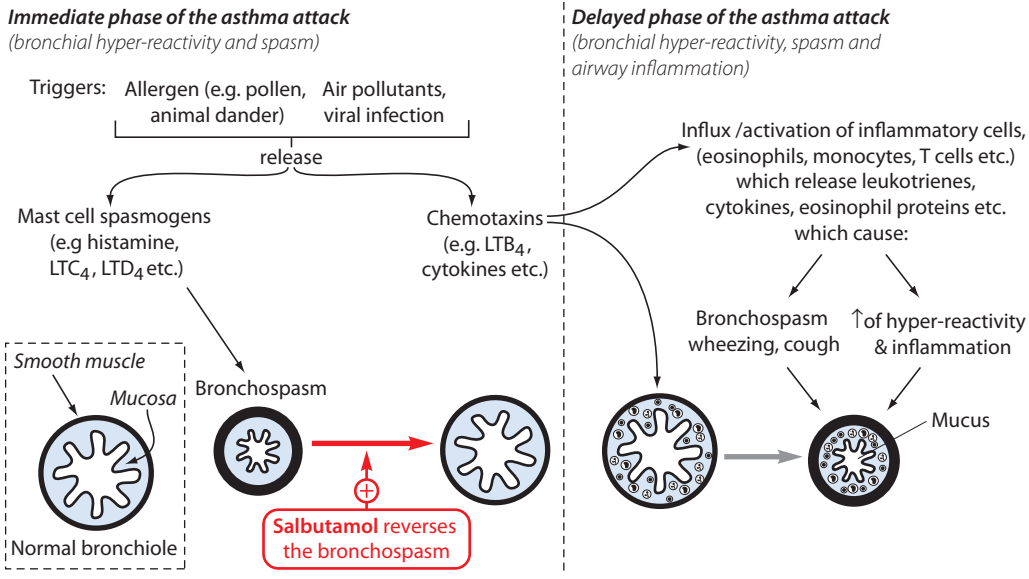
Clinical use For the acute asthmatic attack – used 'as needed'. To prevent exercise-induced asthma. For chronic obstructive airways disease.

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

Special points Selective β_2-agonists are first-line drugs for the the immediate phase i.e. the acute attack; ineffective on the delayed phase.

R&D 7e Ch 27, pp 341; D&H 2e Ch 25, pp 62-63

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



Salmeterol

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. Long-acting (8–12h); Mostly metabolised by P450 with significant amount lost in faeces.

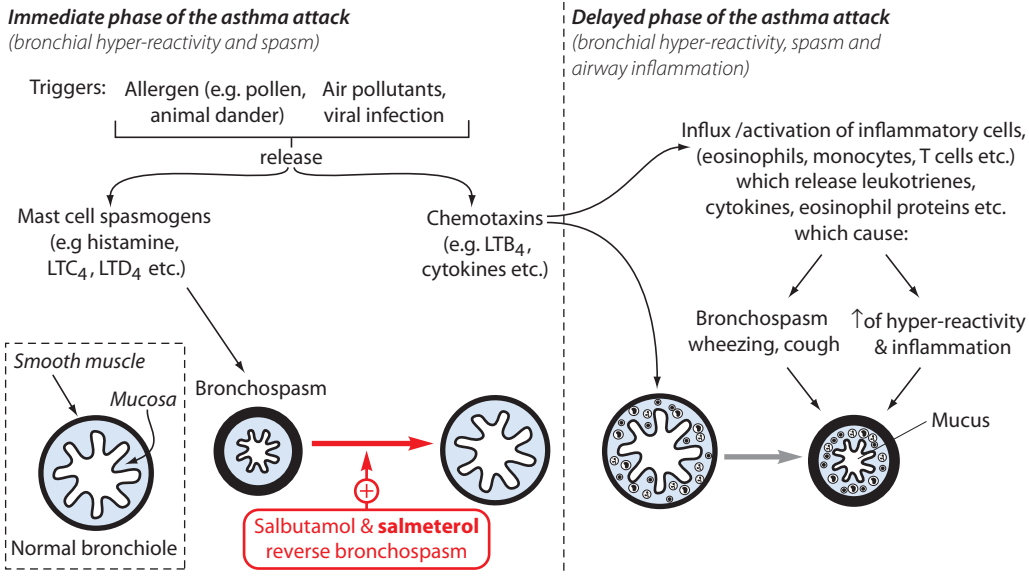
Clinical use To prevent bronchconstriction with exercise-induced asthma or at night in patients needing prolonged bronchodilator therapy. For chronic obstructive pulmonary disease.

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.

R&D 7e Ch 27, pp 340-341; D&H 2e Ch 25, pp 62-63

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



Theophylline

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.

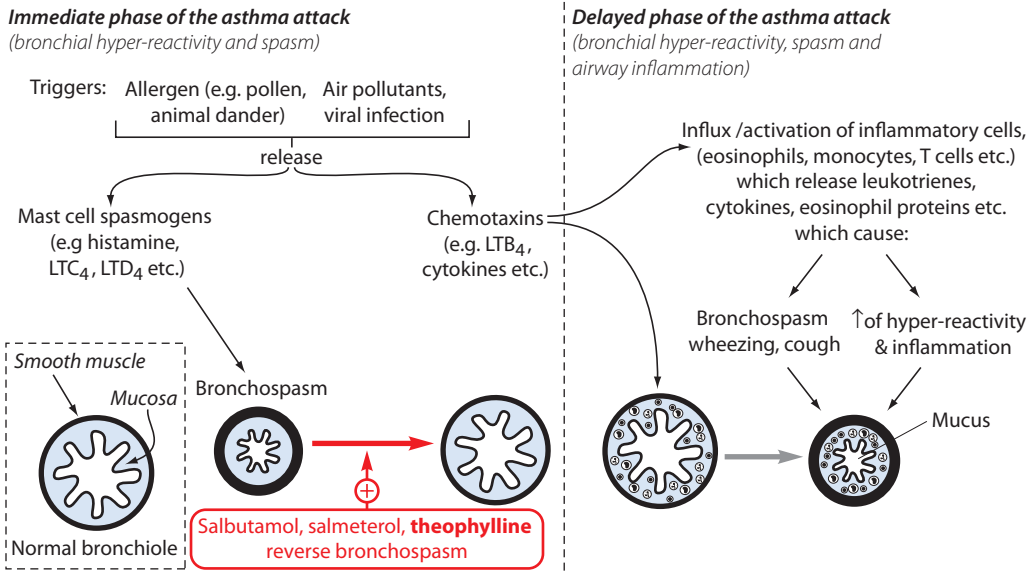
Clinical use A second-line drug for chronic asthma not adequately controlled by β_2-agonists. Aminophylline i.v. is used for severe acute asthma.

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

Special points Plasma levels should be monitored.

R&D 7e, Ch 27, pp 340-341; D&H 2e Ch 25, p 63

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



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

MOA The drug is an antagonist at the cysteinyl leukotriene receptor, (*CysLT*$_1$) on which the bronchospasmic mediators LTC_4, LTD_4 and 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.

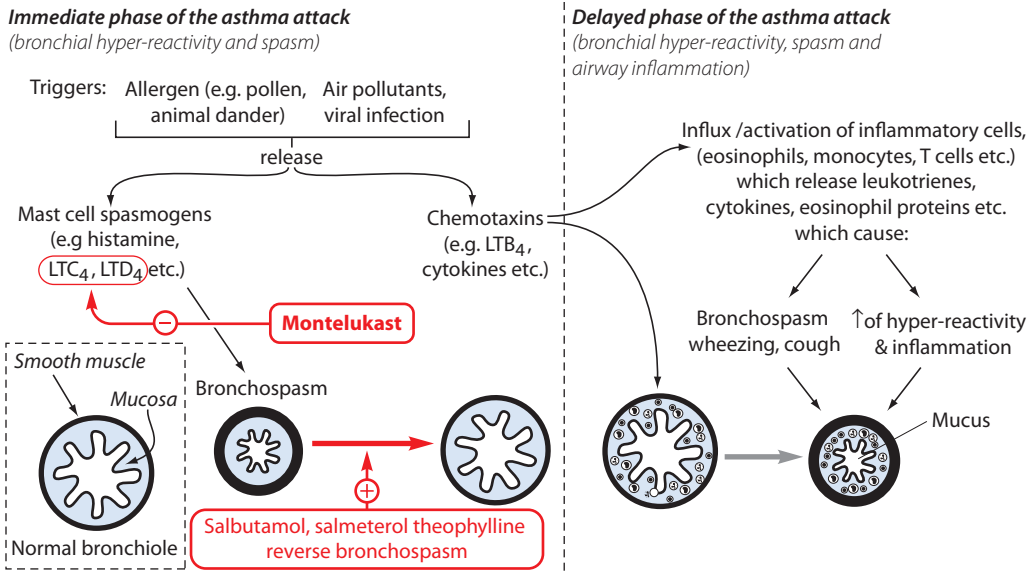
Clinical use A third-line drug for asthma, used as adjunct to inhaled corticosteroids and long-acting β_2-agonists. Effective in aspirin-induced asthma.

Unwanted effects Few.

Special points Easy for children to take.

R&D 7e, Ch 27, p 340; D&H 2e Ch 25, p 63

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



Ipratropium

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

MOA Competitively antagonises acetylcholine action on muscarinc receptors.

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

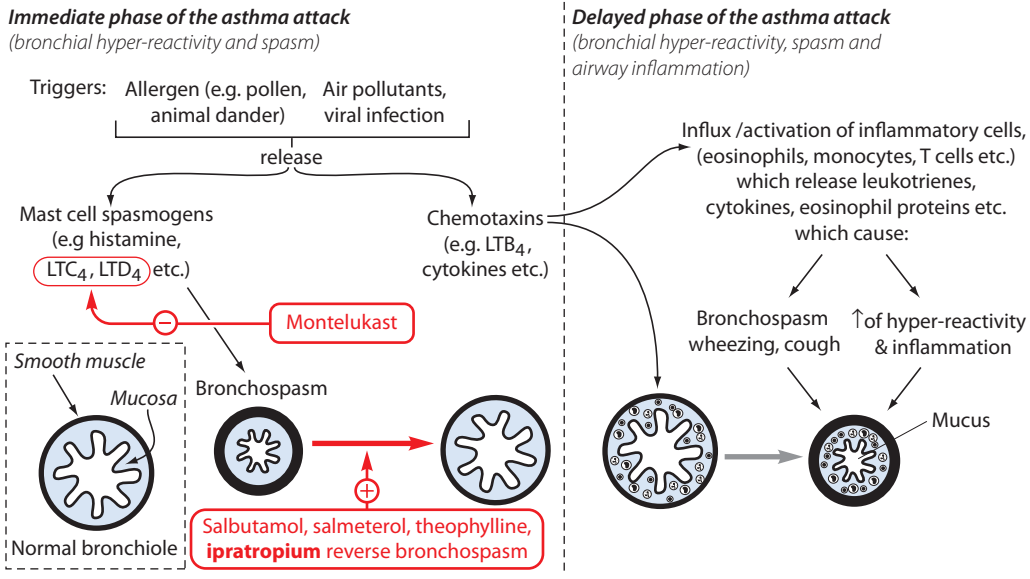
Clinical use For asthma as adjunct to β_2-agonist & corticosteroids; for chronic obstructive pulmonary disease.

Unwanted effects Few.

Special points Useful in patients intolerant of β_2-agonists.

R&D 7e Ch 27, p 342; D&H 2e Ch 25, pp 62-63

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



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.

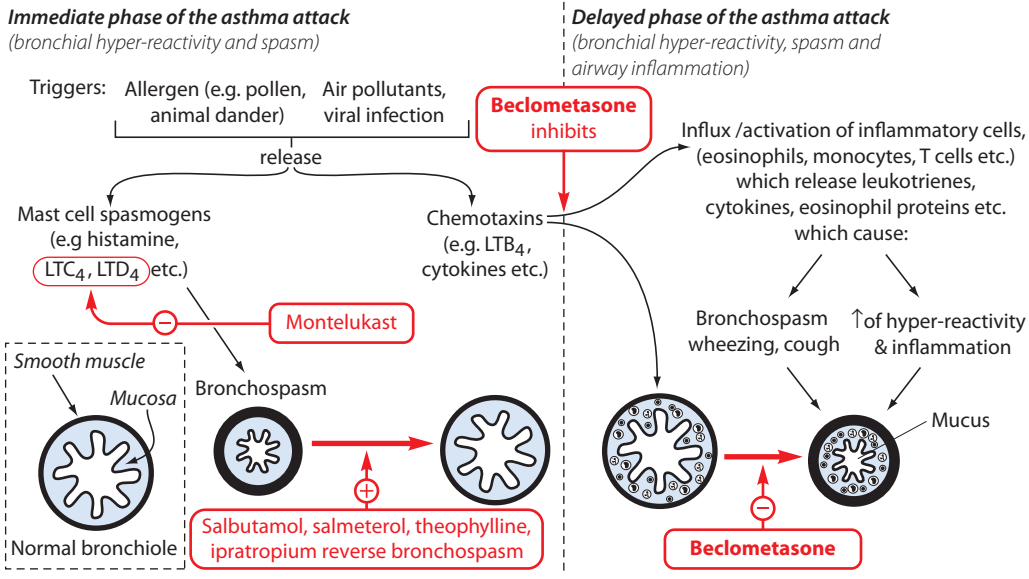
Clinical use Added to bronchodilator therapy if this is inadequate. An i.v. glucocorticoid (e.g. hydrocortisone) is life-saving in acute severe asthma (status asthmaticus).

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



Omalizumab

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.

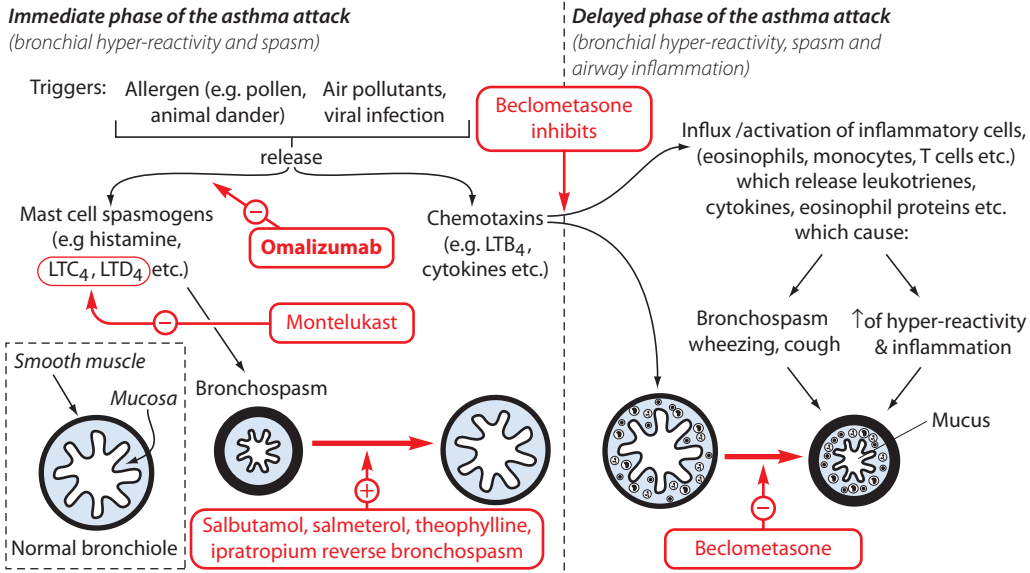
Clinical use For persistent allergic asthma not completely controlled with inhaled corticosteroid plus long-acting β_2-agonist.

Unwanted effects Hypersensitivity reactions.

Special points Needs expert administration.

R&D 7e Ch 27, p 338

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



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.

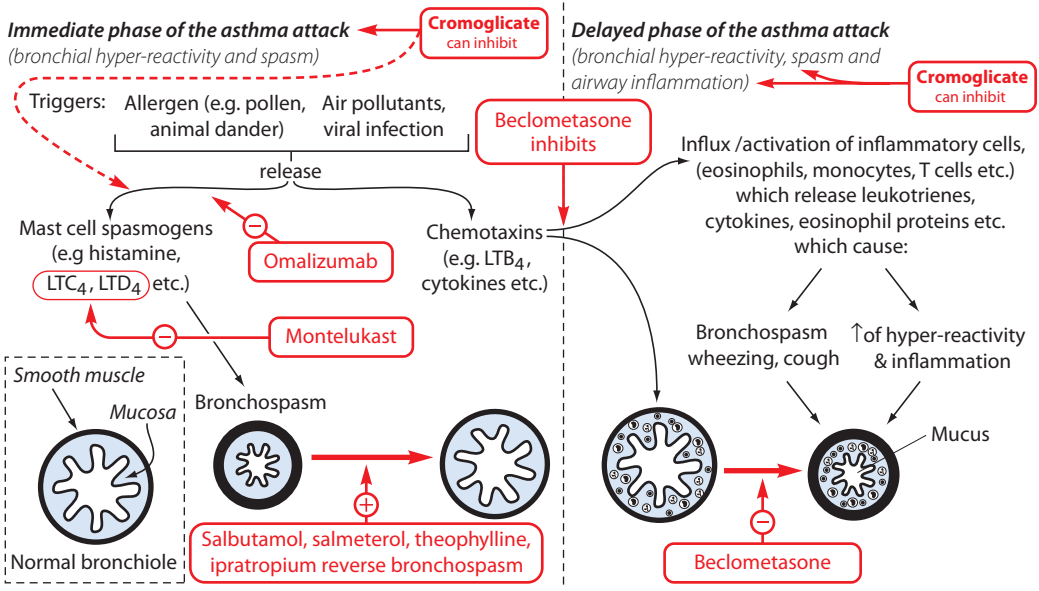
Unwanted effects Irritation of throat by the powder.

Special points None.

R&D 7e Ch 27, p 343; D&H 2e Ch 25, p 63

How might the main drugs given here be introduced gradually, in five steps, in a patient whose asthma is difficult to control?

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



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?

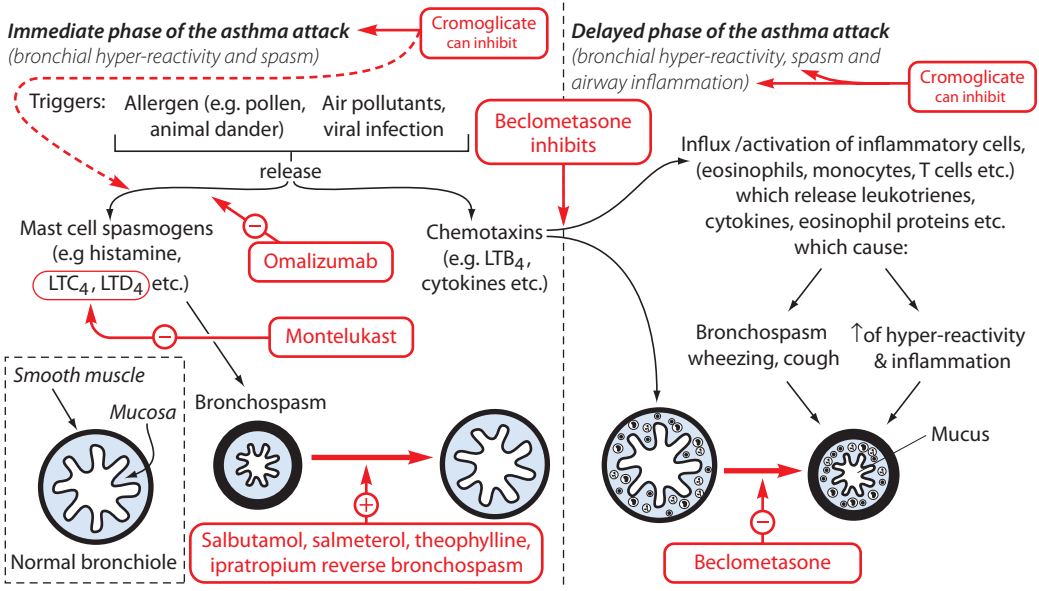
Step 4 If asthma is still not adequately controlled, add *other drug(s).* How would it/they be given?

Step 5 If asthma is still not adequately controlled, add *another drug.* How would it be given?

R&D 7e Ch 27, pp 340-343; D&H 2e Ch 25, p 63

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



Step 1 Patient is started on a short-acting bronchodilator such as salbutamol. Taken by inhalation 'as needed' – up to once daily.

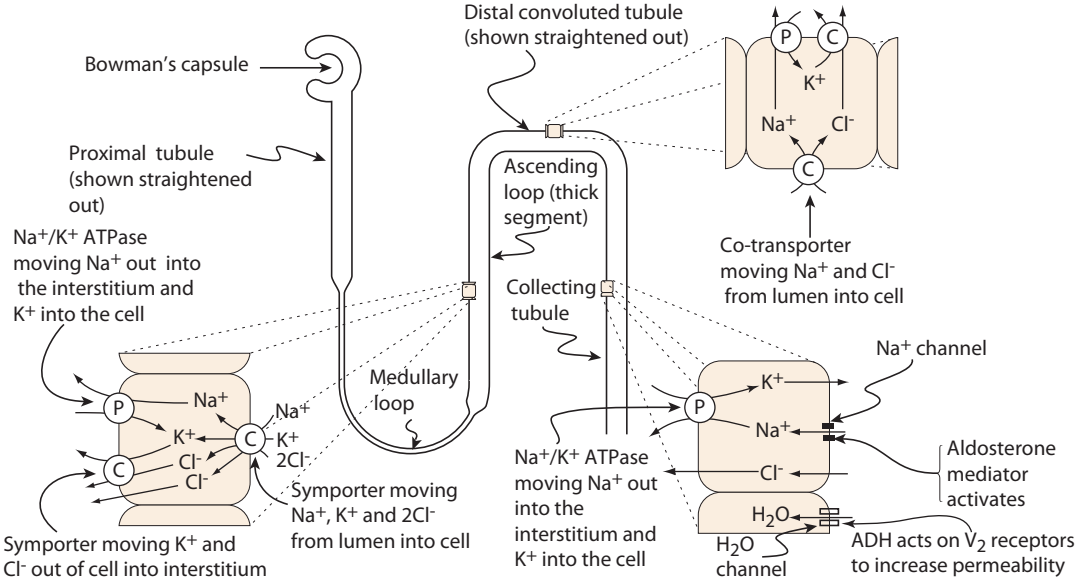
Step 2 If inhalation of the short-acting bronchodilator is needed more than once a day, regular inhaled beclometasone is *added*.

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*.

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



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.

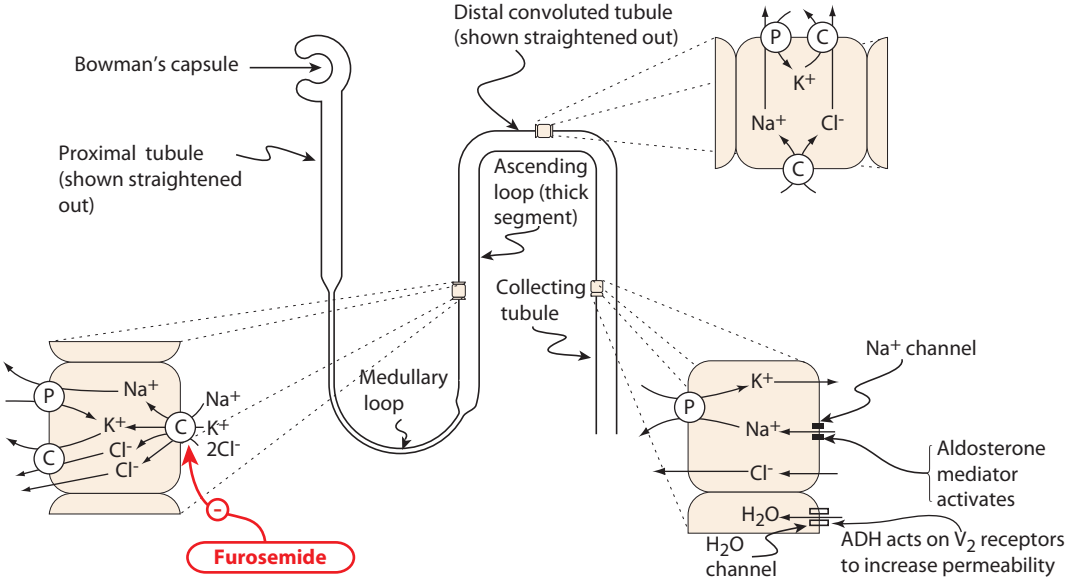
Abs/Distrb/Elim Given orally (can be given i.v. in emergencies), well absorbed, reaches site of action by being secreted into the proximal tubule. Half-life 90min.

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



Hydrochlorothiazide

Actions Causes moderate degree of diuresis by inhibiting NaCl reabsorption in the distal tubule. Increases K^+ and H^+ excretion. Decreases excretion of Ca^{2+} and uric acid; increases excretion of Mg^{2+}. Some vasodilator action.

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

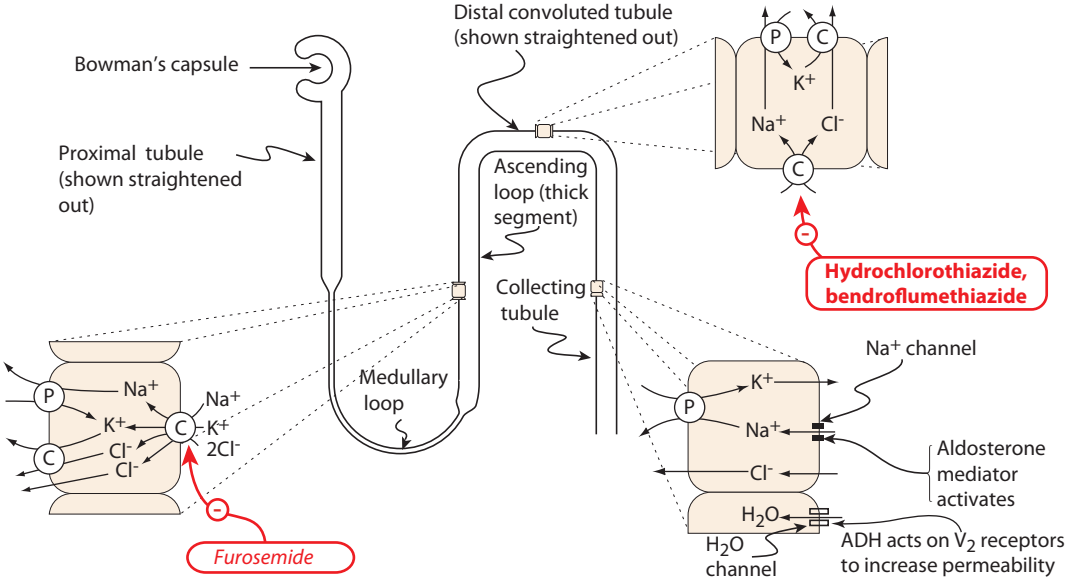
Abs/Distrb/Elim Given orally; reaches site of action by being secreted into the proximal tubule. Half-life 90min.

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.

R&D 7e Ch 28, p 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



Actions Inhibits sodium reabsorption in the distal nephron; has limited diuretic effficacy. Reduces K^+ excretion.

MOA Inhibits the sodium channel in the luminal membrane of the collecting tubule, reducing sodium influx.

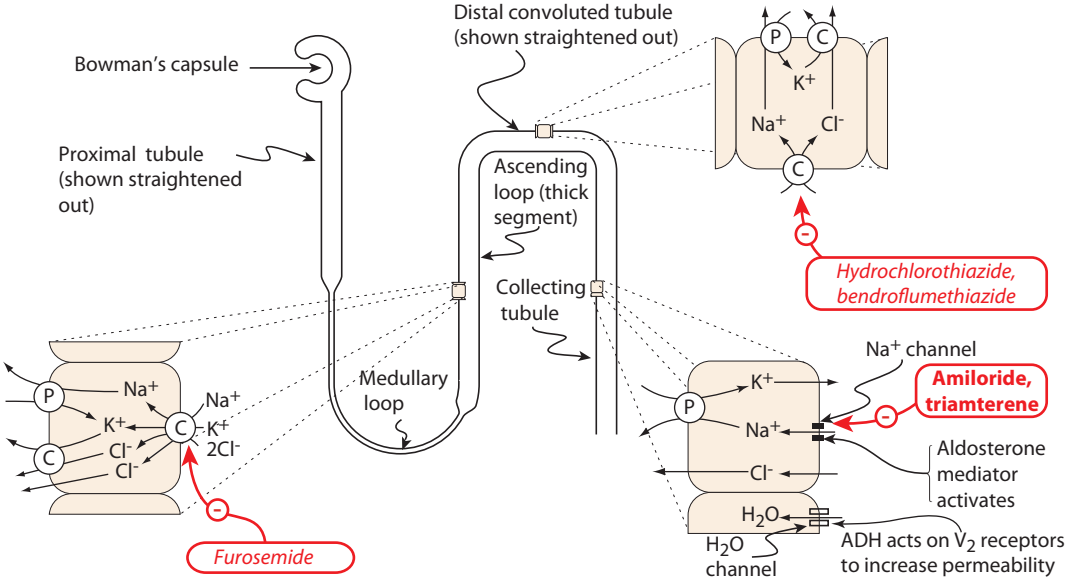
Abs/Distrb/Elim Given orally. Triamterene has more rapid onset and shorter duration of action than amiloride.

Clinical use Given with K^+-losing diuretics (thiazides, loop diuretics) to limit K^+ loss.

Adverse effects Hyperkalaemia; may cause acidosis.

R&D 7e Ch 28, p 356; 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



Spironolactone

Actions Inhibits sodium reabsorption in the distal nephron; has limited diuretic effficacy. 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.

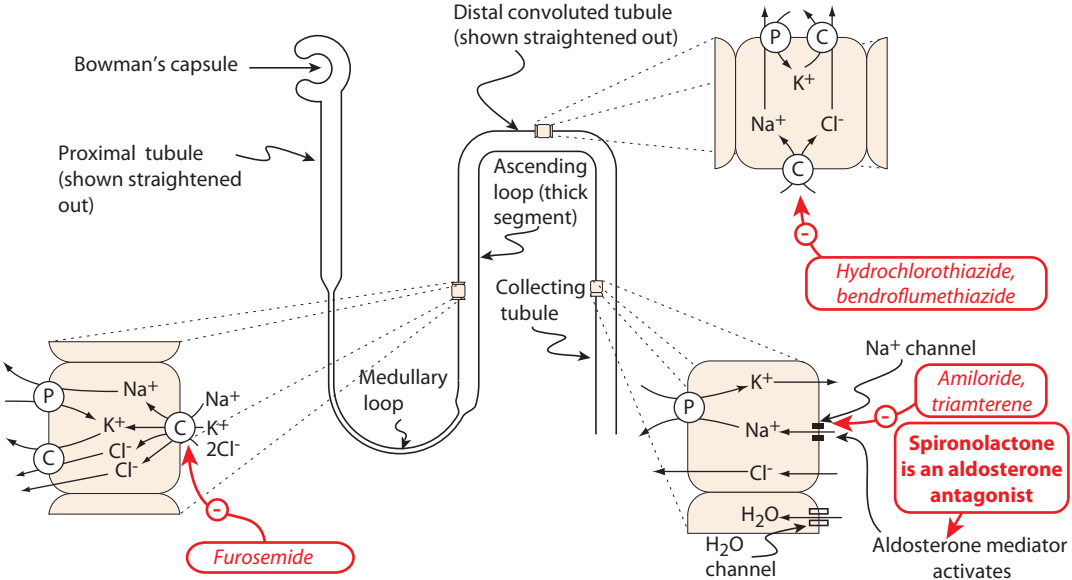
Abs/Distrb/Elim Given orally, gives rise to active metabolite, canrenone, which has a plasma half-life of 16h. Eplerenone has no active metabolite and a shorter half-life.

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).

R&D 7e Ch 28, p 355; 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



Mannitol

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.

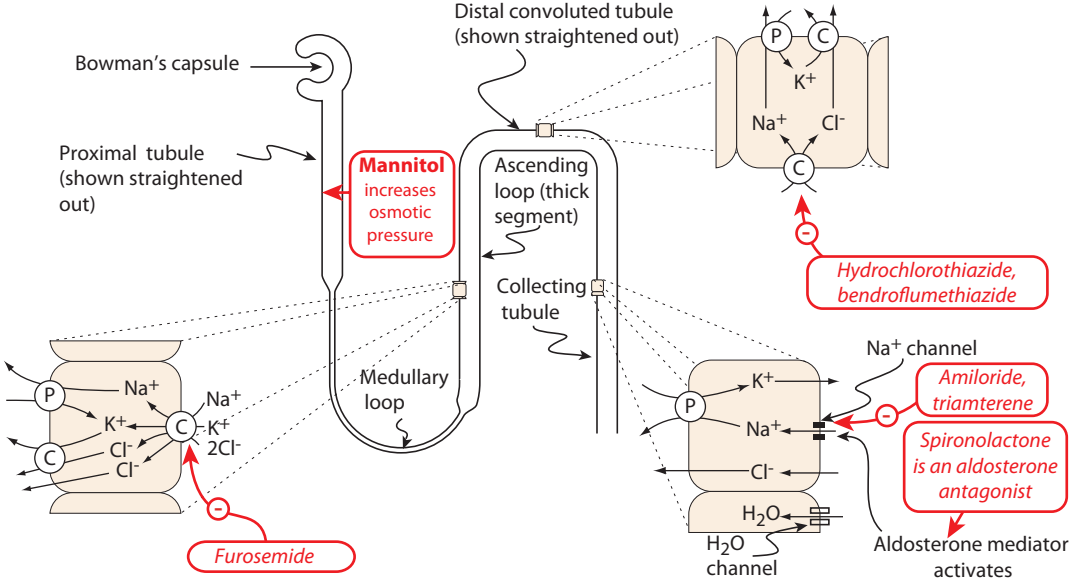
Abs/Distrb/Elim Given intravenously, not metabolised, excreted in about 30min.

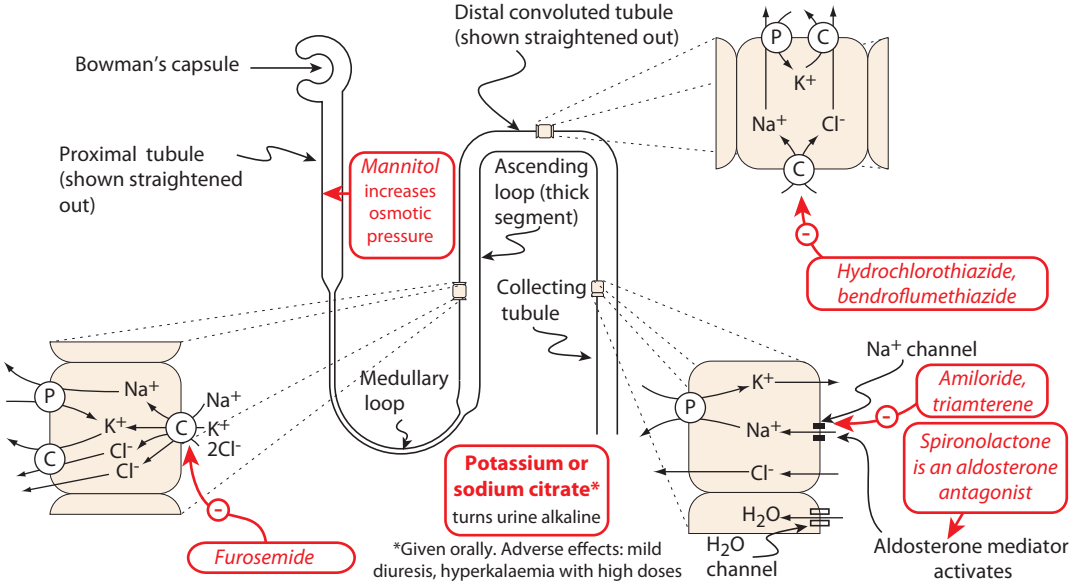
Clinical use Cerebral oedema; increased intraocular pressure.

Adverse effects Temporary expansion of the extracellur fluid compartment and hyponatraemia due to osmotic extraction of intracellular water. Pulmonary oedema may occur.

R&D 7e Ch 28, p 356; D&H 2e Ch 26, pp 64-65

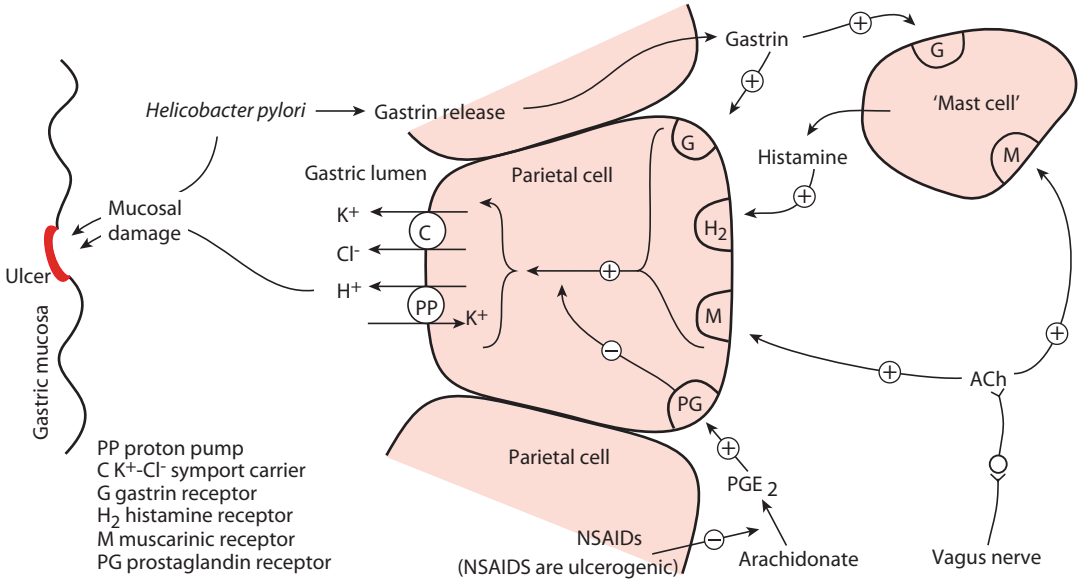
Diagram of the nephron with 3 tubular cells shown enlarged





R&D 7e Ch 28, pp 356-357

Factors influencing gastric HCl secretion and the development of gastric ulcers



Cimetidine

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).

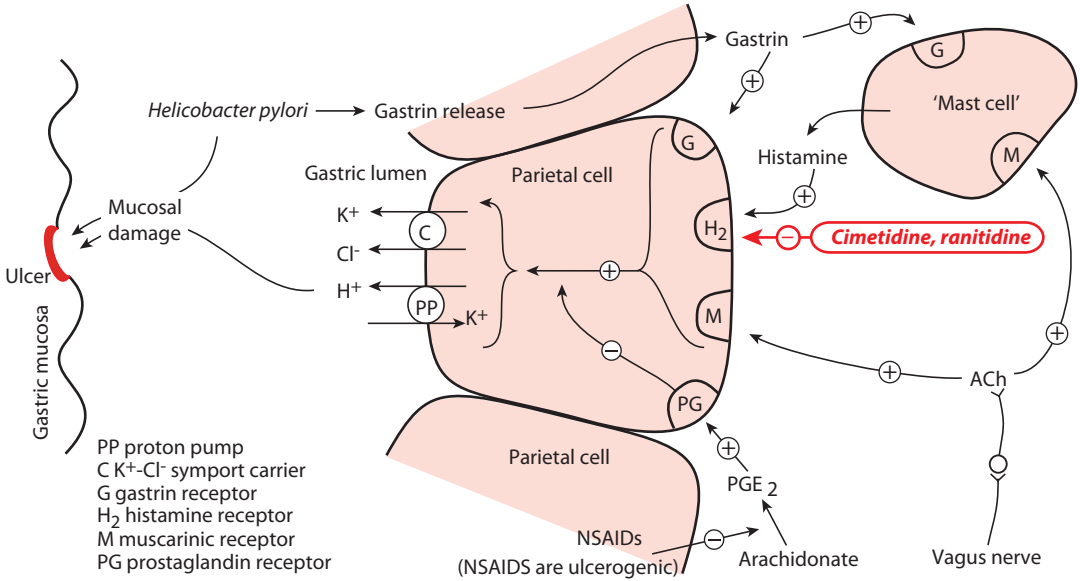
Clinical use Peptic and duodenal ulcers. Gastro-oesophageal reflux disease. NSAID-induced ulcers (with discontinuation of NSAID).

Adverse effects Uncommon. Headache, GIT disturbances. Confusion, disorientation in elderly. Antiandrogenic effects with cimetidine but not other H_2 blockers – gynaecomastia in men and galactorrhoea in women.

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.

R&D 7e Ch 29, p 363; D&H 2e Ch 27, p 66

Factors influencing gastric HCl secretion and the development of gastric ulcers



Omeprazole

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.

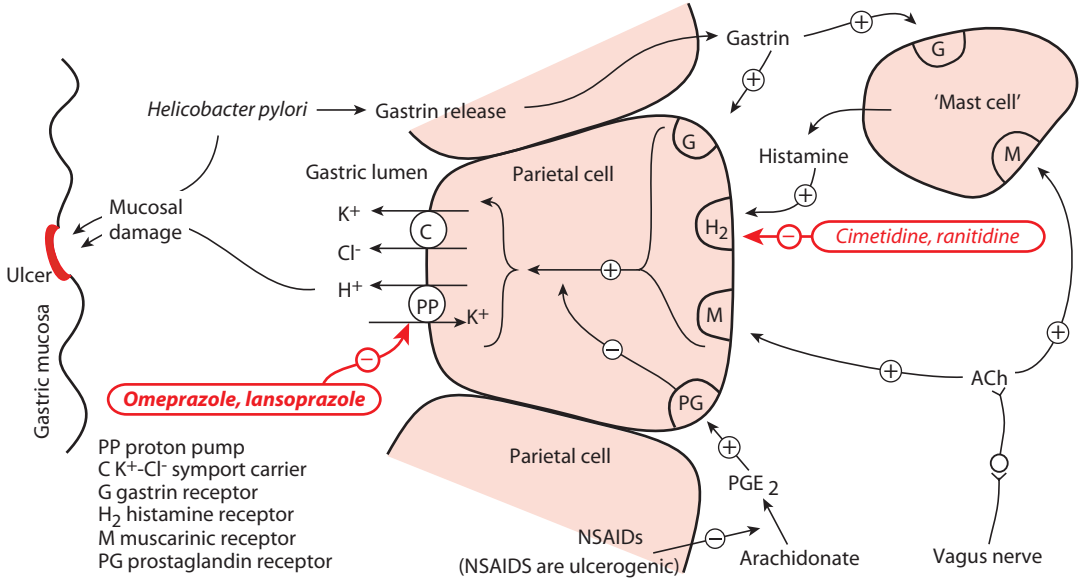
Abs/Distrib/Elim Mainly eliminated by rapid P450 metabolism in liver ($T_{0.5}$,1–2h), but duration of action is long (2–3days) because of covalent binding. The production of new PP molecules determines the rate of recovery. Needs enteric coating to prevent action of acid before absorption.

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 H_2 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.

R&D 7e Ch 29, p 363; D&H 2e Ch 27, p 66

Factors influencing gastric HCl secretion and the development of gastric ulcers



Clarithromycin

Actions Bactericidal.

MOA Kills bacteria by binding to their ribosomes to inhibit protein synthesis.

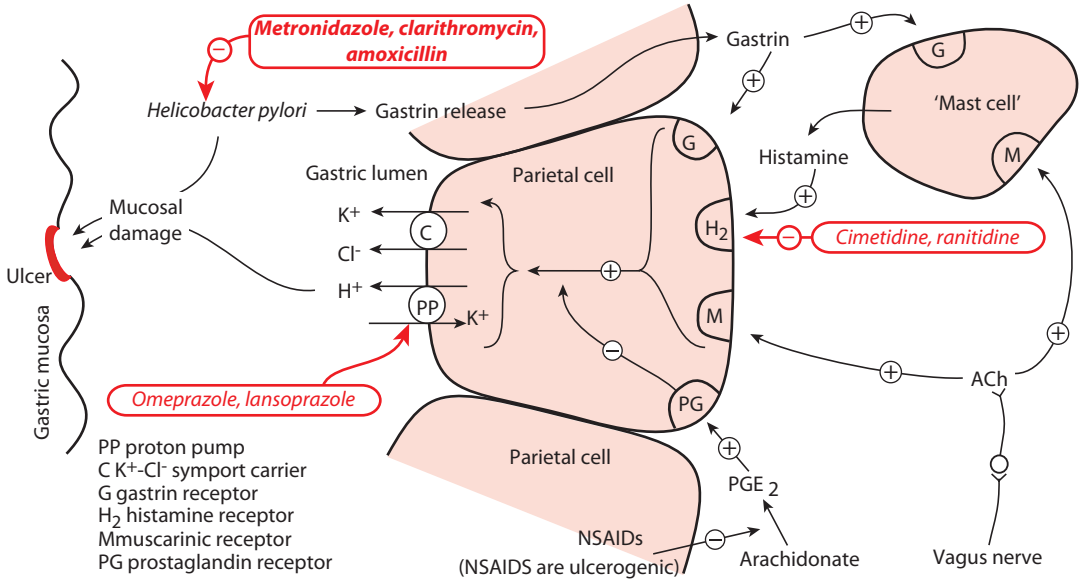
Abs/Distrib/Elim Active orally. Metabolised by liver (with significant first-pass metabolism). $t_{½}$ 3–4h.

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.

R&D 7e Ch 29, pp 364-365; D&H 2e Ch 27, p 66

Factors influencing gastric HCl secretion and the development of gastric ulcers



Bismuth chelate

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.

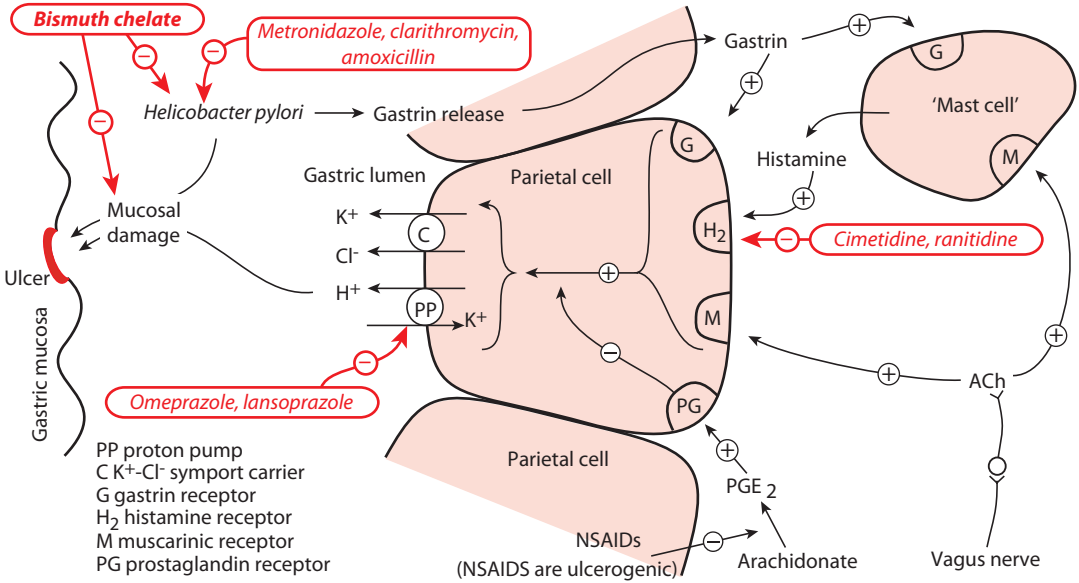
Abs/Distrib/Elim Very little (1%) of oral dose is absorbed into the systemic circulation.

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.

R&D 7e Ch 29, p 365; D&H 2e Ch 27, p 66

Factors influencing gastric HCl secretion and the development of gastric ulcers



Sucralfate

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.

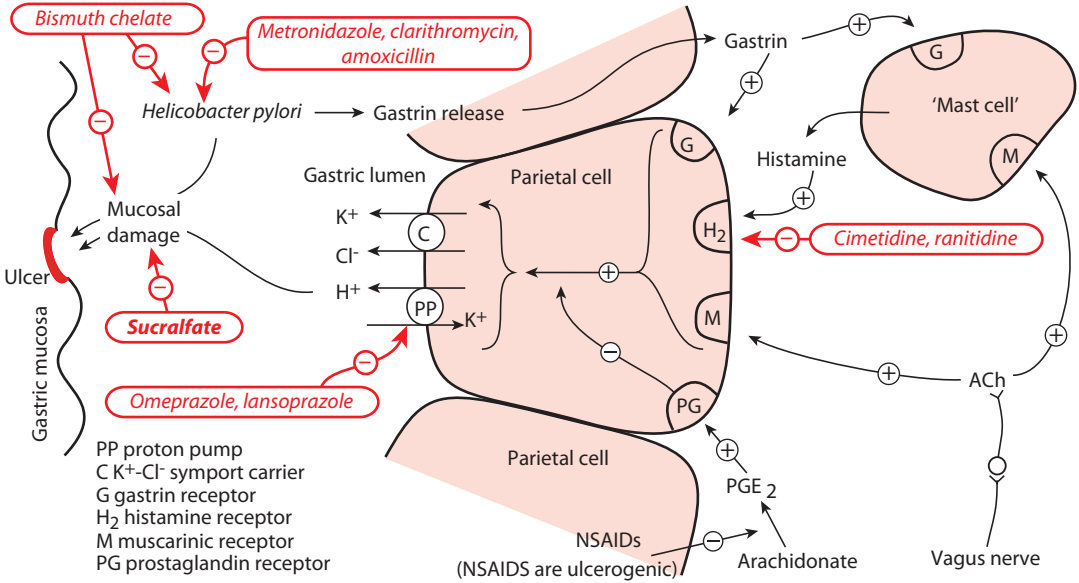
Clinical use Gastric and duodenal ulcer. Gastro-oesophageal reflux disease.

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.

R&D 7e Ch 29, p 365; D&H 2e Ch 27, p 66

Factors influencing gastric HCl secretion and the development of gastric ulcers



Aluminium hydroxide

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). $NaHCO_3$ and $CaCO_3$ are absorbed and may have significant systemic actions.

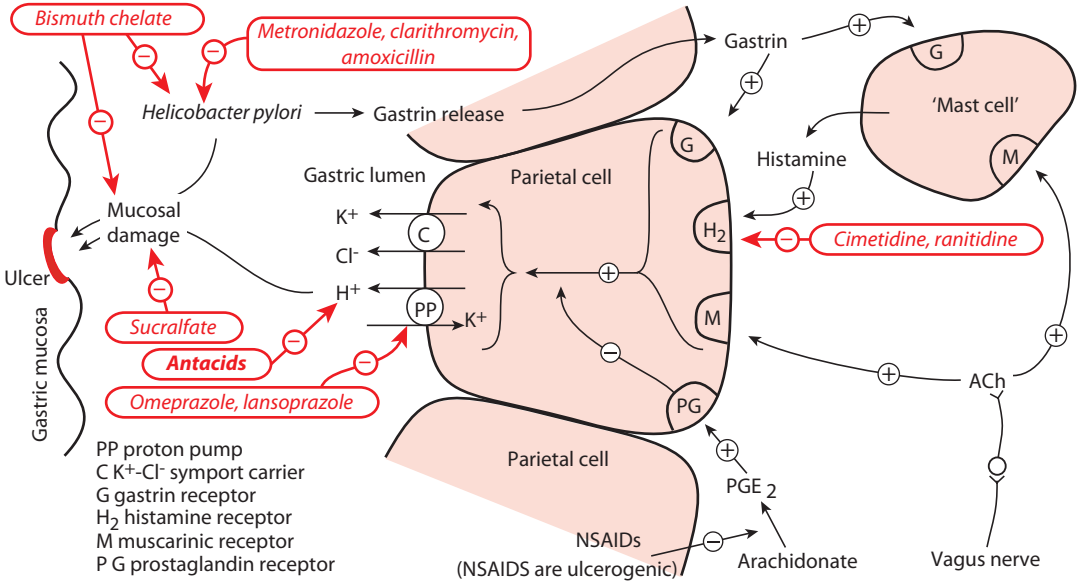
Clinical use Short-term symptom relief for duodenal ulcers. Gastro-oesophageal reflux diseaseNeeds to be taken 5–7 times daily.

Adverse effects $Al(OH)_3$ causes constipation. $Mg(OH)_2$ has a strong laxative action (osmotic purgative). $NaHCO_3$ and $CaCO_3$ release CO_2 which causes belching and also metabolic alkalosis.
$CaCO_3$ causes hypercalcaemia.

Special point Calcium and aluminium salts complex with orally administered tetracyclines to prevent their absorption.

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



Misoprostol

Actions Promotes gastric ulcer healing. Combats the ulcerogenic action of NSAIDs.

MOA Activates prostaglandin receptors (EP_3 subtype) to inhibit acid secretion. Effects mediated by G_i-mediated inhibition of adenylate cyclase. Additionally stimulates bicarbonate and mucus secretion.

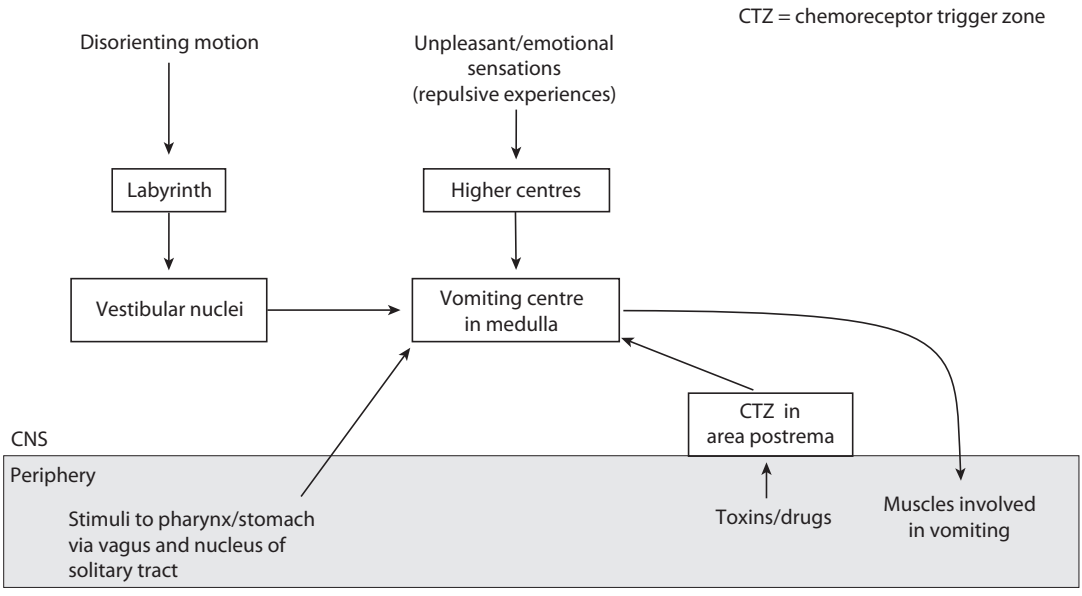
Abs/Distrib/Elim Well absorbed orally. Rapidly hydrolysed to free acid which is the active moiety. $T_{0.5}$ 30–40min.

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.

R&D 7e Ch 29, p 362; D&H 2e Ch 27, p 66

The central control of vomiting and stimuli resulting in emesis



Promethazine

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'.

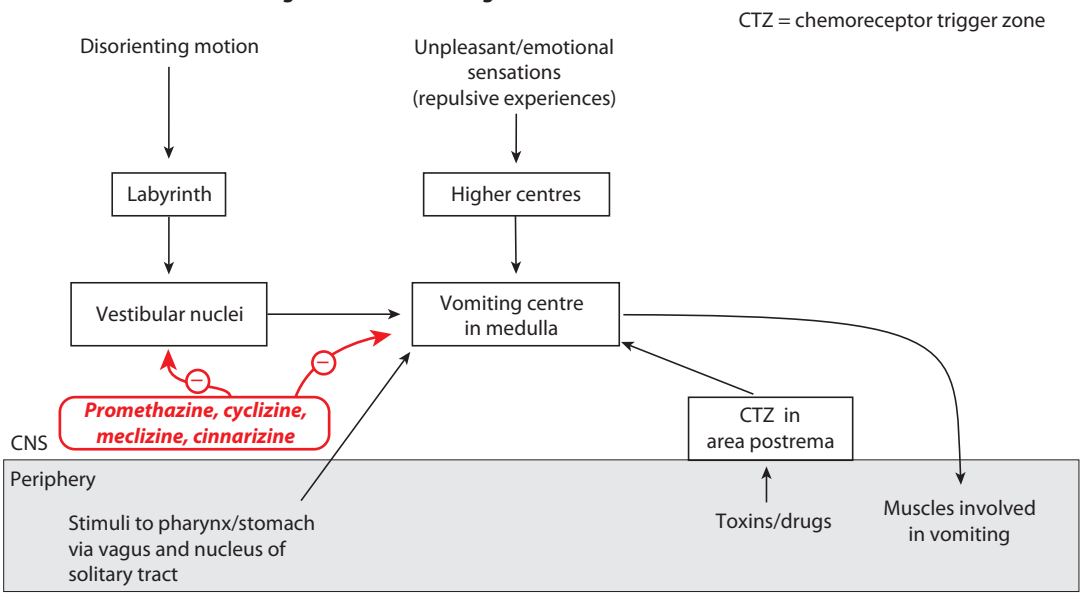
Abs/Distrib/Elim $T_{0.5}$ 10h. Significant first-pass metabolism. Meclizine longer $T_{0.5}$.

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.

R&D 7e Ch 29, p 366; D&H Ch 27, p 67

The central control of vomiting and stimuli resulting in emesis



Scopolamine

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.

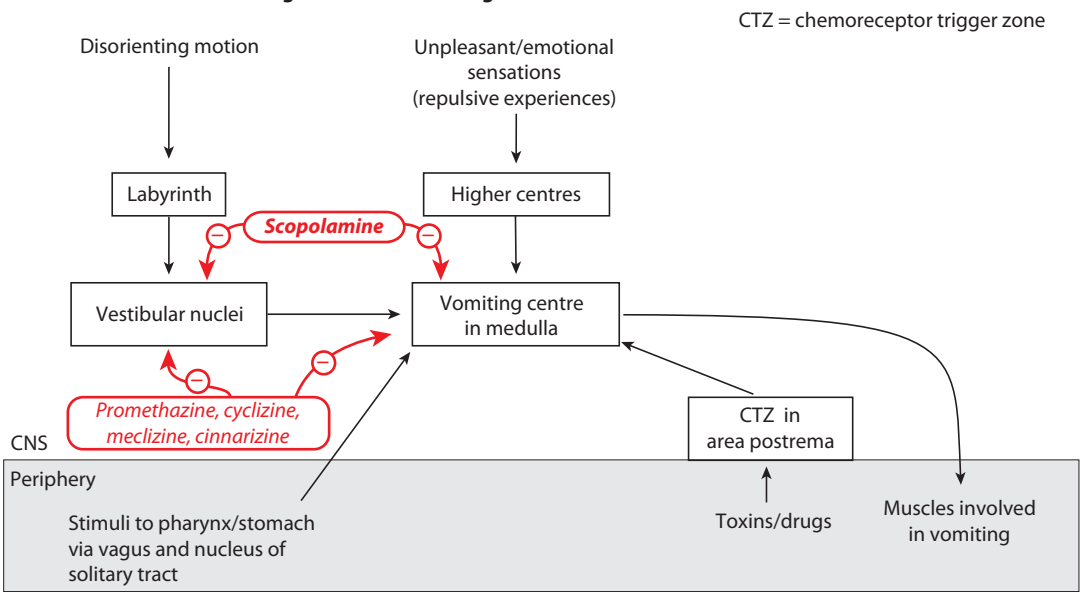
Abs/Distrib/Elim Active orally ($t_{½}$ 5h). A transdermal patch applied behind ear is particularly effective, lasting for up to 3 days.

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.

R&D 7e Ch 29, p 366; D&H 2e Ch 27, p 67

The central control of vomiting and stimuli resulting in emesis



Ondansetron

Actions Antiemetic.

MOA Reversible competitive antagonism at 5-HT_3 receptors in the CTZ and at the sensory endings of vagal afferents in the GIT.

