Pharmacokinetics

- are the processes which determine the levels of a drug and why blood levels can vary between different people i.e. ‘what the patient does to the drug’:
  - absorption
  - distribution
  - metabolism
  - elimination/excretion

Absorption

- crosses gut wall by:
  1. passive diffusion
     - the most common mechanism
     - depends on:
       - formulation (enteric coating, particle size, diluents e.g. lactose, binding agents e.g. syrups, lubricants e.g. talcs, disintegrating agents e.g. starch)
       - solubility (particle size, ambient pH, drug pKa - when pH = pKa, 50% of the drug is ionized)
     - to be absorbed by passive diffusion, a drug must be unionized since it is more lipid soluble; in an acid pH (stomach), basic drugs will be largely ionized and will not be absorbed
     - the un-ionized fraction of a drug is 10000 times more lipid soluble than the ionized portion)
  2. active transport
  3. pore filtration – passive movement of water soluble substances of low molecular weight (<200 Da) is via aqueous channels (diameter less than 4 Å)
  4. pinocytosis

oral administration

- occurs mainly in the small intestine
- influenced by:
  1. gastric emptying - delayed by drugs with anticholinergic properties e.g. TCAs, MAOIs, opiates
  2. gastric pH - affects basic drugs e.g. TCAs
  3. intestinal mobility - increased by anxiety
  4. food - greatest absorption from an empty stomach, food increases absorption of DIAZEPAM
  5. intestinal flora/enzymes - CHLORPROMAZINE is sulphated leading to reduced absorption, TYRAMINE by gut wall MAO
  6. area for absorption
  7. blood flow
- rectal administration
  - minimal 1st pass metabolism
  - no acidic gastric environment
  - frequent use can be irritant

- intramuscular
  - avoids 1st pass metabolism
  - influenced by:
    1. solubility - lipid soluble, low molecular weight drugs, are rapidly absorbed
    2. rate of absorption - increased by exercise, and reduced by heart failure
    3. drug formulation - fatty esters are added to depot preparations which slowly hydrolyses, releasing the active drug
    4. precipitation - can crystallize

- intravenous
  - rapid entry to systemic circulation
  - carries risks of injection

Distribution
- well perfused regions (e.g. liver, kidney) will have higher levels more rapidly than poorly perfused regions such as fat

protein binding:
- many drugs are bound to albumin, globulins, and glycoproteins
  - 95-99 % bound include: DIAZEPAM, CHLORPROMAZINE, AMITRIPTYLINE, IMIPRAMINE
  - 90-95 % bound include: PHENYTOIN, VALPROATE, CLOMIPRAMINE
- it is only the ‘free’ fraction that can be active
- protein binding is reduced in:
  - hepatic disease
  - renal disease
  - cardiac failure
  - malnutrition
  - carcinoma
  - surgery
  - burns
  - last stage of pregnancy
- drug assays measure total amount of drug (bound and free)

blood brain barrier:
- lipophilic/ lipid soluble drugs cross easily
- ionized drugs (highly acidic/ basic) cross slowly
- more permeable when intracranial infection
- LEVODOPA crosses by active transport
- LITHIUM diffuses
Metabolism

- most metabolism occurs in the liver, with other sites including the gut, kidney, skin, brain, and lung
- differences in drug metabolism account for most of the variability seen in blood drug levels

- **hepatic transformation:**

<table>
<thead>
<tr>
<th>FROM</th>
<th>BY</th>
<th>TO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td>Drug</td>
<td>oxidation&lt;br&gt;hydroxylation&lt;br&gt;dealkylation&lt;br&gt;reduction&lt;br&gt;demethylation&lt;br&gt;acetylation&lt;br&gt;methylation</td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td>Metabolite</td>
<td>glucuronidation&lt;br&gt;sulphation</td>
</tr>
</tbody>
</table>

