1. Drug Receptor Interactions
Dr MJCroucher

**Pharmacology:** "the science of the properties of drugs and their side effects on the body"
- Pharmacology can be divided into two main areas: pharmacokinetics + pharmacodynamics

**Pharmacokinetics:** "the study of how drugs are handled within the body, including their absorption, distribution, metabolism + excretion"
This is concerned with...
- how drug concentration changes with time
- how drugs pass across cell membranes
- how often drugs should be given
- what the effect of long-term administration may be
- how drugs interact with each other
(it also addresses how individual variations affect all these things)

**Pharmacodynamics:** "the interactions of drugs with cells and their mechanism of action on the body"
It includes factors such as...
- How drugs bind to cells
- Uptake of drugs into cells
- Intracellular metabolism of drugs

**BASIC CONCEPTS + TERMINOLOGY**

**Drug:** "a chemical that affects physiological function in a specific way"
- This rules out substances like water, which affects physiological function in a non-specific way

**Drug target sites:** "protein complexes key to drug mechanism of action"
When a drug is administered, it first must interact with 1 of 4 target sites:
- Cell Receptors
- Ion channels
- Transport systems
- Enzymes

1) **Cell Receptors**
- Effectively proteins which usually sit within cell membranes therefore are exposing an active site waiting to be activated by neurotransmitters or hormones.
  - NB: steroid hormone receptors are intracellular
- There are 4 main families of receptors; differentiated on the basis of the protein structure of the receptor + the biochemical/transduction system the receptor interacts with in the cell

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionotrophic receptors (ligand-gated channels)</td>
<td>Metabotropic receptors (G-protein coupled)</td>
<td>Kinase-linked receptors</td>
<td>Intracellular steroid type receptors</td>
</tr>
<tr>
<td>Location</td>
<td>Membrane</td>
<td>Membrane</td>
<td>Membrane</td>
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<tr>
<td>Effector</td>
<td>Channel</td>
<td>Enzyme or channel</td>
<td>Enzyme</td>
</tr>
<tr>
<td>Coupling</td>
<td>Direct</td>
<td>G-protein</td>
<td>Direct or indirect</td>
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<tr>
<td>Speed</td>
<td>Milliseconds</td>
<td>Seconds</td>
<td>Minutes</td>
</tr>
<tr>
<td>Examples</td>
<td>Nictonic Ach receptor</td>
<td>Muscarinic Ach receptor</td>
<td>Insulin receptor</td>
</tr>
</tbody>
</table>
Receptor structure

- **T1 receptors** = 4-5 subunits with an external binding domain. Specific transmembrane segment forms the channel pore.
- **T2 receptors** = no subunits, but 7 transmembrane segments. Binding domain sits within the transmembrane segments, thus giving a smaller external domain. G-protein coupling domain lies within cytoplasmic loops.
- **T3 receptors** = single transmembrane segment with large external binding domain. Binding initiates signal to cytoplasmic catalytic domain \(\rightarrow\) enzymatic response
- **T4 receptors** = similar classic receptor structure, except all intracellular. DNA binding domain lies within zinc fingers (these wrap around the nuclear DNA + promote gene transcription)
Receptors often initiate sequences involving different 2nd messenger molecules. You should be aware of these (do not need to learn diagram!!)

Receptors are also defined by their specific agonists + antagonists

**Agonists:** a drug or other substance that acts on the cell receptor to activate it, initiating a response. Examples include:
- acetylcholine at acetylcholine receptors
- nicotine

the normal dose-response curve has a hyperbolic shape, whereas the log dose-response curve has a sigmoidal shape.

**Antagonists:** a drug or other substance that binds to the cell receptor without activating it, thus blocking the receptor active site and inhibiting the normal response.

NB: the term agonist + antagonist are specifically used for drugs acting on receptors (not enzymes, where they may act as enzyme activators or inhibitors)

### 2) Ion channels

Selective pores in the lipid bilayer in the cell membrane, which can be opened to promote the movement of ions down their electrochemical gradient.

There are 2 main types of ion channels, differentiated by their mechanism of gates:
- **Voltage-sensitive**: channel opens in response to a change in membrane potential, e.g. Ca2+ channels (VSCC)
- **Receptor-linked**: channel opens in response to the activation of a receptor (for info about receptor activation, see above) e.g. acetyl choline activates nAChR, which in turn opens an ion channel
Drugs may interact with one or both types of ion channels. Examples of drugs include:

- **Local anaesthetics** – interact with/block v-sensitive Na+ channels on pain conduction neurones, thus reducing the perception of pain
- **Calcium channel blockers** – e.g. Nitradipline; very useful in the treatment of CV disorders, for example as anti-hypertensives + anti-angina drugs

3) **Transport systems**
Specific carrier molecules that transport substances against their concentration gradient
These are energy dependent
Examples include:

- Glucose transporter in hepatocytes
- Neurotransmitter transport e.g. active reuptake of noradrenaline into nerve terminals in the sympathetic NS
- Na+/K+ ATPase

Drugs may interact with transport systems in order to mediate their action. Examples include:

- **TCAs** (tricyclic anti-depressants) – in clinical depression, the Na5HT transporter in the brain is not fully functional. TCAs slows down the postsynaptic reuptake of NA into the nerve terminals thus prolonging the effect of NA
- **Cardiac glycosides** – act to slow down the Na/K ATPase, leading to an increase in intracellular Na+. this is useful in cardiac failure, as the increase in intracellular Na+ leads to an increased force of contraction, e.g. Digoxin

4) **Enzymes**
Catalytic proteins that increase the rate of reaction, without changing the reaction
A number of drugs interact with enzymes in 3 ways:

- **Enzyme inhibitors** – act to slow enzyme function, e.g. neostigmine: an anticholinesterase which slows down the rate of degradation of acetylcholine thus enhancing its action
- **False substrates** – act to subvert normal pathways by introducing a new substrate, e.g. Methyldopa: anti hypertensive drug which subverts the normal noradrenaline synthesis pathway by introducing a different precursor \( \rightarrow \) local vasodilation
- **Prodrugs** – essentially drugs which interact with an enzyme to form the active component which then has an effect on the body, e.g. chloral hydrate which is converted to the active trichloroethanol

NB: unwanted (non-therapeutic) effects of drugs are also mediated by enzymes, e.g. Paracetamol overdose (10-15x normal dose) saturates the metabolism enzyme system in the liver, leading the alternative metabolic pathways which involve the formation of free radicals + generation of toxic metabolites which cause irreversible liver + kidney damage – there is a delay in the organ damage by \( \sim 24-48 \) hrs, therefore treatment for overdose needs to happen in the first 12 hours to prevent the irreversible damage.

Non-specific drug action
There are drugs whose action are mediated solely by their own physiochemical properties, and do not involve the 4 main drug-target sites.
Examples of these include:

- **General anaesthetics** – interact with synaptic transmission in the brain, but the specific interaction is unknown
- **Antacids** – used in the treatment of indigestion, dyspepsia and the symptoms of ulceration (in conjunction with anti-ulceration drugs)
  o Antacids are bases, therefore have no specific action, but their effects result from the general equation acid + base \( \rightarrow \) salt + water
- **Osmotic purgatives/laxatives** – act to draw water into the large intestine causing softening/expansion of faeces and promotion of excretion
NB: **plasma protein binding**: plasma protein binding sites e.g. albumin, act to allow storage of drugs in the body in a protein-bound form. This allows transport of the drug, but does not mediate any action of the drug. Not all drugs can/will exist in a pp bound form.

**DRUG-RECEPTOR INTERACTIONS**

Further terminology...

- **Affinity**: the strength (Avidity) of drug binding to receptor
- **Efficacy/intrinsic activity**: the ability of the drug to induce a response in the receptor post-binding (i.e. through a conformational change in the receptor)
- **Potency**: the powerfulness of a drug, depending on its affinity and efficacy
- **Full agonist**: an agonist which has the ability to induce a max response in tissue post-binding
- **Partial agonist**: an agonist which can only produce a partial response in tissue, and in conjunction with a full agonist may act with antagonistic activity
- **Selectivity**: the preference of a drug for a receptor (this is not specificity; specific suggests one drug one receptor. In fact the adverse effects of many drugs are caused by the binding to their non-preferred receptors)
- **Structure-activity relationship**: referring to the fact that the activity of a drug is closely related to the structure of the drug, therefore small changes in the structure may produce large effects on its action
  - This is like the lock + key theory, and is useful in drug design; small changes to an agonist may in turn form an antagonists, as well as altering the pharmokinetics of the drug
- **Receptor reserve** refers to the fact that in many tissues, not all receptors need to be occupied in order to achieve the maximal tissue response
  - With regards to physiological tissue, this results in an increased sensitive + speed of response

**ANTAGONISTS**

Agonists show affinity + efficacy for receptors. However antagonists have no efficacy, therefore post receptor-binding they do not induce a response. In turn they prevent agonists from binding and inducing the normal response from the receptor.

**Competitive antagonists** bind to the same site as the agonist, therefore reducing the number of agonist molecules which can bind to the receptor, therefore reducing the normal agonist response

- They are surmountable; therefore by increasing the concentration of the agonist, you can overcome a competitive antagonist block
- Dose-response curve shows parallel displacement to the RIGHT
- E.g. 1) **atropine** = acetyl CoA muscarinic antagonist
- E.g. 2) **propranolol** = non-selective β1/2 blocker

**Irreversible antagonists** bind either tightly to the same site as the agonist (by covalent bonds as opposed to the normal hydrogen bonding/electrostatic forces), or at a different site to the agonist.

- These are insurmountable, therefore the maximal normal response cannot be achieved regardless of whether the concentration of agonist is increased further.
- Dose-response curve shows shift of curve to the right + decreased maximal tissue response
- E.g. **hexamethonium** – nicotinic antagonist; binds to the ion channel + blocs the flow of Na+
2. Introduction to the autonomic nervous system
Dr Christopher John

There are 3 principle efferent outputs from the CNS: autonomic, somatic + neuroendocrine
- **Autonomic** is responsible for involuntary control, and accounts for the innervation of exocrine glands, smooth muscle, cardiac muscle, as well as being involved in metabolism + host defence.
- **Somatic** is the innervation of the muscle, including the diaphragm and respiratory muscles.
- **Neuroendocrine** system is responsible for growth, metabolism, reproduction, development, salt + water balance as well as host defence.

The basic branches of the ANS are the sympathetic + parasympathetic
- **sympathetic** = fight + flight
- **parasympathetic** = rest + digest

These states are either end of the spectrum, but generally speaking we exist somewhere in the middle of the spectrum with a balance between sympathetic and parasympathetic control, and these branches are usually found to antagonise one another.

Within the different body tissues (i.e. targets of the ANS), the innervation of sympathetic + parasympathetic is rarely equal and there tends to be dominance of one branch of the ANS. Examples include:
- **Lung tissue** – sympathetic NS in the lung causes dilation, whereas parasympathetic control causes constriction of the airways. Here the parasympathetic NS tends to dominate to maintain a partial constriction of the airways which allows for finer control.
- **The eye** – sympathetic NS tends to dilate the pupil, whereas the parasympathetic NS tends pupil constriction. Again parasympathetic dominance occurs to maintain partial constriction.

**NB:** innervations of smooth muscle tends to favour parasympathetic dominance to allow for finer control, i.e. if you have partial constriction you have the ability to constrict further but also dilate.
- **The heart** (NB: cardiac tissue is different than smooth muscle) – the sympathetic NS tends heart rate increase, and the parasympathetic tends heart rate decrease. Again parasympathetic dominance allows for more control of the heart rate.
- **Blood vessels** – the parasympathetic NS tends not to innervate blood vessels, therefore the sympathetic NS is completely dominant. However it needs to be able to both constrict + dilate the blood vessels. The balance of action on the blood vessels is thus dependent on the presence of receptors in the tissues, and varies depending on the location of blood vessels within the body.

**PRINCIPLE TARGETS + FUNCTIONS**
In most cases, the actions of the two branches of the ANS act to antagonise each other, but in some cases they have the same effect, e.g. in the salivary glands. However the difference here is that the two branches result in different types of secretions.

**ANATOMICAL STRUCTURE**
**General** features:
- 2 neurone set up; pre=ganglionic + post-ganglionic fibres
- Neurones innervate together in ganglion

**Parasympathetic** features:
- Cranial sacral outflow
- Long pre-ganglionic fibre
- Short post-ganglionic fibre
- Ganglia tend to lie within the innervated tissue
- Only neurotransmitter involved is Ach, therefore all cholinergic synapses
Sympathetic features:
- Thoracolumbar outflow
- Short pre-ganglionic fibre
- Long post-ganglionic fibre
- Ganglia form just outside spinal cord in the paravertebral chains
- Preganglionic fibres release Ach, but post-ganglionic fibres vary:
  - Postganglionic fibres to effector organs release noradrenaline
  - Some preganglionic fibres innervate the adrenal medulla, thus the gland acts as the ganglion releasing noradrenaline (+~20%NA + little dopamine) via the bloodstream to effector organs
  - Postganglionic innervation to sweat glands release Ach

NB: the enteric nervous system is the local nervous system of the digestive tract, consisting of the submucosal and myenteric plexus. The somatic nervous system consists of 1 long motor neurone with Ach release to skeletal muscle.

**CHOLINOCEPTORS + ADRENOCEPTORS**
Acetylcholine is a neurotransmitter which requires receptor binding in order to produce an effect, and is then broken down within ms by acetyl cholinesterases.

There are two types of Ach receptors:
- **Nictonic receptors** – membrane bound receptors present at autonomic ganglia
  - These are Type 1 ionotrophic receptors, thus produce rapid responses via ion channel opening
  - Stimulated by nicotine + acetylcholine
  - Blocked by hexamethonium
- **Muscarinic receptors** – tend to be found in the effector organs innervated by post-ganglionic parasympathetic fibres, thus mediating effector responses:
  - These are type 2 G-protein coupled receptors, thus require the generation of 2nd messenger molecules → slower responses
  - Stimulated by muscarine + acetylcholine
  - Blocked by atropine

There are 3 subtypes of muscarinic cholinceptors:
- M1 – found in neural tissues
- M2 – found in cardiac tissues
- M3 – found in exocrine + smooth muscle

There are also many subtypes of adrenoceptors. These are found at all effector organs innervated by post-ganglionic sympathetic fibres. These mediate the effects of NA on the sympathetic effector organs (+ circulating in the bloodstream)

The subtypes include:
- Alpha 1
- Alpha 2
- Beta 1
- Beta 2

Summary of receptor locations within the ANS:
- Nictonic cholinceptors are found at all pre-ganglionic nerve terminals
- Muscarinic cholinceptors are found at all parasympathetic post-ganglionic nerve terminals + sympathetic port-ganglionic fibres innervating sweat glands
- Adrenoceptors are found at sympathetic post-ganglionic nerve terminals in their effector organs

NB: Drugs may interact with nictonic, muscarinic or adrenergic receptors; resulting in different effects
BIOSYNTHESIS + METABOLISM OF THE AMINE NEUROTRANSMITTERS

All amine transmitter synthesis follows a similar set of stages:

1. Precursor is taken up into pre-synaptic nerve terminal
2. Precursor is enzymatically converted into the active transmitter, and then packaged into vesicles
3. Following pre-synaptic nerve terminal depolarisation (with associated increased intracellular Ca2+), the vesicles fuse and release the transmitter into the synapse
4. The transmitter then binds with the receptor on the effector cell, is broken down and its degradation products are taken back up into the nerve terminal.

Acetyl choline synthesis follows this norm...

- Precursor = acetyl CoA + choline
- Enzymatic conversion = choline acetyl transferase
- Enzymatic degradation = acetylcholine esterase (with choline + acetate released as the degradation products)

Noradrenaline synthesis is slightly more complex...

- Precursor is tyrosine
- Tyrosine is then hydroxylased into DOPA by tyrosine hydroxylase
- DOPA is then decarboxylated to form Dopamine, which is then packaged into vesicles
- Within the vesicle, dopamine is hydroxylased to form noradrenaline by dopamine beta hydroxylase
- NA is then released from the vesicle like normal...
- There are 2 uptake systems for NA tissue reuptake:
  - Uptake 1 – neural reuptake + degradation by MAO-A (monoamine oxidase A) to form secondary metabolites
  - Uptake 2 – extraneural uptake and degradation via COMT

NB: this is very important in pharmacodynamics

Generally speaking, drug targets are proteins, thus when considering a specific biosynthesis/metabolism system, you can determine what the possible enzyme/receptors could be targeted.
3. Mechanism of Drug Action
Dr MJ Croucher

**DRUG ANTAGONISM**

There are 4 main types of drug antagonists...

1) **Receptor blockade**

See notes from lecture 1 on competitive + irreversible antagonists.
NB: “use-dependency”: this refers to the fact that some irreversible antagonists act by blocking ion channels (e.g. hexamethonium – blocks v-gated Na+ channels on nictonic receptors), therefore the effect of the antagonist is seen more quickly on rapidly firing neurones. This provides a degree of variation between antagonist effect on different neurones; allows a degree of selectivity useful for local anaesthetic and the blocking of pain perception neurones.

2) **Physiological antagonism**

Here, drugs may act on different receptors in the same tissue to induce the opposite effect.
E.g. noradrenaline acts to induce vascular constriction → BP increase, whereas histamine acts on different receptors to induce vascular dilatation and BP decrease.

3) **Chemical antagonism**

This is a relatively rare event, whereby two drugs interact in solution.
For example, chelating agents e.g. dimercaprol, form complexes with heavy metals, allowing them to be more easily in urine.
This is very useful in treatment for heavy metal poisoning.

4) **Pharmacokinetic antagonism**

Here, the antagonists act to reduce the concentration of the active drug at the site of action.
The ways in which pharmacokinetic antagonism occurs include:
- Decrease absorption
- Increase metabolism
- Increase excretion

A good example of this is barbiturate interaction with warfarin...
- Barbiturates are very good enzyme inducers; this means that if they are administered repeatedly (e.g. for treatment of epilepsy), the metabolising system within the liver increases.
- This can pose a problem with co-administering another drug metabolised by the same enzymes, as in turn their activity will be reduced.
- E.g. in treatment of atrial fibrillation in an epileptic, warfarin dose must be monitored very carefully in order to ensure the warfarin dose is sufficient to achieve the required effect.
- NB: barbiturates also interact with other anti-convulsants + TCAs in this way.

**DRUG TOLERANCE**

“the gradual reduction in responsiveness to a particular drug, following repeated administration”
- Usually appears within days-weeks of administration.
E.g. benzodiazepines: anti-epilepsy drugs.
- These are very good for single seizure treatments, but if given as treatment for epilepsy over a long period; patients most often develop tolerance.

There are various factors which may influence drug tolerance...

1) **Pharmacokinetic factors** – increase the rate of metabolism of the drug, i.e. enzyme inducing
   E.g. barbiturates + alcohol
2) **Loss of receptors** – by membrane endocytosis, leading to receptor “down-regulation”
   
   E.g. beta-adrenoceptors

   NB: receptor *up-regulation* does not relate to drug tolerance. An example of receptor up-regulation is in burns patients.
   
   - Cholinergic innervation of skeletal muscle may be lost during burns, therefore the tissue responds by increasing the number of receptors on the membrane surface in order to compensate for the loss of innervation.
   - This is also known as deinnervation supersensitivity.

3) **Receptor desensitization** – the receptor remains on the cell surface, but undergoes a conformational change therefore can no longer bind with an effective response
   
   E.g. nicotinic acetyl CoA receptor at the neuromuscular junction

4) **Exhaustion of mediator stores** – with repeated stimulation of a system, any required mediator stores may be exhausted therefore reducing the tissue response
   
   E.g. amphetamines; central stimulant, which crosses the BBB + sits on the noradrenaline transporter
   
   - The amphetamine is then taken up into the neurone, causes a release NA from vesicles into the synaptic cleft
   - With repeated amphetamine administration, the NA neurones cannot synthesis the NA fast enough therefore vesicle stores deplete

5) **Physiological adaption** – this is a homeostatic response to the effect of a drug, in which the body tries to keeps effects within a set range.
   
   This is most important in tolerance to drug side effects, and is the mechanism by which adverse effects are often reduced.

NB: read this in conjunction with lecture 1 notes...they are related!!
4. Pharmacokinetics
Nigel J Gooderham

The journey of a drug...FOR ALL AMAZING DUCKS MAKE EGGS

**Formulate Administration Absorption Distribution Metabolism Excretion**

**FORMULATION:** the process of making a medicine containing a drug

- A single drug may be available in a number of different formulations that have been designed for use via different routes of administration, e.g. sterile solution for IV injection, or as an ointment

A medicine contains the drug in question + also include a number of other materials called excipients.

- These excipients may be added to aid the manufacture of the medicine, to improve its chemical/biological stability or to increase its acceptability to the patient by improving its flavour, fragrance, or appearance (e.g. sugar, chalk, lactose, talc, chalk, salts + alcohol)

In addition, several different formulations may have been designed for use with the same route of administration, e.g. liquids, syrups, tinctures, powders, soluble tablets, capsules + enteric-coated tablets all have been formulated for oral use.

**ADMINISTRATION:** drug actions may be systemic or local, and this is the primary consideration for administration.

Administration routes can be divided into enteral + parenteral routes

- **Enteral** routes include sublingual, buccal, oral + rectal.
  - These are easier, and patients can be relied on to self-administer.

- **Parenteral** routes include intravenous, intramuscular, subcutaneous, percutaneous + inhalation
  - These tend to be more invasive and often require administration by a medical professional (exceptions to this include asthmatics, diabetics etc)

The oral route is the most common + convenient:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permits self-medication</td>
<td>Inappropriate for drugs which:</td>
</tr>
<tr>
<td>Does not require rigorously sterile preparations</td>
<td>- Are labile in acid pH of stomach</td>
</tr>
<tr>
<td>Incidence of anaphylactic shock is lower (than IV)</td>
<td>- Undergo extensive “first pass” metabolism</td>
</tr>
<tr>
<td>Capacity to prevent complete absorption (vomiting)</td>
<td>Requires patient compliance</td>
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The intravenous route delivers the drug directly into the circulating blood:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>Slow injection necessary (to avoid toxic bolus)</td>
</tr>
<tr>
<td>Avoids poor absorption/destruction in the GI tract</td>
<td>Higher incidence of anaphylactic shock</td>
</tr>
<tr>
<td>Permits careful control of blood levels</td>
<td>Medical professional required (usually)</td>
</tr>
<tr>
<td></td>
<td>Complications possible (embolism, phlebitis, pain)</td>
</tr>
</tbody>
</table>

Inhalation is via the lungs and respiratory tract:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal for particles, gases, volatile liquids, aerosols</td>
<td>Possible localised effect within the lung (unless desired)</td>
</tr>
<tr>
<td>Enormous surface area of alveolar membranes available</td>
<td></td>
</tr>
<tr>
<td>Simple diffusion mechanism + phagocytosis</td>
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</table>
The **intramuscular route** delivers the drug into connective tissue as a reservoir in a muscle block:

<table>
<thead>
<tr>
<th>Advantages</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Relatively high blood flow, increased during exercise</td>
<td>Possible infection + nerve damage (especially in gluteal region)</td>
</tr>
<tr>
<td>Enables DEPOT THEORY (prolonged absorption from pellet, microcrystalline suspension or solution in oily vehicle)</td>
<td></td>
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The **subcutaneous route** delivers the drug into connective tissue spaces under the skin:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local administration, dissemination can be minimised for local effect</td>
<td>Pain, abscess, tissue necrosis</td>
</tr>
<tr>
<td>Enables DEPOT THEORY</td>
<td></td>
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</tbody>
</table>

The **percutaneous route** is across the skin:

<table>
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<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local application + action</td>
<td>Local irritation + skin reactions</td>
</tr>
<tr>
<td>Lipid soluble compounds diffuse readily</td>
<td>Alteration of skin structure (e.g. steroids)</td>
</tr>
</tbody>
</table>

**ABSORPTION**: drugs will either be water-soluble or lipid-soluble, but have to traverse both aqueous + lipid environments within the body, i.e. when crossing a membrane a drug must be soluble in the lipid bilayer, as well as in the aqueous phase of the membrane core. Transfer across membranes is achieved by different mechanisms of transport...

- Passive diffusion (most common, important in the absorption of water-soluble drugs)
- Facilitated diffusion
- Active transport (important in drug excretion)
- Pinocytosis
- Filtration
- Paracellular transport

**Lipid-soluble drugs**, e.g. anaesthetics, are usually small volatile molecules that can easily “dissolve” into membranes

**Water-soluble drugs** (most drugs) are usually weak acids or bases. They ionise within the physiological environment of the body. This poses a problem for absorption of the drug, as it is only the unionised form of the drug which is able to cross the lipid-layer of the cell membrane. Here we must consider the mechanism by which the passive diffusion of water-soluble drugs across membranes occurs – **PH PARTITION HYPOTHESIS**

- Theory proposed by Brodie; highlighting 3 important factors to consider when thinking about the process of absorption of a drug:
  - The lipid solubility of the unionised drug (constant specific to each drug)
  - The pKa of the drug (measure of acid dissociation constant of the drug, i.e. weakly acidic drugs = higher pKa > strongly acidic drugs)
  - The pH of the surrounding medium at the site of absorption (e.g. GI tract fluid, blood)
- Drugs are absorbed when in their unionised state, therefore rate of absorption is dependent on the amount of drug present in an unionised form.
- The pH partition hypothesis can be illustrated by considering a well-known drug, aspirin. **Aspirin** is a very useful anti-inflammatory + anti-pyretic drug, which is available in a number of dosage forms:
  - Aspirin tablets
  - Soluble aspirin
  - Enteric-coated aspirin (sugar + wax coated; coating remains intact in dilute acid but quickly dissolves in alkali)
Aspirin as a pKa of about 3.4 and the pH of the stomach is ~3, so it will not be ionised in the stomach and is preferentially absorbed. In contrast, the pH of the intestine is higher, therefore a smaller proportion of the aspirin exists in unionised form thus is absorbed more slowly. This information is useful when considering reason for aspirin use:

- When quick pain relief is needed, soluble aspirin will be rapidly absorbed in the stomach.
- For chronic intake (e.g. for arthritis), enteric-coated aspirin is appropriate as it will undergo slow absorption in the small intestine following the dissolving of the enteric coating in the basic pH of the intestine.

Only after a substance has entered the blood or lymph can it be said to be truly absorbed. The lymph (eventually) drains into the vascular system mainly via the thoracic duct. Once within the vascular system a drug can be distributed throughout the various tissues + body fluids.

**DISTRIBUTION:** there are main factors which influence drug distribution around the body...

Regional blood flow

- **Extracellular binding** – if the drug has an affinity to a particular protein, it may bind to the protein, thus existing in a non-active bound form. This prolongs the half-life of the drug.
- **Capillary permeability** – may vary between tissues. Tissues may also vary, i.e. the difference between some tissue + renal, hepatic, brain + placental tissue. This needs to be considered depending on the intended target tissue of the drug.
- **Localisation in tissues** – this sometimes occurs with drugs, and can be useful if a specific target tissue distribution is wanted, but can also pose a problem if the desired effect is more systemic.

**EXCRETION:** In the human body, there are 2 major routes of drug excretion...

- **Kidney** – this is ultimately responsible for the elimination of most drugs. In the glomerulus, drug-protein complexes are not filtered (unbound drugs are), active secretion of acids + bases then occurs in the proximal tubule with lipid-soluble drugs being reabsorbed in the distal tubules.
- **Liver** – some drugs are concentrated in the bile (usually large molecular weight conjugates), and then eliminated from the body via biliary excretion.
  - This involves active transport systems into the bile (involving bile acids + glucuronides)
  - **Enterohepatic cycling** is where the drug/metabolite is excreted into the gut (via biles), but then is reabsorbed and taken into the liver to be excreted again. This can lead to drug persistence.
- **Other routes** (usually of little quantitative importance) include the lungs, skin, GI secretions, saliva, sweat, breastmilk, genital secretions.

**PHARMACOKINETICS**

"the variation with time of drug concentration in the blood/plasma"

- Clinical analysis is used to derive mathematical parameters to describe the drug’s journey through the body; the half-life + thus the required dosage/dosing frequency
• Pharmacokinetic principles relate specifically to the variation with time of drug concentration and the rates of change.

Bioavailability: the proportion of the administered drug that is available within the body to exert its pharmacological effect
• It is the amount that enters the systemic circulation in an unchanged form after the administration of the product
• Clearly the concept of bioavailability is not confined to drugs, but can be applied to any chemical to which people are exposed
• It is important for a drug to be bioavailable so that the correct concentration can enter the systemic circulation and have its desired effect on the body. The measurement of bioavailability won’t always reflect the effectiveness of a drug though, as the target tissue may not be in the systemic circulation (e.g. topical agents + GI drugs)
• The bioavailabilities of different formulations are assessed by comparing the areas under the plasma level-time curves of the drug after:
  o IV administration of the drug (100% bioavailable)
  o Administration of an identical dose of the medicine by the intended route (e.g. oral)

In the case of oral administration, several factors may influence bioavailability:
• The physiochemical characteristics of the drug – ionisation in the gut will decrease bioavailability
• Gastrointestinal pH – the drug form may change depending on the acidic/alkaline environment (refer back to pH partition hypothesis for more detail)
• Whether or not the drug is passively or actively transported. If the drug is actively transported, it will be absorbed in any form (whereas passive requires unionised + is the usual route)
• Gastrointestinal motility can decrease transit time which reduces absorption
• Particle size of the drug – smaller = absorbed better
• Physicochemical interaction between drug + gut contents (e.g. the chemical interaction between calcium + tetracycline antibiotics – degradation and binding/precipitate formation interfere with absorption

Bioequivalence
• Once the patent on a new drug has expired, it is possible for any drug company to manufacture + market the drug
• This often means that cheaper examples (generic) of the same drug can be made, in which the formulation is slightly different.
• Thus regulatory authorities lay importance on evidence of bioequivalence, which is evidence that the generic product behaves sufficiently similar to the existing one to be substituted for it without causing clinical problems
• This is particularly important when a drug has a narrow therapeutic index/therapeutic window, as too much of the drug will be toxic, while too little will be ineffective. This applies to drugs like Digoxin, Warfarin, Lithium + cytotoxic drugs

Presystemic metabolism/first pass metabolism
• Bioavailability can also be influences by the biology of the human gut. The drug can be metabolised to inactive products by microbes within the gut lumen, enzymes present in the gut wall + enzymes in the liver
• The bioavailability is thus altered since the newly absorbed drug does not gain access to the general circulation until it has existed in the liver (via the hepatic portal vein)
• A drug which undergoes 100% metabolism could be therapeutically useful if the target is the gut, or if the prodrugs + active metabolites are being used
• Good bioavailability can be achieved for drugs that undergo extensive first pass metabolism by using other routes than oral.

NB: various illnesses could also affect the bioavailability of drugs, such as diseases of the gut wall, liver diseases, inherited disorders and blood flow disorders.
Apparent volume of distribution: the volume in which a drug appears to be distributed
  • This is an indicator of the pattern of distribution

Biological half-life: the time taken for the concentration of drug (in blood/plasma) to fall to half its original value
  • This is important when considering dosing frequency

Clearance: the volume of blood/plasma from which a drug is completely removed in a unit time
  • This is related to the volume of distribution + rate at which the drug is eliminated
  • If clearance involves several processes, then total clearance is the sum of these processes.
  • Effectively clearance determines the speed at which the active drug is removed from the body
Xenobiotics are usually lipophilic molecules. Their metabolism tends to reduce or eliminate pharmacological/toxicological activity, as it converts lipophilic chemicals to polar derivatives which are readily excreted.

The liver is the major organ of drug metabolism. Hepatic “first pass” metabolism can be extensive.

- This is the phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation
- It is the fraction of lost drug during the process of absorption which is greatly related to the liver (hepatic) + gut wall (stomach + small intestine = pre-hepatic)

NB: Metabolism can also occur in other organs (e.g. gut, kidneys, skin, brain etc)

There are 3 types of metabolic change:
In phase I reactions...
- Oxidation/reduction creates new functional groups
- Hydrolysis unMASKS new functional groups

Examples of oxidation reactions include cytochrome P450 mediated oxidation, oxidation by CYP, aliphatic oxidation, aromatic oxidation, N-demethylation, O-demethylation, N-oxidation, and alcohol oxidation. Other examples of phase I reactions are reduction and hydrolysis.

Phase I reactions prepare a drug for Phase II metabolism by introducing a functional group such as -OH, -NH2, -SH or -COOH.

- These reactions often generate a biologically inactive product (exception = prodrug: administered drug dependent on metabolism by the body in order to form the active drug. This can be a solution to protect the drug from 1st pass metabolism).
- They have little effect on drug polarity, and sometimes produce toxic metabolites.

In phase II reactions...

Phase II reactions are discrete reactions which have specific enzymes for each reaction. They include:
- **Glucuronidation** (glucuronyl transferase)
- Methylation (methyl transferase)
- Sulphation (sulphotransferase)
- Acetylation (acetyl transferase)
- Amino acid conjugation (acyl transferase)
- Conjugation with glutathione (glutathione-S-transferase)

Phase II reactions are conjugation reactions which utilise OH, NH2, SH, and COOH. They involve a high energy intermediate/conjugating agent such as UDPGA for glucuronidation or PAPS for sulphation
The importance of drug metabolism:

- The biological half-life of the chemical is decreased
- The duration of exposure is reduced
- Accumulation of the compound in the body is avoided and potency of the biological activity of the chemical can be altered
- The pharmacology/toxicology of the drug can be governed by its metabolism
6. Cholinomimetics
Dr Martin Croucher

“Cholinomimetic drugs mimic activation of the parasympathetic nervous system”

Muscarinic effects are those that can be replicated by muscarine, and abolished by low doses of the antagonist atropine

- Actions correspond to those of parasympathetic stimulation
- After atropine blockade of muscarinic actions larger dose of acetylcholine can induce effects similar to those caused by nicotine.

There are 3 main muscarinic receptor subtypes:
- M1: salivary glands, stomach, CNS
- M2: heart
- M3: salivary glands, bronchial/visceral smooth muscle, sweat glands, eye
- M4/M5: CNS

All of these are type 2 G-protein coupled receptors; with 7 transmembrane segments, and cytoplasmic loops with associated G-protein subunits.

- M1, M3 and M5 receptors are G-protein coupled to IP3 and DAG second messengers. M2 and M4 are G-protein coupled to cAMP second messengers.
- Receptors are generally excitatory, apart from M2 on the heart which is inhibitory; responsible for a decrease in heart rate

Nicotinic receptors are ligand-gated ion channels, with 5 subunits (α, β, γ, δ, ε).

- The subunit combination determines the ligand binding properties of the receptor. For example...
  - A muscle type has the combination 2α β δ ε
  - a ganglion type receptor has 2α 3β

NB: The effects of Ach are relatively weak on nicotinic receptors

Muscarinic cholinergic target systems
Eye:
Consider parasympathetic innervation/activity:

- Contraction of the ciliary muscle as seen in accommodation for near vision
- Contraction of sphincter pupillae (circular muscle of the iris) to constrict the pupil (miosis) and improve drainage of intraocular fluid
- Lacrimation (tears)

In glaucoma, and increased intraocular pressure is produced by a decreased drainage of aqueous humour via the canals of Schlemm anterior to the iris. Treatment involves stimulating the smooth muscle in the iris by a muscarinic
agent, causing contraction of the sphincter pupillae which opens the pathway for drainage therefore reducing the pressure.

Heart:
- ACh effects on M2 acetylcholine receptors in atria and nodes decreases cAMP and consequently decreases Ca2+ entry and increases K+ efflux, which leads to decreased cardiac output and decreased heart rate.
- Also known as having a negative ionotrophic + chronotrophic effect

Vasculature:
- Most blood vessels do not have parasympathetic innervation, but rather M3 acetylcholine receptors on vascular endothelial cells
- Acetylcholine then acts to stimulate NO release; induces vascular smooth muscle relaxation
- Overall effect is to reduce total peripheral resistance.
- Muscarinic agonists can thus be used as a possible treatment for hypertension

Summary – the Cardiovascular System:
Effects of parasympathetic activity include...
- Decreased heart rate (bradycardia)
- Decreased cardiac output (due to decreased atrial contraction)
- Vasodilation (due to stimulation of NO production)
All of these combined can lead to a sharp drop in blood pressure.

Non-vascular smooth muscle:
Smooth muscle that does have a parasympathetic innervation responds in the opposite way to vascular muscle, i.e. it contracts
- Lungs; bronchoconstriction
- Gut; increased peristalsis + gut motility
- Bladder; promotes bladder emptying

Exocrine glands:
- Salivation
- Increased bronchial secretions
- Increased gastro-intestinal secretions (including gastric HCl production)
- Increased sweating (SNS-mediated)

So in summary, muscarinic effects on the body include...
- Decreased heart rate
- Decreased blood pressure
- Increased sweating
- Difficulty breathing
- Bladder contraction
- Gastrointestinal pain

CHOLINOMIMETIC DRUGS

There are two classes of cholinomimetic drugs: directly acting and indirectly acting cholinomimetics...

Directly acting
These include choline esters and alkaloids:
- Acetylcholine (a choline ester) is of no therapeutic use because it does not differentiate between nicotinic and muscarinic receptors and it is rapidly degraded.
- Nicotine (alkaloid) stimulates all autonomic ganglia and thus increases both sympathetic and parasympathetic activity. It is not used clinically but is an important component of cigarette smoke.
These include physostigmine and neostigmine.

Clinically relevant examples include bethanechol and pilocarpine.

Pilocarpine is an alkaloid derived from leaves of the South American shrub Pilocarpus.

- It is a partial agonist for many muscarinic responses with a half-life of about 3 to 4 hours
- It is less effective on GI smooth muscle and the heart, but is particularly useful in ophthalmology as a local treatment for glaucoma; given as eyedrops with a high lipid solubility therefore diffuse easily across the cornea + stimulate circular muscle to open, draining the fluid.
- Side effects of this can be predicted from the action of muscarinic receptors, and include blurred vision, sweating, GI disturbance + pain, hypotension and respiratory diseases

Bethanechol is a choline ester, similar in structure to acetylcholine but with the addition of a methyl group which makes it resistant to degradation (i.e. longer lasting)

- It is an M3 Acetylcholine receptor agonist
- It is orally active with limited access to the brain and a half-life of about 3 to 4 hours
- It is used to assist bladder emptying or to enhance gastric motility
- Side effects include sweating, impaired vision, nausea, bradycardia, hypotension and respiratory difficulty

Directly acting

These increase the effect of normal parasympathetic nerve stimulation by inhibiting the action of acetylcholinesterase and thus preventing the breakdown of acetylcholine. They therefore have the potential to increase cholinergic activity in ALL cholinergic synapses. There are two types of anticholinesterases:

- **Reversible** anticholinesterases include physostigmine, neostigmine and donepezil
- **Irreversible** anticholinesterases include ecohthipate, dyflos and sarin

The effect of cholinesterase inhibitors/anticholinesterases include:

- **Enhanced muscarinic activity (at low dose)**
- Further enhancement of muscarinic activity with increased transmission at all autonomic ganglia (at moderate dose)
- A high dose can be toxic, showing a depolarising block at all autonomic ganglia (thus inhibiting any neural activity by preventing further depolarisation)

**Cholinesterase enzymes** metabolise acetylcholine to choline and acetate. There are two types of cholinesterases which differ in distribution, substrate specificity and function:

- **Acetylcholinesterase** (AChE) – also known as true or specific cholinesterase; found I all cholinergic synapses (both central and peripheral)
  - It has a very rapid action (hydrolysis occurs at over 10,000 reactions/second)
  - It is highly specific for acetylcholine
- **Butryrylcholinesterase** (BChE) – also known as pseudocholinesterase; not found in cholinergic synapses, but rather in plasma and most tissues (e.g. liver, skin)
  - Has broader substrate specificity than AChE and hydrolysis other esters such as suxamethonium (skeletal muscle relaxant)
  - It is the principle reason for low plasma acetylcholine
  - It shows genetic variation which influences the duration of action of the drugs it normally metabolises

NB: the most clinically important anticholinesterase drugs will block both enzymes about equally.