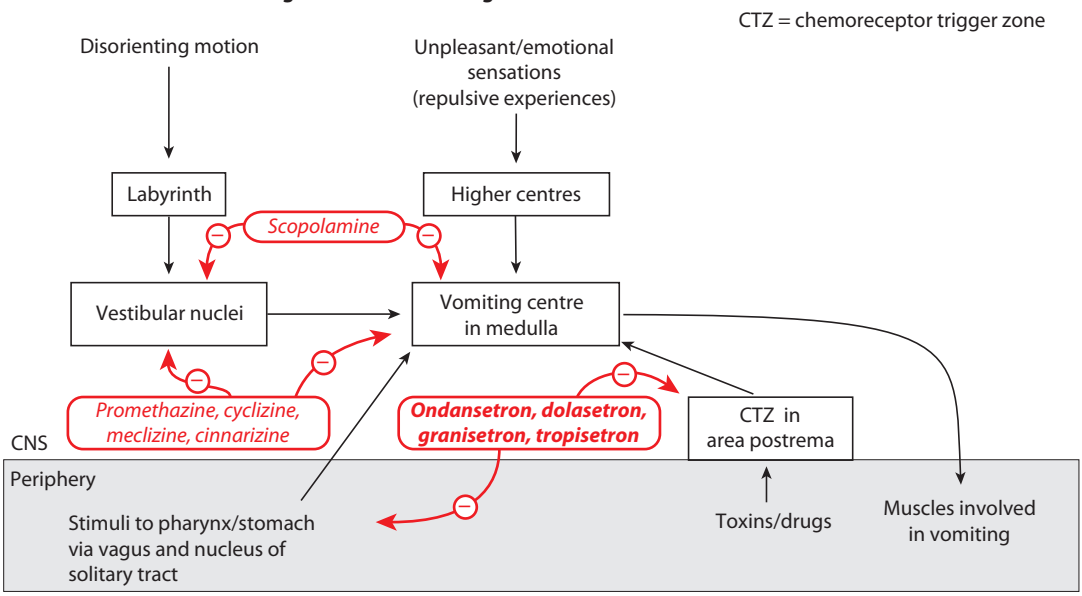
Abs/Distrib/Elim Given orally or i.v. (if vomiting). $T_{0.5}$ 4–6h. Metabolised by cytochrome P450 system in liver.

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



Chlorpromazine

Actions Antiemetic. Antipsychotic (see card 23.01).

MOA Reversible competitive antagonism of dopamine D_2 receptors in CTZ. Some of the side effects are due to antagonism of other receptors (e.g. adrenoceptors and histamine receptors).

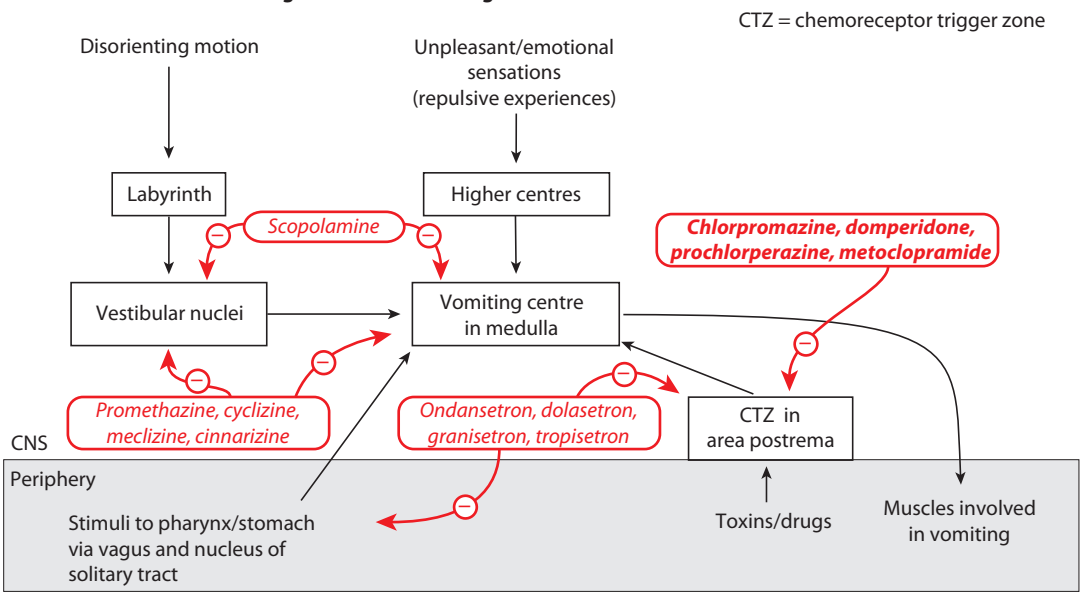
Abs/Distrib/Elim Oral administration. $T_{0.5}$ 15–30h. (P450 metabolism in liver.)

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).

R&D 7e Ch 29, p 367; D&H 2e Ch 27, p 67

The central control of vomiting and stimuli resulting in emesis



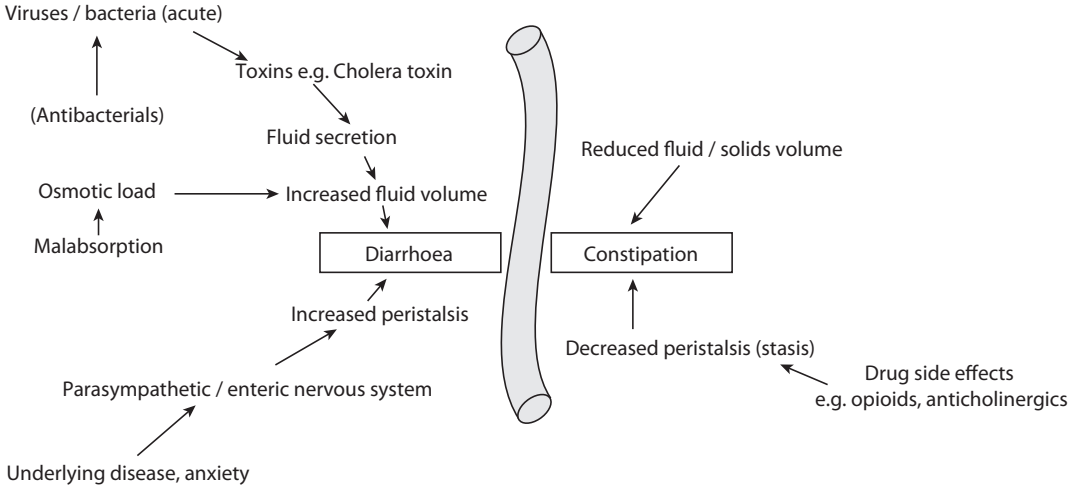
Dexamethasone Mechanism of antiemetic action is not established. High doses used for nausea and vomiting of chemotherapy (esp. cisplatin). Generally used in combination with other antiemetics.

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.

R&D 7e Ch 29, p 367; D&H 2e Ch 27, p 67

Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action



Magnesium sulfate

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.

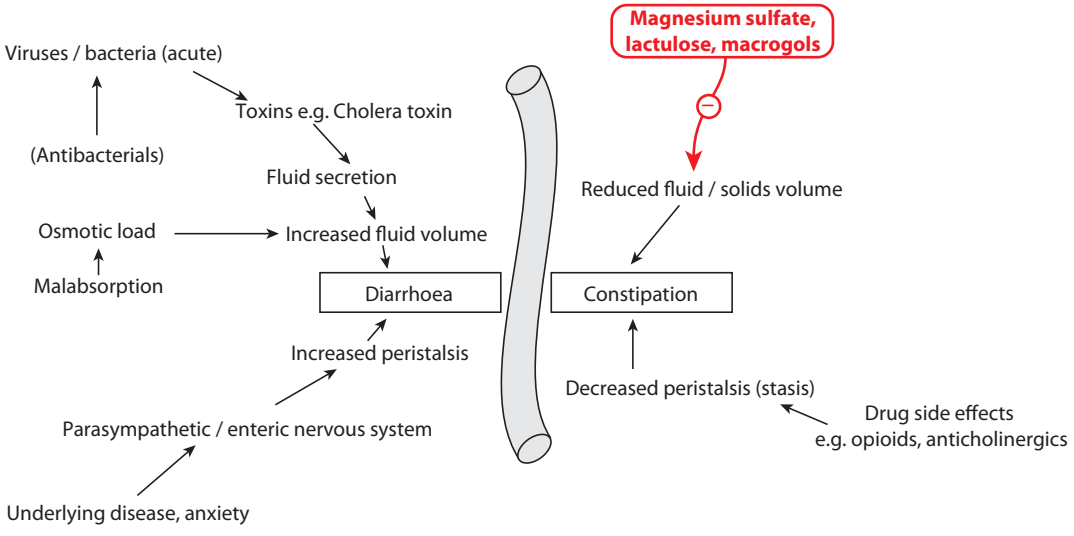
Abs/Distrib/Elim Taken orally. Not absorbed.

Clinical use Bowel cleansing prior to surgery or examination ($MgSO_4$). Constipation (macrogols and lactulose). The effects of lactulose develop after 2–3 days.

Adverse effects Abdominal cramps. Few systemic actions because of low absorption.

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



Actions Purgative.

MOA These agents are poorly absorbed and, being hygroscopic, form a soft faecal mass which distends the gut to promote peristalsis.

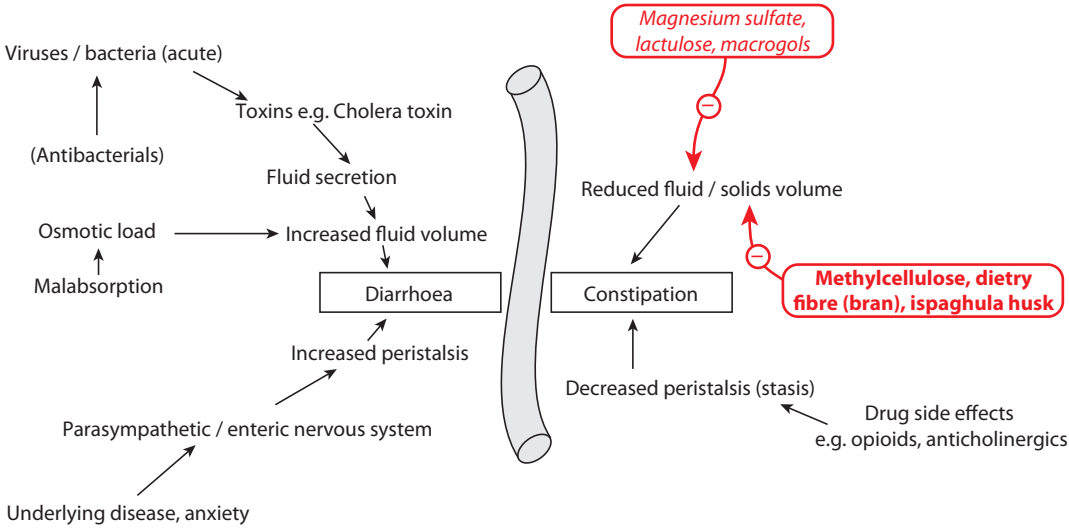
Abs/Distrib/Elim Taken orally. Not absorbed.

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.

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



Lubiprostone

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.

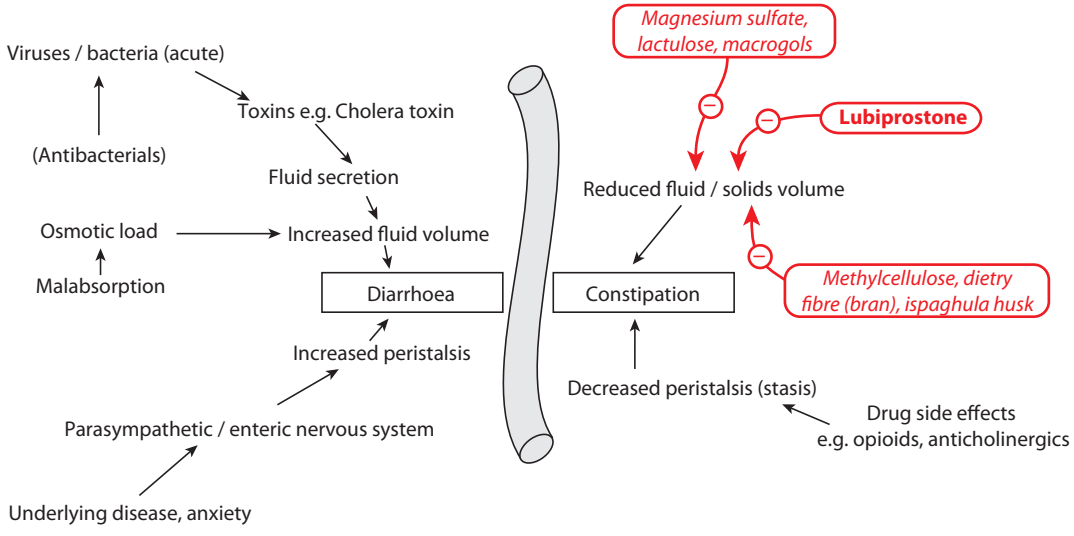
Abs/Distrib/Elim Oral administration. Local action in the gut – little systemic absorption.

Clinical use Chronic constipation. Irritable bowel syndrome with constipation.

Adverse effects Nausea. Diarrhoea.

(Too new to be in R&D or D&H)

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.

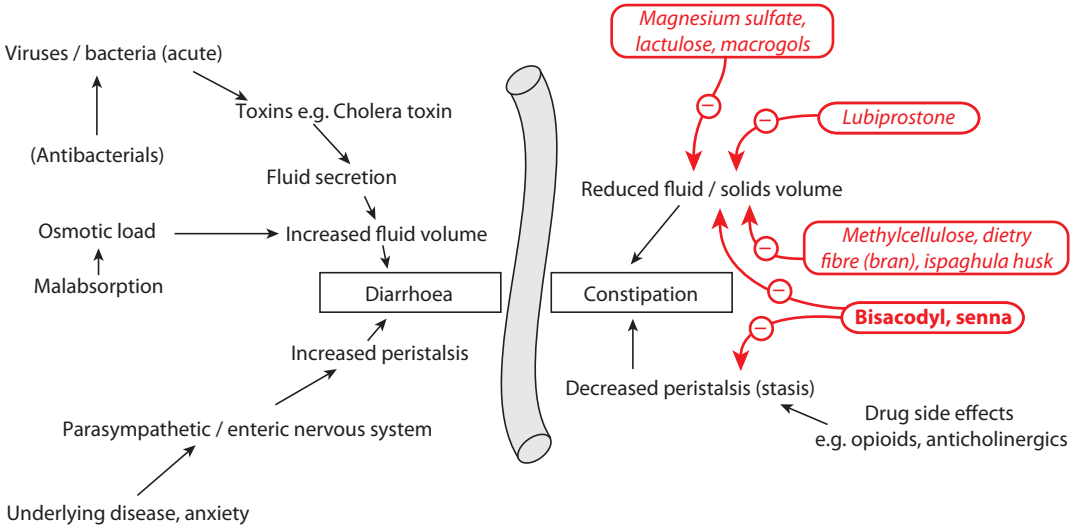
Abs/Distrib/Elim Oral or rectal administration. $T_{0.5}$ 16h. Senna is activated in the colon by bacteria.

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



Actions Softens/lubricates the stool to allow easier passage along gut and defaecation.

MOA Surfactant with emulsifying action.

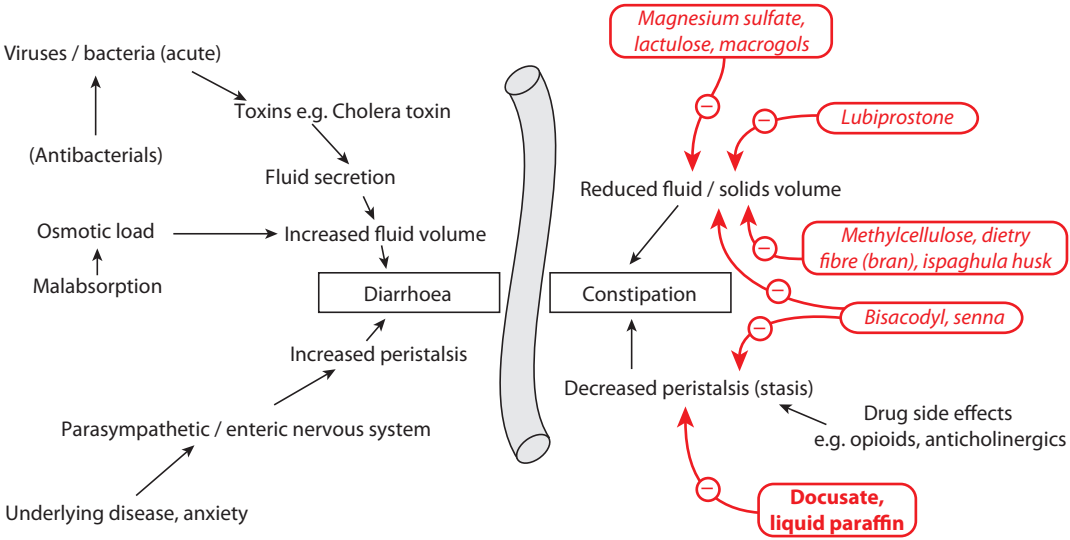
Abs/Distrib/Elim Docusate is given orally or rectally, arachis oil rectally.

Clinical use Constipation. Haemorrhoids.

Adverse effects Well-tolerated – possible abdominal cramping. Liquid paraffin may impair the absorption of fat-soluble vitamins.

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.



Loperamide

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).

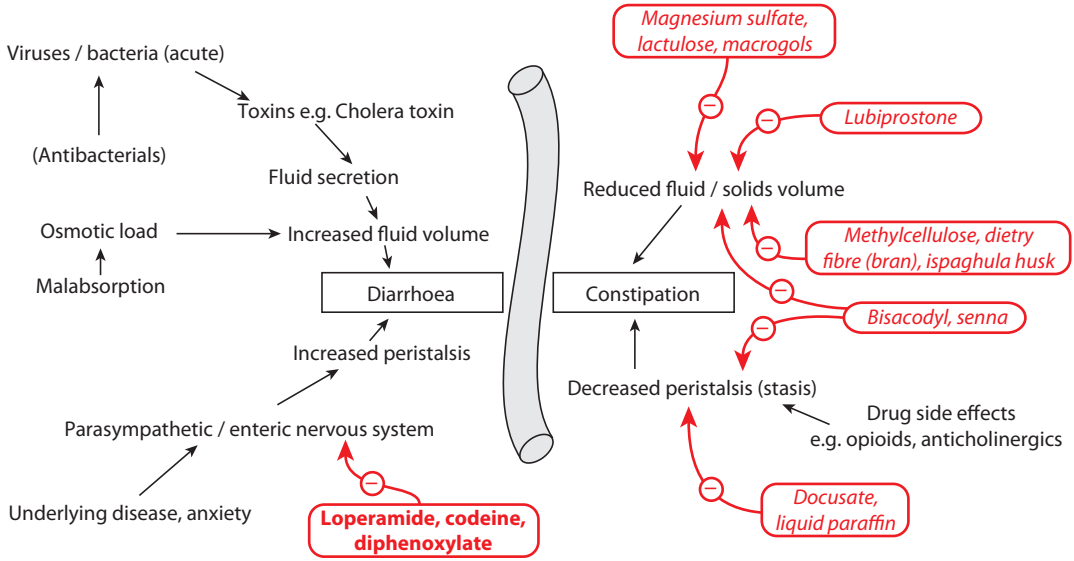
Abs/Distrib/Elim Oral administration. Metabolised by hepatic cytochrome P_{450} system. $t_{½}$ 10h. Diphenoxylate is hydrolysed to an active metabolite.

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.

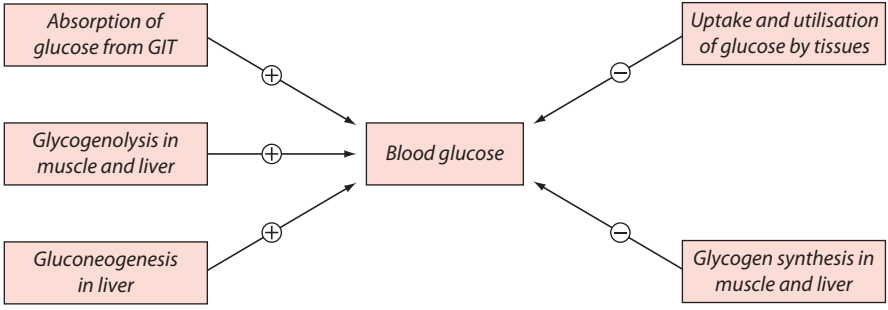
R&D 7e Ch 29, p 369; D&H 2e Ch 27, p 67

Processes in the GIT involved in constipation and diarrhoea which are potential targets for drug action



NOTES

The main processes determining blood glucose concentrations



Actions Promotes tissue uptake and storage of glucose, amino acids and fats. Acutely lowers blood glucose. Inhibits hepatic glycogenolysis and gluconeogenesis. Increases glycogen synthesis in muscle/liver. Inhibits lipolysis. Stimulates protein synthesis. Longer-term effects on growth and gene expression.

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.

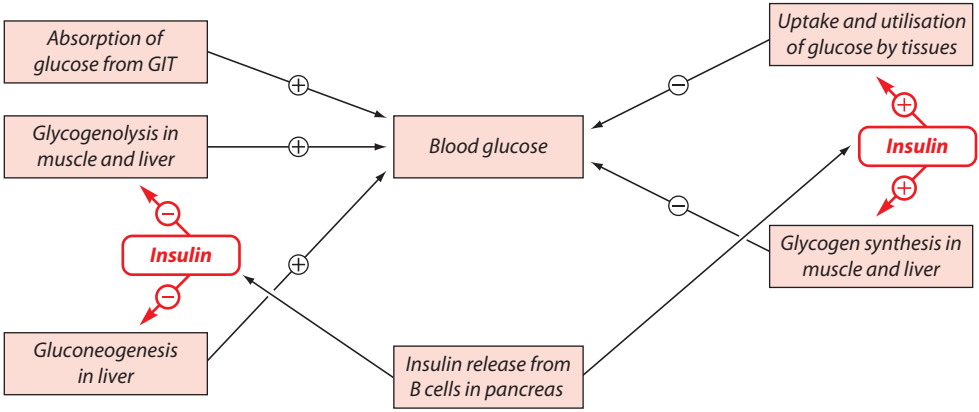
Clinical use Life-long treatment of type 1 diabetes. Also for type 2 diabetes not controlled by oral hypoglycaemic agents. Soluble insulin also for emergency i.v. treatment of diabetic ketoacidosis.

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.

R&D 7e Ch 30, pp 372-376; D&H 2e Ch 28, pp 68-69

The main processes determining blood glucose concentrations



Glibenclamide

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.

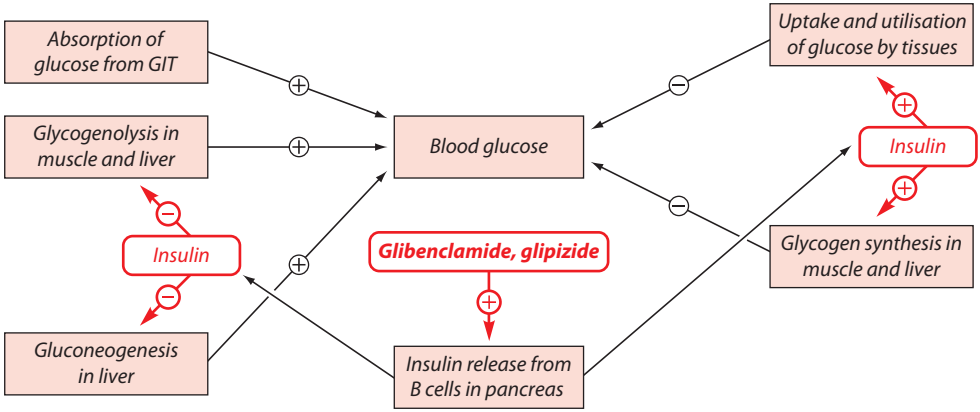
Abs/Distrb/Elim Given orally they bind extensively to plasma proteins. Half-lives: glibenclamide 10h, tolbutamide 4h, glipizide 4h, glimepiride 5h. Actions prolonged in patients with renal disease.

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.

R&D 7e Ch 30, p 380; D&H 2e Ch 28, p 69

The main processes determining blood glucose concentrations



Metformin

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.

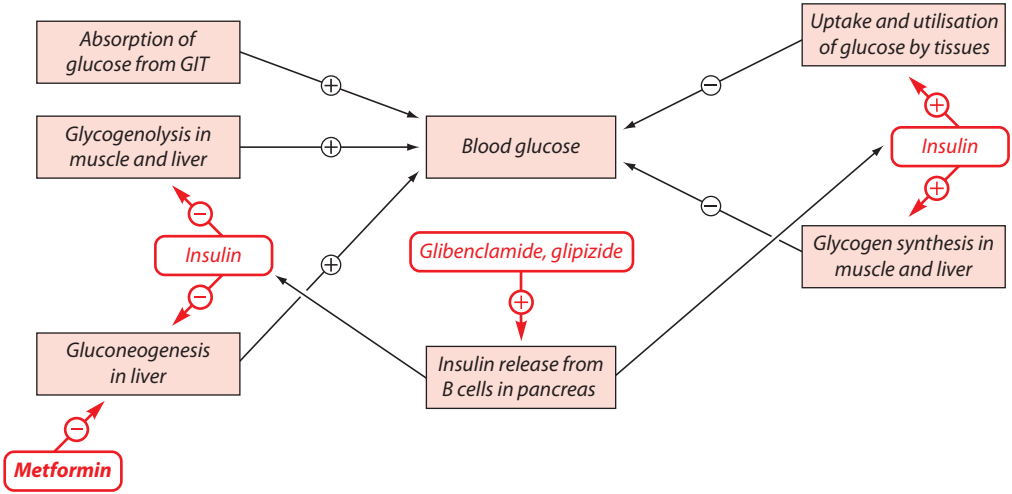
Abs/Distrb/Elim Given by mouth. Half-life 3h. Mostly excreted unchanged in urine (avoid in patients with renal insufficiency).

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.)

R&D 7e Ch 30, pp 379-380; D&H Ch 28, p 69

The main processes determining blood glucose concentrations



Repaglinide

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_{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.

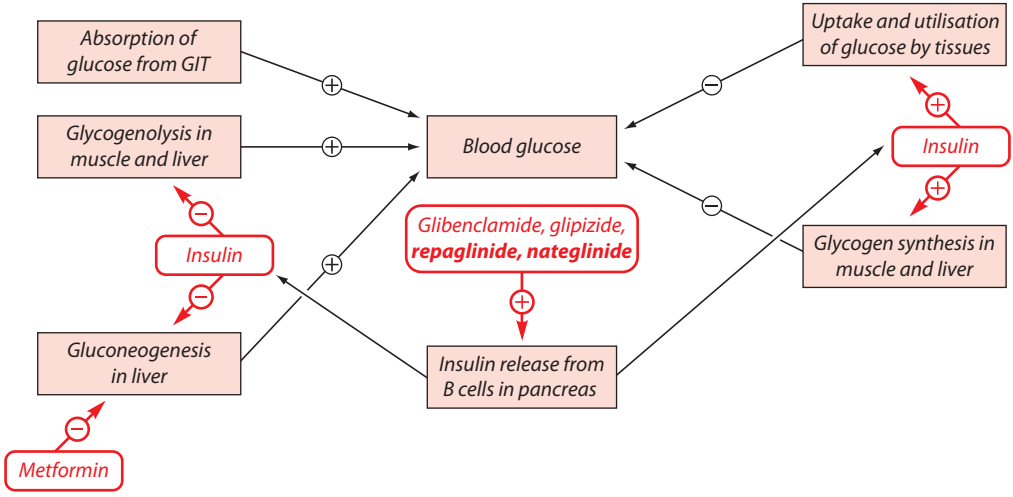
Abs/Distrb/Elim Quick onset and short duration of action. Half-life 1h. (Its actions can be reduced by drugs that induce hepatic P450 enzymes, e.g. carbamazepine.) Nateglinide half-life 1.5h.

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).

R&D 7e Ch 30, p 381; D&H 2e Ch 28, p 69

The main processes determining blood glucose concentrations



Rosiglitazone

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.

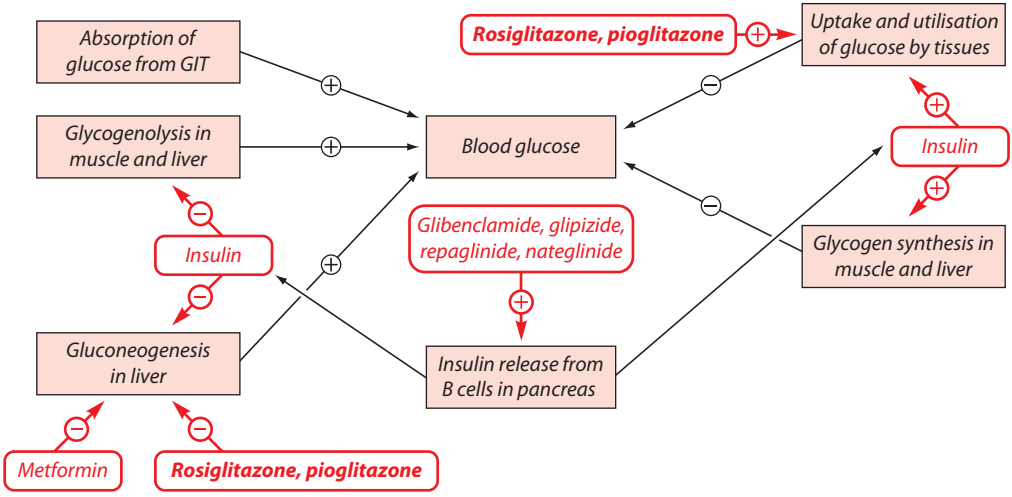
Abs/Distrb/Elim Rapid oral absorption, highly bound to plasma proteins. Eliminated mainly by P450 metabolism in liver. (Interactions may occur with drugs inhibiting or inducing cytochrome P450.) Short half-life (7h) but some activity of metabolites.

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



Actions Delays carbohydrate absorption from intestine.

MOA Inhibits intestinal α-glucosidase and pancreatic α-amylase so reduces the rise in blood glucose which follows a meal. α-glucosidase is the enzyme responsible for breaking down starches and oligosaccharides to yield the absorbable monosaccharides.

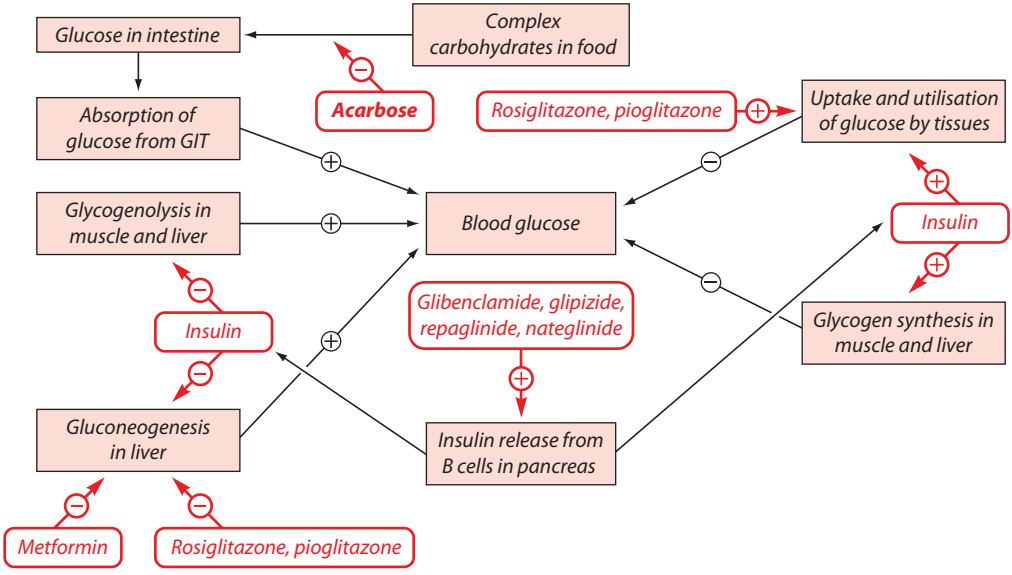
Abs/Distrb/Elim Metabolised in GIT by bacteria and digestive enzymes. Half-life 2h.

Clinical use Type 2 diabetes mellitus not controlled by other drugs.

Adverse effects Gastrointestinal discomfort – flatulence, diarrhoea.

R&D 7e Ch 30, p 382; D&H 2e Ch 28, p 69

The main processes determining blood glucose concentrations



Glucagon

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 β-adrenoceptors. It elevates blood glucose by stimulating hepatic gluconeogenesis and glycogenolysis and by inhibiting glycogen synthesis.

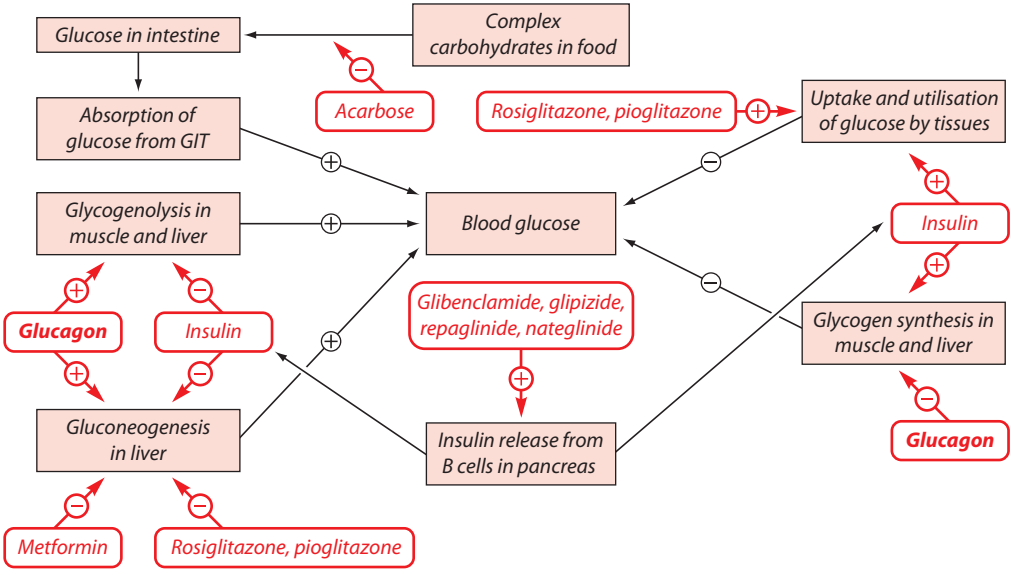
Abs/Distrb/Elim Glucagon is a peptide hormone which must be given by injection. Plasma half-life 5min.

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 β-adrenoceptor antagonists.)

Adverse effects Uncommon. Cardiac stimulation in patients taking β-blockers or with phaeochromocytoma.

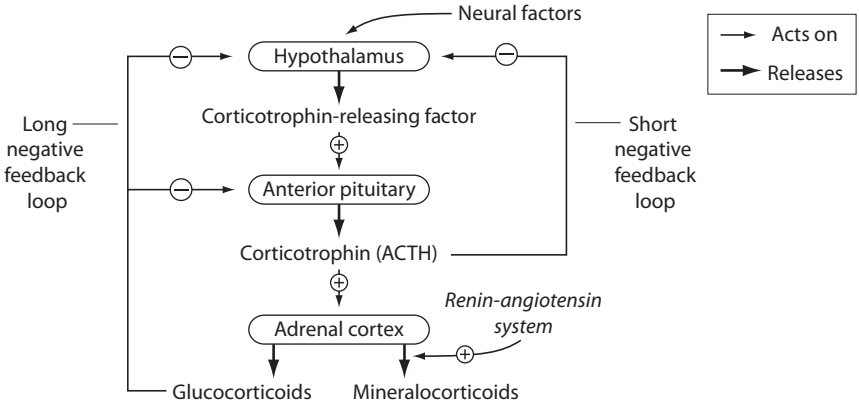
R&D 7e Ch 30, pp 376-377; D&H 2e Ch 28, p 69

The main processes determining blood glucose concentrations



Notes

The figure outlines the synthesis and release of the endogenous corticosteroids.



Hydrocortisone

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.

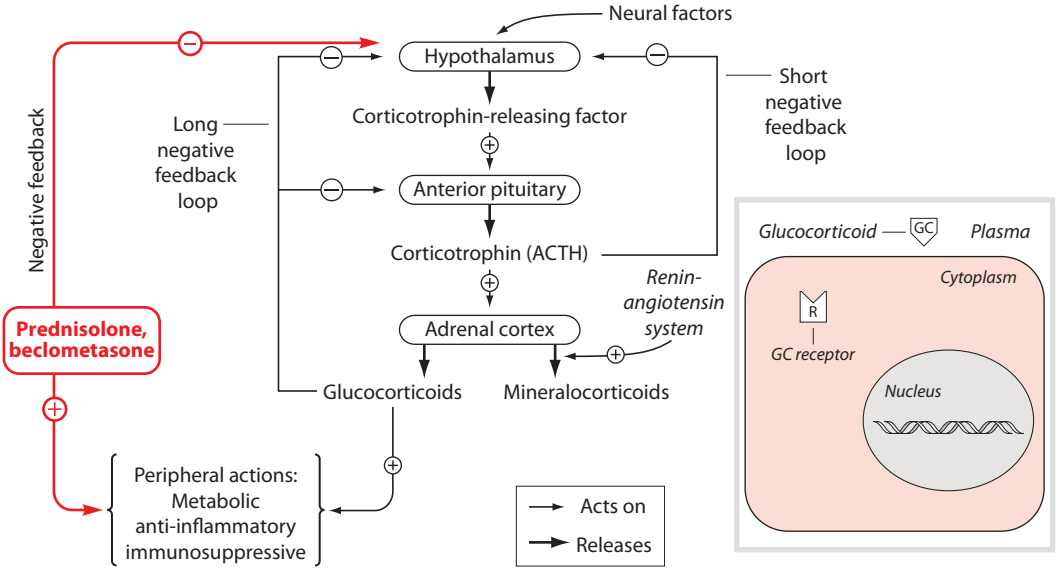
Similar drugs Prednisolone (short-acting; oral, injectable). Triamcinolone (intermediate-acting; i.m. injection, topical). Dexamethasone (longer-acting; oral, injectable) . Beclometasone (given by inhalation).

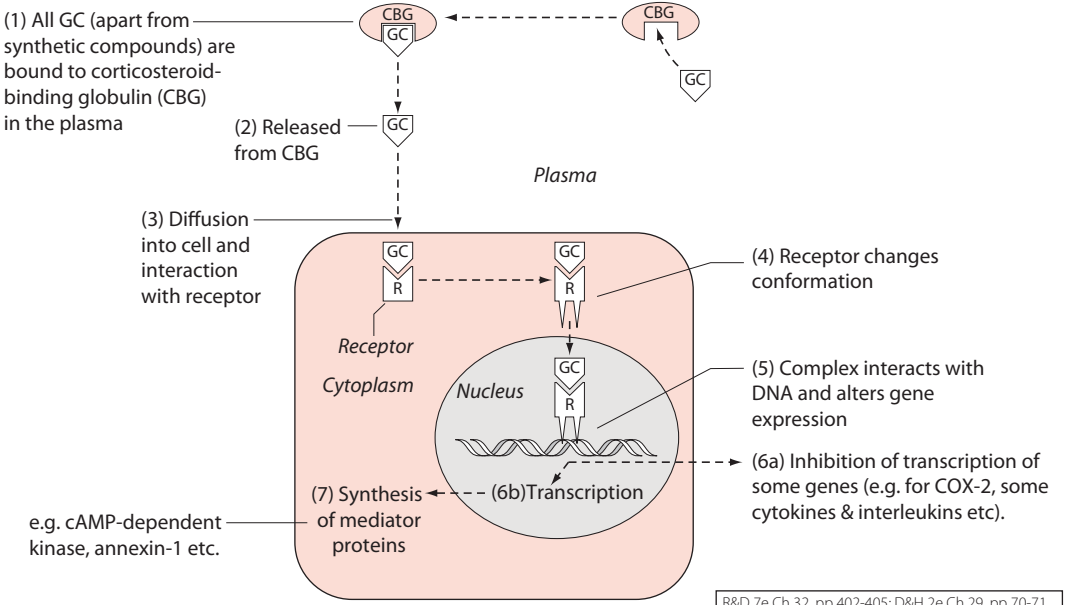
Clinical use Inflammatory, hypersensitivity and autoimmune diseases (rheumatoid arthritis, asthma, anaphylactic shock etc.); to prevent graft rejection; in some cancers.
Replacement therapy in adrenal failure.

Adverse effects See card 16.03.

R&D 7e Ch 32, pp 400-401; D&H 2e Ch 29, pp 70-71

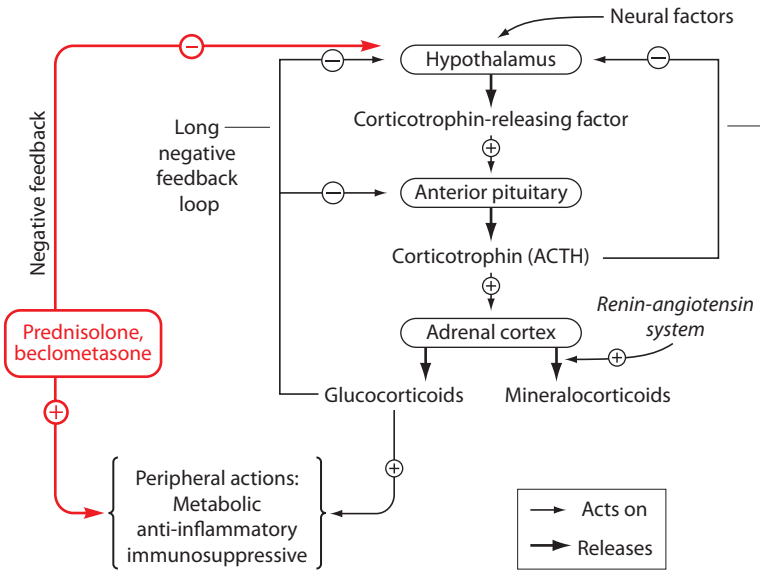
The figure outlines the synthesis and release of the endogenous corticosteroids.

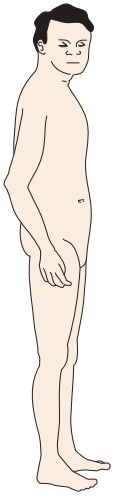




R&D 7e Ch 32, pp 402-405; D&H 2e Ch 29, pp 70-71

The figure outlines the synthesis and release of the endogenous corticosteroids.





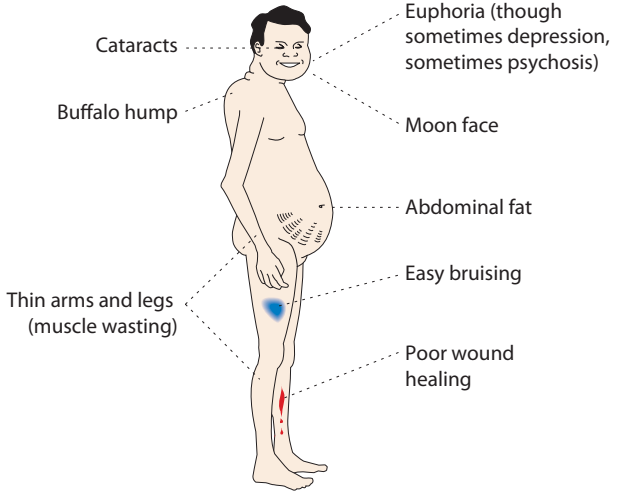
Before prolonged corticosteroid therapy

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 syndome

* When used thus, the metbolic actions are unwanted

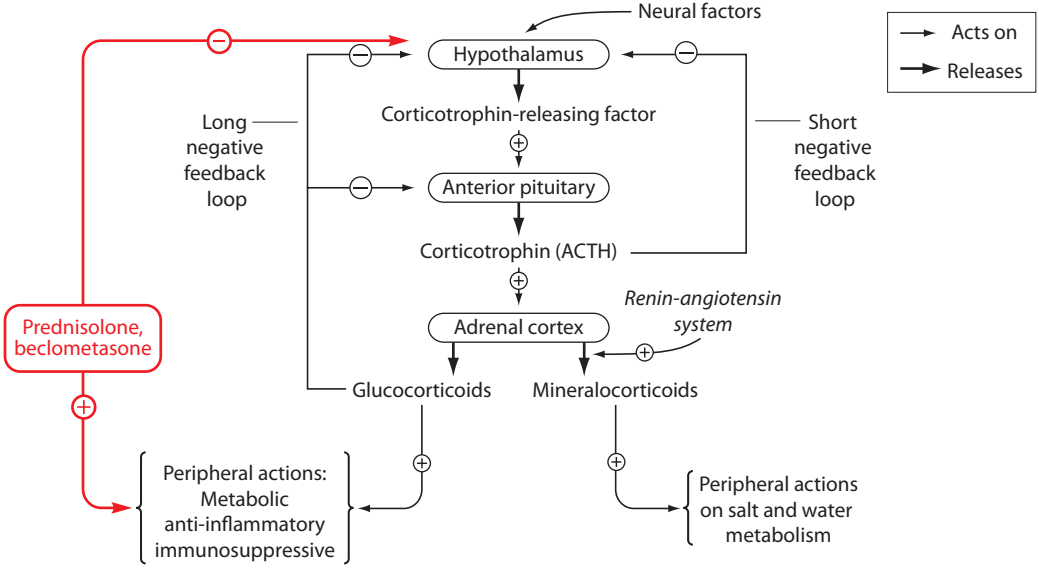
B. Used in corticosteroid **deficiency** there are few adverse actions



Iatrogenic Cushing's syndrome (after prolonged glucocorticoid therapy)

R&D 7e Ch 32, pp 403- 406; D&H 2e, Ch 29, pp 70-71

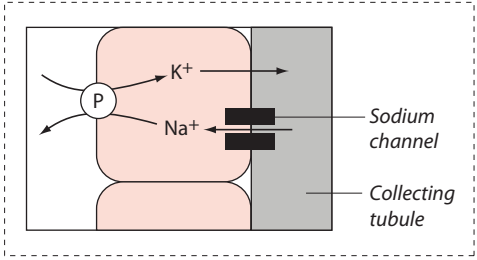
The figure outlines the synthesis and release of the corticosteroids.



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).

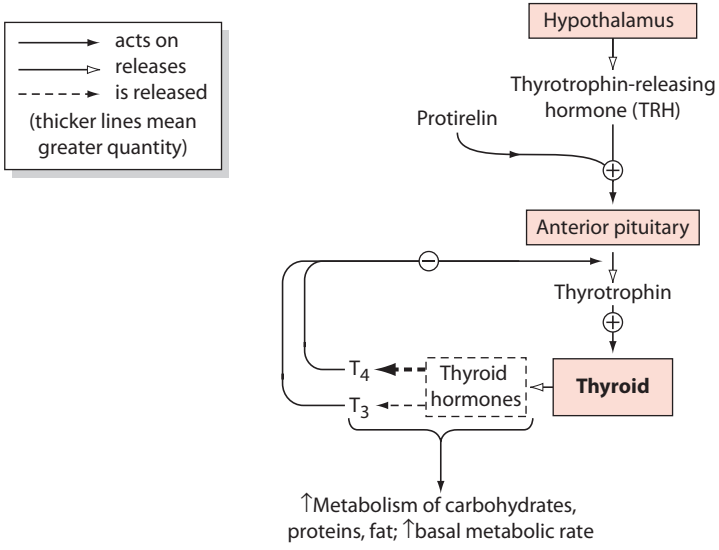


Abs/Distrb/Elim Given orally.

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



Carbimazole

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.

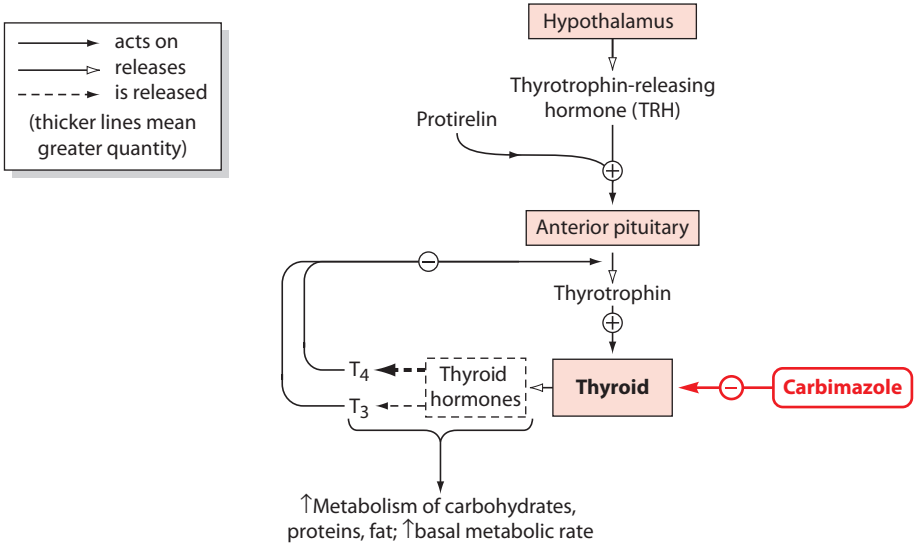
Clinical use Hyperthyroidism; to control the disease before surgery.

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.

R&D 7e Ch 33, pp 414- 415; D&H 2e Ch30, p 73

Outline of the control and actions of thyroid hormone system



Levothyroxine

Actions Increased metabolism of carbohydrates, proteins and fats; increase in basal metabolic rate.

MOA The drug enters cells and is converted to T_3 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 T_4.

Abs/Distrb/Elim Given orally. Has long half-life.

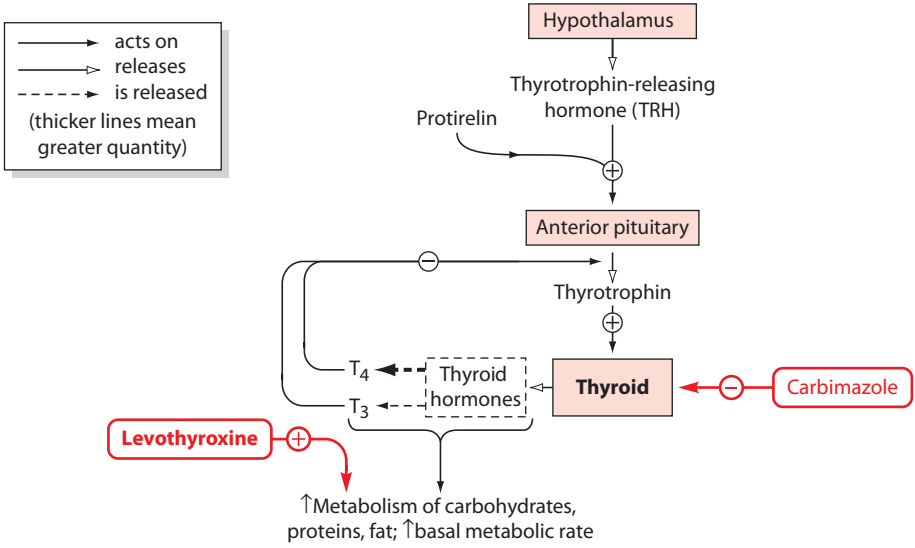
Clinical use Hypothyroidism. Liothyronine is used for myxoedema coma.

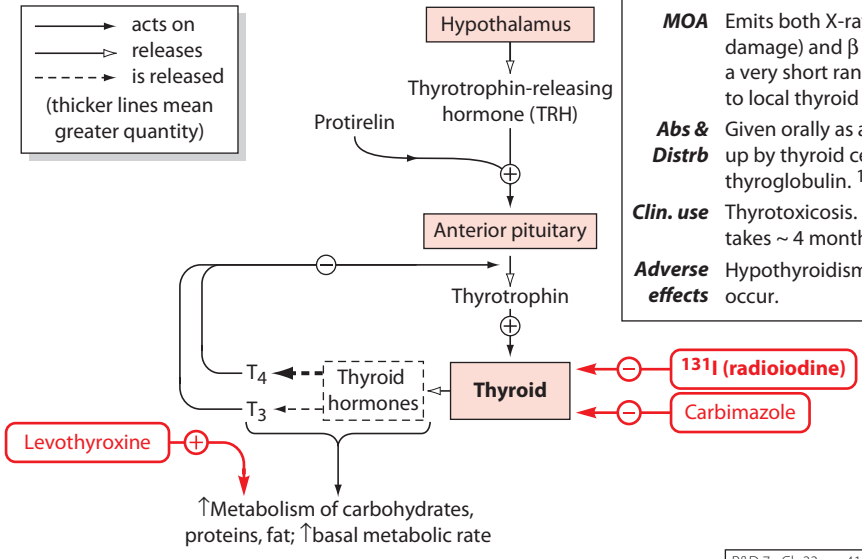
Adverse effects Nervousness, palpitations, insomnia, heat intolerance, weight loss.

Special points Best given on an empty stomach since some foods can interfere with absorption.

R&D 7e Ch 33, p 415; D&H 2e Ch 30, pp 72-73

Outline of the control and actions of thyroid hormone system





Radioactive iodine (^{131}I):

MOA	Emits both X-rays (which do no damage) and β 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.

R&D 7e Ch 33, pp 413-415; D&H 2e Ch 30, pp 72-73

Schematic outline of bone formation

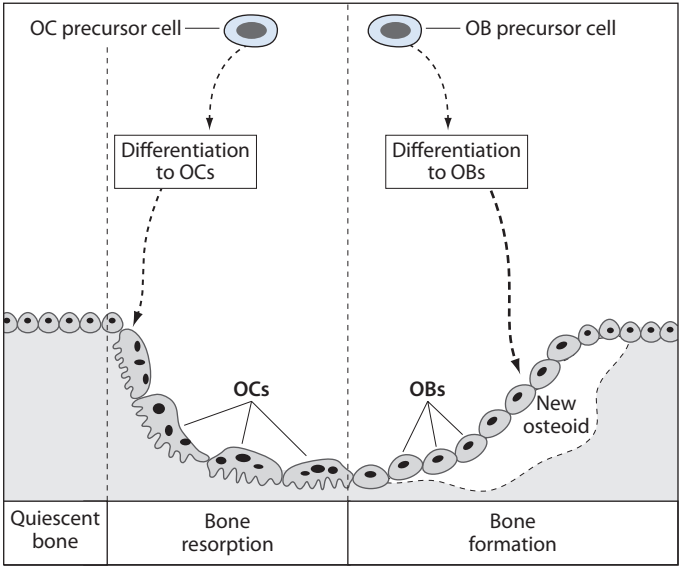
The bone remodelling cycle:

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.



A bisphosphonate that modifies bone remodelling (Similar drug: pamidronate)

Alendronate

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.

Clinical use Postmenopausal osteoporosis (either alone or with an oestrogen).
Paget's disease of bone.
Glucocorticoid-induced osteoporosis.
Malignant hypercalcaemia.
Bone secondaries in breast cancer.

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.

R&D 7e Ch 35, p 438; D&H 2e Ch 31, pp 74-75

Schematic outline of bone formation

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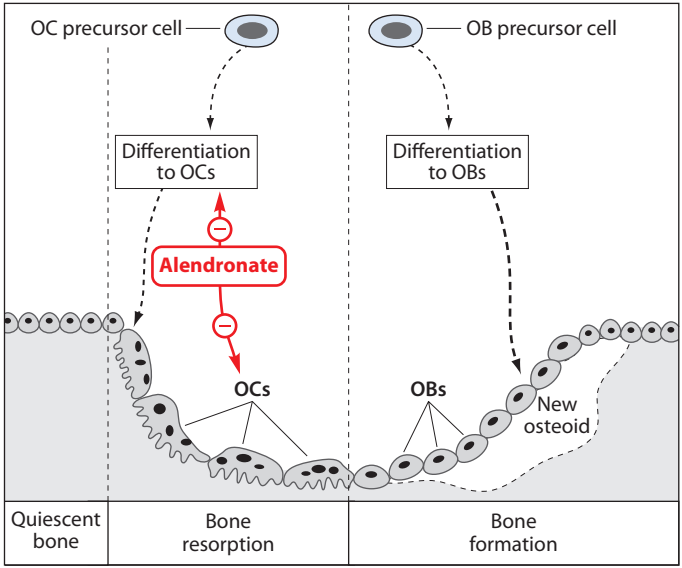

A recombinant form of parathyroid hormone (Similar drug: parathyroid hormone)

Teriparatide

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.

R&D 7e Ch 35, p 439; D&H 2e Ch 31, pp 74-75

Schematic outline of bone formation

The bone remodelling cycle:

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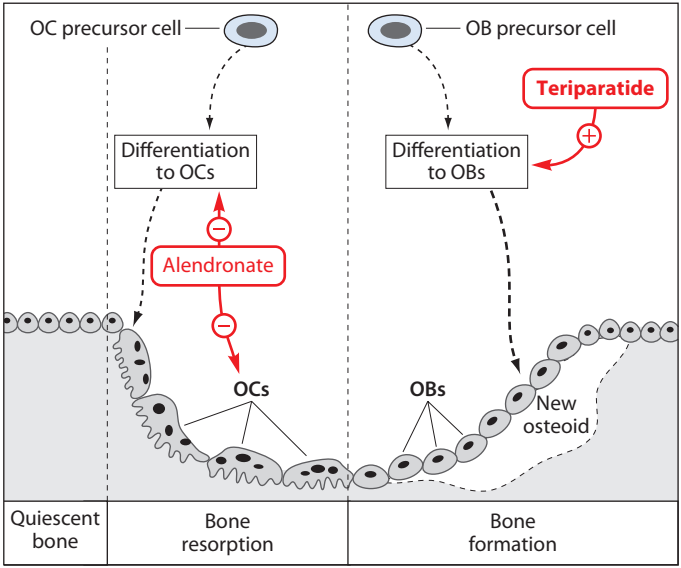

Raloxifene

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.

R&D 7e Ch 35, pp 438-439; D&H 2e Ch 31, pp 74-75

Schematic outline of bone formation

The bone remodelling cycle:

Bone resorption

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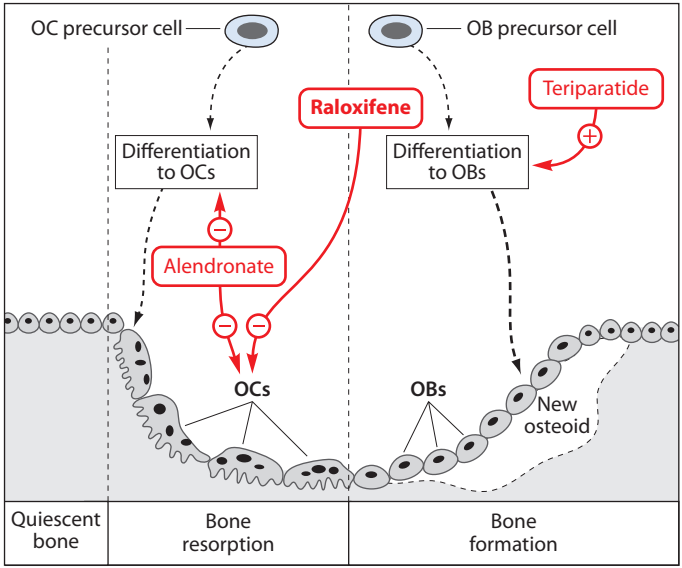
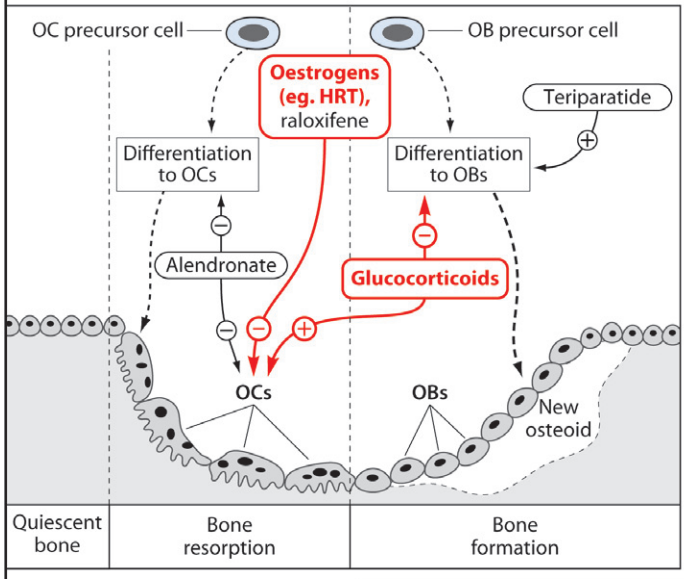


Oestrogens are important in maintaining bone integrity in females and the decrease in their levels at menopause results in osteoporosis. Oestrogen preparations (see figure) are not the first choice for this condition because of the risk of breast cancer.