- hydroxylation and acetylation are under genetic control
  - hydroxylation:
    - poor metabolisers will have higher levels and hence more side effects
    - autosomal dominant
    - 8% of Caucasians
    - affects PHENYTOIN, ISONIAZID
  - acetylation:
    - enzyme is N-acetyltransferase
    - fast and slow acetylators - depends on amount of enzyme
    - fast: slow = 40: 60 in Europe, 85: 15 in Japan
    - effects MAOIs

- **enzyme induction**
  - enhances metabolism
  - usual enzyme is cytochrome P<sub>450</sub>
  - drugs inducing own metabolism include:
    - CARBAMAZEPINE, PHENOTHIAZINES, CHLORAL HYDRATE

<table>
<thead>
<tr>
<th>Metabolism induced by</th>
<th>Affects metabolism of</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARBITURATE</td>
<td>BARBITURATE, CHLORPROMAZINE, OCP, TCAS, PHENYTOIN</td>
</tr>
<tr>
<td>PHENYTOIN</td>
<td>OCP, TCAS, PHENYTOIN</td>
</tr>
<tr>
<td>CARBAMAZEPINE</td>
<td>PHENYTOIN, TCAS (reduced levels)</td>
</tr>
</tbody>
</table>

- **enzyme inhibition**
  - some drugs rely on this for their therapeutic effect e.g. DISULFIRAM inhibits aldehyde dehydrogenase
• PHENOTHIAZINES and HALOPERIDOL inhibit TCA metabolism

Elimination
• majority of drugs excreted by kidney
• acidic urine is good for the excretion of basic drugs (TCAS, AMPHETAMINES)
• acidic drugs are passively reabsorbed

Pharmacokinetics in the elderly

| absorption          | • less acid in stomach – increased gastric pH  
|                    | • reduced rate of gastric emptying  
|                    | • reduced intestinal blood flow  
| distribution       | • decreased body weight  
|                    | • decreased albumin  
|                    | • decreased % of body water  
|                    | • increase % of body fat  
| metabolism         | • slowing of hepatic blood flow  
|                    | • reduced hepatic transformation  
| excretion          | • reduced GFR, but doesn’t affect plasma creatinine due to reduced muscle mass  
|                    | • half life of lithium is increased by 50-100 %  

Pharmacokinetics in Pregnancy
• most drugs cross the placenta

| absorption          | • no change  
| distribution        | • increase in plasma volume and total body water  
|                    | • decreased plasma albumin - TOTAL drug may fall but FREE drug remains the same  
| metabolism          | • probably increased  
| excretion           | • increased GFR by 70 %  

Plasma Concentration - Time relationships

First-order (exponential) kinetics

- applies to most drugs at therapeutic concentrations
- a constant *fraction* of the drug is cleared in unit time - metabolism or elimination of the drug depends on its concentration
- the **half-life** \( (t_{\frac{1}{2}}) \) is the time taken for concentration to reach half of its previous value and is constant for all concentrations

![Graph of plasma concentration over time for first-order kinetics]

Zero-order (saturation) kinetics

- a constant *amount* of drug is cleared in unit time
- metabolic processes with limited capacity become saturated, i.e. elimination rate reaches a maximum
- e.g. ALCOHOL, PHENYTOIN (1st order at low concentrations, zero-order at higher concentrations), ASPIRIN

![Graph of plasma concentration over time for zero-order kinetics]
Volume of distribution

- the actual volume cannot be measured, but the *apparent volume of distribution* can be represented as:

\[
C_0 = \frac{D}{V_d}
\]

- \(C_0\) = plasma concentration
- \(D\) = intravenous dose

- if a drug is highly protein-bound then \(V_d\) will appear to be reduced, and will be close to the plasma volume
- e.g. DIGOXIN = 420 L, CHLOROQUINE = 13,000 L
- Increased volume of distribution is associated with:
  - increased lipid solubility
  - low rate of protein binding
  - increasing age
  - higher body weight
  - shorter duration of drug action