**Reversible anticholinesterase drugs**

These include physostigmine and neostigmine (alkaloid carbamyl esters)

- These drugs compete with acetylcholine for the active site on the anticholinesterase enzyme, and donate a carbamyl group to the enzyme, blocking the active site and preventing acetylcholine from binding.

- **Muscarine** (alkaloid) is selective for muscarinic receptors; it is not used clinically but is the cause of mushroom poisoning.
• The carbamyl group is then removed by slow hydrolysis (takes minutes rather than milliseconds). This increases the duration of acetylcholine activity in the synapse.

**Physostigmine** is a naturally occurring tertiary amine from Calabar beans. It primarily acts at the postganglionic parasympathetic synapse, with a half-life of about 30 minutes. It is used in the treatment of glaucoma; aids intraocular fluid drainage + to treat atropine poisoning, particularly in children

**Irreversible anticholinesterase drugs**
These include organophosphate compounds such as ecothiopate, dyflos, parathion + sarin
- They rapidly react with the enzyme active site, leaving a large blocking group which is stable and resistant to hydrolysis.
- Recovery of the cholinesterase active site thus requires production of new enzymes, which takes days to weeks
- Only ecothiopate is in clinical use, but the others are commonly used as insecticides + nerve gas

**Ecothiopate** is a potent inhibitor of acetylcholinesterase. Following its administration, reactivation of the cholinesterase enzymes occurs by slow hydrolysis (taking several days)
- It is used as eye drops in the treatment of glaucoma, acting to increase intraocular fluid drainage with a prolonged duration of action
- Its systemic side effects include sweating, blurred vision, GI pain, bradycardia, hypotension and respiratory difficulty.

**Anticholinesterase drugs + the CNS**
Only non-polar organophosphates (e.g. physostigmine) can cross the blood brain barrier. At low doses, this results in excitation with possibility of convulsions, but at high doses this can result in unconsciousness, respiratory depression + death
- **Donepezil** and **tacrine** are examples of drugs used for treatment of the CNS; used as an Alzheimer's treatment as Ach is important in learning in memory
  - The effect of the drugs is to potentiate central cholinergic transmission, relieving the Alzheimer's symptoms. However they have no effect on degeneration.

**Organophosphate poisoning**
Accidental exposure to organophosphates e.g. DYFLOS (used in insecticides, or deliberate use as nerve agents) can cause severe toxicity. They are highly lipid soluble and are readily absorbed through the nasal mucosa, skin, lungs etc. poisoning may easily occur if adequate precautions (e.g. protective clothing) are not taken.
- Poisoning is seen by an increased muscarinic activity, CNS excitation and a resulting depolarising neuromuscular block
- Treatment is **atropine**, artificial respiration and **pralidoxime**. Atropine targets the muscarinic receptors on effector organs, whereas pralidoxime is non-selective in the Ach receptors it targets.
- The phosphorylated enzymes then “age” within a few hours

**SUMMARY**
- Two main classes of cholinomimetics – direct agonists and indirect inhibitors of cholinesterase enzymes
- Clinically relevant cholinomimetics act at muscarinic receptors
- Cholinomimetics decrease heart rate and cardiac output, increase exocrine gland activity, increase non-vascular smooth muscle contractility and cause miosis
- High doses of cholinomimetics not only activate the parasympathetic nervous system, but can activate the sympathetic nervous system and cause depolarising NM blockade
INTRODUCTION
Definitions
There are two important concepts when considering receptors: affinity and efficacy...

• The strength with which an agonist binds to a receptor refers to its affinity.
• Once the drug has bound the receptor, the ability to transduce a response and activate intracellular signalling pathways refers to efficacy
• Agonists show affinity and efficacy (binding + response)
• Antagonists show affinity with NO efficacy (binding + NO response)

In any tissue, there are thousands of receptor molecules and agonist molecules. If an agonist binds to a receptor, it binds for mere milliseconds to produce a response and then unbinds. This process is continuous until it is cleared from the synapse by enzymes etc.

• A competitive antagonist acts in a similar way except it does not induce a response.
  Increasing the concentration of the antagonist means that the likelihood of the antagonist binding to a receptor (as opposed to agonist binding) increases

Cholinoceptors
There are two groups of cholinoceptors (Ach receptors): nicotinic and muscarinic...

• Nicotinic receptors are present at ALL autonomic ganglia, therefore a drug interfering with nicotinic cholinoceptors has the ability to interfere with the whole of the autonomic nervous system
• Muscarinic receptors are present within the effector organs of the parasympathetic nervous system, as well as the sweat gland innervated by the sympathetic nervous system. This means that the effect of a drug interfering with muscarinic receptors will be much more specific

NICOTNIC RECEPTOR ANTAGONISTS
There are a few types of nicotinic receptor antagonists, but the clinically useful ones are ganglion blocking drugs which in fact are not technically receptor antagonists.

• There are two ways that you can interfere with an ion-channel linked receptor; blocking the receptor or blocking the ion channel itself. Ganglion blocking drugs block the ion channel, thus preventing ions from moving through the channel pore.
• Ganglion blocking drugs interfere with both parasympathetic and sympathetic action, with widespread effects.

Clinically useful examples include Hexamethonium and Trimetaphan (hexamethonium has historical relevance but is no longer in clinical use)

“Use-dependent block” is a term that refers to the fact that these drugs work most effectively when the ion channels are open. Therefore, the more agonist present at the receptor, the more opportunity for the antagonist to block the channel, thus the more useful and effective these drugs can be.

• This is because if there is more agonist, more ion channels are open and so more can be blocked
• These drugs only result in incomplete block, i.e. there do not completely switch off function but slow it down and so reduce it considerably.
Drug Action
These drugs have the capacity to interfere with the entire autonomic nervous system. The effects that these drugs have on the body are **tissue specific**, as it depends which branch of the autonomic nervous system **predominates** in a particular tissue.

- If the sympathetic predominates, then those effects will be lost
- If the parasympathetic predominates, then those effects will be lost by the use of these drugs

**Sympathetically dominated** tissues include the **kidneys** (increase renin secretion, sodium + water retention) and **blood vessels** (particularly vasoconstriction in the gut)

- Administering a nicotinic cholinoreceptor antagonist therefore shows a **hypotensive effect**. Blood pressure falls because these sympathetically driven responses in the kidneys and blood vessels to increase blood pressure are reduced

**Parasympathetically dominated** tissues are more common, and include the following...

- In the **eyes**, parasympathetic action acts to maintain a level of partial pupil constriction at rest. This allows them to dilate or constrict further when necessary. Administering ganglion blocking drugs will thus cause the pupils to dilate
- In the **lungs**, the parasympathetic system is also the predominating effect in a similar way to the eye, relating to smooth muscle control. The bronchioles are always partially constricted under parasympathetic control so that further dilation or constriction can occur when required. These drugs then tend to cause bronchodilation when the parasympathetic effect is lost.
- The same effect is seen in the **bladder, ureters and GI tract**. The drugs can therefore cause bladder dysfunction, loss of GI motility, tone and secretions
- **Exocrine secretions** are reduced overall, e.g. saliva, sweating, GI secretions are all reduced

Hexamethonium is historically important, as it was the **first anti-hypertensive** we had. It has a very **generalised action**, therefore the **side-effect profile** was very large, e.g. loss of bladder control, pupil dilation and loss of GI motility. It was therefore superseded by more selective agents.

Trimetaphan is currently the only ganglion blocking drug we have, but it is not used very often as it is **very potent**. It is used during surgery when a controlled hypotension is needed, but is a very **short acting** drug so the effects are lost quickly.

Receptor blockade antagonists interfere with the receptor, not the channel (unlike ganglion blocking drugs). These are found widely in the world of **toxins** and **venoms**. In contrast to most therapeutic drugs, these tend to be **irreversible** (they bind covalently and therefore prevent the ion channels from opening > **total loss of autonomic function**). An example of this is **alpha-bungarotoxin** (common krait snake venom), which targets the skeletal muscle of the somatic nervous system causing paralysis of the skeletal muscle and diaphragm > suffocation and death.

**MUSCARINIC RECEPTOR ANTAGONISTS**
Muscarinic receptor antagonists are therapeutically more useful, as they are more specific; only targeting parasympathetic effector organs and sweat glands. Examples include the plant-derived...
Muscarinic receptor antagonists of similar chemical structure; atropine and hyoscine. Atropine is from Deadly Nightshade, and atropine poisoning is sometimes seen in children if they eat the berries.

Muscarinic receptor antagonists will affect the parasympathetic nervous system, with the exception of sweat glands. In short they will affect pupil constriction, bronchoconstriction, bladder function, salivary production, sweating, heart parasympathetic inflow and also gut secretions.

In the CNS, the parasympathetic nervous system is very important in terms of attention, memory, and also certain sleep pathways. Atropine and Hyoscine have effects on the CNS, particularly binding to M1 and M5 receptors that are important in the brain; however we do not yet know how these drugs have their effects.

- Atropine and Hyoscine have different effects, only in low doses. In low doses Atropine causes mild restlessness or agitation, whereas Hyoscine is quite a good sedative.
- At higher doses both drugs cause CNS agitation.

**Uses and Examples**

Tropicamide is a muscarinic receptor antagonist, which acts on receptors within the iris of the eye to cause pupil dilation. This is used in eye exams in order to examine the retina (see eye practical)

Muscarinic receptor antagonists are also very good for anaesthetic premedication. Particularly in certain types of surgery where intubation is required, these drugs will cause the airways to dilate (useful when administering a gas mask). They also dry the throat a bit, which reduces the risk of aspiration, as well as slightly increasing heart

- They also will reduce secretions in the lungs, which is very important as inhaling secretions can lead to things like pneumonia. They will also reduce secretions in the mouth such as saliva.
- A muscarinic receptor antagonist removes the effect of parasympathetic effects on the heart, i.e. slowing heart rate and reducing contractility. Anaesthetic reduces rate and contractility anyways, so it is helpful to remove the parasympathetic influence to avoid doubling the effect of slowing down the heart.
- If the right drug is chosen, something like Hyoscine has sedative effects too, which is useful in anaesthetic premedication.

Another use for Hyoscine is neurological, for example using a Hyoscine patch in motion sickness.

- Muscarinic receptors are very important in relaying information from the labyrinth of the inner ear to the vomiting centres.
- A lot of motion sickness is mediated by the labyrinth of the inner ear, and a lot of people are very sensitive to changes in posture and position.
- Muscarinic receptor antagonists reduce the flow of information from the labyrinth (periphery) to the brain (CNS), thus reducing this nausea.

Muscarinic receptor antagonists can be used in treating Parkinson's disease, although they are not first line treatment.

- In the brain, nigrostrial dopamine neurons are very important in fine control of movement. These neurons are lost in Parkinson's disease, and consequently the obvious signs of Parkinson's disease start to show
- Muscarinic receptors actually have a negative effect on dopamine signalling from these neurons. In a healthy individual this is just another level of control within the system. In someone with Parkinson's disease, they have lost 60-70% of the dopamine producing neurones, so the negative effect of the muscarinic receptors is unwanted.
- It's important that the last few remaining dopamine neurons can function normally, so the antagonists take out the M4 receptors and consequently the inhibitory effect is lost and the last few D1 dopamine neurons can fire at a maximum rate.
There are muscarinic receptor antagonists that are used in treating asthma and COPD. For example, Ipratropium Bromide is the drug important within the lungs.

- The difference between Ipratropium Bromide and Atropine is a large quaternary amine structure - this localises the response.
- It is administered as an aerosol, but as it is positively charged it doesn’t get out of the lungs very well (doesn’t cross lipid membrane), so it is held localised within the lungs. The drug removes the effect of bronchoconstriction, and this helps in obstructive airway diseases.

Muscarinic receptor antagonists can also be used in Irritable Bowel Syndrome.

- Knocking out parasympathetic effects within the gut reduces smooth muscle contraction, gut motility and gut secretions. This relieves some of the symptoms of irritable bowel syndrome.

There are of course unwanted side effects of muscarinic receptor antagonists. This can be remembered by:

- **Hot as hell** (decreased sweating interferes with thermoregulation)
- **Dry as a bone** (reduced secretions everywhere)
- **Blind as a bat** (due to effects on accommodation ability of ciliary muscle - cyclopegia)
- **Mad as a hatter** (high dose effect CNS agitation, restlessness, confusion, etc)

There is also the chance of poisoning, which is predominantly seen in young children.

- This is treated with an anti-cholinesterase such as Physostigmine.
- A massive amount of Atropine overloads the system and all ACh receptors are blocked.
- An anti-cholinesterase will prevent ACh breakdown in the synapse, so ACh levels will start to out-compete the Atropine. Slowly over time the body will clear the Atropine from the body.

Botulinum Toxin comes from a bacteria *Clostridium Botulinum*, and is generally regarded as the most deadly and potent toxin in the world.

- If it could be aerosolised, enough to cover a 2p coin could wipe out the whole of London! The reason it is so toxic is that it interferes with exocytosis (ACh release from the nerve terminals).
- It binds to the **SNARE complex**, which would usually allow vesicles to fuse with the membrane and release ACh.
- Botulinum Toxin prevents this and so vesicles remain in the nerve. It is estimated that you only need 2 or 3 Botulinum molecules per nerve to knock out the entire system.
- is, however, used clinically as **Botox**. It is injected usually in the face to remove wrinkles. This goes back to the effect of ACh on skeletal muscle, as Botox locally paralyses the skeletal muscle.
Adrenoceptors are receptors for the natural endogenous ligands of adrenaline and noradrenaline.

- The sympathetic chains of the spinal cord send short pre-ganglionic neurones to the ganglia that release Ach into nicotinic receptors to activate the post-ganglionic neurones, which then release noradrenaline at the nerve terminals onto adrenoceptors on effector organs such as the heart, gut, eyes, lungs, etc.

There are 4 main types of adrenoceptor: \( \alpha_1 \), \( \alpha_2 \), \( \beta_1 \) and \( \beta_2 \). The \( \beta \) receptors have greater selectivity for adrenaline, and \( \alpha \) receptors have greater selectivity for noradrenaline. All adrenoceptors can be activated by noradrenaline and adrenaline.

- All adrenoceptors are G-protein coupled, also known as “7-transmembrane type receptors” because of their structure.
- The \( \alpha_1 \) receptors act through the phospholipase C system; triggering reactions to increase inositol triphosphate and diacylglycerol in the cell (IP3 + DAG)
- The \( \alpha_2 \) receptors act to decrease cyclic AMP via the adenyl cyclase system
- Both \( \beta \) receptors result in an increase in cyclic AMP via the adenyl cyclase system

There is a specialised arm of the sympathetic nervous system where the pre-ganglionic fibres synapse in the adrenal medulla.

- The adrenal medulla has chromaffin cells, which release adrenaline and noradrenaline directly into the bloodstream.
- Circulating adrenaline and noradrenaline then act systemically

Another specialised part of the sympathetic nervous system is the sweat glands – here the post-synaptic neurones release Ach onto muscarinic receptors.

**DIRECTLY ACTING SYMPATHOMIMETICS**

**Directly acting sympathomimetics** mimic the actions of noradrenaline/adrenaline by binding to and stimulating adrenoceptors. They are used principally for their actions in the CVS, eyes and lungs.
**Noradrenergic Nerve terminals**  
Review of synthesis, release, reuptake and metabolism of noradrenaline.  
- Tyrosine is taken up into the nerve terminal and is converted into DOPA under the action of **tyrosine hydroxylase**.  
- DOPA is converted into dopamine by **DOPA decarboxylase**  
- Dopamine enters vesicles where it is converted to noradrenaline under the action of dopamine  
- β-hydroxylase.  
- When the nerve-terminal is depolarised, noradrenaline is then released into the synaptic cleft  
Noradrenaline binds to α1 and β adrenoceptors in the tissues, and this is then inactivated by uptake mechanisms.  
- Uptake 1 is present in the **pre-synaptic** nerve terminal, which leads to metabolism by monoamine oxidase (MAO) enzymes present in mitochondria  
- Uptake 2 occurs in the **extra-neuronal** tissue, leading to degradation by COMT enzymes  
**NB:** α2 receptors are located on the pre-synaptic terminal to inhibit more noradrenaline release. This is part of the limiting activity once the neurotransmitter is released to prevent over-stimulation. They are pre-synaptic **autoinhibitory** receptors.  

Sympathomimetic drugs are used mainly for their actions on heart, blood vessels, eyes and lungs. Many are derivatives of the catecholamine **adrenaline** (epinephrine), a polar compound.

**Adrenaline**  
Adrenaline is **synthesised** from noreadrenaline in the pre-synaptic nerve terminal via the action of phenylethanolamine N-methyltransferase.  
- It is often called the emergency hormone of the fight or flight response  

**Use in Allergic reactions and anaphylactic shock:** can lead to hypotensive crisis and breathing difficulties unless treated quickly  
- During an anaphylactic reaction, a large amount of **histamine** is released from mast cells.  
- There are histamine receptors on **blood vessels**, which cause the vascular smooth muscle to relax > decrease in peripheral resistance > hypotension  
- Histamine receptors on the **bronchial smooth muscle of the lungs** cause bronchoconstriction > narrowing of airways > breathing difficulties  
- Adrenaline is used (IV and autoinjector delivery systems = EpiPen) to reverse severe and potentially life-threatening hypotension and bronchoconstriction  
Adrenaline has **actions on α1 receptors in blood vessels and also on the β2 receptors.**  
- These receptors are not equally distributed throughout the vasculature; there are more β2 receptors in the blood vessels going to skeletal muscle. Adrenaline causes an increased blood flow to skeletal muscle by dilating the blood vessels. This in fact causes a further decrease in peripheral resistance and thus blood pressure.  
- However, there is a massive vasoconstriction caused by actions on the α1 receptors found in the skin, mucous membranes, spleen, gut, viscera, salivary glands, etc. This brings blood pressure back up again, overall the α1 effects win out.  
It also acts on the **β1 receptors on the heart**, particularly the SA node regulating pacemaker tissue  
- Adrenaline both increases the speed at which the heart beats and the force of contraction  
- Increased heart rate and contractility cause an increase in cardiac output which raises blood pressure further to treat the hypotensive crisis.  

β2 receptors are also present in the smooth muscle **present in the trachea and bronchi.**  
- Adrenaline acts to cause smooth muscle relaxation when acting on these receptors.  
- This opens up the airways so the constrictor mediators (eg histamine) can be opposed  
- Adrenaline also stops inflammatory mediators from being released in the airways  

**Use in treating COPD** (chronic bronchitis, emphysema and asthma emergencies)  
- The important factors here are the bronchodilator actions of the **β2 receptors** and the suppression of inflammatory mediator release.
Use in acute management of heart block: via IV administration. Heart block is a severe life-threatening condition in which the heart has failed for whatever reason

- Adrenaline increases peripheral resistance via α1 receptors and so increases return of blood to the heart
- It also increases heart rate (chronotropic) and force of contraction (inotropic) to increase cardiac output (β1 receptors on the heart).
- However, caution and regulation must be observed as over-stimulation of the heart is possible. This is either caused directly or by reflex tachycardia.

Use in anaesthesia:

- Can be used intravenously in spinal anaesthesia to maintain blood pressure
- Can also be used to prolong the duration of local anaesthesia via local administration. The vasoconstrictor effects of the adrenaline prolongs the duration of action by keeping the local anaesthetic where it has been injected for longer. This minimises doses as the site of action becomes more concentrated.

Use in glaucoma (eye drops).
Glaucoma is the 2nd leading cause of blindness worldwide, often caused by a raised intraocular pressure leading to damage of the optic nerve.

- Adrenaline may decrease the production of aqueous humour, which will decrease the intraocular pressure
- This is via an α1 mediated vasoconstriction, whereby the amount of blood supplied to the ciliary processes is decreased and so less aqueous humour can be produced

Unwanted effects of adrenaline are due to effects on:

- Secretions: reduced and thickened mucous > dry mouth
- CNS: minimal, as adrenaline doesn’t cross the BBB very well
- CVS effects:
  - Trachycardia, palpitations, arrhythmias
  - Cold extremeties (due to vasoconstriction), severe hypertension
  - Overdose may cause cerebral haemorrhage and pulmonary oedema from extreme hypertension
- GI tract: minimal effects but may slow gut movement
- Skeletal muscle: stimulation of the beta receptors may cause a tremor

Pharmacokinetics

- Administration of adrenaline varies depending on what it is being used for – intravenous, intramuscular, locally in eye drops or topically
- It is generally poorly absorbed orally, and is metabolised very quickly in the gut, liver and other tissues due to the presence of MAO and COMT throughout the body, so the duration of action is a matter of minutes

Phenylephrine is a drug that has a selective action on α1 adrenoceptors with relatively little action on the others. It is chemically related to adrenaline but is more resistant to COMT degeneration.
Its clinical uses include...
- It is a good vasoconstrictor, given intravenously or topical leg in anaphylactic shock or along with local anaesthesia
- It can also be used as a mydriatic in eye drops to dilate the pupils; this is useful for inspecting the eye prior to minor procedures. The radial muscles all have α1 adrenoceptors causing pupil dilation via constriction when stimulated.
- Also found in nasal decongestants; not to treat the cold or flu virus, but vasoconstrictor actions minimise plasma and dry-up secretions

Clonidine is a drug that is selective for α2 adrenoceptors, which are uniquely located pre-synaptically and act as autoinhibitory receptors to reduce the amount of noradrenaline released into the synaptic cleft
- One of the uses of clonidine is in the treatment of hypertension and migraine (oral or iv administration) as this reduces the amount of noradrenaline released in vascular smooth muscles > reduced sympathetic tone
- Sympathetic outflow can also be reduced via central action in the brainstem within the baroreceptor pathway

Isoprenaline is a drug that acts selectively on β adrenoceptors
It is based on the structure of adrenaline, but the slight difference means that it is less susceptible to metabolism by MAO than adrenaline > longer plasma half life (by ~ 2 hours)
Clinical uses include...
- It is used to treat heart block (cardiogenic shock, acute HF or MI) when given intravenously
- Was used to treat asthma due to actions on β2 adrenoceptors, but CV effects meant this often resulted in fatal reflex tachycardia or dysrhythmias therefore discontinued.

Dobutamine is a drug that is selective for β1 receptors and has very little β2 action and lacks isoprenaline’s reflex tachycardia effect, it is used to treat heart block.
- It is administered by intravenous infusion. It has a very short plasma half life of 2 minutes, and is rapidly metabolised by COMT.

Salbutamol is otherwise known as Ventolin, and acts selectively on β2 receptors
It is a synthetic catecholamine derivative with relative resistance to MAO and COMT therefore has a much longer duration of action
Its clinical uses include...
- Treatment of asthma (either oral or inhalation); causes the relaxation of bronchial smooth muscle and the inhibition of bronchoconstrictor mediator release from mast cells
- Treatment of threatened uncomplicated premature labour (iv administration)

Unwanted actions:
- Can have some reflex tachycardia, but not as severe as isoprenaline
- Some tremor due to B2 action
- Caution must also be taken with cardiac patients, patients with hyperthyroidism and diabetics (B2 receptors mobilise glycogen)

INDIRECTLY ACTING SYMPATHOMIMETICS
Indirectly acting sympathomimetics are drugs that act at the adrenergic nerve terminal as opposed to the adrenoceptors.

Cocaine
This acts to prevent Uptake 1 (no MAO metabolism) so there is more catcholamines at both the synaptic cleft of noradrenergic terminals but also dopaminergic terminals in the brain

Actions and unwanted actions:
- Key CNS effects are euphoria, excitement and increased motor activity. This may result in a psychological dependence syndrome (with depression, deterioration of motor performance and learned behaviours after withdrawal)
- **Unwanted** effects include activation of the vomiting centres, CNS depression of medullary centres, respiratory failure and death
- **CV effects** include tachycardia, vasoconstriction and raised blood pressure
- **Other** effects include experience of tremors and convulsions

**Pharmacokinetics**
- Cocaine is well **absorbed** from all sites, and readily crosses the BBB unlike adrenaline and NA
- It is **metabolised** by plasma esterases and hepatic enzymes, with a plasma half-life of about 30 minutes
- It is **excreted** in urine

**Tyramine** is a **dietary amino acid** found in foods such as cheese, red wine and soy sauce. Its **actions** include...
- Some weak **agonistic** activity in its own right at post-synaptic adrenoceptors
- **Competes with catecolamines for Uptake 1**, ie competes to be taken up into adrenergic nerve terminals
- **Displaces noradrenaline** from intracellular storage vesicles into cytosol
  - Noradrenaline and tyramine compete for sites on MAO, causing excess cytoplasmic noradrenaline to leak through the neuronal membrane and act on post-synaptic adrenoceptors

Under **normal conditions**, this is not a problem as tyramine undergoes extensive first pass metabolism, and has a short half-life thus does not pose as strong competition, and does not enter the CNS
- However **when MAO’s are inhibited** (eg when MAO inhibitors eg antidepressant drugs like phelazine are taken), ingestion of foods containing tyramine may cause a hypertensive crisis (competition with noradrenaline > excess NA action). This is known as the **“cheese-reaction”**
Types of Adrenoceptors

- $\alpha_1$ = vasoconstriction, relaxation of the GI tract
- $\alpha_2$ = inhibition of transmitter release, contraction of vascular smooth muscle, CNS actions
- $\beta_1$ = increased cardiac rate and force, relaxation of GI tract
- $\beta_2$ = bronchodilation, vasodilation, relaxation of visceral smooth muscle, hepatic glycogenolysis
- $\beta_3$ = lipolysis

Adrenoceptor antagonists

- Non-selective: ($\alpha_1+$ $\beta_1$) Labetalol
- $\alpha_1+$ $\alpha_2$: Phentolamine (non-selective alpha)
- $\alpha_1$: Prazosin
- $\beta_1$ + $\beta_2$: Propranolol (non-selective beta)
- $\beta_1$: Atenolol (also known as cardioselective)

SNS antagonists and false transmitters have many clinical uses, for example in hypertension, cardiac arrhythmias, angina, modifying plasma lipid levels and glaucoma.

**HYPERTENSION** is the sustained diastolic arterial pressure greater than 90mmHg.

- This is associated with an increased risk of other diseases, and the underlying cause is rarely diagnosed. Idiopathic hypertension is known as essential hypertension.
- The diastolic BP is the pressure the system is under at rest. This is not designed to survive at a higher pressure, therefore poses a risk.
- The main elements that contribute to hypertension include blood volume, cardiac output and peripheral vascular tone.
Blood vessels are solely supplied by the SNS in the periphery. This means that the tissue targets for antihypertensive drugs are:

- **Sympathetic nerves** (that release the vasoconstrictor noradrenaline)
- The **kidney** (which regulates blood volume via the renin-angiotensin-aldosterone system)
- The **heart** (which controls cardiac output)
- The **arterioles** (which determine peripheral vascular resistance)
- The **CNS** (Which determines blood pressure set point and regulates some systems involved in blood pressure control)

### B-ADRENOCEPTOR ANTAGONISTS

**β-blockers** can be classified as to whether they are non-selective (eg propranolol), cardioselective (eg atenolol) or whether they have some additional α1 antagonist activity. They work primarily by competitive antagonism of b1 adrenoceptors, although b2 antagonism may be important but this is not clear.

**Mode of action:**
- In the CNS to reduce sympathetic tone
- In the heart to reduce heart rate and cardiac output
- In the kidney to reduce renin production (principal effect)
- A common feature in their anti-hypertensive action is a reduction in peripheral resistance.

NB: they also have a pre-synaptic effect; presynaptic beta receptors have a positive effect on the synthesis and release of NA, therefore b1-antagonists block this presynaptic facilitation. This may contribute to the antihypertensive effect but its importance is not known.

**Unwanted effects** are due to the wide distribution of beta receptors within the SNS, and include:
- **Bronchoconstriction:** this is of little importance in the absence of airway disease, but in asthmatics or COPD patients, the bronchoconstriction caused by B-adrenoceptor antagonists may be life-threatening
- **Cardiac failure** is another unwanted effect. Patients with heart disease may rely on a degree of sympathetic drive to the heart to maintain an adequate cardiac output. Removal of this drive by b-receptor blockers will thus produce a degree of cardiac failure.
- **Hypoglycaemia:** the SNS responds to hypoglycaemia by producing symptoms that are useful in warning diabetic patients (eg sweating, palpitations, tremor) of the urgent need for carbohydrate. Use of β-antagonists are dangerous to such patients as it takes away this warning system. β1-selective agents may have advantages since glucose release from the liver is controlled by β2 receptors.
- **Fatigue** is due to the reduced cardiac output and muscle perfusion. Cold extremities are because of the loss of B-receptor mediated vasodilation in cutaneous vessels. Bad dreams may also be an unwanted effect due to effects on the CNS.

**Propranolol** is a non-selective B-blocker.
- In a subject at rest, it causes very little change in heart rate, cardiac output or arterial pressure. However it reduces the effect of exercise or stress in these variables
- Being non-selective, propranolol produces all of the typical adverse effects

**Atenolol** is a B1 selective drug, commonly known as cardioselective.
- It mainly antagonises the effects of noradrenaline on the heart, but will affect any tissue with B1 receptors
- It produces less effects on the airways that non-selective drugs, but is still not safe with asthmatic patients as some B2 blockad e does still occur

**Labetalol** is a dual acting B1 and a1 antagonist (with a ratio of B1:a1 of 4:1)
- This drug lowers blood pressure via a reduction in peripheral resistance
- No long-term change in heart rate or cardiac output seen, though decrease in TPR is significant
- This decrease in TPR is caused by decreased renin secretion and peripheral subcutaneous vasodilation
A-ADRENOCEPTOR ANTAGONISTS

**Non-selective antagonists** cause a rapid fall in arterial pressure, as alpha receptors are the main mediators of peripheral resistance.
- This is due to the subcutaneous vasodilation > increased blood flow through cutaneous and splanchnic vascular beds, with only slight effects on vascular smooth muscle
- A side-effect of this is a postural hypotension induced reflex tachycardia (B-receptors show reflex response to fall in arterial pressure)

**Phentolamine** was the **first non-selective alpha antagonist**
- Blockade of a1 receptors > vasodilation > fall in TPR + BP
- Blockade of a2 receptors > loss of inhibition of NA release from pre-synaptic nerve terminals > increased NA release > enhanced reflex tachycardia
- Other effects include increased GIT motility > diarrhoea
- No longer used clinically

**Prazosin** is a **selective a1 receptor antagonist**
- This produces vasodilation and a fall in arterial pressure, but less reflex tachycardia. However the hypotensive effect is dramatic
- This is due to the fact that there is no block of presynaptic a2 receptors therefore no change in synthesis and release of NA
- However cardiac output also decreases as dilation of the capacitance vessels > fall in venous pressure as well as arterial pressure
- Also has a modest effect on cholesterol metabolism > modest decrease in LDL and increase in HDL causing it to become more popular again as an antihypertensive

**Methyldopa** is a false transmitter, which can also be used as an antihypertensive agent.
- In the same way that DOPA is taken up into vesicles, methyldopa is taken up, decarboxylated and hydroxylated to form the false NT **alpha-methyl-norepinephrine**.
- This is released into the synaptic cleft, but not deaminated by MAO so tends to accumulate more than NA therefore displacing it from synaptic vesicles

**Mode of action** differs slightly to that of NA:
- **Less active on a1 receptors** therefore less effective in causing vasoconstriction
- **More active on presynaptic a2 receptors**, therefore auto-inhibitory feedback mechanism operates more strongly therefore reducing NT levels below normal

**NB:** also stimulates vasopressor centre in brainstem to inhibit sympathetic outflow
- **Indications for use:** Renal blood flow is well maintained with methyldopa, and so is widely used in hypertensive patients with **renal insufficiency or CVD**. It is also recommended in **hypertensive pregnant women**, as it has no adverse effects on the foetus despite crossing the placenta
- **Adverse effects** include dry mouth, sedation, orthostatic hypotension and male sexual dysfunction

**ARRHYTHMIAS**
The other clinical use of adrenoceptor antagonists is to control arrhythmias: **abnormal or irregular heartbeats**
- Arrhythmias pose a serious problem with exercise, or in people that have had myocardial infarction
- An increase in **sympathetic tone** can stimulate myocardial adrenoceptors and precipitate or aggravate arrhythmias. Particularly after myocardial infarction there is an increase in sympathetic tone.
- **AV conductance** also depends critically on sympathetic activity, and the refractory period of the AV node is increased by β-adrenoceptor antagonists, interfering with AV conduction in arterial tachycardias, to slow ventricular rate.
**Anti-arrhythmics**

There are 4 classes of anti-arrhythmics.
- Class II anti-arrhythmic drugs act to decrease sympathetic drive and increase the refractory period of AV conductance

**Propanolol** is a non-selective B-antagonist which also acts as a class II anti-arrhythmic (mainly due to B1 antagonism)
- The drug helps to reduce the mortality of patients with a myocardial infarction
- It is particularly useful in arrhythmias that occur during exercise or mental stress, where increased sympathetic drive acts to increase heart rate

**ANGINA**

This is a pain that occurs when oxygen supply to the myocardium is insufficient for its needs, ie during excitement or exertion.
- The pain is distributed across the chest, and radiates to the arm and neck

There are 3 types of angina:
- **Stable** angina = pain on exertion when there is an increased demand on the heart. This is due to a fixed narrowing of the coronary vessels eg atheroma
- **Unstable** angina = pain with increasingly less exertion, culminating with pain at rest. This could be due to a platelet-fibrin thrombus associated with a ruptured atheromatous plaque, but without complete occlusion of the vessel. This poses a serious risk for infarction.
- **Variable** angina = occurs at rest; caused by coronary artery spasm, associated with atheromatous disease

A patient with angina requires treatment that allows the heart to do the same job without causing the same increase in pressure and demand. **B-adrenoceptor antagonists** reduce myocardial oxygen demand by...
- Decreasing heart rate
- Decreasing systolic pressure
- Decreasing cardiac contractile activity

At **LOW** doses, **B1 selective agents** like Metoprolol reduce heart rate and myocardial contractile activity without affecting bronchial smooth muscle
- At **HIGH** doses, this selectivity is lost and activity resembles that of Propanolol

**Adverse effects** include: fatigue, insomnia, dizziness, sexual dysfunction, bronchospasm, bradycardia, heart block, hypotension and decreased myocardial contractility

**Contraindications**: bradycardia (<55bpm), broncospasm, hypotension, AV block, or severe congestive failure

**PLASMA LIPID LEVELS**

**A1-antagonists** are used to modify plasma levels of low density lipoprotein (LDL) cholesterol.
- Overall LDL cholesterol levels are reduced as well as very low density lipoproteins (VLDL) levels and **total triglyeride** levels
- There is also an increase in high density lipoprotein (HDL) cholesterol levels and this therefore reduces one of the risk factors associated with **coronary artery disease**

**GLAUCOMA**

This condition is characterised by an **increase in intraocular pressure**. It is usually caused by poor drainage of the aqueous humour. If untreated, it permanently damages the optic nerve, causing blindness.

**Aqueous humour** is produced by the blood vessels in the **ciliary body** via the actions of carbonic anhydrase.
- It flows into the posterior chamber through the pupil and into the anterior chamber
- It then drains into the trabecular network and into the veins and the canal of Schlemm
- The production of aqueous humour is indirectly related to blood pressure and blood flow in the ciliary body, ie increased blood flow eventually leads to increased production
Non-selective B-antagonists eg carteolol hydrochloride, levobunolol hydrochloride and timolol maleate reduce the rate of aqueous humour production by blocking receptors on the ciliary body. Selective B-antagonists like Betaxolol hydrochloride have also been shown to be effective.

NB: other uses of B-antagonists include controlling anxiety related symptoms, migraine prophylaxis and benign essential tremor.
10. Neuromuscular Blocking Drugs
Dr M Croucher

NEUROMUSCULAR TRANSMISSION
A neuromuscular junction is the synapse of the axon terminal of a motoneuron with a motor end plate, the highly excitable region of muscle fibre plasma membrane responsible for initiation of action potentials across the muscle’s surface, ultimately causing the muscle to contract. The neurotransmitter involved in neurotransmission at the NMJ is acetylcholine. The NMJ is the location where the neurone activates muscle to contract. This is a step in the excitation-contraction coupling of skeletal muscle:

1. **Action potential** arrives at pre-synaptic nerve terminal, and voltage sensitive calcium channels open. Calcium ions flow from the extracellular fluid into the pre-synaptic terminal cytosol.
2. The **influx of calcium ions** causes the neurotransmitter-containing vesicles to fuse with the nerve terminal cell membrane through SNARE proteins.
3. Fusion results in the emptying of the acetylcholine into the synaptic cleft (exocytosis).
4. **Acetylcholine** diffuses into the synapse and binds to the nicotinic acetylcholine receptors bound to the motor end plate.
5. These receptors are **ligand-gated ion channels** (nAChR) and when they bind acetylcholine, they open, allowing **sodium ions to flow in** and **potassium ions to flow out** of the muscle’s cytosol.
6. Because of the differences in electrochemical gradients across the plasma membrane, more sodium moves in than potassium moves out, producing a local **depolarisation** of the motor end plate known as **end-plate potential** (EPP).
7. This depolarisation spreads across the surface of the muscle fibre and continues the excitation-contraction coupling to contract the muscle.
8. The action of acetylcholine is terminated with the enzyme **acetylcholinesterase** degrades part of the neurotransmitter and the rest of it diffuses away.
9. The choline produced by the action of acetylcholinesterase is recycled - it is transported, through **reuptake**, back into the pre-synaptic terminal, where it is used to synthesise new ACh molecules.
The **nicotinic acetyl-choline receptor** is made up of 5 sub-units.
- These are all arranged symmetrically around a central pore.
- Each subunit comprises 4 transmembrane domains with both the N and C terminus located extracellularly.

There are various **sites of drug action** for drugs that affect the musculoskeletal system...
- **CNS processes** are affected by spasmolytics like Diazepam and Baclofen.
- **Conduction** of nerve action potential in the **motor neuron** is affected by local anaesthetics.
- **Acetylcholine release** is affected by Ca\(^{2+}\) entry blockers, and **choline reuptake** is blocked by hemicholinium.
- **Propagation** of action potentials along muscle fibres is prevented by spasmolytics like Dantrolene.

The final site at which drugs can act is at the **neuromuscular junction**; preventing depolarisation of the motor end-plate and post-synaptic action potential initiation. These drugs are known as **neuromuscular blocking drugs**.

**NEUROMUSCULAR BLOCKING DRUGS**

**Neuromuscular blocking drugs** act post-synaptically. There are two types of these drugs:
- **Non-depolarising** neuromuscular blockers are **competitive antagonists**, eg Tubocarine and atracurium.
- **Depolarising** neuromuscular blockers are **agonists**, eg suxamethonium (succinylcholine).

These drugs do not affect consciousness, pain sensation, but affect respiratory muscles therefore respiration must always be assisted until the drug is inactive or antagonised.

**Tubocarine** is naturally occurring quaternary ammonium compound (alkaloid) found in a south American plant. It was a prototype, and now a range of synthetic drugs are now available as **Non-depolarising neuromuscular blocking drugs**.

- **Mode of action**: it is a competitive nicotinic Ach receptor antagonist, and a 70-80% block is necessary to achieve the desired effects.
  - Produces a **graded block**, in which there are different proportions of fibres blocked.
- **Pharmacokinetics**: it is **administered** intravenously (highly charged), and it does not cross the BBB or placenta. Its **onset of action** is within 2 or 3 minutes, and the **duration of action** is between 40 and 60 minutes. It is **not metabolised**, but is **excreted** 70% in the urine and 30% in bile, so care must be taken if the patient has their renal or hepatic function impaired.

**Effects**: tubocarine causes **flaccid paralysis**
- First, the **extrinsic eye muscles** are affected (patient experiences double vision).
- 2\(^{nd}\) the **small muscles** of the face, limbs and pharynx are affect.
- Finally the **respiratory muscles** are affected.