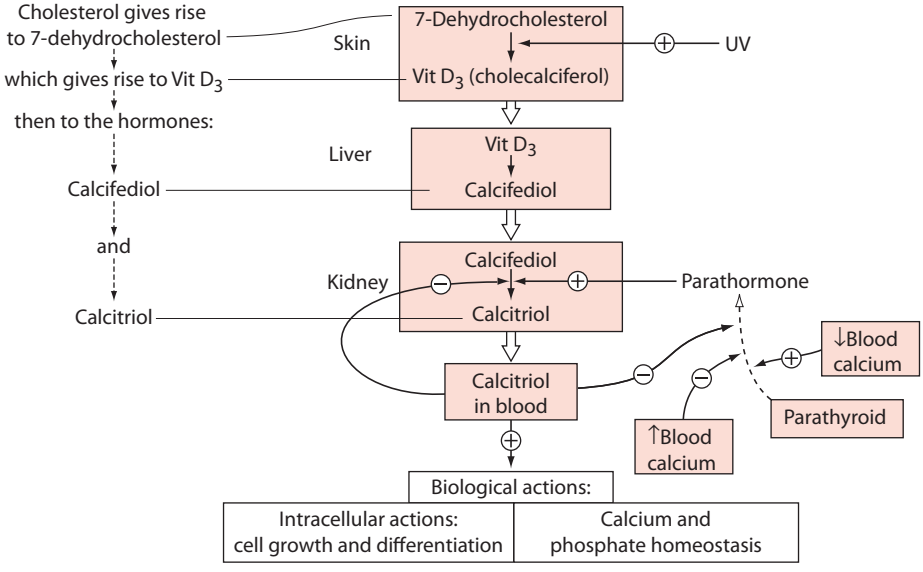
Large or long-continued doses of **glucocorticoids** can cause osteoporosis by inhibiting OB differentiation and activity and stimulating OC activity.

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).



R&D 7e Ch 35 pp 435-437; D&H 2e Ch 31, pp 74-75

The vitamin D family, parathyroid and calcium metabolism



A preparation of vitamin D_2

Ergocalciferol

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.

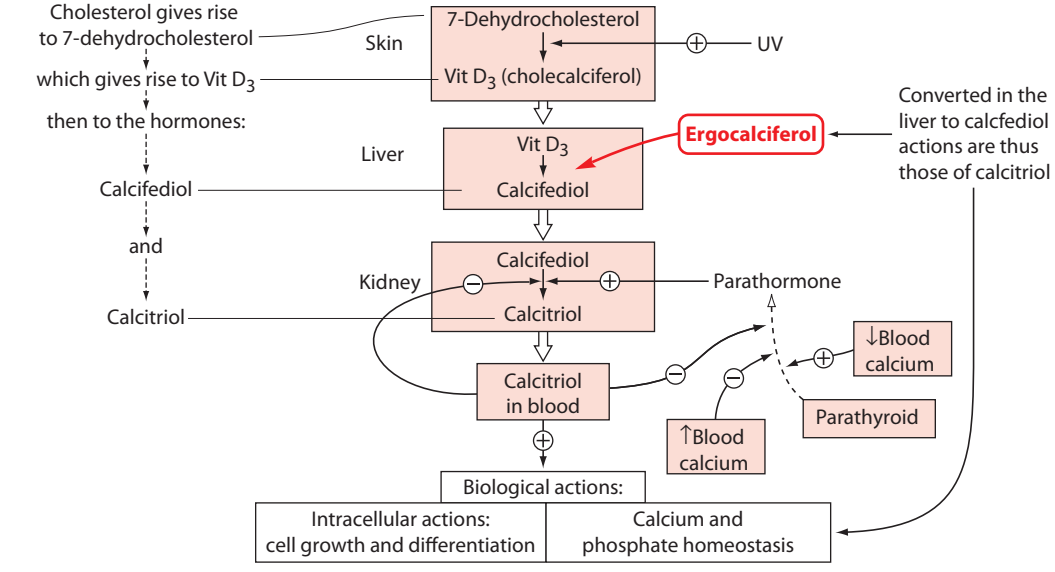
Clinical use Rickets; the hypocalcaemia of hypoparathyroidism; the osteodystrophy of renal failure.

Adverse effects Excessive intake can cause hypercalcaemia; if this persists renal calculi may result.

Special points Serum calcium levels should be monitored.

R&D 7e Ch 35, p 439; D&H 2e Ch 31, pp 74-75

The vitamin D family, parathyroid and calcium metabolism



A secosteroid that has all the actions of vitamin D_2 and vitamin D_3

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/Distrb/Elim Given orally it needs bile salts for absorption. Can be given by i.v. injection.

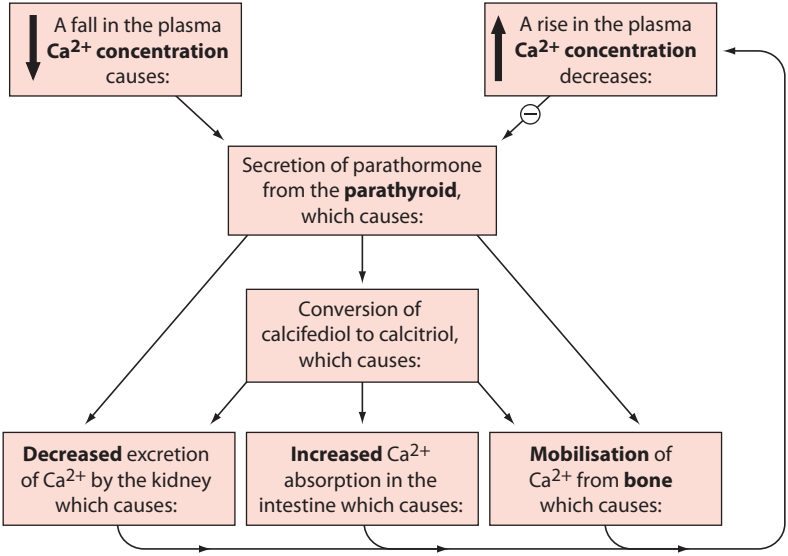
Clinical use The osteodystrophy of chronic renal failure which is due to decreased calcitriol; postmenopausal osteoporosis.

Adverse effects Excessive intake can cause hypercalcaemia; if this persists renal calculi may result.

Special points Serum calcium, phosphate and and creatinine levels should be monitored.

R&D 7e , p 439; D&H 2e Ch 31, pp 74-75

Calcium homeostasis, parathyroid and bone



Calcitonin

Actions Lowers 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.

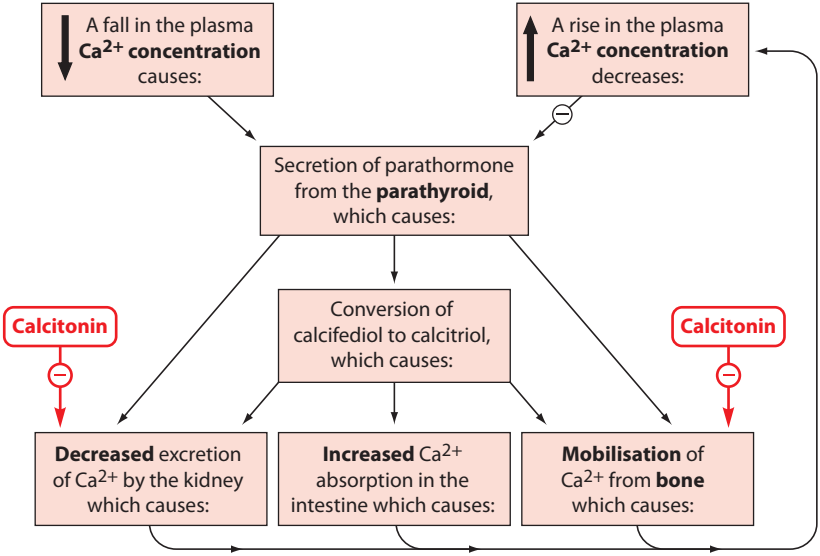
Abs/Distrb/Elim Given by subcut. or i.m. injection or by nasal spray. Plasma half-life is 4–12min; action lasts several hours.

Clinical use Hypercalcaemia; Paget's disease; the prevention of postmenopausal osteoporosis.

Adverse effects GIT disorders; facial flushing; taste disturbances; dizziness; muscle pain.

R&D 7e Ch 35, p 437; D&H 2e Ch 31, pp 74-75

Calcium homeostasis, parathyroid and bone



Cinacalcet

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.

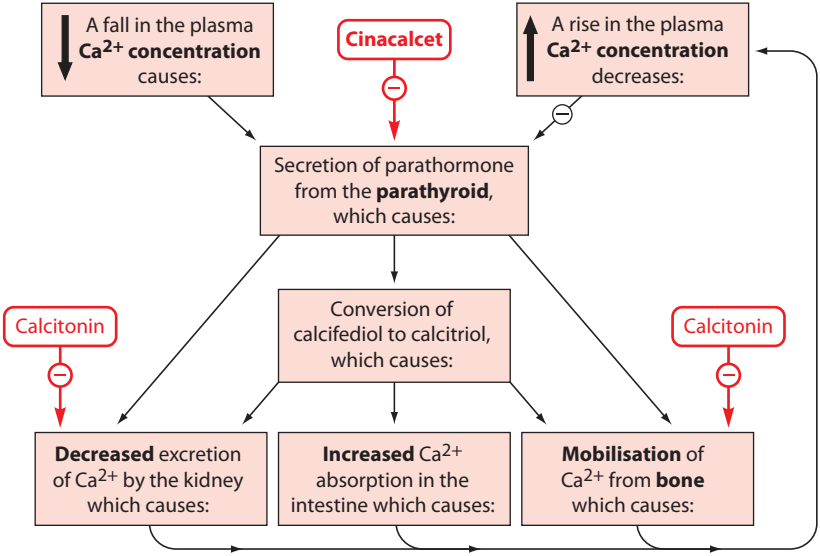
Adverse effects Excessive intake can cause hypercalcaemia; if this persists renal calculi may result.

Special points Serum calcium, phosphate and and creatinine levels should be monitored.

R&D 7e Ch 35, p 440; D&H 2e Ch 31, pp 74-75

A 69-year-old woman slips on her front steps, falls and breaks her arm. Probable diagnosis? Drug treatment? Which drugs and why?

Calcium homeostasis, parathyroid and 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.

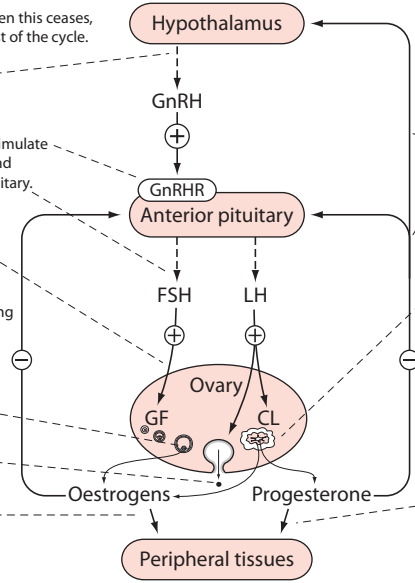
Drugs to be considered:

A drug which ***decreases bone resorption*** and thus prevents futher 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.

R&D 7e Ch 35 ; D&H 2e Ch 31, pp 74-75

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

. . . to act on GnRH receptors in the ant. pit to stimulate release of follicle-stimulating hormone (FSH) and luteinising hormone (LH) from the anterior pituitary.

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.

Ethinylestradiol + norethisterone

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.

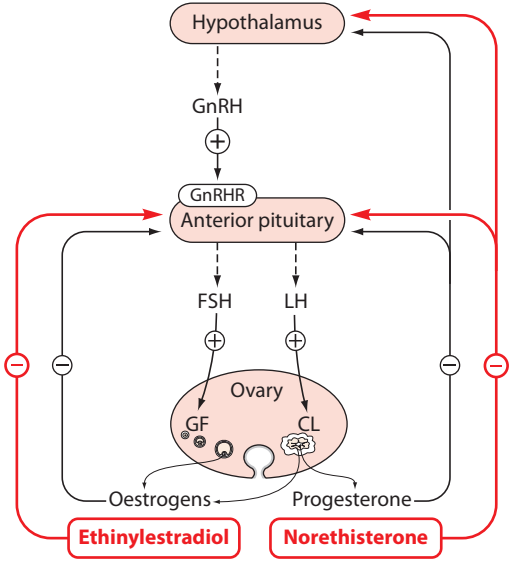
Abs/Distrb/Elim Given orally.

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.

R&D 7e Ch 34, pp 425-426; D&H 2e Ch 32, pp 76-77

The figure shows the hormonal control of the menstrual cycle



Clomifene

Action & MOA Acts on the anterior pituitary to inhibit the negative feedback action of endogenous oestrogens thus increasing gonadotrophin release.

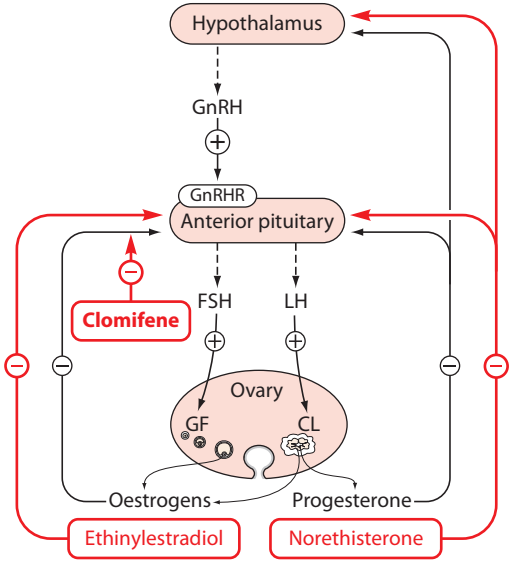
Abs/Distrb/Elim Given orally.

Clinical use Treatment of infertility.

Adverse effects Menopausal-like hot flushes; ovarian enlargement. Sometimes visual symptoms (after images). GIT disturbances may occur.

R&D 7e Ch 34, pp 424-425; D&H 2e Ch 32, pp 76-77

The figure shows the hormonal control of the menstrual cycle



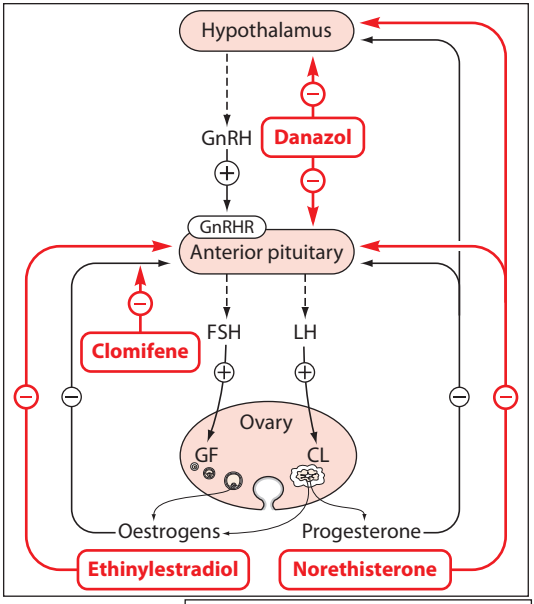
Danazol

Action & MOA Inhibits gonadal function by suppressing the mid-cycle surge of gonadotrophins.

Abs/Distrb/Elim Given orally, $T_{0.5}$ >15h.

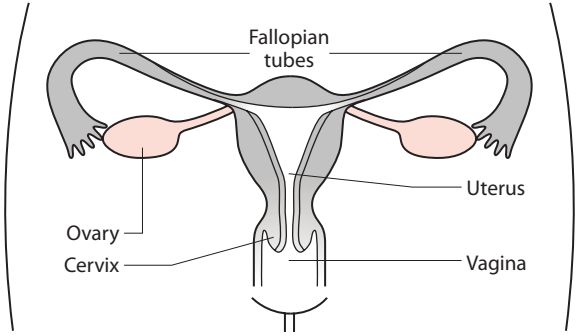
Clinical use Treatment of endometriosis.

Adverse effects Moderate effects are common: weight gain, acne, hot flushes, amenorrhoea, masculinisation (hirsutism, deepening of voice etc.).



R&D 7e Ch 34, pp 424-425; D&H 2e Ch 32, pp 76-77

The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries



Oxytocin

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.

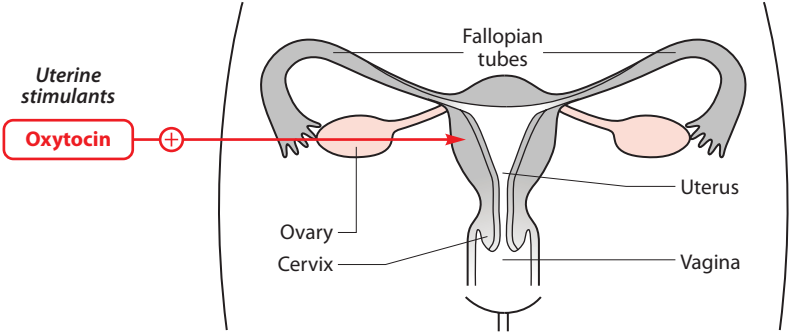
Clinical use To induce or augment labour when the uterine muscle is not functioning adequately.
To prevent or treat post-partum bleeding due to uterine atony.
To treat haemorrhage due to incomplete abortion.

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.

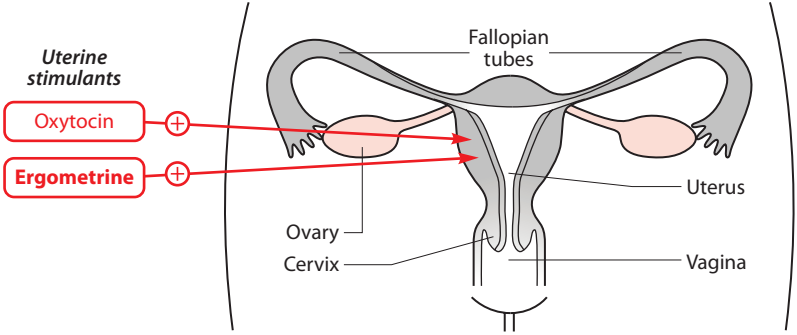
Abs/Distrb/Elim Given orally, i.m. or i.v. Rapid onset of action. Duration: 3–6h.

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.

R&D 7e Ch 34, pp 427-428; D&H 2e Ch 32, p 77

The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries



Carboprost

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.

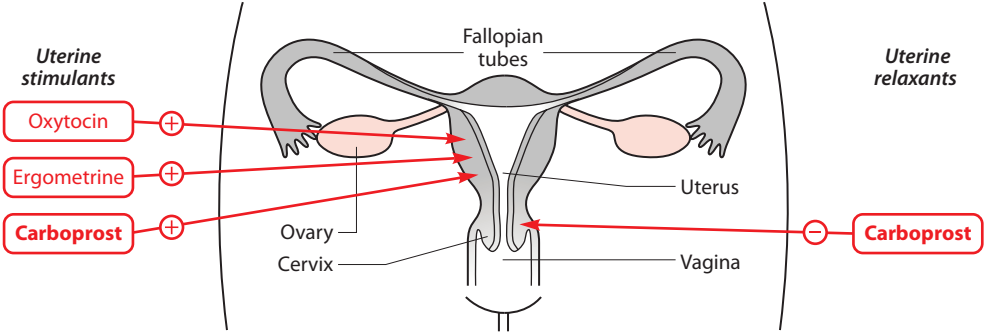
Clinical use To treat post-partum haemorrhage unresponsive to oxytocin or ergometrine.

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.

R&D 7e Ch 34, p 428; D&H 2e Ch 32, pp 76-77

The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries



Ritodrine

Actions Inhibits spontaneous and oxytocin-induced contractions of the pregnant uterus.

MOA Activates β-adrenoceptors on uterine smooth muscle causing relaxation.

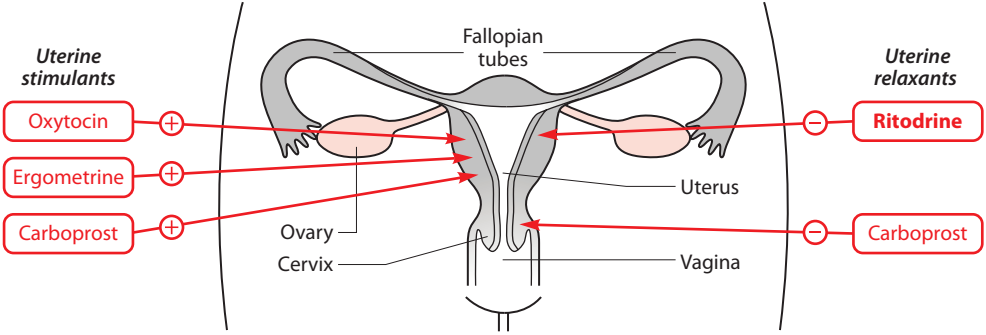
Abs/Distrb/Elim Given by i.v. infusion.

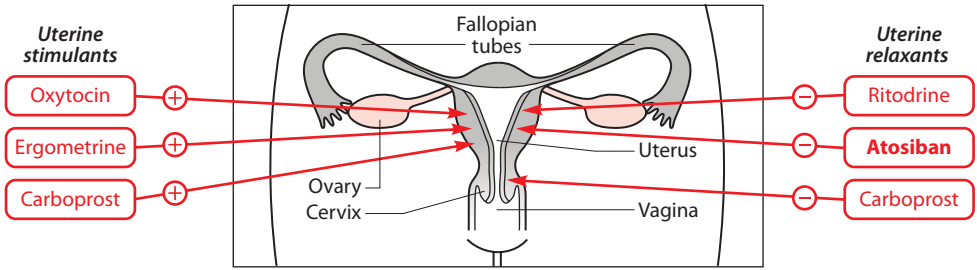
Clinical use To delay pre-term labour.

Adverse effects GIT disturbances; headache, dysrhythmias, vasodilatation, hypersensitivity reactions.

R&D 7e Ch 34, p 428; D&H 2e Ch 32, p 77

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.

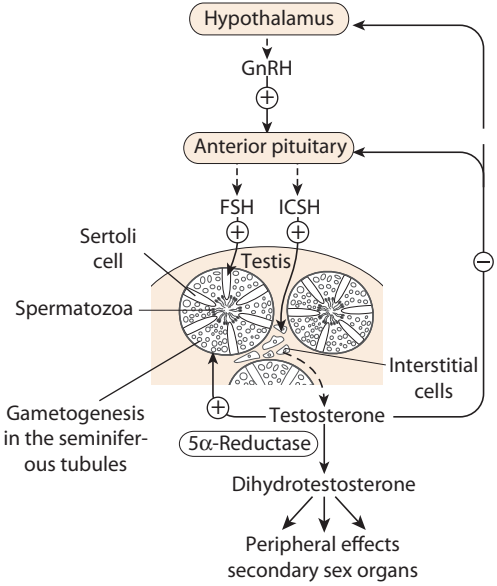
Abs/Distrb/Elim Given by i.v. injection.

Clinical use To delay pre-term labour.

Adverse effects GIT disturbances, tachycardia, hypotension, dizziness, headache.

R&D 7e Ch 34, p 428; D&H 2e Ch 32, p 77

Hormonal control of the male reproductive system



Testosterone

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.

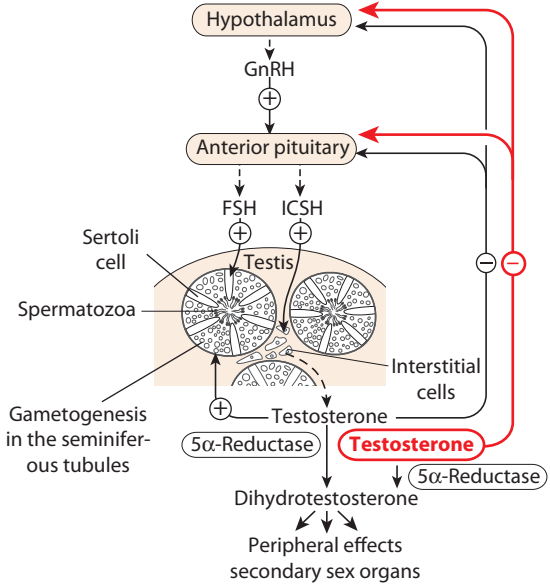
Abs/Distrb/Elim Administration can be oral, buccal, by i.m. injection or transdermally.

Clinical use Replacement therapy in hypogonadism.

Adverse effects Eventual decrease of gonadotrophin release resulting in infertility; oedema due to salt and water retention.

R&D 7e Ch 34, pp 422-423; D&H 2e Ch 32, pp 77-78

Hormonal control of the male reproductive system



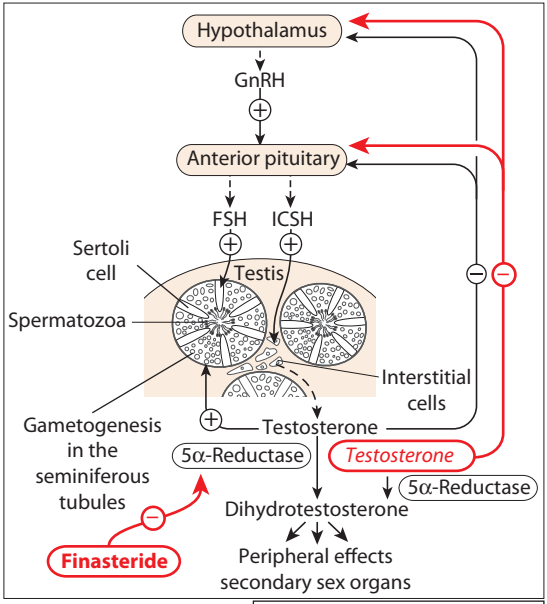
Finasteride

Action & MOA Finasteride inhibits the 5α-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; $T_{0.5}$ ~7h

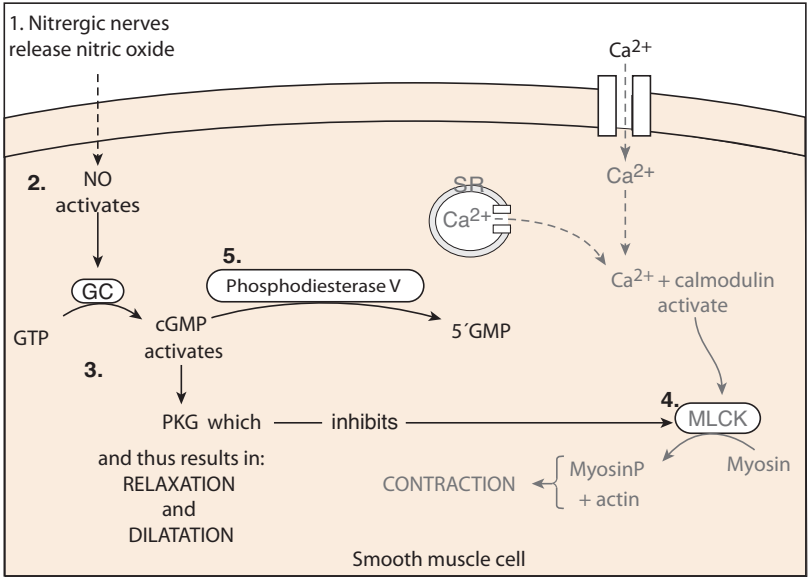
Clinical use Benign prostatic hyperplasia (but note that α-adrenoceptor blockers are more effective). Flutamide is used to treat prostate cancer.

Adverse effects Erectile dysfunction; libido loss.



R&D 7e Ch 34, p 424; D&H 2e Ch 32, p 77

The mechanisms controlling the contraction and relaxation of the smooth muscle of the corpora cavernosa



NO = nitric oxide

GC = guanylate cyclase

MLCK = myosin light chain kinase

PKG = protein kinase G

SR = sarcoplasmic reticulum

Sildenafil

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.

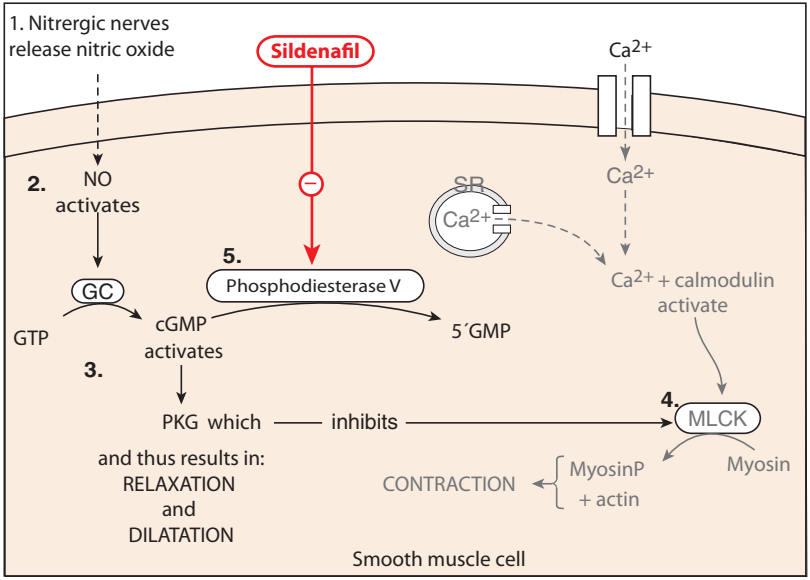
Clinical use For erectile dysfunction.

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



NO = nitric oxide

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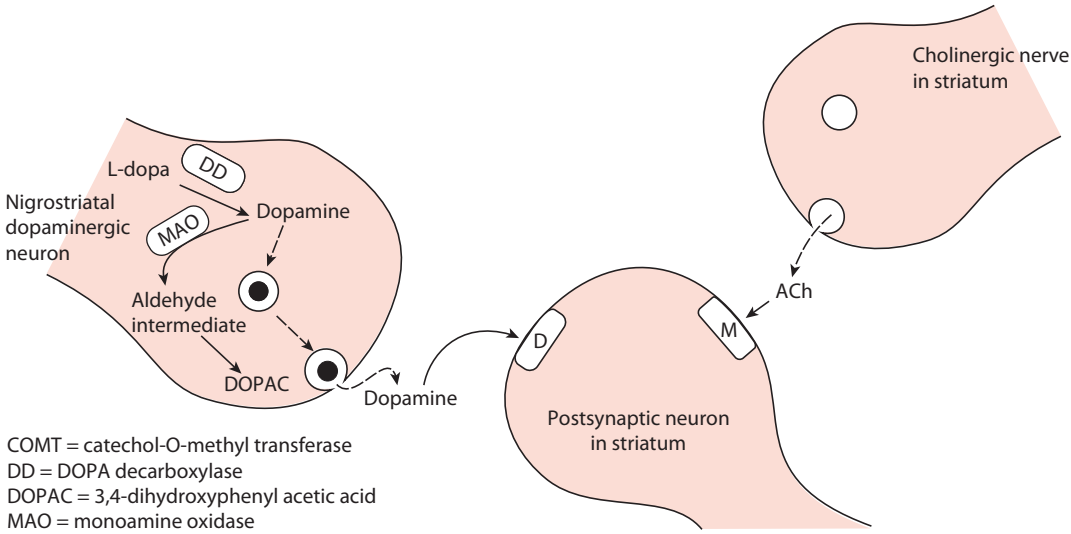
Notes on the female and male reproductive systems

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



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).

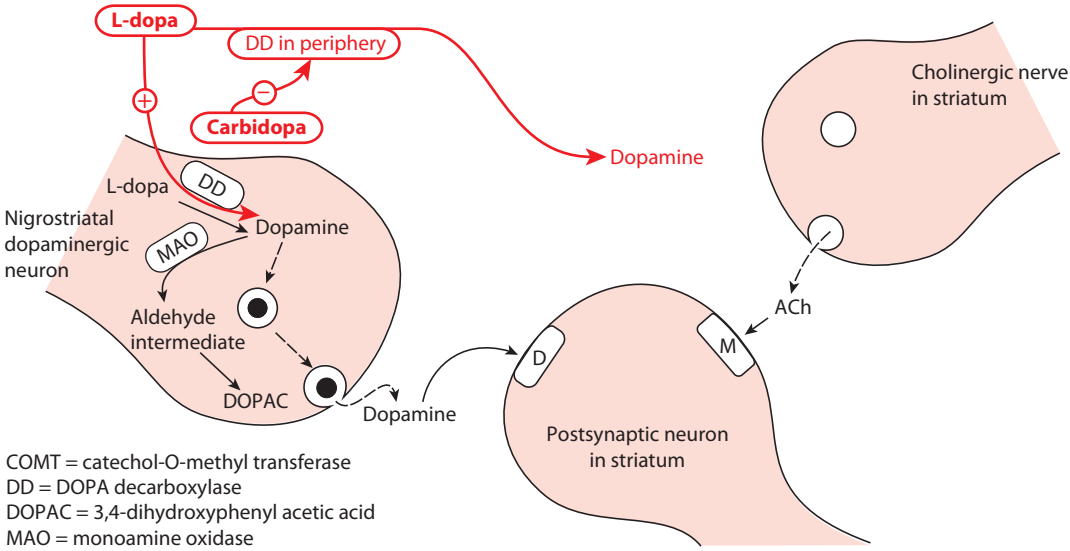
Abs/Distrib/Elim Oral admin. Levodopa $T_{0.5}$ 1–2h when co-administered with carbidopa.

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).

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



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Entacapone

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.

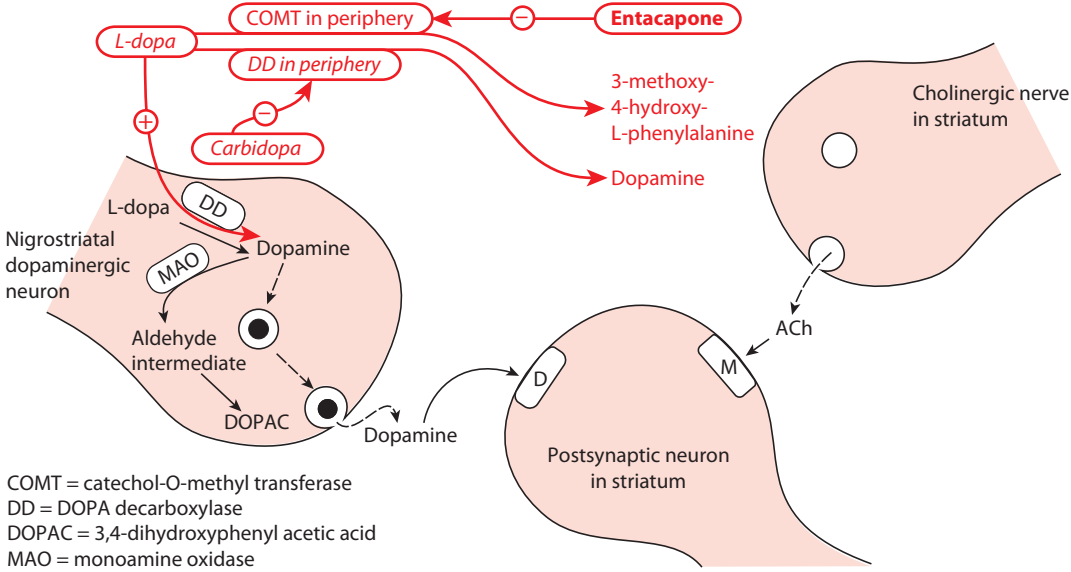
Abs/Distrib/Elim Oral admin. Short $T_{0.5}$ (1h) necessitates dosing several times/day.

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.

R&D 7e Ch 39, p 487; D&H 2e Ch 36, p 85

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

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.

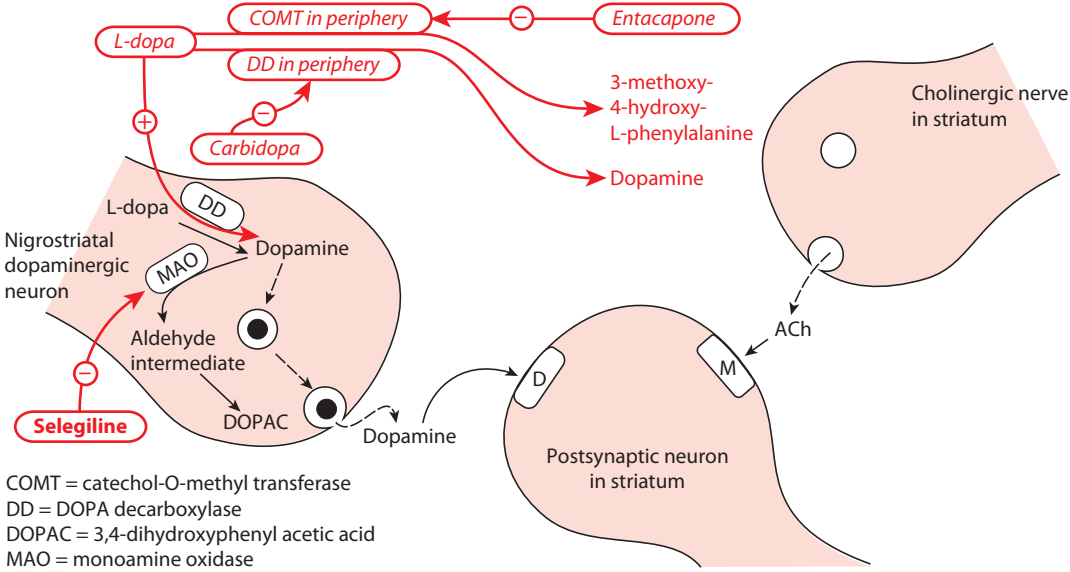
Abs/Distrib/Elim Oral admin. (but low bioavailability), $t_{½}$ 2h. Rasagiline $T_{0.5}$ 3h.

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



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Bromocriptine

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.

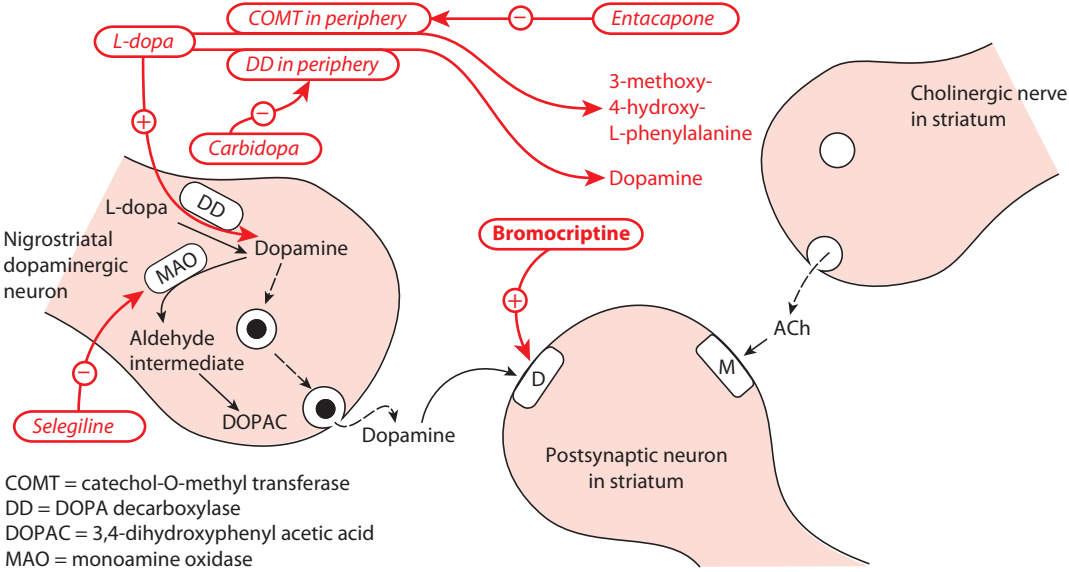
Abs/Distrib/Elim Dopamine agonists have longer $T_{0.5}$s than levodopa and provide a more continuous control of symptoms. $T_{0.5}$: bromocriptine 12h, pramipexole 12h, ropinirole 6h.

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.

R&D 7e Ch 39, p 488; D&H 2e Ch 36, p 85

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

Amantadine

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.

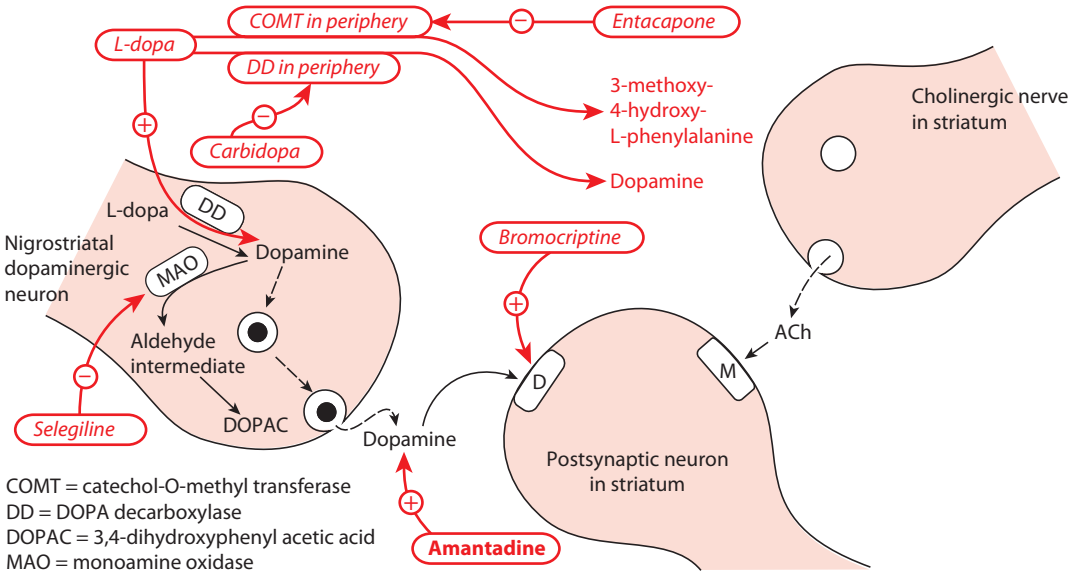
Abs/Distrib/Elim Oral admin. Most excreted unchanged in urine. $T_{0.5}$ 17h.

Clinical use Parkinson's disease. Generally less effective than levodopa, dopamine agonists or MAO_B 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 .

R&D 7e Ch 39, p 489; D&H 2e Ch 36, p 85

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



Benztropine

Actions Antiparkinsonian.

MOA Reduces muscarinic actions of ACh in striatum. (Restores 'balance' between dopaminergic and cholinergic activities.) Action is probably on M_1 receptors

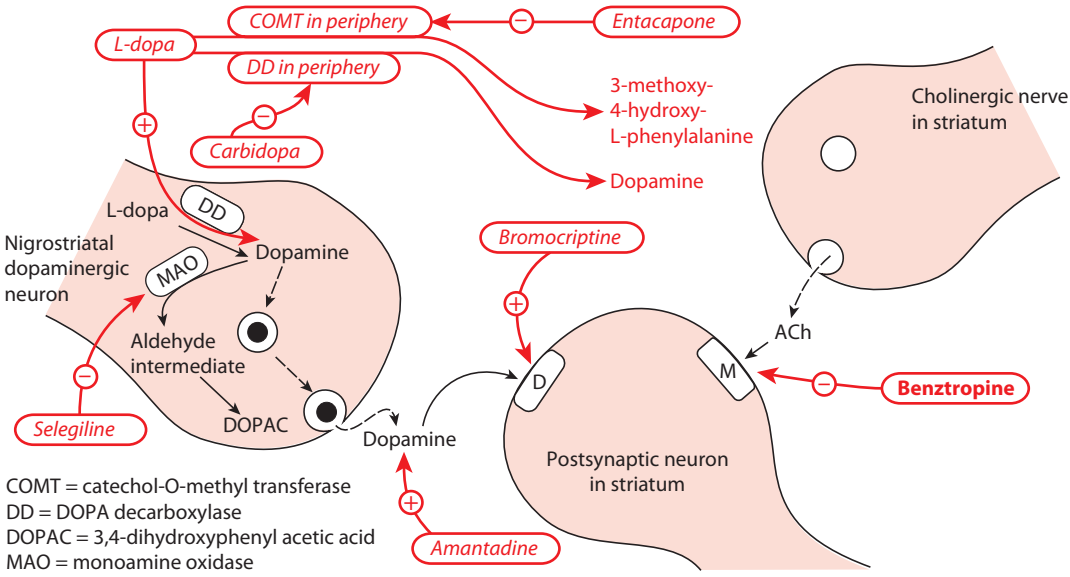
Abs/Distrib/Elim Orally active. Long $T_{0.5}$ – 36h. Trihexyphenidyl $T_{0.5}$ 3–4h.

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.

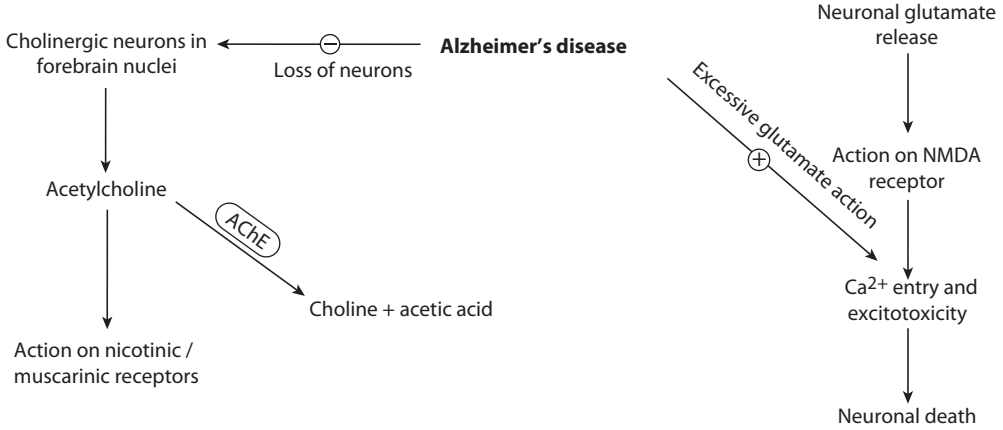
R&D 7e Ch 39, p 489; D&H 2e Ch 36, p 85

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



Notes

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

Donepezil

Actions Ameliorates symptoms of Alzheimer's disease.

MOA Reversible inhibition of acetylcholinesterase. Enhances cholinergic transmission in the cerebral cortex and hippocampus.

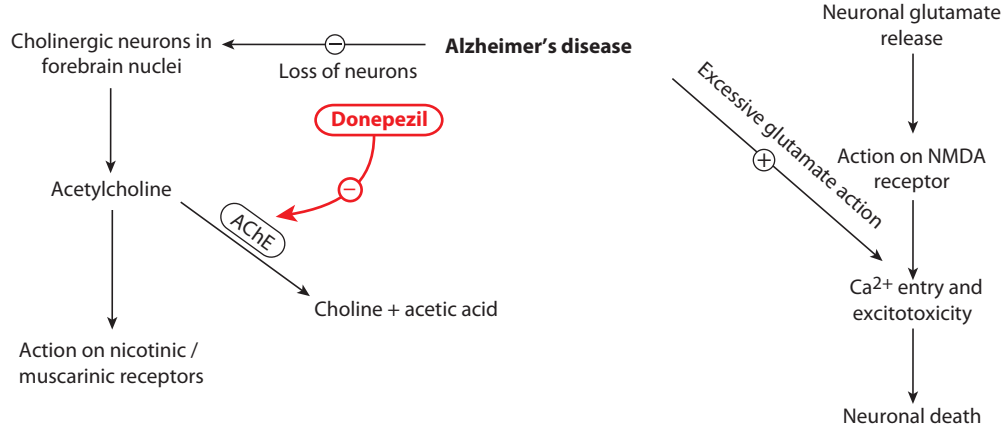
Abs/Distrib/Elim Orally active. Donepezil has long $T_{0.5}$ of 70h. Galantamine $T_{0.5}$ 7h. Rivastigmine has a short half-life 1.5h.

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.

R&D 7e Ch 39, pp 283-284; D&H 2e Ch 36, pp 84-85

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 Open channel block of NMDA receptors. Prevents Na^+ and, more importantly, Ca^{2+} entry into the neurone, so reducing glutamate excitotoxicity. Normal glutamatergic transmission continues.

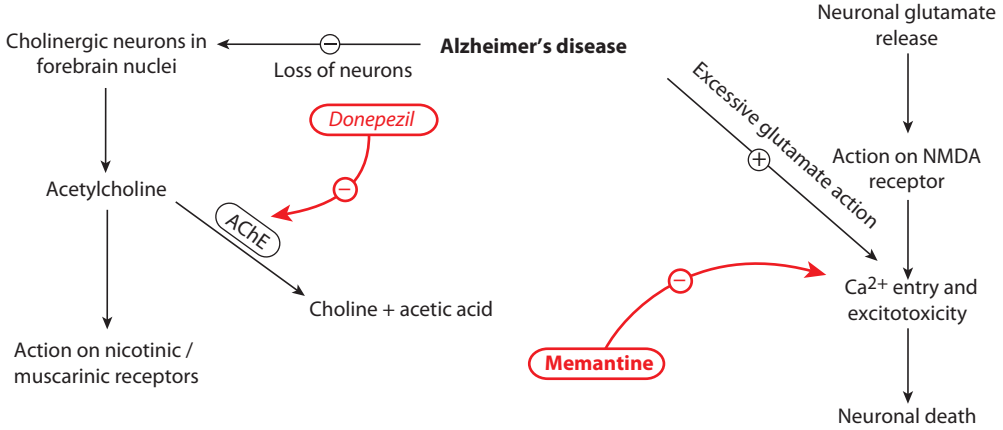
Abs/Distrib/Elim Oral admin. $T_{0.5}$ 60–80h.

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.

R&D 7e Ch 39, pp 483-485; D&H 2e Ch 36, p 85

Cholinergic and glutamatergic transmission are targets for drug action in Alzheimer's disease.

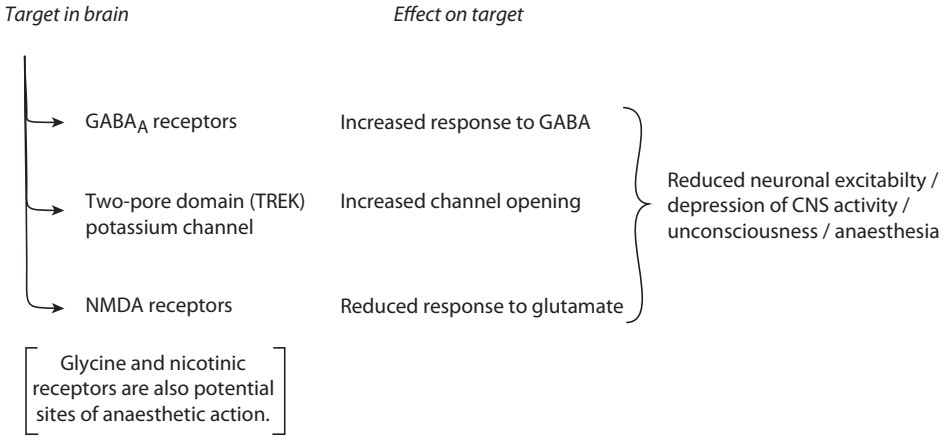


Alzheimer's disease is associated with a loss of neurons and shrinkage of brain tissue, particularly in the hippocampus and basal forebrain. The loss of cholinergic neurons in particular is believed to be associated with the impairment of learning and memory. Excitotoxicity, mediated by NMDA receptors, may also be important in neuronal death.

AChE = acetylcholinesterase
NMDA = N-methyl D-aspartate

Notes

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.

Actions CNS depressant. Causes unconsciousness. Only weakly analgesic.

MOA Potentiates GABA action on $GABA_A$ receptors and opens K^+ channels (TREK type) to reduce neuronal activity, especially in cerebral cortex, thalamus and hippocampus. Lipid solubility important for action.

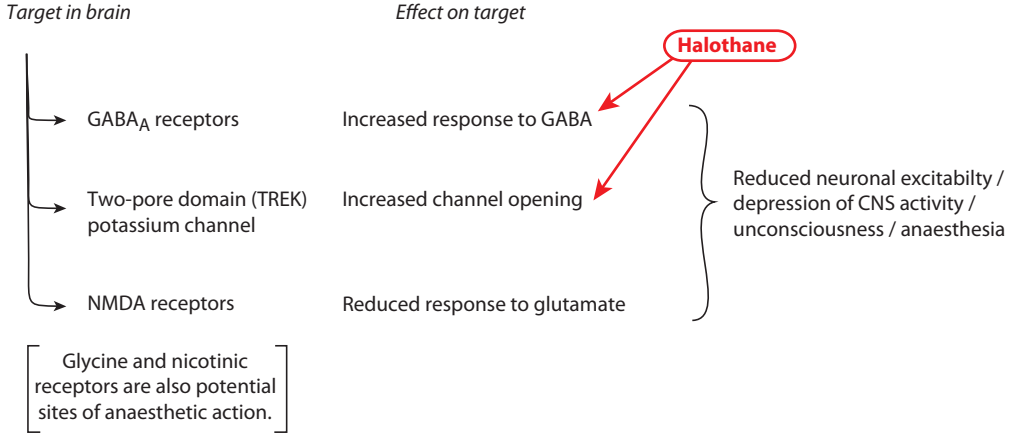
Abs/Distrib/Elim Given by inhalation with oxygen. Rate of equilibration with body and onset of anaesthesia depends on the 'blood/gas solubility'. Halothane has a medium onset of action – desflurane and sevoflurane (with lower blood/gas solubilities) a fast onset. Mostly eliminated unchanged by the lungs.

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.

R&D 7e Ch 40, pp 498-500; D&H 2e Ch 37, p 86

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.

Nitrous oxide

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.

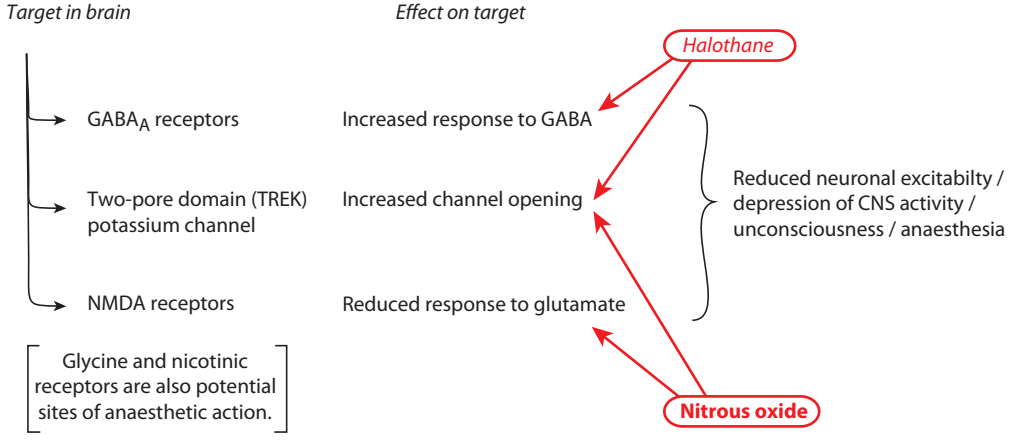
Abs/Distrib/Elim Administered by inhalation. Low blood/gas partition coefficient results in rapid onset and offset of action. Eliminated unchanged via lungs. No metabolism.

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'.

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.



Inhalation anaesthetic agents in general act at high (mM) concentrations and have less well-defined targets than the more potent intravenous agents.

Actions Ultrashort-acting anaesthetics. All have only weak analgesic action.

MOA Binds to particular site (different to benzodiazepine binding site) on $GABA_A$ receptor to enhance opening of intrinsic Cl^- channel by GABA. Higher concentrations directly activate receptor.

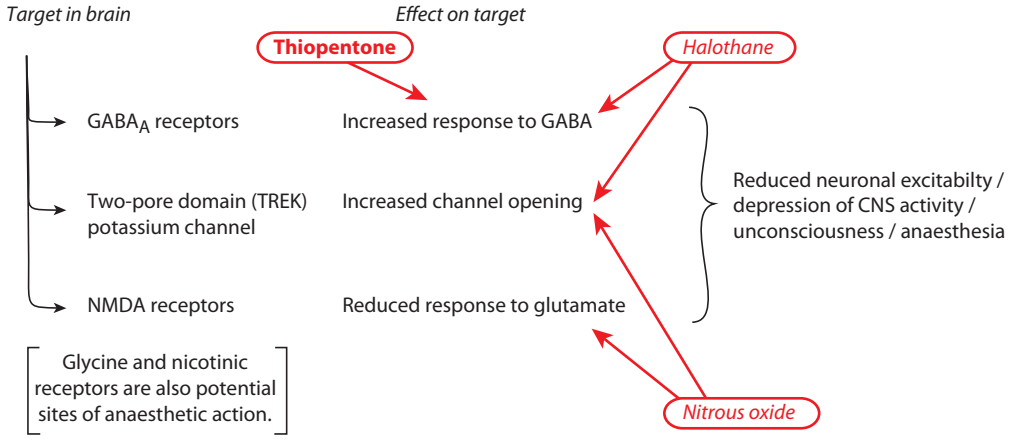
Abs/Distrib/Elim I.v. injection. Very lipid soluble allowing rapid CNS penetration. Rapid onset (20s) and short acting (5–10min). Short duration due to rapid redistribution in body, particularly to muscle. Thiopental is slowly metabolised ($T_{0.5}$ 8–10h) and may produce a 'hangover'. Propofol is rapidly 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.



Inhalation anaesthetic agents in general act at high (mM) concentrations and have less well-defined targets than the more potent intravenous agents.

Ketamine

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.

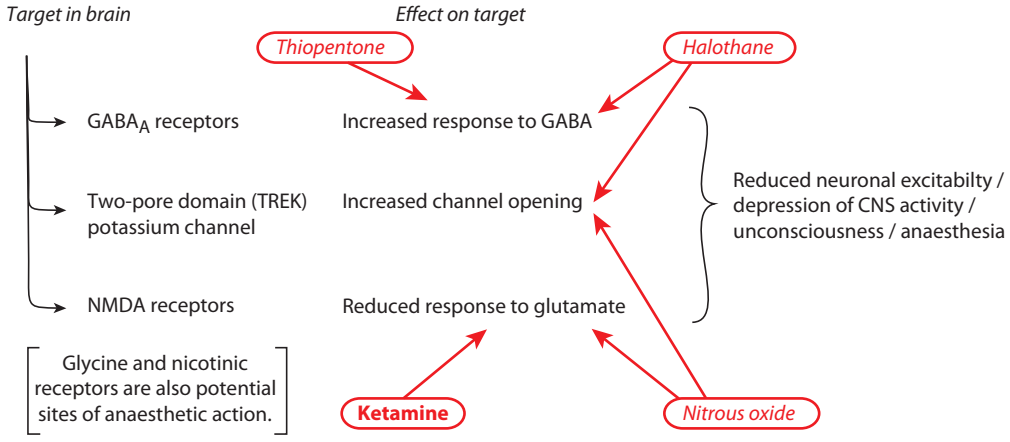
Abs/Distrib/Elim I.v. or i.m. admin. Rapid onset and short duration of action following i.v. dosing. Metabolised in liver; $T_{0.5}$ 2.5h.

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.

R&D 7e Ch 40, pp 496-497; D&H 2e Ch 37, pp 86-87

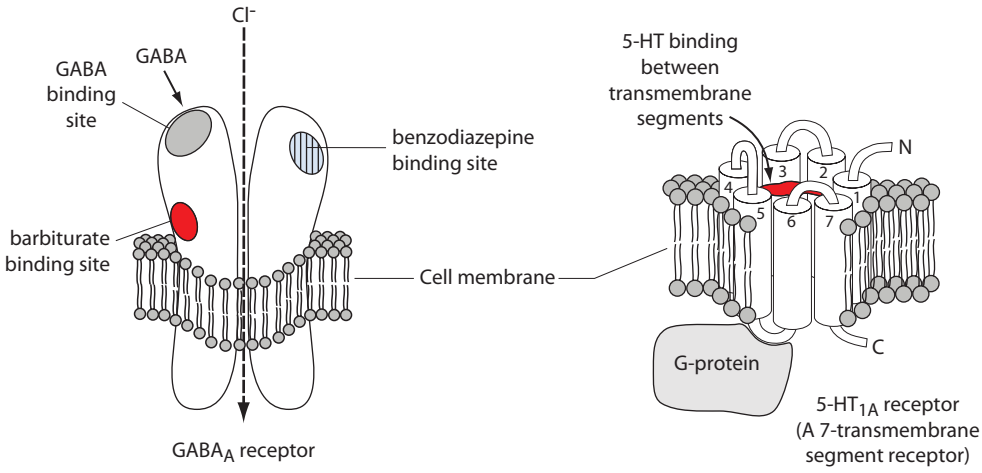
Established/possible targets for anaesthetic agents are indicated in the diagram.



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.



Diazepam

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.

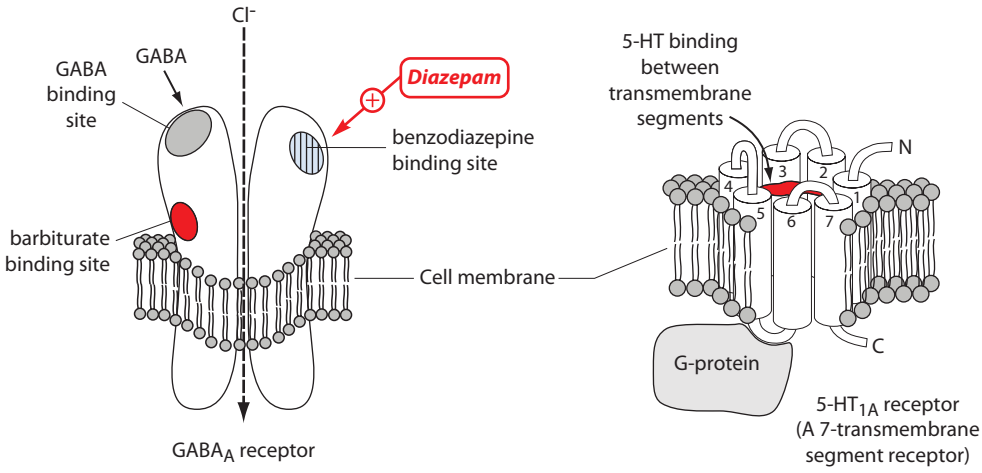
Abs/Distrb/Elim Given orally. Diazepam is long acting due to active metabolite with long $T_{0.5}$. Nitrazepam and temazepam have a medium duration. Oxazepam is short acting.