Bioavailability

- bioavailability (oral) = \(\frac{AUC_{oral}}{AUC_{intravenous}}\)
- AUC is the area under the curve:

![Graph showing the comparison between intravenous and oral bioavailability](image)

Repeated dosing

- applies to 1st order kinetics only
- at steady state, the rate of intake will equal the rate of clearance
- time to reach steady state (or 97 % of steady state conc.) will equal \(5 \times t_{1/2}\)

The therapeutic index

- is equal to the toxic dose, divided by the therapeutic dose of the drug:

\[
TI = \frac{\text{toxic dose}}{\text{therapeutic dose}}
\]
therapeutic dose

- it is therefore inversely proportional to the therapeutic dose, and proportional to the toxic dose of the drug
Pharmacodynamics

- ‘what the drug does to the patient’

Distribution of neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Distribution</th>
</tr>
</thead>
</table>
| Acetylcholine (Ach) | 1. basal ganglia  
2. cerebral cortex  
3. basal nucleus of Meynert |
| Dopamine (DA) | 1. tuberoinfundibular (c.f. Prolactin secretion)  
2. mesocorticolimbic (c.f. Schizophrenia)  
3. nigrostriatal (c.f. Parkinson’s)  
4. ventral tegmental area |
| Serotonin (5-HT) | 1. brain stem - raphe nucleus, pons  
2. cerebral cortex  
3. limbic system |
| Noradrenaline (NA) | 1. brain stem - locus coeruleus  
2. reticular activating system |
| GABA | 1. cerebral cortex  
2. striato-nigral |
| Opiate (Op) | 1. periaqueductal grey matter |
| Glutamate (Glu) | 1. cortex and striatal pathways |

Receptor types

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subtype</th>
<th>Main actions of natural agonist</th>
<th>Drug Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
</table>
| Adrenoceptor | α₁ | • contraction of vascular smooth muscle  
• increased contractile force of the heart | ISOPROTENEROL, PHENYLEPHRINE | PRAZOSIN |
| | α₂ | • contraction of vascular smooth muscle  
• reduced NA release | CLONIDINE | YOHIMBINE |
| | β₁ | • increased contractile force of the heart | DOPAMINE, DOBUTAMINE | ATENOLOL, METOPROLOL |
| | β₂ | • relaxation of smooth muscle | SALBUTAMOL | |
| Cholinergic | Muscarinic | heart rate, secretion, gut motility, broncho-constriction | PILOCARPINE | ATROPINE, BENZTROPINE, ORPHENADRINE, IPRATROPium |
| | Nicotinic | contraction of striated muscle | | SUXAMETHONIUM, TUBOCURARINE |
| Histamine | H₁ | broncho- | | CHLORPHENIRAMIN |
Constriction, capillary dilation

<table>
<thead>
<tr>
<th>H₂</th>
<th>↑ gastric acid</th>
<th>E, TERFENADINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>D₁-like (D₁, D₃), D₂-like (D₂, D₃, D₄)</td>
<td>CNS neurotransmitter</td>
</tr>
<tr>
<td>Opioid</td>
<td>μ (mu), δ (delta), κ (kappa)</td>
<td>CNS neurotransmitter</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-HT₁, 5-HT₂₆, 5-HT₂₇, 5-HT₃</td>
<td></td>
</tr>
<tr>
<td>GABA</td>
<td>GABAₐ, GABAₐβ</td>
<td></td>
</tr>
</tbody>
</table>

**Neurotransmission**
- Neurotransmitters may open or close ion channels in the neuronal membrane and can do this directly or by activating adjacent proteins.
- Their time-course of action is produced by their altering the properties of voltage-gated ion channels.
- The release of neurotransmitters represents the ‘final common pathway’ of all neuronal functions.