NB: recovery is in the reverse order.
- Its **clinical uses** include the relaxation of skeletal muscles during surgical operations so that less anaesthetic is needed.
- It is also used to permit **artificial ventilation**.
- The actions can be **reversed** by **anticholinesterases** like Neostigmine, co-administered with Atropine.
The main *unwanted effects* are:
- Ganglion block + histamine release from mast cells
- Ganglion blockade > decreased peripheral resistance > Hypotension and reflex tachycardia
- Histamine release > bronchospasm, excessive bronchial and salivary secretions
- Apnoea also caused by histamine release

Atracarium is another antagonist of ACh at the post-synaptic site at the NMJ. It is a non-depolarising neuromuscular blocker like Tubocurarine, but its **effects have a shorter duration.**

Suxamethonium (Succinylcholine) is a *depolarising* neuromuscular blocker. It has a structure related to acetylcholine, and is a **post-synaptic nAChR agonist**
- This causes **excitation for a long period of time**, and so action potentials can no longer be produced as the **cell cannot repolarise** because the membrane potential is above the threshold and ion channels are inactivated.
- It is degraded by **Butyrylcholinesterase** (a plasma enzyme).
11. Clinical Applications of Antagonists of the Parasympathetic Nervous System

Dr Mike Schachter

The Parasympathetic Nervous System consists of the cranio-sacral outflow of the autonomic nervous system. It is responsible for the “rest and digest” state of the body, and is widely distributed around the body. Its actions on specific organs include:

- **Eye** – lacrimation (production of tears; there are tears that are produced continuously for lubrication and killing of bacteria, emotionally triggered tears are sympathetically driven), accommodation for near vision (miosis = pupil constriction, lens shape change to becomes more convex to shorten focal length. Eyes also converge, but this is not PS driven)
- **Salivary glands + submandibular parotid glands** – secretion
- **Bronchi** – bronchosecretion + increased mucous secretion (function is unknown. NB: the bronchi has no sympathetic innervation, but has adrenergic receptors ie sympathetic receptors)
- **Heart** – negative chronotropy + ionotropy (slowing HR + contractility)
- **Stomach** – increased motility + acid/protease secretion (aiding digestion)
- **Gut** – increased motility + secretion
- **Bladder** – detrusor contraction + relaxation of internal sphincter (helps empty bladder, although voluntary control is dominant)
- **Genitals** – erection

**MUSCARINIC ANTAGONISTS**

The wide distribution of the PNS means that muscarinic antagonists/anti-cholinergic agents have a range of target tissues.

**Effect on heart rate**

- **Atropine** (muscarinic antagonists made from the berries of the nightshade plant) is used to alter heart rate. Following a myocardial infarction, patients often have increased vagal (PNS) activity that causes bradycardia.
- Severe bradycardia may cause reduced blood pressure, cardiac output as well as reduced cardiac perfusion. This may in turn worsen the damage of the MI.
- Intravenous atropine is therefore administered in the short-term following an MI

**Effect on the bronchi**

- Drugs are used to modify bronchial function in treatment of COPD and asthma.
- **Ipratropium** and **Tiotropium** are administered via an inhaler/nebuliser.
  - Ipratropium is administered once daily
  - Tiotropium is an older drug, thus is required up to 4-5 times daily
- This is an example of where a drug is administered to the target organ, which reduces the systemic absorption of the drug and avoids hepatic metabolism of the drug. This allows for lower doses to be used.
- In treatment of asthma, beta agonists are the preferential treatment thus anti-cholinergics are used as 2nd line treatment. However in treatment of COPD, or in acute situations, anticholinergics are preferable
- They cause bronchodilatation, and reduced secretion

**Effect on the Bladder**

- There are anti-cholinergics, such as **Oxybutynin** and **Tolterodine**, which are considered to be bladder-selective.
- They are administered orally to treat an overactive bladder (resulting from CNS problem such as MS or spinal injury), incontinence (common problem in the elderly) or enuresis (bed-wetting)
- They act to decrease bladder emptying by decreasing detrusor activity and increasing the activity of the internal sphincter
Other uses of peripheral anti-muscarinics

- **In the Eye:** tropicamide dilates the pupil to allow detailed examination of the retina. It is used preferentially because of its short duration of action (few hours)
- **In the Gut:**
  - The mechanism of IBS is not fully understood, but mebeverine seems to have an therapeutic benefit, and is used because it appears to stay in the gut and avoid absorption
  - Anticholinergics have been a suggested treatment for peptic ulcers, but there are preferential treatments such as proton-pump inhibitors (which are used to reduce acid secretion to virtually zero)
  - This is also true for treatment of diarrhoea; anticholinergics would work (reduce motility), but immodium is preferable (non-absorbable opioid)

Adverse Effects

Despite that some anti-muscarinics are supposedly selective, there tends to always be some systemic absorption and hence systemic effect.

- **Eyes:** dry eyes (reduced secretion), blurred vision with some discomfort (paralysis of accommodation, loss of light reflex),
  - increased intraocular pressure (this happens in patients susceptible to glaucoma; as the pupil dilates, you block the drainage of aqueous humour from the anterior chamber of the eye therefore increasing the pressure which causes pain and may lead to irreversible damage)
- **Salivary Glands:** dry mouth. This shows that there is some systemic effect even when given locally)
- **Bronchi:** bronchodilatation + reduced secretion is not ADVERSE, it’s a beneficial effect!
- **Heart:** tachycardia (usually not noticeable)
- **Gut:** constipation (inevitable consequence)
- **Bladder:** urinary retention (does not affect everyone, but especially in elderly men with prostatic hypertrophy. Causes increased risk of infection and may require catheterisation)
- **Genitals:** Erectile dysfunction (same as TCA)

**NOTE: the clinical importance of the balance between sympathetic and parasympathetic tone in the cardiovascular system**

- At any given moment, there is a degree of sympathetic AND parasympathetic activity in the CV system
- This balance may shift depending on the surrounding environment, for example when you are scared
- **HEART RATE VARIABILITY** is a result of changes in this balance. This can be measured using a long stretch of ECG readings by reading the R-wave intervals
- R-R intervals in healthy individuals should show a lot of variability; this reflects the effect of parasympathetic activity and is associated with a reduced risk of cardiac arrhythmias
- However, in diabetes/autonomic neuropathy, there is a loss of this variability, which is associated with an increased risk of dangerous cardiac arrhythmias
- HRV can therefore be used as an estimator of cardiovascular risk

Centrally Acting Anti-Muscarinic Drugs

Virtually all receptors found in the periphery of the body are also found in the brain (this is even true for gut hormone receptors, they just aren’t all used in the brain!)

3 anti-muscarinic drugs are used for their central effects on the body:

- hyoscine
- benzhexol
- procyclidine
These have a few clinical uses:

- **Motion sickness**
- **Parkinson’s Disease** – seen to improve tremor, but dopamine-based treatment shows a wider range of beneficial effects therefore is preferential
- **Drug-induced Parkinsonism** – a parkinson’s-like disease which is more severe in presentation
  - Treatment of psychotic illness, eg schizophrenia, often tries to target dopamine receptors in the brain.
  - An adverse effect of this treatment is the targeting of the dopamine receptors involved in movement (those affected in Parkinson’s)
- **Acute Dystonic Reactions** involve a sudden outburst of involuntary, jerky movements mainly affecting the head and neck
  - **Oculo-gyrice crisis** is an example of this; a reaction to anti-psychotic drugs which involves the eyeballs rotating upward into the orbit. This is very painful, and often leaves the patient functionally blind
  - Treatment of this crisis involves emergency intravenous anti-muscarinics, which results in improvement within 30-40 seconds
12. Drugs and the Cardiovascular System I
Alun Hughes

Introduction + context
• Ischaemic heart disease + cerebrovascular disease dominate total deaths in both high-income and low/middle-income countries around the world
  o Account for more than 30% of UK deaths
• Drugs affecting the cardiovascular system also dominate prescriptions in the UK
  o However, they do not always pose the greatest expense as many have become cheaper

RENIN-ANGIOTENSIN SYSTEM
The renin-angiotensin aldosterone system (RAAS) is primarily responsible for fluid and blood pressure regulation
• Angiotensinogen (precursor) is produced in the liver, and enters the circulation where it is cleaved by Renin (enzyme produced in the kidney) to form Angiotensin I
  o Renin production is increased by decreased BP, decreased renal Na reabsorption, decreased renal perfusion pressure and an increased sympathetic drive
• Angiotensin I is converted to angiotensin II by the action of angiotensin converting enzyme (ACE).
  o NB: this will also convert a number of kinins, eg Bradykinin, into their active molecules
Angiotensin II then has various effects on its target organs, via AT1 receptors:
• Brain – SNS activation + thirst
• Blood Vessels – vasoconstriction
• Kidney – increased salt and water retention
• Adrenal cortex – aldosterone secretion
It also has many other effects that contribute to cardiovascular and metabolic disease.

There are therefore 3 targets for drugs acting on the RAAS
• Renin inhibitors (prevent cleavage of angiotensinogen to Ang I)
• ACE inhibitors (prevent conversion of Ang I to Ang II + conversion of kinins to active substances)
• Angiotensin II Receptor antagonists (ARB) (prevent action of Ang II)

Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
• ACE inhibitors, eg Enalapril, inhibit the somatic form of ACE, thus preventing the conversion of Ang I to Ang II
  o NB: there is also a germline form of ACE, which is significantly different therefore not affected
• These are used in conditions which confer an increased cv risk, include:
  o Hypertension
  o Heart failure
  o Post MI
  o Diabetic nephropathy
  o Progressive renal insufficiency
  o Patients at high risk of CV disease

**Angiotensin Receptor Blockers (ARB or AIIA)**
• ARBs, eg losartan, act as antagonists of type 1 (AT₁) receptors for Ang II, preventing the renal and vascular actions of Ang II.
• They are widely used in hypertension as an alternative to ACE inhibitors as they have fewer side effects (suggested that their tolerability is comparable to that of a placebo)
• They are also used in chronic heart failure in patients who cannot tolerate ACE inhibitors

**Renin Antagonists**
• For example, Aliskiren, inhibits the enzyme activity of renin
• These have limited clinical experience as of yet

**Adverse Effects**
Drugs targeting the RAAS are generally well tolerated, especially angiotensin receptor blockers. However side-effects that do occur include:
• Cough – basis is not well understood, thought that bradykinase is indicated (mainly ACE inhibitors)
• Hypotension
• Urticaria (hives) + angioedema (red swellings) – very rare (ACE inhibitors mainly)
• Effect on renal sodium handling > hyperkalaemia (requiring K supplements or K sparing diuretics)
• Fetal injury
• Renal failure (in predisposed patients with limited perfusion of kidney)

**CALCIUM ANTAGONISTS**

**Importance of Calcium**
- A rise in intracellular calcium is a key step in excitation-contraction coupling in both cardiac and vascular myocytes. While the mechanisms differ, influx of Ca²⁺ through L-type voltage-operated calcium channels forms the basis of contraction.
  • Inhibiting calcium entry will thus interfere with cardiac contraction, electrical conduction in the heart and vascular smooth muscle contraction

**Molecular mechanisms**
The L-type calcium channel is a voltage-dependent calcium channel which is dependent on cell membrane potential
  • As the cell depolarises towards a more positive potential, the channel opens and allows calcium influx

There are 3 subclasses of CCB which interact with the receptor at difference sites, thus exerting different electrophysiological effects:
• Dihydropyridine binds to the extracellular domain of the receptor
• Diltiazem and Verapamil bind to the intracellular domain of the receptor

**Classification of CCBs**
Functionally, CCBs can be divided into 2 classes:
• **Rate-slowing** drugs, which exert both cardiac and smooth muscle effects
  o Phenylalkylamines (e.g. Verapamil)
  o Benzothiazepines (e.g. Diltiazem)
• **Non-rate slowing** drugs, which only exert smooth muscle action and have little direct effect on the heart
  o Dihydropyridines (e.g. amlodipine)
CCBs have a wide range of uses in CV disease:
- **Hypertension** (mainly dihydropyridines)
- **Angina** arising from ischaemic heart disease
- **Paroxysmal supraventricular tachycardias** and **atrial fibrillation** (usually Verapamil, as it has more marked CV effects)
  - NB: this assumes that there are no abnormal conduction pathways

**Mechanism of Action** at clinical doses
- Verapamil and Diltiazem reduce Ca2+ entry into cardiac and smooth muscle cells
  - This results in a negative ionotropic effect (reduces contractility). Verapamil exerts a greater effect than diltiazem
  - NB: verapamil also inhibits AV node conduction
- Dihydropyridines inhibit Ca2+ entry into vascular smooth muscle cells

**Adverse Effects**

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<td>Ankle oedema (increased peripheral vasodilation)</td>
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<td>Constipation (effect on GI smooth muscle)</td>
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**BETA BLOCKERS**

Beta adrenoceptors are widely distributed in the body. There are two classes of beta-adrenoceptors: B1 and B2. However from a cardiovascular perspective, the B1 receptors are the principal therapeutic target

**Sympathetic control of the Heart**

The principle mechanism of action of beta blockers is to interfere with the sympathetic control of the heart
- Sympathetic neurons innervating cardiac muscle release noradrenaline on depolarisation.
- NA acts on the B1 receptors on cardiac myocytes, to increase heart rate, contractility and excitability
- Competitive antagonists, ie beta blockers thus tend to have a negative ionotropic + chronotropic effect

Beta blockers, eg Atenolol (B1 selective/cardioselective) thus have a wide **range of uses:**
- Angina
- Post myocardial infarction (reduce mortality)
- Cardiac dysrhythmias (due to effect on cardiac excitability)
- Chronic heart failure
- Hypertension (reduced CO, reduced renin release)
- Also thyrotoxicosis, glaucoma, anxiety states, migraine prophylaxis, benign essential tremor

**Hypertension**

Beta blockers are no longer the 1st line of treatment of hypertension in the UK. This is because they do NOT reduce peripheral resistance. However they still have other effects which may in turn affect blood pressure:
- Reduce cardiac output
- reduce renin release by the kidney
- may diminish noradrenaline release by sympathetic nerves,
- lipophilic agents (e.g. propranolol) exert central sympatho-inhibitory actions.
**Adverse Effects**
At clinically used doses, most drugs have some systemic action. This is true for cardioselective/B1 selective beta blockers. When used at clinical doses, they have some action on b2 receptors, which accounts for most of their unwanted effects:

- Worsening of cardiac failure
- Bradycardia (excessive slowing > heart block)
- Bronchoconstriction (action on B2 receptors)
- Hypoglycaemia (in diabetics on insulin, the symptoms will be masked which is dangerous)
- Increased risk of new onset diabetes (mechanism not fully understood; increased insulin resistance and reduce pancreatic secretion)
- Fatigue
- Cold extremities and worsening of peripheral arterial disease (B2 effect: reduced blood perfusion of the limbs)
- Impotence
- CNS effects (lipophilic agents) e.g. nightmares
  - NB: atenolol is water-soluble thus is used preferentially

**ORGANIC NITRATES AND RELATED AGENTS**
The molecular mechanisms of these drugs was only recently understood.

- Organic nitrate is absorbed particularly in smooth muscle cells
- It undergoes degradation into nitrite free radical, which then is converted to nitric oxide
- Nitric oxide is an endogenous vasodilator; it acts on the enzyme guanylate cyclase to increase cyclic GMP production
- Cyclic GMP then acts to vasodilate the smooth muscle

**Uses of nitrates** in the cardiovascular system

- Angina
- Acute and chronic heart failure
- BP control during anaesthesia (nitrates are easy to titrate, thus allowing for fine control of BP)

**Mechanism of action**

- Nitrates directly release NO in smooth muscle cells (see above for explanation), eg *glyceryl trinitrate*
- They also may stimulate guanylate cyclase to cause the vasodilation, eg *nicorandil*
- This reduces venous return, which reduces the preload. Reduced peripheral resistance also reduces the afterload, therefore the heart does not need to work as hard

NB: organic nitrates also have some other minor effects not on the cardiac myocytes

- antiplatelet agents (process of NO release also occurs in platelets)
- coronary artery vasodilators (not that important in terms of angina)

**Pharmacokinetics**
Organic nitrates are an example of drugs where their pharmacokinetics are important...

- Nitrates undergo extensive ‘first pass’ metabolism by the liver
  - As a consequence, *glyceryl trinitrate* is often given sublingually (absorbed by buccal mucosa, thereby avoiding first-pass metabolism) for rapid relief of angina - has a short half life (~5 mins).
  - Longer acting forms of nitrate (e.g. *isosorbide mononitrate* can be given orally, or glyceryl trinitrate via a transdermal patch) are available for sustained actions

**Unwanted effects**

- Nitrates can cause hypotension, headaches, and flushing as a result of vasodilation
- Excessive/prolonged use of nitrates is also associated with tolerance
  - This is one of the reasons that GTN is used for immediate relief as opposed to long-term treatment. If prolonged treatment is required, it is given in varying intervals
ANTIDYSRHYTHMICS

Disturbances of rhythm

Abnormalities of cardiac rhythm are very common. **Treatment** consists of 3 different aims:

- The principle aim is to reduce sudden death due to a major disturbance eg Ventricular fibrillation
- Prevent stroke, especially in atrial fibrillation whereby a thrombus forms in the atrium, and breaks off and embolises to the brain
- The third aim is to alleviate symptoms

**Management** of rhythm disturbances is a complex, multi-factorial process which is usually undertaken by specialists. It may involve:

- Cardioversion
- Pacemakers
- Catheter ablation therapy
- Implantable defibrillators
- Drug therapy

Classification of Rhythm Disturbances

The most basic classification is the **association with heart rate**:

- Bradyarrhythmias decrease heart rate
- Tachyarrhythmias increase heart rate

They then are classified based on their **site of origin**:

- Supraventricular arrhythmias arise from the atria and conduction tissue, and require treatment with for example amiodarone, verapamil
- Ventricular arrhythmias arise in the ventricle, and require treatment with for example flecainide or lidocaine
- Complex arrhythmias have multiple sites of origin (supraventricular and ventricular) and require treatment with for example disopyramide

**NB:** the **Vaughan-Williams classification of anti-arrhythmic drugs** classifies drugs according on their effect on cardiac action potential and their mechanism of action. This includes:

- I – sodium channel blockers
- II – beta adrenergic blockers
- III – potassium channel blockers (which prolong repolarisation)
- IV – calcium channel blockers

This method of classification is useful in research, but is rarely used in a clinical setting

**Antiarrhythmics**

**Adenosine** is used intravenously to terminate supraventricular tachyarrhythmias

- Its use is favoured because of its short duration of action (20-30s) thus is consequently safer than verapamil in an acute setting
- **Mechanism of action:** It is an endogenous mediator produced by the metabolism of ATP, which acts on adenosine type 1 receptors (in the heart) to hyperpolarise cardiac tissue and thus slow conduction through the AV node
- **Adverse effects** include chest pain, shortness of breath, dizziness and nausea

**Amiodarone + dronedarone** have a wide use in supraventricular and ventricular tachyarrhythmias

- **Mechanism of action:** complex action involving multiple ion channel blocks, as well as some effect on thyroid gland
- **Adverse effects:**
  - Amiodarone accumulates in the body (t½ 10-100days) therefore producing a number of adverse effects including photosensitive skin rashes,
hypo/hyperthyroidism (contains iodine), pulmonary fibrosis, corneal deposits, neuro + GI disturbances
  o Dronedarone is a more recent drug, and is non-iodinated. It is thus less toxic than amiodarone but also less effective

**Cardiac Glycosides**
Cardiac glycosides, with **Digoxin** being the most prominent member, have both a cardiovascular and CNS effect.

- **CVS effect**: inhibition of Na-K ATPase, resulting in an accumulation of intracellular Na+. This increases intracellular Ca2+ via Na+/Ca2+ exchanger, thus having a positive inotropic effect
- **CNS effect**: increased vagal outflow, which causes an increased refractory period and reduced rate of conduction through the AV node (negative chronotropic effect)
- **Uses**: it can be used in atrial fibrillation, and relieves symptoms in chronic heart failure
- **Pharmacokinetics**: digoxin has a narrow therapeutic window, and a long half life (t½ = 40 hours), therefore digoxin toxicity is a risk
  o An immune Fab (digibind) is available to treat digoxin toxicity; to “mop- up” the digoxin
- **Adverse effects**
  o Any anti-arrhythmic agent can also induce a new dysrhythmia, eg AV conduction block, ectopic pacemaker activity
  o Digoxin is often taken in conjunction with a diuretic. Associated hypokalaemia and hypomagnesaemia again lower the threshold for digoxin toxicity

**NB**: **Ivabradine** is a relatively new agent with a selective **mechanism of action**.
- It blocks IF channels in the SAN, thus preventing sodium and potassium from entering the SAN therefore slowing rate of contraction (ie negative chronotropic)
- It has use in angina in patients with a normal sinus rhythm
- However it its **contraindicated** in:
  o Severe bradycardia
  o Sick sinus syndrome
  o 2nd/3rd degree heart block
  o cardiogenic shock
  o following a recent MI
- **adverse effects** include bradycardia, 1st degree heart block and ventricular/supraventricular arrhythmias

**Cardiac Inotropes** are agents that increase the force of cardiac contractions
- They are used to treat acute heart failure in some situations (eg after cardiac surgery, cardiogenic shock, septic shock)
- **Dobutamine** is a B1 adrenoceptor agonist that stimulates cardiac contraction without a major effect on heart rate. This has a use in an acute setting.
- Inhibitors of phosphodiesterase, such as **milrinone**, have inotropic effects by inhibiting breakdown of cyclic amp in cardiac myocytes
  o Despite this, so far has a limited use as they have a reduced survival in chronic heart failure

**ALPHA BLOCKERS + SYMPATHOLYTICS**
Alpha blockers are antagonists of a1-adrenoceptors. They can be competitive (eg doxazosin) or irreversible (phenoxybenzamine)
- **Competitive drugs**, eg **doxazosin**, are used occasionally in combination with antihypertensives in resistant hypertension
  o However their routine use has declined since they were shown to be associated with an increased rate of chronic heart failure
Irreversible drugs, eg phenoxybenzamine (taken in conjunction with a beta blocker) is used to provide long-lasting alpha blockade in catecholamine tumours (pheochromocytoma)
  - Surgical removal of a pheochromocytoma often causes hypersecretion of catecholamines. An irreversible antagonist is required (to ensure catecholamines cannot surmount the receptor)

Centrally acting sympatholytics, eg clonidine (α2 adrenoceptor agonist) and moxonidine (imidazoline agonist) inhibit sympathetic outflow from the brain
  - These are occasionally used as antihypertensives

**VASOCONSTRICTORS**

**Sumitriptan** is 5HT-1d receptor agonist
  - It acts to constrict some large arteries (particularly cerebral) and inhibits trigeminal nerve transmission
  - It is used to treat migraine attacks, but contraindicated in patients with coronary disease
  - Other ergot alkaloids are also used in migraine, and probably act as a partial agonist of 5HT1 receptors but there usefulness is limited by marked side-effects

**Sympathomimetic agents**

For example, adrenaline (the endogenous catecholamine), is produced by the adrenal gland to provide circulatory support in cardiac arrest and anaphylactic shock
  - This is via B1 receptor action in the heart, and alpha1 mediated peripheral vasoconstriction

**THERAPEUTIC APPLICATIONS**

**Angina**

Angina is chest pain arising from myocardial ischaemia, which is due to an imbalance between oxygen supply to and demand from the heart
  - Myocardial oxygen supply is affected by coronary blood flow and the arterial oxygen content
  - Demand from the heart depends on the work it is carrying out; this is increased by increased heart rate, preload, afterload and intrinsic contractility

An increased supply or reduced demand for oxygen leads to a reduction in myocardial ischaemia

**Pharmacological Applications**

In angina, most drugs work by reducing oxygen demand on the heart
  - **Beta-blockers** are used to reduce heart rate and contractility
  - **Calcium channel blockers** are vasodilators, therefore ensuring less resistance to blood flow ie reduced afterload
  - **Nitrates** work by dilating veins, therefore reducing the venous return and thus the preload.
    - This is at the expense of the cardiac output

**Treatment combinations:**

- Beta blocker (or CCB in beta-blocker intolerant patient) to provide background anti-anginal cover by slowing heart rate
- Glyceryl trinitrate for symptomatic relief

**Preventative measures**

- Statins (lower LDL cholesterol)
- Aspirin (to inhibit platelet activation)

**Hypertension**

Hypertension is blood pressure that is greater than 140/90mmHg
  - It is a common condition affecting 1 billion people worldwide
  - It results in an increased risk of myocardial infarction, stroke, heart failure and renal disease
Blood pressure control is a complex process involving multiple systems, but regulating BP is core to cardiovascular treatment

- We still do not know what causes hypertension in more than 90% of patients = essential hypertension
- There is no clear single cause of hypertension in the majority of cases and treatment is directed at the physiological regulators of blood pressure

**Treatment**

Typically patients require at least 2 drugs of different classes to control BP

- Angiotensin converting enzyme inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB)
- Calcium antagonist (long acting dihydropyridine)
- Thiazide diuretic
- Other CVD prevention measures (e.g. statin to lower LDL cholesterol)

NB: Beta blockers are no longer first line agents for hypertension in UK but may have a role in younger patients, particularly young women who plan to become pregnant as other treatments dangerous for fetus

**Chronic Heart Failure**

Chronic heart failure is impaired cardiac function due to ischaemic heart disease, hypertension or cardiomyopathy that results in

- fluid retention
- oedema
- fatigue

This results from either depressed cardiac output, or increased filling pressures. It is a serious condition with a high mortality that is increasingly common due to the ageing population and the increased 5 year survival post 1st MI

**Neuroendocrine Compensatory Mechanisms in CHF**

- Regulation of CO is complex, and thus treatment requires multiple drugs.
- The key elements involved include the kidney, heart, blood vessels and other systems (CNS, conversion of Ang I > Ang II in the lungs)

![Diagram of CHF mechanisms]

**Treatment**

Typically, patients will receive...

- Diuretic – reduces salt and water retention
- ACE inhibitor/ARB – reduces salt and water retention
- Beta blockers – reduce hear rate and improve survival
- Spironolactone – aldosterone antagonist
- Digoxin
The reason drugs are abused is due to their ability to cause euphoria by targeting particular pathways in the brain.

- The mesolimbic system and pathways originating in the ventral tegmental area go up into the nucleus accumbens to release dopamine.
- It is this release of dopamine into the nucleus accumbens that causes the euphoric feeling, as this is also the natural reward pathway, which can usually be activated by exercise, feeling good, etc. Drugs of abuse artificially hijack this system.
- Mechanism of action: rewarding stimulus > dopamine release from axons terminals of neuron (cell body in ventral tegmental area) into the nucleus accumbens

### ROUTES OF ADMINISTRATION

There are several classical routes of administration for these drugs of abuse:

- **Snorting (intra-nasal)** - drug has to cross the mucous membranes of the nasal sinus into the blood, then into the systemic circulation back to the heart, then eventually up to the brain (slow absorption)
- **Eating (oral)** - drug has to be absorbed in the gastrointestinal tract, pass through the liver, then go back into the circulation (very slow absorption)
- **Smoking (inhalation)** – relatively fast transfer of the drug across the small airways and thin alveoli into the blood. The close proximity of the pulmonary circulation to the heart means drugs have fast access to the brain (rapid absorption + distribution)
- **Injecting (intra-venous)** is also fast, but the drug has to get round the systemic circulation back to the heart before going up to the brain. But this route is also quite rapid absorption.

In general, the faster the rate of absorption, the faster you feel the euphoria, the more addictive the drug.

### CLASSIFICATION

- **Narcotics (painkillers)** are opiate like drugs, such as heroin and morphine
  - These work by increasing dopamine release into the nucleus accumbens, via GABA secretion interference
  - Opiates bind to u opiate receptors on the GABAergic neuron cell body to suppress them, therefore suppressing GABA release > more dopamine release
- **Depressants** are ‘downers’, which slow down the CNS. These include alcohol, benzodiazepines (valium), and barbiturates
- **Stimulants** are ‘uppers’, and are probably the largest class of addictive drugs, which tend to speed everything up in the CNS.
  - These include cocaine, amphetamine (speed), caffeine, metamphetamine (crystal meth), and mephedrone (meow meow)
• **Miscellaneous** drugs have several effects and properties (e.g. stimulant as well as hallucinogenic), and these drugs include cannabis and ecstasy (MDMA).

**CANNABIS**
Cannabis is a genus of flowering plants. The active component of the drug (cannabinoids) can be found in all parts of the plant (stalk, lead, seeds, flowers, etc), in various forms:

- This can often be found in the form of **Marijuana** (crushed, dried leaves)
- Cannabinoids are secreted from glandular ‘trichomes’ within the plant. These are released as a **resin (Hashish)**, potent in cannabinoids
- **Hash oil** is made whereby solvent extraction can concentrate the cannabinoids even further

The plant itself contains well in excess of 400 different compounds, of which there are 60 cannabinoids, the most active one being **tetrahydrocannabinol (THC)**.

**Pharmacokinetics**
The pharmacokinetics of cannabis are slightly unusual.
- It is most commonly smoked, and in this case only about 50% of the total dose will get into the bloodstream (this is because some of it is swallowed, some is released back into the air, etc)
- Following administration, there is rapid absorption and thus the euphoric effects have a rapid onset
- Cannabis can also be eaten, in which case only 10% of the total dose gets into the systemic circulation, because of first pass metabolism in the liver
  - Orally administered cannabis also has a delayed onset of action, therefore the euphoric effects take longer to come into effect but will last longer

**Fat (adipose tissue)** determines how much THC gets into different tissues and how long it stays there. Cannabis enters fat and sits there for a very long time, which is what makes the pharmacokinetics complicated. It is very lipid soluble, but as time goes on, the equilibrium shifts and it is released back from the fat into the circulation.

Cannabis is **metabolised** in the liver and is **excreted** in the urine.
- About 25% of the dose is excreted, but about 65% of the dose is metabolised and secreted in the bile, so it undergoes enterohepatic recycling (secreted in bile, reabsorbed in the gut, reabsorbed in the blood).
- **Enterohepatic recycling** is a problem as the major metabolite is 11-hydroxyTHC (an active metabolite). This means that the administered dose, plasma concentration and urine concentration does not really correlate with intoxication

**Pharmacodynamics**
In fact, we have an endogenous compound cannabinoid system within the body.
We produce endogenous cannabis like substances e.g. endogenous anandamide (generated from arachidonic acid)
- This binds to CB1 receptors in the brain (hippocampus, cerebellum, cerebral cortex, basal ganglia) to produce euphoric effects; these are probably the most prevalent G-protein coupled receptors in the brain
- CB2 receptors are found on white blood cells (immune cells)
These are both G-protein coupled receptors, and downstream signalling involves a down regulation of adenylyl cyclase. Binding of cannabis to its CB1 receptor results in the inhibition of GABA secretion, which increases dopamine release in the nucleus accumbens

**Risks/Effects**
- A major risk of cannabis is that it can cause **psychosis and schizophrenia** in naïve users.
- A current hypothesis involves the anterior cingulate cortex acting as an amplifier or filter for integrating emotional and cognitive processing. It determines how we act on certain impulses etc. Cannabis interferes with this system, and so there is **less inhibition** to do or say things that are inappropriate.
• The "munchies" are a result of the effect on the hypothalamus. The hypothalamus is the major site that integrates feeding signals in the body, and cannabis acts on receptors here to interfere with appetite in a way that increases food intake.
• Profound memory loss is also associated with chronic cannabis use due to the effects on limbic regions of the brain. The amnesic effects are also due to the decrease in the production of Brain Derived Neurotrophic Factor (BDNF).
• Cannabis also has an alcohol like effect on psychomotor performance (cerebral cortex), so the ability to carry out certain skills will be interfered with.
• immunosuppressant.
• nother effect is interference with TRPV1 receptors, causing tachycardia and profound vasodilation, which can lead to reddening conjunctivae.
• Chronic cannabis users have many of the same problems that cigarette users have, due to carbon monoxide and carcinogens produced in smoke.

Cannabis in disease
In certain diseases, up-regulation of the CB receptors can be used to try to mitigate the disease.
• For example, in multiple sclerosis and schizophrenia, activating CB1 receptors and CB2 receptors has a beneficial effect as it stops the toxic necrosis of the neurons in the brain.
• Up-regulation of the system can also affect things like fertility, obesity or stroke.

Cannabis in pharmacology
There are a certain number of drugs produced that actually target the cannabinoid system.
• Dronabinol and Nabilone are agonists that bind to and activate the endogenous receptors to try to increase appetite in AIDS patients and cancer patients. It is also used to treat nausea and vomiting.
• Sativex is a more recent drug, and is another agonist of the receptors used to treat neuropathic pain within multiple sclerosis.
• Rimonabant is an antagonist used as an anti-obesity agent. It blocks the receptors and therefore prevents the effect on appetite. One of the problems with obesity drugs is that appetite and reward are closely associated; therefore depression can be a problem.

COCAINE
Cocaine is derived from the plant Erythroxylum coca, where you can extract 0.1 to 0.9% of the lead to get cocaine. There are different forms of cocaine:
• The most basic is paste, found mainly in the developing world. You can extract about 80% of the active drug using this method.
• The medicinal form of the drug is cocaine hydrochloride, where the paste is dissolved in an acidic solution. If this is heated, however, it breaks down, so you can't smoke it.

Cocaine paste and cocaine hydrochloride are suitable for intravenous, oral or intranasal administration.
• Crack cocaine is relatively simple to prepare, as it just needs to be precipitated with an alkaline solution.
• Freebase cocaine is where you take the precipitate and dissolve it in a non-polar solvent like ammonia, and then use ether to extract the freebase cocaine.

Crack cocaine and freebase cocaine are suitable for inhalation.

Pharmacokinetics
The onset of action is within seconds following smoking/injection; this contributes to the addictive potential of the drug
• You tend to lose a lot more of the dose if you smoke it than if you inject it, as you may swallow some or lose it in the air.
• Injecting and inhaling also has a shorter duration of action compared to oral administration. However snorting tends to have a longer half life than injecting, therefore is more commonly used.
• Within 20 to 90 minutes most of it is broken down and excreted in the urine. The liver produces various metabolites. The other thing is that plasma cholinesterases break down and metabolise cocaine. This is why the half life is so short,

Pharmacodynamics
• Cocaine has a local anaesthetic effect, with a number of drug targets (e.g. sodium channels). Cocaine blocks sodium channels to prevent nerve conduction. This is the major therapeutic use of cocaine, still used in certain procedures even now.
  o Cocaine also binds to and inhibits monoamine transporter proteins. It influences the transport of neurotransmitters. Cocaine blocks the transporters, e.g. for serotonin, dopamine and noradrenaline.
• In terms of euphoria, cocaine directly affects the mesolimbic neurons.
  o It binds to the dopamine transporter present on the terminals of dopaminergic neurons and prevents the reuptake of dopamine. If you prevent dopamine being removed from the synapse in the nucleus accumbens, the effect is prolonged, and this is how the euphoria is caused.
• Other effects in the CNS manifest themselves as behavioural measures. It is a stimulant, and enhances CNS effects.
  o An overdose can induce severe effects like irritability, hostility, anxiety, and insomnia.
• Because of the cardiovascular effects of cocaine, complications may occur in susceptible individuals.
  o Cocaine increases the production of endothelin 1 (a powerful vasoconstrictor) and decreases NO production (a vasodilator).
  o There is increased platelet activation, increased sympathetic stimulation and an overall increase in heart rate, hence the link between cocaine use and sudden death.

NICOTINE
A single cigarette has very little nicotine - 95% of the cigarette smoke is volatile matter (nitrogen, carbon monoxide, benzene, hydrogen cyanide, all the nasty things that cause cancer)
• Nicotine (5% of the particulate smoke) is a plant-derived alkaloid that is contained within tar droplets, which are very lipid soluble and pass down into the lungs and onto the bloodstream.

Pharmacokinetics
There are numerous routes of possible administration of nicotine:
• Nicotine spray (intranasal) contains about 1 mg of nicotine (20-50% gets into the bloodstream).
• Nicotine gum contains 2 to 4 mg of nicotine (50-70% gets into the bloodstream)
• Cigarettes contain about 9-17 mg of nicotine (only about 20% gets into the bloodstream)
• Nicotine patches contain about 15 to 22 mg which are applied over 24 hours (70% gets into the bloodstream transdermally).

Nicotine itself has a pKa of about 7.9, and cigarette smoke is relatively acidic.
• This means that most of the nicotine in smoke is actually ionised, which means very little is absorbed into the bloodstream via the mucous membranes of the mouth - nearly all of it is absorbed in the lungs, because the alveoli are so thin it doesn’t matter if its ionized
• The spray, gum and patch are buffered to make them as close to the pKa of nicotine as possible so that the nicotine is absorbed as much as possible (ie so it remains unionized)

The cigarette is clearly the quickest route of administration - very high levels achieved very quickly.
• The spray is also quite rapid.
• Oral administration always shows the slight delay, and the patch has very low levels over a long time.
With the spray, gum and patch, the aim is to remove the nicotine “spike”, which tends to encourage the individual to take another cigarette. To wean people off cigarettes, you want a low level of nicotine over a long period of time.

The half-life of nicotine is a couple of hours. It is broken down predominantly (70-80%) in the liver by hepatic cytochrome P2A6 into cotinine, and this is excreted in the urine. The relatively quick clearance is why there is repetitive abuse of the drug.

**Pharmacodynamics**
Nicotine acts on nicotinic acetylcholine receptors in the ANS. There are 5 subunits that make up the receptor.

- Binding causes opening of the Na+ channels, causing depolarisation and subsequent action potentials at all ganglia and the adrenal medulla
- Generally, the alpha4 and beta2 subunits are what nicotine binds to produce its effects
- Nicotine binds to the nicotinic acetylcholine receptors on the cell bodies of the dopaminergic neurons in the ventral tegmental area. This stimulates them, and activates them to release dopamine into the nucleus accumbens
  - This is a less potent effect than that achieved with cocaine in terms of producing euphoria, and the feeling wears off during the day

**Side effects**
The main side effects of nicotine are *cardiovascular*:

- Increased heart rate and stroke volume
- Profound vasoconstriction (particularly in coronary arterioles and skin) and vasodilation in skeletal muscle
- Increased lipolysis
- Increased platelet activity because of enhanced thromboxane A2 and reduced nitric oxide

In combination, the heart is working harder than it should, the blood flow to the heart is reduced, and the likelihood that the vessels supplying the heart will get blocked increases – strong CV risk

**Metabolic effects** of nicotine:

- Increased metabolic rate
- Appetite suppressant

Although these should contribute to weight loss, a study following smokers who quit showed a 6.7%-9.8% weight gain after 2 years

NB: there is evidence that nicotine actually protects against Parkinson’s disease, as it increases brain cytochrome P450, which metabolises a lot of neurotoxins in the brain

- It is also protective against Alzheimer’s disease, as it decreases beta-amyloid toxicity and the build up amyloid precursor proteins (APP) which are thought to be of pathological importance

**CAFFEINE + CHOCOLATE**
Theoretically caffeine could induce euphoria

- Adenosine (which binds to adenosine receptors on mesolimbic neurons and post-synaptically within the nucleus accumbens) tends to decrease dopamine content within the synapse
- Caffeine inhibits these adenosine receptors, and so this will reduce the suppression by adenosine, and the amount of dopamine will increase to produce euphoria.
- However, most coffee is low dose in caffeine, and it is taken orally, so the effects are slow.

Chocolate falls under the same category as any other natural rewarding stimuli. It does not hijack the reward system, it just stimulates it.
15. Alcohol
Dr Chris John

Burden of alcohol for Medicine
In 2009 and 200910 there were about 28,000 hospital admissions per year because of alcohol. There are also about 33,000 deaths per year because of alcohol, with a total cost to the NHS of about £3 billion a year. It is the underlying factor behind a third of all A&E attendances.