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).

R&D 7e Ch 43, p 535; D&H 2e Ch 38, p 88

The important anxiolytic and hypnotic drugs act on $GABA_A$ or $5HT_{1A}$ receptors.



Zolpidem

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.

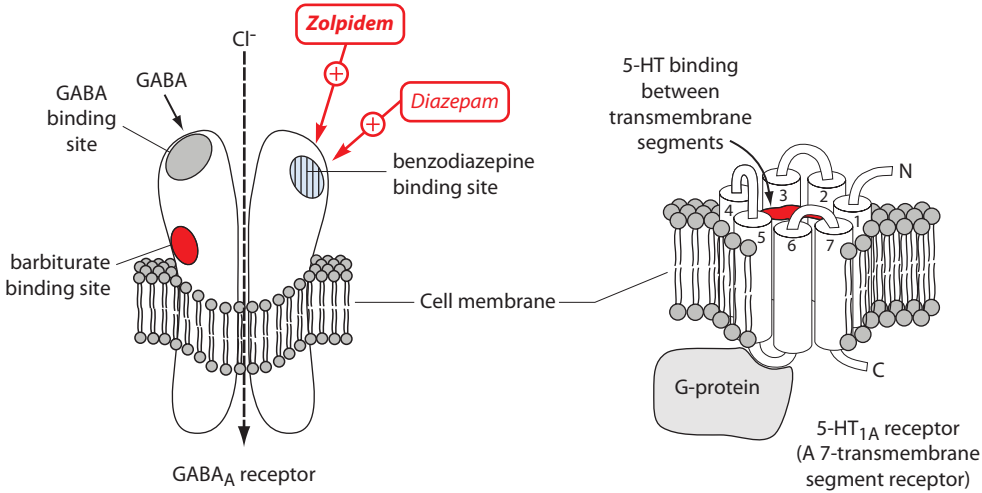
Abs/Distrb/Elim Oral admin. Zolpidem and zopiclone are short acting ($t_{½}$ 2–3 and 6h respectively): zaleplon very short acting.

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 $GABA_A$ or $5HT_{1A}$ receptors.



Flumazenil

Actions Antagonises actions of benzodiazepines and zolpidem-like drugs.

MOA Competitive binding to the benzodiazepine binding site on $GABA_A$ receptor.

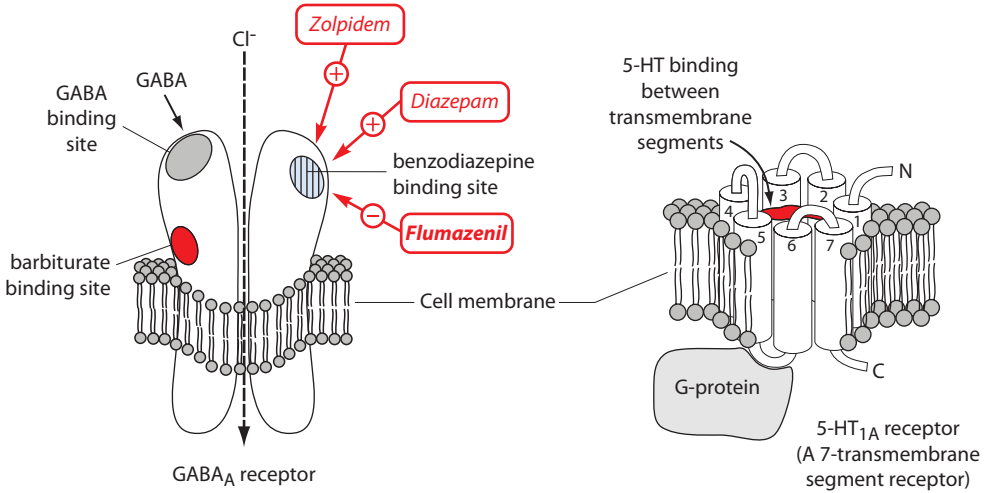
Abs/Distrb/Elim Given intravenously. Short $T_{0.5}$ 1–2h, so will need repeat doses to antagonise the longer-acting benzodiazepines.

Clinical use Treatment of overdose of benzodiazepines or zolpidem.

Adverse effects Anxiety, palpitations, insomnia. Convulsions.

R&D 7e Ch 43, pp 535-537; D&H 2e Ch 38, p 88

The important anxiolytic and hypnotic drugs act on $GABA_A$ or $5HT_{1A}$ receptors.



Actions CNS depressant. Hypnotic, anxiolytic.

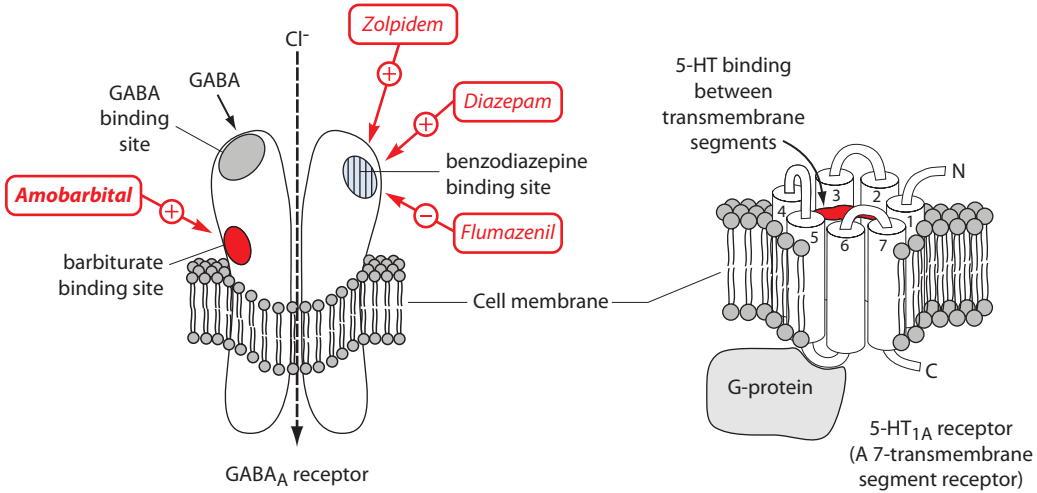
MOA Binds to barbiturate binding site on $GABA_A$ receptor to increase action of GABA. At higher concentration can increase channel opening in absence of GABA.

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.

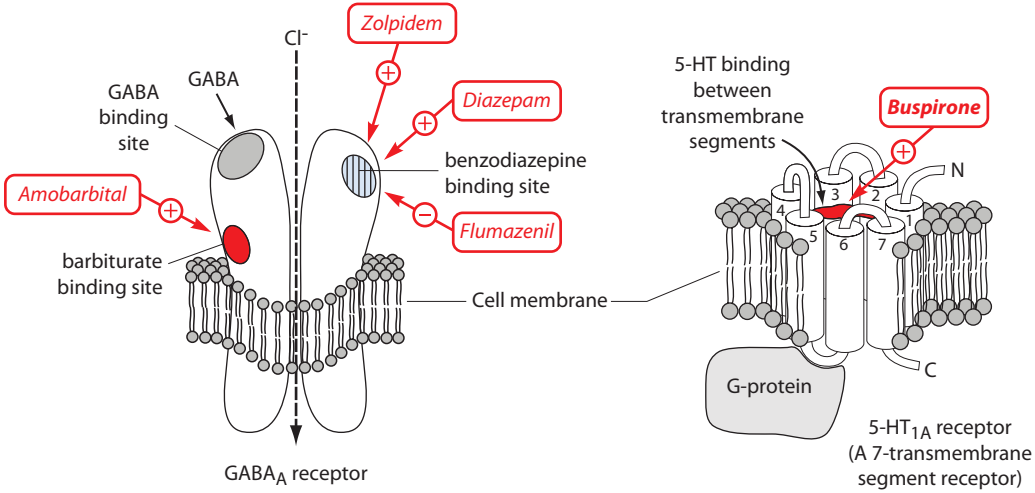
Abs/Distrb/Elim Given orally, but significant first-pass metabolism. $T_{0.5}$ 2–3h, but effects are longer lasting, possibly due to metabolite with similar action.

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.)

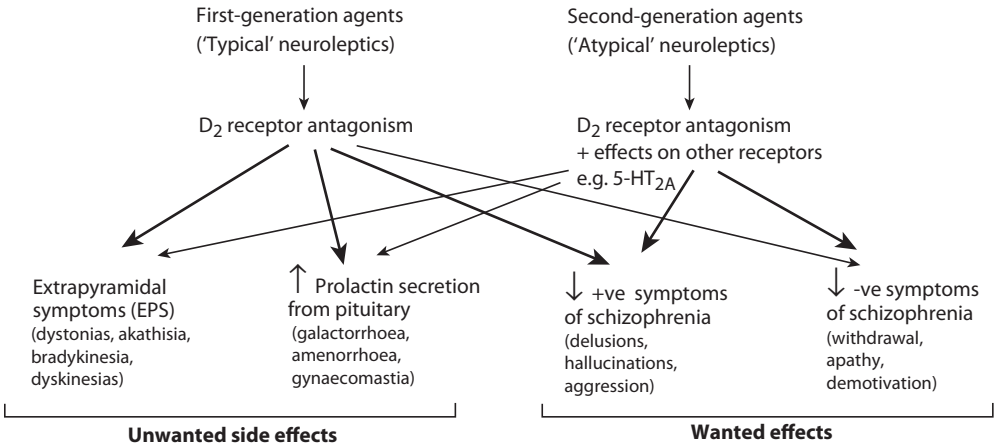
R&D 7e Ch 43, pp 438-439; D&H 2e Ch 38, p 88

The important anxiolytic and hypnotic drugs act on $GABA_A$ or $5HT_{1A}$ receptors.



Notes

Diagram illustrating the effects of first- and second-generation antipsychotics



Chlorpromazine

Actions Antipsychotic. Apathy and inertia. Reduced aggression. Antiemetic.

MOA Competitive antagonism of dopamine D_2 receptors in the mesolimbic/mesocortical pathways. Clinical benefits are delayed although receptor block is immediate, suggesting that slower changes in neurotransmission occur.

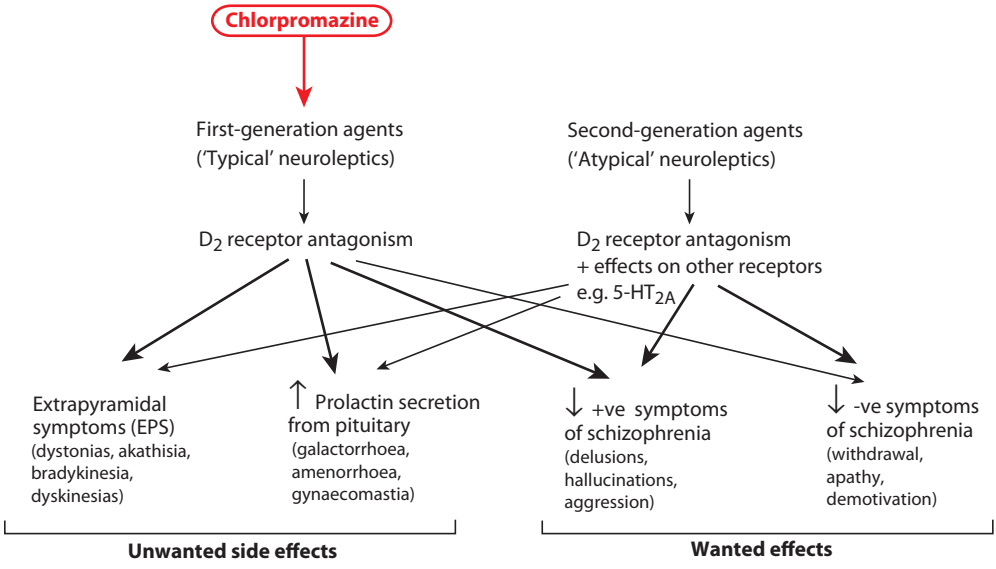
Abs/Distrib/Elim Given orally or by i.m. injection. $t_{½}$ 16–32h. Fluphenazine decanoate available as i.m. depot formulation.

Clinical use Schizophrenia (less effective against –ve symptoms) and other psychotic states. Manic phase of bipolar disorder. Tourette's syndrome. Nausea & vomiting. Aggression in children. Persistent hiccups.

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 (α-adrenoceptor antagonism). Rare, but serious, neuroleptic malignant syndrome. Hypersensitivity reactions. Agranulocytosis. Hepatotoxicity.

R&D 7e Ch 45, pp 555-556; D&H 2e Ch 39, pp 90-91

Diagram illustrating the effects of first- and second-generation antipsychotics



Haloperidol

Actions Antipsychotic. Apathy. Reduced aggression. Antiemetic

MOA Competitive antagonism of dopamine D_2 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.

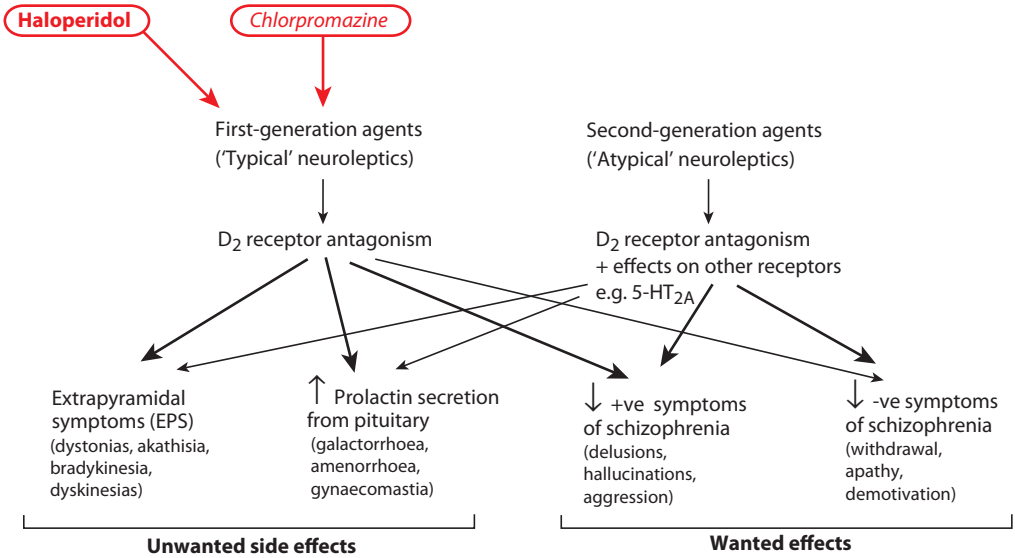
Abs/Distrib/Elim Oral or i.m. admin. (Also i.m. depot.) $t_{½}$ 12–36h.

Clinical use Schizophrenia (less effective against negative symptoms) and other psychotic states. Mania. Aggressive behaviour. Tourette's syndrome. Nausea & vomiting. Persistent hiccup.

Adverse effects Marked EPS. Hyperprolactinaemia. Little sedative, hypotensive or antimuscarinic actions. Neuroleptic malignant syndrome.

R&D 7e Ch 45, pp 555-556; D&H 2e Ch 39, pp 90-91

Diagram illustrating the effects of first- and second-generation antipsychotics



Flupentixol

Actions Antipsychotic. Antidepressant (tricyclic-like) activity.

MOA Competitive antagonism of dopamine D_2 receptors in the mesolimbic/mesocortical pathways. Clinical benefits are delayed although receptor block is immediate, suggesting that more complex changes in neurotransmission occur.

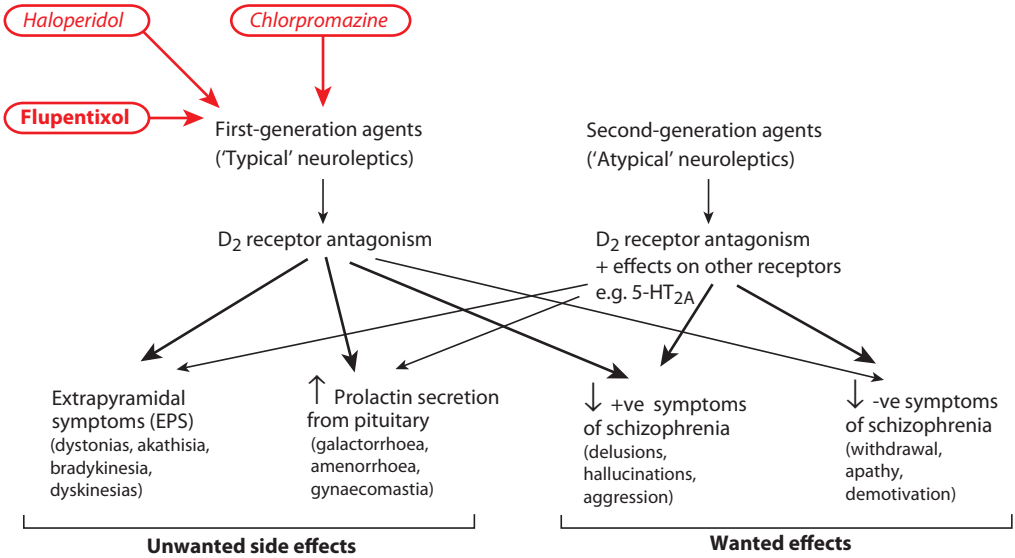
Abs/Distrib/Elim Effective orally but most often used as i.m. depot formulation. $T_{0.5}$ 19–39h.

Clinical use Schizophrenia and other psychotic states. Bipolar disorder. Depression.

Adverse effects EPS. Hyperprolactinaemia. Neuroleptic malignant syndrome.

R&D 7e Ch 45, p 556t; D&H 2e Ch 39, pp 90-91

Diagram illustrating the effects of first- and second-generation antipsychotics



Clozapine

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, $5HT_2$, α_1 adrenoceptors, and H_1 histamine receptors. Higher affinity for D_4 than other dopamine receptors.

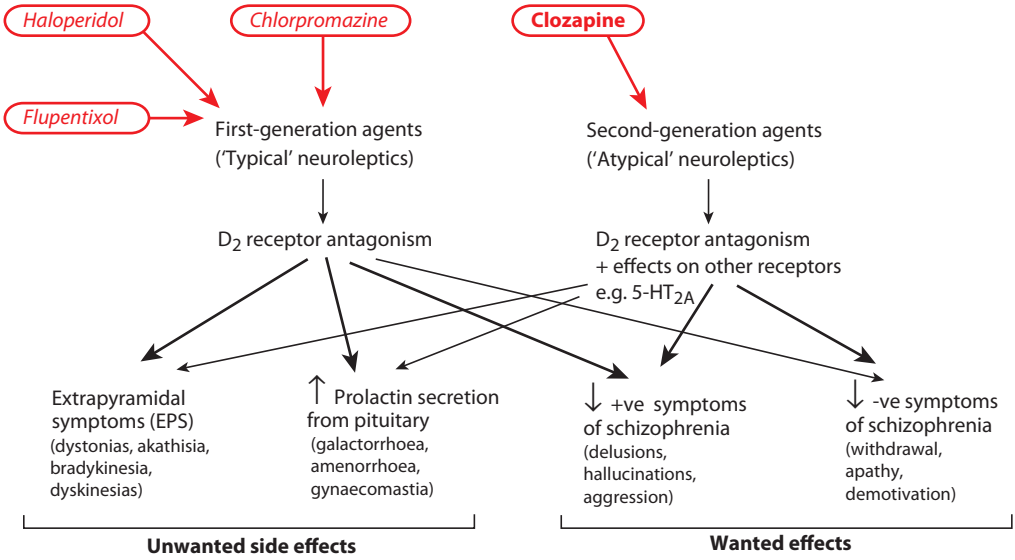
Abs/Distrib/Elim Orally active. $t_{½}$ 12h.

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.

R&D 7e Ch 45, pp 560-561; D&H 2e Ch 39, pp 90-91

Diagram illustrating the effects of first- and second-generation antipsychotics



Risperidone

Actions Antipsychotic. Effective against +ve and -ve symptoms of schizophrenia.

MOA Potent antagonist of D_2 and $5HT_{2A}$ receptors and α_1 adrenoceptors. As for other atypical agents, a combination of D_2 and $5HT_{2A}$ antagonism may be important in modifying activity in the mesolimbic and mesocortical pathways.

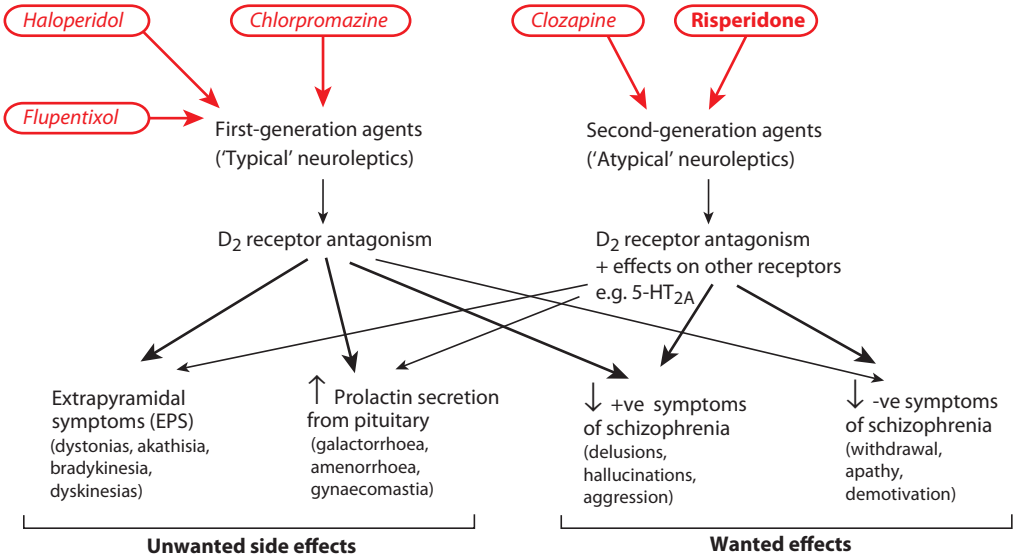
Abs/Distrib/Elim Oral and i.m. depot admin. Hepatic P450 metabolism. $t_{½}$ 3–20h. Active metabolite is longer acting.

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.

R&D 7e Ch 45, p 557t; D&H 2e Ch 39, pp 90-91

Diagram illustrating the effects of first- and second-generation antipsychotics



Quetiapine

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.

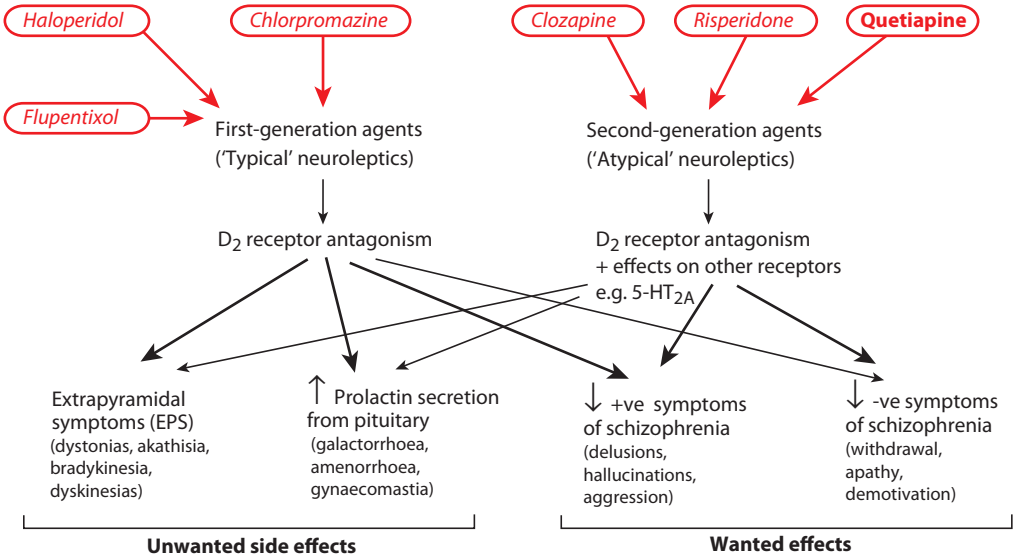
Abs/Distrib/Elim Oral admin. Short (6h) half-life.

Clinical use Schizophrenia and other psychotic states. Bipolar disorder.

Adverse effects Weight gain. Minor EPS and hyperprolactinaemia. Sedation. Postural hypotension. Constipation, dry mouth (antimuscarinic actions). Rarely, neuroleptic malignant syndrome.

R&D 7e Ch 45, p 557t; D&H 2e Ch 39, pp 90-91

Diagram illustrating the effects of first- and second-generation antipsychotics



Aripiprazole

Actions Antipsychotic. Effective against +ve and -ve symptoms.

MOA Modification of dopaminergic transmission in the mesolimbic/mesocortical pathways. Aripiprazole binds strongly to dopamine D_2 receptors but has partial agonist activity which may explain its low incidence of EPS. $5HT_{2A}$ antagonism is probably important.

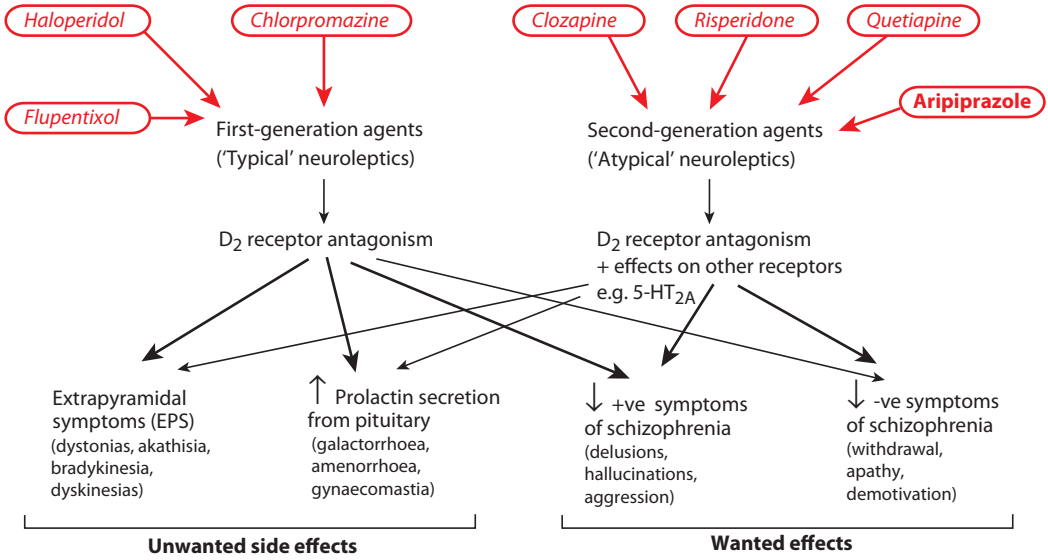
Abs/Distrib/Elim Oral admin. Long (75h) half-life.

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.

R&D 7e Ch 45, p 557t; D&H 2e Ch 39, pp 90-91

Diagram illustrating the effects of first- and second-generation antipsychotics



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 α_1 adrenergic receptors.

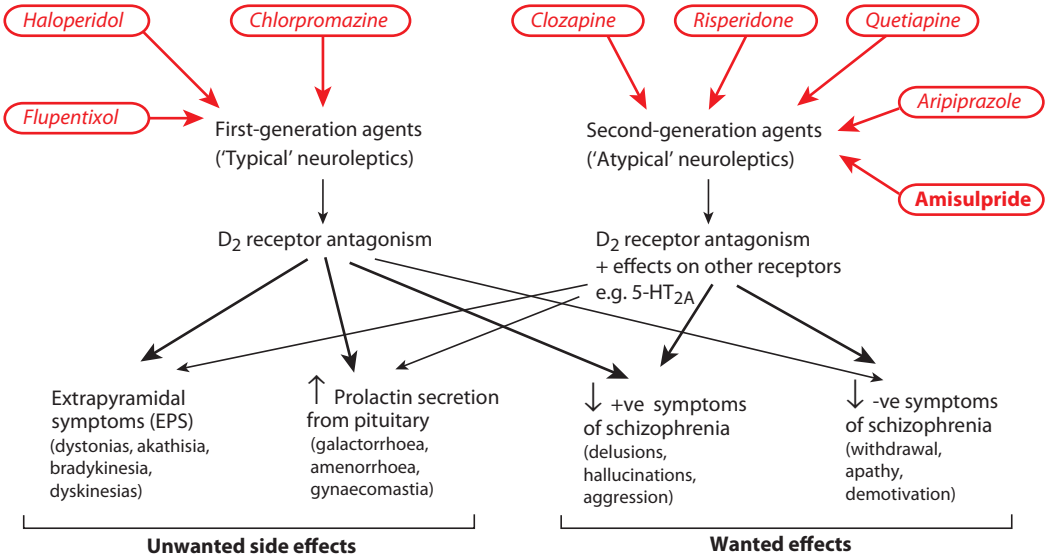
Abs/Distrib/Elim Mostly excreted unchanged in kidney. $t_{½}$ 12h.

Clinical use Schizophrenia.

Adverse effects Hyperprolactinaemia. Insomnia. Anxiety. Weight gain. Constipation and dry mouth.

R&D 7e Ch 45, p 562; D&H 2e Ch 39, pp 90-91

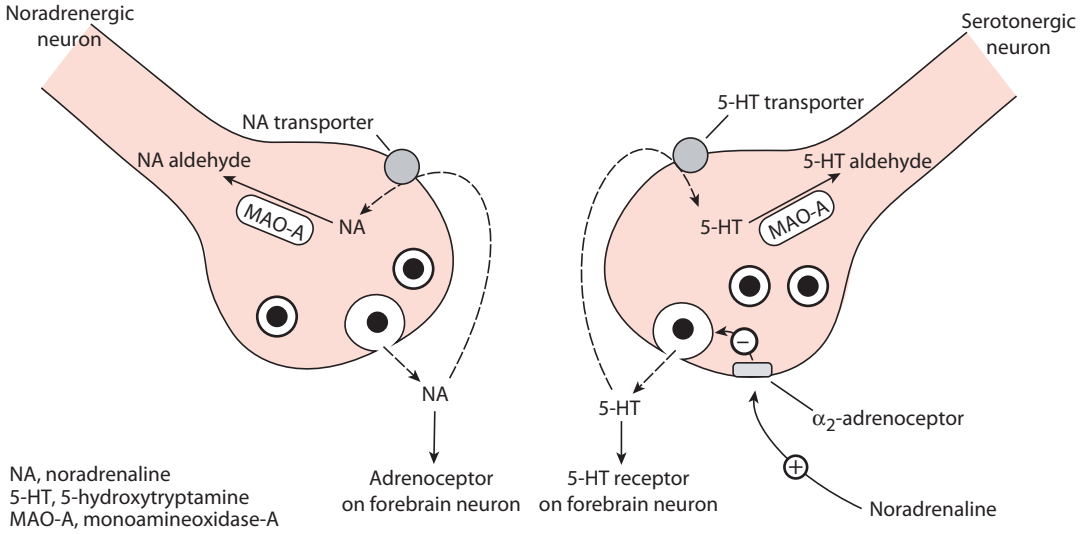
Diagram illustrating the effects of first- and second-generation antipsychotics



Drug	↓+ve symptoms	↓-ve symptoms	EPS	Prolactin secretion	Anti-muscarinic	Anti-histamine	α-block
Chlorpromazine	+++	+	+++	++	+++	+++	++++
Haloperidol	+++	+	+++++	++	+	+	+
Fluphenazine	+++	+	++++	++	++	+	+
Flupentixol	+++	+	++++	++	+	+++	+
Clozapine	++++	++++	+	0	++++	++++	+++
Risperidone	+++	+	++	++	+	++	++
Olanzapine	+++	+	+	+	+++	+++	++
Quetiapine	++	+	+	0	+	+++	+
Aripiprazole	++	+	+	0	+	++	++
Amisulpride	++	+	++	++	+	+	+

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



NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

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.

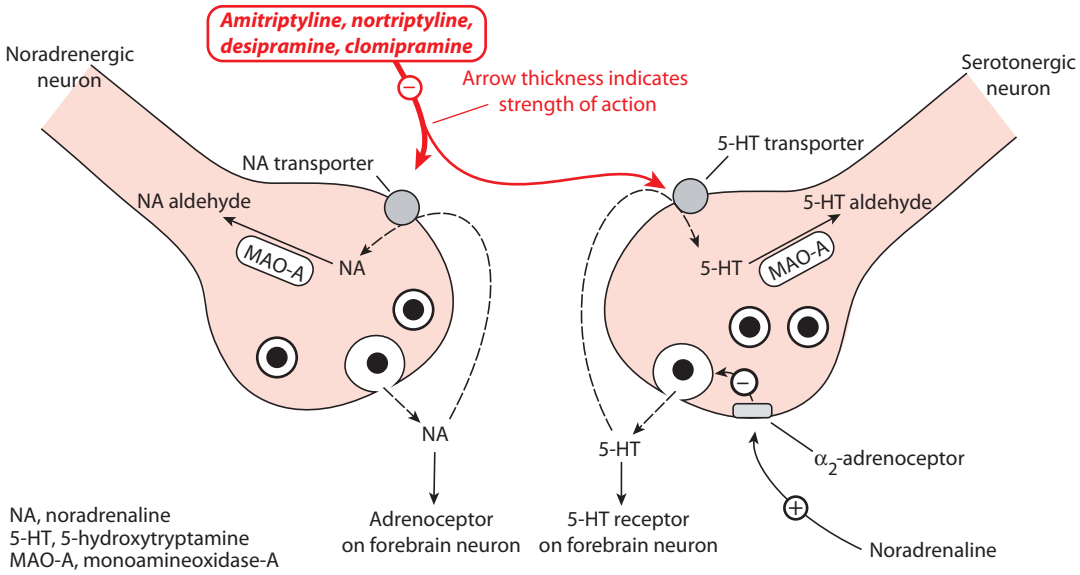
Abs/Distrib/Elim Oral administration. Metabolised in liver by cytochrome P450 system with subsequent conjugation reactions. Plasma half-life 12–24h (influenced by P450 inhibitors or inducers). Strong protein binding.

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 (α_1-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



Fluoxetine

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. $T_{0.5}$ 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.

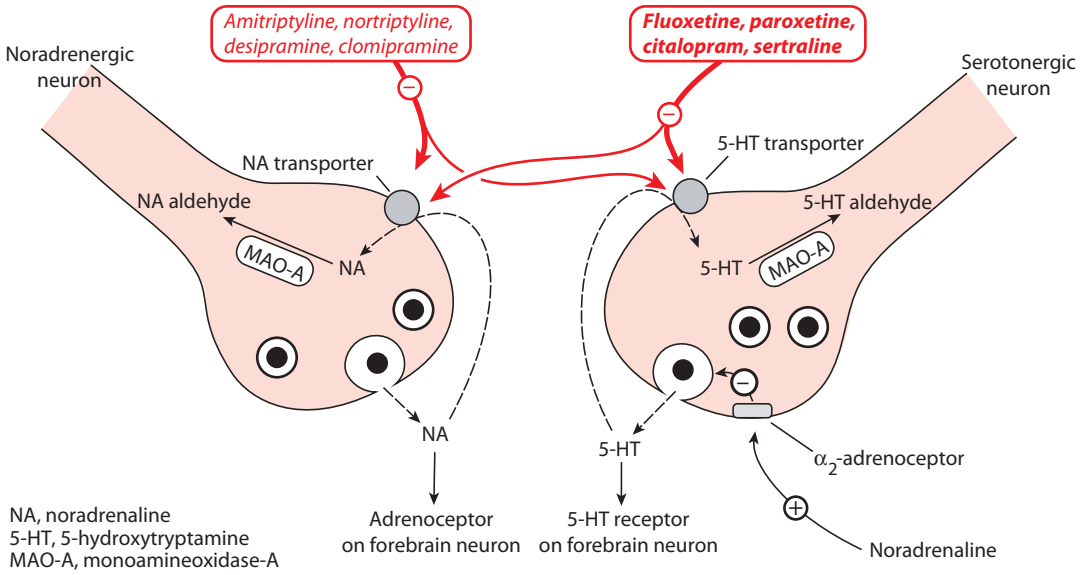
Clinical use Widely prescribed. Depression. Obsessive–compulsive disorder. Panic disorder. Bulimia nervosa.

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.

R&D 7e Ch 46, pp 573-574; D&H 2e Ch 40, pp 92-93

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



Venlafaxine

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.

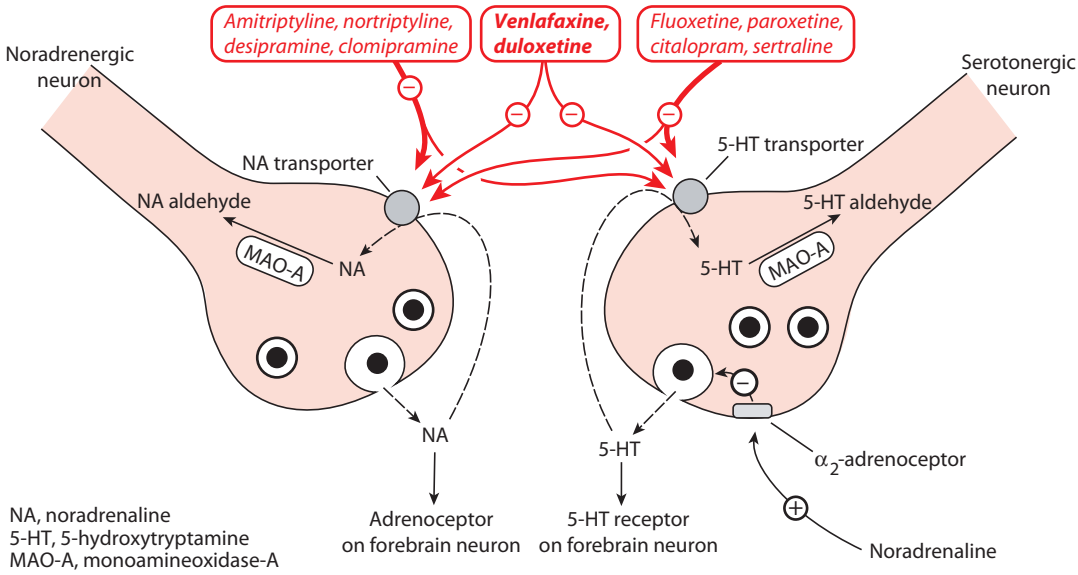
Abs/Distrib/Elim Oral administration. Half-life 5h (active metabolite – desmethylvenlafaxine. $T_{0.5}$ 11h) Metabolised in liver by cytochrome P450 system. $T_{0.5}$ of duloxetine 12–24h.

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.

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



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.

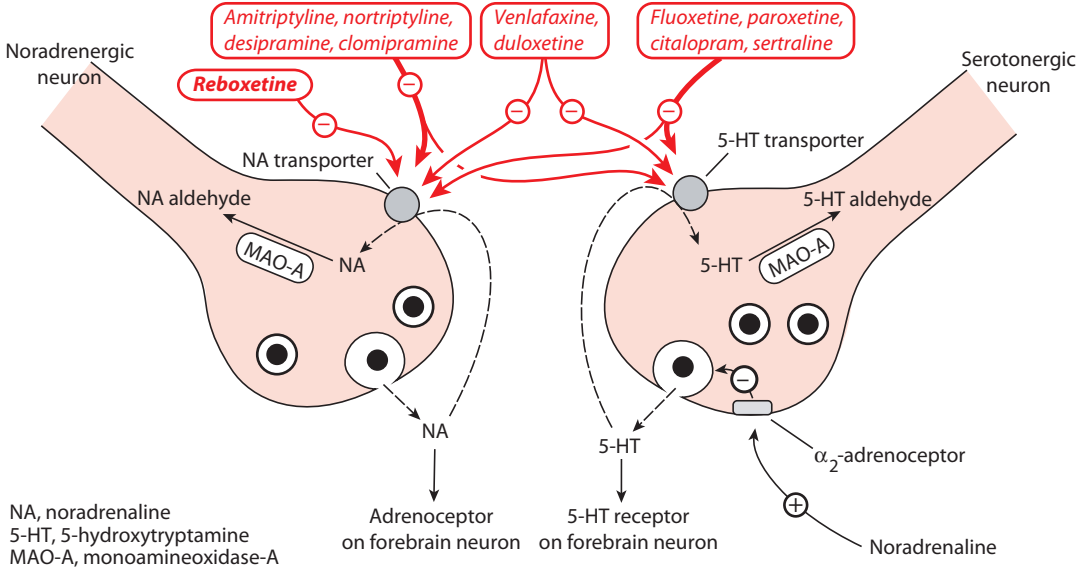
Abs/Distrib/Elim Oral administration. Metabolised in liver by cytochrome P450 system. Plasma half-life 15h (influenced by P450 inhibitors or inducers).

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.

R&D 7e Ch p 577; D&H 2e Ch 40, pp 92-93

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



Actions Antidepressant.

MOA Phenelzine and isocarboxacid 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.

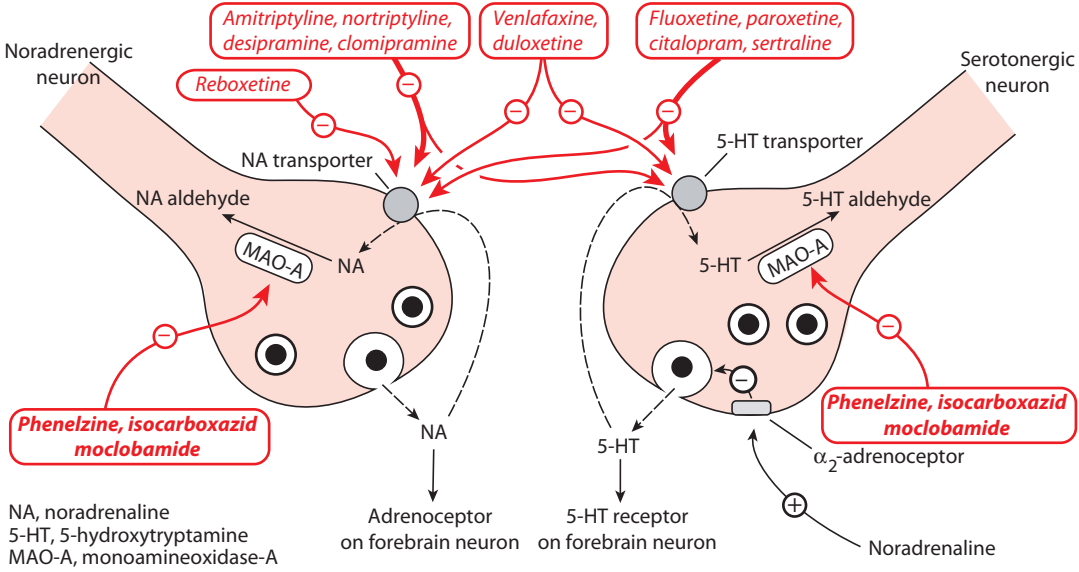
Clinical use Depression; may have particular value for atypical depression. Social phobia. Clinical effect takes some days to develop.

Adverse effects Postural hypotension. Headache. Insomnia. Sexual dysfunction. Dry mouth, urinary retention. Convulsions with overdose. Increased risk of suicide in young patients. Cheese reaction with dietary tyramine – hypertensive crisis. Cheese reaction is less pronounced with moclobemide (since MAO-B is still functional).

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



Actions Antidepressant.

MOA Antagonist at presynaptic α_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).

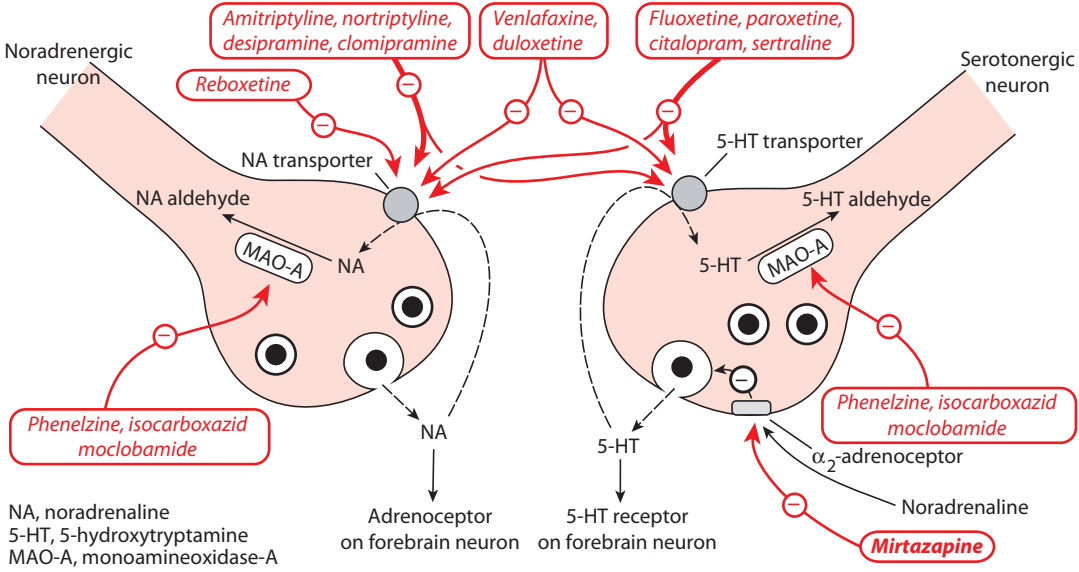
Abs/Distrib/Elim Oral admin. Subject to hepatic cytochrome P450 metabolism. $t_{½}$ 30h. Longer in elderly and those with liver/ renal impairment.

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.

R&D 7e Ch 46, p 577; D&H 2e Ch 40, pp 92-93

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



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.

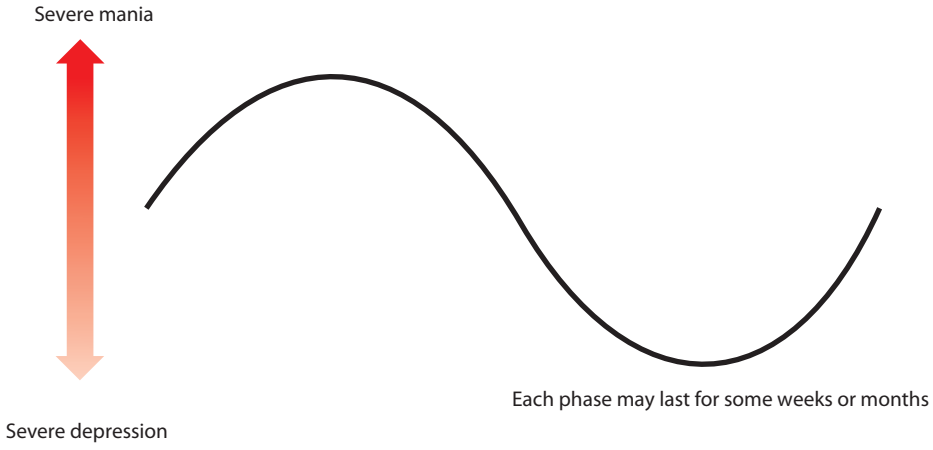
Abs/Distrib/Elim Oral admin. Extensive hepatic metabolism by Cyt P450 yields active metabolites which contribute to antidepressant action. $T_{0.5}$ 20h.

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.

R&D 7e Ch 46, p 577; D&H 2e Ch 40, pp 92-93

Bipolar disorder (manic-depressive illness) is characterised by mood changes which swing between mania and depression.



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.

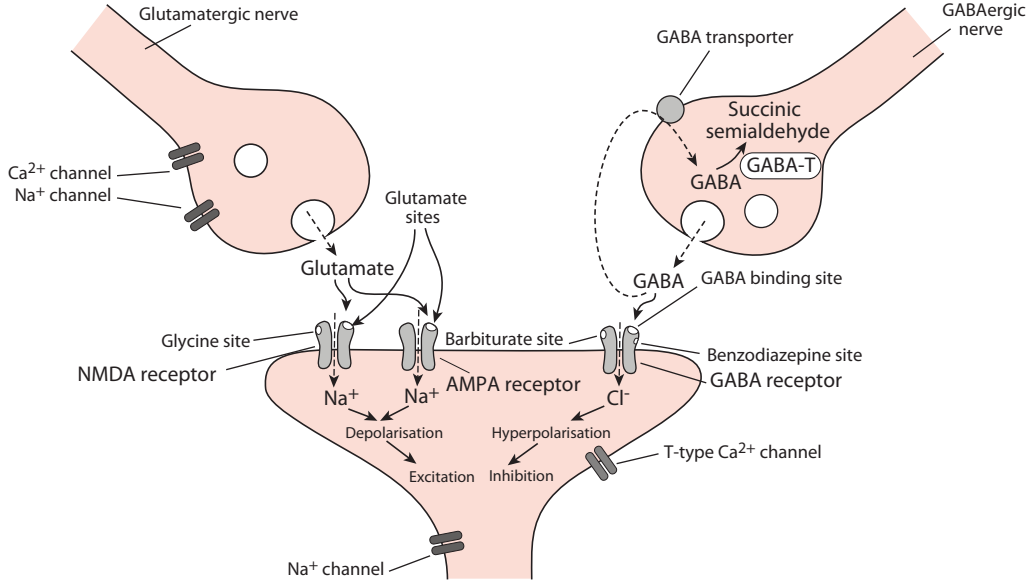
Clinical use Bipolar (manic-depressive) disorder, mania and as adjunct to other agents in unipolar depression. Clinical effect develops over 3–4 weeks.

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



Carbamazepine

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.

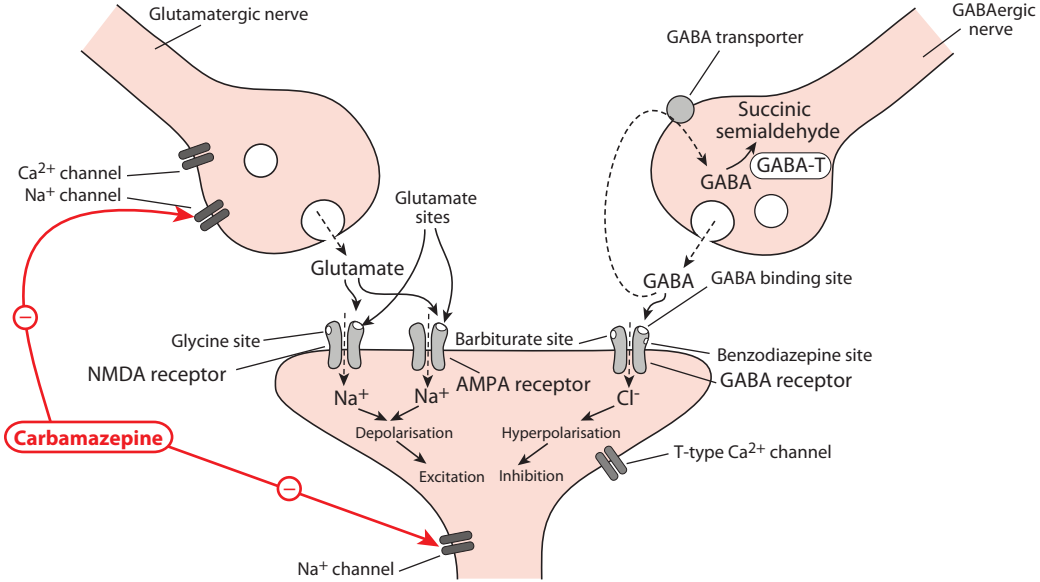
Clinical use Partial and generalised seizures (tonic-clonic), but not absence seizures. Also neuropathic pain and bipolar disorder. Phenytoin also used for status epilepticus. Saturable elimination of phenytoin makes it useful to monitor its plasma concentration.

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.

R&D 7e Ch 44, p 546; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



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.

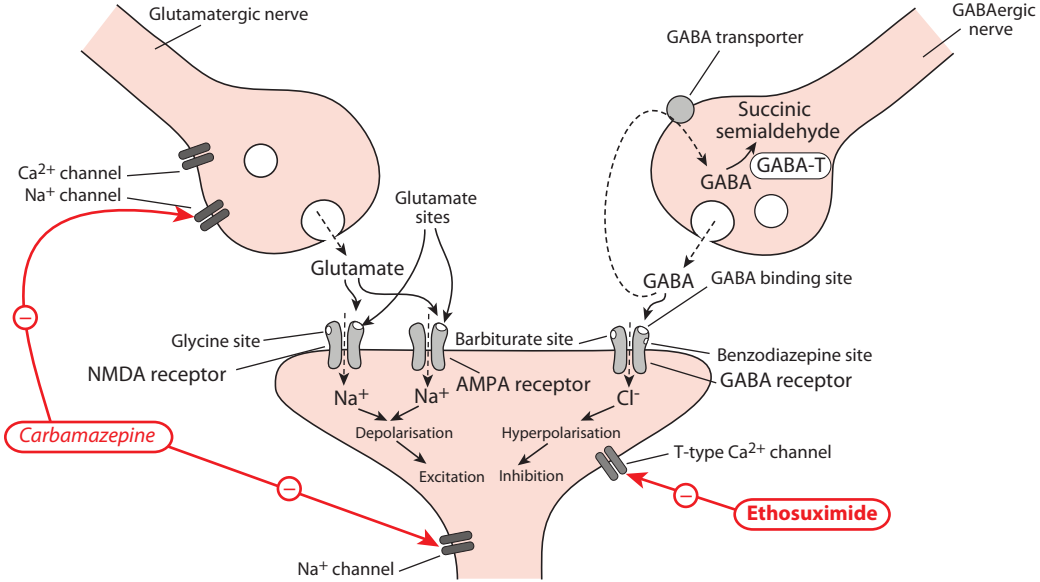
Abs/Distrib/Elim Oral admin. Oxidised by cytochrome P450 system. $T_{0.5}$ 50h.

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.

R&D 7e Ch 44, p 548; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



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.

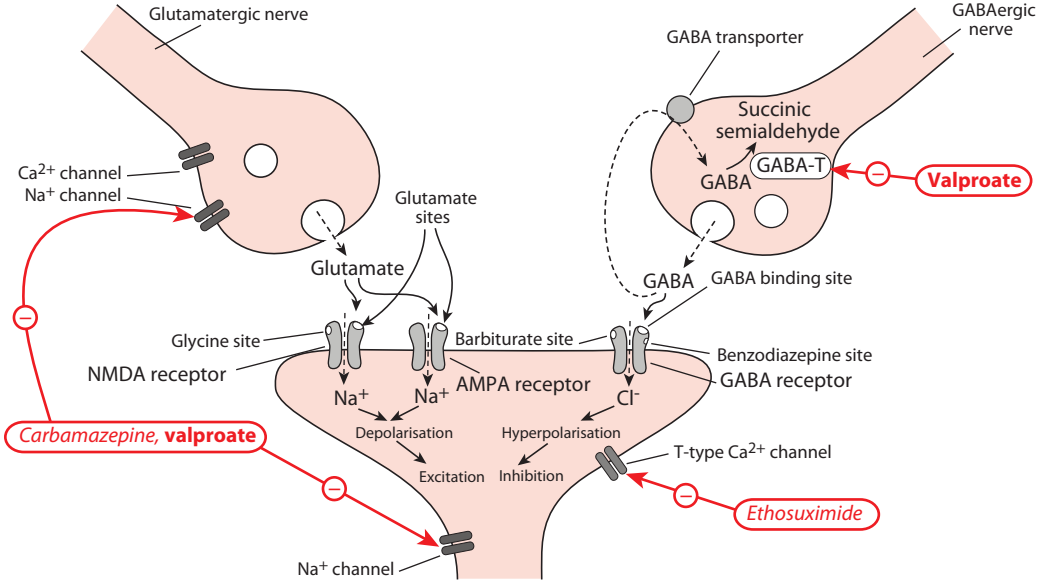
Abs/Distrib/Elim Oral admin. Subject to glucuronidation and mitochondrial oxidation. $T_{0.5}$ 9–16h.

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



Actions Anticonvulsant. Also hypnotic and anxiolytic (see set 22).

MOA Interacts with benzodiazepine binding site on $GABA_A$ 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.

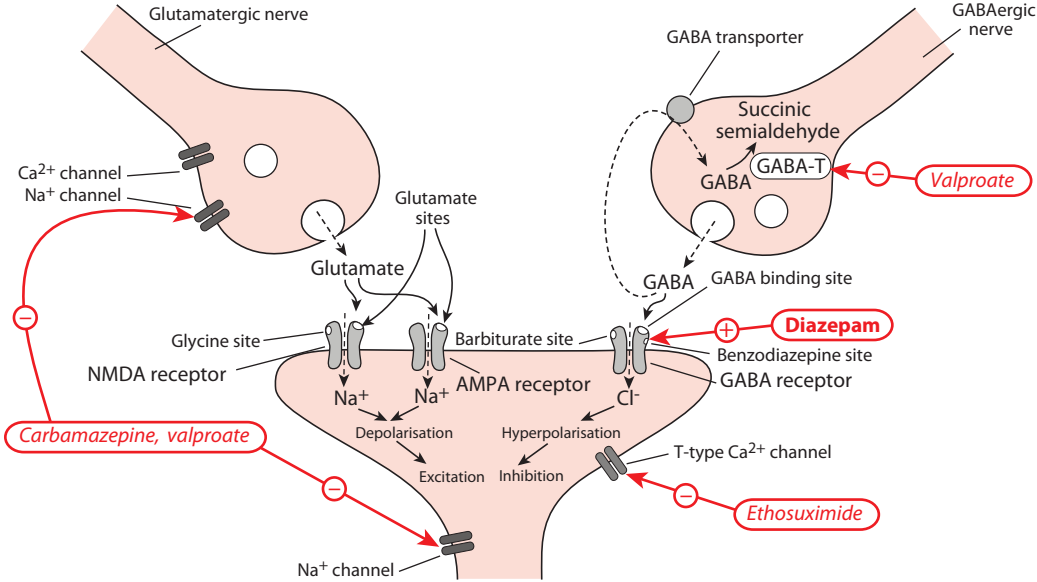
Abs/Distrib/Elim Given orally (i.v. for status epilepticus). Active metabolite of diazepam has a longer half-life (60h) and contributes significantly to actions. Metabolised by P450 system and glucuronide conjugation.

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).

R&D 7e Ch 44, p 548; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



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.

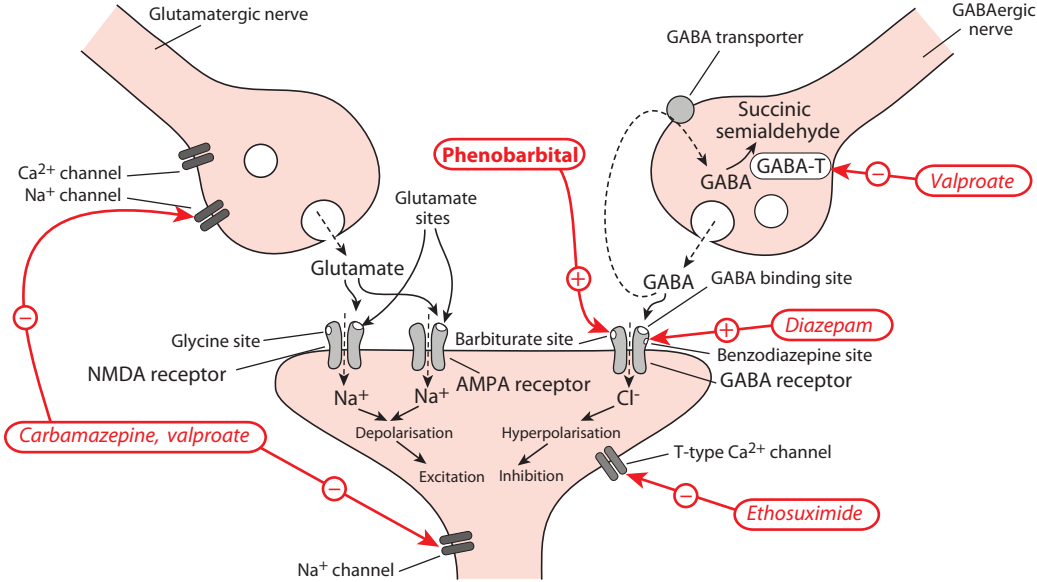
Abs/Distrib/Elim Oral admin. Some drug is excreted unchanged, but majority of drug is oxidised in liver. $T_{0.5}$ 50–100h.

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.

R&D 7e Ch 44, p 548; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



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.