**Calcium channels**
- Neurotransmitter release is Calcium-dependent.
- Ca²⁺ channels open in response to membrane depolarisation and generate electrical and chemical responses.
- Ca²⁺ entry into the cell carries a depolarising charge that contributes to paroxysmal phenomena such as epileptiform or pacemaker activity.
- Multiple types of Ca²⁺ channel exist:
  1. Low-voltage activated (LVA)
  2. High-voltage activated (HVA)
     a) T subtype (‘transient’)
        i) T channels are important in pacemaker depolarisation in heart cells
     b) L subtype (‘long lasting’)
        i) L channels are involved in heart muscle contraction, and substance P and noradrenaline release in the CNS
        ii) Only L channels are sensitive to blockade by Ca²⁺ channel-blocking drugs
     c) N subtype (‘neither T nor L’)

- Ca\(^{2+}\) channel blockade probably accounts for some neuroleptic side effects – for example, diphenylbutylpiperidines (PIMOZIDE) are as effective channel blockers as DILTIAZEM or VERAPAMIL.
- The cardiac and ejaculatory side effects of THIORIDAZINE are probably caused by Ca\(^{2+}\) channel blockade.

**Phosphatidylinositol (PI) metabolism**

- protein kinase C (PKC) is a Ca\(^{2+}\)-dependent enzyme concentrated at presynaptic nerve terminals close to or in conjunction with synaptic vesicles.
- it is activated by diacylglycerol (DAG), a cleavage product of a group of membrane lipids called phosphatidylinositols.
- PKC in turn potentiates neurotransmitter release.
- LITHIUM blocks the activation of PKC by DAG.

**Second messengers**

1. receptor-neurotransmitter complex $\rightarrow$ G protein binding to receptor-neurotransmitter complex $\rightarrow$ adenylate cyclase activation (or inhibition) $\rightarrow$ cyclic AMP
2. neurotransmitter binding $\rightarrow$ hydrolysis of phosphatidylinositol biphosphate $\rightarrow$ diacylglycerol (DAG) and inositol triphosphate (IP\(_3\)).
   - DAG activates protein kinase C.
   - IP\(_3\) causes endoplasmic reticulum calcium release, in turn activating calmodulin-dependent protein kinase.

---

**Fig. 7.3** The proposed mechanisms of action of noradrenaline and acetylcholine (ACh) in blocking the slow Ca\(^{2+}\)-activated K\(^+\) conductance.
Receptors

- have a life-span of 7-30 days

Receptor families

<table>
<thead>
<tr>
<th>‘Superfamily’</th>
<th>Neuroreceptor/ Ion channel</th>
</tr>
</thead>
<tbody>
<tr>
<td>G protein-coupled receptors</td>
<td>• visual pigments</td>
</tr>
<tr>
<td></td>
<td>• noradrenergic</td>
</tr>
<tr>
<td></td>
<td>• muscarinic cholinergic</td>
</tr>
<tr>
<td></td>
<td>• serotonergic</td>
</tr>
<tr>
<td></td>
<td>• GABA&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
<tr>
<td>Ligand-gated ion channels</td>
<td>• nicotinic cholinergic</td>
</tr>
<tr>
<td></td>
<td>• GABA&lt;sub&gt;A&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>• glycine</td>
</tr>
<tr>
<td>Voltage-gated ion channels</td>
<td>• Na&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• K&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Voltage-gated ion channels

- sodium, potassium, and calcium channels consists of a principal transmembrane subunit which constitutes the core of the ion channel
- different cell types contain varying numbers of subunits for sodium, potassium, and calcium channels
- depolarization leads to a sequence of conformational changes in individual α subunits – as each subunit changes, an open ion channel is formed by movement of the helical arrangement of amino acids that constitutes each subunit
- these voltage-sensitive ion channels require the movement of protein-bound positive charges from the intracellular to the extracellular surface of the membrane