DOSING
Recommended amounts
There are two important things to consider when figuring alcohol dosing: absolute amount and units. % Alcohol by volume (ABV) is also very important

- Absolute amount = % ABV x 0.78 (g/100ml)
- Units = %ABV x vol (ml) / 1000 (1 unit = 8g of absolute alcohol)

There is no consistency with doses of alcohol in different drinks. However there are safe recommended amounts of alcohol:

- Men: < 21 units per week
  o They are at low risk if they consume <4 units at least once a week
  o They are at high risk if they consume >8 units at least once a week
- Women: <14 units per week
  o They are at low risk if they consume <3 units at least once a week
  o They are at high risk if they consume >6 units at least once a week

NB: in the general population age 16-24, 42% of males and 36% of females exceed that of the low risk intake

Blood levels
In terms of blood levels and observable effects of alcohol...

- 20-40mg/ml – minimal effects (1/2 pint – 1 pint)
- Up to 50mg/ml – very little effects on motor skills
- Up to 80mg/ml (legal driving limit) – x4 increased likelihood of car accident
- Up to 150mg/ml (gross intoxication of 90% of population) – 25x more likely
- 300mg/ml (coma)
- 400-500mg/ml (death)

NB: alcohol has a relatively narrow therapeutic window

PHARMACOKINETICS
Administration
Alcohol is administered mostly orally. However it has complicated pharmacokinetics

- Once administered, 20% of alcohol is absorbed in the stomach, and 80% in the ileum
- This is why the speed of onset is directly related to gastric emptying. If the stomach is full, the alcohol sits in the stomach and the absorption is poor. The alcohol then moves into the blood at a much slower rate, and it is alcohol in the blood that has the effect
- If you drink on an empty stomach, drinking fluid stimulates gastric emptying, so the alcohol passes straight through to the small intestine and large proportion of the dose is absorbed into the bloodstream

Metabolism
Of the original dose ingested, about 90% is metabolized in the body and 10% is expired unchanged in the breath (basis of a breathalyzer test)

- Of the 90% metabolized in the body, 85% is metabolized in the liver
- There are two important enzymes in the liver: alcohol dehydrogenase and mixed function oxidase. These both break down into acetaldehyde
  o 75% of this is done by alcohol dehydrogenase
  o 25% of this is done by mixed function oxidase
Therefore, acts on numerous targets:

- The CNS is functionally complex, and ethanol has a low potency; it has a low selectivity. It tends to show some CNS excitability.

If we consider the primary Acute Effects and efficacy, there is also no alcohol receptor, therefore it binds to a huge number of targets with low affinity and efficacy.

Acute Effects

If we consider the primary effect on the CNS, alcohol is a depressant. However, depending on the personality of the individual, and the environment (social/non-social setting), alcohol in low doses tends to show some CNS excitability.

- Alcohol affects GABA, both pre- and post-synaptically. It facilitates chloride ion influx and therefore promotes the effects of GABA. It also has an inhibitory effect pre-synaptically via the generation of the neuroactive steroid called Allopregnenolone, which has a stimulatory effect on releasing GABA.
- In terms of targets in the CNS, there are NMDA receptors and calcium channels.
  - Evidence suggests that alcohol can bind to NMDA receptors (stimulatory) to reduce function, and decreasing the effects of excitatory neurotransmitters.
  - There is also dampening down of calcium channel activity. NT release is calcium dependent, therefore down-regulating calcium entry shows a depressant effect.

The CNS is functionally complex, and ethanol has a low potency; therefore, there is low selectivity. It therefore acts on numerous targets:

- In terms of euphoria, the obvious targets are GABA and NMDA. Decreased GABA and increased NMDA action should increase euphoria.

**Rate of consumption** also has an important effect.

- Oral administration has to pass through first past hepatic metabolism in order to enter the systemic circulation to produce its effects.
- If your liver is better at metabolizing the alcohol, less alcohol will ever reach the systemic circulation.
- However, the liver enzymes can be SATURATED, therefore causing a greater increase in blood ethanol levels. If you give a dose over a longer period of time, you allow normal function of the enzymes to be regained and you never see the same level of blood ethanol – the individual will never be as intoxicated.

**Differences between sexes**

- 15% of alcohol is absorbed in the stomach. ADH also acts here, generating acetaldehyde. However, women have about 50% less ADH in the stomach, therefore are less able to metabolise it thus it has a greater effect.
- Women also have more fat than men, therefore they have a smaller volume of body water (50% compared to 59%). As alcohol is a water soluble compound, this means alcohol is more concentrated in women.

**Further metabolism**

Acetaldehyde (toxic metabolite) is then converted to acetic acid. This again involves ADH (in both the liver and stomach).

- We have a drug used to treat alcoholics; Disulfiram (ADH inhibitor). This causes the toxic build up of acetaldehyde following alcohol consumption, which makes patients feel very unwell.

NB: the effects of disulfiram is similar to that seen by the genetic polymorphism that affects ADH. Asians have a low capacity to metabolise acetaldehyde, therefore find drinking often a very unpleasant experience.

**PHARMACODYNAMICS**

Alcohol has incredibly low pharmacological potency; it is a very simple chemical structure (ethanol is C2H5OH) therefore is not particularly selective.

There is also no alcohol receptor, therefore it binds to a huge number of targets with low affinity and efficacy.

One of the main reasons why you can increase your tolerance/capacity for alcohol is due to the action of the MFO system. If you regularly drink alcohol, your MFO enzyme is upregulated, therefore your capacity to metabolized alcohol becomes a lot greater.
In the aldehyde dehydrogenase pathway, alcohol uses up its function to cause euphoria. However at high doses this disinhibition stops.

If we consider the **effects on the Brain** more specifically, we see that certain regions of the brain appear to be more sensitive to alcohol than others, for example the cortical region (both in terms of sensory and motor function). As alcohol is a depressant, we can predict effects on different parts of the brain if we know their function:

- **Corpus callosum** (role in communication between L + R hemisphere) > disconnect between rules/logic + impulse feelings (alcohol = more impulsive)
- **Hypothalamus** (regulating appetite, body temp, emotional behavior, pain, sensation) > loss of regulation (alcohol = munchies, emotional, no pain)
- **Reticular activating system** (regulates consciousness) > impaired consciousness (at very high dose)
- **Hippocampus** (involved in memory formation) > loss of memory
- **Cerebellum** (movement + coordination) > stumbling
- **Basal ganglia** (perception of time) > loss of sense of time

The **effects on the cardiovascular system** are easier to understand.

- Cutaneous vasodilation (fascial flushing) is related to decreased calcium entry and increased vasodilating prostaglandins

NB: it is difficult to know whether it is alcohol itself or acetaldehyde which causes these effects.

- Alcohol seems to have a depressant effect on arterial baroreceptors, which reduces the stimulation of the PNS + reduces inhibition of the SNS. The increased SNS drive causes an increased heart rate (tachycardia)

There are also **effects on the endocrine system**.

- Alcohol increases diuresis (polyuria), both by way of volume and a direct effect on ADH (anti-diuretic hormone)
- It reduces ADH secretion, which stimulates diuresis. This is linked to reduced potassium entry into the posterior pituitary

**Chronic Effects**

With long term alcohol consumption, there are chronic **effects on the CNS**.

- Cortical atrophy and a decreased volume of cerebral white matter > dementia
- Cerebellar cortex degeneration > ataxia
- Dementia and ataxia lead to WERNICKE-KORSAKOFF SYNDROME, which is encephalopathy related to the 3rd ventricle and aqueduct
- This eventually leads to KORSAKOFF’S PSYCHOSIS, which is related to the interference with memory (involving the dorsomedial thalamus) which is irreversible. There is a massive link with W-K syndrome to thiamine deficiency, and poor dietary intake of thiamine is often associated with alcoholics (who tend to get most of their calories from alcohol)

There are also classic chronic **effects on the liver**.

In the aldehyde dehydrogenase pathway, alcohol uses up all of the NAD+ stores.

- This affects every metabolic pathway requiring NAD+, and results in a shift away from gluconeogenesis and glycolysis towards ketogenesis, lipid production and fat deposition. This leads to an increase of storage of fats as triacylglycerol in the liver = FATTY LIVER (this is completely reversible, occurs following all alcohol consumption)
- If fatty liver deposits occurs chronically, you start to see inflammatory changes in the liver. There is generation of pro-inflammatory cytokines and free radicals which leads to inflammation of the liver and HEPATITIS
• Inflammation will trigger fibroblasts to start laying down connective tissue, so you start to lose active liver tissue and hepatocyte regeneration = CIRRHOSIS (this is irreversible, and is the stage at which transplants need to be considered depending on extent of damage)

There also appear to be some **beneficial effects on the cardiovascular system**. Evidence suggests that there is a reduced mortality from coronary artery disease, increased HDL levels, increased tPA levels and a reduction in platelet aggregation

In the **gastrointestinal tract**, 15% of alcohol is metabolized to acetaldehyde. Acetaldehyde results in damage to the gastric mucosa, and is carcinogenic therefore poses and increased risk of stomach cancer.

With regards to the **endocrine system**, alcohol stimulates ACTH which leads to increased cortisol synthesis which causes a Cushing’s like syndrome. It is also linked with a decreased testosterone secretion > gynaecomastia.

**HANGOVER**
Symptoms peak as blood alcohol concentration reaches zero, so it is thought that hangover is a **rebound excitation effect**.

• Alcohol deprives you of good quality sleep because of the rebound excitation of the CNS
• Symptoms of a hangover include **nausea and vomiting** (irritant to vagus to vomiting centre), **headache** (vasodilation), **fatigue** (sleep deprivation, rebound), **restlessness** and **muscle tremors** (rebound), **polyuria** and **polydipsia** (decreased ADH secretion).
16. Haemostasis + Thrombosis
Dr Sohag Saleh

HAEMOSTASIS BASICS
Blood vessels act as transportation routes for blood. Blood flows through the circulatory system within blood vessels being pumped by the hear and provides oxygen and essential nutrients for all the cells of the body

• Blood is not a homeogenous liquid and can be more accurately described as heterogenous colloidal suspension, containing numerous cell types, proteins, lipoproteins and immunoglobulins
• If a vessel is damaged it is imperative that blood loss is minimized and the body repairs this as soon as possible.

Haemostasis is an essential physiological process where blood coagulation prevents excess blood loss.

• It occurs when an impermeable platelet and fibrin plug or clot is formed at the site of vessel injury
• All the components for haemostasis are already present within the blood so that they are immediately available when required

Occasionally blood can coagulate within an intact blood vessel.

Thrombosis: A pathophysiological process where blood coagulation occurs within an intact blood vessel and obstructs blood flow.

• The clot becomes life-threatening if it dislodges from the vessel (embolises) and becomes trapped in another vessel
• To prevent this occurring there are a number of physiological anticoagulants already present within the blood.
• Thrombosis can occur within the venous or arterial system:
  o Venous thrombosis (red thrombi) have high fibrin components
  o Arterial thrombosis (white thrombi) have high platelet components

Atherosclerosis
Arterial blood flow is much faster than the blood flow through the veins, therefore it is much harder to form a blood clot. However formation of an atherosclerotic plaque within the subendothelial layer of the blood vessel wall will often form a thrombus within the plaque.

• If the plaque ruptures the thrombus is released into the bloodstream, and if this lodges within a coronary artery it can cause a myocardial infarction

Virchow’s Triad
This triad addresses why thrombi may form within intact blood vessels. Virchow addresses 3 factors which influence the formation of thrombi:

• The rate of blood flow – when blood flow is slow or stagnating, supplies of anticoagulant factors are not replenished and there is an adjustment of balance in favour of coagulation for example during long haul flights
• The consistency of blood – in certain conditions the blood may contain more procoagulation factors than anticoagulation factors, eg Factor V Leiden disease (factor V doesn’t function)
• The blood vessel wall integrity – damaged endothelia results in the blood being exposed to tissue factor, eg in atherosclerosis
Blood

<table>
<thead>
<tr>
<th>Total constituents</th>
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<tr>
<td>Blood cells (45%)</td>
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<td>Blood plasma (55%)</td>
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<tr>
<td><strong>Serum</strong></td>
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<tr>
<td><strong>Clotting factors</strong></td>
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<tr>
<td>Erythrocytes (99%)</td>
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</tr>
<tr>
<td>Thrombocytes</td>
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<td>Water (90%)</td>
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<td>Electrolytes (e.g. Na+, Cl, HCO₃⁻)</td>
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<td>Proteins (e.g. albumin)</td>
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<tr>
<td>Lipoproteins (e.g. cholesterol)</td>
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<tr>
<td>Pro-coagulants</td>
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<tr>
<td>Prothrombin</td>
</tr>
<tr>
<td>Fibrinogen</td>
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<tr>
<td>Clotting factors V, VII-XIII</td>
</tr>
<tr>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Tissue factor pathway inhibitor</td>
</tr>
<tr>
<td>Protein C</td>
</tr>
<tr>
<td>Protein S</td>
</tr>
<tr>
<td>Antithrombin III</td>
</tr>
<tr>
<td>Plasminogen</td>
</tr>
</tbody>
</table>

Blood plasma consists mainly of water, but also contains numerous other substances including lipoproteins and a variety of factors involved in the clotting process.

**Coagulation Cascade**
It is too complicated to try and learn the clotting cascade, therefore there is a simplified theory to break down the cascade into 3 stages:

**Cell based theory of coagulation**
1. **Initiation** – small scale production of thrombin (targeted by anticoagulants)
2. **Amplification** – larger scale thrombin production on platelets surface (targeted by antiplatelets)
3. **Propagation** – thrombin mediated generation of fibrin strands (targeted by thrombolytics)

**ANTICOAGULANTS**
- Target the initiation stage of cell based theory. Tissue factor bearing cells activate clotting factors V + X forming Va-Xa complex known as the prothrombinase complex (usually do not come into contact with each other)
- The prothrombinase complex activates factor II (prothrombin) > factor IIa (thrombin)
- Under normal circumstances, antithrombin (AT-III) will normally inactivate thrombin (endogenous anticoagulation) to prevent continuation of the cascade into the amplification process

There are 4 types of anticoagulants which target different aspects of this process:
- Direct thrombin inhibitors
- Heparin + derivatives
- Factor Xa inhibitors
- Vitamin K antagonists

**Direct Thrombin Inhibitors**
Inhibit thrombin directly, eg **Hirudin + Lepirudin**
- They are administered subcutaneously and are licensed for treatment of heparin induced thrombocytopenia
- **Dabigatran** is the first orally available direct thrombin inhibitor and was only recently approved for the prophylaxis of venous thromboembolism during surgery

**Heparin and derivatives**
Heparin exerts a conformational change and thus activates antithrombin-III making it more potent at inactivating thrombin. It is a natural anticoagulant found on mast cells in the body.
- In addition, its derivatives (low molecular weight heparins) also inhibit factor Xa.
• Heparin has a short half life and is not orally available – must be given at regular intervals or by continuous infusion. The low molecular weight heparins, eg Dalteparin are more effective at inhibiting factor Xa and have longer half lives. They do not require continuous infusion but still are not orally available.

Factor Xa inhibitors
• Fondaparinux (Fpx) was the first direct factor Xa inhibitor but requires once daily subcutaneous administration
• Rivaroxaban is the first orally available, and was only recently approved for the prophylaxis of venous theomboembolism during surgery

Vitamin K antagonists
• Vit K is essential for the production of many different clotting factors
• Warfarin is still the most commonly used oral anticoagulant even though it has a long delay of onset (5 days)
• It has a narrow therapeutic window, unpredictable pharmacokinetics and numerous drug interactions which makes its administration more complex and requires INR monitoring

ANTI-PLATELETS
These target the amplification stage in the cell based theory of coagulation. This involves the activation and aggregation of platelets
• Activation: If the AT-III does not inactivate thrombin, thrombin activates the platelets (via PAR receptors) which induces a conformational shape change (more stellate appearance) which then produces a number of other clotting factors, and ADP
  o Thrombin also releases endothelial bound vWF (von Willebrand factor), which activates factor II (prothrombin) > IIa (thrombin)
• Aggregation: ADP acts on the active platelets via P2Y receptors, leading to platelet aggregation and formation of a clot

There are different pharmacological targets for platelet activation, ie anti-platelets

PAR antagonists
• Thrombin acts on the protease activated receptor (G-protein 7 transmembrane) located on the surface of platelets
• These receptors are linked to Gαq pathway, therefore activation leads to rise in intracellular Ca2+
• This rise in calcium causes a change in shape in the platelet, and causes release of the ADP from dense granules.
• Pharmacology: atopaxar + vorpaxar are in phase III clinical trials, and would act to inhibit this process by preventing platelet activation

ADP receptor agonists
• ADP released from the active platelet has both autocrine and paracrine effects which activate P2Y receptors
• P2Y receptor antagonists are in clinical use, eg Clopidogrel + Prasugrel

Cyclo-oxygenase inhibitors
• PAR activation also liberates arachidonic acid. The action of COX on arachidonic acid in plateletes generates thromboxane A2 (pro-coagulant molecule)
• Pharmacology – low dose 75m aspirin is a COX inhibitor, therefore prevents breakdown of arachidonic acid into pro-coagulant molecules
• At higher doses it inhibits endothelial COX in addition to platelet COX. Usually endothelial COX helps produce the prostacyclin PGI2 (protective with anticoagulant activities), therefore this natural anticoagulant activity is lost
**Glycoprotein IIb/IIa receptor antagonists**
- TXA2 activation by COX causes expression of the glycoprotein receptor on the surface of platelets and these play an important role in platelet aggregation
- **Pharmacology**: antagonists licensed for the treatment of thrombotic disorders, eg abciximab, eptifibatide, tirofiban

**THROMBOLYTICS**
Targets propagation phase: generation of fibrin strands (large scale thrombin converts fibrinogen to fibrin). The fibrin strands wrap around the clot, with the eventual formation of a thrombus within the intact blood vessel.

**Fibrinolytics/clot busters**
These are effective at removing pre-formed clots (anticoagulants/antiplatelets are ineffective).
They convert plasminogen to plasmin, which is a natural protease that degreases fibrin strands
- **Alteplase** is a recombinant tissue type plasminogen activator that is indicated for the treatment of acute MI + ischaemic stroke. It activates plasmin that then degrades fibrin, dissolving the clot – needs to be given within 12 hours of symptom onset
- **Streptokinase** is a bacterial product that is cheap and effective at binding to plasminogen causing a conformational change that exposes the active site – tolerance develops after first administration as it is bacterial therefore body develops immunity
- **Reteplase/tenectepase** are also licensed for acute MI

**TREATMENT OF THROMBOSIS**
Venous red thrombi have a fibrin component – better for anticoagulants
Arterial thrombi are primarily treated with anti-platelets
- Anticoagulants – used for deep vein thrombosis
- Anticoagulants/thrombolytics – pulmonary embolism
- Anti-platelets /thrombolytics – stroke
- Thrombolysis – acute coronary syndrome
- Anti-platelets/anticoagulation – atrial fibrillation
- Anti-platelets – aortic aneurism
17. Atherosclerosis + Lipoprotein Metabolism
Dr Mike Schachter

ATHEROSCLEROSIS

Lipoproteins + Lipid Metabolism
LDL is low density involved in atherosclerosis
HDL is high density, and is considered protective in atherosclerosis

**LIPID METABOLISM**

![Diagram of lipid metabolism]

**EXOGENOUS PATHWAY**

- Dietary fat (triglycerides + cholesterol)
- Intestine
- Chylomicron
- LPL
  - Free Fatty Acids
- Adipose Tissue and Skeletal Muscle
  - Chylomicron remnant

**ENDOGENOUS PATHWAY**

- Liver
  - Remnant receptor
  - Blood Vessel (Atheroma formation)
  - LPL
  - VLDL
  - VLDL
  - IDL
  - LDL

The **Exogenous metabolic pathway** of lipids is concerned with the transport and utilisation of dietary fats

- Dietary fat is broken down in the gastrointestinal tract into cholesterol, fatty acids and mono- and diglycerides. These molecules, together with bile acids, form water-soluble micelles that carry the lipid to absorptive sites in the duodenum
- Normally, virtually all triglyceride (TG) is absorbed, compared with only 50% of cholesterol. Following absorption in the duodenum, chylomicrons are formed which enter the bloodstream via intestinal lymphatics and the thoracic duct
- On entering the plasma, rapid changes take place in the chylomicron. It is hydrolysed by the enzyme lipoprotein (LP) lipase releasing the triglyceride core, free fatty acids and mono- and diglycerides for energy production or storage
- The residual chylomicron undergoes further delipidation, resulting in the formation of chylomicron remnants. These are taken up by a number of tissues. In the liver they undergo lysosomal degradation, and are either used for a variety of purposes including remanufacture into new lipoproteins, production of cell membranes or excretion as bile salts

The **Endogenous metabolic pathway** of lipids is concerned with the breakdown of the chylomicron remnants

- Whilst chylomicrons transport triglyceride from the gut to the liver, VLDL is the analogous particle that transports triglycerides from the liver to the rest of the body. Triglycerides
together with cholesterol, cholesterol ester and other lipoprotein particles are transported in VLDL in the bloodstream, where VLDL undergoes delipidation with the enzyme lipoprotein lipase in a similar way to chylomicrons; this is the endogenous pathway of lipid metabolism.

- Lipoprotein lipase is the main enzyme used in the lipolysis of large VLDL particles, whereas hepatic lipase reacts with the small VLDL and IDL particles.
- It has been shown that small dense LDL particles are the most atherogenic. They are absorbed by macrophages within the arterial wall to form lipid-rich foam cells, the initial stage in the pathogenesis of atherosclerotic plaques.
- The enterohepatic circulation provides a route for the excretion of cholesterol and bile acids.

**NB: Reverse cholesterol transport** – as cholesterol cannot be broken down within the body, it is eliminated intact. Therefore it is taken out of the tissues and transported back to the liver via HDL.

- HDL begins as a lipid-deficient precursor which transforms into lipid-rich lipoprotein. In this form it transfers cholesterol either directly to the liver or to other circulating lipoproteins to be transported to the liver for elimination.

**Atherosclerosis**
An inflammatory fibroproliferative disorder; involving cell proliferation following deposition of lipids in the arteries leading to the formation of an atherosclerotic plaque.

The **pathogenesis of atherosclerotic plaques** involves 7 stages:

- Endothelial damage
- Protective response resulting in production of cellular adhesion molecules
- Monocyte + T-lymphocytes attachment to "sticky" surface of endothelial cells
- Migration through the arterial wall to subendothelial space
- Macrophage uptake of oxidized LDL-cholesterol
- Formation of lipid-rich foam cells
- Fatty streak + plaque formation

The key first event is the movement of LDL into the subendothelium, where it is oxidized by macrophages and smooth muscle cells.

**Endothelial dysfunction**
If the endothelium is intact + functioning normally, you are far less likely to start the atherosclerosis

- Endothelial dysfunction in atherosclerosis is characterised by a series of early changes that precede lesion formation
- The changes include greater permeability of the endothelium, up-regulation of leucocyte and endothelial adhesion molecules and migration of leucocytes into the artery wall.

**Fatty streak formation** is the first recognizable lesion of atherosclerosis

- It is caused by the aggregation of lipid-rich foam cells (derived from macrophages + T cells), within the intima (innermost part of artery wall)
- A complex series of steps is then involved in the development of this streak, including smooth-muscle cell migration, T-cell activation, foam cell formation and platelet adherence/aggregation
- Fatty streaks are common; they may increase in size, remain static or even disappear. Very few form a complex plaque.

**Formation of the complicated atherosclerotic plaque**
The development of an atherosclerotic plaque indicates an advanced stage in the atherosclerotic process, and results from the death and rupture of the lipid-laden foam cells in the fatty streak

- Migration of vascular smooth muscle cells to the intima and laying down of collagen fibres results in the formation of a protective fibrous cap over the necrotic lipid core
• The fibrous cap is the crucial component of the mature atherosclerotic plaque as it separates the highly thrombogenic lipid-rich core from circulating platelets and other coagulation factors.
• Stable atherosclerotic plaques are characterized by a necrotic lipid core covered by a thick vascular smooth muscle rich fibrous plaque.

The **unstable atherosclerotic plaque**

An atherosclerotic plaque may cause complications as a result of its size, reducing lumen diameter and blood flow, its tendency to rupture, or following its erosion.

• Plaque erosion or rupture occurs in plaques that are intrinsically vulnerable.
• Factors that may influence plaque vulnerability include hypertension, high turbulent flow, an increased number of inflammatory cells, a thin fibrous cap with few smooth muscle cells or collagen fibres.
• Both erosion and rupture causes a haemorrhage from the plaque microvessels. This can lead to thrombus formation on the site of the plaque and vessel occlusion.
• Plaque formation can also cause hardening of the arteries, resulting in weakening and thinning of the vessel wall, leading to aneurysm and possibly haemorrhage.
• The vulnerable atherosclerotic plaque must be distinguished from a stable plaque. A patient suffering from a vulnerable plaque may not appear to have a severely reduced lumen area, but the cap may be very thin. Intravascular ultrasound can be used to distinguish between the two plaques, but this is very difficult.

### Types of atherosclerotic lesions

![Diagram of atherosclerotic lesions](image)

**CHOLESTEROL**

**LDL cholesterol**

LDLs are strongly associated with atherosclerosis and CHD events in patients with established CHD (history of angina pectoris, MI etc) and in those without CHD.

• 10% increase in LDL results in a 20% increase in CHD risk.
• This association is also modified by other risk factors including low HDL, smoking, hypertension and diabetes. This modification is apparent especially when total cholesterol and LDL cholesterol are only moderately elevated.

**HDL cholesterol**

Has a protective effect for risk of atherosclerosis and CHD. The lower the HDL cholesterol level, the higher risk of atherosclerosis and CHD.
- This has been shown in both patients with CHD and asymptomatic subjects, in men and women, and is independent of LDL cholesterol and other risk factors
- Tends to have a reciprocal relationship with triglycerides
- Low HDL is also associated with an atherogenic lifestyle, as HDL cholesterol is lowered by smoking, obesity and physical inactivity

**Triglycerides**
Associated with an increased risk of CHD, but poorly understood
- This link is complex, it may be related to low HDL and more atherogenic forms of LDL cholesterol (small dense particles). The small dense particles are most likely to penetrate the vascular wall, and are more likely to be oxidized which is much more atherogenic
- Normal triglyceride: <200mg/dl (2.3mmol/l)
- Very high triglycerides: >1000mg/dl – at high risk of acute pancreatitis
- The effects of cholesterol are not equally bowed

**Cholesterol as a modifiable risk factor**
- In the US, 37% have elevated total cholesterol (5.2mmol/l)
- 58% patients with established CHD had elevated cholesterol.
- 10% reduction in total cholesterol results in 15% of CHD mortality, and 11% reduction in total mortality. However the risk cannot be totally eliminated
- LDL-cholesterol is the primary target to prevent CHD

**DRUG THERAPIES**
There are different classes of drugs used to target cholesterol.
- They have all shown varying degrees of efficacy in delaying the progression of atherosclerosis and some have also been shown to reduce MI and sudden death
- A combination of two agents may be used to achieve greater efficacy in cases of severe hypercholesteraemia. However the most convincing evidence has been demonstrated with statins, and at present they are the first-line drugs in the treatment of dyslipidaemias.

**Statins**
**Mechanism of action**
- The body obtains cholesterol and triglyceride either by synthesising them in the liver or from the diet or storage sites in adipose tissue.
- The cholesterol synthesis pathway is a complex process involving many biochemical pathways and feedback mechanisms in the liver.
- Statins inhibit the HMG-CoA reductase, the enzyme involved in the rate-limiting step in the formation of cholesterol, which is usually responsible for two-thirds of the body’s cholesterol.
- In response to this the hepatocytes up-regulate and increase the number of LDL receptors, increasing binding and removal of LDL cholesterol and LDL precursors from the plasma.
- This results in an increase in HDL levels although the mechanism involved has not been fully established

**Effects**
- Although statins work in the same method, they have varying pharmacological properties (seen opposite)
- The main adverse effects of

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency on Enzyme IC₅₀ (mM)</th>
<th>Cell Selectivity log ratio</th>
<th>Hepatic Metabolism by 3A4</th>
<th>Elimination Half Life (h)</th>
<th>Max % Effect on LDL-C</th>
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</table>
Loses cholesterol from HDL to LDL, therefore inhibiting this protein would prevent this

- Effects of statins on lipids: rule of 6; doubling the dose only results in a 6% reduction in LDL
- Clinical trial findings were that statins decrease LDL cholesterol by 25 to 35%, and there are benefits are various LDL cholesterol levels, evident soon after therapy in some studies. Studies support treatment in various patient groups, including women, the elderly and diabetics.
- COCHRANE review of the therapeutic use has shown some reservation in using statins in primary prevention.
- Statins in patients with normal LDL + raised CRP is very controversial

**Bile acid sequestrants**
These bind to bile acids and prevent reabsorption. The effect on the liver is to increase synthesis and excretion of the cholesterol from the liver. However this does not have a significant effect on triglycerides.

- However, compliance can be a problem as patients may object to the taste and texture, and common adverse events are gastrointestinal bloating, nausea and constipation

**Nicotinic acid**
B-complex vitamin used in therapy at very high doses – multitude of effects on HDL, LDL + triglycerides a well as effects on clotting etc (indicated for all dyslipidaemias except congenital lipoprotein lipase deficiency)

- Small trials (eg HATS) shows large reduction in risk. However the value has been limited by the incidence of adverse effects
- Averse effects include flushing, skin problems, GI disease, liver toxicity, hyperglycaemia and hyperuricaemia
- They are also very expensive, and the dosing is difficult

**Fibrates**
These are effective triglyceride-lowering drugs, and as such, are effective for patients with type III hyperlipoproteinaemia.

- However they have not had the quality or size of trials that statins have, and in the majority of patients they only moderately reduce LDL cholesterol
- Their main mechanism of action is the activation of PPAR alpha receptors (peroxisome proliferator activated receptors)
- They act on receptors in the liver and adipose tissue, resulting in a decreased level of plasma fatty acids and triglycerides
- They have a wide range of mechanisms of action, but have too have many other effects on inflammatory responses, thrombosis, etc therefore are not usually used

**Ezetimibe**
Absorbed then activated as glucuronide in the liver, it is then secreted into bile into the GIT where it blocks cholesterol absorption (85% is endogenous)

- Studies have shown reduces LDL significantly
- It is good in combination with the statins to increase the effect on LDL, but there is no hard data on the end-point (ie reducing CV events, death)
- Outcome trials are to be carried out in 2-3 years time

**NB: Cholesterol ester transfer protein**
Loses cholesterol from HDL to LDL, therefore inhibiting this protein would prevent this

- Eg of this drug is torcetrapib, but trial showed increase in mortality. Reason for this is the associated with increased BP through an increased aldosterone synthesis. This is known as an off-target effect
- However similar drugs are still under trial!
18. Adverse Drug Reactions
Dr Mike Schachter

ADVERSE DRUG REACTIONS
Adverse drug reactions may be caused by either preventable mediation errors, or unpredicted medication event that results in harm to the patient.

Epidemiology of ADRs
ADRs have a substantial morbidity + mortality, being...
- 4th-6th leading COD among hospitalized patients
- 6.7% of serious ADRs incidence
- 0.3-7% of all hospital admissions
- 30-60% preventable

Description of ADRs is by onset, severity + type
- **Onset** may be acute (within 1hr), subacute (1-24hours) or later (>2 days)
- **Severity** may be mild (requiring no change in therapy), moderate (changes required + treatment/hospitalization) and severe (disabling/life-threatening)
  - Severe ADR results in death/life-threatening, requires/prolongs hospitalization, causes disability/congenital anomalies and requires intervention to prevent permanent injury.

Classification
Classifications of ADRs have evolved, and may be either dose-related or time related. The most recent classification divided ADRs into 5 types, remembered by the pneumonic ABCDE (A=augmented pharmacological effect, B=bizarre, C-chronic, D=delayed, E=end-of-treatment)
- **TYPE A** – extension of pharmacological effect (usually predictable + dose dependent)
  - This is usually responsible for 2/3rd of ADRs, eg atenolol + heart block, anticholinergics + dry mouth, NSAIDs + peptic ulcer
  - This is common and usually not very dangerous
- **TYPE B**- idiosyncratic/immunological reactions (usually not predicatable and rare).
  - Includes allergy and “pseudoallergy”
  - Examples include chloramphenicol + aplastic anaemia, ACE inhibitors + angioedema
- **TYPE C** – associated with long-term drug use, and involves dose accumulation.
  - Examples includes methotrexate and liver fibrosis, and antimalarials and ocular toxicity
- **TYPE D**- delayed effects (sometimes dose independent)
  - may exhibit carcinogenicity (eg immunosuppressants)
  - may show teratogenicity= produce fetal malformation (eg thalidomide)
- **TYPE E** – this includes...
  - withdrawal reactions (opiates, benzodizepans, corticosteroids)
  - rebound reactions (clonidine, beta-blockers)
  - “adaptive” reactions (eg neuroleptics + major tranquilsers)
  - eg Clonidine effect: BP increases after treatment to higher than initial level

Allergies
Types of allergic reactions
- **Type I** – immediate, anaphylactic (IgE mediated)
  - Eg anaphylaxis with penicillins
- **Type II** – cytotoxic antibody (IgG + IgM mediated)
  - Eg methyldopa and haemolytic anaemia
- **Type III** – serum sickness (IgG + IgM mediated)
  - Forms antigen-antibody complexes, eg procainamide-induced lupus
- **Type IV** – delayed hypersensitivity (T cell mediated)
  - Eg contact dermatitis
**Pseudoallergies**

Not immunologically determined; these are pharmacologically determined “allergic” responses

- Eg aspirin/NSAIDs > bronchospasm (block COX activity in bronchial smooth muscle, therefore diverting arachidonic acid to make glucotrienes which causes bronchospasm in large amounts)
- ACE inhibitors > cough, angioedema
  - (kininase breaks down bradykinin; accumulation of these in the lung cause cough)

**DOts**

DOts classification is a new three dimensional classification system based on dose relatedness, time relatedness and patient susceptibility.

**Dose relatedness:** Traditionally, immunological and certain other adverse drug reactions have been considered not to be dose related. However, effects of drugs involve interactions between chemical entities and are therefore subject to the law of mass action. This implies that all drug effects, beneficial or adverse, are dose related

- It is clearer to divide adverse drug reactions into reactions that occur at:
  - supratherapeutic doses (toxic effects)
  - reactions that occur at standard therapeutic doses (collateral effects)
  - reactions that occur at subtherapeutic doses in susceptible patients (hypersusceptibility reactions)

- Collateral effects include those that occur due to a different pharmacological effect from the therapeutic action and those that occur through the therapeutic pharmacological effect but in another tissue.

**Time relatedness:** Many pharmacological effects depend on both the concentration of the drug at the site of action and the time course of its appearance there.

- **TIME-INDEPENDENT reactions:** occur at any time during treatment, independent of the duration of the course. They typically occur either due to:
  - Change in dose or concentration at site of action (pharmaceutical effect, ie increased bioavailability, or pharmacokinetic effect, eg worsening renal function)
  - pharmacological response altered without a change in concentration (pharmacodynamics effect, eg due to hypokalaemia)

- **TIME-DEPENDENT reactions:** are of 6 subtypes:
  - Rapid (rapid administration)
    - Eg digoxin induced hypertension
  - First dose (do not necessarily occur with further treatment)
    - Eg ACE inhibitor induced hypotension
  - Early (tolerance develops to the adverse reaction)
    - Eg nitrate induced headache
  - Intermediate (occurs after some time, risk of developing intermediate reaction increases initially, but after period of time it diminishes)
    - Eg venous thromboembolism caused by antipsychotics
  - Late (risk increases with time)
    - Eg corticosteroid induced osteoporosis
  - Delayed (carcinogenic or teratogenic effects)
    - Eg thalidomide

**Patient Susceptibility**

Studies show different sources of susceptibility to adverse drug reactions, including:

- Genetic
- Age
- Sex
- Altered physiology eg pregnancy
- Exogenous factors
- Disease
Causes
Common causes include:
  
  - Antibiotics
  - Antineoplastics*
  - Anticoagulants
  - CV drugs *
  - Hypoglycaemics
  - Antihypertensives
  - NSAID/analgesics *
  - CNS drugs *
*account for 2/3 of fatal ADRs
ADR frequency increases with the number of medications they take. This shows the importance of prescribing the minimal number of medications necessary

Detection
  
  - Subjective report – patient complaint
  - Objective report – direct observation, abnormal findings (OE, lab test, diagnostic procedure)

The problem is the number of patients you are likely to need for the event to occur is very large. This means that rare events will probably not be detected before the drug is marketed.

Yellow Card Scheme
Voluntary scheme introduced after thalidomide disaster; can be used by doctors, dentists, nurses, etc. It includes blood products, vaccines, contrast media.
  
  - For established drugs, only serious or new adverse reactions are reported
  - With new drugs (black triangle drugs), you report ANY suspected adverse reaction

Process of reporting
ADR suspected > ADR confirmed (high probability) > frequency estimated > prescribers informed

DRUG INTERACTIONS

Incidence
The true incidence is difficult to determine, as data for drug-related hospital admissions do not separate out drug interactions, it is easier to focus on ADRs. There is also a lack of availability of comprehensive databases providing information about drug interactions

Other limitations
  
  - Difficulty in assessing OTC and herbal drug therapy use
  - Difficulty in determining contribution of drug interaction in complicated patients
  - Drug interactions are sometimes the principle cause of ADRs with specific drugs, eg statins

There are 3 types of Drug Interactions:
  
  - Pharmacodynamic – relating to the drug’s effect in the body
    - eg receptor site occupancy, interactions at different receptors
  - Pharmacokinetic – related to body’s effect on the drug
    - Ie absorption, distribution, metabolism, elimination
  - Pharmaceutical – drugs interactions outside the body
    - This mostly concerns IV infusions

Pharmacodynamic
These are additive, synergistic or antagonistic effects on the body resulting from co-administration of two or more drugs. Examples include:
  
  - Synergistic actions of antibiotics
  - Overlapping toxicities of ethanol and benzodiazepines
  - Antagonistic effects of anticholinergics (eg amitriptyline + acetylcholinesterase inhibitors)

Pharmacodynamics drug interactions are often deliberate, ie two medications are prescribed to be co-administered as their combined effect is useful
Pharmacokinetic
Pharmacokinetic drug interactions may result from alteration in absorption/protein binding, changes in metabolism or alteration in elimination
- **Alterations in absorption** include chelation = irreversible binding of drugs in the GI tract.
  - Examples of this include tetracycline binding to calcium ions
- **Protein binding interactions** involve competition between drugs for protein or tissue binding sites, that may result in an increase in free drug concentration that enhances the pharmacological effect
  - NB: many interactions that were previously thought to be protein binding interactions are NOT usually clinically significant, with the exception of warfarin
- **Drug metabolism and elimination** has 3 possible routes:
  - Excretion unchanged by kidney
  - 1st phase metabolized by liver + excreted (largely oxidation, reduction + hydrolysis)
  - 1st phase + 2nd phase metabolism (conjugation; glucuronidation, sulphation + acetylation), with excretion by kidney

Drug metabolism interactions
- Drug metabolism may be inhibited or enhanced by coadministration of other drugs. The cytochrome P450 system has been the most extensively studies, and appears to be the most crucial for the handling of commonly used drugs.
- However, phase 2 metabolic interactions are now under research

Cytochrome P450 Substrates
Few clinically used drugs are metabolized by a single predominant isozyme of P450; it is far more common for drugs to be metabolized by more than one isozyme.
- If a drug is co-administered with CYP450 inhibitor, not all isozymes may be inhibited. This means that some isozymes may “pick up slack” for the inhibited isozyme, allowing drug metabolism to continue
- The most common isozymes involved in drug metabolism are CYP3A4 + CYP2D6

Cytochrome P450 inhibitors/Inducers

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Inducers</th>
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<tbody>
<tr>
<td>Cimetidine (H2 receptor antagonist: inhibits gastric acid secretion)</td>
<td>Rifampicin (antibiotic)</td>
</tr>
<tr>
<td>Erythromycin (antibody)</td>
<td>Carbazepine (anti-convulsant)</td>
</tr>
<tr>
<td>Ketoconazole (antifungal)</td>
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</tr>
<tr>
<td>Ciprofloxacin (antibody)</td>
<td></td>
</tr>
<tr>
<td>Ritonavir (HIV drug)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (SSRI = selective serotonin reuptake inhibitor = antidepressant)</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
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</table>

Drug elimination interactions almost always take place in the renal tubule.
- An example of a good interaction is between probenecid and penicillin
- An example of a bad interaction is between lithium, and thiazides

Deliberate interactions
Sometimes drug interactions can have a therapeutic benefit, therefore the drugs are coadministered and the interaction is deliberate. This includes:
- levodopa + carbidopa
- ACE inhibitors + thiazides
- penicillins + gentamicin
- salbutamol + ipratropium
**19. Diuretics**

*Dr Chris John*

**Diuretics** are drugs that act on the renal tubule to promote the excretion of Na+ and Cl-. This increases the osmolarity of the tubular fluid, therefore decreasing the osmotic gradient across the epithelia. The end result of this is the increased loss of water in the urine = **diuresis**.