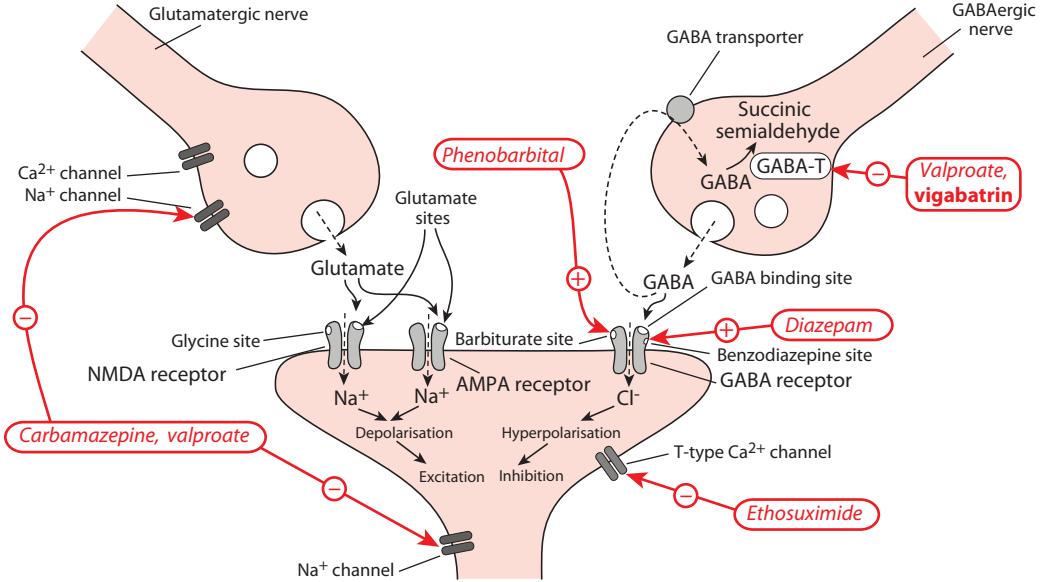
Abs/Distrib/Elim Oral admin. Mostly excreted unchanged. $T_{0.5}$ 10h, though irreversible enzyme inhibition prolongs drug action.

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.

R&D 7e Ch 44, p 549; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



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.

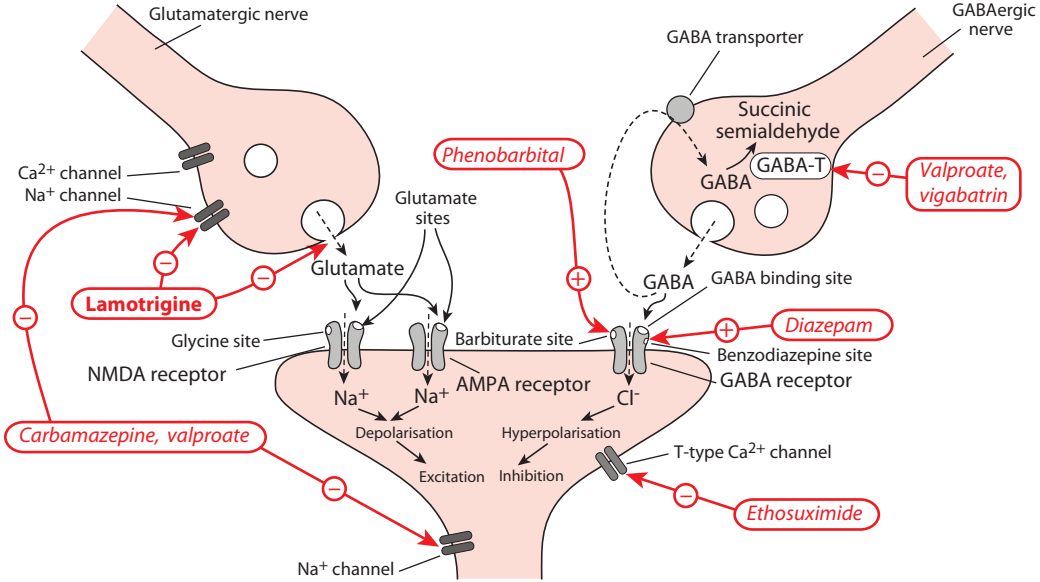
Abs/Distrib/Elim Oral admin. Subject to hepatic glucuronidation. $T_{0.5}$ 24–36h.

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.

R&D 7e Ch 44, p 549; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



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.

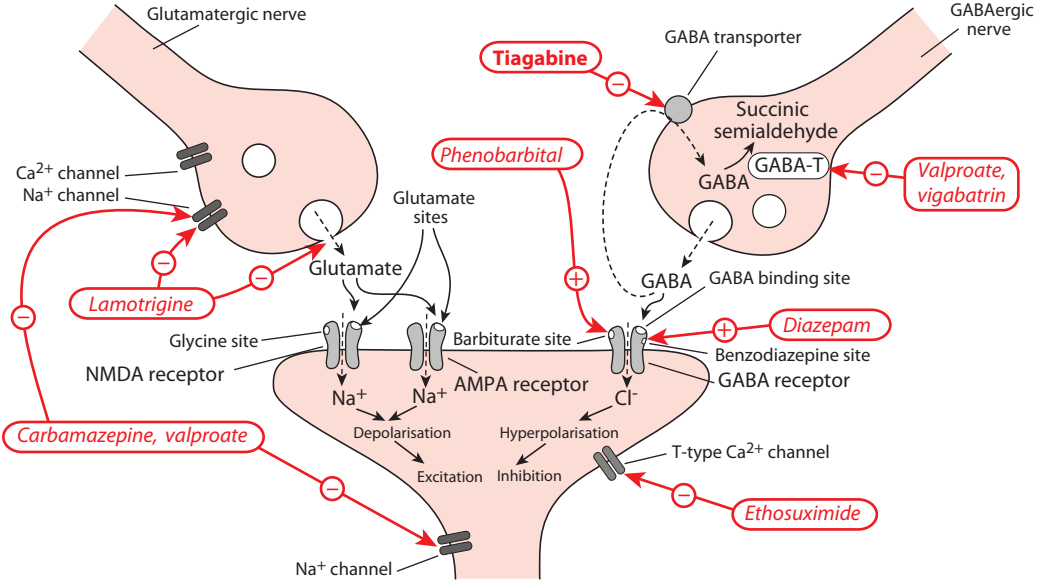
Abs/Distrib/Elim Orally active. P450 metabolism in liver. $T_{0.5}$ 7h.

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



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.

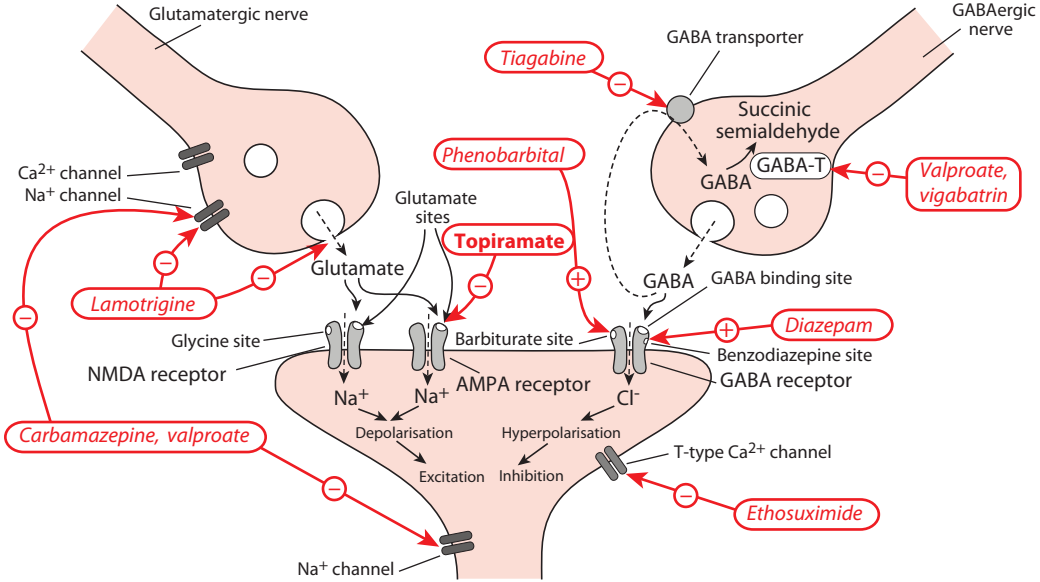
Abs/Distrib/Elim Oral admin. Mostly excreted unchanged in urine with some hepatic metabolism. $T_{0.5}$ 21h.

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.

R&D 7e Ch 44, p 549; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



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.

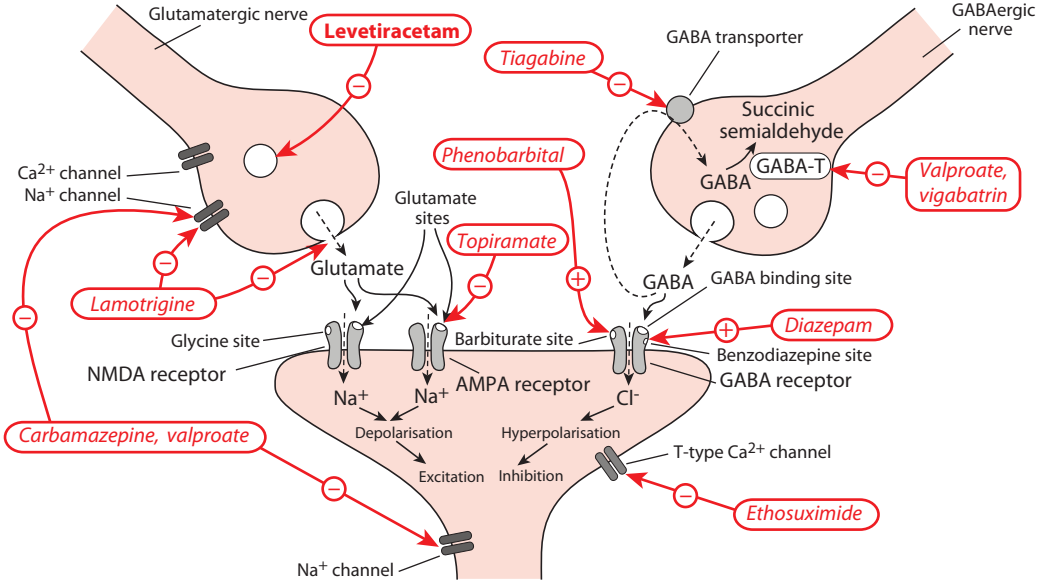
Abs/Distrib/Elim Oral admin. Mostly excreted unchanged. $T_{0.5}$ 7h.

Clinical use As an adjunct to other anticonvulsants in the treatment of partial seizures.

Adverse effects Sedation, dizziness, paraesthesia. Few drug interactions.

R&D 7e Ch 44, p 549; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



Actions Anticonvulsant. Analgesic.

MOA Action is attributed to binding to the α_2-δ-1 and α_2-δ-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.)

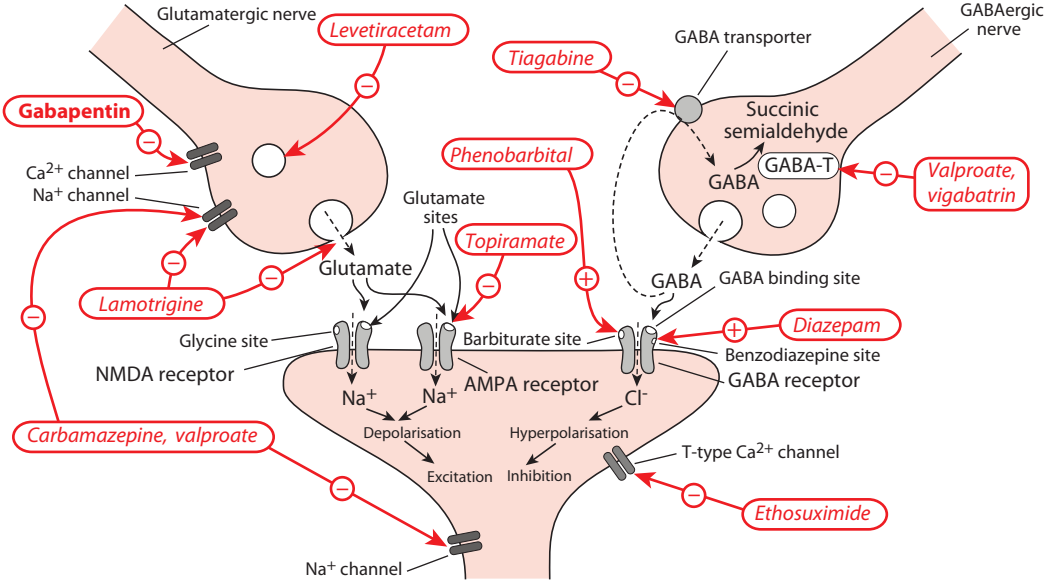
Abs/Distrib/Elim Oral admin. Excreted unchanged. $T_{0.5}$ 6h (longer with renal impairment).

Clinical use Adjunctive treatment for partial seizures. Widely used to treat neuropathic pain (see set 26).

Adverse effects Sedation, dizziness and unsteadiness.

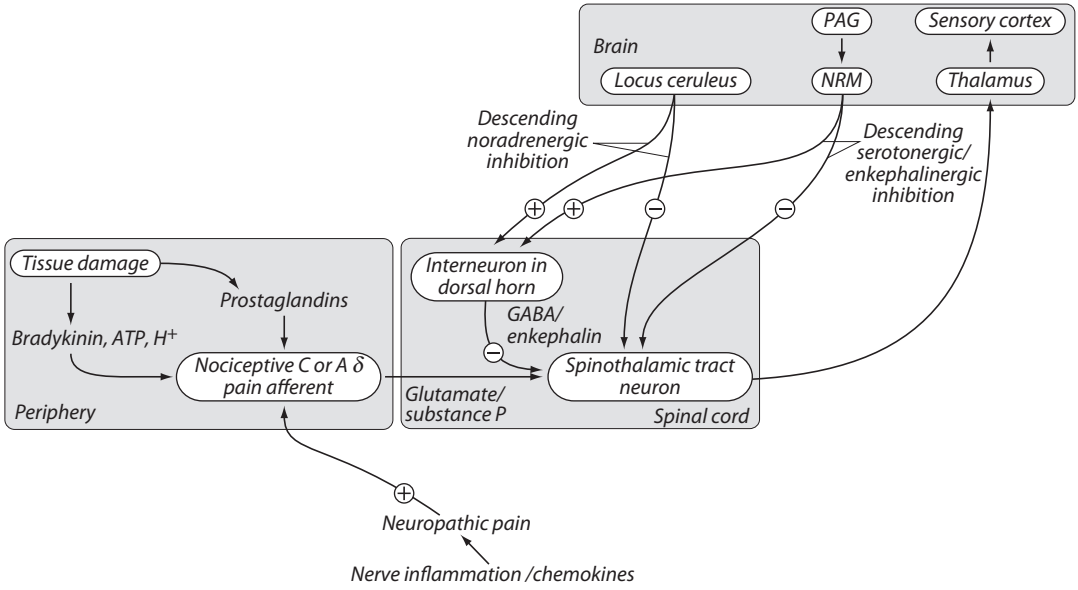
R&D 7e Ch 44, p 549; D&H 2e Ch 41, pp 94-95

Potential sites of action of antiepileptic drugs



Notes

Simplified diagram of pain pathway from periphery to brain



Morphine

Actions Analgesia. Sedation. Euphoria/reduced anxiety. Physical/psychological dependence. Cough suppression and respiratory depression. Inhibition of gut motility.

MOA Activates μ opioid receptors in the brain and spinal cord to inhibit pain transmission and modify the central perception of pain. Activation of κ 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.

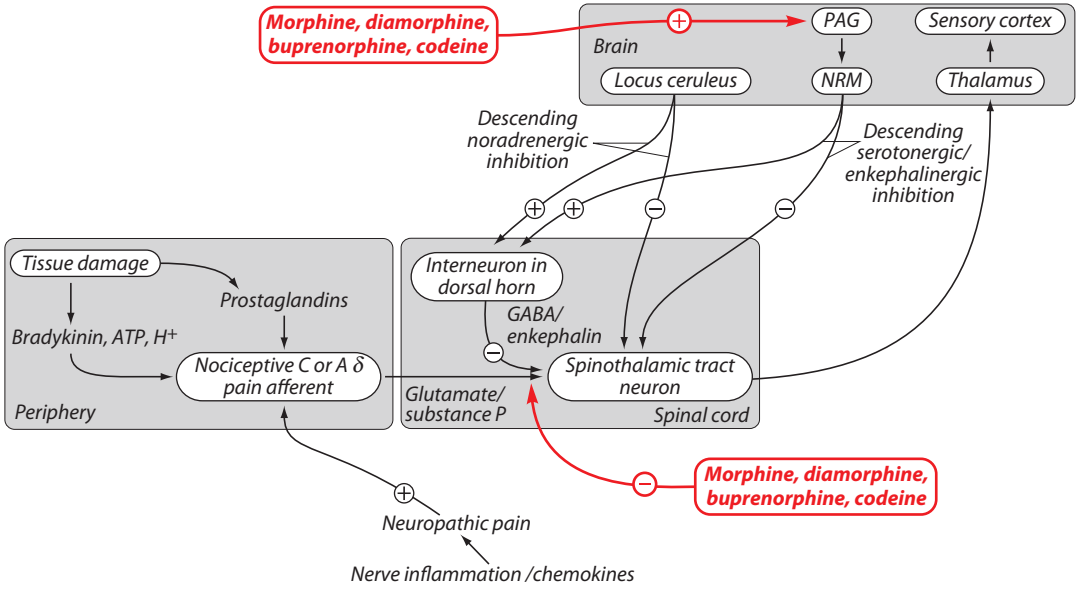
Abs/Distrb/Elim Oral or s.c., i.m. injection. Glucuronic acid conjugation in liver: $t_{0.5}$ 3–4h. The actions of diamorphine and codeine are due, at least in part, to metabolism to morphine. Buprenorphine $T_{0.5}$ 12h.

Clinical use Moderate to severe chronic and post-operative pain (codeine – mild pain). Epidural anaesthesia. Neuropathic pain. Treatment of painful cough. Diarrhoea.

Adverse effects Hypotension. Constipation, nausea, vomiting, drowsiness, dizziness. Tolerance, dependence and withdrawal effects (much less with codeine). Larger doses – coma with respiratory depression.

R&D 7e Ch 41, pp 510-513; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



Actions Analgesia. Euphoria. Physical/psychological dependence. Respiratory depression. Inhibition of gut motility. (Antimuscarinic effects of pethidine cause tachycardia.)

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).

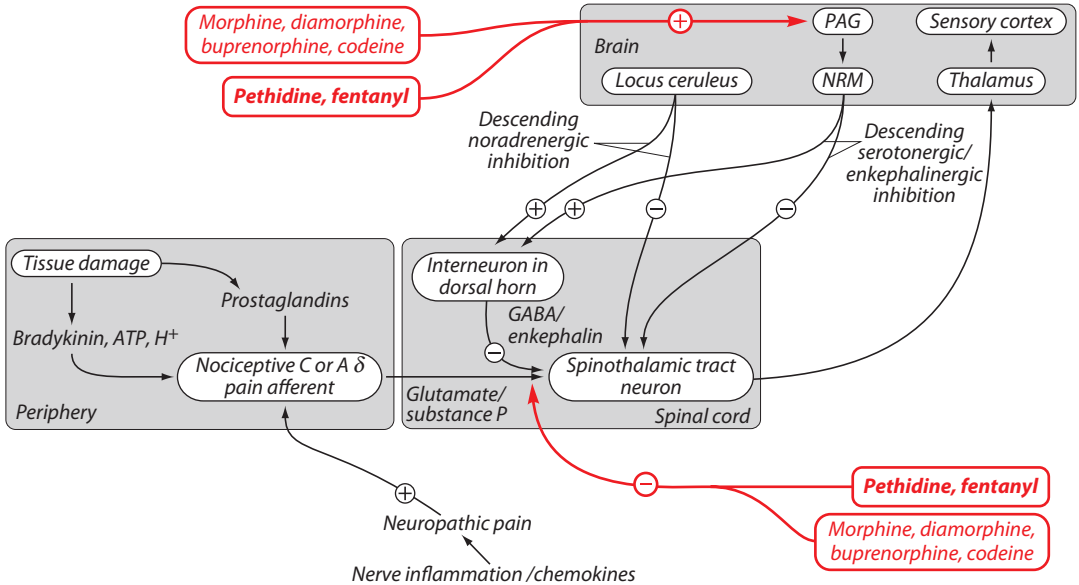
Abs/Distrb/Elim Oral/ i.m. admin. Subject to hydrolysis and P450 oxidation – $T_{0.5}$ 3–5h. Fentanyl is also available as a patch for transdermal admin. for long-term effects. Remifentanil has a very short half-life (0.1h).

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.

R&D 7e Ch 41, p 520; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



Methadone

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.)

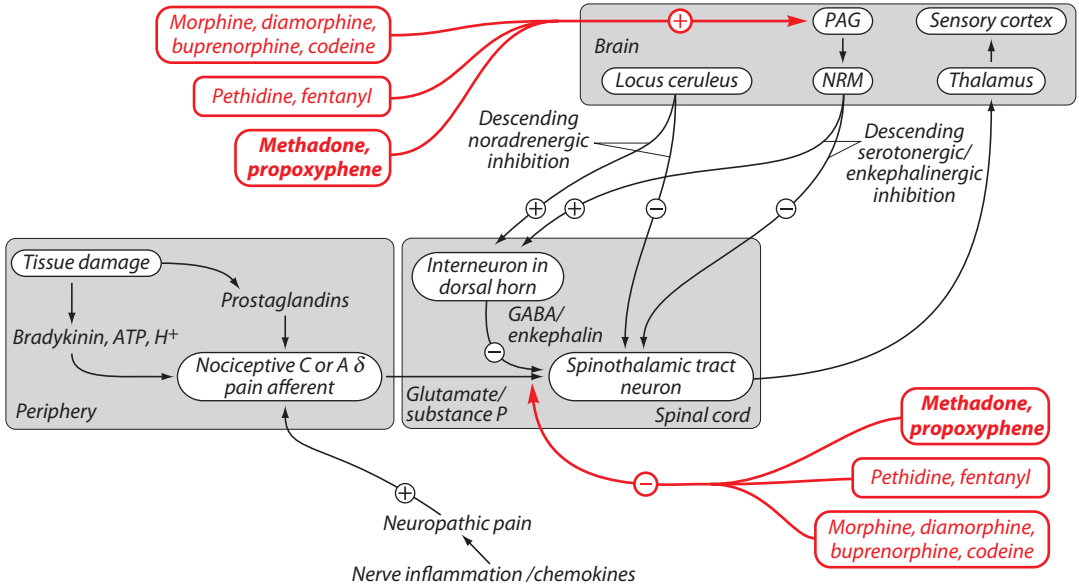
Abs/Distrb/Elim Oral absorption. Long duration of action. P450 metabolism in liver $T_{0.5}$ 15–40h. Propoxyphene $T_{0.5}$ 6h.

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.

R&D 7e Ch 41, pp 519-520; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



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-HT_3 receptor antagonists.

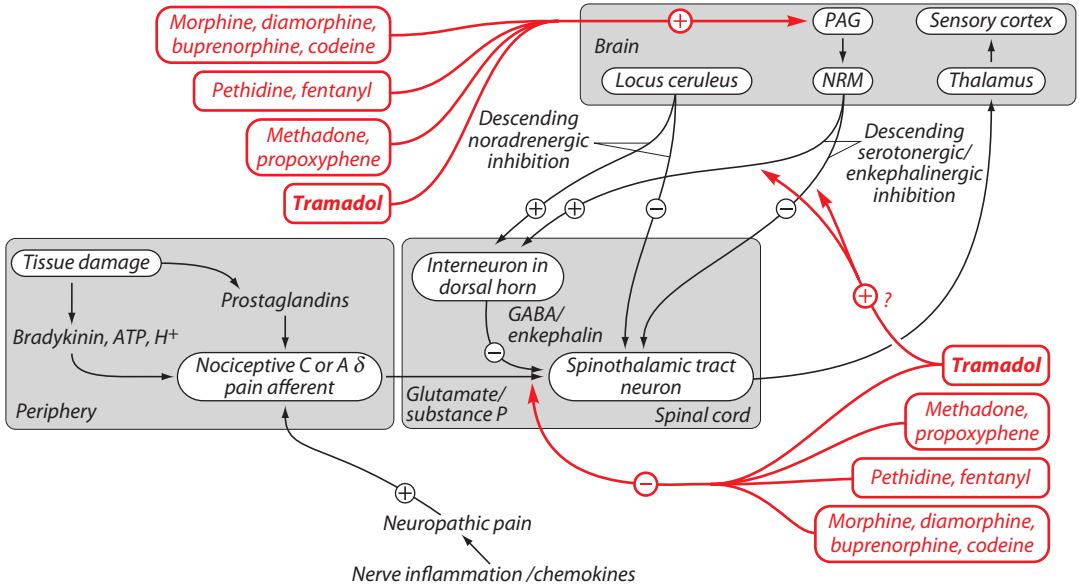
Abs/Distrb/Elim Oral admin. Subject to hepatic demethylation and conjugation, $T_{0.5}$ 6h.

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.

R&D 7e Ch 41, p 520; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



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.

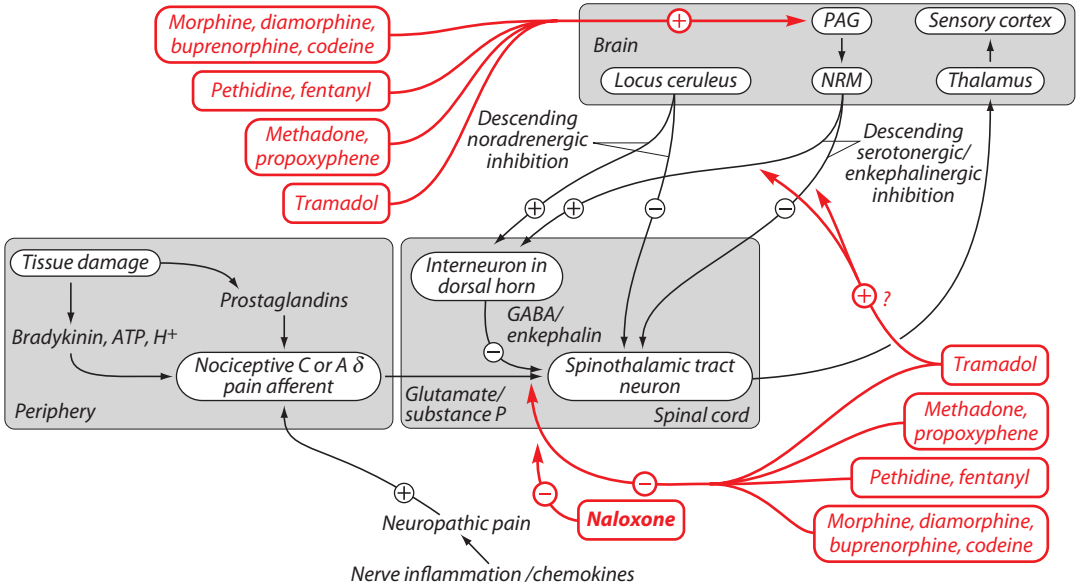
Abs/Distrb/Elim Given by injection (i.v., i.m. or s.c.) (very low oral bioavailability). Conjugated with glucuronic acid in liver, short $t_{½}$:1–2h. Naltrexone is orally active and has a $t_{½}$ of 4h though action is extended by an active metabolite with $t_{½}$ of 13h.

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.

R&D 7e Ch 41, p 520; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



Ibuprofen

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.

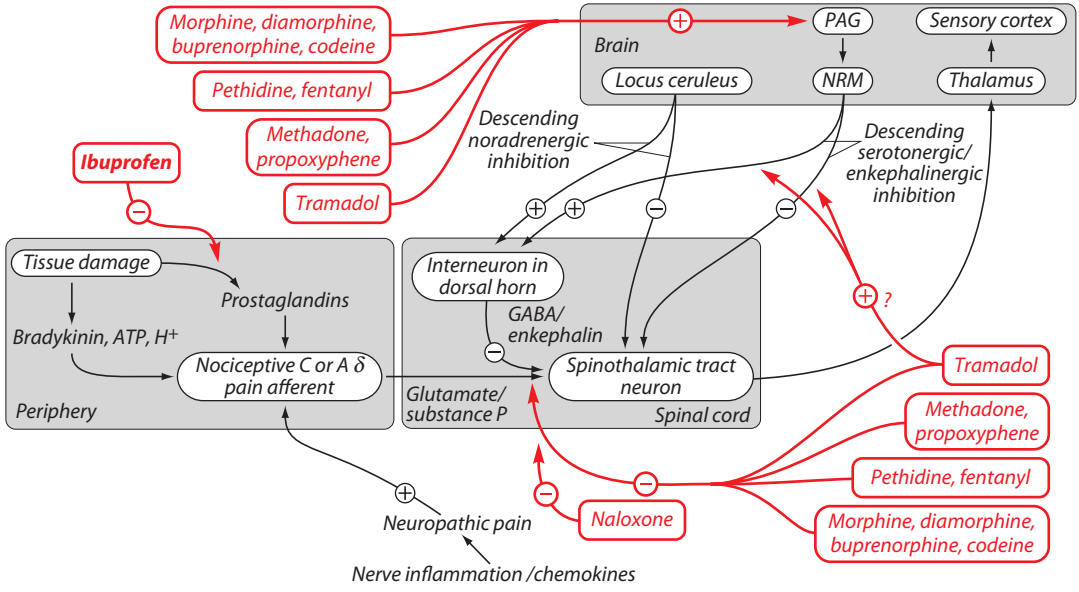
Abs/Distrb/Elim Oral admin. Metabolised by P450 system, $T_{0.5}$ 2h. Aspirin is rapidly hydrolysed to yield salicylate which is also a COX inhibitor. Naproxen $T_{0.5}$ 14h. Paracetamol $T_{0.5}$ 2–3h.

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.

R&D 7e Ch 41, p 521; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



Carbamazepine

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.

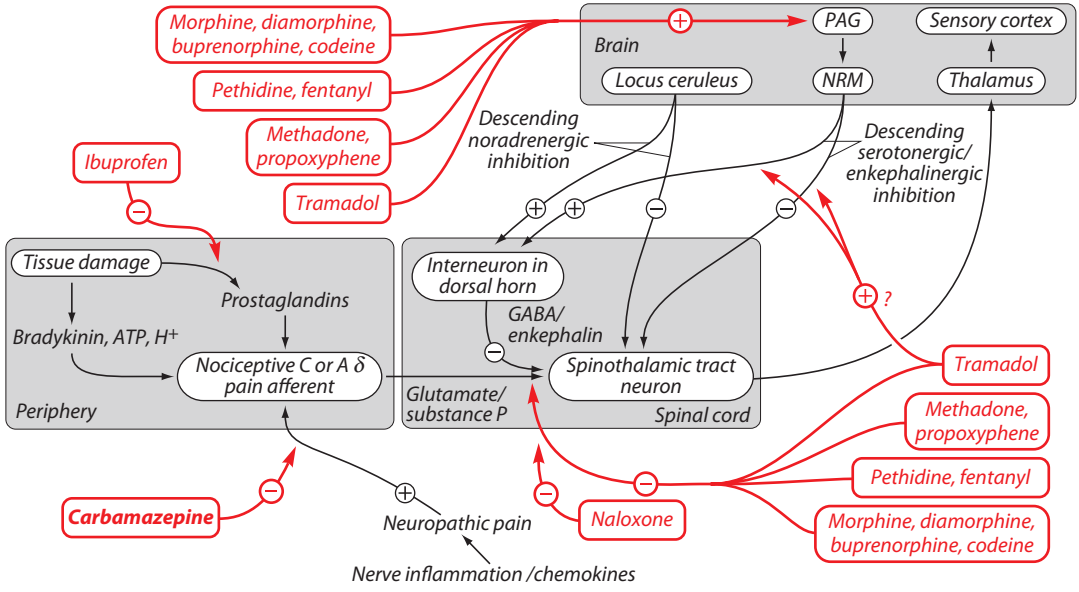
Abs/Distrb/Elim Oral administration. Active P450 metabolite.

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.

R&D 7e Ch 41, p 521; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



Amitriptyline

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.

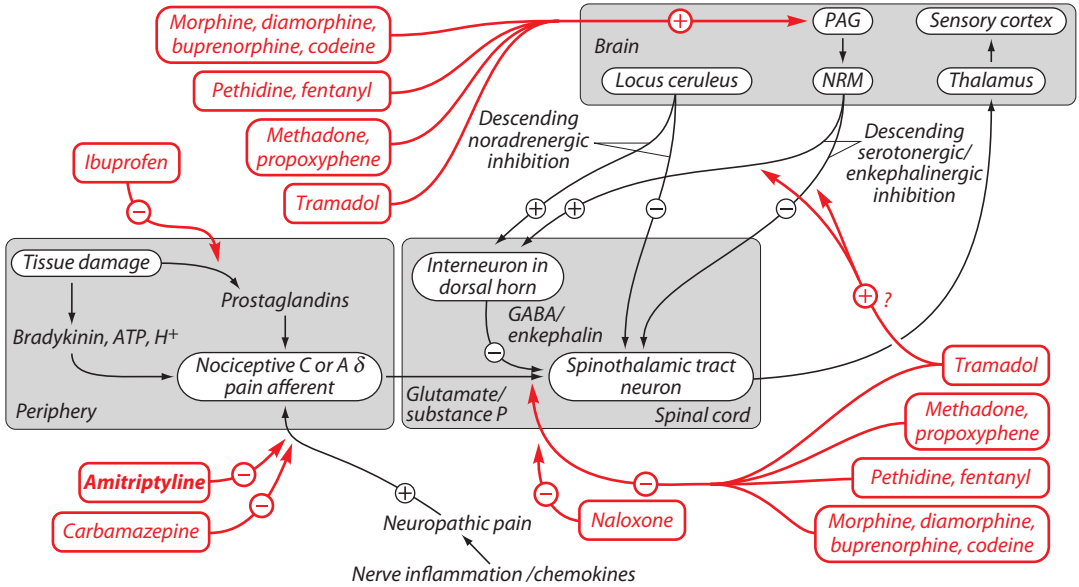
Abs/Distrb/Elim Oral administration. Hepatic P450 metabolism (nortriptyline is a metabolite of amitriptyline). $T_{0.5}$ 12–24h.

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 (α_1-adrenoceptor antagonism). Overdose potentially fatal due to cardiac dysrhythmia, severe hypotension, seizure and CNS depression. Increased risk of suicide in young patients.

R&D 7e Ch 41, p 521; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



Gabapentin

Actions Reduction of neuropathic pain. (For antiepileptic action see set 25).

MOA Effectiveness in neuropathic pain is due to binding to the α_2-δ-1 and α_2-δ-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.

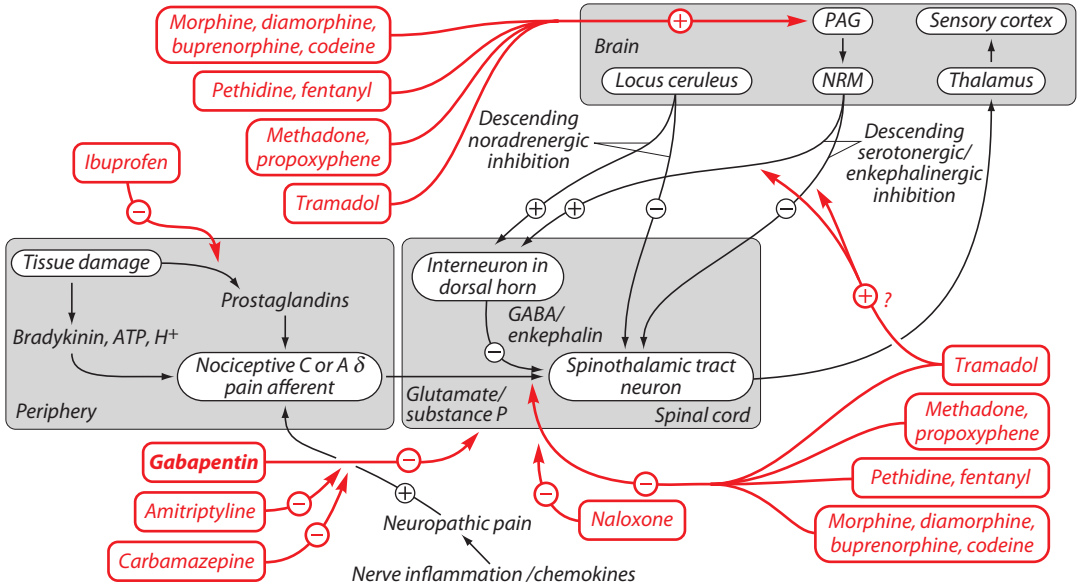
Abs/Distrb/Elim Oral admin. Excreted unchanged. $t_{½}$ 6h.

Clinical use Postherpetic and trigeminal neuralgia. Pregabalin is also used for painful diabetic peripheral neuropathy.

Adverse effects Sedation, dizziness and unsteadiness.

R&D 7e Ch 41, p 521; D&H 2e Ch 42, p 96

Simplified diagram of pain pathway from periphery to brain



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_{1B} and 5-HT_{1D} receptors. Activation of 5-HT_{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. $T_{0.5}$ 1.5h. May be given s.c. if migraine is accompanied by vomiting.

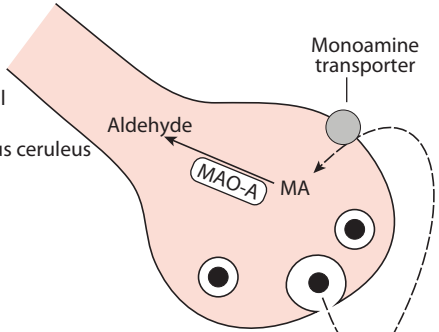
Clinical use Acute migraine attack. Sumatriptan is also effective in cluster headache.

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_2 receptor antagonist).

R&D 7e Ch 15, pp 201-202; D&H 2e Ch 12, p 36

Dopaminergic, noradrenergic and serotonergic transmission as targets for CNS stimulants and psychotomimetics



MA, monoamine
DA, dopamine
NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

Amfetamine

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.

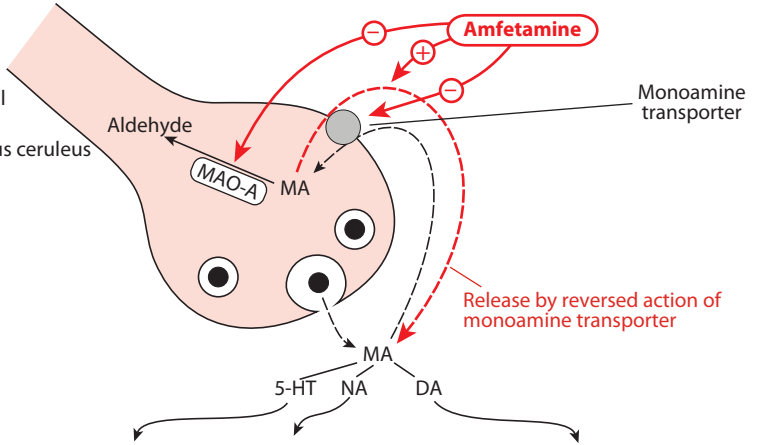
Clinical use Attention deficit hyperactivity disorder (ADHD), narcolepsy.

Adverse effects Aggression, restlessness, insomnia, paranoia. Anorexia, weight loss. Psychotic states/ hallucinations. Dependence. Dehydration/hyperthermia (MDMA). Hypertension. Sudden death in patients with pre-existing cardiac abnormalities.

R&D 7e Ch 47, pp 584-586; D&H 2e Ch 43, p 99

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, monoamineoxidase-A

Actions Euphoria, alertness and other effects like amfetamine. Sympathomimetic actions: tachycardia, vasoconstriction with increased blood pressure etc. Local anaesthesia.

MOA Inhibits action of monoamine transporters (but unlike amfetamine-like drugs is not transported and does not provoke monoamine release). Local anaesthetic action due to Na^+ channel block (see card 28.03).

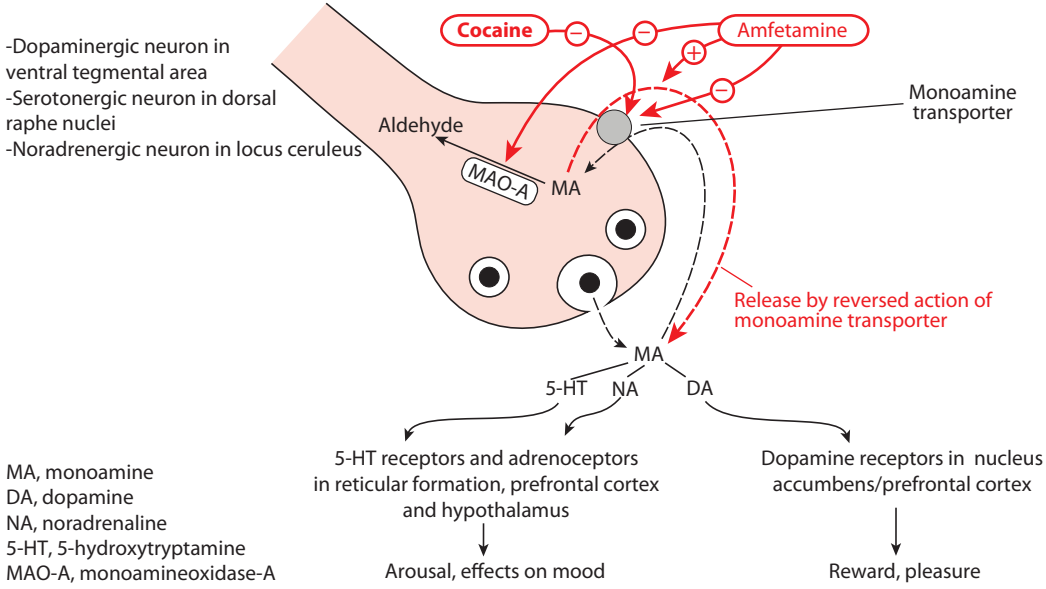
Abs/Distrib/Elim Abusers favour i.v. or nasal admin. (The free base 'crack cocaine' is volatile and is smoked.) $T_{0.5}$ 1h.

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.

R&D 7e Ch 47, p 587; D&H 2e Ch 43, p 99

Dopaminergic, noradrenergic and serotonergic transmission as targets for CNS stimulants and psychotomimetics



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 nucei by 5-HT_{1A} receptors and modulation of dopaminergic activity in the mesolimbic pathway. Mescaline acts partly by inhibiting MA reuptake.

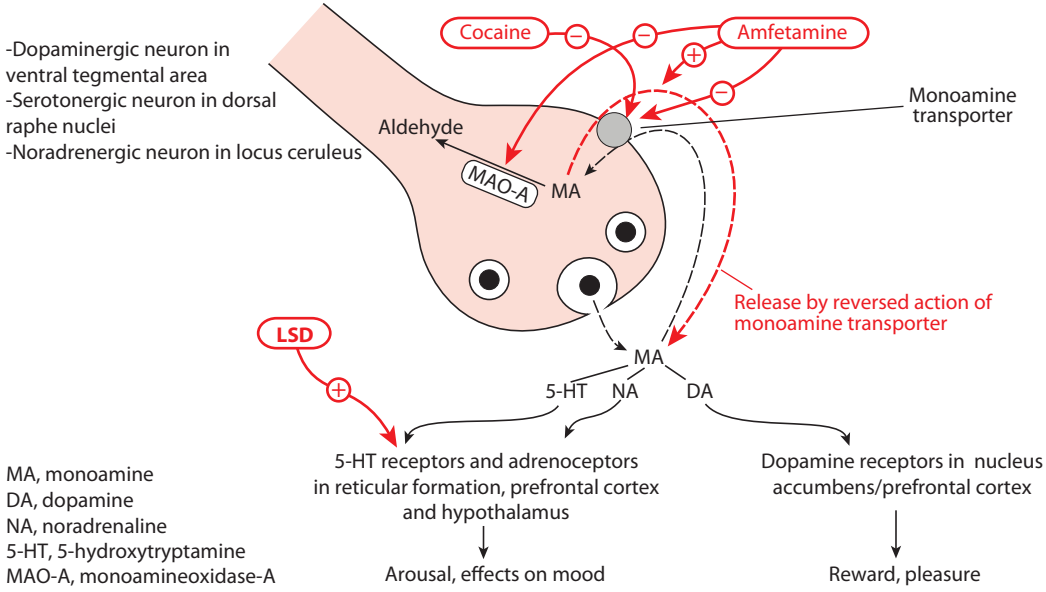
Abs/Distrib/Elim Effective orally. LSD $T_{0.5}$ 3h. DMT has a low oral bioavailability so may be smoked.

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.

R&D 7e Ch 47, p 589; D&H 2e Ch 43, p 99

Dopaminergic, noradrenergic and serotonergic transmission as targets for CNS stimulants and psychotomimetics



Phencyclidine

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.

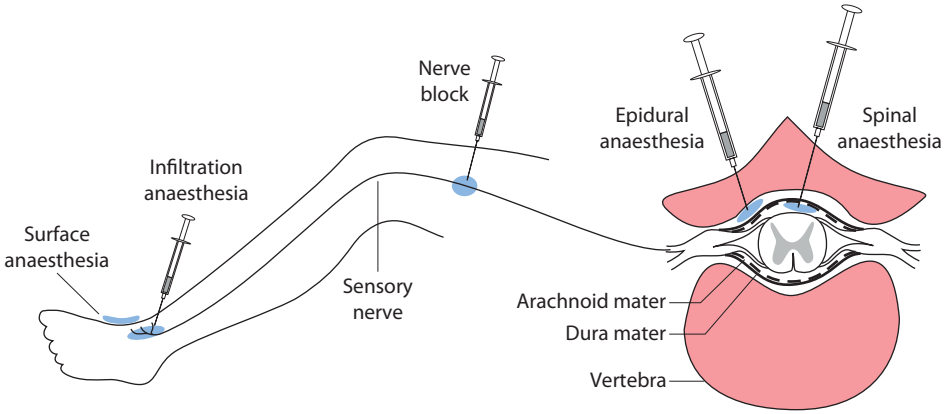
Abs/Distrib/Elim Most commonly absorbed by inhalation of smoke but also orally active. $T_{0.5}$ 10–90h.

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.

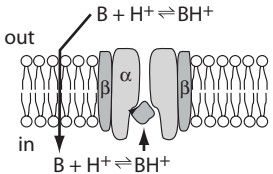
R&D 7e Ch 47, p 590; D&H 2e Ch 43, p 99

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).



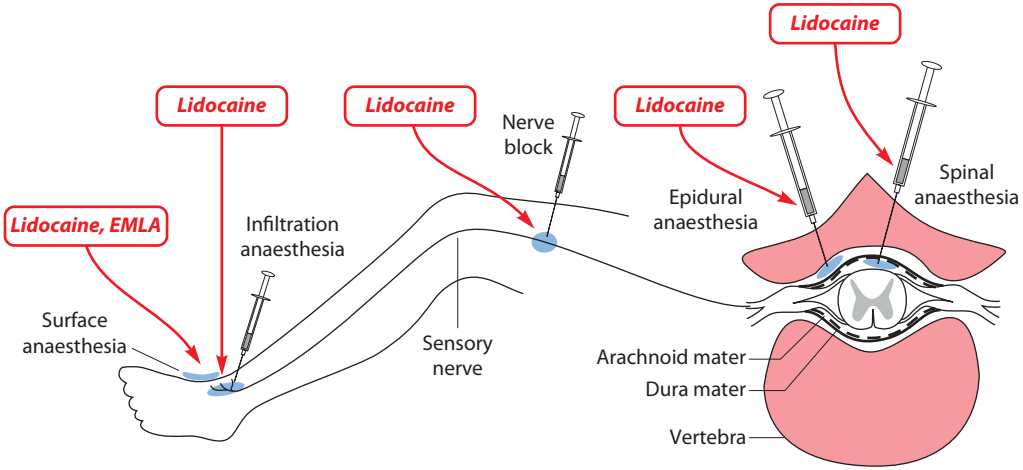
Abs/Distrb/Elim Topical application (gel, solution, patch) or injection. Penetrates membranes readily. Lidocaine, like other amide LAs, is metabolised mainly in the liver by P450 system. $t_{½}$ 2h.

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.

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.



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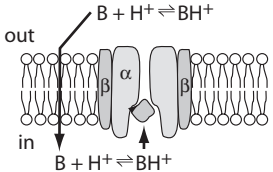
MOA Use-dependent block of voltage-gated Na^+ channels from inside of cell membrane. Penetrates cell membrane in its lipid-soluble, uncharged form. (See fig.) Less active in inflamed tissue, where the lower pH increases ionisation of the weakly basic local anaesthetic (LA).



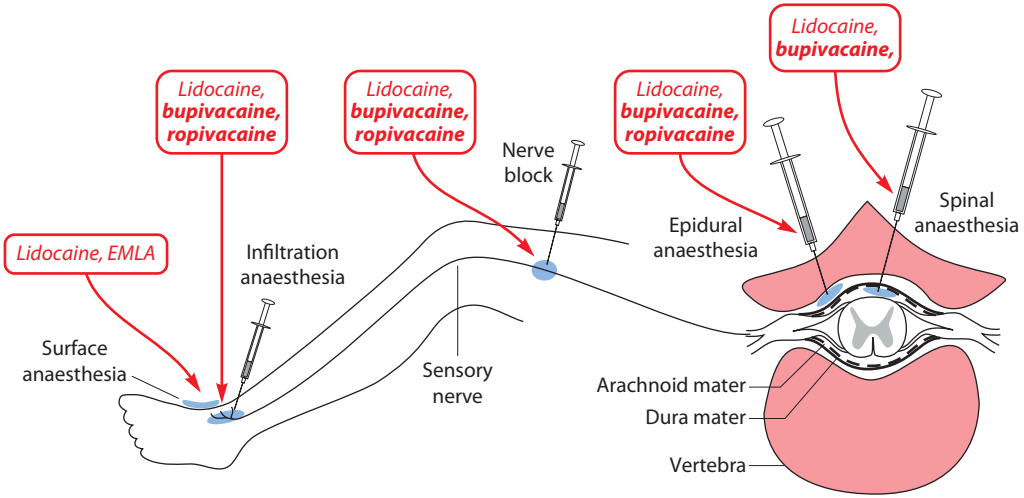
Abs/Distrb/Elim These drugs are amides metabolised by P450 system in liver, eventually yielding glucuronides. They are longer acting than other LAs. Bupivacaine $T_{0.5}$ 2–3h.

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.)

R&D 7e Ch 42, pp 526-528; 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.



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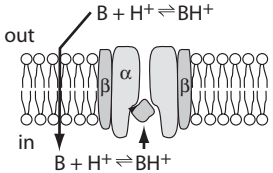
MOA Use-dependent block of voltage-gated Na^+ channels from inside of cell membrane. Penetrates cell membrane in its lipid-soluble, uncharged form. (See fig.) Less active in inflamed tissue, where the lower pH increases ionisation of the weakly basic local anaesthetic (LA).



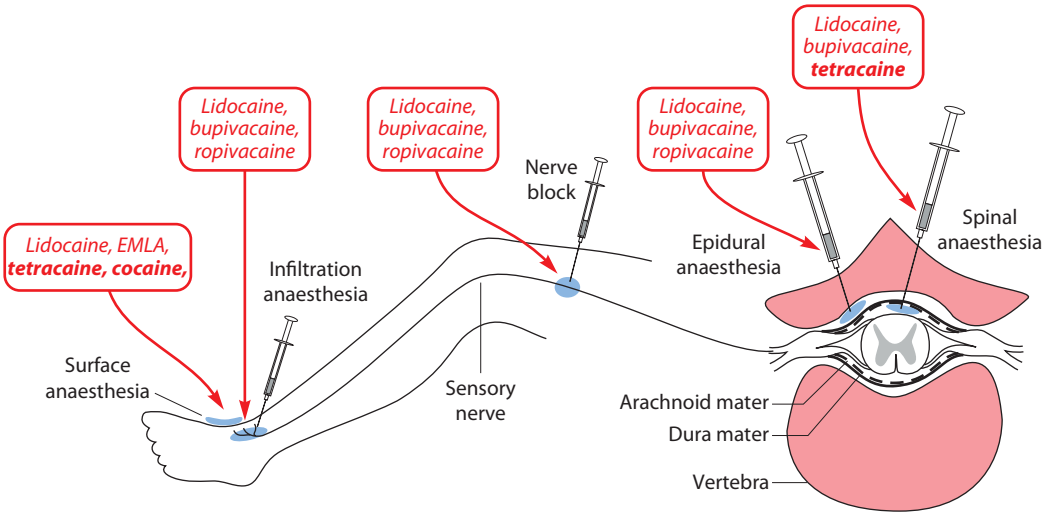
Abs/Distrb/Elim Ester-type LAs are in general shorter acting than lidocaine or bupivacaine, being mainly hydrolysed by plasma esterases. (Plasma $T_{0.5}$ is only a few minutes, but duration of action is increased due to slower removal from site of injection, especially so for the very lipid-soluble 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).

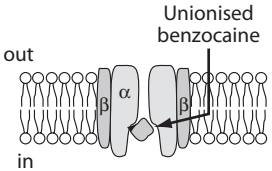
R&D 7e Ch 42, pp 526-529; D&H 2e Ch 44, p 100

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 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.).



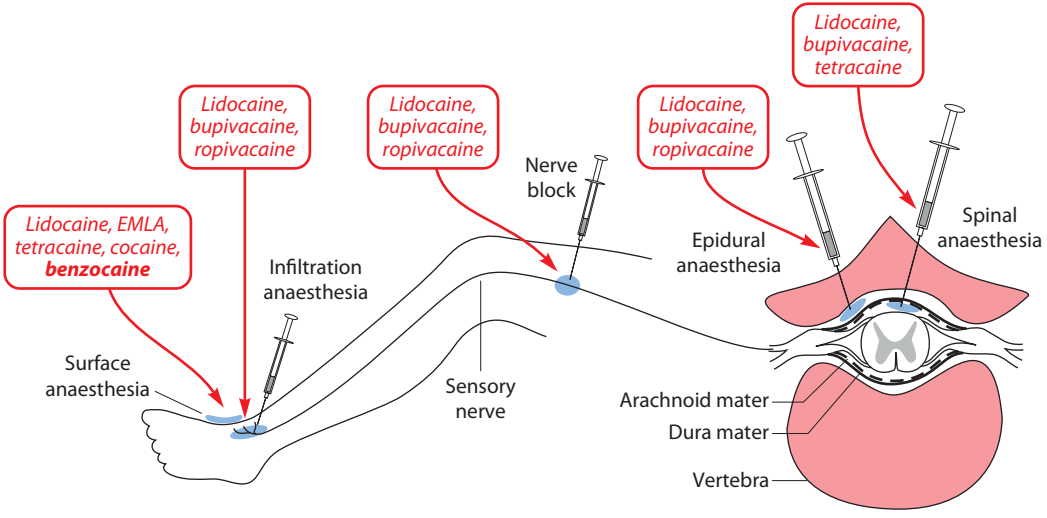
Abs/Distrb/Elim Topical application as gel, ointment or powder (low aqueous solubility). High lipid solubility allows rapid penetration of mucous membranes.

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.

R&D 7e Ch 42, p 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.



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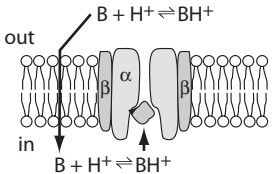


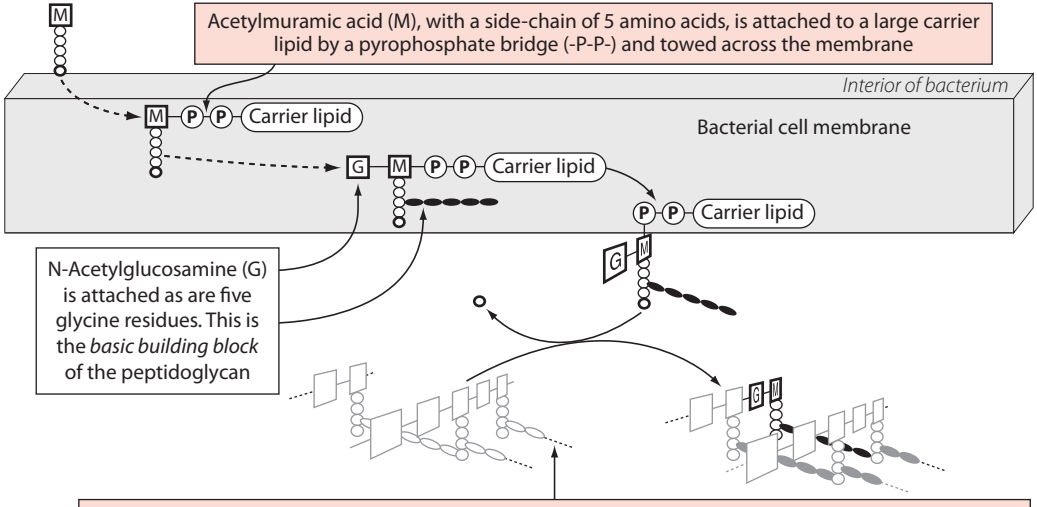
Abs/Distrb/Elim Articaine is an amide-type LA (like lidocaine) but has an additional ester group which can be rapidly hydrolysed to give a short plasma half-life (30min).

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.

R&D 7e Ch 42, pp 527-528; D&H 2e Ch 44, p 100

Peptidoglycan synthesis and the site of action of drugs



Benzylpenicillin

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 phenoxymethyl penicillin can be given orally.

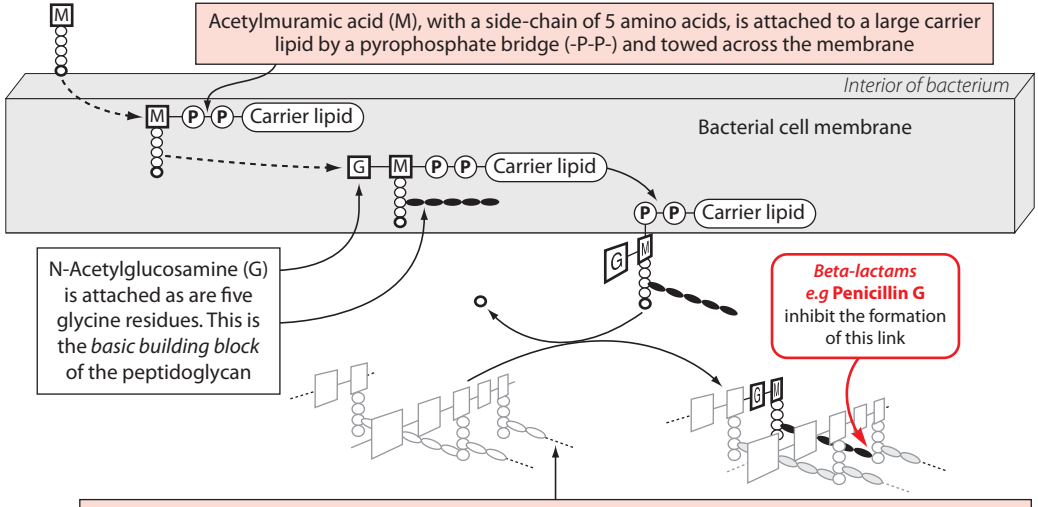
Clinical use Streptococcal, gonococcal, meningococcal infections; also anthrax, dipththeria, gas gangrene.

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).

R&D 7e Ch 50, p 627; D&H 2e Ch 47, pp 107-108

Peptidoglycan synthesis and the site of action of drugs



A β-lactamase-resistant penicillin antibacterial agent (Similar drug: temocillin)

Flucloxacillin

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).

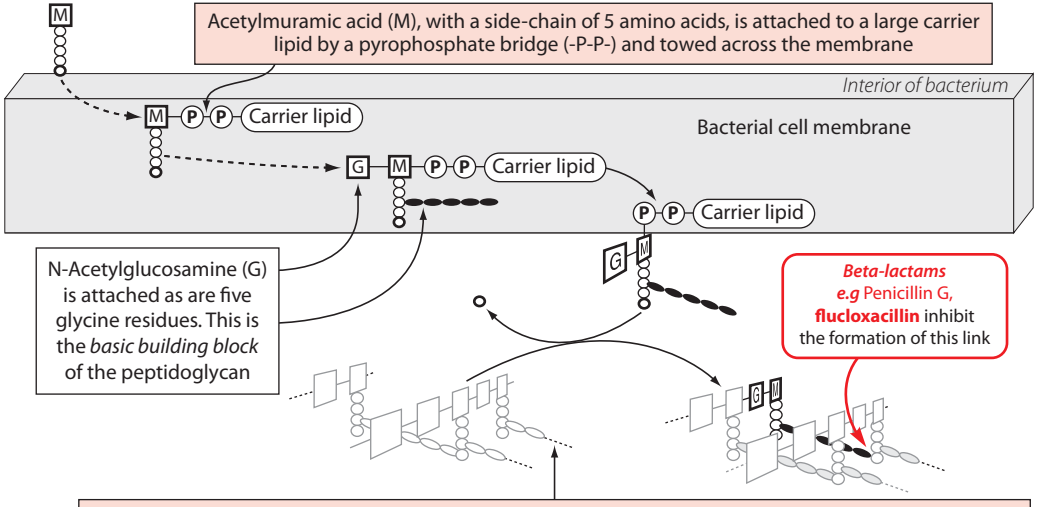
Clinical use Penicillin-resistant staphylococci infections.