G protein-coupled receptors

G-proteins

- consist of 3 subunits (alpha, beta, and gamma)
- located on the intracellular surface of the plasma membrane
- have 3 roles:
  1. regulation of ion channels
  2. control of the cAMP system
  3. control of the inositol system
- they can be subdivided by their susceptibilities to bacterial toxins:
  1. cholera toxin only
  2. pertussis toxin only
  3. both toxins
  4. neither toxin
- for neurotransmitter binding, the following types of G protein may be involved:
  • Gs – stimulate adenylate cyclase
• **Gi** – inhibit adenylate cyclase
• **Go**
• **Gq**

**G-protein coupled receptors**

• 3 extracellular loops
• 3 intracellular loops
  • the cytoplasmic loop between spans 5 and 6 is probably the G protein regulation site
• 7 membrane-spanning sites
• the N-terminal is extracellular
• the C-terminal is intracellular

**Inhibitory amino acid neurotransmission (IAA)**

**Glycine receptors**

• the post-synaptic glycine receptor (GlyR) is a large membrane-spanning glycoprotein
• it is a ligand-gated ion channel
• agonists:
  • taurine
  • β-alanine
• antagonists:
  • strychnine – which has its own binding site on GlyR close to the integral ion channel
• in Parkinson’s disease and motor neurone disease, GlyR-strychnine binding sites are reduced
**GABA neurotransmission**

GABA synthesis and breakdown

Glutamic acid

\[ \text{glutamic acid decarboxylase} \]

\[ \text{GABA} \]

\[ \text{GABA transaminase (GABA-T)} \]

Glutamic acid + Succinic semialdehyde

**GABA receptors**

- heterotetrameric protein consisting of four subunits which may be either $\alpha$ or $\beta$

- $\text{GABA}_A$: increased Cl$^-$ ions, via a receptor-gated ion channel
- $\text{GABA}_B$: coupled to adjacent Ca$^{2+}$ channels by G proteins; binding between GABA at the receptor selectively opens K$^+$ channels and closes Ca$^{2+}$ channels
- $\text{GABA}_A$ receptors are more widely distributed than $\text{GABA}_B$ receptors and may have important roles in the control of receptor sensitivity

- the $\text{GABA}_A$ receptor has at least 4 sites at which ligands may bind; each of these sites may be occupied simultaneously:
  1. the GABA agonist/antagonist (2 sites on the $\beta$ subunit)
  2. picrotoxin (where agents that block GABAergic transmission may bind)
  3. benzodiazepine (on the $\alpha$ subunit)
  4. CNS depressant drugs (e.g. barbiturates) where agents may bind and prolong GABAergic activation of the integral ion channel

- occupation of both of the 2 binding sites for GABA is necessary to open the chloride channel

- $\text{GABA}$
  - synthesized from glutamate by *glutamic acid decarboxylase*
  - after release, GABA is either restored in vesicles or destroyed by *GABA transaminase*
Excitatory amino acid neurotransmission (EAA)

Transmitters

- the most abundant EAAs are glutamate and aspartate, as well as cysteic acid and homocysteic acid

Receptors

- EAA effects are mediated through at least 5 different receptor systems:

<table>
<thead>
<tr>
<th>Receptor type</th>
<th>Mechanism of transduction</th>
<th>Second messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA</td>
<td>ligand-gated ion channel</td>
<td>calcium, IP$_3$/DAG</td>
</tr>
<tr>
<td>• NMDAR1-2</td>
<td>(Ca$^{2+}$)</td>
<td></td>
</tr>
<tr>
<td>Quisqualate (Q)</td>
<td>ligand-gated ion channel</td>
<td>IP$_3$/DAG</td>
</tr>
<tr>
<td>Kainate (KA)</td>
<td>ligand-gated ion channel</td>
<td>calcium, IP$_3$/DAG</td>
</tr>
<tr>
<td>• GluR5-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• KA1-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP4, AMPA</td>
<td>ligand-gated ion channel</td>
<td></td>
</tr>
<tr>
<td>• GluR1-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabotropic glutamate receptor (mGluR)</td>
<td>G protein coupled</td>
<td>calcium, IP$_3$/DAG</td>
</tr>
<tr>
<td>• mGluR1-6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Q or K are widely distributed – they are highly concentrated in the cerebellum
- NMDA receptors are coupled intracellularly to GlyR and also to a binding site for PCP (phencyclidine)
- PCP and σ opiate receptor activation antagonises the excitatory effects of NMDA activation but does not affect Q or K receptors