**THE KIDNEY**

The kidney is the target organ for the action of all subtypes of diuretics. The gross structure renal tubule can be divided into 4 sections:

- The proximal convoluted tubule
- Loop of Henle
- Distal convoluted tubule
- Collecting duct

The kidney filtrate passes through the lumen of the entire tubule, and reabsorbed substances move from the lumen into the interstitium, and eventually into the bloodstream.

**Proximal Convoluted Tubule**

**Passive transport**

- Both sodium and water freely diffuse across the apical membrane into the tubule cells along their concentration gradient
- This concentration gradient is maintained by the Na/K ATPase on the basal membrane, which transports sodium from the cell into the interstitium and eventually into the bloodstream
- Sodium ions exert and osmotic pressure which drives water movement into the interstitium. The oncotic pressure of plasma proteins within the renal capillaries also exert a pull driving water transport
- There are large gap junctions between the PCT cells, which allow for paracellular movement of sodium, chloride, bicarbonate, water and some drugs to diffuse along their concentration gradients

**Active transport**

- On the apical membrane, there is a Na/H exchanger protein that allows sodium to be reabsorbed into the PCT cell in exchange for H+ ions. The Na+ the binds to this transporter is also able to bind to glucose or amino acids, therefore allowing the reabsorption of glucose and amino acids to occur
- For the Na/H exchanger to function, there must be a supply of H+ ions within the cytoplasm of the PCT cell. This is maintained by **carbonic anhydrase enzyme**. There are two subtypes of CA enzyme.
  - In the CYTOPLASM of the PCT cell, CA combines carbon dioxide and water to generate H+ ions and HC03- ions.
    - The HC03- ions are then used for co-transport of sodium into the interstitium on a basal membrane transporter
    - The H+ ions are used to drive the Na+ (and glucose/amino acid) exchanger on the apical membrane
A subtype of CA enzyme in the TUBULE LUMEN uses the H+ ions that are secreted into the lumen (by the Na/H exchanger), and combines them with luminal HCO3- ions to form CO2 + H2O (which then freely diffuse into the PCT cell cytoplasm to be recycled).

The PCT is most significant site of filtrate reabsorption in the kidney; it shows significant Na reuptake, water reabsorption, bicarbonate (65-70%), glucose + amino acid reabsorption. Only 30% of the filtrate is then passed on to then loop of Henle.

Loop of Henle
There are two parts to the loop of Henle; the descending limb and ascending limb.

Descending limb
The descending limb is completely permeable to water. Within the lumen fluid is roughly isotonic, but the interstitial fluid is hypertonic. This means that water freely diffuses across the cell into the interstititium.

Ascending limb
The ascending limb is more complicated. It is completely impermeable to water, and possesses various transmembrane carrier proteins.

• On the apical membrane, there is a sodium, chloride + potassium co-transporter (Na+/2x Cl-/K+).
• On the basal membrane, there is a Na+/K+ co-transporter and a K+/Cl- co-transporter. This means that most of the ions are absorbed into the interstitium, making it more hypertonic and the luminal fluid more hypotonic.
• NB: some K+ diffuses freely back into the lumen, and some Cl- diffuses freely into the interstitium.

Countercurrent principle
The countercurrent principle is the means by which water reabsorption is maximised in the loop of Henle.

To understand this principle, first consider a loop filled with isotonic luminal fluid, and an isotonic interstitium...

• As luminal fluid moves around the ascending limb, sodium, chloride and potassium are reabsorbed into the interstitium, leaving water behind. This makes the interstitial space hypertonic, and the luminal fluid hypotonic.

More fluid then flows into the tubule.
• As luminal fluid passes through the descending loop, water freely flows into the hypertonic intersitium to equilibrate the osmolarity of the lumen and intersitium
  - NB: the osmolarity of BOTH the intersitium + lumen will now be greater than the osmolarity of the luminal fluid
• As the luminal fluid then passes through the ascending limb, more ions are reabsorbed making the intersitium even more hypertonic.

More fluid then flows into the tubule. This cycle continues, with a "countercurrent" flow within the descending and ascending limb. More ions continue to be extracted making the intersitium progressively more hypertonic, increasing the osmotic gradient between the tubular fluid and interstitial space

NB: the most concentrated part of the interstitium is the bottom of the loop.

**Distal Convoluted Tubule**
The relatively dilute filtrate is then passed onto the DCT. However it does still contain some ions which need to be extracted

The DCT is impermeable to water, but has some important carrier proteins.

- A sodium channel and sodium/chloride co-transport protein lie on the apical membrane. The concentration gradient which drives this transport is maintained by the Na/K exchanger and Cl/K co-transporter on the basal membrane
- NB: this distal tubule is under the influence of Aldosterone. Ang II stimulates aldosterone secretion by the adrenal cortex. This enters the DCT and binds to mineralocorticoid receptors which direct the production of the apical sodium channels and basal Na/K ATPase
- In the later distal tubule, aquaporin molecules are inserted on either side of the cell (AQP2 on apical membrane, AQP3/4 on basal membrane) which regulate water movement from the lumen to intersitium. This is under vasopressin control

**The collecting duct**
The collecting duct is very similar to the later distal tubule. However there is also free movement of potassium (from the interstitium > lumen) and chloride (from the lumen > interstitium). The collecting duct is the site of remaining water reabsorption, to prevent excess water from being excreted.
**DIURETICS**

There are 5 main classes of diuretics, each with a different mechanism of action:

- **Osmotic diuretics**, eg mannitol - act on entire kidney tubule
- **Carbonic anhydrase inhibitors**, eg acetazolamide – act principally on PCT
- **Loop diuretics**, eg frusemide (furosemide) – act on ascending loop of Henle
- **Thiazides**, eg bendrofluazide (bendroflumethiazide) – act on early DCT
- **Potassium sparing diuretics**, eg amiloride, spironolactone – act on late DCT and collecting duct

The last 3 classes are of greatest clinical importance.

**Osmotic diuretics**
- These are an example of a drug with no protein target, they just increase the osmolarity of the kidney filtrate, resulting in less water reabsorption and thus more water excretion
- **Mannitol** is a pharmacologically inert substance which is freely filtered into the lumen, but then poorly reabsorbed. It therefore decreases water reabsorption where the nephron is freely permeable to water, including:
  - Proximal convoluted tubule
  - Descending loop of Henle
  - Collecting duct
- **Clinical uses**: not generally used for kidney-related issues, but for:
  - Prevention of acute renal failure
  - Decreasing intra-cranial pressure/intraocular pressure
- **Unwanted effects** include and increased ECF volume, which may be associated with hyponatraemia > nausea, vomiting and pulmonary oedema

**Carbonic anhydrase inhibitors**
- Carbonic anhydrase allows you to extract bicarbonate from the lumen of the PCT (by converting it to CO2 + H2O which are freely absorbed) and generate bicarbonate within the PCT cells (along with H+ ions which are important for driving the apical membrane Na/H exchanger)
- CA inhibitors, eg Acetazolamide, will therefore increase bicarbonate and sodium loss, and thus water loss. Increased tubular fluid osmolarity also decreases water reabsorption in the collecting duct.
- These are relatively weak diuretics, as they only act on the PCT and further reabsorption of sodium occurs in later parts of the kidney
Clinical uses:
- Renal stones – as uric acid deposits are more likely to form in an acidic environment
- Metabolic alkalosis (as it results in increased HCO3- loss)
- Decreasing intra-ocular pressure
- Altitude sickness

Unwanted effects: increased delivery of HCO3- to the DCT increases K+ loss, which might cause hypokalaemia. There is also a reduced H+ excretion, resulting in alkaline urine (normal urine is acidic) and metabolic acidosis

Loop diuretics
- These are the most potent diuretics.
- The most common example is frusemide, which acts on the ascending limb of the loop of Henle. It blocks the sodium-chloride-potassium co-transporter, which means that more ions are passed on to the DCT and collecting duct
- This reduces the osmolarity of the medullary interstitium, therefore less water is reabsorbed.
- An increased delivery of sodium to the distal tubule also increases the amount of K+ lost (via Na/K exchange)
- Loop diuretics can result in 15-30% more of your filtrate being lost (large volumes of water, with Na+, Cl-, K+ + Ca2+/Mg2+ loss)

Clinical uses:
- Oedema (heart failure, pulmonary, renal, hepatic or cerebral)
- Moderate hypertension
- Hypercalcaemia
- Hyperkalaemia

Unwanted effects:
- Hypovolaemia
- Hypotension
- Metabolic alkalosis

Thiazides
- These are mild diuretics which are used as first line treatment of hypertension in the elderly
- Eg Bendrofluazide; blocks the Na+/Cl- co-transport protein in the early DCT (inhibiting 5-10% of Na+ and Cl- reabsorption).
  - This results in an increased osmolarity of the tubule, with a corresponding decrease in water reabsorption in the collecting duct
  - Increased delivery of Na+ results in an increase K+ loss, as well as increased Mg2+ and Ca2+ reabsorption

Clinical uses:
- Hypertension
- Cardiac failure
- Idiopathic hypercalciuria
- Resistant oedema
- Nephrogenic diabetes insipidus (here they have a paradoxical effect whereby they act with an anti-diuretic effect)

Unwanted effects:
- K+ loss
- Metabolic alkalosis
- Diabetes mellitus (S/E = inhibition of insulin secretion)
Potassium sparing diuretics

These are taken to act against potassium loss, acting in the late DCT. There are two different classes of K+ sparing drugs:

- Aldosterone receptor antagonists, eg spironolactone
- Inhibitors of aldosterone-sensitive Na+ channels, eg amiloride

Any other diuretic that has acted in the earlier tubules of the kidney results in increased Na+ and Cl- deposition in the DCT. This results in increased K+ loss, via the basal membrane Na/K exchanger

- Potassium sparing diuretics act to inhibit Na+ reabsorption in the late DCT, and therefore inhibit the concomitant K+ secretion. This results in an increased tubular fluid osmolarity > increased water loss, with an increased H+ retention > increased uric acid loss
- They result in a small increase in urine volume, with a small Na+ loss. They are not particularly useful on their own, but are often taken in conjunction with other diuretics

- **Clinical uses:**
  - Amiloride is taken in conjunction with K+ losing diuretics
  - Spironolactone is used in primary and secondary hyperaldosteronism

- **Unwanted effects:**
  - Hyperkalemia + metabolic acidosis
  - Spironolactone > gynaecomastia, menstrual disorders + testicular atrophy
INTRODUCTION
Anti-emetics/anti-nausea drugs are indicated only when the cause of the nausea/vomiting is known, otherwise they may mask the diagnosis of a potentially serious condition eg digoxin toxicity, diabetic ketoacidosis

Vomiting pathways and stimuli
There are different stimuli that may trigger vomiting pathways:
- From peripheral organs: pharynx, stomach, duodenum, heart, bladder, uterus, viscera + testicles (eg being punched)
- From endogenous toxins/drugs: infections, cancer, chemotherapeutic agents, radiation damage, morphine, estrogen (in early pregnancy), recovery from general anaesthesia
- Motion sickness
- Pain, repulsive sights/smells, emotional factors

Stimuli from peripheral organs stimulate the visceral afferent pathway. Visceral afferents are nerve endings in the viscera with 5HT3 receptors (serotonin receptors). They transmit signals to the vomiting centre either via:
- the nucleus of the solitary tract (which involves muscarinic Ach receptors and type 1 histamine receptors)
- the chemoreceptor trigger zone (which lies on the floor of the 4th ventricle, is close association with the medulla but OUTSIDE the blood brain barrier – this involves dopamine type 2 and 5HT3 receptors)

Endogenous toxins/drugs also tend to stimulate the 5HT3 pathway (visceral afferent)

The Labyrinth and Vestibular nuclei are important in motion sickness information, and involve muscarinic Ach and type 1 Histamine receptors. It is though that the vestibular nuclei then communicate with chemoreceptor trigger zone via CSF
In contrast, pain, repulsive sights/smells and emotional factors activate the Sensor afferent CNS pathways. These transmit signals to higher centres for integration, involving muscarinic Ach and type 1-histamine receptors. The higher centres then stimulate the vomiting centre
PROMETHAZINE
This is a phenothiazine derivative. Its mode of action is to act as a competitive antagonist at H1, AchM and D2 receptors (order of potency of antagonistic action H1>AchM>D2)

- It therefore acts centrally (vestibular nuclei, NTS, higher centres + vomiting centre) to block the activation of the vomiting centre

Clinical uses
Use as an antiemetic:
- Motion sickness – normally prophylactically
- Disorders of the labyrinth, eg Meniere’s
- Hyperemesis gravidarium
- Pre/post-operatively

Other uses
- Relief of allergic symptoms
- Anaphylactic emergency
- Night sedation + insomnia

Unwanted effects
- Dizziness
- Tinnitus
- Fatigue
- Sedation (although excitation in excess)
- Convulsions
- Anti-muscarinic side-effects

Pharmacokinetic considerations
- Administer orally
- Onset of action 1-2 hours, peak at 4 hours
- Duration of action 24 hours

METOCLOPRAMIDE
This is a dopamine receptor antagonist
Its mode of action is to act at D2, H1 and AchM receptors (order of potency). It has two sites of action:
- Centrally, especially at the chemoreceptor trigger zone
- Acts in the GIT, to increase smooth muscle motility, accelerate gastric emptying and accelerate transit of intestinal contents

Pharmacokinetic considerations
- As it causes faster transit through the gut, co-administered drugs will move faster through the system, which may affect their bioavailability. This is especially important for drugs of a narrow therapeutic window, ie digoxin
- Faster transit may also compromise nutrient supply. This is especially important in diabetes mellitus
- May be administered orally; rapidly absorbed and undergoes extensive first pass metabolism
- May also be given intravenously
- Crosses BBB and placenta

Clinical use
Used to treat nausea and vomiting associated with:
- Uraemia (severe renal failure)
- Radiation sickness
- GI disorders
- Cancer chemotherapy (eg cisplatin; requires high doses)

Unwanted effects
In CNS:
- Drowsiness
- Dizziness
- Anxiety
Extrapyramidal reactions (Parkinsonian-like syndrome; rigidity, tremor, motor restlessness)

NB: no anti-psychotic actions

**In the endocrine system**
- Hyperprolactinaemia (blocking dopamine > increased prolactin)
- Galactorrhoea
- Disorders of menstruation

**HYOSCINE**
This is an anti-muscarinic drug. Its mode of action is to act on AchM, D2 + H1 receptors (order of potency AchM > D2 = H1). It acts centrally, especially in the vestibular nuclei to block the activation

**Clinical use**
- Prevention of motion sickness
- Little effects once nausea/emesis is established
- Pre-operative

**Unwanted Effects**
Typical anti-muscarinic side effects include:
- Drowsiness
- Dry mouth
- Cyclopegia
- Mydriasis
- Constipation (although this only tends to occur at high doses)

**Pharmacokinetic considerations**
- Can be administered orally (peak 1-2 hours), intravenously or transdermally

**ONDASETRON**
This is a 5HT3 receptor antagonist which acts to block transmission in visceral afferents and the chemoreceptor trigger zone.

**Clinical uses**
- Main use in preventing anti-cancer drug-induced vomiting, especially following cisplatin treatment
- Radiotherapy-induced sickness
- Post-operative nausea and vomiting

**Unwanted effects**
- Headache
- Flushing/sensation of warmth
- Constipation

**Pharmacokinetic considerations**
- Well absorbed, therefore oral administration + excreted in urine
INTRODUCTION
Peptic ulcers may be gastric or duodenal, but the treatments are relatively similar

The integrity of the **gastrointestinal mucosal barrier** is important in maintaining a disease free state. The following **protective factors** lubricate ingested food and protect the stomach from attack by acid and enzymes:

- Mucus from gastric mucosa creates a gastrointestinal barrier
- Bicarbonate ions trapped in mucus generate a pH of 6/7 at mucosal surface
- Locally produced prostaglandins stimulate mucus and bicarbonate production (paracrine action) and inhibit gastric secretion

However there are other factors we need to convert food into a thick semi-liquid paste (chime) which have the **potential to damage** the mucosal barrier

- Acid secretion from parietal cells of the oxyntic glands in the gastric mucosa
- Pepsinogens from the chief cells which can erode the mucus layer

Normally, the protective and destructive factors are in a state of harmony, ie balanced.

**Peptic ulcer disease** is the imbalance of the protective and potentially damaging factors. There are many factors that may contribute to the underlying pathology of damage to the mucosal GI barrier, for example:

- Helicobacter pylori infection (may also play a role in pathogenesis of gastric cancer)
- Increased acid secretion
- Reduced bicarbonate secretion
- Reduced thickness of mucus layer
- Increase in pepsin type I
- Decreased mucosal blood flow

The **cause** of peptic ulcer disease is not fully understood, despite affecting 1 in 10 of the population in developed countries

- However genetic redisposition, stress and smoking are known risk factors.
- Food type and alcohol consumption are also suggested risk factors

The **aims of drug treatment** of peptic ulcer disease are to eliminate the cause of mucosal damage and promote ulcer healing.

**ANTIBIOTICS**
These are used to eliminate **Helicobacter Pylori**, which is a Gram negative bacterium. Clinical importance of H. pylori:

- 50-80% of the population worldwide are chronically infected (low grade infections which causes gastritis)
- 10-20% of these cases go on to develop peptic ulcer disease or neoplasia
- Almost 100% of patients with duodenal ulcers and 80-90% with a gastric ulcer are infected with H. pylori

**H. Pylori infection**

- The **risk factors** for acquiring infection are known, and the **methods of transmission** are uncertain although spread is linked to socioeconomic conditions and contact with animals + contaminated species
- With regards to treatment, 90% eradication should be aimed for in 7-14 days.
  - Infection may be difficult to eradicate; however, if eradication is successful, the recurrence of a duodenal ulcer after healing falls from 80% to 5%
**Triple Therapy** is currently the best practice in treating peptic ulcer disease. A single antibiotic is not sufficiently effective. This is partly due to the development of resistance

1. **Metronidazole** (active against anaerobic bacteria and protozoa) or **amoxicillin** (broad spectrum antibiotic) are used depending on the pattern of local resistance
2. **Clarithromycin** is an antibiotic with a macrolide structure. It works by inhibiting the translocation of bacterial tRNA.
3. **Proton pump inhibitors** (PPIs) improve antibiotic efficiency (possibly by increasing gastric pH which improves the stability and absorption of the antibiotic)

Another example of a drug combination used in triple therapy is **H2 receptor antagonists, clarithromycin and bismuth.**

There are 3 problems associated with triple therapy

- Compliance (high prevalence of nausea associated with treatment)
- Development of resistance (although vaccinations are being developed)
- Adverse response to alcohol (especially metronidazole, which interferes with alcohol metabolism)

**INHIBITORS OF GASTRIC SECRETION**

**Gastric Acid Secretion**

Parietal cells contain an extensive secretory network called canaliculi (foldings of membrane to increase surface area), from which HCl is secreted by active transport into the stomach. The enzyme responsible for this active transport is H+K+ ATPase, which transports the H+ ions against a steep concentration gradient.

**HCl formation**

- Carbonic anhydrase converts one molecule of CO2 and one H2O into a bicarbonate and hydrogen ion
- The bicarbonate ion is then exchanged for a chloride ion on the basal cell (HCO3- diffuses into venous blood)
- Potassium + chloride ions freely diffuse into the canaliculi, and then hydrogen ions are pumped out of the parietal cell into the canaliculi in exchange for potassium ions, via H+/K+ ATPase
- Hydrogen + chloride ions then combine within the canaliculi, to form HCl which moves into the stomach

Normally the H+/K+ ATPase is stored in vesicles within the parietal cells, but they are released and the cells secrete acid in response to 3 types of stimuli:

- Histamine type 2 receptors (most important)
- Acetylcholine (from PNS activity via vagus nerve + enteric nervous system)
- Gastrin (least significant)

**Pathway to secretion**

- Upon stimulation, adenylate cyclase is activated within parietal cells.
- This increases intracellular cyclic AMP, which leads to the activation of protein kinase A
- PKA phosphorylates vesicle proteins involved in the transport of H+/K+ ATPase from the cytoplasm to the cell membrane
**Proton Pump Inhibitors**
Proton pump inhibitors like Omeprazole inhibit basal and stimulated gastric acid secretion from the parietal cells by over 90%

**Mechanism of Action**
- PPIs are irreversible inhibitors of the H/K ATPase.
- They are inactive at neutral pH, but in the acidic environment of the canaliculi, they are protonated and rearranged into their active form.
- The active form then binds covalently to the gastric proton pump, deactivating it
- The fact that PPIs are only activated in an acidic environment concentrates their action in the stomach and minimizes their effect on ion pumps elsewhere in the body

**Uses:**
- Component of triple therapy
- Peptic ulcers resistant to H2 antagonists
- Reflux oesophagitis

**Pharmacokinetics:**
- Orally active
- Administered as enteric coated slow-release formulation
- Duration of action 2-3 days (due to accumulation in canaliculi)

**Histamine Type 2 Receptor Antagonists**
H2R antagonists, eg cimetidine and ranitidine, inhibit gastric secretion by approximately 60% and are less effective at healing ulcers than PPIs.

**Mechanism of action**
Competitive antagonism of histamine at the parietal cell H2 receptor suppression normal acide secretion via two mechanisms:
- Histamine released by ECL cells in the stomach is blocked from binding on the parietal H2 receptors > reduced acid secretion
- When bound, other substances that promote acid secretion (gastric/Ach) also have a reduced effect

They are orally administered and well absorbed with few side effects. However withdrawal from treatment often results in relapses, therefore are seen to be less useful than PPIs

**Antimuscarinics**
Although Ach is important in stimulating acid secretion, antimuscarinics have little use as anti-ulcer drugs.

**CYTOPROTECTIVE DRUGS**
These drugs enhance mucosal protection mechanisms and/or build a physical barrier over the ulcer

**Sucralfate** is a polymer containing aluminium hydroxide and sucrose octasulphate.

**Mechanism of action**
- It acquires a strong negative charge in an acid environment, ie the stomach. This negatively charged compound then binds to positively charged groups in large molecules such as proteins/glycoproteins, forming gel-like complexes
- These gel-like complexes coat and protect the ulcer, limiting H+ diffusion and pepsin degradation of mucus
- Other effects include increasing prostaglandin production, mucus and bicarbonate secretion, and reducing the number of H. pylori bacteria.

**Side effects:**
- Most of the orally administered drug remains in the gastrointestinal tract
- This may causes constipation, as well as reducing absorption of some other drugs eg antibiotics and digoxin

**Bismuth chelate** is a drug that acts like sucralfate, and is used in triple therapy for resistant cases.
**Misoprostol** is a stable prostaglandin analogue that mimics the action of locally produced prostaglandins to maintain the gastroduodenal mucosal barrier

- It is used in the prevention of NSAID induced gastric ulcers. NSAIDs block the COX enzyme required for endogenous prostaglandin synthesis from arachidonic acid

**Mechanism of action**

- It acts on the gastric parietal cells, inhibiting acid secretion via G-protein coupled receptor mediated inhibition of adenylate cyclase, which leads to decreased intracellular cyclic AMP and decreased proton pump activity
- At lower doses, it may also stimulate increased secretion of the protective mucus that lines the gastrointestinal tract, and increase mucosal blood flow thereby increasing mucosal integrity

**Unwanted effects**

- Diarrhoea
- Abdominal cramps
- Uterine contractions
- Contraindicated in pregnancy, as is also used in abortion as it induces premature labour.

**ANTACIDS**

These are mainly salts of Al3+ and Mg2+.

- They undergo a neutralization reaction to neutralize stomach acid, therefore raise the gastric pH and reduce pepsin activity
- They are primarily used for non-ulcer dyspepsia (indigestion/upset stomach), as well as for heartburn and gastroesophageal reflux disease
- They also have some use in reducing duodenal ulcer recurrence rates

**Gastroesophageal reflux disease**

GERD results from the reflux of stomach and duodenal contents into the oesophagus, resulting in inflammation (oesophagitis)

- Occasional/uncomplicated GERD is commonly known as heart burn, and can be treated by self-medication with antacids and H2 antagonists
- Chronic GERD may cause Barrett’s Oesophagus (pre-malignant mucosal cells) and potentially oesophageal adenocarcinoma
  - This is treated with PPIs (or H2 antagonists)
  - They are also combined with drugs that increase gastric motility and emptying (eg dopamine type 2 receptor antagonists such as **metoclopramide**)**
INTRODUCTION

Clinical Uses
The major clinical uses of NSAIDs are:

- **Analgesic** (relief of mild-to-moderate pain)
  - Toothache, headache, backache
  - Some post-operative pain
  - Dysmenorrhea (menstrual pain)
- **Antipyretic** (reduction of fever) eg in influenza
- **Anti-inflammatory** (reduction of inflammation) in many diseases such as:
  - Rheumatoid arthritis
  - Osteoarthritis
  - Other musculo-skeletal inflammation
  - Soft tissue injuries (Strains/sprains)
  - Gout

Many people in the UK take NSAIDs. They are widely prescribed and often available over the counter without a prescription. They are being taken by 15% of the elderly population at any one time. Although usually safe when used correctly, they can have extremely serious side-effects, particularly with long term use or when used at high therapeutic doses. They are responsible for 1200 deaths per year.

Mechanism of action
NSAIDs inhibit the production of a specific family of inflammatory lipid mediators called prostanoids.

- These are derived from arachidonic acid, and include prostaglandins, prostacyclins and thromboxanes
- NSAIDs inhibit the enzyme COX (cyclo-oxygenase), which is the rate-limiting step for the production of all prostanoids (converts arachidonic acid > prostaglandin H2)
- Prostanoids are ubiquitous compounds, found in most tissues. They cannot be stored, but are released immediately when they are synthesized
  - They act through a large number of different, specific prostanoids receptors to produce a highly complex array of actions, some, but not all of which, are pro-inflammatory
- The diversity of actions of prostanoids explains why inhibiting their synthesis with NSAIDs can have many unwanted effects.

Isoforms of COX

**COX-1** is constitutive (i.e. it is present all the time)

- It is found in nearly all cell types (it is ubiquitous) and its actions are physiological (main roles are in the regulation of homeostatic functions)

**COX-2** is mainly inducible (i.e. it is made in response to specific stimuli).

- COX-2 is also very widespread. It is made predominantly (but not exclusively) by pro-inflammatory cells such as leukocytes.
Again, it does have a role to play in the regulation of some physiological functions but its actions are primarily pro-inflammatory (pathological)

Both COX isoforms catalyse two different reactions:
- The first step is an oxygenation, which converts arachidonic acid to PGG2
- The second step is a peroxidation, catalysed by a different part of the enzyme, which converts PGG2 to the product PGH2

PROSTANOIDS + NSAIDS
Prostanoids are found in most tissues, and are not pre-formed and stored, but rather are synthesized and metabolized quickly.
- They are receptor mediators for G-protein coupled receptors.
- These are all G-protein coupled, with many cAMP second messenger systems. The overlap of affinity of the different receptors of the prostanoids, as well as physiological and pathological actions, makes their effects extremely complex

If we consider their effects on Prostaglandin E2 (PGE2)...
- Analgesic action = lowers pain threshold. Stimulation of PG receptors on nerve endings sensitizes nociceptors to chemical and thermal stimuli which cause pain, therefore blocking perception of PGE2 > raising threshold of the nociceptors thus reducing perception of pain
- Pyrogenic action = PGE2 stimulates hypothalamic neurons initiating a rise in body temperature (thus responsible for internal thermostat), therefore by blocking its production we can prevent this increase in body temp (although only temporary)
- Anti-inflammatory action = PGE2 has complex effects on immune and inflammatory pathways ...
  - It enhances Th1 cell differentiation and also Th17 cell expansion. These cells often contribute to autoimmune conditions, as Th1 cells produce IFN-γ and Th17 cells produce IL-17, both of which contribute to immune inflammation, which can cause the binding of antibodies to self-tissue.
  - The anti-inflammatory actions of NSAIDs are not explained by the inhibition of PGE2 alone, the inhibition of other prostanoids is important.

NB: Role of PGE2 in gastric cytoprotection
- This explains the undesirable effects of NSAIDs.
- PGEs downregulates gastric acid secretion, and stimulates the release of mucus and bicarbonate onto the stomach surface
- This protects the stomach lining (cytoprotective), therefore prolonged use of NSAIDs may result in increased HCl production and a reduction/loss of the protective mucus and bicarbonate > increased risk of gastric ulceration

Consequences of Prostanoid inhibition
The consequences of inhibiting all the prostanoids can be difficult to predict with accuracy; sometimes NSAIDs tilt the balance between mediators, for example in the airways:
Here, COX enzymes can catalyse the conversion of arachidonic acid to prostanoids, which cause bronchodilation. However 5-lipoxygenase (LOX) enzymes catalyse the conversion of arachidonic acid to leukotrienes, which cause bronchoconstriction.

- If NSAIDs are used, prostanoid production will be blocked and there will be no bronchodilation; bronchospasm will therefore occur as there are only the effects caused by leukotrienes.
  - This is especially true for asthmatics, therefore this is a possible test for asthma

- Dual COX and LOX inhibitors are under development, although they are nothing close to clinical trials yet.

**NSAIDs**

**Ibuprofen and Indomethacin**

- Typical non-selective NSAIDs which inhibit COX reversibly
- Inhibit both COX-1 and COX-2 (with equal efficacy)
- Have anti-inflammatory, analgesic and anti-pyretic actions

**Aspirin**

This is a unique NSAID, as it binds irreversibly to COX enzymes, as well as with higher avidity to COX 1

- The consequences of this irreversibility are that its actions are longer-lasting, and can only be reversed by de novo synthesis of new enzymes.
- Its high affinity for COX 1 (+ its irreversibility) is also the unique property which allows it to be used for long-term treatment to reduce platelet aggregation.
  - Thromboxane A2 are produced by platelets, enhancing platelet aggregation
  - PGI2 is produced by endothelial cell, and inhibits platelet aggregation
  - A standard NSAID will have no effect. But Aspirin inhibits all of thromboxane production by COX1 by platelets. The platelets do not have a nucleus, therefore are unable to synthesise more enzymes and thus this effect is profound.
  - However prostacyclin is also synthesised by COX2, so the relative inhibition is less. Endothelial cells can also synthesise new COX enzymes, therefore the inhibition again is less.
  - Inhibition of PGI2 is proportional to inhibition of COX-2. Anti-platelet actions of Aspirin are due to the very high degree of COX-1 inhibition which effectively suppresses TxA2 production by platelets, as well as the covalent binding which permanently inhibits platelet COX-1. It is also helped by the relatively low binding capacity to inhibit COX-2.
  - The major side-effects of aspirin seen at therapeutic doses are:
    - Gastric irritation and ulceration
    - Bronchospasm in sensitive asthmatics
    - Prolonged bleeding times
    - Nephrotoxicity

**NSAID side effects**

**Reasons for NSAID use**

Patients taking NSAIDs for their analgesic properties tend to take them occasionally, and so there is a relatively low risk of side effects. Patients taking NSAIDs for their anti-inflammatory properties often take them for sustained periods and in high doses, and so there is a relatively high risk of side effects.

**How can we obtain the desirable therapeutic effects whilst avoiding unwanted side-effects?**

It was previously believed that COX-2 was pathological, and COX-1 was physiological, though we now know that this is not true. But this misconception was central to the development of selective COX-2 inhibitors.

**COX selective NSAIDs**

- The two isoforms COX-1 and COX-2 are structurally slightly different, as COX-2 has a wider active site.
This means that COX-2 can be inhibited selectively
- Celecoxib selectively inhibits COX-2, and so there is less effect on COX-1 mediated processes than conventional NSAIDs such as Ibuprofen and Indomethacin, resulting in fewer risks of gastric ulceration

- Comparing the relative risks of CVS/GI side effects associated with NSAID use shows that non-selective NSAIDs result in parallel increase in risk of side-effects, however:
  - COX-1 selective (eg aspirin) results in more GI damage per unit dose
  - In contrast, COX-2 selective results in much less GI effects, but a much larger increase in CVS-side effects
- COX-2 inhibitors may selectively inhibit PGI2 production and spare Txa2 production leading to more platelet aggregation.
  - Although this mechanism is unclear, there is debate over the safety of the COX-2 inhibitors, therefore NICE guidelines recommend they are only used in patients at high risk of GI side effects

**Strategies for limiting effects of NSAIDs**
- Topical application
- Administration with omeprazole or other proton pump inhibitor to protect the stomach

**Paracetamol**
This is a good analgesic for mild-to-moderate pain, and has antipyretic activity.
- However it does not have any anti-inflammatory effect so is NOT an NSAID
- Despite its common use, the mechanism of action is poorly understood.
  - Hypotheses have included a third isoform of COX (COX-3), cannabinoid receptor action, interaction with endogenous opioids, but the most recent hypothesis is due to a central effect

**Side-effects**
- Paracetamol is generally a very safe drug, but overdose may cause irreversible liver failure
- This is because high levels of a minor metabolite of paracetamol (N-acetyl-p-benzoquinoneimine) are produced.
  - This metabolite is normally safely conjugated with glutathione, but if a lot of paracetamol is taken, the glutathione levels are depleted and the metabolite oxidises thiol groups of key hepatic enzymes and causes cell death, resulting in organ failure.
- The antidote for paracetamol poisoning is to add a compound with a –SH group, usually intravenous Acetylcystine, or occasionally oral methionine
- Prompt treatment is required to prevent death, however legal restrictions on sales of paracetamol have significantly reduced the number of successful suicides in the UK
INTRODUCTION

Opiates refer to the alkaloid derivative of the poppy, Papaver somniferum. There are about 50 different opiate-like substances found within the poppy, and they have been used medicinally by humans for a very long time.

- By far the most prevalent opiate found in the poppy is Morphine. Anywhere between 9-15% of the opiates found within an opium poppy is morphine. The second highest concentration is Codeine. These are two natural opiates. After this there are Thebaine and Papaverine.

Chemical structure

The most important feature of the chemical structure of all the opiates is their tertiary amine group; conferring the pharmacological actions of the drug, particularly analgesic action. Altering this structure is a good target for antagonists, which may work by making this a quaternary amine group.

- Other important features are the hydroxyl groups at positions 3 and 6. Drug companies have worked to modify these side groups in order to produce more potent drugs like heroin and codeine.
- Heroin and codeine are produced by simple modifications of morphine at these hydroxyl side groups.
  - Heroin (di-acetyl-morphine) is acetylated, therefore has acetyl groups at positions 3 and 6, making it much more potent than morphine
  - Codeine (a natural opiate; methyl-morphine) has a methyl group at position 3, making it less potent than morphine
- Other drugs have a much more complicated structure, and cannot be so easily compared to morphine.
  - Methadone still has a tertiary amine, so is still considered a natural opiate
  - In contrast, Fentanyl may be 80x more potent than morphine, but it has little structural similarity

Pharmacokinetics

Morphine

- Can be orally administered (40-50% bioavailability)
- Is extensively metabolized by the liver into morphine-6-glucuronide (glucuronidation = large glucuronide groups attached at position 6), with effects taking action after about 30 minutes
- More commonly, morphine is administered intravenously in a hospital setting
- It is then almost completely metabolized in the liver, and then picked up by the kidney to be excreted in the urine
- Morphine-6-glucuronide is an active metabolite, and probably more potent than morphine, therefore it contributes to the pharmacological effects
- A large proportion of morphine-6-glucuronide ends up in the bile, secreted into the gut where it is liberated from morphine
- At physiological pH, morphine is largely ionized – can be seen that the pharmacokinetics are relatively complicated

Codeine is largely an orally administered drug, in contrast to intravenous morphine

- This means that only 5-10% of the total possible effect is seen, so it appears a lot less potent than it actually is

Fentanyl is very lipid soluble, therefore is administered in various preparations such as lollipops (buccal), patches (dermal), intranasal spray
It is a lot more orally bioactive than morphine or codeine. A large proportion of the drug gets into the systemic circulation via the mucous membranes, with its bioavailability between 50-100%.

**Heroin** is metabolized in a similar way to morphine, but in addition it is metabolized by esterases in the blood.
- This means the half-life of heroin is much shorter; a property which makes it more addictive.

**Methadone** is commonly used as a morphine/heroin replacement, often for weaning off addicts.
- It is very lipid soluble, and has rapid and efficient distribution around the body.
- This means the half-life is much longer than the other opiate (up to 150 hours), therefore maintaining a low level of opiate within the blood for a long time.

**Mechanism of action**
Opiates act via specific “opioid” receptors.
- These are endogenous receptors, synthesized because we have **endogenous opioid peptides** produced in the body, including endorphins, enkaphalins and dynorphins/neoeendorphins.
- There are 3 types of opioid receptors, to which the endogenous opioids bind with different affinity. The most important is the **µ receptor**, which mediates most of the pharmacological effects, but there are also **δ** and **κ receptors**.
  - **Endorphin** release is classically associated with exercise, and the feeling of a “high”. Endorphins pretty much bind to all three types, but particularly to µ receptors. Which are found in the brainstem, and thalamus
  - **Enkephalins** activate delta receptors best; found in the nucleus accumbens, cerebral cortex and amygdala
  - **Dynorphins** activate kappa receptors, which are found in the limbic system, diencephalon, brainstem and spinal cord

**Cellular mechanism**
- Opioids binding to their G-protein coupled receptors > decrease adenylate cyclase activity, which dampens down the capacity of the neurone to produce cAMP, and as a result cellular signalling is decreased.
- At the membrane level, they increase the capacity for K+ to leave (hyperpolarisation), and decrease the capacity for Ca2+ to enter the cell. This decreases the ability to excite the neurone and release transmitters. This is a depressant effect.

**PHARMACOLOGICAL ACTIONS**
The main clinical use of opioids is analgesia, although in the past they were marketed as antitussives (act via depression of the cough centre).
- Illegally, they may also be used to induce euphoria.
- Side effects of opioids include: depression of respiration (action on medulla), stimulation of chemoreceptor trigger zone (> nausea/vomiting), pupillary constriction and GI effects.
Analgesia

In terms of analgesic use, the opioids decrease pain perception and increase pain tolerance.

**Ascending pathways:**
- From the periphery, sensory afferent neurons transmit signals of painful stimuli to the spinal cord (where there is a level of processing), and this information is then transmitted to the thalamus.
- The thalamus is the central integrating centre, and information is the relayed to the cortex.

After pain has been relayed to the brain, there are **descending inhibitory pathways:**
- The peri-aqueductal grey (PAG) area in the midbrain is where the information is first sent to. This is the part involved in pain tolerance.
  - This is then passed on to the nucleus raphe magnus (NRM). From the medulla, the inhibitory neurons are sent down the spinal cord to diminish the feelings of pain.
- The nucleus reticularis paragigantocellularis (NRPG) is a system activated before the information is relayed to the brain. So an aspect of descending inhibition is sent down even before the information is sent to the brain (auto feedback).
  - The NRPG is the part involved in pain perception. It activates the NRM to try to suppress the sensations of pain.
- The hypothalamus is very important, and can either increase or decrease the descending inhibition.

The locus coeruleus (LC) (noradrenaline producing neurones) is strongly linked to the **stress response.** It is a nucleus in the brainstem associated with physiological responses to stress and panic.
- As long as the sympathetic nervous system is activated, the LC inhibits our ability to sense pain, e.g. during exercise.