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.

R&D 7e Ch 50, p 627; D&H 2e Ch 47, pp 107-108

Peptidoglycan synthesis and the site of action of drugs



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.

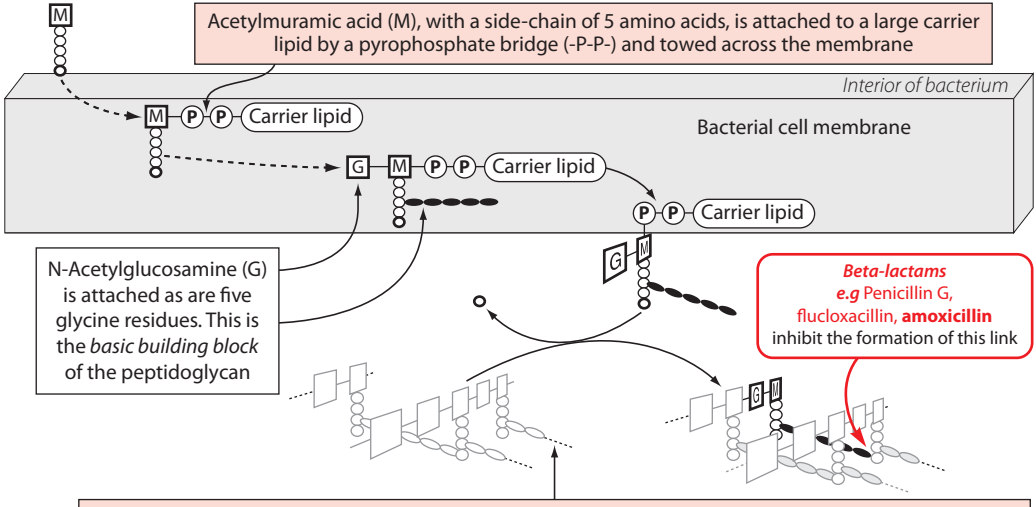
Clinical use Gram-negative bacteria as well as streptococcal, gonococcal, meningococcal infections, anthrax, dipththeria, gas gangrene.

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.

R&D 7e Ch 50, p 627; D&H 2e Ch 47, pp 107-108

Peptidoglycan synthesis and the site of action of drugs



Piperacillin

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).

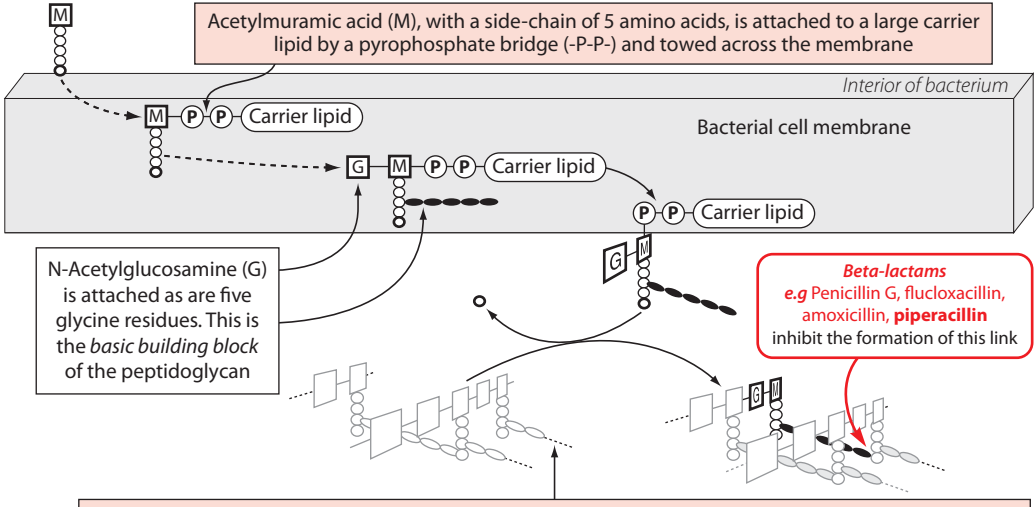
Clinical use Gram-negative bacterial and *Pseudomonas aeruginosa* infections.

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



A second-generation cephalosporin β-lactam antibiotic (Similar drug: cefaclor)

Cefuroxime

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.

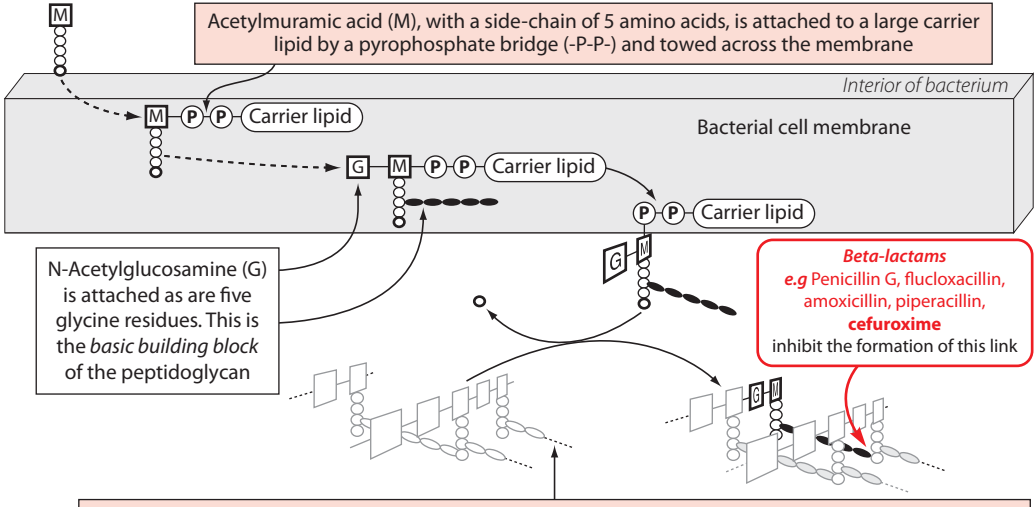
Abs/Distrb/Elim Given orally. i.m. or i.v. Passes into all body fluids; excreted in the urine (blocked by probenecid).

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.

R&D 7e Ch 50, p 627-628; D&H 2e Ch 47, pp 107-108

Peptidoglycan synthesis and the site of action of drugs



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.

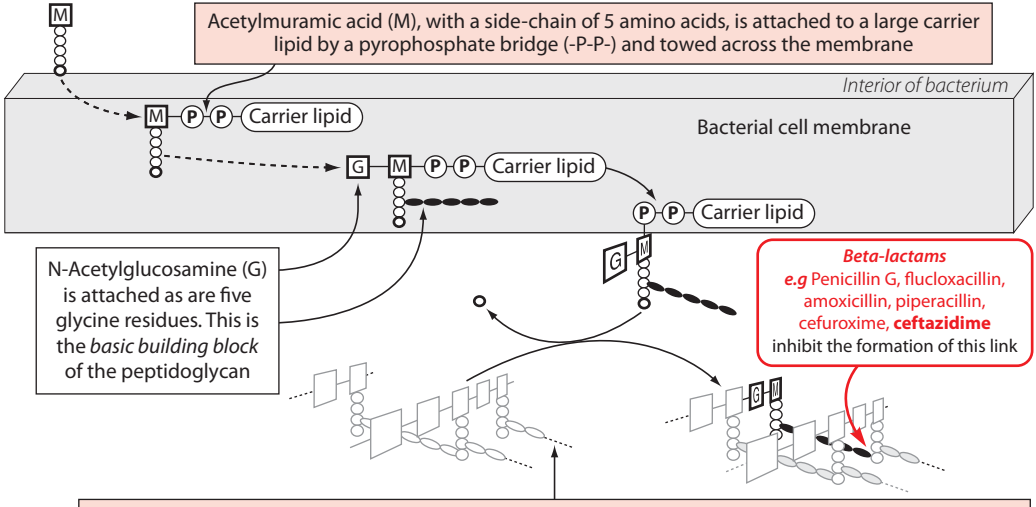
Clinical use Gram-positive & Gram-negative bacterial and *Pseudomonas aeruginosa* infections.

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).

R&D 7e Ch 50, p 627-628; D&H 2e Ch 47, pp 107-108

Peptidoglycan synthesis and the site of action of drugs



Imipenem

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.

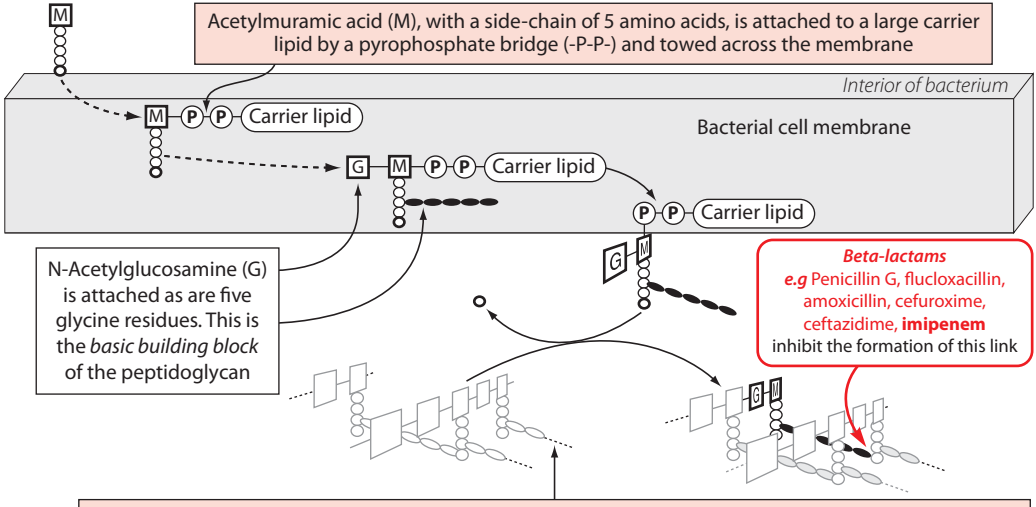
Clinical use Broad spectrum: active against Gram-positive, Gram-negative and anaerobic bacteria. Not active against MRSA. Used to treat severe polymicrobial hospital-acquired infections, e.g. septicaemia, pneumonia, complicated urinary infections.

Adverse effects GIT disturbances, rashes, injection site reactions.

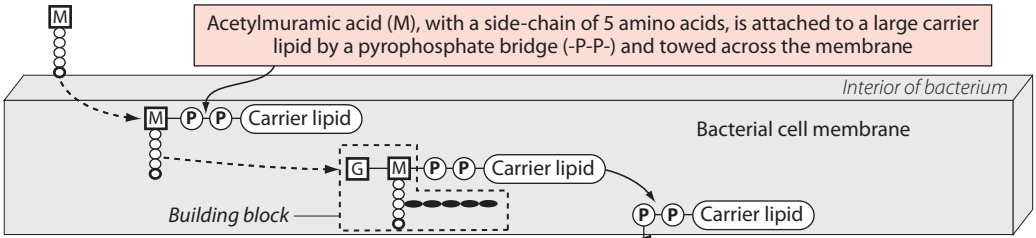
Similar drugs Meropenem.

R&D 7e Ch 50, p 628; D&H 2e Ch 47, pp 107-108

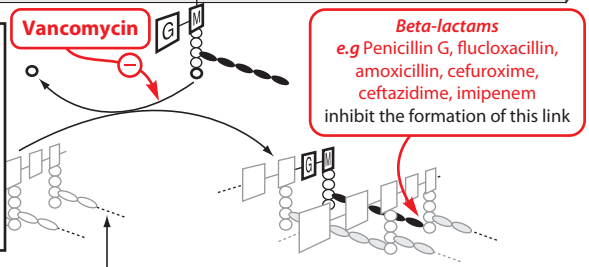
Peptidoglycan synthesis and the site of action of drugs



Vancomycin



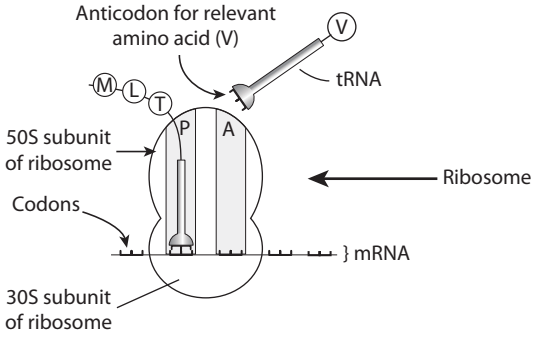
Action & MOA	Bactericidal; interferes with cell wall synthesis in dividing bacteria.
Abs/Distrb/ Elim	Given orally for local effect in the mouth,otherwise i-v; renal excretion
Clinical use	MRSA infections, pseudo-membranous colitis
Advers effects	Reversible hearing loss; rarely: renal failure



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.**

R&D 7e Ch 50, p 628; D&H 2e Ch 47, p 108

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/Distrb/Elim Given orally, absorption impaired by milk and by calcium, magnesium and iron preparations.

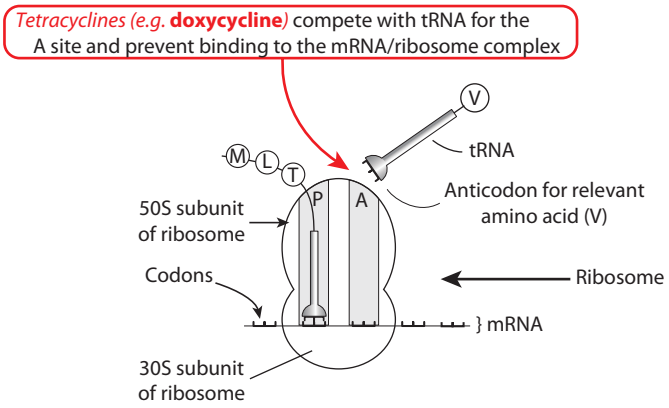
Clinical use A drug of choice for chlamydial, rickettsial and brucella infections. Effective in infections with mycoplasma and *Haemophilus influenzae*. Used in sinusitis, prostatitis, syphilis, Lyme disease and in treatment/prevention of malaria (see card 31.02).

Adverse effects Staining of the teeth, GIT disturbances, anorexia, flushing, tinnitus. Rare: hepatotoxicity pancreatitis, hypersensitivity reactions.

Similar drug: Minocycline (has broader spectrum), demeclocycline.

R&D 7e Ch 50, p 629; D&H 2e Ch 47, p 110

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).

Gentamicin

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.

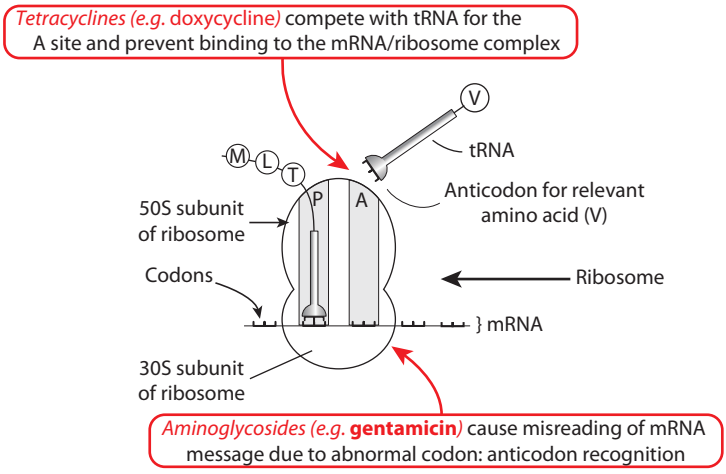
Adverse effects Dose-related ototoxicity and nephrotoxicity. GIT disturbances, rash, blood disorders can occur; ↑ ototoxicity with loop diuretics; ↑ effect of neuromuscular blockers.

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



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).

Chloramphenicol

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.

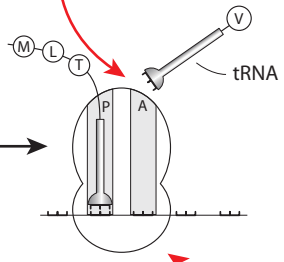
Adverse effects Dose-related bone marrow depression. 'Grey baby' syndrome in neonates who lack the relevant inactivating enzyme: circulatory collapse, flaccidity, vomiting. Aplastic anaemia in a few genetically predisposed individuals.

R&D 7e Ch 50, p 630; D&H 2e Ch 47, p 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

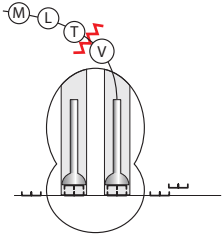
A transfer RNA with growing peptide chain is in the P site. The Incoming tRNA carries valine (V).



Aminoglycosides (e.g. gentamicin*)* cause misreading of message due to abnormal codon: anticodon recognition

Chloramphenicol inhibits transpeptidation

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



Erythromycin

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, diptheria, prostatitis, whooping cough, campylobacter enteritis.

Adverse effects GIT disturbances. Less frequent: allergic reactions, cholestatic jaundice.

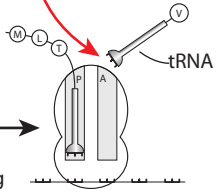
Similar drugs Clarithromycin and azithromycin.

R&D 7e Ch 50, p 631; D&H 2e Ch 47, pp 108-110

Bacterial protein synthesis and the antibiotics that act thereon

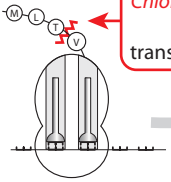
Tetracyclines (e.g. doxycycline*)* compete with tRNA for the A site and prevent binding to the mRNA/ribosome complex

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

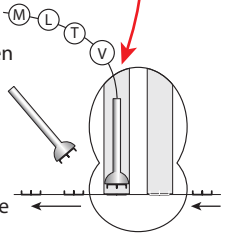


Chloramphenicol inhibits transpeptidation

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.

Macrolides (e.g. **erythromycin***)* inhibit translocation



Clindamycin

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.

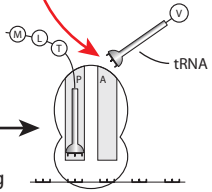
Adverse effects GIT disturbances, skin rashes, jaundice, pseudomembranous colitis.

R&D 7e Ch 50, p 633; D&H 2e Ch 47, p 110

Bacterial protein synthesis and the antibiotics that act thereon

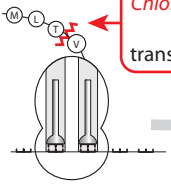
Tetracyclines (e.g. doxycycline) compete with tRNA for the A site and prevent binding to the mRNA/ribosome complex

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

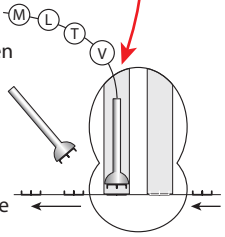


Chloramphenicol inhibits transpeptidation

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



Quinupristin + dalfopristin

Actions Inhibit bacterial protein synthesis by disrupting the translation of mRNA into protein.

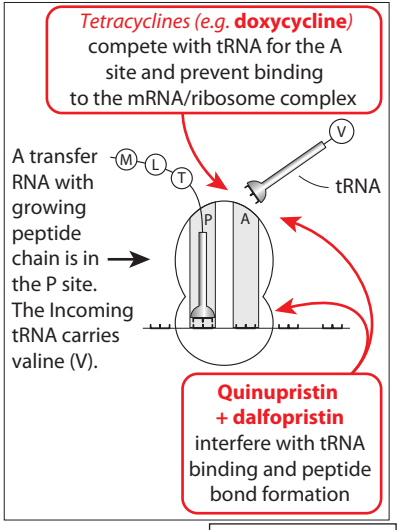
MOA Dalfopristin inhibits the binding of the aa-tRNA to the ribosome and the formation of the peptide bonds; quinupristin causes dissociation of the peptidyl-tRNA.

Abs/Distrib/Elim Given by i.v. infusion, metabolised in the liver; $T_{0.5}$1–3h.

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*.

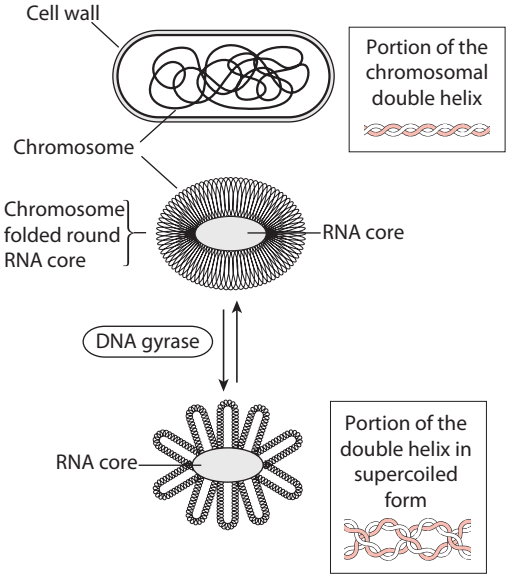
Adverse effects GIT disturbances, headache, joint and muscle pain, rash, pruritis, infusion site reactions, anaemia, leucopenia.

Special points Inhibits the metabolism and thus increases action of ciclosporin, midazolam, nifedipine, antidysrhythmics (lidocaine, disopyramide).

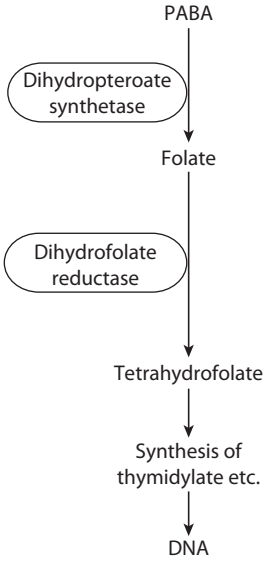


R&D 7e Ch 50, p 633

The bacterial chromosome



Folate metabolism



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.

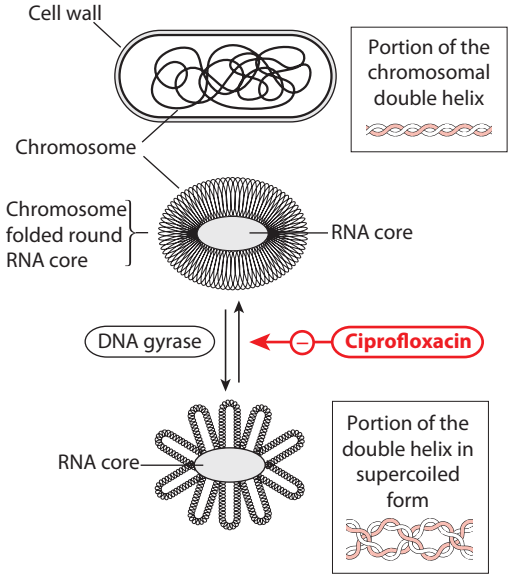
Clinical use Active against Gram-positive organisms; particularly effective against Gram-negative bacteria. Used for infections of the urinary tract, the GIT and bones & joints; for respiratory tract infections not caused by pneumococci; for gonorrhoea and septicaemia caused by sensitive organisms.

Adverse effects GIT upsets, headache, dizziness, rashes. Rare: tendon damage, CNS effects (seizures, insomnia) due to competition with GABA binding to its receptors.

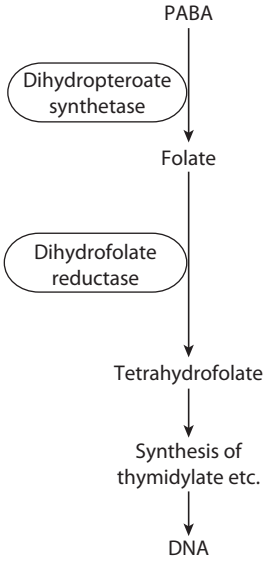
Similar drugs: Norfloxacin, levofloxacin.

R&D 7e Ch 50, p 632; D&H 2e Ch 47, p 110

The bacterial chromosome



Folate metabolism



Co-trimoxazole

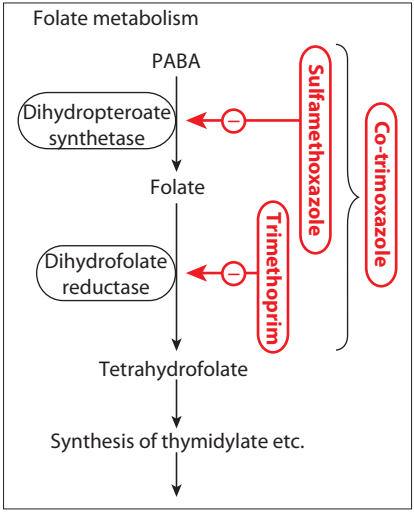
Actions Both sulfamethoxazole and trimethoprim interfere with bacterial folate metabolism and thus with DNA synthesis.

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.



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.

A nicotinic acid derivative that is an antituberculosis drug

Isoniazid

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).

R&D 7e Ch 50, p 634; D&H 2e Ch 47, p 111-112

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.

Drug 3 given for 2-month initial phase only.

Drug 4 given for 2-month initial phase only.

Different countries may have different regimens.

Rifampicin

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.

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.

Pyrazinamide

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.

R&D 7e Ch 50, p 635; D&H 2e Ch 47, pp 111-112

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.

Pyrazinamide

Drug 4 given for 2-month initial phase only.

Different countries may have different regimens.

Ethambutol

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*

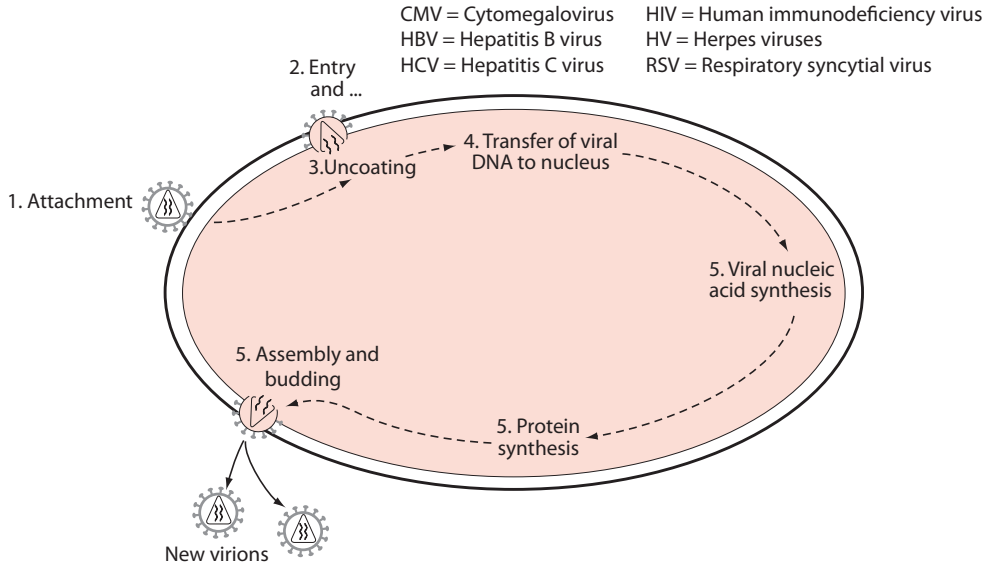
Drug 2 given for 2-month initial and 4-month continuation therapy: *Rifampicin*

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



Zidovudine

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.

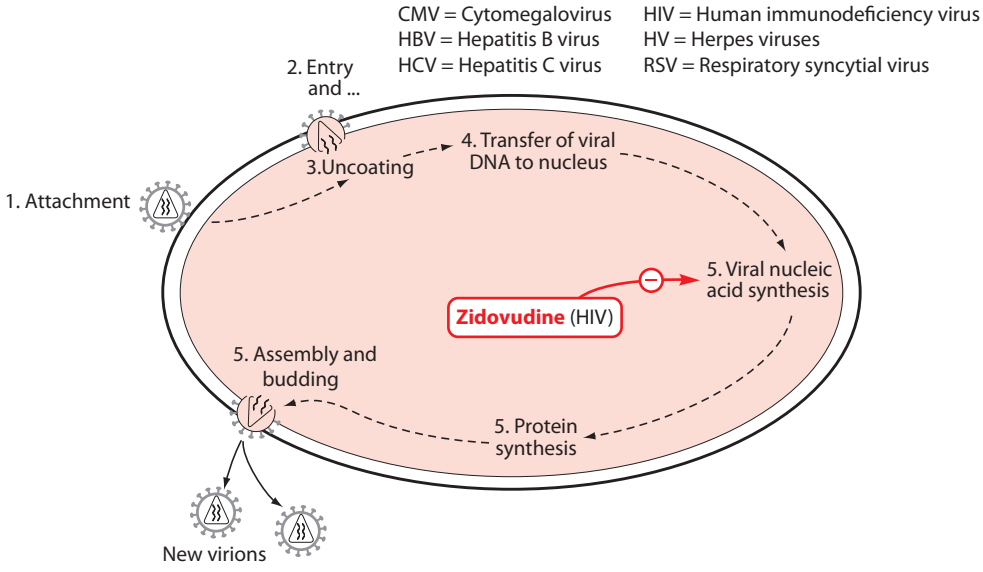
Clinical use Human immunodeficiency virus infection in combination with other agents. Slows progress of the disease without curing the infection.

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



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.

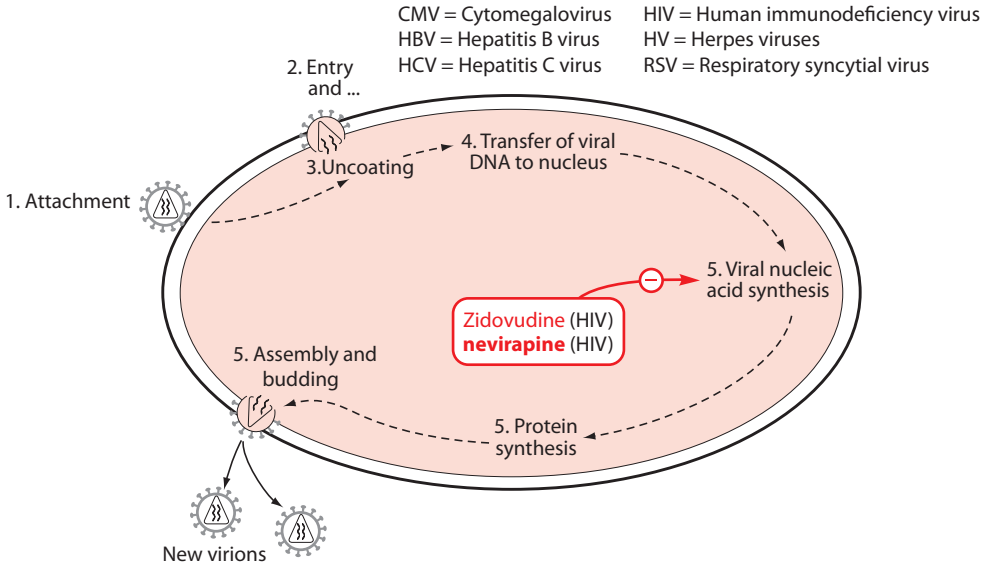
Abs/Distrb/Elim Given orally; the concentration in the CSF is 45% of the plasma level.

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



Saquinavir

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.

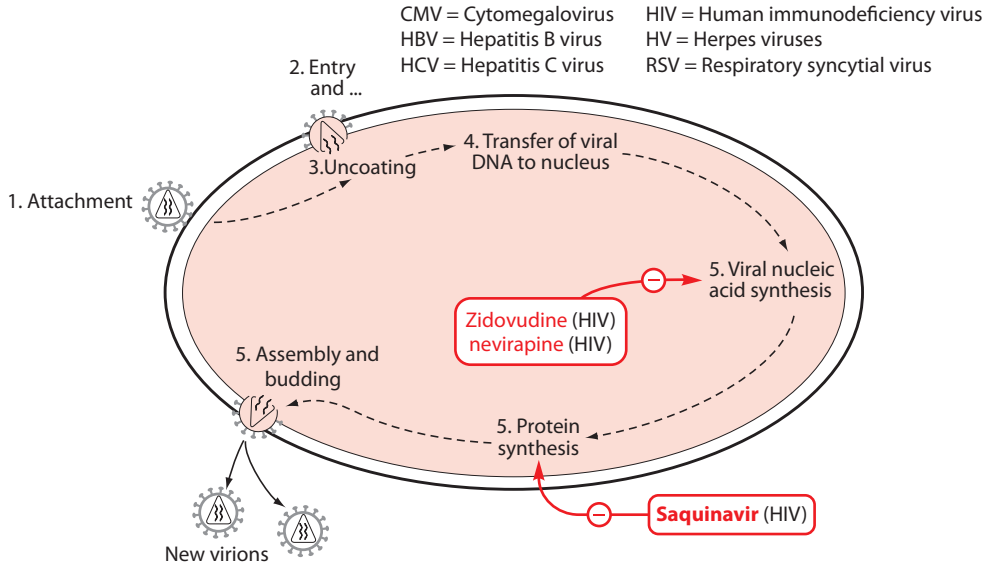
Abs/Distrb/Elim Given orally, extensive first-pass metabolism. Elimination $t_{1/2}$ 12h.

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.

R&D 7e Ch 51, p 643; D&H 2e Ch 48, p 114

A schematic diagram of virus infection of a mammalian cell



Enfuvirtide

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.

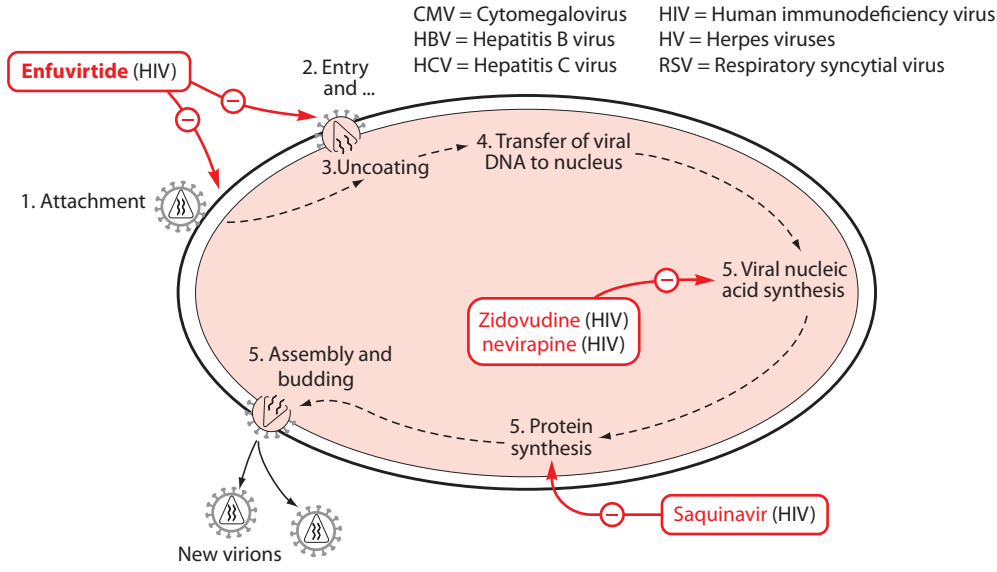
Abs/Distrb/Elim Given by subcut. injection. Elimination $t_{1/2}$ ~4h.

Clinical use HIV-1 infection in combination with other antiretrovirals.

Adverse effects Hypersensitivity reactions.

R&D 7e Ch 51, p 645; D&H 2e Ch 48, p 114

A schematic diagram of virus infection of a mammalian cell



Aciclovir

Actions Interferes with viral nucleic acid synthesis.

MOA Converted by viral and host cell kinases to aciclovir triphosphate which selectively inhibits viral DNA polymerase.

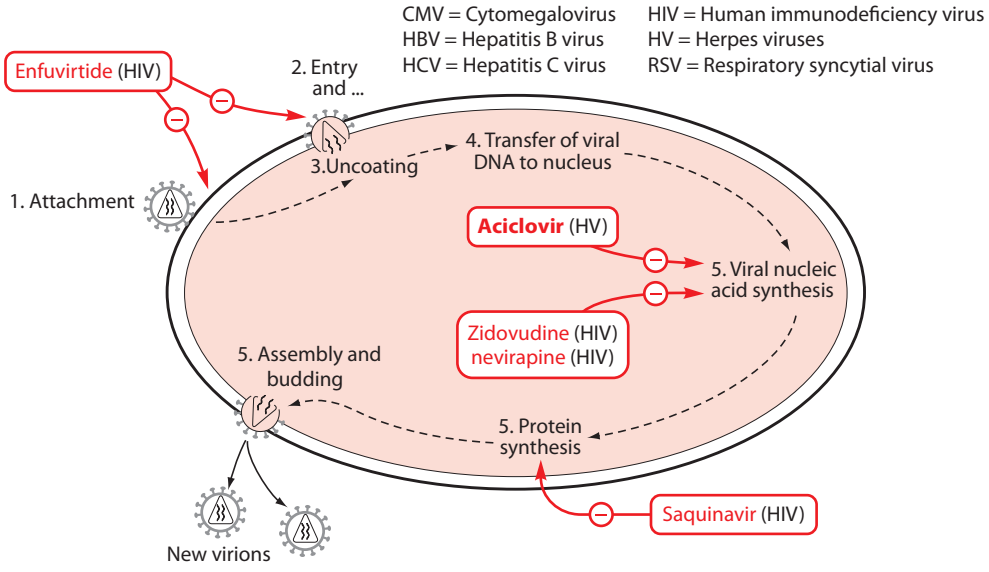
Abs/Distrb/Elim Given orally, i.v. (slowly) or topically; is degraded fairly rapidly within the host cell. CSF concentration is ~50% of plasma level.

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.

R&D 7e Ch 51, pp 644-645; D&H 2e Ch 48, p 114

A schematic diagram of virus infection of a mammalian cell



Ganciclovir

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.

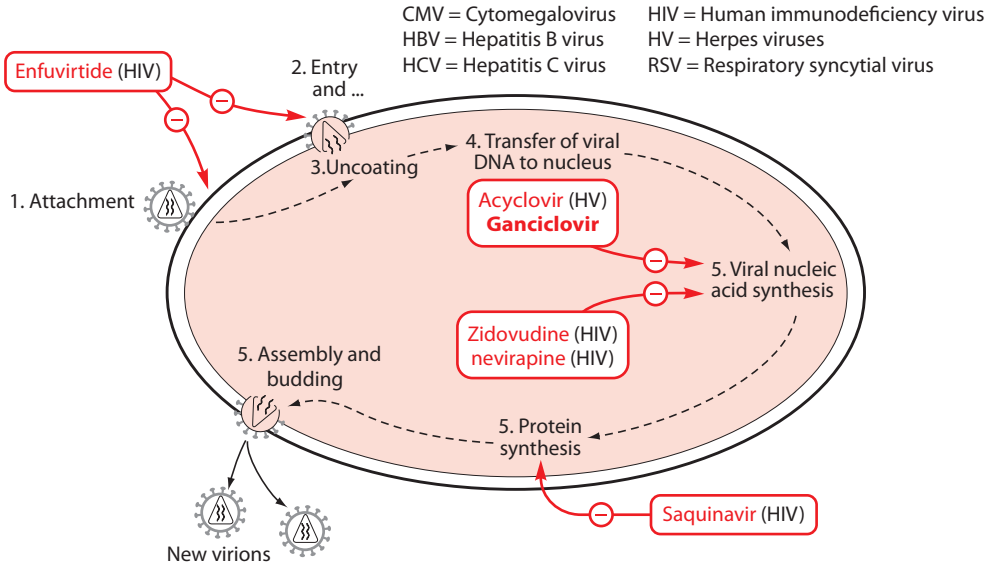
Abs/Distrb/Elim Given intravenously; $t_{1/2}$ 4h but persists in host cells for 18-20h.

Clinical use Cytomegalovirus infection (common in AIDS & immunocompromised patients).

Adverse effects Bone marrow depression; therefore used only for life-threatening infections.

R&D 7e Ch 51, p 645; D&H 2e Ch 48, p 114

A schematic diagram of virus infection of a mammalian cell



Actions Reduces viral replication.

MOA Inhibits neuraminidase which is necessary for virion release.

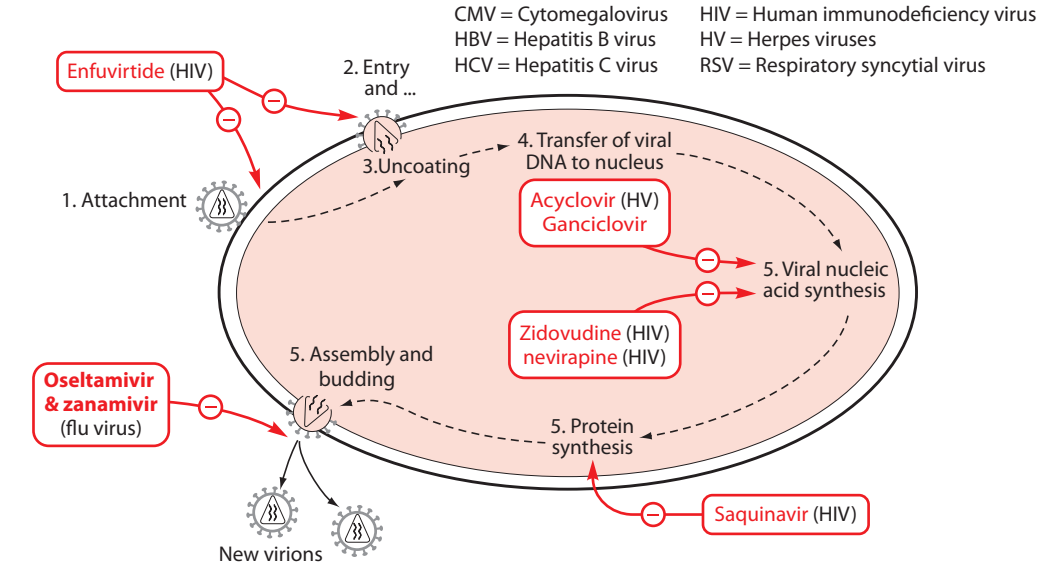
Abs/Distrb/Elim Given orally – within 48h of onset of symptoms for post-exposure prophylaxis. Zanamivir is given intranasally.

Clinical use Prevention and treatment of infections with influenza viruses A and B.

Adverse effects GIT disturbances, headache, dizziness, rashes; very rarely hepatitis.

R&D 7e Ch 51, p 645; D&H 2e Ch 48, p 114

A schematic diagram of virus infection of a mammalian cell



Palivizumab

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.

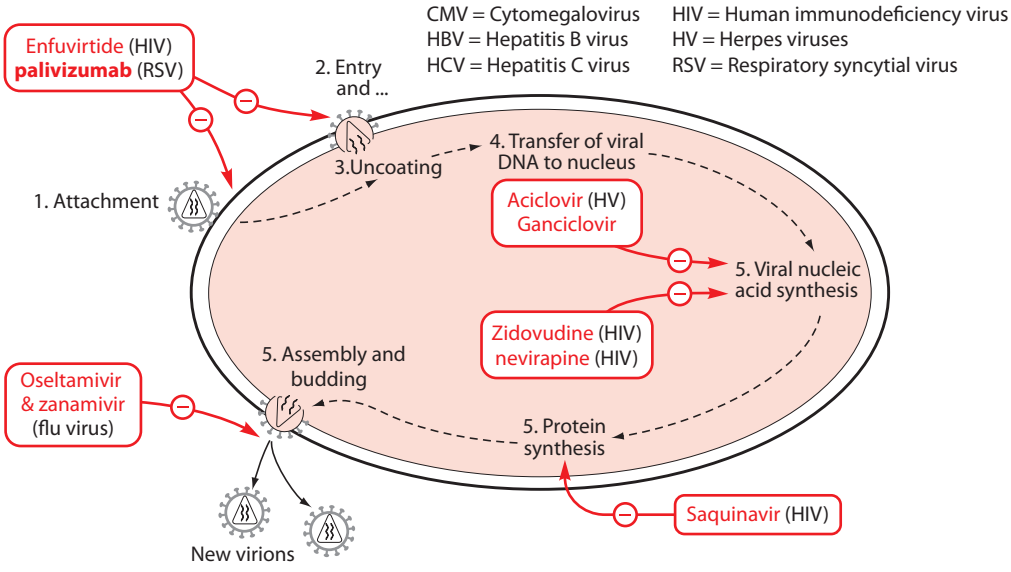
Abs/Distrb/Elim Given by intramuscular injection.

Clinical use For respiratory syncytial virus infection in children. (Needs specialist prescription and administration.)

Adverse effects Hypersensitivity reactions against the monoclonal antibody are possible.

R&D 7e Ch 51, p 646; D&H 2e Ch 48, p 114

A schematic diagram of virus infection of a mammalian cell



Interferon-alpha

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.

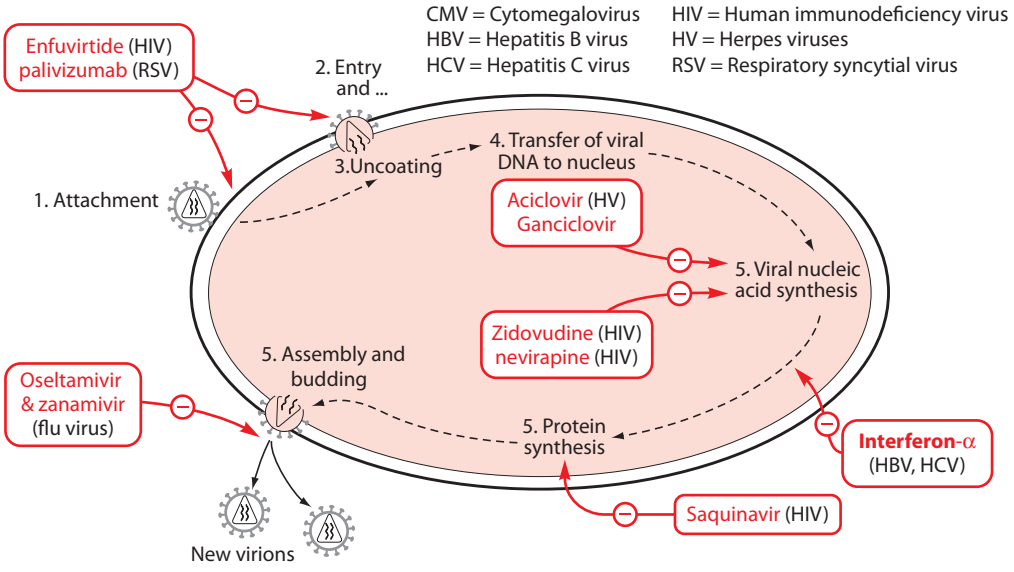
Abs/Distrb/Elim Given i.v.; $T_{0.5}$ 2–4h. Peginterferon-alfa2a has a longer $t_{½}$.

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.

R&D 7e Ch 51, p 646; D&H 2e Ch 48, p 114

A schematic diagram of virus infection of a mammalian cell



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

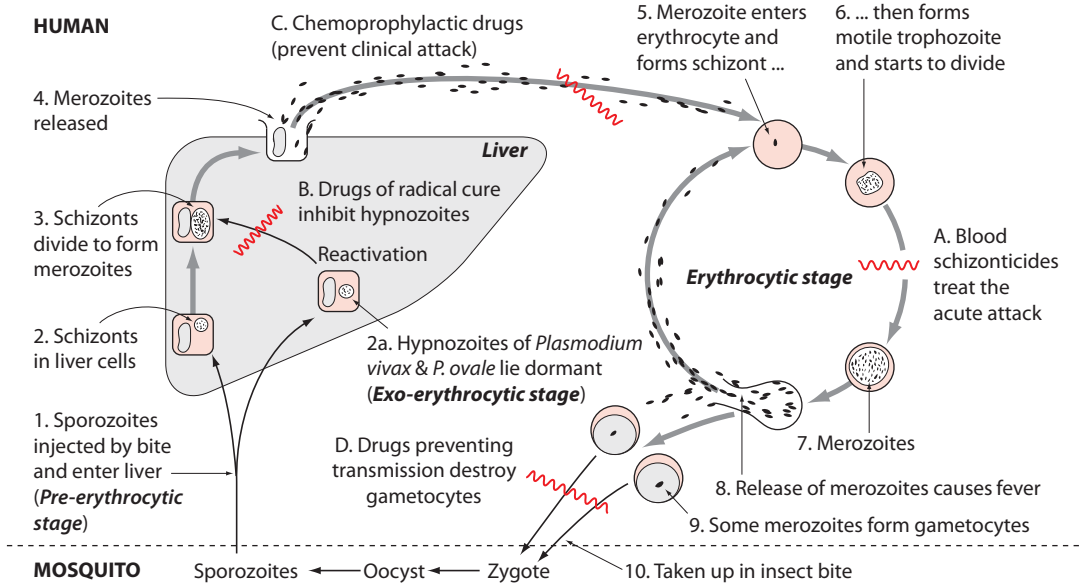
Either a non-nucleoside reverse transcriptase inhibitor, e.g. nevirapine, enfuvirtide

OR a protease inhibitor, e.g. saquinavir, atazanavir.

*referred to as **h**ighly **a**ctive **a**nti**r**etroviral **t**herapy (HAART).

R&D 7e Ch 51, pp 646-647; D&H 2e Ch 48, p 114

The malarial cycle and the sites at which drugs can affect it



Chloroquine

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.

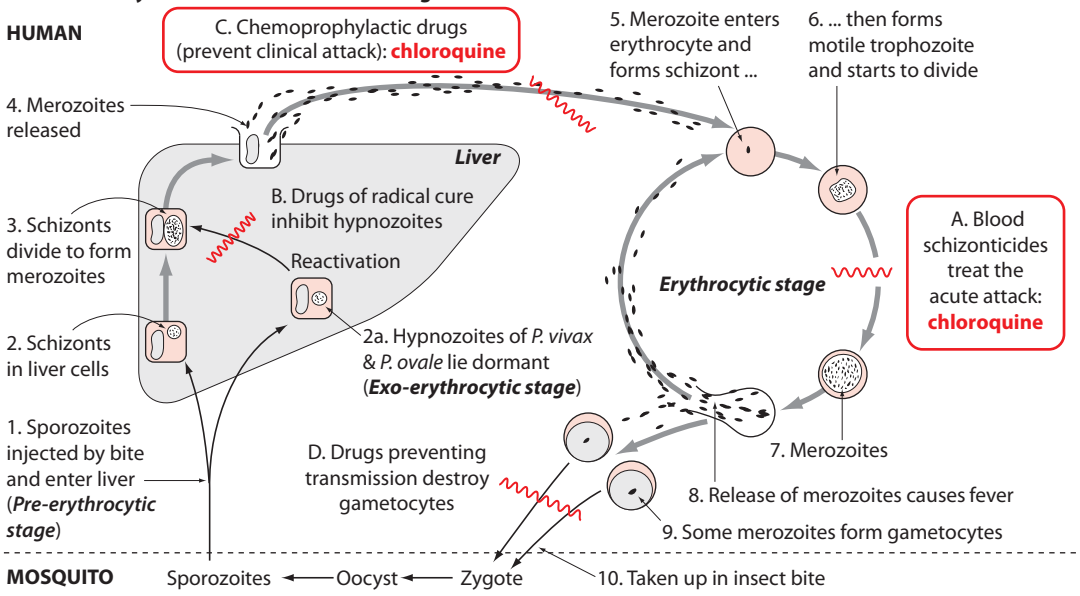
Clinical use To treat acute attacks of benign malaria *(Plasmodium vivax, P. ovale, P. malariae)*.
For chemoprophylaxis of benign malaria and of chloroquine-sensitive falciparum malaria.
To treat rheumatoid arthritis and lupus erythematosus (see card 3.10).

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.

R&D 7e Ch 53, pp 659-660; D&H 2e Ch 49, pp 115-116

The malarial cycle and the sites at which drugs can affect it



Quinine

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, $t_{½}$ 10h but can be given by i.v. infusion. It partially concentrates in parasitised red blood cells. Metabolised in liver; $t_{½}$ 10h.

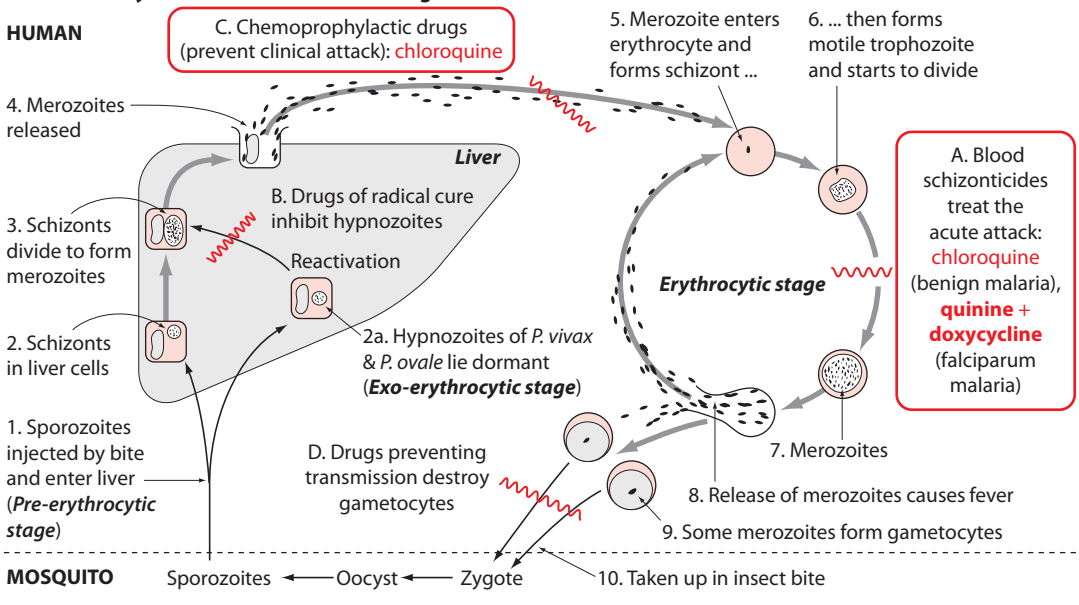
Clinical use To treat acute attacks of malignant malaria (*P. falciparum*). Often given in combination with (or followed by) doxycycline or clindamycin or pyrimethamine + sulfadoxine (see cards 29.09 & 31.06).

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



Mefloquine

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.

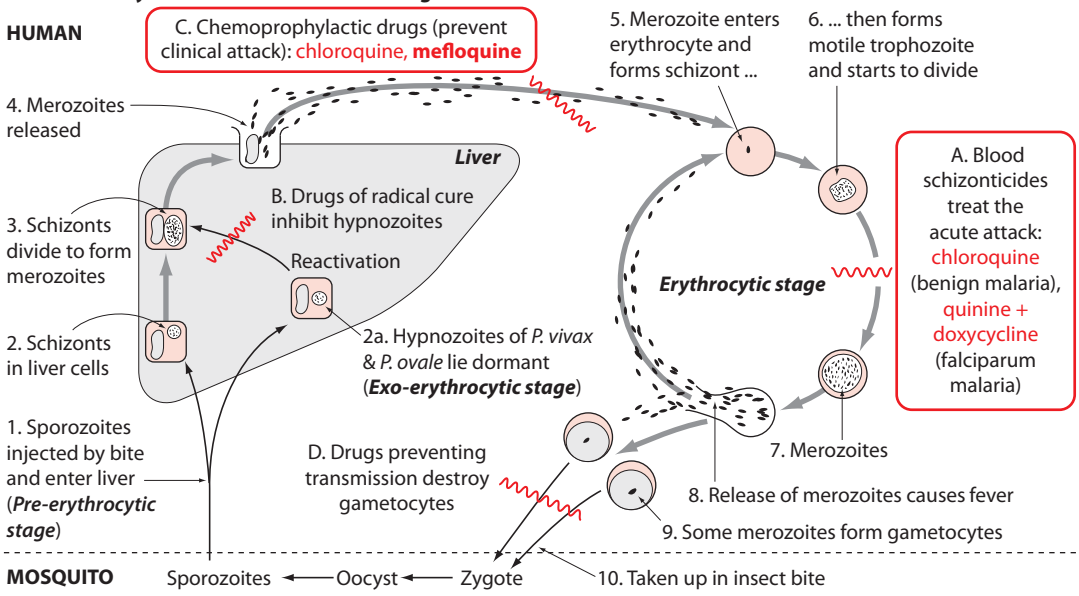
Clinical use For chemoprophylaxis of falciparum malaria in areas where it is chloroquine resistant.

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.

R&D 7e Ch 53, p 661; D&H 2e Ch 49, pp 115-116

The malarial cycle and the sites at which drugs can affect it



Actions Kills hypnozoites in the liver. Kills gametocytes.

MOA Not really known.

Abs/Distrb/Elim Given orally, rapidly metabolised; $t_{1/2}$ 3–6h.

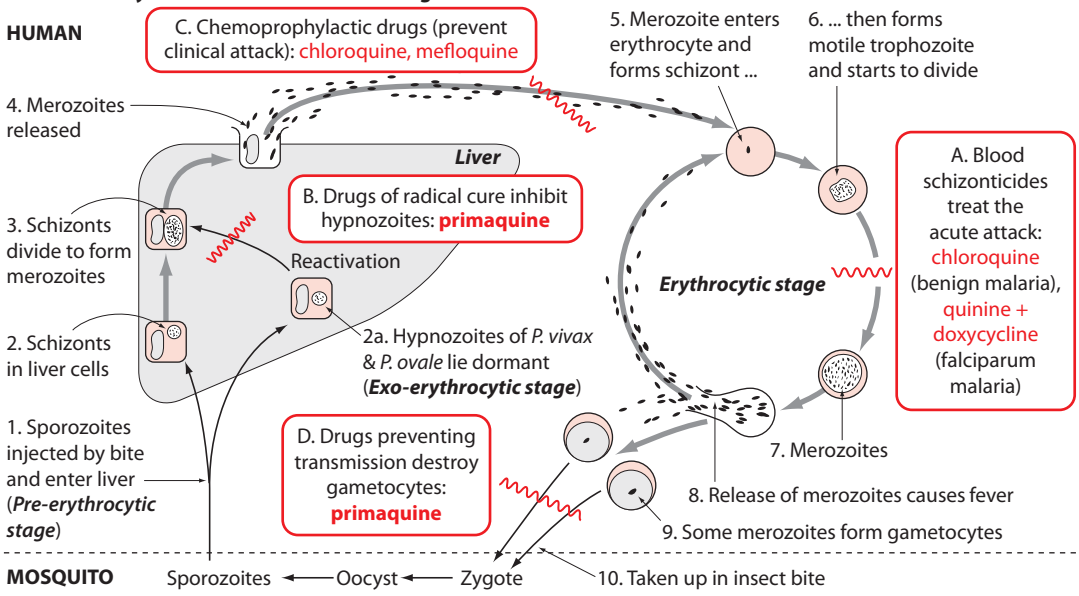
Clinical use For radical cure of *P. vivax* and *P. ovale* by eliminating the exo-erythrocytic stage. Given as adjuct to chloroquine treatment of the acute attack.

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.

R&D 7e Ch 53, p 662; D&H 2e Ch 49, pp 115-116

The malarial cycle and the sites at which drugs can affect it



Actions A slow blood schizonticide.

MOA Inhibits the malaria parasite's dihydrofolate reductase (DHFR) and thus interferes with its thymidylate synthesis.

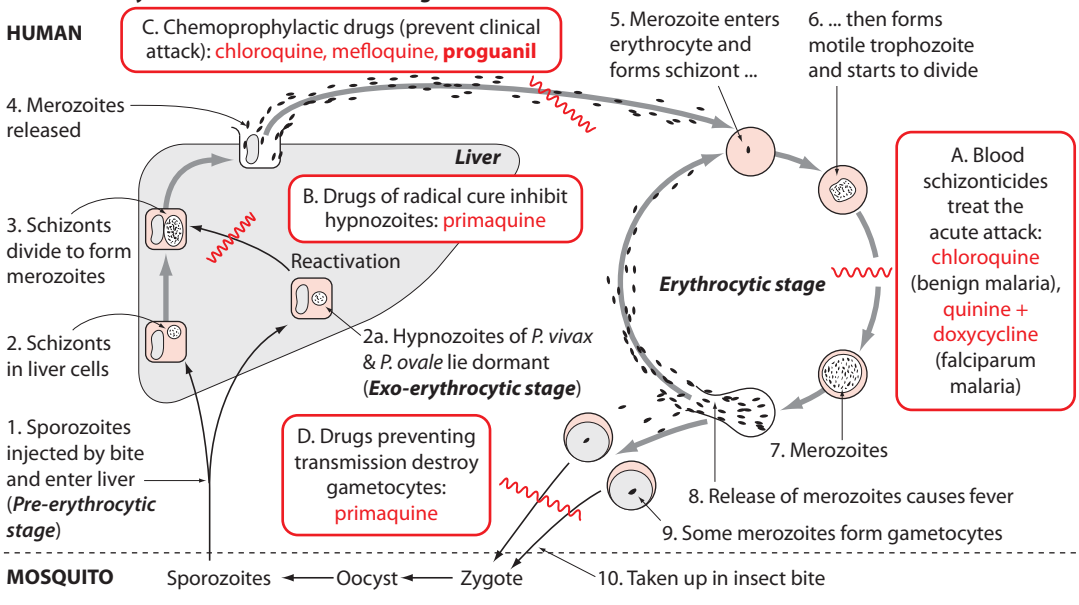
Abs/Distrb/Elim Given orally, $T_{0.5}$ 16h.