Mechanism

- NMDA receptors have a very high conductance, and are usually blocked by a Mg$^{2+}$ ion
- under certain conditions, such as activation of AMPA receptors, which conduct the bulk of glutamate transmission, the magnesium ion leaves the channel, so unblocking it and allowing calcium influx
- this influx of calcium activates cellular enzymes that bring about changes in neuronal excitability and synaptic function
Cholinergic neurotransmission

Acetylcholine synthesis and breakdown

Acetyl coenzyme A + choline

\[ \text{Choline acetyltransferase} \]

acetylcholine

\[ \text{Cholinesterase} \]

Choline + Acetic (ethanoic) acid

- synthesis of acetylcholine can be increased by choline administration because the enzyme is not fully saturated

Nicotinic receptors

- are ligand-gated ion channels, and when activated, produce a rapid increase in cellular permeability to Na\(^+\) and K\(^+\)
- they are present in the brain, particularly the thalamus and cerebellar cortex

Muscarinic receptors

- are G protein coupled and are not necessarily linked to ion channels
- exist in varying subtypes: M\(_1\), M\(_2\), and M\(_3\)
- M\(_1\) and M\(_3\) activate a G protein that stimulates PLC activity, and thereby resulting in the release of intracellular Ca\(^{2+}\)
- M\(_2\) receptors activates Gi proteins which inhibit adenylate cyclase, and open K\(^+\) and close Ca\(^{2+}\) channels
- M\(_1\) receptors are concentrated in the sympathetic ganglia, stomach, and corpus striatum
- M\(_2\) receptors are found in the hind brain, cerebellum, and heart

Drugs affecting acetylcholine release

- black widow spider venom produces a rapid release of Ach and also causes morphological changes in the presynaptic storage vesicles

Drugs affecting nicotinic receptors

- nicotinic receptors are specifically blocked by α-bungarotoxin

**agonists:**

- nicotine – small doses of nicotine produce increased cortical release of Ach and electrocortical arousal
- DMPP
- PTMA

**antagonists:**

- TUBOCURARINE is a nicotinic receptor antagonist at the neuromuscular junction
• SUCCINYLCHOLINE is also an antagonist but it depolarises the receptor for a long period of time

Drugs affecting muscarinic receptors
• *agonists:*
  • MUSCARINE
  • PILOCARPINE
  • ARECHOLINE
  • METHACHOLINE
  • CARBACHOL
• *antagonists:*
  • ATROPINE
  • SCOPOLAMINE
  • tricyclic antidepressants
Noradrenergic neurotransmission

Noradrenaline synthesis and breakdown

L-tyrosine

\[ \text{tyrosine hydroxylase} \]

\[ \text{L-DOPA (3,4-dihydroxyphenylalanine)} \]

\[ \text{aromatic-L-amino-acid decarboxylase} \]

Dopamine

\[ \text{dopamine } \beta\text{-hydroxylase} \]

Noradrenaline

\[ \text{COMT} \]

\[ \text{MAO} \]

normetanephrine

3,4-dihydroxyphenylglycoaldehyde

MHPG

3,4-dihydroxyphenylglycol

3,4-dihydroxymandelic acid

VMA (Vanillyl mandelic acid)

- CARBIDOPA inhibits peripheral aromatic-L-amino-acid decarboxylase
- DISULFIRAM inhibits dopamine $\beta$-hydroxylase
- synthesis of NA can also be disrupted by the structurally similar precursor $\alpha$-METHYLDOPA

Drugs affecting the storage of noradrenaline

- Rauwolfa alkaloids (e.g. RESERPINE) and TETRABENAZINE disrupt NA storage and inhibit NA uptake into storage vesicles