If we look at the **dorsal horn of the spinal cord** itself, the descending neurons can either:
- synapse directly with neurons in the spinal cord, inhibiting the transmission of information.
- Synapse with the short inhibitor interneurons of the substantia gelatinosa, thus indirectly inhibiting the transmission of pain perception.

**Analgesic action of opioids**
Opioids have a profound effect within the dorsal horn. They suppress the relay of information from the periphery to the brain. There is a huge concentration of opioid receptors within the spinal cord.
- Opioids are depressants, and they decrease the ability of information to be passed from sensory afferents to spinothalamic neurons > decreased pain perception.
- Opioids increase pain tolerance by activating the PAG, and by activating the NRPG. This will increase activation of the descending inhibitory pathway.

**Euphoria**
Opioids produce euphoria by acting on u-receptors on the mesolimbic dopamine neurons arising in the ventral tegmental area and terminating in the nucleus accumbens.
- It is dopamine released in the nucleus accumbens which causes euphoria.
- GABA would normally suppress this effect. Opiates suppress GABA by binding to μ receptors on the cell body. This increases dopamine, and there is a euphoric response.
Anti-tussives

Opioids are also very good anti-tussive agents, particularly codeine (suggests methylation at the 3 position is particularly important)

- A cough is where there is irritation in the upper airways, so sensory afferents are activated. This information is relayed by the vagus to the cough centre
- The cough centre has a high concentration of serotonin receptors in the dorsal raphe nucleus. From here, information is sent back to the airways and a cough is initiated.
- Acetylcholine and neurokinins are very important in mediating the cough
- Codeine both inhibit the receptor activation within the cough centre, and suppresses the release of ACh and NK within the upper airways.

Unwanted actions

Respiratory depression

- This occurs to some degree with any dose of opioid; they act on central chemoreceptors which signal to the medulla to increase/decrease respiration, which normally respond to arterial CO2 pressure
- Opioids densities the chemoreceptors (via μ receptors), therefore > loss of sensitivity to arterial CO2 and thus the ability of the medulla to control respiration
- This is the main cause of death in overdose

Nausea/vomiting

Opioids act centrally within the chemoreceptor trigger zone

- Normally, the trigger zone is naturally suppressed, but may be activated by signals from the stomach and intestines
- Opioids cause you to lose this inhibition. They activate the trigger zone, relaying information to the medullary vomiting centre > vomiting reflex

Miosis (“pin-prick pupils”)

Normally, light hits the retina, this information is relayed via the optic nerve to the pretectal nucleus, to the Edinger-Westphal nucleus, to the oculomotor nerve, to the ciliary ganglion and to the iris

- Opioids cause stimulation of the oculomotor nerve, which signals via the ciliary ganglion > pupillary constriction
- This is a diagnostic feature of heroin overdose.
  - Normally, when someone is unconscious, there are dilated pupils as CNS function is depressed (> loss of partial constriction)
  - However, in a heroin overdose, the pupils are massively constricted due to the large number of opioid receptors within he oculomotor nucleus.

Effect on GI tract

The enteric nervous system is the nervous system of the gut. Within this system, there is a huge concentration of opioid receptors (μ and κ)

- As opioids are depressant drugs, they decrease gastric emptying and GI motility
- This leads to increased water absorption and constipation.

Hospital time is often increased because of the opioids used to treat pain resulting in large GI disturbances

Allergy

Many patients seem to experience an allergic response to opioids

- This is not anaphylaxis, but rather a G-protein receptor mediated activation of mast cells and release of histamine
- Present with pruritis (itching), urticaria (hives), and hypotension (due to vasodilation)
PROBLEMS ASSOCIATED WITH LONG-TERM USE

**Tolerance** to opioids seems to be due to a direct tissue tolerance

- When we take opioids for a long time, are tissues respond via an increased number of a group of molecules called **arrestins**
- These molecules cause receptor internalization. There are then less receptors and therefore opioids have less of a response thus require a higher dose to achieve the same effect

**Dependence**

There is a profound **physical withdrawal** associated with opioids.

- Present evidence suggests it has something to do with increased activation of the adenylate cyclase system
- When you remove the opioids, there is already a massive up-regulation of the adenylate cyclase system and so you get the reaction because it is far more active than it should be
- Patients suffering withdrawal will present with psychological craving, muscle tremors and diarrhoea
- Over time the body should return to normal function

**Overdose**

A patient suffering from an opiate overdose may present with:

- Coma
- Respiratory depression
- Pin-point pupils
- Hypotension

The **treatment** for overdose is the opioid receptor antagonist **Naloxone**. It is given intravenously in emergency situations.
24. Pharmacology of IBD
Dr Sue Smith

INTRODUCTION
The two major forms of inflammatory bowel disease (IBD) are:

- **Ulcerative colitis (UC)**
- **Crohn’s disease (CD)**

However the distinction between the two may be incomplete in some patients. They are both autoimmune disease, but their pathogenesis is incompletely understood.

- They are believed to be triggered by an abnormal response to bacterial lipopolysaccharide, so the pathogenesis is believed to be associated with a defective interaction between mucosal immune system and gut flora
- Genetic factors are important, especially in CD (this is generally more extensively studied than UC)

**Immune surveillance in the Gut**
There are about $2 \times 10^{14}$ bacteria in the gut, therefore it is very important that the immune system identifies pathogenic ones from commensals. There is complex and tightly regulated interplay between hosts and microbes of the gut, and disrupted innate immunity leads to:

- uncontrolled inflammation
- physical damage to the epithelium
- leakiness of tight junctions

**PATHOLOGY**

**Ulcerative colitis**

- Th2 mediated autoimmune reaction, with Th2 cytokines involved e.g. IL-13
  - T cell clones have a limited capacity to expand, and no there are no detected defects in T cell apoptosis
- There are about 10 genes implicated in UC to date
- Ulcerative Colitis is confined to the mucosa and submucosa, and begins in the rectum. It may spread proximally, but remains confined to the colon.
- Inflammation is continuous. Abscesses, fissures, and fistulae are not a feature, and surgery is curative.

**Crohn’s disease**

- Here, there is a strong genetic component, with about 20 genes implicated
  - An example of this is NOD2; gene that codes for an intracellular receptor for a bacterial peptidoglycan
  - It has a pivotal role in innate immunity, and mutations lead to abnormal cytokine responses. Homozygotes therefore have a 10-30 fold increased risk of CD
- Th1 mediated disease, with important Th1 cytokines including IFN-gamma and TNF-alpha
  - IL-17 and IL-23 are also important
  - Associated with florid T cell expansion and defective apoptosis
- Crohn’s is not confined to the mucosa and submucosa, but rather can affect any part of the GI tract
- Inflammation may be patchy and discontinuous, and abscesses, fissures and fistulae are common
- May recur following resection
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<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
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<tbody>
<tr>
<td>Autoimmune disease</td>
<td>Th2 mediated</td>
<td>Th1 mediated</td>
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<tr>
<td>Gut layers affected</td>
<td>Only mucosa and submucosa</td>
<td>All layers</td>
</tr>
<tr>
<td>Regions of the gut affected</td>
<td>Only the colon</td>
<td>Any region</td>
</tr>
<tr>
<td>Inflamed areas</td>
<td>Continuous</td>
<td>Patchy</td>
</tr>
<tr>
<td>Abscesses/fissures/fistulae</td>
<td>Not a feature</td>
<td>Are a feature</td>
</tr>
<tr>
<td>Surgery</td>
<td>Is curative</td>
<td>Not always curative</td>
</tr>
</tbody>
</table>

**EPIDEMIOLOGY**
- Incidence: 10 - 20 new cases/100,000 population/year
- Prevalence: 100 - 200 /100,000 population
- UC is more common than CD
- Peak incidence 20 – 40 years
- More common in women
- Increased incidence in first degree relatives
- Marked differences between ethnic groups

**CLINICAL FEATURES**
Severity of symptoms depends on the **extent** and **location** of disease. Patients may get:
- rectal bleeding with mucous discharge
- diarrhoea
- abdominal pain
- anorexia
- weight loss
- ever
- other extra-GIT symptoms
This is rarely fatal, due to modern therapy, but it dramatically reduces the quality of life.

**MEDICAL TREATMENT**
Treatment falls into two parts, the **treatment of the active disease** and the **maintenance of remission** in order to prevent relapse. When medical treatments fail, surgery may be necessary.
Treatments for IBD fall into 1 of 3 categories:
- Supportive therapies
- Treatments for the reduction of inflammation and relief of symptoms
- Curative therapies

**Supportive therapies**
These are mainly used as **acute** medical treatment, and may involve:
- Blood transfusion/oral iron
- Fluid/electrolyte replacement
- Antibiotics (not clear whether any bacterial species are causative)
Nutrition-based therapies can also be considered supportive therapies but are used for **maintenance** of remission. These include:
- Enteral nutrition
- Probiotics
- Omega 3 fatty acid supplements

**Treatment to reduce inflammation and relief of symptoms**
Treatment of symptoms involves treatment of the active disease itself. **Glucocorticoids** such as Prednisolone are used, and **Aminosalicylates** such as Mesalazine are used. Treatment also aims to prevent relapse, again using Mesalazine, but also **immunosuppressives** such as Azathioprine.

**Aminosalicylates**
These are anti-inflammatory drugs, including Mesalazine or 5-aminosalicylic acid (5-ASA) or Olsalazine (2 linked 5-ASA molecules), have no immunosuppressive action.
They are useful in the treatment of active Ulcerative Colitis and for maintenance of remission, but they are ineffective in Crohn's disease.

The mechanisms of anti-inflammatory action include:

- Reducing free radicals
- Upregulating endogenous antioxidant systems
- Reducing leukocyte infiltration

**Pharmacokinetics:**

- **Mesalazine** is absorbed in the small bowel and colon.
- **Olsalazine** is metabolised by colonic flora, and is absorbed in the colon
- **5-ASA** requires methods of controlling site of absorption, therefore is delivered topically (suppositories, enemas) in pH-dependent capsules which only release in the small intestine
  - slow-release microspheres are used to spread the action across the small and large bowel, which leads to the gradual release of 5-ASA as it travels through the bowel (33% in upper SI, remainder in distal ileum and colon)
  - topical 5-ASA has been shown to be superior to topical steroids in inducing remission of UC

There is a “step-up” approach to UC treatment (seen in pyramid opposite)

**Glucocorticoids**

These are powerful anti-inflammatory and immunosuppressive drugs, and include **Prednisolone**, **Fluticasone** and **Budesonide**.

- They are derived from the hormone cortisol, and activate intracellular GC receptors which then act as:
  - positive transcription factors, increasing the expression of anti-inflammatory genes, or, more frequently....
  - Negative transcription factors, reducing the expression of pro-inflammatory genes
- They act on many cell types and have powerful anti-inflammatory actions including:
  - A reduction in the influx and activation of pro-inflammatory cells
  - Reduced production of the mediators > vasodilation, fluid exudation, inflammatory cell recruitment and tissue degradation
- Additionally, GCs are potent immunosuppressive drugs, causing reductions in antigen presentation, cell proliferation and clonal expansion
- In terms of use, GCs are on the decline for ulcerative colitis, but can be used topically or intravenously if severe. However they remain the drug of choice for inducing remission for Crohn's disease

Because of structural similarities between synthetic GCs and the endogenous hormone, cortisol, GCs tend to have many unwanted side effects. The incidence and severity of side effects are closely related to the dose and duration of GC given.

**Unwanted effects of GCs are:**

- Osteoporosis
- Increased risk of Gastric ulceration
- Suppression of HPA axis
- Type II diabetes
- Hypertension
- Susceptibility to infection
- Skin thinning, bruising and slow wound healing
- Muscle wasting and buffalo hump
GCs play a key role in the management of CD, so strategies have been developed for minimising unwanted effects. These strategies include:

- use of tapered doses
- use of drugs with a high therapeutic index such as fluticasone
- topical administration (particularly of budesonide which has a high first pass metabolism in the liver and GIT)

Because of their unwanted effects, GCs are best used to treat active disease rather than to maintain remission and prevent relapse.

### Immunosuppressive Therapies

A number of different immunosuppressive agents have been tried for the treatment of IBD, but many have not been successful

- **Azathioprine** has demonstrated a significant degree of success in both UC and Crohn’s
- **Cyclosporine** has also proven useful in severe cases of Crohn’s

#### Azathioprine

**Use:**

- In ulcerative colitis, it is useful for maintaining remission
- In Crohn’s, it is useful for maintaining remission, but also for inducing remission (with treatment >17 weeks)
  - It may also enable a reduction in glucocorticoid dose as well as postponement of colostomy

**Mechanism:** It is a pro-drug activated in vivo by gut flora to 6-mercaptopurine; this interferes with purine biosynthesis hence affects DNA synthesis and cell replication

**Actions:**

- It impairs –
  - Acquired immune responses
  - Lymphocyte proliferation
  - Mononuclear cell infiltration
  - Antibody synthesis

- It enhances T cell apoptosis

**Unwanted effects:**

- Bone marrow suppression
- Because it is metabolized by the enzyme xanthine oxidase, it should not be administered with drugs that inhibit this enzyme, eg allopurinol, as the build up of 6-mercaptopurine > blood disorders

#### Curative (biological) Therapies

**Anti-TNFalpha antibodies**, such as **Infliximab** and **Adalimumab** are approved for use in IBD. Other antibodies may be effective, but have more severe side effects.

Anti-TNFα is used successfully in the treatment of Crohn’s Disease.

- It is potentially curative rather than simply palliative, and it is also successful in some patients with refractory disease and fistulae. There is some evidence of effectiveness in Ulcerative Colitis.

### Mechanism of action

- The mechanism of action indicates that TNF-alpha plays an important role in pathogenesis of IBD. The actions of anti-TNFalpha include:
  - reduces activation of TNF α receptors in the gut
  - Reduced production of other cytokines, infiltration and activation of leukocytes is reduced
  - Also binds to membrane associated TNF-alpha, mediating complement activation and inducing cytolyis of cells expressing TNF-alpha
    - Promotes apoptosis of activated T cells
Pharmacokinetics
- Curative therapies are usually given intravenously, and they have a very long half-life (9 ½ days).
- Benefits can last for 30 weeks after a single infusion, but most patients will relapse after 8 to 12 weeks. Therefore, repeat infusions must be done every 8 weeks.

Adverse effects
- Increased incidence of infections
- May reactivate dormant TB
- Increased risk of septicaemia
- Worsening of heart failure
- Increased risk of demyelinating disease
- Increased risk of malignancy
- Can be immunogenic – therefore given with azathioprine to suppress immune response. However immunomodulators increase the risk of TB and malignancy further
- Possible risk of anaphylaxis
Dr Martin Croucher

GABA-MEDIATED NEUROTRANSMISSION
Revision of amino acid transmitters
Reminder: principle amino acid transmitters in the CNS include GABA, glycine, glutamate, asparate and L-homocysteate
- Glycine is mainly a spinal cord inhibitory amino acid, whereas GABA is mainly active in the brain. They are both neutral amino acids. GABA is considered the most important AA inhibitory transmitter in the brain.
- Glutamate is the key excitatory amino acid in the brain, although aspartate is also shown to have some effect. There are not many developed drugs that interact with glutamate transmission, but these are under development. These are both acidic amino acid, ie have an additional carboxyl group.

GABA
Chemical structure: NH2-CH2-CH2-CH2-COOH
GABA has a wide distribution throughout the brain. There are some areas with particularly high concentrations:
- the cerebral cortex, cerebellum, hippocampus, corpus striatum (basal ganglia) and the hypothalamus.
- The dorsal horn of the spinal cord; function here is to modulate primary afferent input to the spinal cord by releasing GABA onto the terminals
- There is little in the PNS
Most central neurons respond to GABA (approx. 30% of synapses have GABA receptors on their surfaces). Type of neurons that utilize GABA:
- Principally short inhibitory interneurons (cell body and terminals are in same brain area – role is to regulate overactivity in different brain areas)
- Some longer tracts, eg striato-nigral, (ascending dopaminergic tract from midbrain to forebrain, this is descending from forebrain to midbrain) and cerebellar
This means it has widespread inhibitory action in the CNS, both pre- and post-synaptic.

Functions
There are 4 main functions:
- Motor activity, reflected in high concentrations of GABA in the cortex, cerebellum and spinal cord
- Extrapyramidal activity, reflected by concentrations in basal ganglia (striato-nigral tract is outside the pyramidal system)
- Emotional behavior, reflected by presence in limbic system eg hippocampus + amygdala
- Endocrine function, reflected by high concentration in hypothalamus

Neurochemistry
Synthesis
- Synthesized from glutamate involving glutamate decarboxylase (GAD)
- One of the important things about GAD is that it is specific for GABAergic neurons; this was important because antibodies can be raised against this protein. This can be utilized by immunohistochemical labeling, in which antibodies are labelled so you can see the different neurons in the brain
- Pathway: important points include:
  o GABA originates from the Krebs Cycle (TCA cycle)
  o Alpha-oxoglutarate is converted into glutamate by GABA transaminase (GABA-T), which is converted into GABA
  o GABA is broken down to succinic semialdehyde, and then again by SSDH to succinate to retrun to the Krebs cycle – this is known as the GABA shunt
Approx. 8-10% of the Krebs cycle activity is used for the GABA shunt, emphasizing its important

**Storage and release**
- Stored in GABAergic vesicles, which contain high affinity transporters in their membranes
- These pick up GABA from the cytoplasm, and transport it into the vesicle
- With the arrival of the action potential in the nerve terminal, depolarization opens voltage sensitive calcium channels. Calcium influx stimulates exocytotic release of GABA

**Receptors**
- GABA then diffuses across the cleft, making contact with receptors on the post-synaptic membrane (may by glutamate neurons etc)
- There are two main types of receptors:
  - GABA-A (type 1 ionotropic; linked to chloride channels)
  - GABA-B (type 2 metabotropic; G-protein coupled)

**Inactivation**
We need to inactivate GABA very quickly, as receptors would desensitize
- The inactivation of GABA is primarily by reuptake into neurons and surrounding glial cells
- This reuptake (ie the transporters, only exist on GABA terminals) is Na+ dependent, energy dependent (ATP dependent) and therefore is saturable
- Once re-uptake has occurred, metabolism occurs

**Metabolism**
GABA is broken down by GABA transaminase to succinic semialdehyde, and then again by succinic semialdehyde dehydrogenase (SSDH) to succinic, which returns to the Krebs cycle
- These enzymes are examples of mitochondrial enzymes
- Inhibitors of GABA metabolism result in a large increase in brain concentrations of GABA. This is associated with an enhancement of GABA-mediated inhibition. Examples of these include (use as anti-convulsants):
  - Sodium valproate (epilim)
  - Vigabatrin (sabril) - binds covalently to GABA-T, inhibiting its action

**GABA RECEPTORS**

**GABA-A Receptors**
These pentameric ionotropic (type 1) receptors (consisting of 5 subunits) are mostly postsynaptic, and have a cellular mode of action.
- Conformational change in the subunits > opening of Cl channels. They result in an increase in Cl- influx into the post-synaptic neurone, leading to hyperpolarization (generates inhibitory post-synaptic potential – IPSP) and inhibition of post-synaptic firing
- **Agonists** of these receptors include: GABA + muscimol (selective GABA-A agonist)
- **Antagonists** of these receptors include:
  - Bicuculline (competitive inhibitor)
  - Picrotoxin (non-competitive inhibitor)
  - Both of these are convulsants, tending to generate seizures by reducing GABA transmission. These are therefore very useful experimental tools, but are not used therapeutically.
- Benzodiapenes + barbiturates both interact with GABA-A receptors, and are therapeutically useful as sedatives

**GABA-B Receptors**
These are mostly presynaptic, and their role is to regulate GABA release
- They inhibit NT release on the presynaptic autoreceptors, as well as heteroreceptors (resulting in a decrease in dopamine release), again with a cellular mode of action:
- They are G-protein linked receptors, therefore require activation of a G-protein in the pre-synaptic cell membrane, resulting in reduced calcium conductance therefore decreasing exocytotic NT release and a decrease in cAMP levels (via inhibition of adenylate cyclase)
- **Agonists** include baclofen (Selective GABA-B), and this is therapeutically useful as a skeletal muscle relaxant acting in the spinal cord.
This is useful in spasticity associated with MS, ie as a spasmolytic

- **Antagonists** include *saclofen* (competitive)

**NB: G-protein coupling**

- G-protein (trimer) sits in membrane, and binding of receptor leads to a conformational change which > diffusion of alpha subunit to beta/gamma receptor+ exchange of GDP > GTP leads to activation of the target protein
- When GTP is replaced by GDP again, the alpha subunit is no longer active and returns to the receptor

**DRUGS AFFECTING GABA TRANSMISSION**

Drugs affecting GABA transmission include Anxiolytics, sedatives and hypnotics.

**GABA-A Receptor Complex**

The GABA-A receptor is composed of 4 main proteins:

- GABA-A receptor
- Barbiturate receptor
- Benzodiazepines
- Chloride channel

GABA modulin allows the BDZ receptor to link to the GABA receptor protein

GABA binds to the GABA receptor protein, activating a linkage between the GABA + BZ receptor protein (modulated by GABA modulin), which leads to opening of the chloride channel protein

- When we give *benzodiazepines*, they bind to their own receptor protein, with 2 main effects:
  - Number 2 show the enhancement of GABA action
  - Number 3 shows enhancement of GABA binding to GABA receptor protein, and this effect is reciprocated
  - BDZ increases the FREQUENCY of opening

- **Barbiturates** bind to the BARB receptor protein. Number 4 shows they have a similar overall effect to BDZ, both in action and binding. However this is NOT reciprocated.
  - NB: at higher concentrations, barbiturates can have a direct effect on the chloride channel (number 6)
  - BARB increase the duration of the opening of the chloride channel
- Bicuculline competes with GABA at its receptor, and flumazenil competes with the BDZ receptor

**NB:** both BDZ + BARB have NO action on their own, ie they have allosteric action (binding to their own sites)

- BARBs are less selective than BZs
- BARBs show some evidence as acting as glutamate antagonists, leading to a decreased excitatory transmission, as well as other membrane effects eg direct opening of the chloride channel (can be thought of as "less clean" drugs)
  - This lack of selectivity may explain the induction of surgical anaesthesia, and low margin of safety (compared to BDZ)
Benzodiazepines (BDZ) + Barbiturates (BARB)

Clinical uses:
These drugs have a wide spectrum of activity.
- **Anaesthetics** – BARBs only, eg thiopentone which induces general anaesthesia very quickly
- **Anticonvulsants** – eg diazepam, clonazepam, phenobarbital
- Anti-spastics, eg diazepam
- Antiolitics: These remove anxiety WITHOUT impairing mental or physical activity (minor tranquillisers – although this term is rarely used as effects are not minor)
- Sedatives: Reduce mental and physical activity WITHOUT producing loss of consciousness
- Hypnotics: induce sleep

Ideally, these drugs:
- Have wide margin of safety
- Do not depress respiration
- produce natural sleep (hypnotics)
- do not interact with other drugs
- do not produce ‘hangovers’
- do not produce dependence

Barbiturates
- **Molecular structure**: classic 6-membered ring with a number of additional groups
- **Examples** include phenobarbital, pentobarbital and thiopentone

These are non-selective CNS depressants, which are have been largely superceded by BDZs (especially as sedatives/hypnotics due to increase in dependence)
- **Their main uses** include:
  - General anaesthetics – thiopentone
  - Anticonvulsants – phenobarbital
  - Sedative/hypnotics – amobarbital (used for severe intractable insomnia not responding to BDZ)
- **Unwanted effects** include:
  - Low safety margins – depress respiration, overdose can be lethal (treated with alkaline diuresis)
  - Alter natural sleep + decrease REM > hangovers/irritability
  - Enzyme inducers, eg liver microsomal enzymes, therefore may interact with the metabolism of co-administered drugs
  - Potentiate effect of other CNS depressants eg alcohol
  - Tolerance, both pharmacokinetic and tissue tolerance
  - Dependence + withdrawal symptoms including insomnia, anxiety, tremor, convulsions and death

NB: much more dangerous than benzodiazepines

Benzodiazepines
- **Molecular structure**: 3 ring structure. There are lots of variations on this structure as there are various BDZs although small differences in structure result in large changes in pharmacokinetic activity
- **Examples** include: diazepam, oxazepam and temazepam. All have similar potencies and profiles (Acting at GABA-A), with varying pharmacokinetics which determine use
- **Pharmacokinetics**
  - Administration: well absorbed orally, with peak plasma within an hour. Can be given IV for status epilepticus for prolonged seizure activity.
  - Distribution: bind plasma proteins strongly, and are highly lipid soluble therefore have a wide distribution
  - Metabolism: extensive hepatic metabolism
  - Excreted in urine as glucuronide conjugates
  - Duration of action varies greatly. Can be divided into:
    - Short-acting
- Long-acting (either have a slower metabolism and/or generate active metabolites)

- **Metabolism:**
  - Short acting: temazepam (t1/2 = 8rs) + oxazepam – metabolized rapidly + excreted in urine
  - Diazepam has a half life of 32 hours, and involves metabolism either via temazepam + oxazepam, or via nordiazepam (which also shows agonist activity)

- **Uses:**
  - Anxiolytics = long acting, eg diazepam (valium)
    - In cases of hepatic impairment, oxazepam is used to prevent toxicity
  - Sedative/hypnotics = short acting, eg temazepam and oxazepam

- **Advantages** over BARBs:
  - Wide margin of safety – overdose only causes prolonged rousable sleep, treated with flumazenil
  - Only mild effect on REM sleep
  - Do not induce liver enzymes

- **Unwanted effects:**
  - Sedation, confusion, ataxia (impaired manual skills)
  - Potentiate other CNS depressants
  - Tolerance (less than BARBs – only tissue tolerance)
  - Dependence leading to withdrawal syndrome similar to BARBs but less intense.
    - Withdraw drug slowly to avoid this
  - Increase in free plasma concentration of different drugs including aspirin, and heparin

**OTHER DRUGS**

**Other sedatives/hypnotics** used clinically include:

**Chloral hydrate**

- Metabolized in the liver to trichloroethanol (Active drug)
- Mechanism of action is not known, but used as has a wide margin of safety therefore used in children and elderly

**Other anxiolytics** used clinically include:

**Propranolol**

- Non-selective beta blocker
- Improves physical symptoms on anxiety such as tachycardia and tremor
- Used for stage fright

**Busiprone**

- 5HT-1A agonist
- slow onset of action (days – weeks)
- few side effects
- downside is that we don't really understand the interaction with the 5HT transmission
26. Anti-Parkinsonian Drugs and neuroleptics
Dr David Dexter

DOPAMINERGIC PATHWAYS

Pathways
- **Nigrostriatal** - Cell bodies originate in the substantia nigra zona compacta (black pigment can be viewed by naked eye) and project to the striatum - Control of Movement, affected in Parkinsons
- **Mesolimbic** - Cell bodies originate in the ventral tegmental area and project to the nucleus accumbens, frontal cortex, limbic cortex and olfactory tubercule - Involved in emotion, affected in Schizophrenia
- **Tuberoinfundibular** system - Short neurones running from the arcuate nucleus of the hypothalamus to the medial eminence & pituitary gland - Regulate hormone secretion

Dopamine synthesis
- Starting product is tyrosine, converted by tyrosine hydroxylase (rate limiting) to DOPA.
- DOPA decarboxylases then converts DOPA to dopamine
- Then normal NT storage + release
- Acts on D1 family (D1 + D5) and D2 family (D2, 3 + 4) of receptors
- Reuptake is followed by either recycling, negative feedback on DA release or metabolism by MAO

PARKINSON’S DISEASE

Epidemiology:
- 3rd most prevalent neurological disorder
- In 1000 of general population, 1 in 100 of those aged over 60
- 4:1 males: females (oestrogen suggested to be protective)
- Familial accounts for 5-7%, idiopathic accounts for 93% of cases (possibly due to combination of environment, oxidative stress which alters protein metabolism)
  - There are a number of “risk genes” involved

Definition: progressive neurodegenerative disorder of movement.
First described by James Parkinson

Cardinal clinical manifestation
Diagnosis requires at least 2 out of 4 of these.
- **Resting tremor**: shaking of the limb when relaxed (also known as pill-rolling tremor)
- **Rigidity**: stiffness, limb feels heavy/weak
- **Bradykinesia**: slowness of movement and initiating movement after thought
- **Postural abnormality**, eg loss of arm-swing, stooped shuffling gait

Other Presenting symptoms
- Difficulty with fine movements –micrographia.
- Poverty of blinking.
- Impassive face.
- Monotony of speech & loss of volume of voice.
- Loss of balance – lack of righting reflex, retroplulsion

Symptoms are unilateral at onset, but spread to both sides of the body, worsening with the patient becoming severely disabled.

Secondary Manifestations
These are the non-motor signs:
- Depression (approx. 45% of patients)
- Pain in limbs due to build up l=of lactic acid from tremor
- Taste-disturbances, and loss of olfaction
- Dementia
• Autonomic dysfunction: constipation, postural hypotension, urinary frequency/urgency, impotence, increased sweating

**Neuropathology**

• Putamen-projecting pathways degenerate significantly
• Lewy bodies (large circular structures with bright core + white surrounding, packed with alpha-synuclein) also present
  o These are probably a defensive mechanism to protect against toxic altered proteins
  o Eventually the proteins spill out and cause toxicity
• Other affected areas include:
  o Cell loss in the substantia nigra
  o Cell loss in locus coeruleus
  o In some cases, the dorsal vagaus nucleus, nucleus basalis of mynert and other subcortical nuclei are affected

NB: it is necessary to lose 80-85% of the dopaminergic neurons and deplete 70% of the striatal dopamine before symptoms appear
• Compensatory mechanisms, eg neurone overactivity + upregulation of DA receptors prevent appearance of symptoms

**Dopamine replacement therapy**

**L-DOPA** is a dopamine replacement therapy
• DOPA does not cross BBB, but L-DOPA can cross in chemotactic trigger zone
• Require DOPA-decarboxylase inhibitor (acting in the periphery to prevent peripheral conversion to dopamine), allowing the L-DOPA to cross the BBB and be centrally converted to dopamine
• Uses:
  o Hypokinesia, rigidity + tremor
  o Effectiveness decreases with time
• Acute side effects:
  o Nausea - prevented by Doperidone (peripheral acting antagonist)
  o Hypotension
  o Psychological effects - Schizophrenia like syndrome with delusions, hallucinations, also confusion, disorientation & nightmares
• Chronic side effects:
  o Dyskinesias - Abnormal movements of limbs & face. Can occur within 2 years of treatment. Disappear if reduce dose but clinical symptoms reappear!
  o "On-Off" effects - Rapid fluctuations in clinical state. Off periods may last from minutes to hours. Occurs more with L-DOPA

**DA-agonists**

This targets the receptors directly, principally the D2 receptors.
• There are many drugs on the market that act as dopamine agonists eg bromocriptine, pergolide, ropinerol
• These have a longer duration of action than L-DOPA, and thus have a smoother and more sustained response. Because of this you get less dyskinesias forming
• Here the actions are independent of dopaminergic neurons
• NB: DA-agonists can be used in conjunction with L-DOPA, or as L-DOPA
• **Adverse effects:**
  o Common - Confusion, dizziness, nausea/vomiting, Hallucinations
  o Rare - Constipation, headache, dyskinesias
• The ergot ring structure of the older agonists caused problems with heart valves, eg bromocryptine.
  o However the more modern preparations, eg pergolide and ropinerol (no ergot ring) have resulted in development of addictive behaviours eg gambling
**MAO inhibitors**
Monoamine oxidase is involved in the breakdown of DA, therefore more is stored in synaptic vesicles and will be released into the synaptic cleft

**Deprenyl (selegiline)**
- Selective for MAO-B, predominates in dopaminergic areas of CNS. Actions are without peripheral side effects of non-selective MAO-I's
- Can be given alone in the early stages of the disease, preserving the naturally synthesised DA in the brain
- Or in combination with L-DOPA, reduce the dose of L-DOPA by 30-50%
- Side effects are rare - hypotension, nausea/vomiting, confusion and agitation.

**Resagiline** – Shown to have neuroprotective properties by inhibiting apoptosis – promotes anti-apoptosis genes
- Early clinical trials suggest that this drug may slow the disease down but subsequent studies not so positive

**COMT**
Catechol O-methyl transferase is present in the CNS and periphery.
- CNS - Prevents breakdown of dopamine in the brain
- Peripheral - COMT in the periphery converts L-DOPA to 3-O-methyl-DOPA (3-OMD).
- 3-OMD and L-DOPA compete for same transport system into the brain, therefore less L-DOPA will cross the BBB so has a smaller effect

COMT inhibitors, e.g Tolcapone, stop 3-OMD formation thus increasing the bioavailability of L-DOPA, Thus more L-DOPA crosses into the brain and is converted to dopamine in the CNS
- This also allows you to reduce L-DOPA dosage!
- You can also use this to boost response to L-DOPA in patients starting to show tolerance

Unfortunately, these have a marked side-effect profile, including CVS effects

**SCHIZOPHRENIA**

**Epidemiology:** affects 1% of the general population

**Clinical features** can be split into positive and negative:
- **Positive** – delusions, hallucinations, thought disorders
- **Negative** – withdrawal, flattening of emotional responses

NB: schizophrenia has a strong hereditary tendency, with first degree relatives suffering in 10%, and monozygotic twin risk rises to 50%

**Onset** is in adolescence, following one of two types:
- Relapsing and remitting (most common)
- Chronic progressive (rare – do not respond to drug treatments as well)

**Aetiology:** unknown but several theories
- Slow viral linked with auto-immune process
- Developmental abnormality

**Neurochemical involvement**
- Excessive dopamine transmission in the mesolimbic and striatal region leading to positive symptoms – mediated through D2 receptors
- Whilst dopamine deficit in pre-frontal region, mediated by D1 receptors leads to negative symptoms

**Evidence:**
- Dopamine agonists e.g bromocriptine can induce various psychotic reactions.
- Typical anti-schizophrenic drugs are dopamine receptor antagonists.
- In drug naïve patients PET scans show increased dopamine receptor numbers.
Neuroleptics
There have been about 50-60 drugs developed so far to treat, but most have failed
Most of the drugs block a variety of other receptors in the CNS and body
  • **Typical neuroleptics** include chlorpromazine, but these are potent antagonists at many receptors therefore BIG side effect profile
  • **Atypical receptors** eg clozapine are not preferable as they have a smaller antagonist activity at other receptors

**Mechanism of action**
  • All neuroleptic drugs are antagonists at dopamine “D2 like” receptors.
  • Most neuroleptics block other receptors e.g. 5-HT, thus accounting for some of their side effects.
  • Clozapine is relatively none selective between D1 and D2 receptors but does have a high affinity for D4 receptors that have been shown to be increased in schizophrenia.
  • Drugs treat positive symptoms but not the negative ones!
  • Also note these have DELAYED effects, takes weeks to work. Initially neuroleptics induce an increase in DA synthesis and neuronal activity, ie compensatory mechanisms to increase DA synthesis to overcome blockade. This declines with time.

**Other actions of Neuroleptics**
  • Anti-emetic effect (blocking of receptors in chemotactic trigger zone)
  • Phenothiazine, effective at controlling vomiting and nausea induced by drugs (e.g chemotherapy)
  • Many neuroleptics also have blocking action at histamine receptors. Drugs developed from neuroleptics are also effective at controlling motion sickness.
  • Endocrine Effects - DA is involved in the Tubero-infundibular system (3rd DA pathway) that regulated prolactin secretion. Neuroleptics increase serum prolactin concentrations which can lead to breast swelling (men & women) and sometimes lactation in women.
  • Blockade of cholinergic muscarinic receptors - typical peripheral anti-muscarinic side effects e.g blurring of vision, increased intra-ocular pressure, dry mouth, constipation, urinary retention.

**Side-effects**
  • Extrapyramidal side effects - Blockade of dopamine receptors in the nigrostriatal system can induce “Parkinson” like side effects.
  • Acute dyskinesias - Related to blockade of dopamine receptors in the striatum which leads to an increase in cholinergic function
    - Develop at onset of treatment, reversible on drug withdrawal or anti-cholinergic drugs.
  • Tardive dyskinesias - Involuntary movements, often involving the face & tongue.
    - Occur in about 20% of patients after several months or years of therapy. Made worse by drug withdrawal or anti-cholinergics.
    - Tardive means induced by dyskinesias.
    - The rate of dyskinesia has declined recently due to tailoring of treatment
INTRODUCTION

**What is general anaesthesia?**

The **clinically desirable effects** of general anaesthesia include:

- loss of consciousness
- suppression of reflex responses
- analgesia
- muscle relaxation
- amnesia

However when we consider general anaesthetics as a group of drugs, the most important effects are those they all share in common, including:

- *inducing loss of consciousness at low concentrations* – this is the defining feature!!
- suppression of reflex responses at high concentrations

**History of general anaesthetics**

- Ether was the first general anaesthetic used in practice, although this was not made public until after the development of a nitrous oxide compound in 1845 which was publicly shown to remove pain

**Types of general anaesthetics**

General anaesthetics can be split into gaseous/inhalation drugs, and intravenous drugs:

- **Gaseous** drugs include nitrous oxide, diethyl ethyl, halothane and enflurane
- **Intravenous** drugs include propofol and etomidate

**MOLECULAR TARGETS**

**The Meyer/Overton Correlation**: “the potency of a GA increases in proportion to its oil: water partition coefficient”

- Refers to the fact that the more lipid soluble the agent, the more effective it is
- This led to the **lipid theory of general anaesthetics** – once a GA is present within the lipid bilayer, it disrupts it to prevent nerve propagation. Therefore the more lipid soluble, the more present in the membrane, the more disruption
- However there are problems with this theory:
  - The disruption of the lipid membrane is very small at therapeutic concentrations
  - The lipid theory didn’t explain how ion channel proteins are affected (as these are key in action potential propagation)
- We now know that the mechanism of action is either to do with:
  - **Reduced neuronal excitability**
  - **Altered synaptic function**

**Mechanism of Action**

**Intravenous agents** produce their actions by altering synaptic function via GABA-a receptors which are predominant within the brain (these are the most abundant, fast inhibitory, ligand-gated ion channels in the CNS)

- The anaesthetic binds to the outside of the receptor to facilitate opening > increased inhibition.
- The subunit composition of the receptor is very important:
  - It is the β3 subunit that is important for the anaesthetic effects, i.e. the suppression of reflex responses etc.
  - α5 subunits are important for amnesia effects.

**Inhalation agents** are more complicated. They work by:

- Also potentiate GABA_A receptor function (and glycine receptors). Less potent than intravenous anaesthetics and show no subunit selectivity (altered synaptic function).
• Inhibits nicotinic acetylcholine receptors (altered synaptic function)
• Facilitate TREK (background leak) potassium channel opening (reduced neuronal excitability due to increase K+ ions) – this is important in suppression of reflex responses

**Nitrous oxide** actually does very little to GABA and glycine.
• One major effect is that it blocks excitatory receptors within the brain, e.g. NMDA-type glutamate receptors.
• At neuronal nicotinic ACh receptors, it is seen that as you increase the concentration of the anaesthetic, the firing rate of these receptors decreases. So these agents act as antagonists at these receptors, but we can’t be sure that this bears relevance to the anaesthetic effects of amnesia or relief of pain.

In terms of reduced neuronal excitability, there are a group of K+ channels (‘background leak’). They are found on nerves, and they cause the nerves to remain hyperpolarised. Inhalation agents open these channels and so increase hyperpolarisation within individual nerves, leading to the suppression of reflex responses.
• Intravenous agents are pretty selective for the GABAA receptors. Inhalation agents are relatively non-selective.

**Neuroanatomical Sites**
• For loss of consciousness, depressed excitability of thalamocortical neurons is important. The thalamus is the major relay centre of the brain, and has profound influence on levels of consciousness
  o The reticular activating neurons are also particularly important, as reduced firing rates > reduced levels of consciousness
• For suppression of reflex responses, depression of the reflex pathways in the spinal cord is important
  o If information cannot pass between the periphery and brain, reflexes are obviously inhibited
• Decreased synaptic transmission in the hippocampus and amygdala is related to amnesia

**CLINICAL SETTING**
This is the consideration of whether to use inhalation vs intravenous anaesthetic.
• Intravenous anaesthetics are relatively straight forward – you inject them directly into the blood, therefore they need to be water soluble (blood=water)
• After it dissolves in the blood, there is a slow movement of the anaesthetic agent from the blood to the brain as the brain is lipid based
Inhalation agents are even more complicated, as they are initially present as a gas, must diffuse across the lipid membrane of the alveoli walls into the blood (water).