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.

R&D 7e Ch 53, pp 661-662; D&H 2e Ch 49, pp 115-116

The malarial cycle and the sites at which drugs can affect it



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.

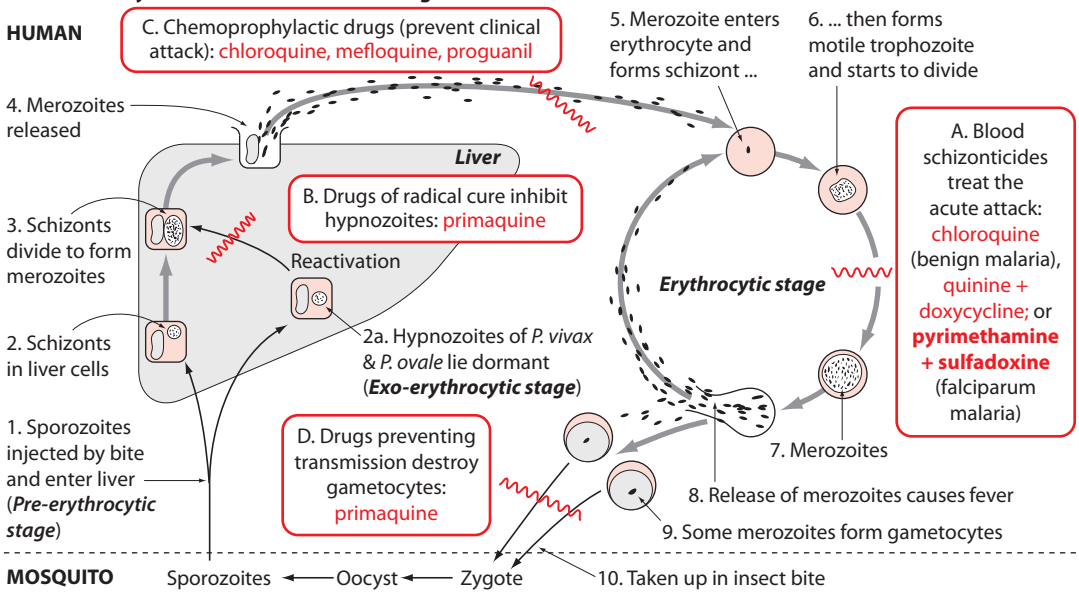
Abs/Distrb/Elim Given orally.

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.

R&D 7e Ch 53, p 661-662; D&H 2e Ch 49, pp 115-116

The malarial cycle and the sites at which drugs can affect it



Artemether + lumefantrine

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: $T_{0.5}$ 3–7h. Lumefantrine: $T_{0.5}$ 4–7 days.

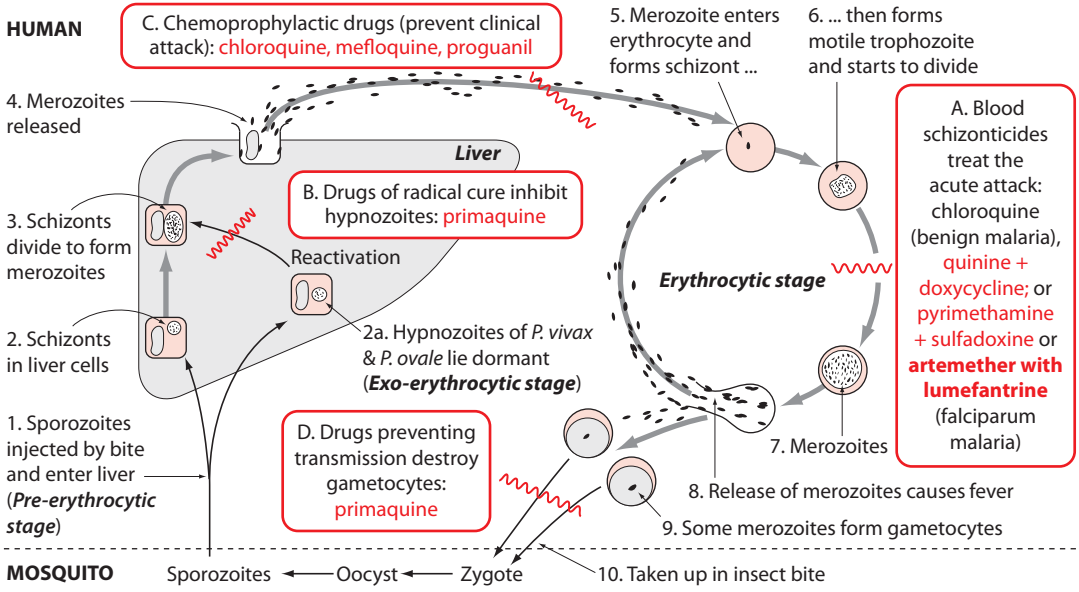
Clinical use To treat acute uncomplicated falciparum malaria.

Adverse effects GIT disturbances, headache, dizziness, parasthesia, myalgia, rash.

R&D 7e Ch 53, p 661; D&H 2e Ch 49, pp 115-116

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



If falciparum malaria in the region is chloroquine resistant, the drugs to be used could be:

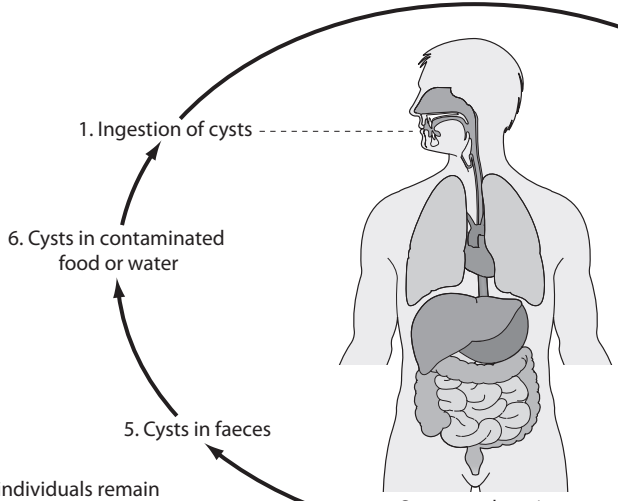
Mefloquine or doxycycline or proguanil + atovaquone

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*.



Metronidazole

Actions Kills the motile forms of *Entamoeba histolytica*.

MOA The trophozoite generates, from the drug, free radicals that damage the trophozoite's DNA.

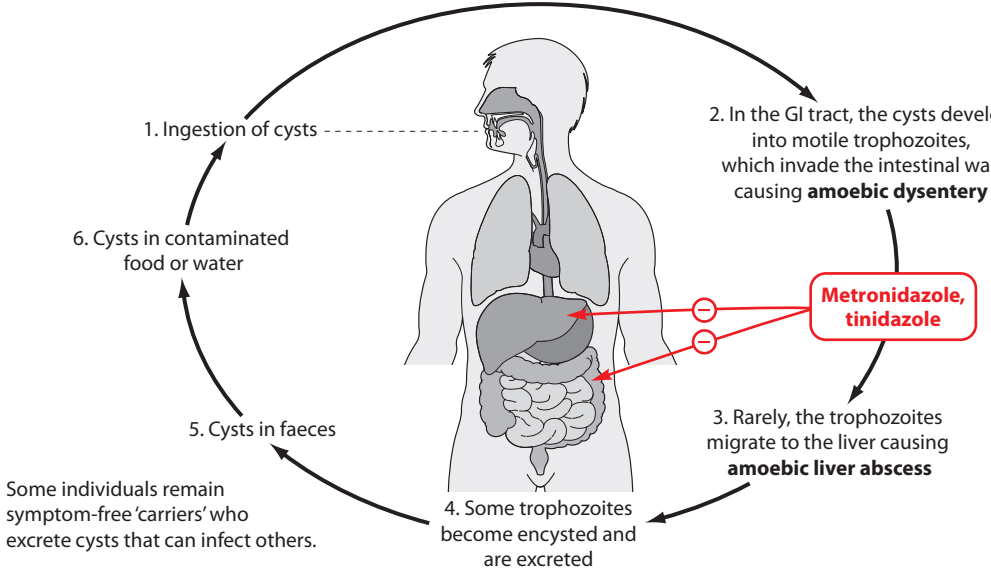
Abs/Distrb/Elim Given orally, can be given i.v. and rectally; $t_{1/2}$ 7h. Tinidazole has longer action.

Clinical use To treat amoebic dystery (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

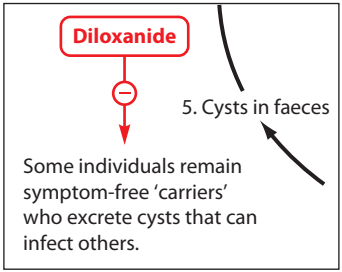
Amoebiasis is caused by the ingestion of the cysts of *Entamoeba histolytica*.

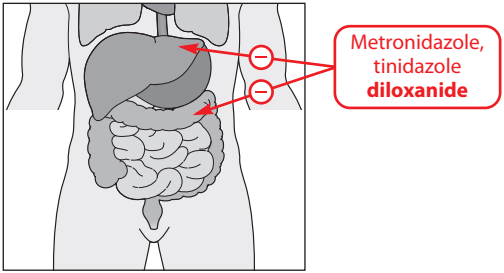


Actions Acts against the non-motile forms of *Entamoeba histolytica*.

MOA Not clearly known.

Abs/Distrb/Elim Given orally, can be given i.v. and rectally; $t_{1/2}$ 7h.



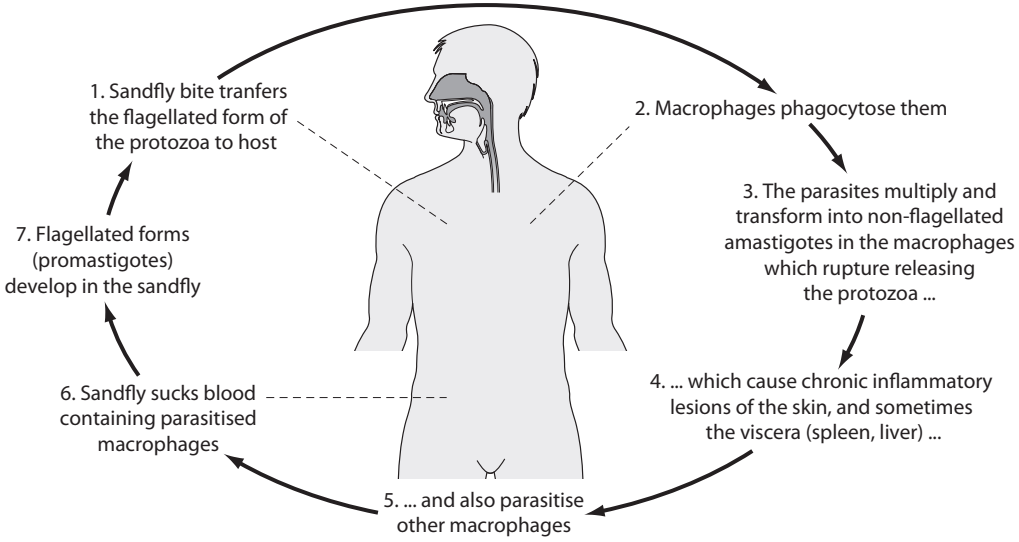


Clinical use To treat amoebic dysentery (*after* treatment with metronidazole); to treat asymptomatic cyst carriers.

Adverse effects GIT disturbances; anorexia. *Occasionally* dizziness, ataxia, myalgia, hepatitis, blood dyscrasias, Can cause disulfiram reactions after alcohol.

R&D 7e Ch 53, p 664; D&H 2e Ch 49, p 116

Leishmaniasis is a disease of the skin and viscera caused by leishmania protozoa transmitted by the bite of a sandfly.



Sodium stibogluconate

Actions & MOA Inactivates the protozoa within the macrophage, possibly by triggering toxic oxygen radicals.

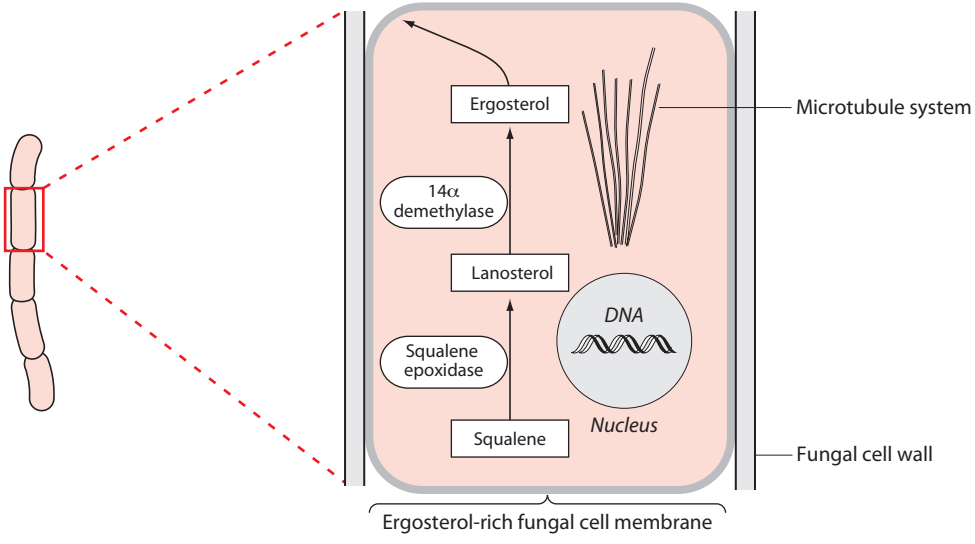
Abs/Distrb/Elim Given i.m. (painful) or by slow i.v. injection daily for 10–20 days.

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.

R&D 7e Ch 53, p 666; D&H 2e Ch 49 p 116

Simplified diagram of a fungal cell



Amphotericin

Actions & MOA Kills fungi by binding to the ergosterol in the fungal cell membane (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.

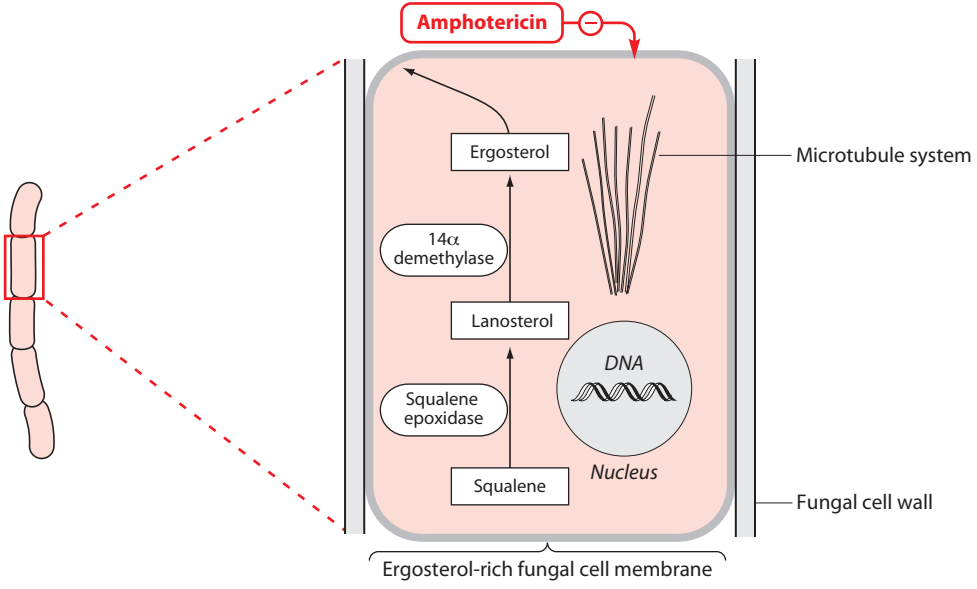
Clinical use Candidiasis; cryptococcal meningitis; histoplasmosis; apergillosis; blastomycosis; coccidiomycosis; mucormycosis.

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.

R&D 7e Ch 52, pp 650-651; D&H 2e Ch 50, p 117

Simplified diagram of a fungal cell



Fluconazole

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.

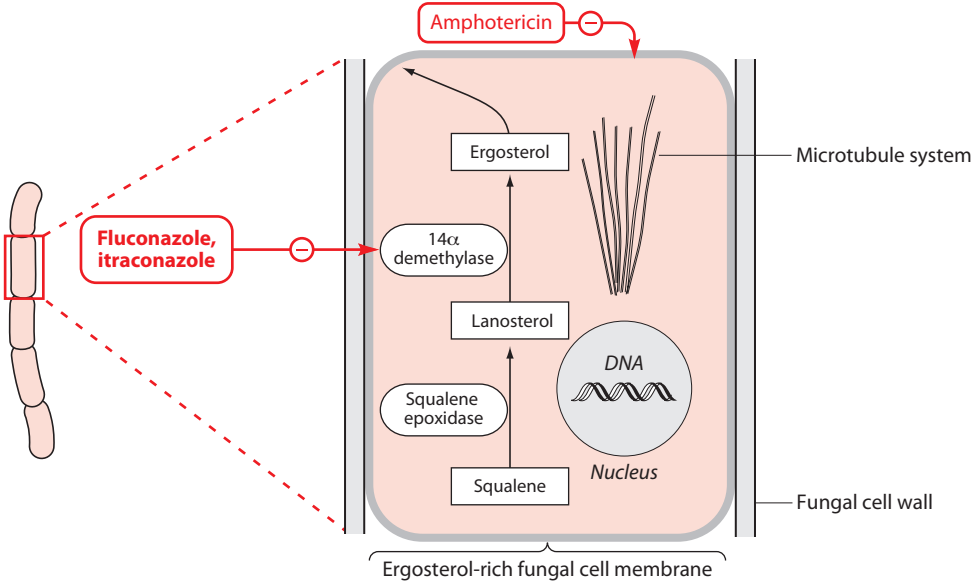
Clinical use Candidiasis: local (dermal, mucosal) and invasive; tinea corporis, tinea cruris & tinea pedis; cryptococcal meningitis; histoplasmosis; blastomycosis; coccidiomycosis.

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.

R&D 7e Ch 52, p 652; D&H 2e Ch 50, p 117

Simplified diagram of a fungal cell



Terbinafine

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.

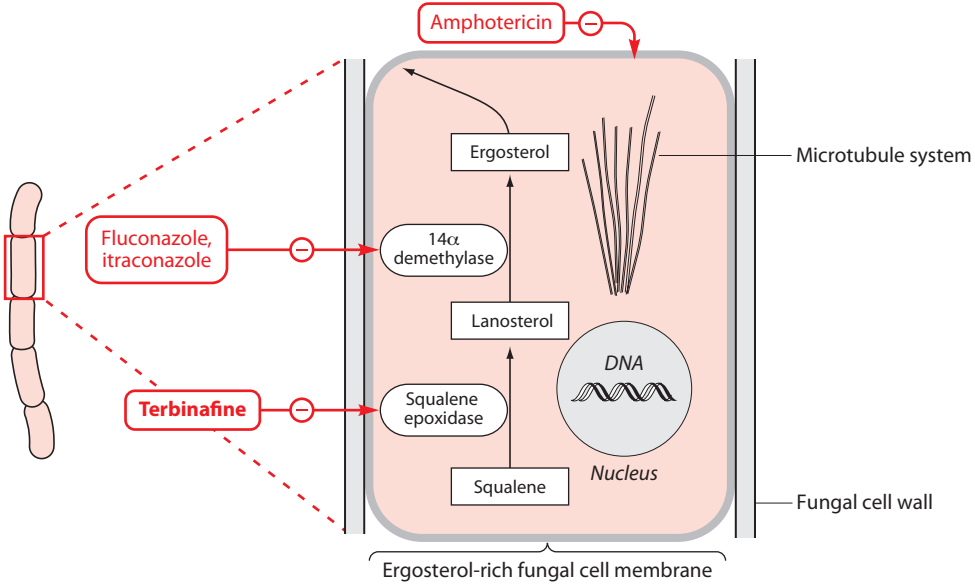
Clinical use Fungal infections of the nails & skin (tinea corporis, tinea cruris & tinea pedis, aka 'ringworm')

Adverse effects GIT disturbances; headache, dizziness, rash.

Drug with similar action Amorolfine; used topically on the nails.

R&D 7e Ch 52, p 653; D&H 2e Ch 50, p 117

Simplified diagram of a fungal cell



Caspofungin

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.

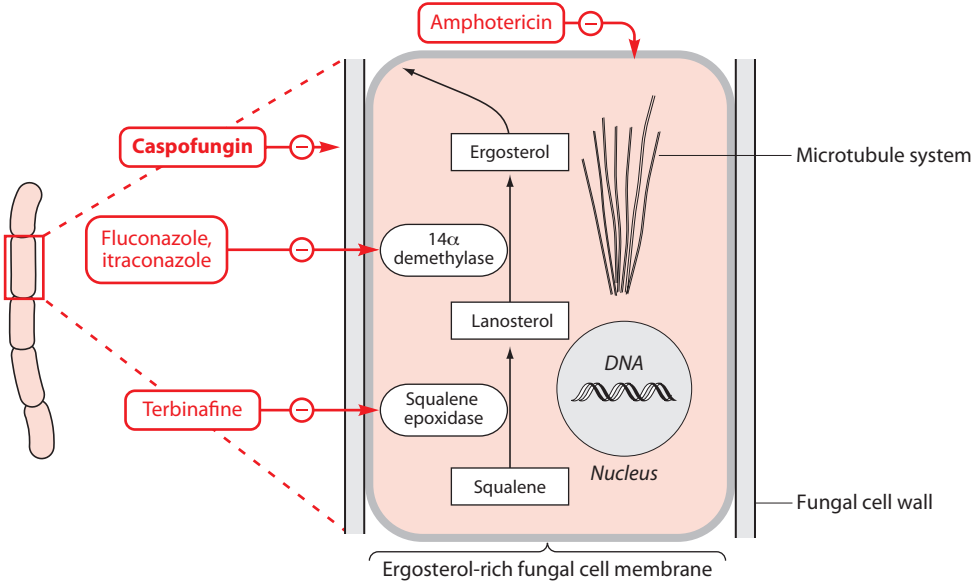
Clinical use Candidiasis; aspergillosis.

Adverse effects GIT disturbances; headache, dizziness, rash.

Drug with similar action Micafungin. Used for invasive candidiasis.

R&D 7e Ch 52, p 652; D&H 2e Ch 50, p 117

Simplified diagram of a fungal cell



Griseofulvin

Action Fungistatic by interefering with mitosis of fungal cells.

MOA Interacts with polymerized microtubules inhibiting spindle formation.

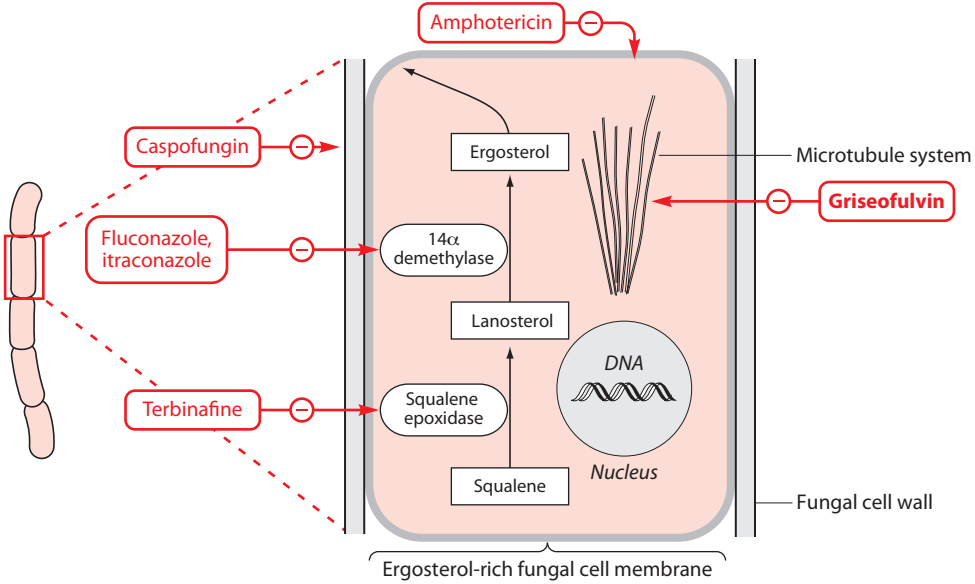
Abs/Distrb/Elim Given orally; taken up by proliferating skin cells, binds to the keratin. Half-life ~24h.

Clinical use Fungal infections of skin, hair and scalp; trichophyton infections in children.

Adverse effects Infrequent: GIT disturbances; headache.

R&D 7e Ch 52, p 651; D&H 2e Ch 50, p 117

Simplified diagram of a fungal cell



Flucytosine

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.

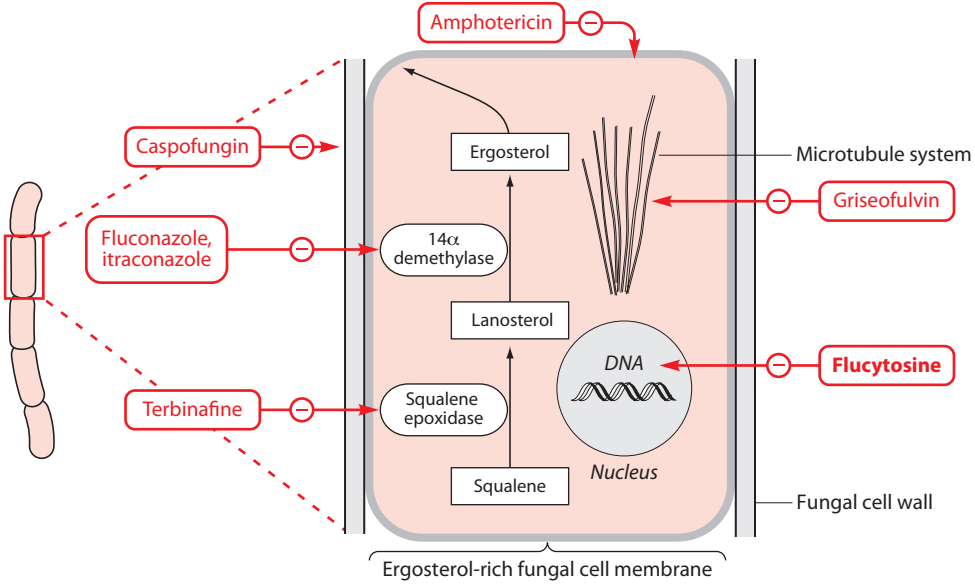
Clinical use Systemic fungal & yeast infections: systemic candidiasis, cryptococcal meningitis.

Adverse effects GIT disturbances; rashes. Less commonly: blood dyscrasias, headaches, confusion, cardiotoxicity.

Special points Resistance can occur, therefore usually given with amphotericin.

R&D 7e Ch 52, p 653; D&H 2e Ch 50, p 117

Simplified diagram of a fungal cell



Notes

Disease/worm	Drugs used
'Thread' worm infection (*Enterobius vermicularis* in UK, *Strongyloides stercoralis* in US)	
Common round worm (*Ascaris lumbricoides*)	
Whip worm (*Trichuris trichiura*)	
Tape worm infection: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tape worm)	
Cysticercosis (infection with larval *Taenia solium*)	
Hydatid disease (*Echinococcus granulosus*)	
Bilharziasis caused by blood flukes /schistosomes (*Schistosoma haematobium, S. mansoni, S. japonicum*)	
Hookworm infection (*Ankylostoma duodenale, Necator americanus*)	
Cutaneous larva migrans (*Ankylostoma caninum*)	
Visceral larva migrans (*Toxacara canis*)	

Mebendazole

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

Disease/worm	Drugs used
'Thread' worm infection (*Enterobius vermicularis* in UK, *Strongyloides stercoralis* in US)	**Mebendazole**
Common round worm (*Ascaris lumbricoides*)	**Mebendazole**
Whip worm (*Trichuris trichiura*)	**Mebendazole**
Tape worm infection: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tape worm)	
Cysticercosis (infection with larval *Taenia solium*)	**Albendazole**
Hydatid disease (*Echinococcus granulosus*)	
Bilharziasis caused by blood flukes /schistosomes (*Schistosoma haematobium, S. mansoni, S. japonicum*)	
Hookworm infection (*Ankylostoma duodenale, Necator americanus*)	**Mebendazole**
Cutaneous larva migrans (*Ankylostoma caninum*)	**Albendazole**
Visceral larva migrans (*Toxacara canis*)	**Albendazole**

Levamisole

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

Disease/worm	Drugs used
'Thread' worm infection (*Enterobius vermicularis* in UK, *Strongyloides stercoralis* in US)	Mebendazole, Albendazole
Common round worm (*Ascaris lumbricoides*)	Mebendazole, **Levamisole**
Whip worm (*Trichuris trichiura*)	Mebendazole
Tape worm infection: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tape worm)	
Cysticercosis (infection with larval *Taenia solium*)	Albendazole
Hydatid disease (*Echinococcus granulosus*)	
Bilharziasis caused by blood flukes /schistosomes (*Schistosoma haematobium, S. mansoni, S. japonicum*)	
Hookworm infection (*Ankylostoma duodenale, Necator americanus*)	Mebendazole
Cutaneous larva migrans (*Ankylostoma caninum*)	Albendazole
Visceral larva migrans (*Toxacara canis*)	Albendazole

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

Disease/worm	Drugs used
'Thread' worm infection (*Enterobius vermicularis* in UK, *Strongyloides stercoralis* in US)	Mebendazole, Albendazole, **Piperazine**
Common round worm (*Ascaris lumbricoides*)	Mebendazole, Levamisole, **Piperazine**
Whip worm (*Trichuris trichiura*)	Mebendazole
Tape worm infection: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tape worm)	Albendazole
Cysticercosis (infection with larval *Taenia solium*)	
Hydatid disease (*Echinococcus granulosus*)	Albendazole
Bilharziasis caused by blood flukes /schistosomes (*Schistosoma haematobium, S. mansoni, S. japonicum*)	
Hookworm infection (*Ankylostoma duodenale, Necator americanus*)	Mebendazole
Cutaneous larva migrans (*Ankylostoma caninum*)	Albendazole
Visceral larva migrans (*Toxacara canis*)	Albendazole

Praziquantel

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 absorbrd, metabolised to inactive products. Plasma half-life 60–90min.

Clinical use Schistosomiasis, cysticercosis.

Adverse effects Few and minor: sometimes GIT disturbances.

Special points Available in the UK from special-order manufacturers.

R&D 7e Ch 54, pp 669-670; D&H 2e Ch 50, p 117

Disease/worm	Drugs used
'Thread' worm infection (*Enterobius vermicularis* in UK, *Strongyloides stercoralis* in US)	Mebendazole, Albendazole, Piperazine
Common round worm (*Ascaris lumbricoides*)	Mebendazole, Levamisole, Piperazine
Whip worm (*Trichuris trichiura*)	Mebendazole
Tape worm infection: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tape worm)	**Praziquantel**
Cysticercosis (infection with larval *Taenia solium*)	Albendazole, **Praziquantel**
Hydatid disease (*Echinococcus granulosus*)	Albendazole
Bilharziasis caused by blood flukes /schistosomes (*Schistosoma haematobium, S. mansoni, S. japonicum*)	**Praziquantel**
Hookworm infection (*Ankylostoma duodenale, Necator americanus*)	Mebendazole
Cutaneous larva migrans (*Ankylostoma caninum*)	Albendazole
Visceral larva migrans (*Toxacara canis*)	Albendazole

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/Distrb/Elim Given orally.

Clinical use Onchocerciasis (drug of choice); strongyloidiasis.

Adverse effects Infrequent: itching, rash, GIT disturbances, dizziness, fatigue.

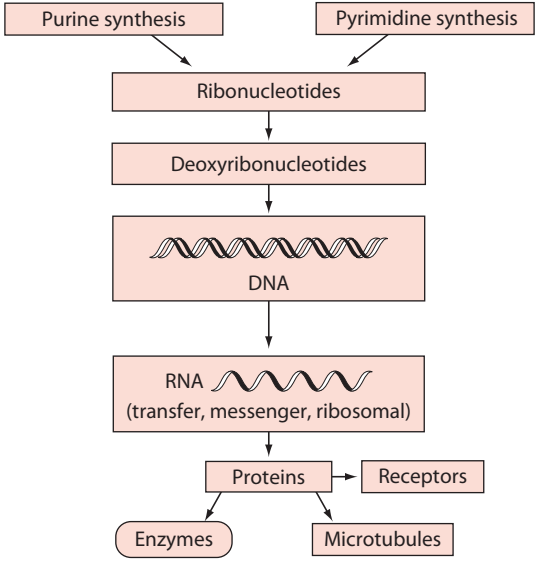
Special points Available in the UK from special-order manufacturers.

R&D 7e Ch 54, p 671; D&H 2e Ch 50, p 117

Disease/worm	Drugs used
'Thread' worm infection (*Enterobius vermicularis* in UK, *Strongyloides stercoralis* in US)	Mebendazole, Albendazole, Piperazine For US 'threadworm': **ivermectin**
Common round worm (*Ascaris lumbricoides*)	Mebendazole, Levamisole, Piperazine
Whip worm (*Trichuris trichiura*)	Mebendazole
Tape worm infection: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tape worm)	Praziquantel
Cysticercosis (infection with larval *Taenia solium*)	Albendazole, Praziquantel
Hydatid disease (*Echinococcus granulosus*)	Albendazole
Bilharziasis caused by blood flukes /schistosomes (*Schistosoma haematobium, S. mansoni, S. japonicum*)	Praziquantel
Hookworm infection (*Ankylostoma duodenale, Necator americanus*)	Mebendazole
Cutaneous larva migrans (*Ankylostoma caninum*)	Albendazole, **ivermectin**
Visceral larva migrans (*Toxacara canis*)	Albendazole

Notes

Diagram of the main targets for anticancer drug therapy



Methotrexate

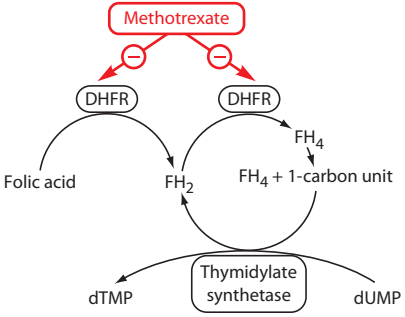
Actions Interferes with purine synthesis and the synthesis of thymidylate and thus with DNA synthesis.

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.

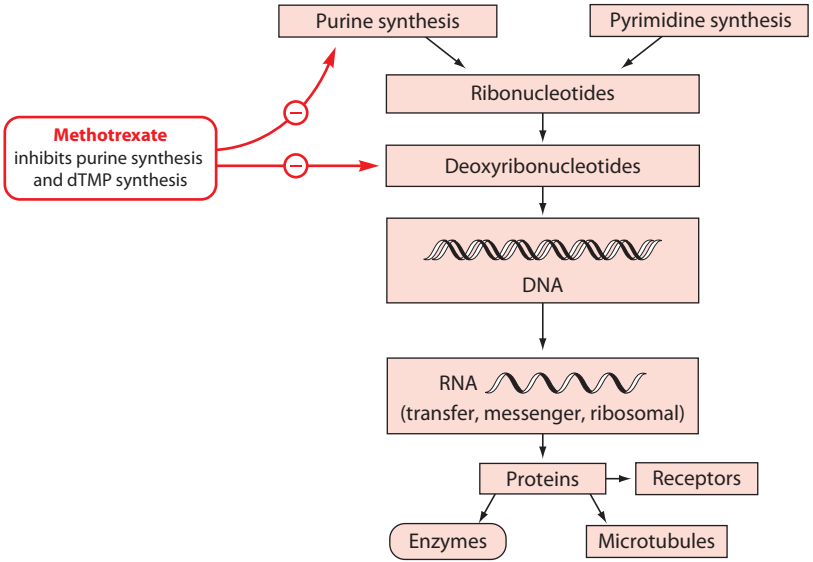


FH_2 = dihydrofolate
FH_4 = tetrahydrofolate
dTMP = thymidylate
dUMP = uridylate

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.

R&D 7e Ch 55, p 680; D&H 2e Ch 46, p 105

Diagram of the main targets for anticancer drug therapy



Fluorouracil

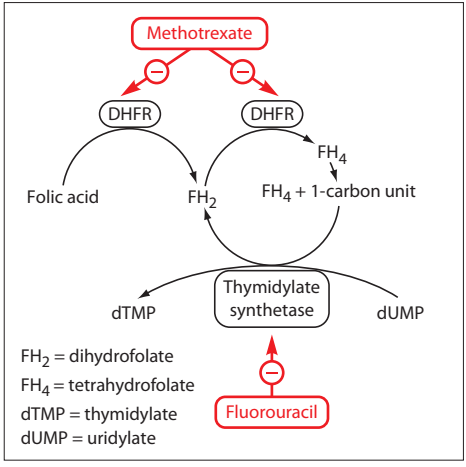
Actions Interferes with the synthesis of dTMP and thus with DNA synthesis.

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.

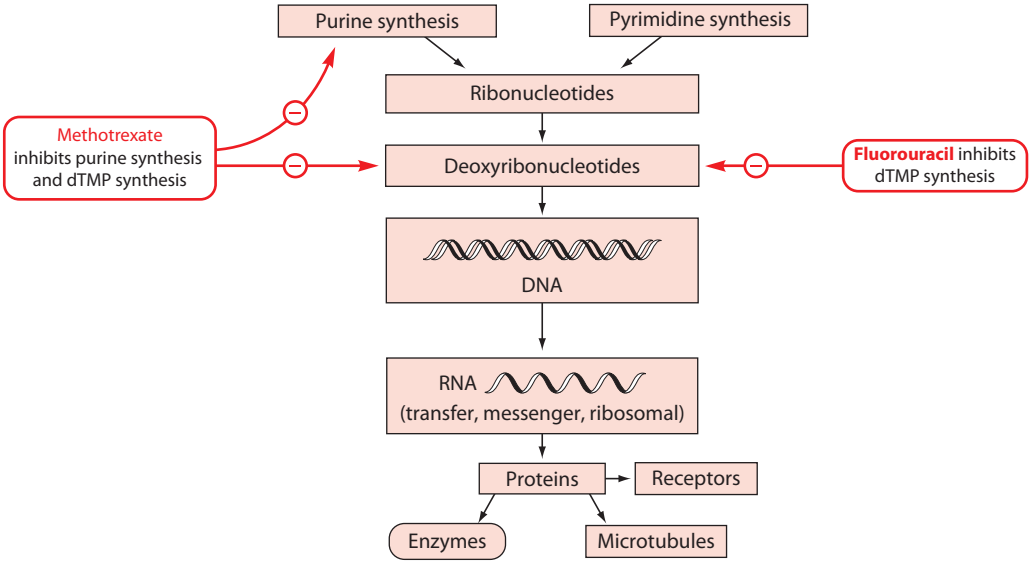
Adverse effects Not common: myelosuppression, GIT disturbances, mucositis. Given long term: desquamation of feet & hands.



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.

R&D 7e Ch 55, p 681; D&H 2e Ch 46, p 105

Diagram of the main targets for anticancer drug therapy



Mercaptopurine

Actions & MOA Purine analogue that inhibits purine synthesis and gives rise to a fraudulent nucleotide.

Abs/Distrb/Elim Given orally.

Clinical use Acute leukemias and chronic myeloid leukemia.

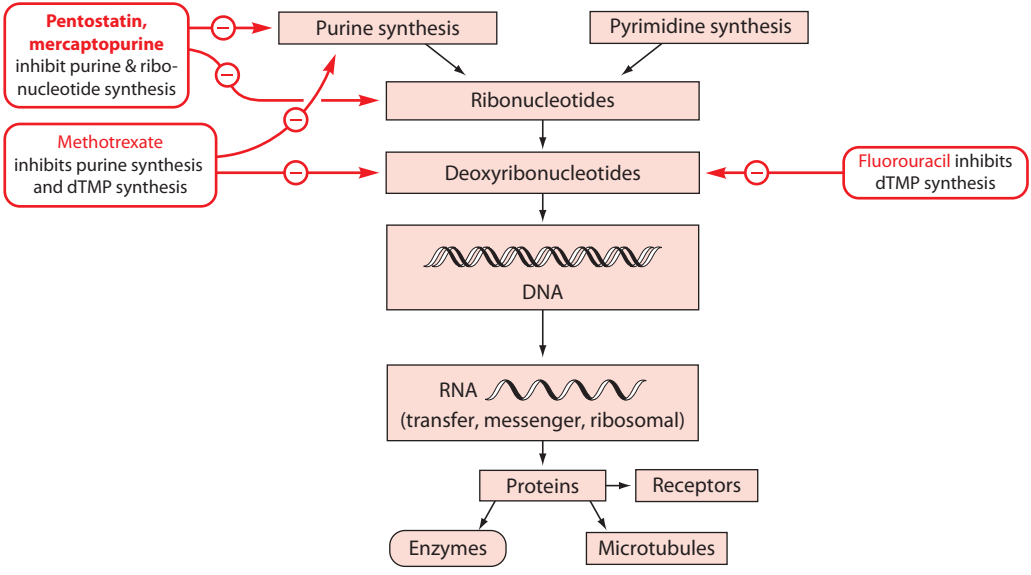
Adverse effects Myelosuppression, hepatotoxicity, immunosuppression. Rare: pancreatitis, GIT ulceration.

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.

R&D 7e Ch 55, p 681; D&H 2e Ch 46, p 104

Diagram of the main targets for anticancer drug therapy



Cytarabine

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.

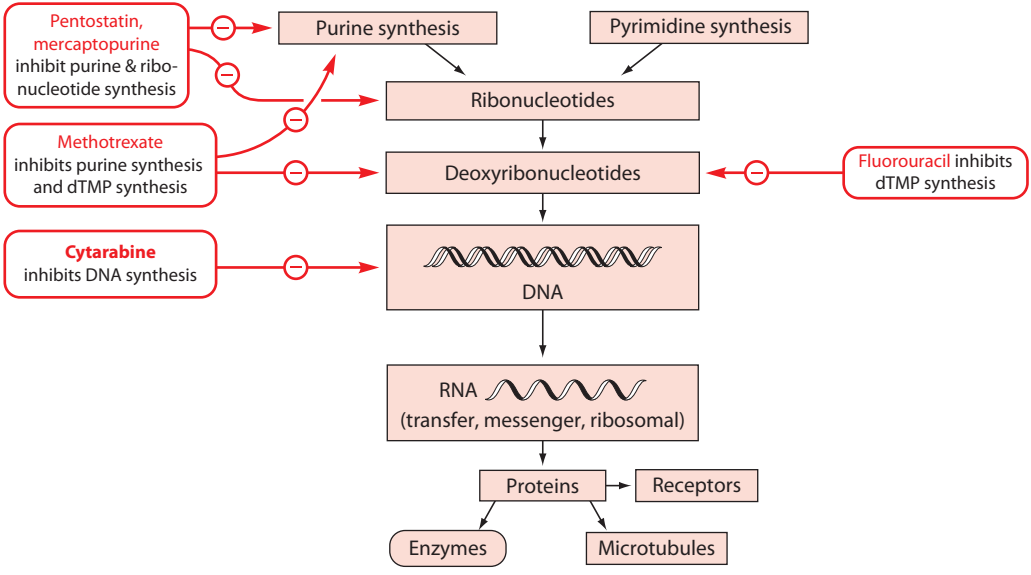
Clinical use Acute myeloblastic leukemia.

Adverse effects Marked myelosuppression. GIT disturbances; cerebellar ataxia.

Special points Careful haematological monitoring necessary.

R&D 7e Ch 55, p 681; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Bleomycin

Actions & MOA Causes DNA fragmentation.

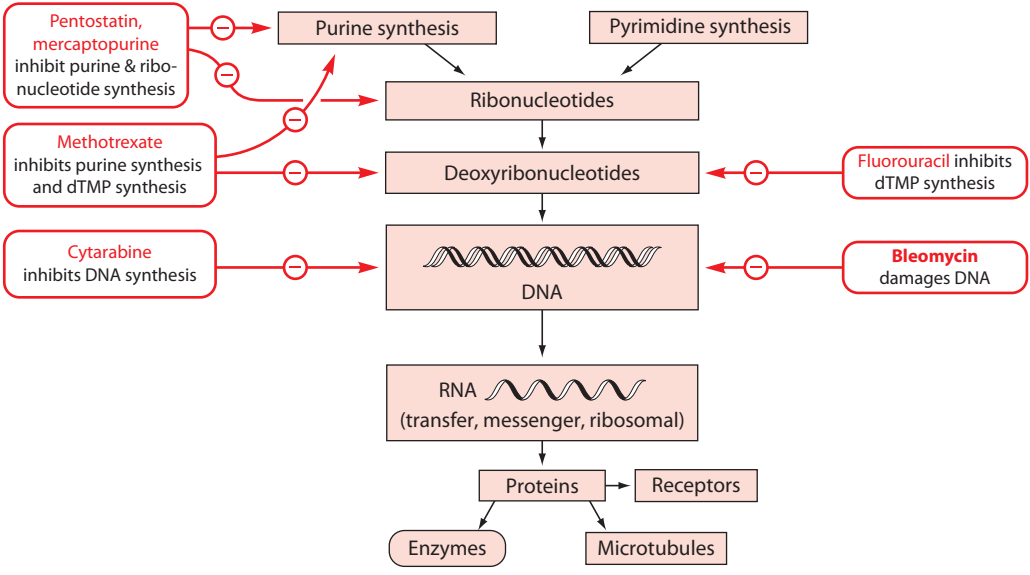
Abs/Distrb/Elim Given i.v. or i.m.

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.

R&D 7e Ch 55, p 682; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Cisplatin

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.

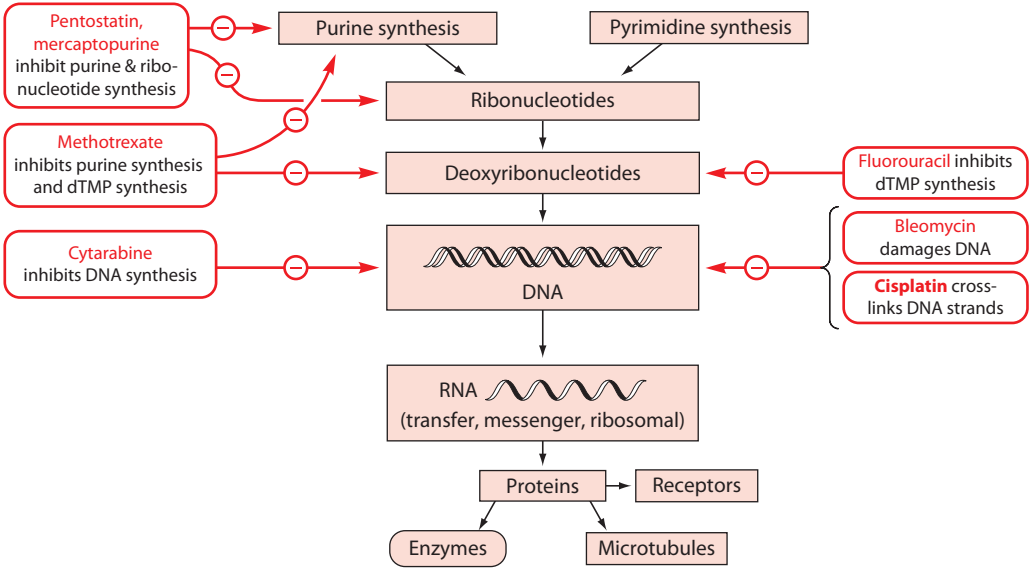
Clinical use Cancers of testes, ovaries, cervix, bladder, lung and head & neck.

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.

R&D 7e Ch 55, p 679; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Cyclophosphamide

Actions & MOA Cross-links DNA by forming covalent bonds with guanine residues on each strand, interfering with cell division and triggering apoptosis.

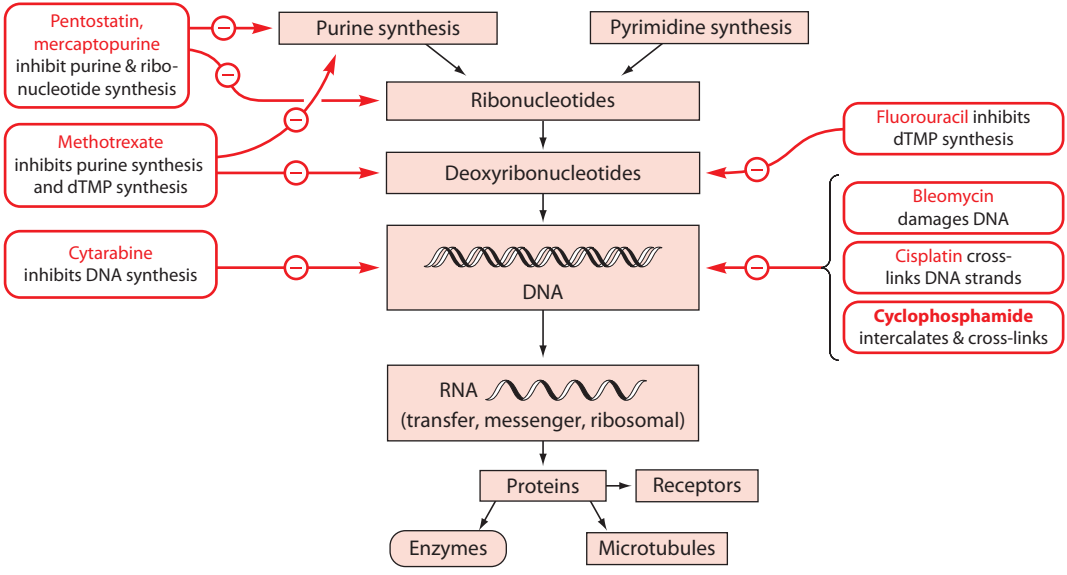
Abs/Distrb/Elim Given orally or i.v. Metabolised in the liver to phosphoramide mustard (the active moiety) and acrolein.

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.

R&D 7e Ch 55, p 678; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Doxorubicin

Actions & MOA Inhibits DNA and RNA synthesis through an effect on topoisomerase II.

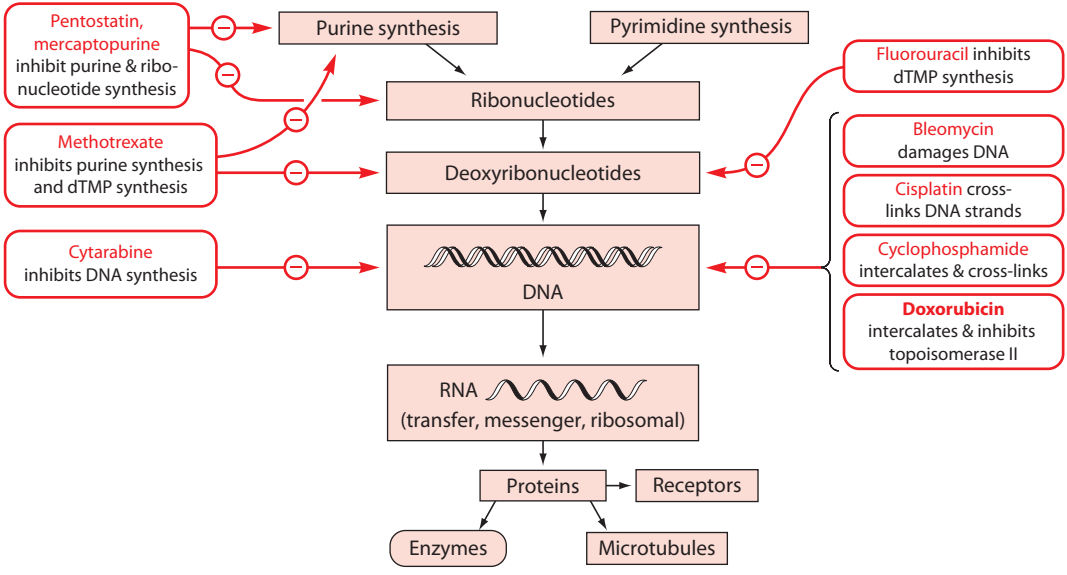
Abs/Distrb/Elim Given by infusion (extravasation can cause tissue damage); by bladder instillation for bladder cancers.

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.

R&D 7e Ch 55, pp 681-682; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Irinotecan

Actions & MOA Binds to and inhibits topoisomerase I, thus interfering with cell proliferation.

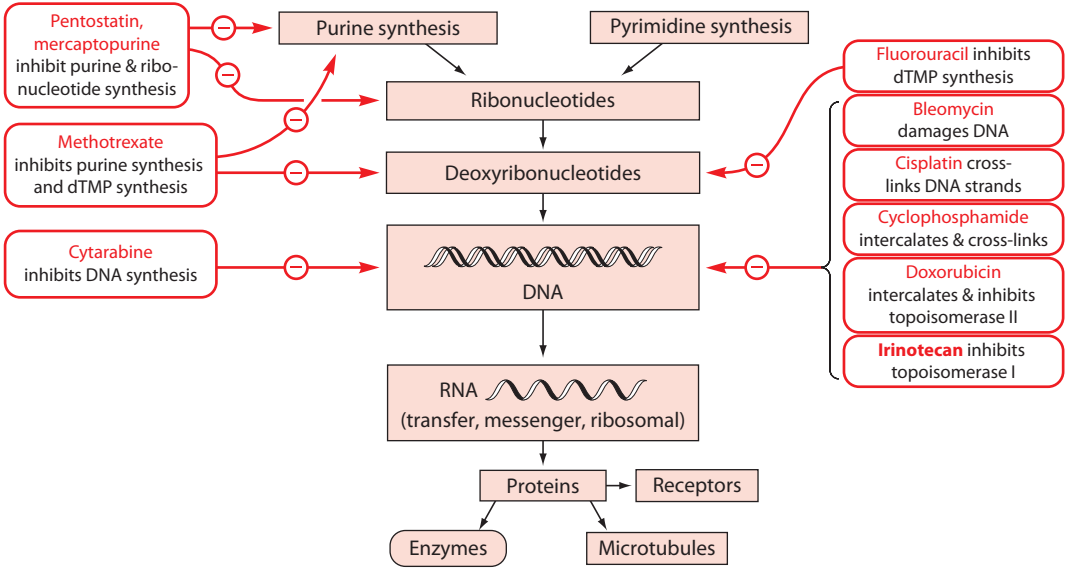
Abs/Distrb/Elim Given by i.v. infusion

Clinical use Metastatic tumours of colon and rectum (in combination with other agents).

Adverse effects GIT disturbances, interstitial pulmonary disease.

R&D 7e Ch 55, p 682; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Dactinomycin

Actions & MOA Intercalates in the DNA and inhibits RNA polymerase and topoisomerase II.

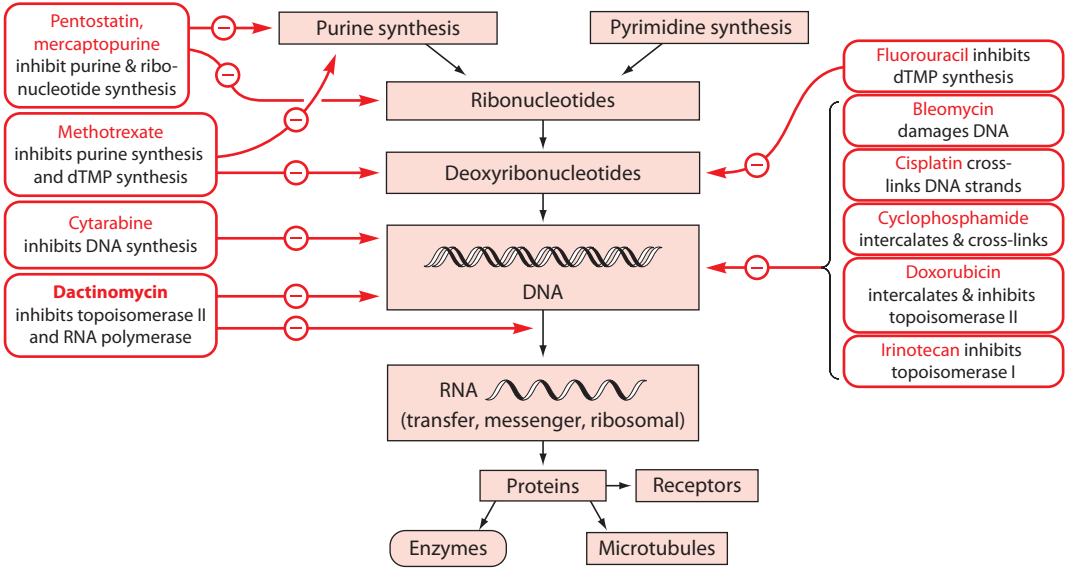
Abs/Distrb/Elim Given by i.v. injection.

Clinical use Paediatric cancers.

Adverse effects Nausea & vomiting; myelosuppression; hair loss.

R&D 7e Ch 55, p 682; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Vincristine

Actions & MOA Binds to tubulin, preventing spindle formation in dividing cells stopping them in mitosis.

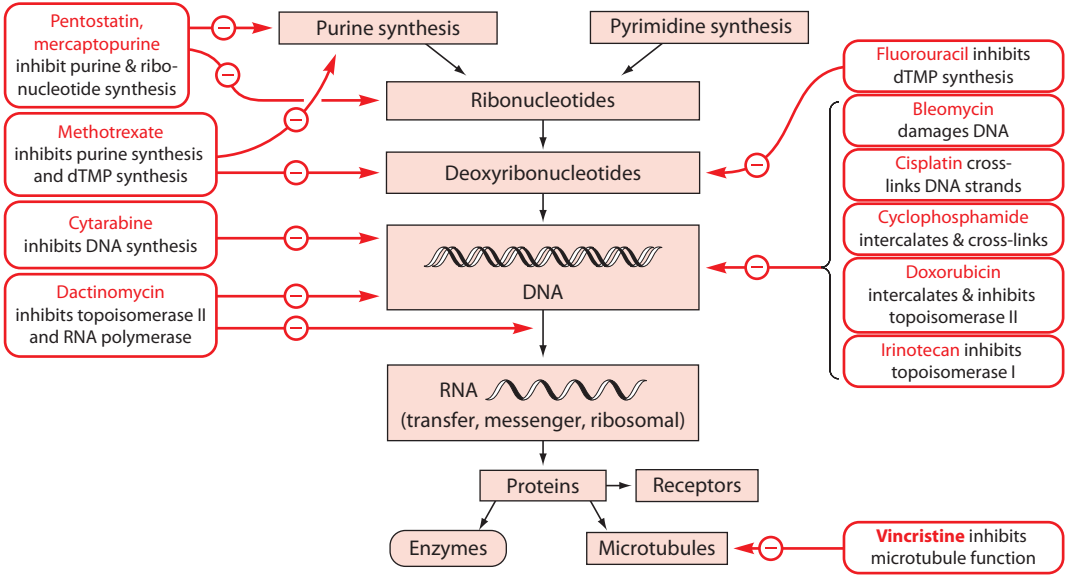
Abs/Distrb/Elim Given by i.v. injection.

Clinical use Leukemias, lymphomas, breast and lung cancers.

Adverse effects Nausea & vomiting; hair loss; **neurotoxicity** (peripheral & autonomic); negligible myelosuppression.

R&D 7e Ch 55, p 682; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Paclitaxel

Actions & MOA Binds to tubulin, keeping microtubules polymerised ('frozen'), preventing spindle formation in dividing cells and stopping them in mitosis.

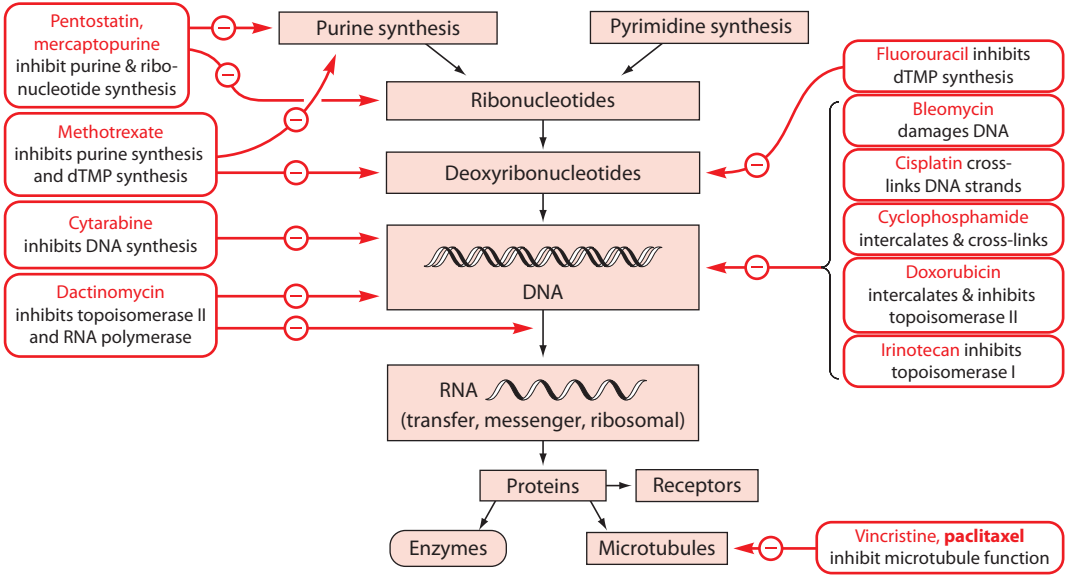
Abs/Distrb/Elim Given by i.v. infusion.