Drugs affecting the release of noradrenaline

- ‘indirectly acting sympathomimetic amines’ such as AMPHETAMINE, TYRAMINE, and EPHEDRINE release NA quickly enough to bind with postsynaptic receptors
- antihypertensive agents such as DEBRISOQUINE, BETHANIDINE, and GUANETHIDINE inhibit NA release from storage, but do not cross the blood-brain barrier
Drugs acting on adrenergic receptors

- noradrenaline acts mostly through alpha receptors, and adrenaline acts mainly through beta receptors
- presynaptic $\beta_1$ receptors facilitate NA release while presynaptic $\beta_2$ receptors are inhibitory – these receptors may be involved in the pathogenesis of affective symptoms

Antidepressants and adrenergic receptors

- there is a close relationship between the potencies of TCAs to occupy postsynaptic $\alpha_1$ adrenoceptors and their sedative-hypotensive effects
  - the tertiary amines (e.g. AMITRIPTYLINE) are more potent at these sites than secondary amines (e.g. NORTRIPTYLINE)
- chronic administration of antidepressants reduces NA-coupled adenylate cyclase activity and also reduces the number of $\beta$ receptors in brain tissue
- the initial increase of NA may be caused by inhibition of NA uptake, blockade of presynaptic inhibitory autoreceptors, or actions at other sites
- MIANSERIN (antagonises $\alpha_2$ receptor leading to increased NA release)
- TCAs, TRAZODONE, MAOIs, and some antipsychotics are $\alpha_1$ antagonists leading to hypotension and sedation

Drugs affecting noradrenaline uptake

- antidepressants and euphoriants such as COCAINE and AMPHETAMINE act rapidly on the presynaptic re-uptake of noradrenaline
- some drugs (tricyclic antidepressants) inhibit the uptake of monoamines from the synaptic cleft
  - secondary amines (DESIPRAMINE, NORTRIPTYLINE) mainly affect noradrenaline, with few drugs having any effect on dopamine

Drugs affecting degradation of noradrenaline

- MAOIs mainly inhibit the action of Monamine Oxidase A, which is more effective in the breakdown of NA and 5-HT
- MAOIs also affect aromatic-L-amino-acid decarboxylase and various other oxidases
Dopaminergic neurotransmission

Dopamine synthesis and breakdown

• see above for synthesis

Dopamine

\[ \text{MAO} \]

3,4-dihydroxyphenylecetaldyhyde

\[ \text{acetaldehyde dehydrogenase} \]

DOPAC (dihydroxyphenylacetic acid)

\[ \text{COMT (catechol-O-methyltransferase)} \]

HVA (homovanillic acid)

• oral administration of L-Dopa increases dopamine synthesis

Dopamine release

• DA is released from central DA terminals by 2 different mechanisms:
  1. energy-dependent:
     • inhibited by nomifensine, benztropine, and cocaine
  2. carrier-dependent:
     • facilitated by amphetamine at concentrations lower than those required to stimulate post-synaptic catecholaminergic receptors

Dopamine receptors

<table>
<thead>
<tr>
<th>TYPE</th>
<th>LOCATION</th>
<th>2° MESSENGER SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁</td>
<td>1. caudate 2. nucleus accumbens 3. olfactory tubercle</td>
<td>cAMP stimulation</td>
</tr>
<tr>
<td>D₂</td>
<td>1. basal ganglia 2. limbic system 3. cerebral cortex</td>
<td>cAMP inhibition</td>
</tr>
<tr>
<td>D₃</td>
<td>1. limbic system 2. nucleus accumbens 3. hypothalamus</td>
<td>cAMP inhibition</td>
</tr>
<tr>
<td>D₄</td>
<td>1. limbic system 2. frontal cortex</td>
<td>cAMP inhibition</td>
</tr>
<tr>
<td>D₅</td>
<td>1. extra-striatal</td>
<td>cAMP stimulation</td>
</tr>
</tbody>
</table>