- It is the **blood-gas partition co-efficient** that is important with regards to general anaesthetics. The higher the blood-gas partition coefficient, the better the anaesthetic dissolves in blood, the slower it crosses into the brain.
- The desired agent has a low blood-gas partition coefficient for quicker induction of anaesthesia, as well as fast recovery. The longer the inhaled anaesthetic remains in gasous form, it can enter and leave the brain very quickly, and be excreted via the lungs/expelled into the air.

**The brain** is not the only large lipid store; fat stores also have an effect on anaesthetics as not only do they have a high lipid store, they also are poorly perfused with blood.

- This means that in a long operation, more anaesthetic will dissolve into adipose tissue, and once it’s there it will sit there for a long time, and so the effects with linger.

Inhalation anaesthetics can be rapidly eliminated, and there is rapid control of the depth of anaesthesia.

- Agents that have low blood-gas partition co-efficients allow this degree of control, which is very useful.

**Intravenous anaesthetics** allow relatively fast induction, but the ability to control the depth of anaesthesia is a lot less. There is also less coughing/excitatory phenomena.

**Choice of Drugs**

- Loss of consciousness induction is using **Propofol**.
- The suppression of reflex responses and maintenance of anaesthesia is using **Enflurane**.
- Other drugs are used to achieve the other clinically desirable end points:
  - Analgesia is achieved using opioids (e.g. IV **Fentanyl**).
  - Muscle relaxation is achieved using good neuromuscular blocking drugs (e.g. **suxamethonium**).
  - Amnesia is achieved using benzodiazepines (e.g. IV **Midazolam**).
Local Anaesthetics (LA) = drugs which reversibly block neuronal conduction which applied locally

INTRODUCTION
Generation of an action potential
If we consider a nociceptive sensory neuron, the resting membrane potential is -70mV

- Sufficient depolarization to reach and/or exceed the threshold potential causes the generation of an action potential. This involves 4 phases, illustrated in the diagram opposite:

All LAs have 3 similar structural group areas:

- Aromatic region, ie a region with benzene like properties
- Basic amine side chain (usually tertiary amines) – meaning most LAs are weak bases
- Bridging group – either an ester linkage, eg cocaine or amide linkage, eg lidocaine
  - It is the bridging group that differentiates different LAs

Mechanism of action
As LAs are basic (pKa 8-9), they ionize fairly easily.

- Any unionized LA is able to diffuse inside the sensory axon, where it then ionizes to reach equilibrium
- The ionized cation form within the axon acts as the active anaesthetic agent, binding to the voltage-sensitive Na+ channels to block the flow of ions, thereby preventing rapid depolarization required for action potential propagation
- This is known as the hydrophilic pathway, and is the most important MOA for local anaesthetics

Effects of local anaesthetics
- Prevent the generation and conduction of action potentials
- Do NOT influence resting membrane potential
- May also influence channel gating and surface tension
- Selectively block small diameter fibres and non-myelinated fibres

ROUTES OF ADMINISTRATION
Surface anaesthesia: LA is applied to the mucosal surface (mouth, bronchial three, etc)
- It is usually applied as a spray, can be a powder
- This is an effective method, but requires relatively high concentrations which can lead to systemic toxicity.

Infiltration anaesthesia: LA is applied directly into the tissues and comes into contact with sensory nerve terminals (usually subcutaneous)
- This is the route used in minor surgery (e.g. removing cysts from under the skin)
- An adrenaline co-injection is given to reduce side-effects and increases the duration of action (vasoconstrictor effect > contain the drug at target for longer)
  - The vasoconstriction effect can also help with bleeding, but it is therefore not given at extremities, because this could lead to ischaemic damage.
**Intravenous regional anaesthesia**: LA is injected **intravenously**, distal to a pressure cuff.
- This is useful in limb surgery
- It diffuses into the surrounding tissue quite rapidly
- However if the cuff is released prematurely, there is a potential for systemic toxicity (should be on for 20 mins)

**Nerve block anaesthesia**: LA is injected close to the **nerve trunks**, e.g. in dental anaesthesia around dental nerves.
- This is widely used, as you can use low doses. However it has slow onset
- The dentist often includes a con-injection vasoconstrictor like Felypressin

**Spinal anaesthesia**: LA is injected into the **sub-arachnoid space** (in the space of CSF) and has effects on the spinal roots.
- This is also known as an "**intra-thecal**" injection.
- It is useful for abdominal, pelvic or lower limb surgery.
- Risks include a drop in blood pressure, and unwanted effects may include a prolonged headache (LA access to the brain)

**Epidural anaesthesia**: LA injected into the fatty tissue of the **epidural space**, and has effects on the spinal roots.
- It is also used in abdominal, pelvic and lower limb surgery, as well as in painless childbirth.
- Disadvantage is that it is slower onset, and you need to use higher doses, so you are more likely to see systemic toxicity.
- However the fact that the area is more restricted means that effects on blood pressure are less likely

### PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Property</th>
<th>Lidocaine</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of LA</td>
<td>Amide</td>
<td>Ester</td>
</tr>
<tr>
<td>Absorption by mucous membrane</td>
<td>Good – widely used in various routes of administration</td>
<td>Good – although only used in surface administration</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hydrolysed in liver, then metabolized by removing the amine side chain (N-dealkylation)</td>
<td>Metabolized in liver and plasma, but non-specific esterases</td>
</tr>
<tr>
<td>Plasma t½</td>
<td>2 hours</td>
<td>1 hour</td>
</tr>
</tbody>
</table>

### UNWANTED EFFECTS

**Lidocaine**
- **CNS effects**: stimulation, restlessness, confusion, tremor
  - These are all paradoxical because they are unexpected.
- **CVS effects**: myocardial depression, vasodilation and hypotension
  - These are all due to Na+ channel blockade.

**Cocaine**
- **CNS effects**: euphoria and excitation.
- **CVS effects**: increased cardiac output, vasoconstriction and hypertension.

NB: The unwanted effects of cocaine are different to all the other anaesthetics; they are all due to sympathetic actions.
Cytotoxic Drugs = drugs that modify the growth of cells and tissues

INTRODUCTION
Cytotoxic drugs are used as anti-cancer agents (eradicating disease, inducing remission + controlling symptoms), to control immune responses in organ transplantation, and to management of autoimmune disease.

- Anything that causes dysregulation in the cell cycle leads to cancer (review cell cycle lecture)
- Cancer is a disease in which there is uncontrolled proliferation and spread within the body of abnormal forms of the body's own cells

The cancer cell phenotype is:
- Disregard of signals to stop proliferating
- Disregard of signals to differentiate
- Capacity for sustained proliferation
- Evasion of apoptosis
- Ability to invade
- Ability to promote angiogenesis

The term neoplasm is often more useful than the word cancer.

- A neoplasm which manifests itself as uncontrolled proliferation (behaviours 1 + 3), is benign
- A neoplasm which manifests as uncontrolled proliferation, invasiveness and metastases is malignant

Problems with anti-cancer therapy
- Difficult to find exploitable differences between cancer cells and normal body cells
- In order to eradicate disease, need to produce a near total cell kill, as the immune system is unable to destroy any remaining cancer cells
- Cancer is usually far advanced before diagnosis
- Tumour cells generally exist in 1 of 3 stages of the cell cycle:
  - Dividing cells – these are sensitive to anticancer treatment
  - Cells no longer able to divide – these do not pose a problem
  - Resting cells (in G0 phase) – these are insensitive to anticancer treatment and will often start dividing again following a course of chemotherapy

CYTOTOXIC DRUGS
These tend to be antiproliferative, but have no affect on invasiveness or tendency to metastasise, therefore affect all rapidly dividing normal tissues

- They are commonly used in combination (ie 2-6 agents), as this is more effective, and reduces the chance of drug resistance
- The effect on normal tissues is responsible for many of the side-effects of cytotoxics

Alkylating agents, eg cyclophosphamide, chlorambucil

- These are highly reactive molecules that covalently bond with nucleophiles.
- The reactive group is a carbonium ion, which finds electrons and binds irreversibly to cell macromolecules, notably DNA, RNA and proteins
- Most are bifunctional, as they have two ends thus can bind to DNA in two different places:
  - The principle target is guanine N7
  - Other targets include N1/N3 of adenine, and N3 of cytosine
- Binding causes intra and/or inter-chain crosslinks, which interferes with transcription and replication
Nitrogen mustards (related to mustard gas) are highly reactive ethylene immonium derivatives, including cyclophosphamide and chlorambucil

Cyclophosphamide is a substrate for cytochrome P450, which metabolises foreign compounds to get rid of them from the body.
- Alone cyclophosphamide is inactive, but oxidised by P450 it is activated, and is able to attack DNA because it becomes extremely reactive.
- Because it is highly reactive, it undergoes metabolism (both enzymatic and non-enzymatic). There are a number of different opportunities to attach DNA because there are several metabolites which have cytotoxic action, e.g. Phosphamide mustard, and Acrolein.

The most potent cytotoxic cyclophosphamide metabolite produced is phosphoramidite mustard.
- This is able to cross-link within the DNA, which completely blocks transcriptional activity

Antimetabolites
These block or subvert pathways in DNA synthesis
- Folate antagonists e.g. Methotrexate, interfere with thymidylate synthesis
  - Folate is essential to synthesise purine nucleotides (A + G)
- Pyrimidine analogues such as fluorouracil interfere with 2'-deoxythymidylate synthesis
  - This prevents deoxynucleotide production
- Purine analogues e.g. Azathioprine inhibits purine synthesis
  - These are incorporated into DNA themselves, and interfere with chain synthesis

Cytotoxic antibodies have direct interaction with DNA, for example:
- Actinomycin D (Dactinomycin) intercalates DNA and interferes with topoisomerase II. This is one of the enzymes which unwind DNA to allow it to be transcribed. By interfering with transcription, you kill the cell
- Doxorubicin inhibits DNA and RNA synthesis by complexing with DNA and preventing the topoisomerase to rejoin it up.
- Bleomycins are metal-chelating glycopeptides antibiotics that degrade DNA.
  - Bleomycins are active against non-dividing cells. It is very toxic, and is administered intravenously. There is a high risk and problem of pulmonary toxicity.

Plant alkaloids include:
- the podophyllotoxins, e.g. etoposide, which inhibits DNA synthesis. It causes cell cycle block at the G2 phase. This compound inhibits topoisomerase II enzymes
- The vinca alkaloids e.g. vincristine act by binding to tubulin and inhibiting polymerisation into microtubules. This prevents spindle formation, so the cell cannot divide and replicate.

Miscellaneous agents include
- hydroxyurea, which inhibits Ribonucleotide reductase, which is involved in the biosynthesis of nucleic acids
- Cisplatin interacts with DNA causing guanine intrastrand cross-links
- Procarbazine inhibits DNA and RNA synthesis and interferes with mitosis at interphase. It is metabolically activated by cytochrome P450 and MAO to alkylate DNA (N7 and O6 of guanine)

Hormones are used in chemotherapy, but aren't technically cytotoxic agents. They can inhibit tumours in hormone-sensitive tissues, for example gonadotrophin-releasing hormone analogues like Goserelin. Examples include prednisolone, fosfostrol and Tamoxifen.

ADVERSE EFFECTS

General toxic effects:
- Myelotoxicity (bone marrow suppression)
- Impaired wound healing
- Depression of growth (in children)
- Sterility
- Teratogenity
- Loss of hair
- Nausea and vomiting

**Fast growing cells**
- Inhibit cell division
- Cell cycle specific drugs = bone marrow, GI tract, epithelium, hair and nails, spermatogonia

**Slow growing cells**
- Introduce DNA mutations
- Cell cycle independent (alkylating agents), Secondary tumours

**IMMUNOPATHOLOGY**
The immune system protects the host from invasion by pathogens etc.
- This can cause autoimmune disease and rejection of allogenic tissue grafts after transplantation.
- Cytotoxic drugs can be used as immunosuppressants, but at much lower doses than used to treat cancer.
- At lower doses, the drugs selectively affect lymphocytes which drive the immune response. Azathioprine, Methotrexate, and Cyclophosphamide are all useful

**SUMMARY**
30. Anti-microbial drugs
Dr David T Dexter

INTRODUCTION
Antimicrobial agents should be toxic for the parasitic cell but innocuous for the host
- This selective toxicity depends on the existence of exploitable biochemical differences between the parasite and host cell
- In reality, the degree of exploitable differences depend on how far apart the host and parasite are in terms of evolutionary development
- E.g. Prokaryotes (cells without nuclei - bacteria) - evolutionary and biochemically very different, easier to kill, whereas eukaryotes (cells with nuclei - protozoa) - likely to be more similar biochemically to cells of the host, more difficult to kill.

Differences between bacteria and eukaryotic cells
Prokaryotic cell structures that differ from eukaryotic cells include:
- Cell Wall – Contains peptidoglycan, supports the underlying membrane which is subject to osmotic pressure.
- Genetic information – No nucleus, genetic material forms a single chromosome.
- Plasma membrane – contain no sterols which may result in differential penetration to chemicals.
- Protein synthesis – Bacterial ribosome's consist of 50s and 30s subunits, whilst mammalian ribosome’s consist of 60s and 40s subunits

ANTIBACTERIAL AGENTS
Drugs which affect folate
Folate is required for DNA/RNA synthesis in both man and bacteria. In men, this is obtained from diet whereas bacteria synthesize their own.
- This bacterial synthesis involves the enzyme dihydropteroate utilises P-aminobenzoic acid for the synthesis of folic acid

Sulphanilamide/Sulphonamide is a structural analogue of P-aminobenzoic acid and competes for the enzyme dihydropteroate (inhibits folate synthesis). It thus interferes with bacterial DNA/RNA synthesis and are bacteriostatic (hold the bacteria in static animation). The host defence system is then required to finish off the bacteria (different to bacteriocidal, where the drug kills the bacteria)
- Pharmacokinetics – Readily absorbed in the GI tract and maximum plasma conc is reached within 4-6 hours.
- Side Effects: Mild/moderate (do not warrant withdrawal) nausea & vomiting, headache, mental depression.
  - Severe (warrant withdrawal) hepatitis type reaction, hypersensitivity reactions, bone marrow suppression.
- Wide spread resistance to these drugs but they are historically/structurally important since they gave rise to many important drugs diuretics (acetazolamide & Thiazides), tuberculostatic agents, oral hypoglycaemics (sulphonylureas)

Differential sensitivity to Folate antagonists
- Folate, in the form of tetrahydrofolate, is used as a co-factor in thymidylate synthesis. The pathway involved can be differentially affected in man and bacteria by folate antagonists
- Pathway is virtually identical in micro-organisms and man, but one of the key enzymes, dihydrofolate reductase, is many times more sensitive to the folate antagonist trimethoprim in bacteria than in man (IC 50 [mmol/l] 0.005 bacteria, 260 man).
- On the other hand the human enzyme is very sensitive to the effects of the folate analogue methotrexate (IC 50 [mmol/l] Inactive bacteria, 0.001 man).
  - This has been put to use in chemotherapy for rapidly dividing cells
  - This shows how you can exploit relative sensitivity differences to enzymes
Trimethoprim

- **Pharmacokinetics**: - oral administration
  - fully absorbed from the GI tract
  - widely distributed throughout the tissues and body fluids.
  - high concentrations in the lungs and kidney, therefore quite effective for treating infections in these tissues
- **Unwanted effects**: - nausea/vomiting and skin rashes. Hypersensitivity - serious - not dose related.
- **Clinical uses**: - For urinary tract and respiratory tract infections

Sequential blockade

**Combination** - co-trimoxazole - sulphasemethazol and trimethoprim.

- Since sulphonamides inhibit folate synthesis, they potentate the actions of trimethoprim.
- combination the drugs - effective at one-tenth or less of what would be needed if each drug was given on its own.

**Pharmacokinetics**: - When given as co-trimoxazole, about two-thirds of each drug is protein bound and about half of each is excreted within 24 hours.

**Clinical uses**: - For infections with pneumocystis carinii, which causes pneumonia in patients with AIDS

Antibiotics which affect Peptidoglycan synthesis

- Peptidoglycan - cell wall of bacteria
- Not present in mammalian cell membranes, therefore excellent target for antibiotics
- In bacteria - cell wall is many layers thick.
  - Each layer consists of multiple backbones of amino sugars with alternating N-acetyl-glucosamine and N-acetylmuramic acid residues – later of which have short peptide side chains which cross-link to form a lattice.
  - Wall is very strong - resist high osmotic pressures.
  - If you stop the formation of this lattice by interfering with cross-linking , you render the bacteria susceptible to osmotic pressures and they bacteria burst
- b-Lactam antibiotics e.g. penicillin inhibits the formation of peptidoglycan, thus preventing formation of the wall and the bacteria burst = Bacteriocidal

B-lactam antibiotics

Examples of these include penicillin, cephalosporins and carbapenems

- These all have a beta-lactam ring their structure, but this is susceptible to breakdown
  - Side rings differ in different molecules
- **Mechanism of action**: Interfere with the synthesis of the bacterial wall peptidoglycan - inhibit the transpeptidation enzyme that cross links the peptide chains attached to the backbone of the peptidoglycan.

Resistance is gradually developing to a lot of the B-lactam antibiotics. There are 3 different mechanisms of resistance:

- Production of b-lactamases by bacteria, which results in breakdown of the B-lactam ring rendering it useless
  - Resistance is genetically controlled and transferred from one bacterium to another.
  - at least 80% of staphylococci now produce b-lactamase
  - **Solution** - use b-lactamase inhibitors e.g. clavulanic acid, functions by covalently binding to the enzyme at or close to its active site.
- Reduction in the permeability of the outer membrane - poor drug to penetrate to the target site.
- Occurrence of modified penicillin-binding sites.

Penicillins

**Types of Penicillin**

- First penicillins - naturally occurring benzylpenicillins. To get industrial quantities was difficult, and they could not be given by oral administration
• Broad spectrum but poor GIT absorbed (given by injection) and are susceptible to b-lactamases.
• Synthetic penicillins – better GIT absorption.

**Pharmacokinetics**

- **Oral administration** – absorption depends on stability in acid and their adsorption on to food (must be taken on empty stomach)
- **Wide bio-distributed** - body fluids, passing into joints, pleural and pericardial cavities, into the bile, the saliva and the milk and across the placenta (can be used for a wide variety of infections)
- **Lipid insoluble** - do not cross readily the blood brain barrier unless the meninges are inflamed - reach effective therapeutic concentrations.
- **Elimination** – mainly renal, 90% is by tubular secretion; this occurs rapidly, and often results in in-tact excretion

Unwanted effects: Relatively free from direct toxic effects.

- Main unwanted effects - hypersensitivity reactions (first exposure results in skin rash or mild discomfort, but subsequent exposure results in anaphylaxis)
- Breakdown products of penicillin combine with host protein - antigenic.
- Most common reactions - skin rashes and fever. More serious - anaphylactic shock.
- Effect on the gut bacterial flora - GI tract disturbances.

**Cephalosporins** (eg cepalexin [oral], cefuroxime & cefotaxime [parenteral])

- **MOA:** - Interfere with peptidoglycan synthesis.
  - Resistance – wide spread - gene encoding for b-lactamase
  - Enzyme is in fact more active in hydrolysing cephalosporins than penicillin.
  - Decreased penetration of the drug due to alterations to outer membrane proteins or mutations of the binding site proteins.
- **Pharmacokinetics:** - Some cephalosporins orally active but most are given parenterally, i.m. or i.v.
  - Widely distributed – enter pleural cavity, pericardial and joint fluids and placenta.
  - *Cefoperazone*, cefotaxime - cross the blood brain barrier - drug of choice for bacterial meningitis.
  - Most Cephalosporins - Excretion by tubular secretion in kidney
    - Exception - 40% of ceftriaxone and 75% of cefoperazone is eliminated in the bile.
  - Since different b-lactam antibiotics may bind to different binding proteins - combine two or even more of these agents and achieve synergistic action between them.
- **Unwanted effects:** - Hypersensitivity reactions - cross reaction occur, about 10% of penicillin sensitive individuals will also be allergic to cephalosporins.
  - Nephrotoxicity - cephradine.
  - Diarrhoea - oral cephalosprins.

**Drugs that inhibit ribosomal function**

Family includes chloramphenicol, erythromycin, tetracyclines and streptomycin. These families affect different stages of ribosome function:

- Chloramphenicol binds to 50S portion and inhibits formation of peptide bond
- Erythromycin binds to 50S portion. Prevents translocation-movement
- Tetracyclines
- Streptomycin

**Tetracyclines** are broad-spectrum antibiotics with many ring structures that are active against many bacteria.

- **MOA:** - Active transported into bacteria - interrupt protein synthesis. Competition with tRNA for the A binding site. By inhibiting protein synthesis, they mainly prevent cell growth + division therefore are considered bacteriostatic, not bactericidal.
- **Spectrum:** - Very wide and includes Gram +ve and Gram –ve
- Widespread resistance –
Aminoglycosides

Pharmacokinetics:

MOA

- binds to the 30S subunit of the ribosome - alteration in codon-anticodon recognition > misreading of the mRNA and hence the production of defective bacterial proteins.

Chloramphenicol

MOA: binds to the 50S subunit of the ribosome - inhibits transpeptidation – inhibits protein synthesis, therefore bacteriostatic

Absorption
- from GIT is irregular and incomplete - improved by the absence of food.
  - Tetracyclines chelate metal ions (e.g. iron), forming a non-absorbable complex - absorption is decreased by the presence of milk, antacids and iron preparations.

Distribution - wide bio - enters most fluid compartments.

Excretion
- of tetracycline is both via the bile and by glomerular filtration in the kidney.
  - Tetracyclines - accumulate if renal function is impaired.
  - Doxycycline - exception, being largely excreted into the gastrointestinal tract via the bile (give to patients with renal impairment)

Unwanted effects:

- Common – GIT disturbances - initially to direct irritation of the molecule on the GI tract (quick effect) and later to modification of the gut flora (longer-term effect)
- Chelate calcium - deposited in growing bones and teeth - staining and sometimes bone deformities.
  - Therefore not be given to children, pregnant women or nursing mothers.
- Demeclocycline - phototoxicity (sensitisation to sunlight).
- Minocycline can produce vestibular disturbances (dizziness and nausea), the frequency of which is dose related.

Gentamicin

MOA: - binding to the 30S subunit of the ribosome - alteration in codon-anticodon recognition > misreading of the mRNA and hence the production of defective bacterial proteins.

Unwanted effects:

- Development of energy-dependent efflux mechanisms which transport the tetracyclines out of the bacterium
- Mutations in ribosome structure – prevent binding.

Pharmacokinetics: - oral or parenterally.

- Absorption from GIT is irregular and incomplete - improved by the absence of food.
  - Tetracyclines chelate metal ions (e.g. iron), forming a non-absorbable complex - absorption is decreased by the presence of milk, antacids and iron preparations.
- Wide bio - distribution - enters most fluid compartments.
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- Minocycline can produce vestibular disturbances (dizziness and nausea), the frequency of which is dose related.
Isoniazid

Exploiting differences between prokaryotic and eukaryotic cells

A combination drug therapy (6 month treatment, so compliance is difficult)

- Penetration through the bacterial cell membrane - dependent on an oxygen-dependent active transport system.
  - Other antibiotics can block this transport system, e.g. chloramphenicol, therefore co-administration should be avoided.
- Their effect is bactericidal and is enhanced by agents that interfere with cell wall synthesis.

- **Resistance:**
  - Inactivation by microbial enzymes - plasmid carried genes
  - Failure of penetration (overcome by concomitant use of penicillin and/or vancomycin which synergises with the aminoglycosides)
  - Mutations that alter the binding-site on the 30S subunit.

- **Spectrum:** - effective against many aerobic Gram -ve and some Gram +ve bacteria. They may be given together with penicillin in infections caused by Streptococcus, Listeria or Pseudomonas aeruginosa.

- **Pharmacokinetics:** polycations & highly polar - not absorbed in the GIT > given i.m. or i.v.
  - Do not enter cells, nor cross the BBB into the CNS.
  - Plasma half life 2-3 hours.
  - Elimination is virtually entirely by glomerular filtration in the kidney.
  - Tissue concentrations increase during treatment – require dose modification with long treatments as completely dependent on kidney.

- **Unwanted effects:**
  - **Ototoxicity** - progressive damage to and destruction of the sensory cells in the cochlea and vestibular organ of the ear.
  - **Nephrotoxicity** – reversible damage to the kidney tubules. Since the elimination of these drugs is almost entirely renal, their nephrotoxic action can impair their own excretion and a vicious cycle can be set up.

**ANTIMYCOBACTERIAL AGENTS**

Mycobacterial infections in man - tuberculosis and leprosy - chronic infections caused by Mycobacterium tuberculosis & leprae respectively.

- Main problem with both infections - micro-organism can survive inside macrophages, unless they are 'activated' T cell lymphokines.
- The WHO has declared tuberculosis to be a global emergency.
- Drug resistant strains which have spread rapidly in prisons and shelters for the homeless, and among persons infected with HIV.
- Inadequate treatment in these cases and in the Third World no treatment at all has compounded the problem.

**Managing resistance:**

A combination drug therapy (6 month treatment, so compliance is difficult)

- A first phase of about 2 months consisting of three drugs used concomitantly: *isoniazid, rifampicin, pyrazinamide* (plus ethambutol if the organism is suspected to be resistant).
- A second, continuation phase of 4 months, consisting of two drugs: *isoniazid and rifampicin*; longer treatment is needed in some situations e.g. meningitis, bone/joint involvement, drug resistant cases.

**Exploiting differences between prokaryotic and eukaryotic cells**

- Rifampicin inhibits RNA synthesis
- Isoniazin inhibits cell wall synthesis
- Ethambutol inhibits

**Isoniazid**

**MOA:** Antibacterial activity - limited to mycobacteria.

- Bacteriostatic on resting organisms and can kill dividing bacteria.
- Passes freely into mammalian cells - effective against intracellular organisms.
MOA is not fully understood but evidence suggests that it inhibits the synthesis of mycolic acids, important constituents of the cell wall and peculiar to mycobacteria.

**Pharmacokinetics:** - Readily absorbed from the GI tract - widely distributed throughout the tissues and body fluids, including the CSF.

- Important - penetrates well into the necrotic tuberculous lesion, therefore can tackle the bacteria producing the lesions
- Metabolism, involves largely acetylation, depends on genetic factors that determine whether a person is a slow (t1/2=3hours) or rapid (t1/2= 1.5 hours) acetylator of the drug, slow acetylators having a better therapeutic response.

Riskampicin

**MOA:** - Binds to and inhibits DNA-dependent RNA polymerase in prokaryotic but not eukaryotic cells.

- One of the most active anti-tuberculosis agents known.
  - Normal antibiotics would only kill extracellular bacteria, therefore reinfection by intracellular bacteria will occur
- Enters phagocytic cells and can kill intracellular micro-organisms.

**Pharmacokinetics:** - oral administration - widely distributed in the tissues and body fluids.

- It is excreted partly in the urine and partly in the bile, some of it undergoing enterohepatic cycling.
- There is progressive metabolism of the drug by deacetylation during its repeated passage through the liver. The metabolite retains antibacterial activity but is less well absorbed from the GI tract.

**Unwanted effect:** - infrequent - occurring in fewer than 4% of individuals e.g. skin eruptions, fever, GI tract disturbances.

Pyrazinamide

**MOA:** Inactive at neutral pH but tuberculostatic at acidic pH, like that of the macrophage environment

- Effective against the intracellular organism in macrophages, - organism will be contained in phagolysosomes at low pH.

**Pharmacokinetics**

- Distribution – Oral – good absorption - widely distributed, penetrating well into the meninges and other tissues.
- Excretion – kidney - glomerular filtration.

**Unwanted effects** - arthralgia (associated with high concentrations of plasma urates which crystallise in the joints). GI tract upsets, malaise and fever are reported.

**Fungal Infections**

**Anti-fungal drugs**

Fungal infections are termed *mycoses* :-

- Superficial infections - Affecting skin, nails, scalp, mucosal membrane.
- Systemic infections - Affecting deeper tissues and organs.

**Primary systemic fungal infections** are rare and generally occur in defined endemic areas of the world.

- In the UK the commonest systemic fungal infection is candidiasis - an infection with a yeast like organism.

**Superficial fungal infections**:

- Dermatomycoses - infections of the skin, nails and hair are caused by dermatophytes. The commonest are due to Tinea organisms e.g. Tinea pedis -causing 'athletes foot'.
- Candidiasis - yeast like organisms which infect the mucous membranes of the mouth (thrush), or vagina, or skin.

**Nystatin** is a polyene macrolide - virtually no absorption from the mucous membranes of the body or from the skin and its use is limited to fungal infections of the skin and GI tract.

**MOA:** - Binds to the cell membrane and interferes with permeability and with transport functions.
• Forms a pore in the membrane, the hydrophilic core of the molecule creating a transmembrane ion channel.
• Selective action, binding avidly to the membranes of fungi - drugs greater avidity for ergosterol (fungal membrane sterol) than for cholesterol, the main sterol in the plasma membrane in animal cells.
• Effective against most fungi and yeasts.

Unwanted effects: - Rare. Limited to nausea and vomiting when high doses are taken by mouth. V.rare - Rash.

**Miconazol**: Azole group of synthetic antifungal agents - broad spectrum of activity.
**MOA**: - Azoles block the synthesis of ergosterol - main sterol in the fungal cell membrane.
• Interacts with the enzyme necessary for the conversion of lanosterol to ergosterol.
• Result - depletion of ergosterol - alters the fluidity of the membrane and this interferes with the action of membrane associated enzymes, affecting the fluidity of the membrane and inhibiting replication
• Additionally - inhibits transformation of candidal yeast cells into hyphae form (the invasive and pathogenic form of the parasite)

**Pharmacokinetics**: - intravenous infusion for systemic infections and orally for infections of the GI tract. It has a short plasma half life.
**Unwanted effects**: - Relatively infrequent, most commonly being GI tract disturbances, blood dyscrasias (rare)

**ANTI-VIRAL DRUGS**

**Viruses**
These are the smallest infective agent - consist of nucleic acids (either RNA or DNA) enclosed in a protein coat or capsid.
• **DNA viruses**: poxvirus (smallpox), herpes viruses (chicken pox, shingles, herpes and glandular fever), adenoviruses (sore throat, conjunctivitis), and papilloma viruses (warts).
• **RNA Viruses**: orthomyxo viruses (influenza), paramyxovirus (measles, mumps), picornaviruses (colds, meningitis, poliomyelitis), retroviruses (AIDS), arenavirus (meningitis, Lassa fever).

They are intracellular parasites with no metabolic machinery of their own.
• In order to replicate, the attach to and enter a living host cell and use its metabolic processes, accessing receptors on the host cell (ie utilising normal membrane constituents eg ion channels, NT receptors, integral membrane glycoproteins).
• The viral coat is removed on entry, and viral proteins are budded off to infect new cells.
• As they share many of the metabolic processes of the host cell, it is difficult to find drugs that are selective for the pathogens.
• However some virus-specific enzymes are potential targets for drugs. Most of these drugs are effective while the virus is replicating.
  o The problem here is that once infection is clinically detectable, the process of viral replication is usually far advanced and chemotherapeutic intervention is very difficult

**Acyclovir** acts by inhibiting nucleic acid synthesis
• This is a guanosine derivative with high specificity for herpes simplex. It is more sensitive than the other herpes viruses which cause glandular fever or shingles - small but reproducible effect against cytomegalovirus (CMV) which can cause glandular fever and retinitis, resulting in blindness in individuals with AIDS.
**MOA**: parent drug is converted to the monophosphate form by thymidine kinase - the virus specific form of this enzyme being very much more effective in carrying out the phosphorylation than the host cells' thymidine kinase.
• The mono form is subsequently converted to the triphosphate by the host cell kinases.
• It is therefore only adequately activated in infected cells.
• Acyclovir triphosphate inhibits viral DNA-polymerase, terminating the chain reaction.
  • 30 times more potent against the herpes virus enzyme than the host enzyme.
• Acyclovir triphosphate is then rapidly broken down within the host cells by cellular phosphatases (hence why frequent application required)

Changes in the viral genes coding for thymidine kinase or DNA polymerase result in **resistance**. This is relatively rare.

**Pharmacokinetics:**

- **Administration** is oral, iv and topically
  - Oral – only about 20% of the dose is absorbed and peak plasma concentrations are reached in 1-2 hours.
  - i.v. infusion results in a plasma concentration 10- to 20- fold higher.
- **Distribution**, including being able to cross the BBB to reach concentrations in the CSF which are 50% of those in the plasma.
- **Excreted** in the kidneys partly by glomerular filtration and partly by tubular secretion.

**Side effects:** these only occur rarely with oral administration, but intravenous administration is associated with some side effects (most due to drug solution, not drugs itself)
- Local inflammation - extravasation of the solution, which is very alkaline.
- Renal dysfunction
- Nausea and headache

**HIV Treatment**

Modern day therapies typically consist of triple combination therapy, including:

**Zidovudine** (AZT; azidothymidine)
- This is an analogue of thymidine, which acts as an active inhibitor of reverse transcriptase enzyme the HIV virus uses

**MOA:**

- Phosphorylated by cellular enzymes to the triphosphate form. This competes with equivalent cellular triphosphates which are essential substrates for the formation of proviral DNA by viral reverse transcriptase (viral RNA-dependant DNA polymerase)
- Incorporation into the growing viral DNA strand results in chain termination, therefore preventing continuation of the DNA synthesis
- Mammalian alpha DNA polymerase is relatively resistant to the effect.
  - However, gamma DNA polymerase in the host cell mitochondrion is fairly sensitive to the compound and this may be the basis of unwanted effects.
    - Interference with mitochondrial function in host cell responsible for side effects

**Pharmacokinetics**

- **Administration:** Oral (bio-availability - 60-80 % due to first pass metabolism)
  - Peak plasma concentration occurs at 30 mins.
  - It can also be given i.v.
- **Distribution:** There is little plasma protein binding so there are no drug interactions due to displacement by other drugs.
  - Zidovudine enters mammalian cells by passive diffusion and in this is unlike most other nucleotides which require active uptake. The drug passes in to the CSF and brain.
- **Metabolism:** Most of the drug is metabolised to inactive glucuronide in the liver
- **Excretion:** 20% of the active form being excreted in the urine.

**Uses for HIV/AIDS**

- **Patients with AIDS** - reduces the incidence of opportunistic infection (such as Pneumocystis carinii pneumonia)
  - Stabilises weight
  - Reverses HIV-associated thrombocytopenia
  - Stabilises HIV associated dementia and reduces viral load.
- If given to **HIV +ve individuals** before the onset of AIDS in combination with other drugs can dramatically prolong the life expectancy.
- **In HIV +ve mothers** it reduces the risk of transmission of the virus to the foetus by 66%.

In subjects who have been accidentally exposed to HIV e.g. hospital worker, rape victims, condom problems etc
Unwanted effects
- Common - anaemia and neutropenia.
- Rare - GI tract disturbances, skin rash, insomnia, fever, headache, abnormalities of liver function, and particularly myopathy.
- Confusion, anxiety, depression, and a flu-like syndrome are also reported.

Resistance: - therapeutic response wanes with long-term use, particularly in late-stage disease.
- Virus develops resistance to the drug due to mutations resulting in amino acid substitutions in the viral reverse transcriptase - these genetic changes accumulate progressively, and can be transferred between individuals
- Decreased activation of zidovudine to the triphosphate, resulting in increased virus load due to reduction in immune mechanisms, therefore decreased response with increased time of treatment
31. Anti-Convulsants
Dr Micheal Johnson

EPILEPSY
Epilepsy is a common serious neurological disorder
- There is a lifetime risk of having an epileptic seizure is 4%
- Active epilepsy affects 1 in 200 people
- 300,000 in UK, >50 million worldwide
- 1000 epilepsy-related deaths per year in UK
- Stigma, social exclusion and under-employment
- 25% have epilepsy resistant to medical treatment
- Costs the NHS £1bn/year

Definitions
- An epileptic seizure is the manifestation of an abnormal and excessive synchronised discharge of a set of cerebral neurones
- Epilepsy is a condition defined as a tendency to recurrent, unprovoked seizures
- Seizures are the clinical manifestation of epilepsy
- Epilepsy is a syndrome, not a disease

NB: the occurrence of a seizure does not in itself mean a diagnosis of epilepsy. Anyone may be affected by a seizure with the appropriate stimulus; the diagnosis of epilepsy implies that the seizures are unprovoked.

Classification
Seizures are classified electroclinically, into those focal and generalized:
- In focal seizures, the epileptogenic zone is a defined cortical region, capable of triggering an epileptic seizure
- Epilepsy is classified as generalized, when extensive areas of the cortex in both cerebral hemispheres can elicit epileptic seizures. From a practical point of view, the patient with generalized epilepsy is considered to have a diffusely abnormal epileptogenic cortex.

Until very recently it was assumed that focal seizures resulted solely from a focal brain injury and generalized epilepsy from diffuse abnormal cortex such as may arise in patients with an inherited predisposition to epilepsy.

In recent years with parallel advances in genetics and neuroimaging, it is clear that focal seizures may arise as result of widespread and diffuse cerebral dysfunction such as a genetic susceptibility, and that generalised seizures may result from a well-delineated focus of neuronal pathology such as a lesion in the mesial frontal lobes (secondary generalised)

Incidence
The incidence of epilepsy varies between 50 and 120 per 100 000 persons per year.
- The incidence appears to vary with age, with two peaks, one early in life and a second in the elderly.
- The first peak is predominantly made up of those epilepsies that have a complex genetic basis, and the second peak in later life is thought to result mainly from environmentally acquired brain injury such as stroke.

Aetiology
The aetiology of epilepsy can be about equally divided into those epilepsies which result from an underlying structural or metabolic brain injury, and those where there is no cause other than an inherited
- The causes of epilepsy can be about equally divided into those where the epilepsy is symptomatic of an
underlying brain injury, and those epilepsies that have no cause other than an inherited predisposition, which we call idiopathic.

- **Symptomatic epilepsy** arises most commonly as a result of an environmentally acquired brain injury from tumour, stroke, infection and head injury, and less commonly, from an inherited brain injury, such as an inherited malformation of cortical development, vascular malformation such as familial cavernomas or metabolic defects such as the inherited progressive myoclonic epilepsies.

- For **idiopathic epilepsy**, only 1 to 2% manifests mendelian inheritance, with majority having polygenic, non-mendelian inheritance. As we mentioned, there has been considerable success in identifying genes for the rare monogenic idiopathic epilepsies, but this success has not yet been translated into a better understanding of the more common idiopathic epilepsies that do not manifest mendelian inheritance.