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.

R&D 7e Ch 55, p 682; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Imatinib

Actions & MOA Inhibits protein kinases important in chronic myeloid leukemia and other malignancies.

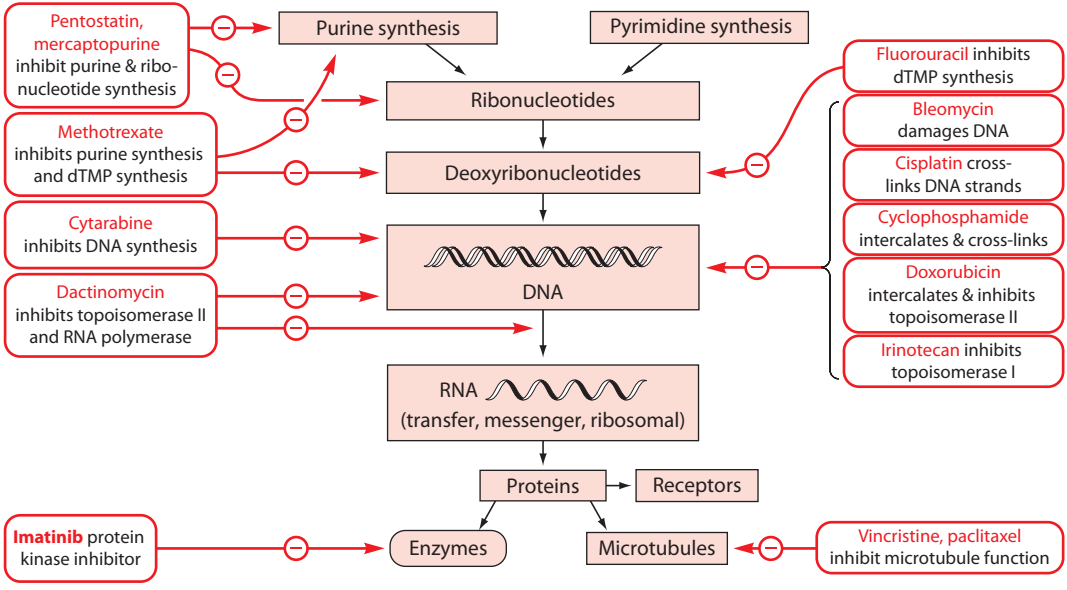
Abs/Distrb/Elim Given orally, well absorbed.

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



Trastuzumab

Actions & MOA Binds to and inhibits the epidermal growth factor receptor (a tyrosine kinase receptor), preventing its activation and inhibiting cell proliferation.

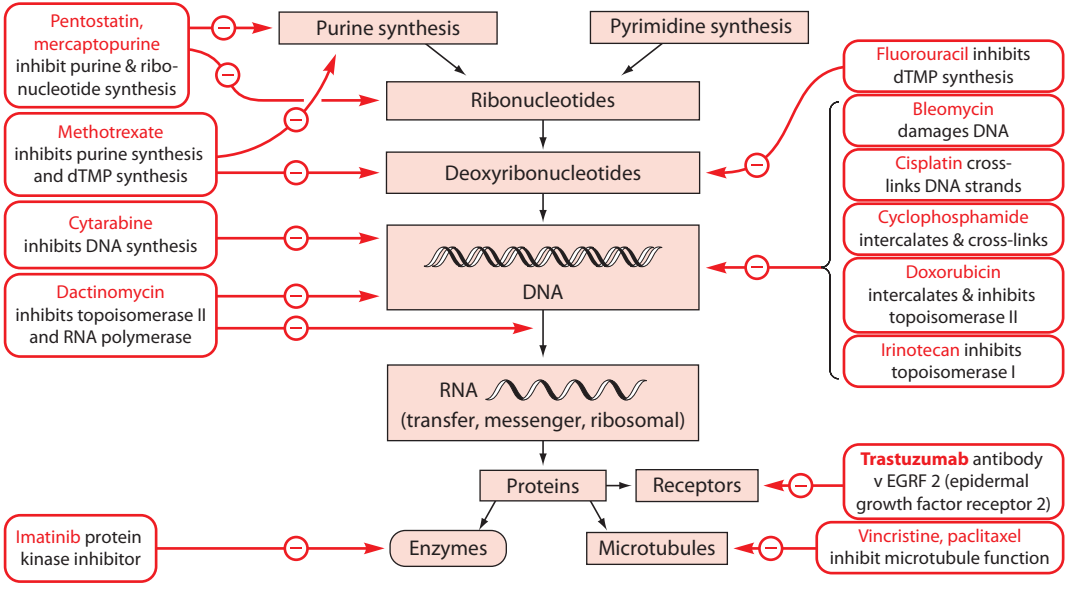
Abs/Distrb/Elim Given by i.v. infusion.

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.

R&D 7e Ch 55, p 684; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



Tamoxifen

Actions & MOA Competes with endogenous oestrogen for the oestrogen receptor, preventing cell activation and proliferation.

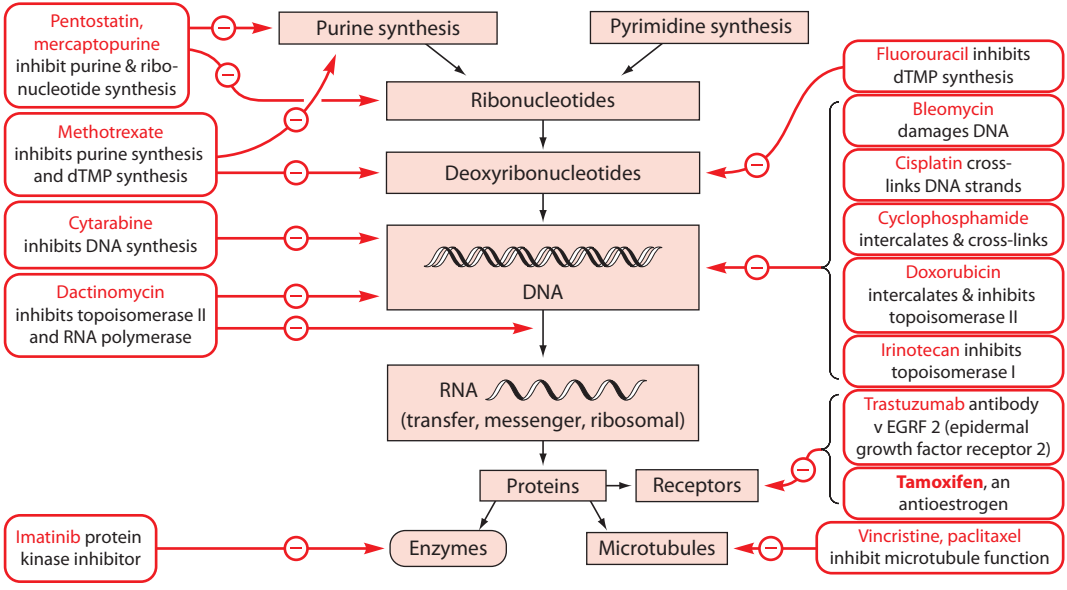
Abs/Distrb/Elim Given orally.

Clinical use Breast cancer.

Adverse effects Hot flushes, GIT disturbances, headache, menstrual irregularities.

R&D 7e Ch 55, p 683; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



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.

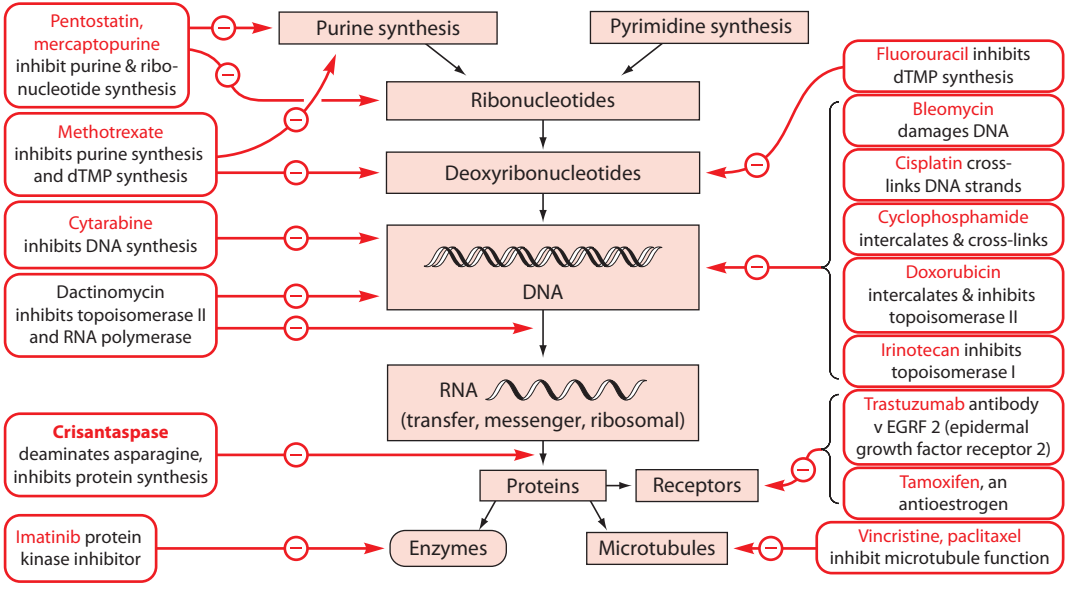
Abs/Distrb/Elim Given i.v., i.m. or subcut.

Clinical use Acute lymphoblastic leukemia.

Adverse effects Nausea & vomiting, CNS depression, liver disorder, anaphylactic reactions, risk of hyperglycaemia.

R&D 7e Ch 55, p 685; D&H 2e Ch 46, pp 104-105

Diagram of the main targets for anticancer drug therapy



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

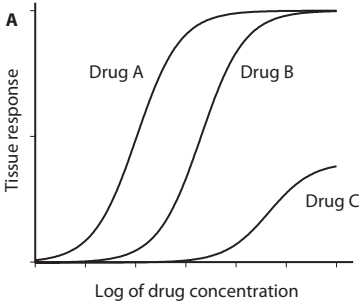
These agents are less likely to have the above cytotoxic actions but have their own adverse effects.

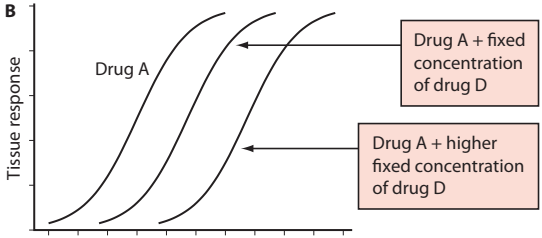
Examples are the drugs that don't affect DNA & RNA synthesis (see the face of this card)

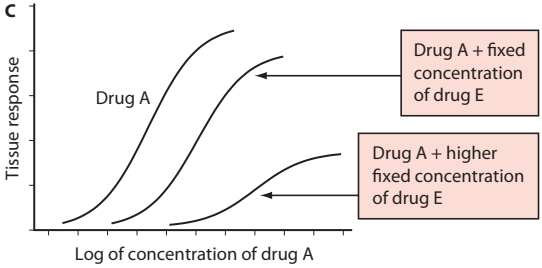
R&D 7e Ch 55 p 676; D&H 2e Ch 46, pp 104-105

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.

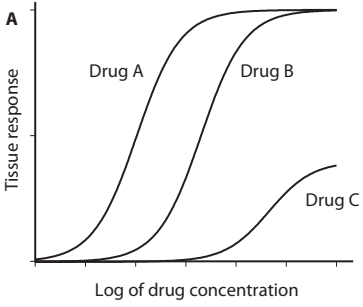
Chemical antagonism – the antagonist combines with the agonist. Very uncommon.

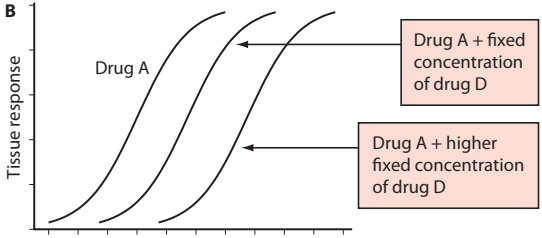
R&D 7e Ch 2, pp 8-14; D&H 2e Ch 1, pp 2-6

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.

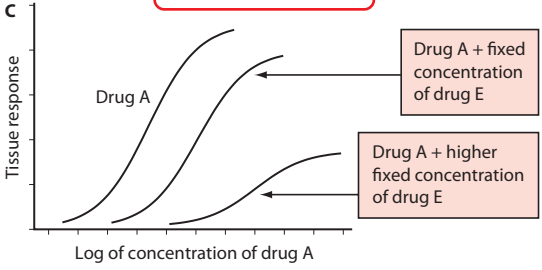
How does the affinity of a drug for its receptor influence its log.dose/response curve?

A, B and C are agonists





D and E are antagonists



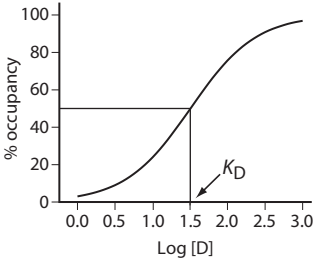
The affinity of a drug, D (agonist or antagonist), for its receptor, R, determines the proportion of receptors which are occupied by the drug, DR. The interaction follows the law of mass action:

$$D + R \rightleftharpoons DR \qquad K_D = ([D] \times [R])/[DR]$$

where [D], [R] and [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:

$$\% \text{ occupancy} = 100^* \frac{[D]}{[D] + K_D}$$

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:



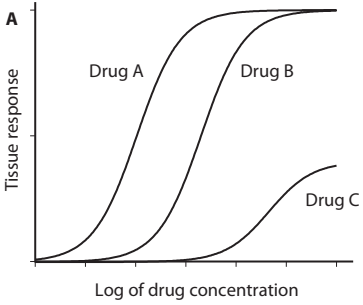
The tissue log.dose/response curve is also invariably sigmoidal. A low K_D value represents a high affinity and the curve will rise at low drug concentrations. If K_D is higher (lower affinity) the curve will appear at higher drug concentrations. Thus in panel A overleaf, drug A would have a higher affinity for the receptor than drug B – assuming they have the same efficacy (see card 35.03)

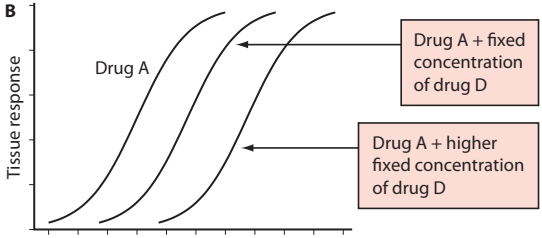
R&D 7e Ch 2, p 8; D&H 2e Ch 1, pp 2-6

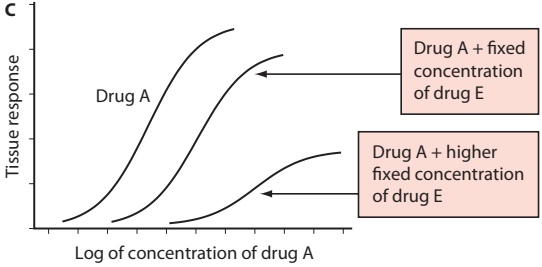
Panel A shows the response of a tissue to drugs A, B and C. Panels B and C show the effects that drugs D and E have on the log.dose/response curves to drug A.

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;

$$A + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} AR \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} AR^*$$

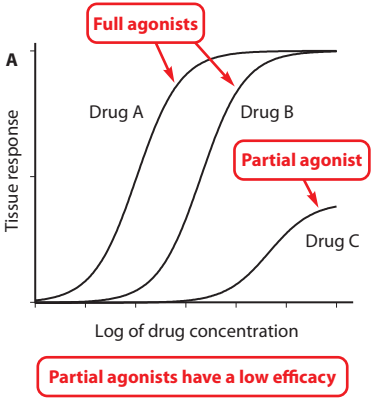
k_{+1} and k_{-1} are the forward and reverse rate constants for agonist binding.

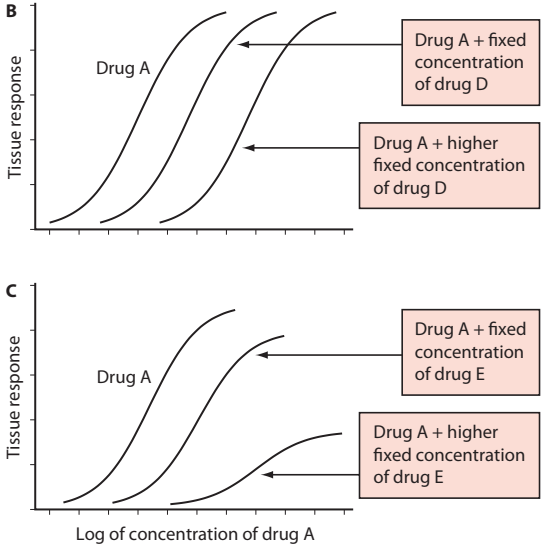
The agonist–receptor complex isomerises to AR* which is the active, open channel form of the receptor, β and α are the forward and reverse rate constants for the isomerisation reaction. It is now easy, for this receptor mechanism, to understand full and partial agonism. For a full agonist β is much greater than α so that many of the channels open. For a partial agonist, with low efficacy, α is greater than β so that few of the receptors isomerise to AR*.

R&D 7e Ch 2, p 8; D&H 2e Ch 1, pp 2-6

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?





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:

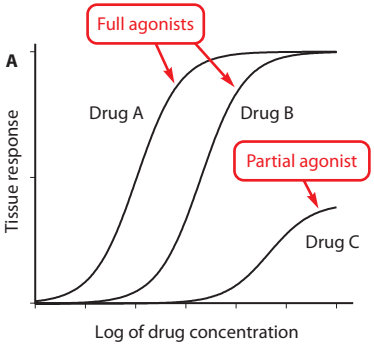
$$r\text{-}1 = \frac{[B]}{K_B}$$

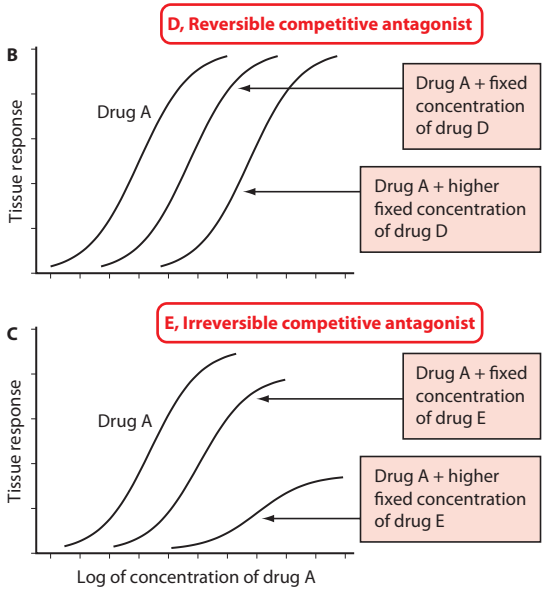
Where [B] is the antagonist concentration and K_B is the dissociation equilibrium constant for antagonist binding.

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).

R&D 7e Ch 2, pp 10-11; D&H 2e Ch 1, pp 2-6

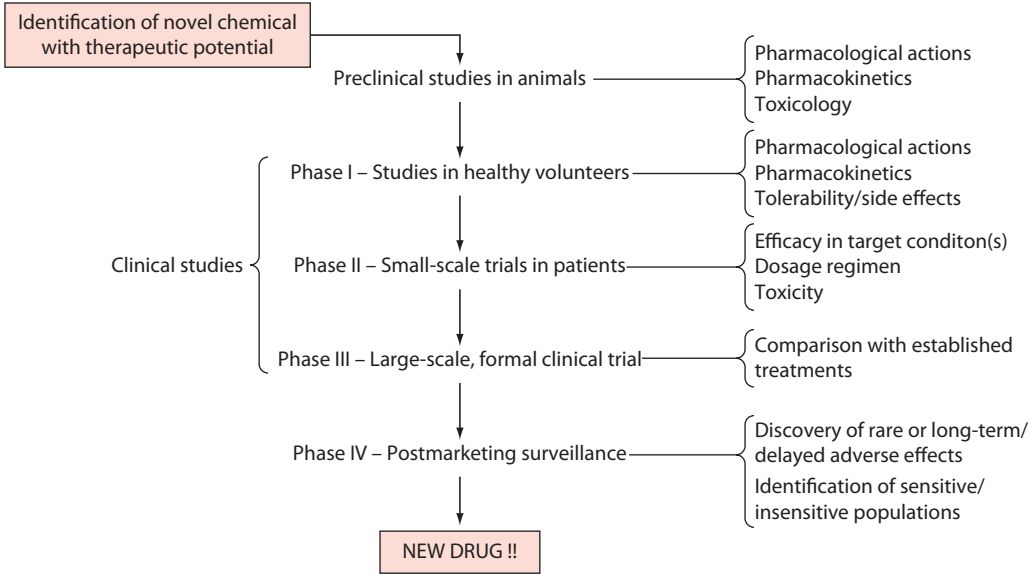
Panel A shows the response of a tissue to drugs A, B and C. Panels B and C show the effects that drugs D and E have on the log.dose/response curves to drug A.





Notes

Key stages in the development and introduction of a 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).

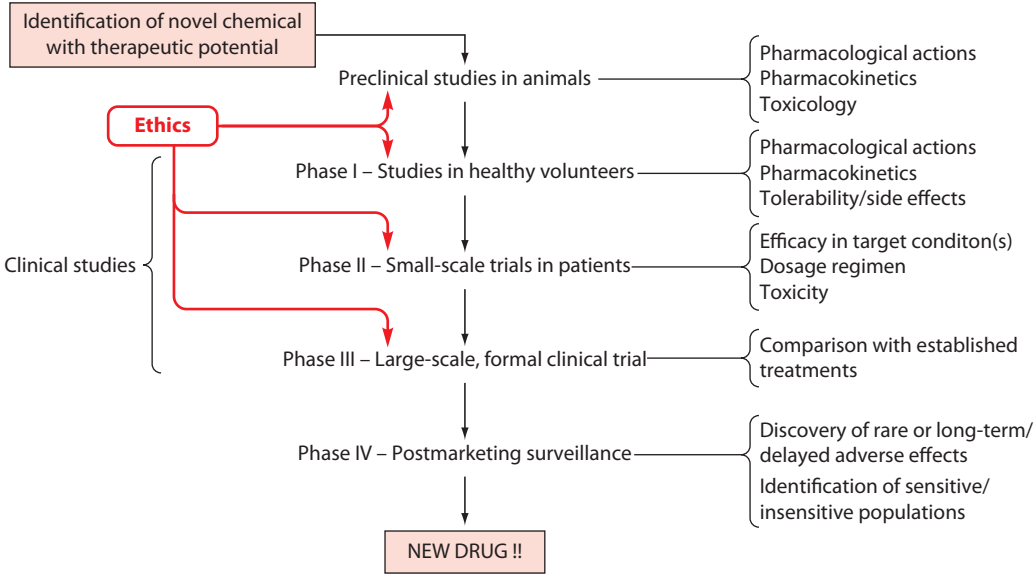
All patients (or guardian) should provide informed consent for participation.

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.

R&D 7e Ch 7, pp 94-98; D&H 2e Ch 5, p 19

Key stages in the development and introduction of a 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

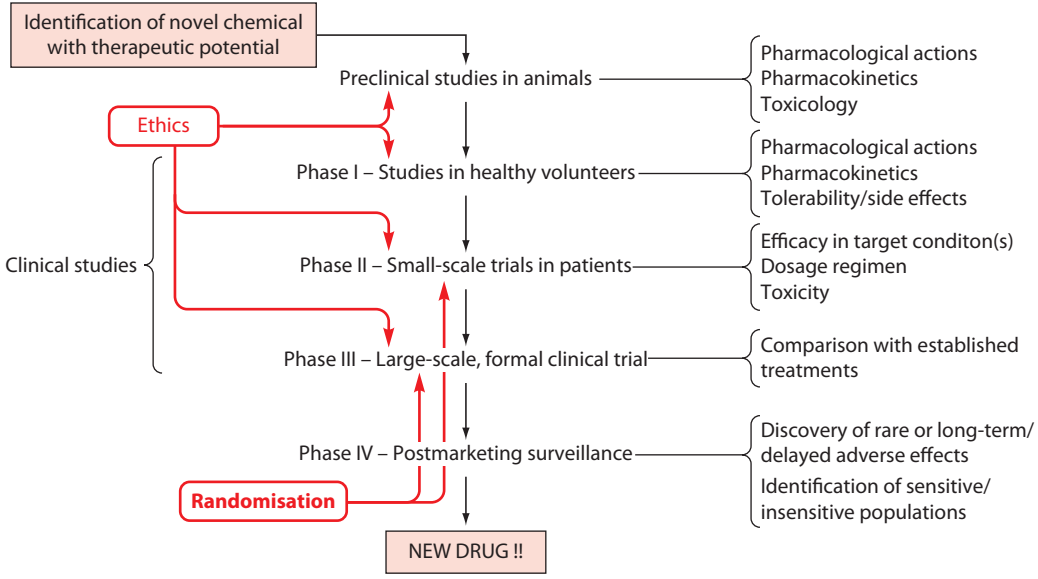
In a small trial, randomisation may not ensure similarity. It may be desirable to make sure that each group has broadly the same numbers of each sex, a similar age spread and that disease severity is comparable. Stratification may also allow groups of individuals who respond more favourably to a particular 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.

R&D 7e Ch 7, p 95; D&H 2e Ch 5, p 19

Key stages in the development and introduction of a new drug

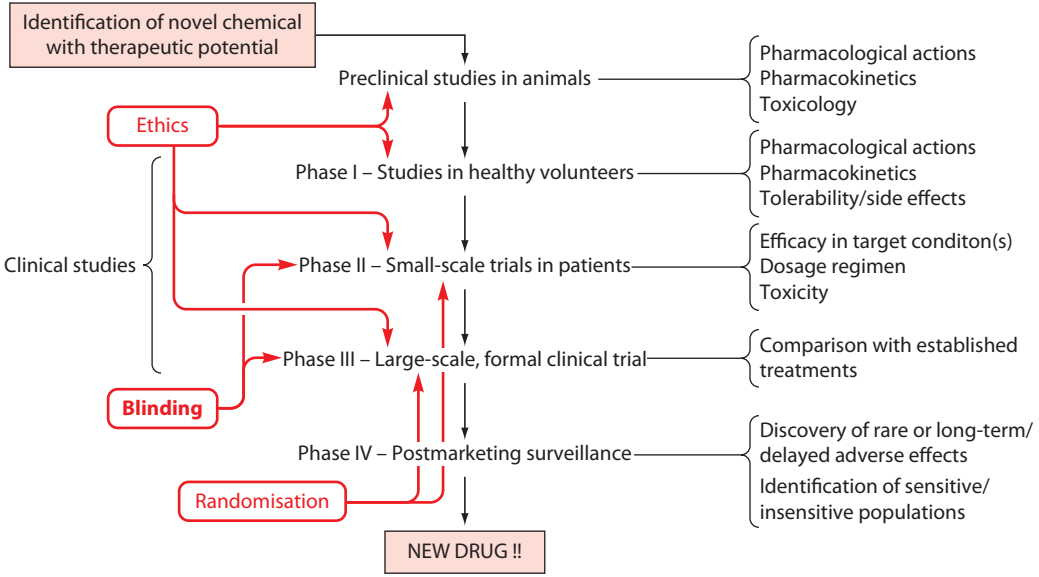


Single blind In single-blind trials patients are not told which treatment they are to receive. The aim is to ensure that any expectations that the patient has does not generate or modify a placebo effect or otherwise influence their assessment of the treatment.

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.

R&D 7e Ch 7, p 95; D&H Ch 5, p 19

Key stages in the development and introduction of a new drug



The therapeutic index (TI) is a simple attempt to quantify the benefit versus risk ratio of a drug.

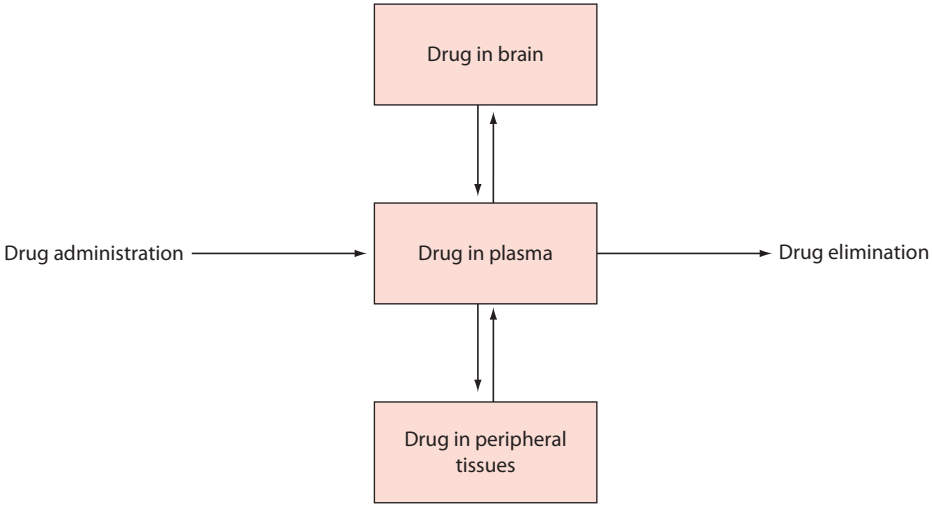
$$TI = \frac{TD_{50}}{ED_{50}} \quad \text{or} \quad \frac{LD_{50}}{ED_{50}}$$

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.

R&D 7e Ch 7, p 97; D&H Ch 5, p 19

Simple diagram of absorption and distribution of a drug
How do lipid solubility and ionisation influence the passage of drugs through cell membranes?



Lipid solubility and ionisation

• 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:

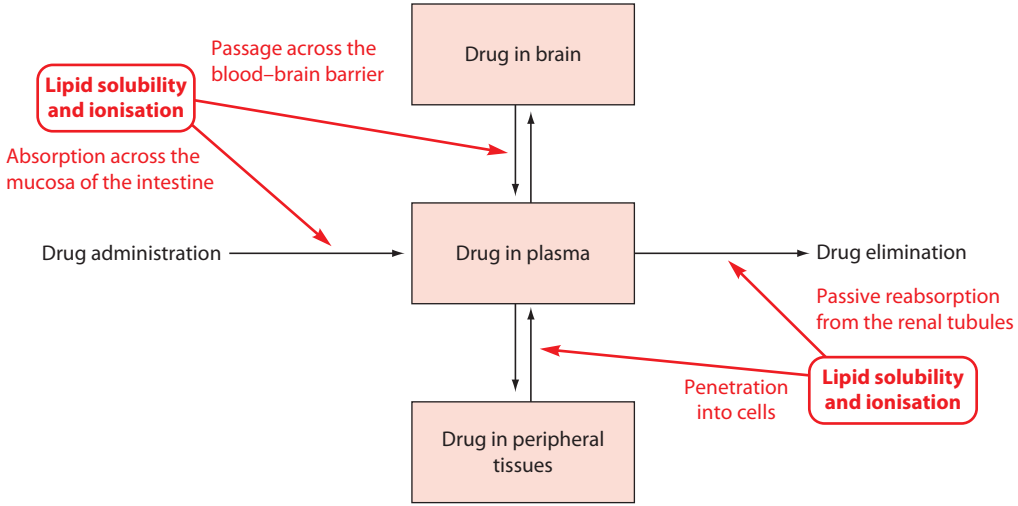
for a weak acid: $\log_{10} c_i/c_u = pH - pK_a$
for a weak base: $\log_{10} c_i/c_u = pK_a - pH$

[Where c_i is the concentration of drug in ionised form, c_u is that in unionised form, pK_a is $-\log_{10}$ of the acid dissociation constant for the drug and 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 pK_a and a strong base has a high pK_a).

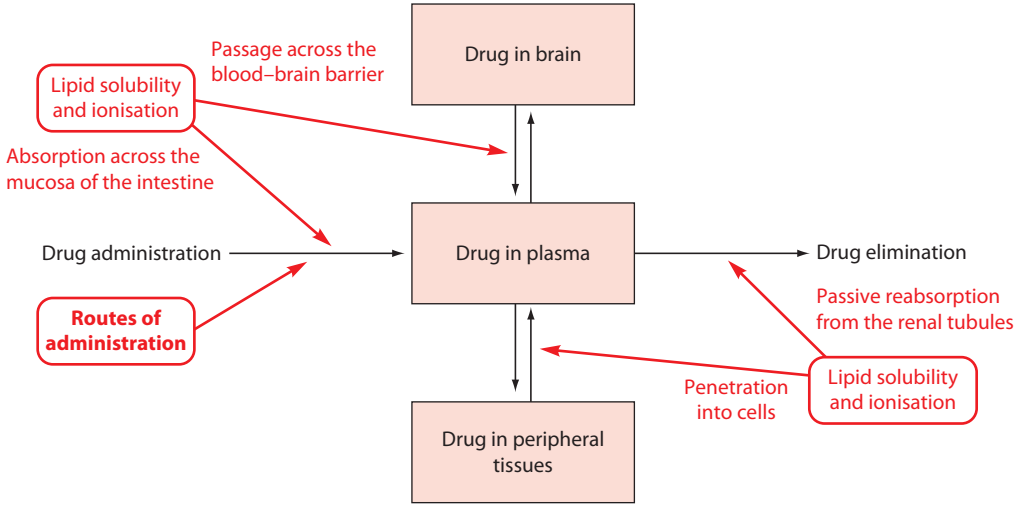
R&D 7e Ch 8, pp 99-101; D&H 2e Ch 6, pp 20-21

Simple diagram of absorption and distribution of a drug
What are the features, advantages and disadvantages of the different routes of drug administration?



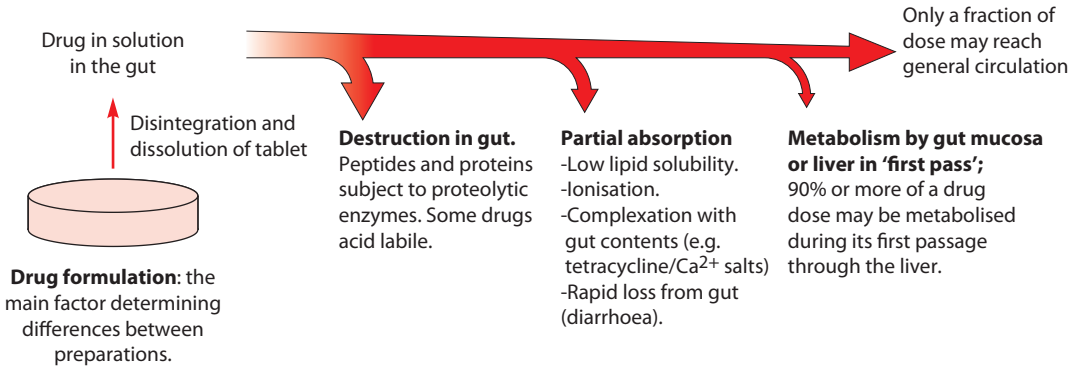
Enteral, i.e. oral, rectal, sublingual	Easy, requires no skill, and little need for sterility. Many drugs, however, are poorly absorbed from the gut and bioavailability (see card 37.03) may be low. Rectal and sublingual admin. largely avoid first-pass metabolism. Rectal route useful for irritant medicines 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'?



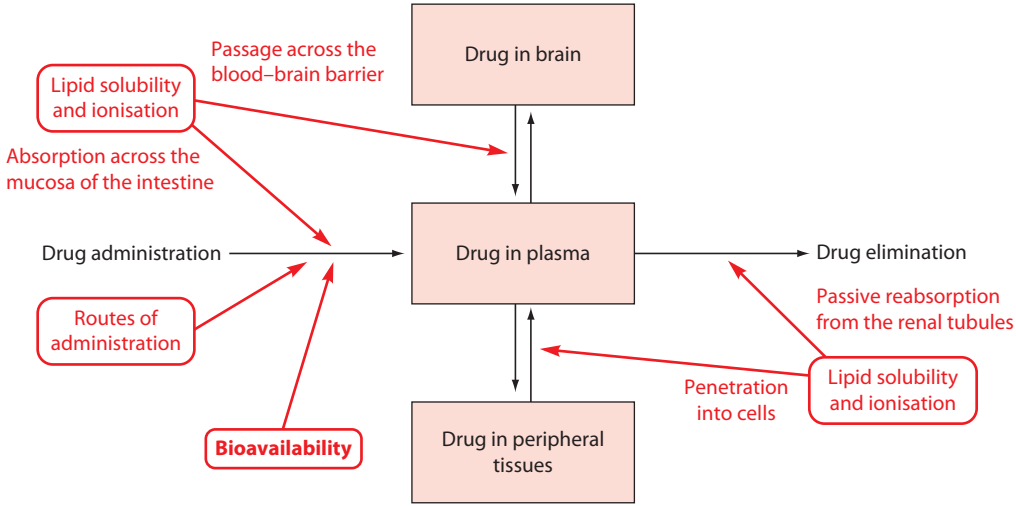
The most useful definition is '**the proportion of the administered dose that reaches the systemic circulation**'. Incomplete release from the dosage form, destruction within the gut, poor absorption and first-pass elimination are important causes of low bioavailability. For drugs with a low therapeutic index it is important that repeat prescriptions provide medicines of equivalent bioavailability (bioequivalence).

Diagram showing factors influencing bioavailability



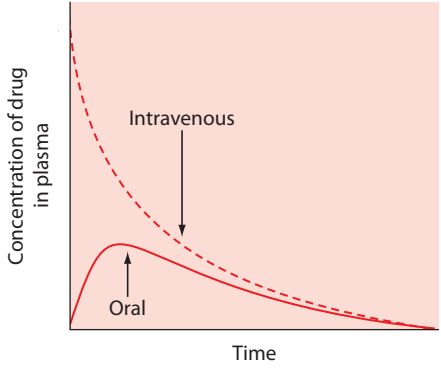
R&D 7e Ch 8, p 108; D&H Ch 6, pp 20-21

Simple diagram of absorption and distribution of a drug
How can the bioavailability of a drug preparation be established?



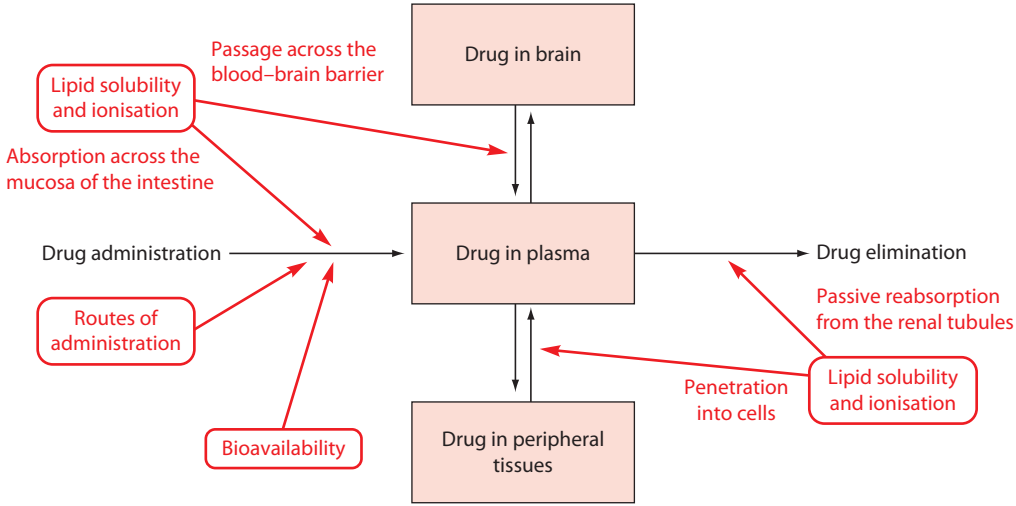
Measurement of bioavailability

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.



R&D 7e Ch 8, p 108; D&H Ch 6, pp 20-21

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?



Many drugs bind to plasma proteins, albumin in general being the most important. α-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.

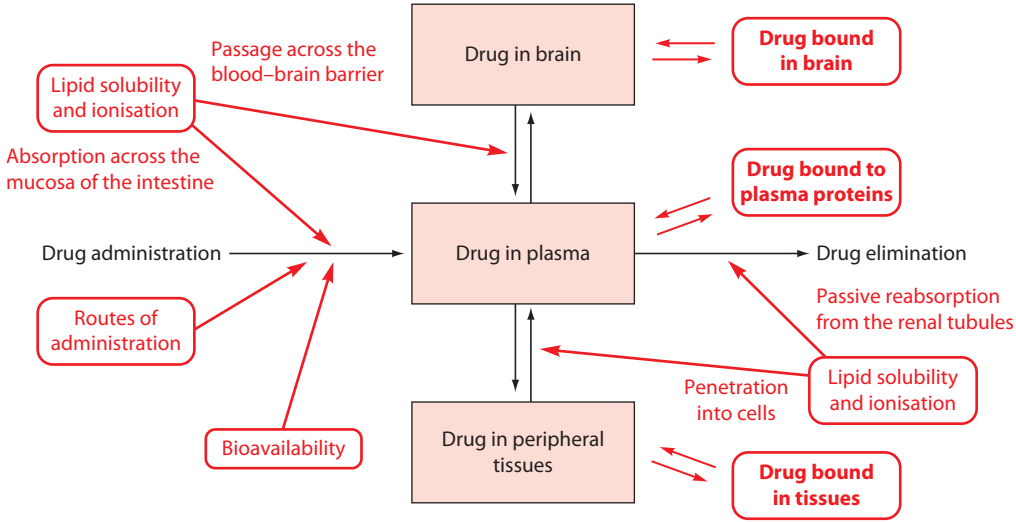
- The reduction in free drug concentration may reduce elimination (by reducing glomerular filtration) or, conversely, protein binding may act to deliver drug to the kidney and liver, and so enhance elimination.

- 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).

R&D 7e Ch 8, pp 103-106; D&H Ch 6, pp 20-21

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:

$$V_d = \text{Dose}/c_p$$

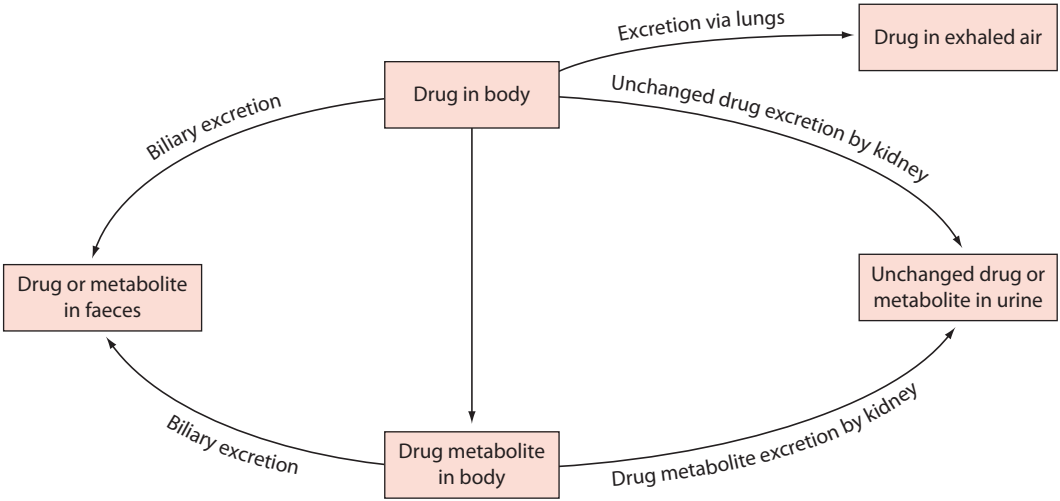
Where c_p is the concentration of drug in the plasma after it has equilibrated in its distribution volume but before a significant fraction has been eliminated. Examples of V_d values (l/kg) are:

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).

R&D 7e Ch 8, p 111; D&H Ch 6, p 21

The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.



Phase I and phase II metabolism

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

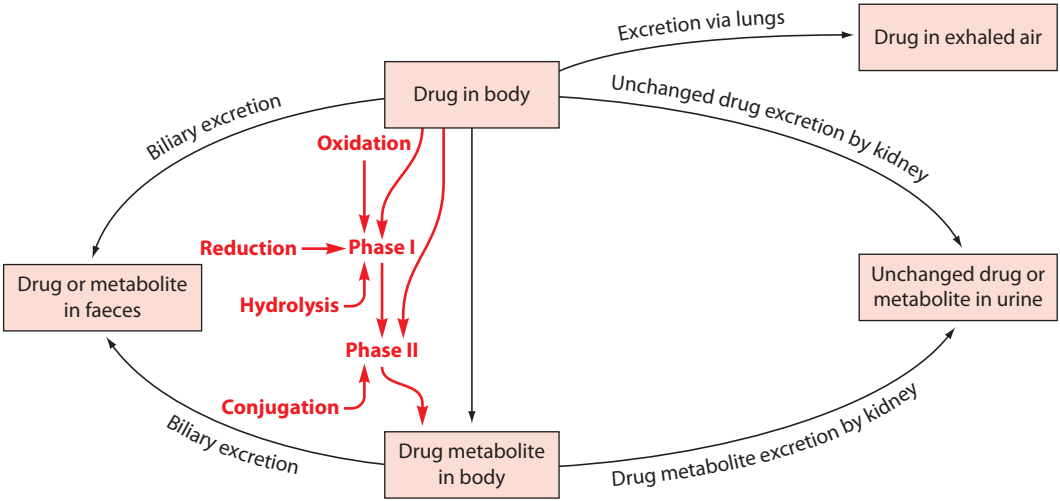
Oxidation	Mainly carried out by the P450 system (see card 38.02) in the liver. Examples: propranolol → 4-hydroxypropranolol (retains β-blocking activity) paracetamol → N-acetyl-p-benzoquinone imine (responsible for hepatotoxicity)
Reduction	Nitrazepam → 7-amino-nitrazepam (nitro reduction) prednisone → prednisolone
Hydrolysis	Often carrried 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

R&D 7e Ch 9, pp 115-117; D&H Ch 7, p 22

The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.



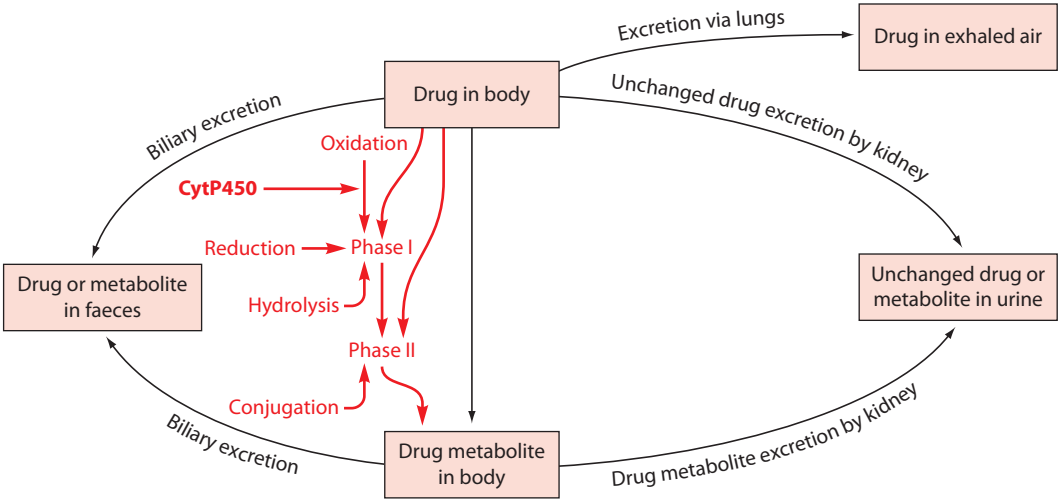
Drug oxidation, usually carried out by the P450 monooxygenase system, is a major route of drug metabolism. The P450 haem proteins are found particularly in the smooth endoplasmic reticulum of the liver. NADPH/cytochrome P450 reductase is generally an essential component of the system.

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.

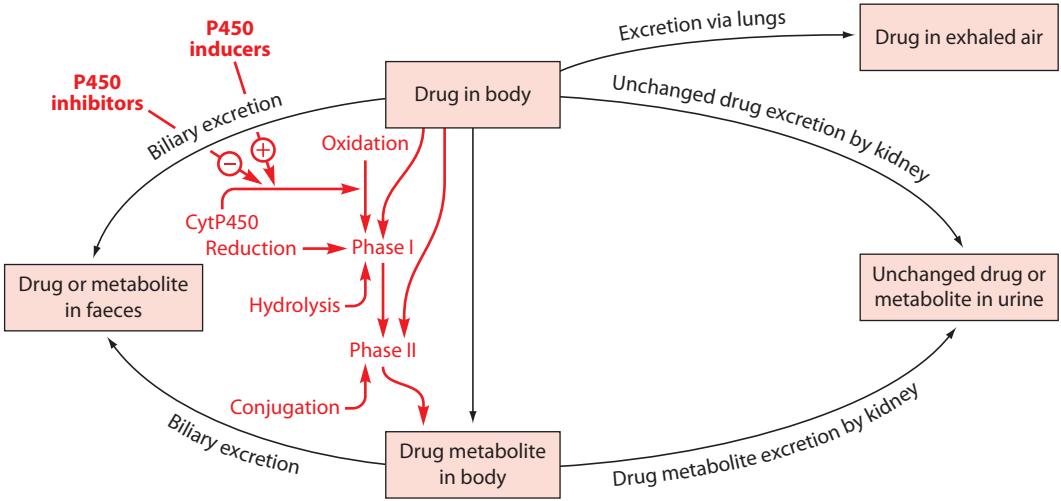


The activity of the P450 system can be increased (induced) or inhibited by drugs or by dietary constituents. This is an important cause of drug interactions. The induction or inhibition of particular P450 isoenzymes will either reduce or enhance the activity of drugs metabolised by the enzyme. Just a few examples are:

Drug metabolising P450s	*Inducers*	*Inhibitors*	*Substrates affected*
CYP1A2	Omeprazole, modafinil	Fluvoxamine, ciprofloxacin, cimetidine, amiodarone	Clomipramine, clozapine, paracetamol
CYP2B6	Phenobarbital, rifampin	Ticlopidine	Bupropion, cyclophosphamide, methadone
CYP2C8	Rifampin	Gemfibrozil, trimethoprim	Paclitaxel, repaglinide
CYP2C19	Carbamazepine, prednisone rifampin	Omeprazole, fluoxetine, topiramate	Omeprazole, diazepam, phenytoin
CYP2C9	Rifampin, secobarbital	Fluconazole, amiodarone	Ibuprofen, tolbutamide, losartan, tamoxifen
CYP2D6	Dexamethasone, rifampin	Fluoxetine, quinidine, terbinafine	Codeine, lidocaine, propranolol
CYP2E1	Ethanol, isoniazid	Disulfiram	Ethanol, paracetamol, halothane
CYP3A4,5,7	Nevirapine, barbiturates, carbamazepine, rifampin	Indinavir, clarithromycin, itraconazole, grapefruit juice	Ciclosporin, terfenadine, simvastatin, buspirone

R&D 7e Ch 9, p 117-118; D&H Ch 7, p 22

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:

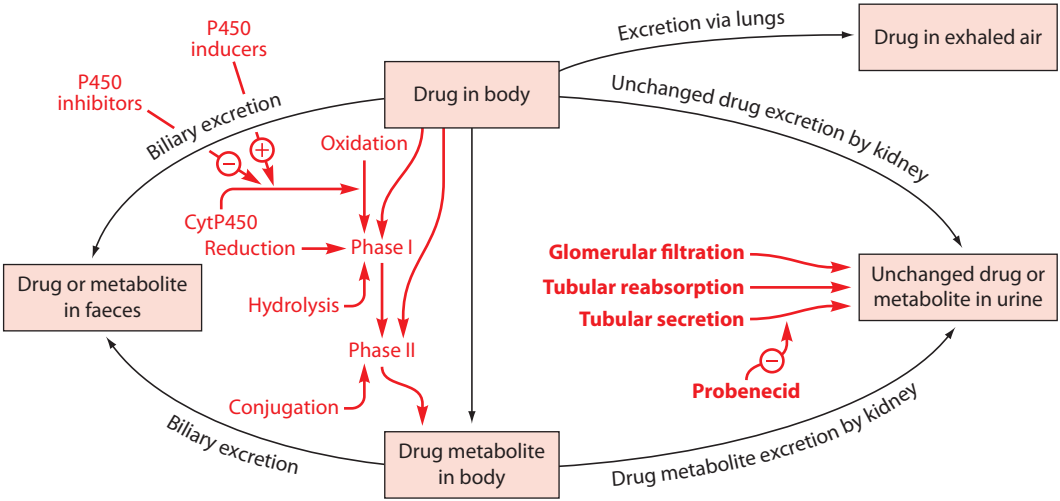
Glomerular filtration Small drug molecules are forced across the glomerular membrane by the pressure in the renal arteries, entering the renal tubule at a concentration equal to that in the plasma. Drug bound to plasma proteins will not be filtered.

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.)

R&D 7e Ch 9, p 119-121; D&H Ch 7, p 23

The concentration of a drug in the body is reduced either by its metabolism or by its excretion unchanged.



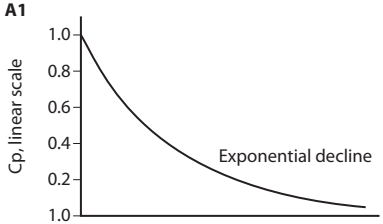
Biliary excretion For some drugs (e.g. cromoglicate, vecuronium) biliary excretion of drug or metabolite is more important than renal excretion. Biliary excretion is by active transport, which is saturable and subject to competition. Drug excreted in bile may be reabsorbed from the intestine and enter an **'enterohepatic circulation'**. Drug tied up in this **'enteric pool'** acts as a reservoir which may increase the drug's half-life.

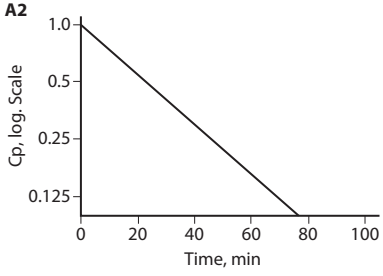
Excretion via lungs Volatile/gaseous agents can be readily excreted via the lungs, which receive the whole of the cardiac output and which have thin membranes which are very permeable to small gas molecules. The main agents lost via the lungs are the gaseous/volatile anaesthetics.

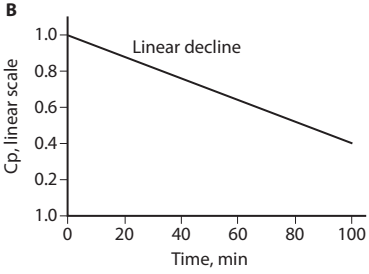
R&D 7e Ch 9, p 119; D&H Ch 7, p 23

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):

$$\ln c_p = \ln c_p(0) - k_{el}t$$

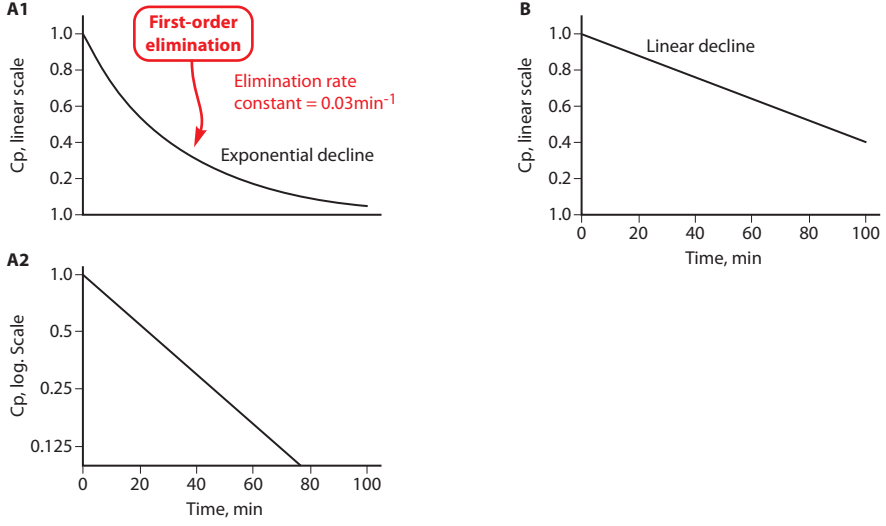
A plot of $\ln c_p$ against time gives a straight line of slope $-k_{el}$.

*Note: A simple exponential decline will only be observed where the body behaves as one compartment – see D&H ref.

R&D 7e Ch 10, pp 124-126; D&H 2e Ch 8, pp 24-25

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 elimination

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):

$$-\frac{dc_p}{dt} = \frac{V_{max} \cdot c_p}{c_p + K_M}$$

Where V_{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:

$$-\frac{dc_p}{dt} \approx V_{max}$$

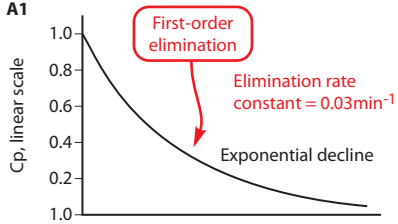
The rate of change of concentration has reached a maximum and is now unaffected by the drug concentration. (C_p declines at a fixed rate (Fig. B overleaf)).

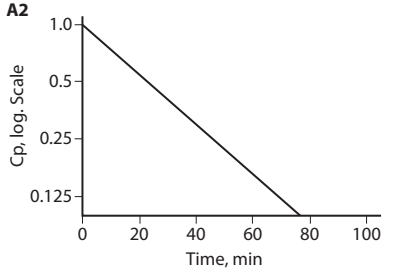
Ethanol is a well-known example of a substance subject to first-order elimination.

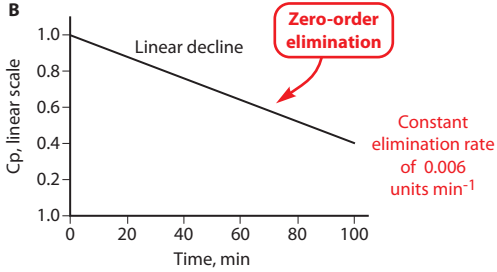
R&D 7e Ch 10, pp 128-129; D&H 2e Ch 8, pp 24-25

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.







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 $t_{½}$ and c_p is made equal to a half of $c_p(0)$ then:

$$t_{½} = 0.693/ k_{el}$$

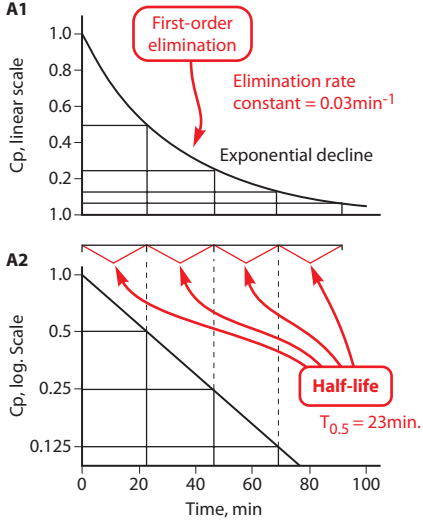
Thus in the example given here $T_{0.5} = 0.693/0.03$, i.e. 23min.

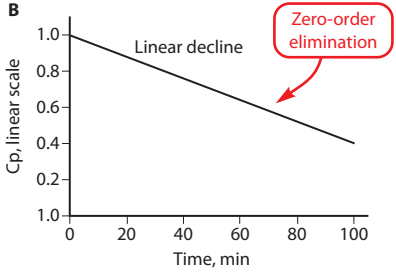
Representative plasma half-lives of drugs, h	
Insulin	0.1
Aspirin	0.25
Penicillin G	0.7
Lidocaine	2.0
Salicylate	4.0
Sulfadiazine	13–25
Atropine	12–38
Chlorpromazine	30
Phenobarbitone	48–120
Digitoxin	200

R&D 7e Ch 10, p 127; D&H 2e Ch 8, pp 24-25

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 $c_p V_d$ multiplied by k_{el}. V_d = volume of distribution. Therefore:

$$Cl = \frac{k_{el} c_p V_d}{c_p} = k_{el} V_d$$

As $k_{el} = 0.693/t_{½}$, clearance = $0.693 V_d/t_{½}$
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}).

R&D 7e Ch 10, p 124; D&H 2e Ch 8, pp 24-25