**Types of seizures**
- Generalised tonic clonic seizure
- Absence seizures
- Focal/partial seizure (temporal lobe type, but can arise from any part of the cortex. Signs determined by part of cortex from which the seizure arises)
  - Here, the same neuronal network is activated every time, and this can be useful for diagnosis
  - 3 stages: Warning/aura, loss of awareness, then automatism (ipsilateral to seizure focus)+ dystonia

**ANTI-EPILEPTIC DRUG (AED) THERAPY**
Treating epilepsy has both benefits and harm:
- **Benefits**: Seizure suppression (reduction in Sz-related harm)
- **Harms**: Psychosocial consequences (illness status, self-esteem, education, employment), Idiosyncratic & dose-related ADRs

The factors influencing decision to treat includes:
- Number of seizures at presentation
- Seizure type and severity
- Cause of seizure
The standard approach is to aim to control seizures with a single AED (this is achieved in 60-70%)

**Abbreviations** (don't need to learn all, just for use in notes)
- CBZ – carbamazepine
- VPA – valproate (sodium)
- LTG – lamotrigine
- PB – phenobarbital
- PHT – phenytoin
- ETX – ethosuximide
- TOP – topiramate
- OXC – oxcarbazepine
- LEV – levetiracetam

**Pharmacodynamics**
Most existing antiepileptic drugs probably act by one or more of these **3 mechanisms**:
1. Enhancing GABA mediated inhibition
2. Inhibiting fast excitatory neurotransmission, principally that mediated by the excitatory neurotransmitter glutamate
3. Inhibiting neuronal action potentials by blocking voltage-gated sodium channels.
4. Neuronal Calcium channels.
5. Unknown
Note:
- Several antiepileptic drugs have more than one mechanism of action. For example, topiramate shown in red probably acts by all 3 mechanisms and it is not possible to say which is the principle mechanism mediating its anticonvulsant effect.
- Note that the known or supposed mechanism of action is not very helpful in choosing drugs for particular types of epilepsy.
- The accepted mechanism of antiepileptic drug action are by no means certain, eg Gabapentin (first marketed as a GABAGergic drug) which works by inhibiting glutamate
  - Another example of serendipitous development: Levetiracetam, is a pyrrolidone derivative licensed in the UK 2001. It was initially developed in the 1980s as a drug with cognitive enhancing effects but early trials were unsuccessful and so it was tried in epilepsy. It is now among the most promising of the new antiepileptic drugs, but its mechanism of action is completely unknown.

Choosing drugs:
NB: if we compare classic and new AEDs we see little difference in effectiveness, but large improvements in tolerability and drug-drug interactions.
- Mechanism of action is poor guide to clinical use
- Partial epilepsy - CBZ or LTG first line
- Generalized epilepsy - VPA or LEV first line
- Many are “broad spectrum” & used in both generalized and partial epilepsy: e.g., VPA, TPM, LTG, LEV
- ESM - childhood absence epilepsy only
- CBZ, VGB, GPT may worsen some generalized epilepsy seizure types(absence and myoclonic seizures)

General pharmacology
- **Pharmacokinetic variation**
  - Bio-availability: age, gender, generic formulations
  - Distribution: Vd (muscle, fat), Protein binding (hepatic/renal disease, pregnancy, age) Metabolism: Biotransformation (Phase I & II enzymes)
  - Excretion: Renal disease, age
  - Drug interactions: Induction/inhibition of liver enzymes
- **Pharmacodynamic variation** - Genetic variation in drug receptor subunit sequence/expression

Principles of AED therapy
- Be clear about indication for AED therapy (see above)
- Discuss risks and benefits with patient
- Accurate classification of epilepsy where possible
- One AED where possible
- Concept of ‘therapeutic range’ overstated - most AEDs, correct dose is minimum dose that controls seizures without intolerable side effects
- Therapeutic drug monitoring of little benefit except in:
  - Phenytoin (but 1/3 still controlled on “sub-therapeutic” levels)
  - Polytherapy (complex drug interactions)
  - Assessing of compliance
  - Suspected toxicity
- Always consider potential for drug interactions
  - Effect of AED on other drugs (including other co-prescribed AEDs)
  - Effect of other drugs on AED, eg contraceptive pill
- Never withdraw drugs suddenly; risk of withdrawal related seizures
- Make one change at a time. If replacing, add-in before withdrawing other

**Importance of this topic:** patients who fail to remit with the first AED, adjunctive treatment with “new AED” is standard care. The criteria for choosing add-on AED is as follows:
- Efficacy (is one AED more effective than another)
• Adverse Effects profile (acute and chronic)
• Pharmacokinetic and drug interactions
• Co-morbidities
• Mechanism of action – less important
• Quality of life

The second drug must be added before the first is removed, ie you only do one step at a time.

**Phenytoin**

The **pharmacokinetics** of phenytoin are complex:

- Hepatic metabolism: oxidation (CYP2C9 > 2C19), followed by hydroxylation then conjugation and renal excretion of non-active metabolites
  - Large inter-individual variation in metabolism
- An important aspect is saturable kinetics; that is concentration dependent. I.e., non-linear kinetics (after the metabolism enzymes are saturated, the drug level rises quickly. This means small increases in dose may precipitate toxicity. To combat this:
  - (Start low (e.g., adult = 100-200mg daily, with increments of 50mg every 2/52 to 300mg daily, then 25mg increments) - unless urgent, when can load IV
- Indications for use: partial epilepsy and staus epilepticus
- Mechanism of action: blockade of v-gated Na channels
- Drug level monitoring is useful, but elimination half-life is 20 hours, therefore monitoring needs at least 5 half-lives following a dose change
- Highly (70-90%) protein bound so free drug levels helpful in some circumstances (displacement by some drugs, low albumin states)
- NB: P450 enzyme inducer - hence large number of important drug interactions

**Side effects:**

- Allergic: rash, vasculitis, fever, hepatitis
- Toxic: ataxia, sedation
- Chronic: gingival hypertrophy, folate deficiency, megaloblastic anaemia, vit K deficiency, depression, hisutism, peripheral neuropathy, hypocalkaemia, osteomalacia and myopathy

**Drug interactions**

**Effects of other drugs on PHT:**

- Amiodarone, Isoniazid - Potent inhibitors of PHT metabolism, with increased PHT levels
- Aspirin - displaces PHT from protein binding - only a prob near sat
- Valproate - displaces PHT from protein binding and also inhibits PHT metabolism. A problem if PHT levels are near saturation, leading to PHT toxicity with normal total PHT levels (measure free PHT levels with this drug combination). Avoid combination where possible.

**Effects of PHT on other drugs:**

- WARFARIN – Induction of CYP450 system so concentration of warfarin decreases. Monitor INRs closely after any change in PHT dose.
- AEDs (e.g., lamotrigine), corticosteroids, cyclosporin, levels all lowered
- Estrogen containing OCP efficacy reduced (50ug estradiol req)

**Carbamazepine**

- Indications: Partial and secondary generalized seizures
- Mechanism of action: Blockade of v-gated Na channels
- Drug level monitoring: Useful
- Elimination half-life: 5-26 hours (x3 daily dosing, unless SR preparations)
- Metabolism: Hepatic oxidation then conjugation. CBZ is a potent hepatic enzyme inducer
- Active metabolites: carbamezepine epoxide
- Drug interactions: Complex drug interaction profile

**Adverse effects**

- Hypersensitivity: rash, hepatitis, nephritis
- Dose related: Ataxia, dizziness, sedation, diplopia
- Chronic: Vit K deficiency, depression, impotence, osteomalacia, hyponatraemia,
Drug interactions:
- Auto-induction
- Effects of other drugs
- Effects of CBZ on other drugs

Valproate
- used in partial or generalised epilepsy. Its mechanism of action is unclear, but it is thought to enhance GABA by a variety of mechanisms.
- Drug level monitoring is not well established, and the clinical effect is poorly correlated with drug levels. The half life of Valproate is between 4 and 12 hours, and metabolism is by hepatic oxidation and then conjugation.
  o Valproate is a potent inhibitor of hepatic enzymes, but it has no active metabolites.
- It has many important drug interactions.

Adverse drug reactions include severe hepatic toxicity (especially in the young), pancreatitis, drowsiness, encephalopathy (ammonia driven), tremor, blood dyscrasias, hair thinning and loss, weight gain, and endocrine effects like PCOS.
- Valproate is a potent inhibitor of both oxidation and glucuronidation, and so Phenytoin, Phenobarbital and Lamotrigine levels are all increased, and Carbamazepine Epoxide levels are increased.
- Levels of Valproate are reduced by hepatic enzyme inducers like Phenytoin, Phenobarbital and Carbamazepine.
- Antacids may impair Valproate absorption. Some NSAIDs, Aspirin and Phenylbutazone displace Valproate from its albumin binding sites and may result in toxicity.

Pharmacology Tutorials/Practicals

Principles of Pharmacodynamics Tutorial

Learning objective: to review and consolidate the essential principles of pharmacodynamics and quantitative pharmacology.

DRUG-RECEPTOR INTERACTIONS

1. Explain in your own words, giving relevant examples where appropriate, what you understand by the following terms:
   a. **Drug**: a chemical that affects physiological function in a specific way
   b. **Drug target site**: a protein upon which a drug acts to mediate its effects
   c. **Receptor**: protein (usually) in a cell membrane which binds with a drug, leading to a response
   d. **Agonist**: a compound which stimulates a response
   e. **Antagonist**: a compound which blocks a response
   f. **Affinity**: the strength of binding
   g. **Efficacy** ("intrinsic activity"): the ability to produce a response when bound
   h. **Potency**: the powerfulness of the drug
   i. **Selectivity (contrast with specificity)**: selectivity describes the preference of a drug from a receptor, whereas specificity suggests it will only bind to a single receptor. Adverse effects to drugs are often the result of drugs binding to non-intended receptors, showing they are not specific.

2. Using the above terminology, differentiate between:
   a. **Full agonist**: stimulates the maximal response of the receptor
   b. **Partial agonist**: stimulates only a partial response to the receptor

3. What are the principle differences between competitive and irreversible antagonists?
a. Differentiate between log dose-response curves to a specific agonist in the presence of
   i. A competitive antagonist
   ii. An irreversible antagonist
   - Competitive antagonists block the receptor binding site temporarily, therefore preventing the drug from binding. However once the antagonist is removed, the active site is exposed and the drug can bind
   - Irreversible antagonists induce a conformational change in the receptor, therefore changing the shape of the active site thus preventing the drug from ever binding even after the antagonist is removed.

4. Describe the four main categories of drug target sites. Give one example of a drug acting at each of these different target sites.
   - Receptors – atropine
   - Ion channels – nAChR
   - Transport systems – cardiac glycosides
   - Enzymes – anticholinesterase

5. Specify four classes of drug that do not act by binding to proteinaceous target sites.
   - Osmotic laxatives
   - General anaesthesia (targets synaptic transmission in the brain)
   - Antiretrovirals (targets RNA)
   - Antacids

6. Define the term “receptor reserve”. What is the physiological importance of this phenomenon?
   - The receptor reserve is a pool of receptors which do not require binding in order to produce a maximal response
   - This is important with regards to irreversible antagonists, even when a maximal response has been produced, there are still spare receptors for agonist binding
MECHANISMS OF DRUG ACTION

7. Briefly explain what you understand by the term “structure-activity relationship”
   - The relationship between the chemical or 3D structure of a molecule and its biological activity.
   - The analysis of SAR enables the determination of the chemical groups responsible for evoking a target biological effect in the organism. This allows modification of the effect or the potency of a bioactive compound (typically a drug) by changing its chemical structure.
   - Medicinal chemists use the techniques of chemical synthesis to insert new chemical groups into the biomedical compound and test the modifications for their biological effects.

8. Differentiate between the four principal types of drug antagonism. Give one example of each.
   - Receptor blockade; this may be competitive or irreversible, eg atropine or hexamethonium
   - Physiological; when 2 drugs may occupy different sites with opposing action, eg noradrenaline + histamine
   - Chemical; this is uncommon, but it is when two substances combine in solution so that the active effect of the drug is lost eg dimercaprol
   - Pharmacokinetic; the antagonist reduces the concentration of the active drug at the site of action, either through increasing elimination or decreasing absorption, eg barbituates

9. Name the four main families of receptors. On what basis are they distinguished?
   - Distinguished by their time-scale of response (shown above), and their molecular structures
     - Kinase linked (response within mins)
     - G-protein coupled (response within secs)
     - Channel-linked (Response within ms)
     - Receptors that control gene transcription (response within hours)

10. Describe the different types of receptor-linked transduction mechanisms and give examples of receptors which utilise each
    - Ionotrophic (ion-linked), eg nicotinic ACh
    - Kinase/tyrosine linked, eg insulin
    - G-protein coupled, eg muscarinic ACh
    - Steroid, eg oestrogen

11. Define “drug tolerance”. Briefly describe the five different cellular mechanisms that may account for, or contribute to, this phenomenon.
    - Drug tolerance is “the gradual reduction in responsiveness to the same drug”
    - Cellular mechanisms include:
      - Receptor damage (causing toxic side-effects)
      - Increased speed of drug metabolism (caused by new enzyme involvement)
      - Receptor desensitisation (via exhaustion of second messenger molecules + mediators), eg amphetamines
      - Physiological adaptation
**Bioavailability Tutorial**

**Pharmacology**, by definition, is concerned with chemicals (drugs) of potential benefit to patients. However, although drugs are developed and tested, the patient actually receives a medicine.

- Medicines are the dosage forms used, which contain the drug in question and also include a number of other materials called **EXCIPIENTS**.
- These excipients may be added to aid the manufacture of the medicine, to **improve its chemical and biological stability** or to **increase its acceptability to the patient** by improving its flavour, fragrance or appearance.

The process of making a medicine containing a drug is called **FORMULATION** and is an important part of the development process in the pharmaceutical industry.

- A drug may be available in a number of **different formulations** that have been designed for use via **different routes of administration**.
- For example, a sterile solution of a drug in isotonic saline may be available for intravenous injection. The same drug also may be available in a pressurised aerosol formulation for (metered dose) inhalation, or as an ointment (or cream, lotion, paste) for application to the skin surface.

In addition, several **different formulations** may have been designed for use with the **same route of administration**, but each may have their own particular advantages.

- For example, liquids, syrups, tinctures, powders, soluble (effervescent) tablets, capsules, tablets and enteric-coated tablets all have been formulated for oral use.

The oral **route for administration** of medicines is the most common and convenient. However other routes of administration have their own applications, advantages and disadvantages...

<table>
<thead>
<tr>
<th>Oral – through the oesophagus</th>
<th>Intra muscular – into connective tissue reservoir in muscle block</th>
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<tbody>
<tr>
<td><strong>Advantages:</strong></td>
<td><strong>Advantages:</strong></td>
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<tr>
<td>it permits self-medication,</td>
<td>relatively high blood flow, increased during exercise</td>
</tr>
<tr>
<td>it does not require rigorously sterile preparations,</td>
<td>enables <strong>Depot therapy</strong> (prolonged absorption from pellet, microcrystalline suspension or solution in oily vehicle).</td>
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<tr>
<td>the incidence of anaphylactic shock is lower (than intravenous),</td>
<td><strong>Disadvantages:</strong></td>
</tr>
<tr>
<td>there is the capacity to prevent complete absorption (vomiting, lavage)</td>
<td>possible infection and nerve damage (especially in gluteal region)</td>
</tr>
<tr>
<td><strong>Disadvantages:</strong></td>
<td></td>
</tr>
<tr>
<td>it is inappropriate for drugs which</td>
<td></td>
</tr>
<tr>
<td>o are labile in acid pH of stomach or degraded</td>
<td>o possible localised effect within lung (unless this is desired)</td>
</tr>
<tr>
<td>o or undergo extensive ‘first-pass’ metabolism,</td>
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<tr>
<td>it requires patient compliance.</td>
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<thead>
<tr>
<th>Inhalation – via lungs and respiratory tract</th>
<th>Intravenous - directly into the circulating blood</th>
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<tbody>
<tr>
<td><strong>Advantages:</strong></td>
<td><strong>Advantages:</strong></td>
</tr>
<tr>
<td>ideal for small molecules, particles, gases, volatile liquids, aerosols</td>
<td>rapid onset of action</td>
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<tr>
<td>enormous surface area presented by alveolar membranes</td>
<td>avoids poor absorption from, and destruction within, the GI tract</td>
</tr>
<tr>
<td>simple diffusion, also phagocytic cells clear particles</td>
<td>permits careful control of blood levels</td>
</tr>
<tr>
<td><strong>Disadvantages:</strong></td>
<td></td>
</tr>
<tr>
<td>possible localised effect within lung (unless this is desired)</td>
<td><strong>Disadvantages:</strong></td>
</tr>
<tr>
<td></td>
<td>possible infection and nerve damage (especially in gluteal region)</td>
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<table>
<thead>
<tr>
<th>Subcutaneous - into connective tissue spaces under skin</th>
<th>Percutaneous - across the skin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages:</strong></td>
<td><strong>Advantages:</strong></td>
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Smith
Advantages:
- local administration, dissemination can be minimised for local effect
- enables depot therapy (as for intramuscular above)

**Disadvantages:**
- pain, abscess, tissue necrosis

- local application and action
- lipid soluble compounds diffuse rapidly (may be assisted by vehicles)

**Disadvantages:**
- local irritation and skin reactions
- alteration of skin structure (e.g. steroids - subcutaneous adipose tissue)

In the following tutorial session we are going to concern ourselves, mainly, with medicines that are taken by the oral (and enteral) route **(enteral routes** - sublingual, buccal, oral, rectal)

1. Describe three different types of formulations that may be used to deliver a drug via the oral route.
   - Syrup, tablet, powder

2. Give three reasons why excipients are added to a drug formulation.
   - Improve chemical + biological stability
   - Provide carrier mechanism
   - Protect the compound from enzymes in the stomach

3. Suggest examples of agents that could be used as excipients.
   - Flavourings
   - Sugar
   - Perfumes
   - Talk
   - Alcohol
   - Chalk
   - Plant extracts

Although it might be thought that the process of formulation would not influence the properties of the drug in the medicine, over the years many examples have been described which show that the action of drugs may indeed be determined by the nature of the excipients included with it.

- For example, in 1969, it was shown that the plasma levels and cardiovascular effects of digoxin varied greatly when patients were given tablets made by different companies in different ways, even though they all contained the same amount of drug. Since then, many cases of this phenomenon have emerged. To explain and understand this variance, the concept of **Bioavailability** has been developed.
- The bioavailability of a drug is the amount of a drug contained in a medicine that enters the systemic circulation in an unchanged form after administration of the product.
- Clearly the concept of bioavailability is not confined to drugs but can be applied to any chemical to which people are exposed.

4. Why is it important for a drug to be bioavailable?
There is a therapeutic window of concentration within the target tissue for which the drug must be in order to achieve the desired effect. If a drug is not bioavailable, it may not reach this desired concentration in the target tissue.

5. Does the measurement of bioavailability always reflect the effectiveness of a drug?
- No, a drug may be very effective but with a low bioavailability, therefore when it is administered its effectiveness is reduced.
- Examples of drugs that are effective but not bioavailable include prodrugs, and drugs which act locally therefore do not need to be systemically bioavailable.
The bioavailability of different formulations are assessed by comparing the areas under the **plasma level - time curves** of the drug after

a) intravenous administration of the drug (100% bioavailable)
b) administration of an identical dose of the medicine by the intended route (e.g. oral).

In the case of oral administration of a medicine, several **factors may influence bioavailability**;

- the physicochemical characteristics of the drug (ionisation in gut)
- gastrointestinal pH
- whether or not the drug is passively or actively transported
- gastrointestinal motility
- particle size of the drug
- physicochemical interaction between drug and gut contents (e.g. chemical interaction between calcium and tetracycline antibiotics)

6. **Explain how the above factors can influence the bioavailability of a drug**

They influence the absorption of the drug in the gut, which directly relates to the bioavailability of the drug because it is the amount of drug absorbed which is related to its concentration in the systemic circulation.

The effects that formulation can have on absorption may be illustrated by considering a well-known drug, aspirin (met in the computer program session). **Aspirin** is a very useful anti-inflammatory and anti-pyretic drug, which is available in a number of **dosage forms**;

- aspirin **tablets** B.P. - ordinary aspirin tablets sold in chemists
- **soluble** aspirin - these are dissolved in water and the solution swallowed
- **enteric-coated** aspirin - these have a sugar and wax coating which remains intact in dilute acid but quickly dissolves in alkali

7. **Aspirin has a pKa of about 3.5. Where would it be preferentially absorbed?**

It would be preferentially absorbed in the acidic environment of the stomach.

8. **When would it be appropriate to take soluble aspirin or tablet/enteric-coated and why would this formulation be advantageous over the others?**

- Soluble aspirin would be appropriate to take for more rapid pain relief as it is quickly absorbed in the stomach
- However tablets or enteric-coated aspirin would not break down as rapidly in the stomach, therefore would not be as quickly absorbed and are thus more suited to slower more prolonged pain relief, or when the patient

Once the **patent** on a new drug has expired, it is possible for any drug company to manufacture and market the drug.

- This often means that cheaper examples (**generic version**) of the same drug can be made, in which the formulation is slightly different. However, not all formulations will be equivalent and this can dramatically alter the bioavailability of the drug.
- Thus, regulatory authorities lay importance on evidence of **Bioequivalence**, that is, evidence that the new ‘**generic**’ product behaves sufficiently similar to the existing one to be substituted for it without causing clinical problems.
- This is particularly important when a drug has a narrow (small) **therapeutic index/window**.

9. **Why is bioequivalence important when prescribing generic versions of a drug which have a narrow therapeutic index?**

If a drug has a narrow therapeutic index, a generic version that is not bioequivalent poses a great risk of either not producing the desired effect or producing toxic effects.
10. Give examples of drugs to which this could apply.
   • Lithium
   • Cisplatin
   • Warfarin
   • Digoxin
   • Cytotoxic drugs

Even if all of the above factors are favourable for drug absorption, bioavailability can still be influenced by the biology of the human gut. The drug can be metabolised to inactive products by...
   • the microbes within the gut lumen
   • enzymes present in the gut wall
   • enzymes in the liver
In each of these latter situations, the bioavailability of the drug is altered by what is known a presystemic metabolism or first pass metabolism since the newly absorbed drug does not gain access to the general circulation until it has exited the liver. Remember, freshly absorbed drug would be taken directly to the liver by the hepatic portal vein.

11. How can good bioavailability be achieved for drugs that undergo extensive first-pass metabolism?
   • Use of a prodrug
   • Alternative route of administration, eg intravenously, sublingual

12. What kind of illness could affect the bioavailability of drugs?
GI disease or an inherited disorder of absorption eg coeliac

13. Under what circumstances could a drug, which undergoes 100% first pass metabolism, be therapeutically useful?
   • Pro-drug
   • If GI absorption is irrelevant, ie the GI tract is the target organ

Drug Metabolism Tutorial
1. Complete the following sentences based on the fundamental concepts of drug metabolism:
   • The major site of metabolism of foreign chemicals/xenobiotics in man is the liver
   • Cytochrome P450 enzymes form a central part of the drug metabolising system and are found in the smooth endoplasmic reticulum. Its principal role is in oxidation of chemicals and hence requires oxygen and the coenzyme NADPH.
   • Phase 1 metabolism typically involves oxidation or reduction reactions (when looking at drug + metabolite, look at group changed and oxidation number) Examples include azoreduction, nitroreduction, amide/ester hydrolysis, hydroxylation, deamination.
   • Phase 2 metabolism typically involves conjugation reactions which increase the polarity of drugs which facilitates excretion. Examples include glucuronidation, acetylation, methylation, sulphations, glutathione conjugation
   • Glutathione (nucleophile with free electrons) is a tripeptide consisting of glutamate, glyceine and cysteine which is most abundant in the liver (+RBC) and reacts with electrophile (+ charged) chemical intermediates

2. Paracetamol Metabolism:
Paracetamol is a widely used analgesic and anti-pyretic drug (the structure is given below). It is taken orally, absorbed and distributed throughout the body enabling pain and fever relief. It is largely metabolised in the liver which results in excretion of paracetamol as non-toxic metabolites. It can cause liver damage after over-dosage. Phase 1 metabolism of paracetamol is mediated by CYP450s and results in the formation of a reactive intermediate, NAPQI, also shown below.
a) What other metabolites of paracetamol would you expect to be formed from phase 2 reactions and name the enzymes/co-substrates necessary, given the list of common phase 2 reactions listed below:

- **Methylation**: of the free OH group, enzyme = methyl transferase, cofactor = SAM
- X - Acetylation: addition of COCH₃ requires free NH₂ (already acetylated)
- **Sulphation**: OH → SO₃⁻, enzyme = sulphotransferase, cofactor = PAPS
- **Glucuronidation**: addition of glucuronide to free O₂⁻ → O₆H₉O₆ (accounts for ~50-55% of paracetamol phase II metabolism), enzyme = UDP-glucuronide transferase, cofactor = UDPGA
- X - Amino acid conjugation: condensation between free NH₂ and COOH → N-C bond
- **Glutathione conjugation**: phase I metabolite has to be an electrophile (+ charge) which it is

b) NAPQI is electrophilic and will be furthered metabolised and detoxified by a phase 2 reaction, discuss this reaction:

- Paracetamol itself is a phase I metabolite of a prodrug, therefore has a free OH group
- The phase I metabolism either gives NAPQI or a compound with two free OH groups (see previous page)
- NAPQI then undergoes glutathione conjugation (addition of :SG)
- Enzyme = glutathione transferase
- Cofactor is not required as substrate just needs to be electrophilic

![Diagram of Paracetamol and N-acetyl-p-benzo-quinone imine (NAPQI)]
c) Based on the metabolic products of paracetamol stated above, suggest what could be used to salvage the toxicity in a case of acute poisoning and explain your mechanistic reasoning.
   • To salvage acute poisoning, you would want NAPQI to undergo the phase II reaction shown above.
   • This requires glutathione (comprised of glutamate, glycine + cysteine). Cysteine is the rate limiter in glutathione synthesis, therefore cysteine is administered (or N-acetylcysteine) either orally or intravenously.

d) A radioactive-labelled paracetamol mass balance study is conducted to study the distribution and metabolism of paracetamol in the rat. Which of the metabolites you have discussed above would you expect to predominantly find in the:
   - bile: compounds MW>300 → bile, therefore glucuronides + glutathione
   - urine: compounds MW<300 → urine therefore polar metabolites, eg sulphates, free N-acetylcysteine (also known as mercapturate; if present in the urine, indicates drug has an electrophilic metabolite)
   - serum: paracetamol (active drug)

e) The plasma half-life of paracetamol in patients with liver damage due to overdosage is over twice that in normal human subjects after a therapeutic dose. Interpret this information given what you know about the metabolism of paracetamol.
   - Liver damage causes the phase II metabolic pathways to be saturated, especially sulphate + glucuronide pathways
   - This causes the patient to run out of cofactors PAPS + UDPGA
   - This means that there is an increased build up of oxidised paracetamol NAPQI, as well as an increased amount of paracetamol remaining which goes into the plasma

f) Acetanilide is a pro-drug of paracetamol - the structure is shown below. Acetanilide causes methemoglobinemia (RBC toxicity) and as a result was removed from the market and replaced with paracetamol. Explain the term pro-drug and show what reaction is involved in the transformation of acetanilide to paracetamol.

Pro-drug: compound which undergoes a reaction, eg phase 1 metabolism, to form the active drug. These are administered to increase the bioavailability of a drug.

3. Prediction of the metabolism of a compound: The compound shown below is a potential hypotensive drug undergoing development. It can be given orally or via a skin patch. The parent form is pharmacologically active.

   a) The major routes of metabolism for this compound are shown below, identify the phase 1 and 2 reactions and name the enzymes/co-substrates involved.
b) What differences in metabolism would you expect for the different sites of absorption; oral or skin.

- Skin absorption would not have any nitroreduction, therefore the other pathways become dominant.
- You can use differences in metabolism for different sites of absorption to avoid pathways with toxic metabolites.

**Drugs in the Eye Practical**

Learning Objectives: to illustrate the effect of anticholinergic and cholinergic agents on the human eye, and to discuss various other principles relevant to ocular pharmacology.

**Anatomy of the Eye**

The eye lies in the front half of the orbit. The exposed surface (the cornea) consists of a central transparent convex portion. This character is obtained by the alignment of the collagen fibres. The iris gives colour to the eye, it is a circular diaphragm forming the posterior boundary of the anterior chamber. It has a central opening known as the pupil. The iris consists of a stroma and an epithelium of two layers. The pupil controls the amount of light entering the eye and is constantly varying in size depending on the action of the iris muscles. There are two types of iris muscles situated in the stroma:

- The circular muscle around the pupil (sphincter pupillae) which causes constriction. It is innervated by the parasympathetic fibres of the 3rd cranial nerve.
- The radial muscle (dilator pupillae) which dilates the pupil. It is innervated by the sympathetic nerves.

The lens is a transparent, bi-convex structure suspended from the ciliary body by zonular fibres and situated between the iris and the vitreous (posterior) compartment. It is elastic and usually under tension, alteration of its shape is under the control of the ciliary muscle which is innervated by parasympathetic fibres.
Pharmacology of the Eye

- **Allergy/inflammation** of the cornea + conjunctiva > topical anti-inflammatory agents, eg corticosteroids
- **Acute eye infections** > topical anti-infective preparations
- **Severe infection** > topical therapy + systemic treatment
- **Removal of foreign bodies/minor surgery** > local anaesthetics, eg cocaine derivatives

- **Surgical preparation** (for inspection of retina + prevention of iritis = iris adhesion to lens in inflammation) > mydriasis (dilation of pupil). This is achieved by either:
  - Anti-muscarinics/anti-cholinergics eg atropine, cyclopentolate, tropicamide (PNS block)
  - Sympathomimetics, eg phenylephrine (SNS stimulation)
- **Inefficient drainage in trabecular meshwork/glaucoma** requires miosis (constriction of the pupil). This is achieved using muscarinic agonists/cholinergic agents eg pilocarpine
  - Beta blockers can also be used to treat glaucoma
- **Chronically sore eyes** with reduced tear secretion, eg Sjogren's syndrome of rheumatoid arthritis > topical agents eg hypromellose + mycolytics
- **Excessive lachrymation** > topical agents eg zinc sulphate
- **Diagnostics/locating damage** > dyes eg fluorescein sodium, rose bengal
- **Cataract** (opacity of the lens) may be caused by administration of either systemic or topical steroids
- **Retina damage** may also be caused by systemic administration of many compounds eg chloroquine, quinine, thioridaine, ethanol
**Aqueous Humour + Glaucoma**

The **aqueous humour** originates from the **ciliary body** epithelium. This consists of two layers of ectodermal cells (containing ATPase and Carbonic anhydrase), with an **intracellular cleft** between that opens onto the aqueous humour side.

- $\text{Na}^+$ is actively absorbed into the intracellular cleft from the stroma, as well as $\text{Cl}^-$ and $\text{HCO}_3^-$ following along an electrical gradient. This creates a hyperosmolar cleft, causing water to flow from the stroma to the cleft.
- Aqueous humour passes through the narrow space between the iris and the lens into the anterior chamber.
- Drainage of aqueous humour occurs through the pores of the **corneo-scleral trabecular meshwork** in the antero-lateral walls of the anterior chamber.
- It then passes through the epithelial walls of the **canal of Schlemm** and returns to the venous circulation.

The **normal intraocular pressure** is about 15mm-Hg (range: 10-20) and is maintained mainly by the balance between the rate of aqueous humour production and the resistance to its return to the venous circulation. A state of glaucoma exists when the intraocular pressure increases such that there is damage to nerve fibres at the optic nerve head which results in progressive optic atrophy.

It is customary to classify **glaucoma** into:

- **Secondary glaucoma**: This is said to be present when an intraocular pressure of more than 20mm-Hg is found in the presence of an ocular disturbance which can reasonably be expected to lead to a raised pressure (e.g. trauma, intraocular neoplasms, neovascular formation, steroid administration).
- **Primary glaucoma**: There are three types and it can be diagnosed when there is no evidence of ocular or general cause of secondary glaucoma.

Glaucoma of all types is estimated to affect more than 1% of the population over the age of 40 years.

- Various pharmacological approaches are available for the treatment of glaucoma during an acute attack and for long-term management including pilocarpine, physostigmine, timolol, adrenaline and carbonic anhydrase inhibitors.
- Alternatives to drugs in the treatment of glaucoma have also been introduced (e.g. laser trabecular surgery).

**Experiment** investigates effect of **Tropicamide** (anticholinergic) and **Pilocarpine** (cholinergic) on:
Are you sure you want to request this document again?
Pindolol competes with **catecholamines** for the beta receptor to lower heart rate and systolic blood pressure, therefore exerts its maximum effect during exercise or in stressful situations when catecholamine output (from the sympathetic nerve endings and adrenal medulla)

**Autonomic influences on blood pressure**

**Beta blockers** decrease the effect of NA on the heart and kidneys – no significant effect on blood vessels
However large amount of beta 2 receptors in vascular supply to skeletal muscle, therefore there is a decrease in dilatation leading to a slight increase in TPR

NB: **Anti-hypertensive drugs**: ACE inhibitors, B-blockers, Calcium channel blockers, Diuretics

**Drugs in Anaphylaxis Tutorial**

**Case history**
Clare had only taken one mouthful of muesli when she felt her mouth itching. She began to feel uncomfortable inside and then vomited. Clare could also feel her throat begining to swell and she had difficulty breathing (dyspnoea). Soon her throat felt as though it was blocked (laryngeal oedema) and she began to feel lightheaded. Clare was taken to the accident and emergency department, by which time respiratory distress, intense erythema and generalised urticaria were evident.

Clare’s treatment began with the intramuscular injection of a drug. Clare made a rapid recovery and was informed that she had experienced an anaphylactic reaction, later found to be due to the nuts in her breakfast cereal.

**What is anaphylaxis?** A severe systemic allergic reaction (type 1 hypersensitivity response)
It involves the potentially life threatening features of:
The most common causes are:
- food (eg. peanuts and other nuts, shellfish)
- insect venom
- drugs (eg. penicillin)
- latex rubber

Common clinical features are:
- respiratory difficulty
- hypotension (circulatory collapse, shock)
- pruritus (generalised itching)
- erythema
- urticarial (hives)
- angio-oedema
- rhinitis/conjunctivitis
- nausea vomiting, abdominal pain

Anaphylaxis is characterised by rapid onset and severity. The full reaction is usually seen after 10-30 minutes. Prompt treatment is essential.

Mechanism
Anaphylaxis occurs when an antigen evokes the production of specific antibodies of the IgE type which bind to receptors for IgE on mast cells and basophils. Subsequent exposure to the antigen results in an interaction between the antigen and the specific IgE antibodies resulting in cross-linking of the IgE antibodies. This leads to activation of the mast cell and the release of preformed mediators, stored in granules (including histamine), as well as of newly formed mediators which are synthesised rapidly. Rapid systemic release of large quantities of mediators cause vasodilation, capillary leakage, mucosal oedema, secretions and smooth muscle contraction resulting in shock and asphyxia.

Preformed mediators:
- Chemotactic factors attract neutrophils and eosinophils
- Proteases degrade the endothelial membrane
- Histamine increases vascular permeability and vasodilation

Newly formed mediators:
- Prostaglandins eg prostacyclin > vasodilation, eg 2 thrombin A2 > platelet aggregation
- Leukotrienes > increased vascular permeability + mucus secretion

Treatment priorities:
- Preservation of airway patency/reversal of bronchospasm
- Maintenance of blood pressure and tissue perfusion

QUESTIONS
1. Stimulation of which branch of the ANS will produce bronchodilation and an increase in blood pressure?
   Sympathetic nervous system

2. Explain how these effects are caused?
   - Adrenal Medulla > adrenaline > B1 receptors > increased HR, B2 receptors > bronchodilation
   - Sympathetic Nerves > noradrenaline > a1 receptors > vasoconstriction of subcutaneous vessels
   - Other effects: pupil dilation, increased secretions, vasodilation in skeletal vessels, decreased motility of GI tract, increased glucose production, relaxation of bladder, hair erection

3. What is the drug of choice for the treatment of anaphylaxis and why?
Adrenaline/epinephrine (EpiPen) > causes bronchodilation + vasoconstriction of peripheral vessels (+ inhibitor mediator release from mast cells)

4. What additional class of drug is often used in the initial treatment of anaphylaxis and why?
   Antihistamine to counteract the major inflammatory mediator produced = histamine
   • Eg of drugs include citixine, chlorphenamine

5. Suggest supporting treatments that may speed recovery
   • IV fluids + Oxygen
   • Selective B2 agonist eg salbutamol
   • Alpha-adrenoreceptor agonists if profound hypotension
   • Corticosteroids

6. How would the taking of a non-selective Beta adrenoceptor antagonists affect the treatment?
   Eg B blocker propranolol > decreased bronchodilation

7. What do you understand by the terms selective and non-selective?
   Selective = higher affinity at one subtype
   Non-selective = equal affinity for all subtypes
Important Drug Interactions

- **Metoclopramide** (D2 antagonist = anti-emetic) – *increases GIT transit* time > decreased absorption of ALL small intestine absorbed oral drugs

- **Sucralfate** (cytoprotective anti-ulcer drug) – *reduces absorption* of drugs such as digoxin

- **Allopurinol** (used for hyperuricemia) = *xanthine oxidase inhibitor* > build up of azathioprine metabolite 6-mercaptopurine

- **Chloramphenicol** (antibacterial) *blocks oxygen-dependent active transport* of gentamicin (antibacterial)

- **Barbituates** (sedative + hypnotic) are *enzyme inducers*, therefore affect hepatic metabolism of drugs

- **Carbazepine** (anticonvulsant) is an *enzyme inducer*, therefore affects hepatic metabolism of drugs

- **Benzodiazepines** (anxiolytics, sedatives + hypnotics) are highly *plasma protein bound*, therefore displace drugs such as aspirin + warfarin from plasma proteins

- **Sodium valproate** (anticonvulsant) is an *enzyme inhibitor*, therefore is contraindicated with enzyme inducers such as phenytoin, phenobarbital + carbazepine

- Phenytoin is a P450 *enzyme inducer*, and has various drug interactions:
  - Inhibits metabolism of amiodarone (anti-arrrhythmic) + isoniazid (anti-myoc bacterial)
  - Displaces aspirin from plasma proteins
  - Displaces and inhibits valproate (anticonvulsant)
  - Decreases warfarin levels – requires INR monitoring

Clinical Applications of Cardiac Drugs

**Heart Failure**: the inability of the heart to maintain adequate blood supply to meet the body’s demands

- **Chronic Heart Failure**: impaired cardiac function due to IHD, Hypertension or cardiomyopathy that results in the development of oedema, fatigue
  - **Left-sided failure** > tachypnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, cardiac asthma
  - **Right-sided failure** > peripheral edema, ascites, hepatomegaly + increased jugular venous pressure
  - **Treatment**:
    - Thiazide diuretic (bendrofluazide)
    - ACE Inhibitor (enalapril, captopril) or ARB (Iosartan)
    - B blocker (atenolol) – contraindicated in Acute HF
- +/- spironolactone (K+ sparing diuretic)
- +/- digoxin (cardiac glycoside - reduces symptoms, used especially if AF present)

  **Acute Heart Failure:** the rapid decompensation of CHF, resulting in potentially fatal respiratory distress.
  - **Treatment:**
    - B1 adrenoceptor agonist (dobutamine)
    - Loop diuretics (frusemide)

**Arrhythmias**
- Calcium channel blockers (verapamil, diltiazem) = Class IV
- B-blockers (atenolol) = Class II
- Amiodarone (general antiarrhythmic)
- Digoxin (for atrial fibrillation)

**Angina:** chest pain caused by myocardial ischaemia resulting from an increased myocardial oxygen demand with reduced supply
- **Treatment**
  - B blockers (atenolol), or calcium channel blockers (verapamil or diltiazem) if intolerant
  - GTN spray – for symptomatic relief
  - Statin/aspirin – to reduce CV risk

**Myocardial Infarction:** occlusion of the coronary arteries leads to prolonged cardiac ischaemia, resulting in myocardial infarction and subsequent cell necrosis
- **Treatment:**
  - Throbolytics – tissue-type plasminogen activator (alteplase) or bacterial plasminogen activator (streptokinase)
- **Following MI,** subsequent treatment to prevent recurrence involves:
  - ACE inhibitors (enalapril, Captopril)
  - B blockers (atenolol)
  - Nicorandil (guanylate cyclase stimulator) – increases O2 supply
  - Warfarin (anti-coagulant) – vitamin K antagonist
    - Heparin is used for PE/DVT
  - Antiplatelets (aspirin or clopidogrel)
  - Statins (for reduction in CV risk)

**Hypertension** (Resting BP > 140/90)
- **Treatment**
  - ACE Inhibitor (enalapril, captopril) or ARB (losartan)
  - Calcium channel blockers (verapamil, diltiazem)
  - Thiazide diuretic (bendrofluazide)
- **For resistant hypertension:**
  - A1 antagonist (prazosin)
  - Centrally acting a2 agonist (clonidine)