Drugs affecting DA receptors

• Antagonists:
  • all antipsychotics affect D₂ receptors to some degree
  • CLOZAPINE has lower D₂ antagonism
• CLOZAPINE is one order more potent at D₄ than D₂ or D₃
• CHLORPROMAZINE is one order less potent at D₄ than D₂
• SULPIRIDE is a relatively pure D₂ antagonist

Drugs affecting DA reuptake
• TCAs will block reuptake of dopamine
• AMPHETAMINE and other drugs which release DA also block its uptake
• anticholinergics such as BENZTROPINE, BENZHEXOL, and ORPHENADRINE inhibit the uptake of DA and also block cholinergic receptors
• RESERPINE can cause Parkinsonism by disrupting DA storage granules and by blocking DA receptors
Serotonergic neurotransmission

- less than 2% of the body’s 5-HT is found in the CNS – the rest is in the enterochromaffin granules of the intestine and in blood platelets

5-HT synthesis and breakdown

L-Tryptophan

\[ \text{tryptophan hydroxylase} \]

5-HP

\[ 5\text{-hydroxytryptophan decarboxylase} = \text{amino acid decarboxylase} \]

5-HT

\[ \text{MAO}_A \]

5-HIAA (5-hydroxyindolacetic acid)

- 5-HT synthesis can be increased by oral tryptophan, and takes place in neurones in both nuclei and nerve terminals

Drugs affecting 5-HT storage

- the Rauwolfia alkaloids and tetrabenazine reduce 5-HT stores by disrupting storage granules
- when 5-HT storage is disturbed, large quantities of 5-HT are released and outside the CNS this causes diarrhoea and abdominal cramps

Drugs affecting 5-HT release

- the amphetamines and some TCAs release 5-HT from storage granules

Drugs affecting 5-HT receptors

- all serotonin receptors are G-protein coupled, except 5-HT\textsubscript{3} which is an ion channel

<table>
<thead>
<tr>
<th>TYPE</th>
<th>LOCATION</th>
<th>2\textsuperscript{ND} MESSENGER</th>
<th>SITE</th>
</tr>
</thead>
</table>
| 5-HT\textsubscript{1A} | pre and post synaptic | cAMP inhibition | 1. hippocampus  
2. raphe nucleus |
| 5-HT\textsubscript{2A} | post synaptic | ?inositol | 1. limbic system  
2. prefrontal & medial frontal cortex |
| 5-HT\textsubscript{2C} | post synaptic | inositol | 1. widespread in forebrain & midbrain  
2. choroid plexus |
| 5-HT\textsubscript{3} | post synaptic | K\textsuperscript{+}/Na\textsuperscript{+} | 1. widespread - including |
amygdala and limbic system

- **agonists:**
  - 5-HT$_{1A}$ receptor agonists are anxiolytic (BUSPIRONE)

- **antagonists:**
  - seen in drugs such as CLOZAPINE and RISPERIDONE
  - may improve negative symptoms
  - 5-HT$_{2A}$ receptors are linked to sexual dysfunction
  - 5-HT$_{2A}$ antagonists improve slow wave sleep
  - 5-HT$_{2C}$ antagonists appear to be anxiolytic and play a role in food intake
  - 5-HT$_{3}$ receptors are linked with nausea

- changes in receptors:
  - decreased post-synaptic 5-HT$_{1A}$ and 5-HT$_{2A}$ seen after long-term antidepressant treatment

**Drugs affecting 5-HT reuptake**

- inhibited by TCAs (tertiary amines) and SSRIs
- PAROXETINE is the most potent inhibitor of serotonin re-uptake
- CITALOPRAM is the most selective
- SSRIs also affect histaminergic, adrenergic, and muscarinic cholinergic receptors, but significantly less than the TCAs

**Drugs affecting 5-HT breakdown**

- MAO$_{A}$ is the main enzyme catalysing the breakdown of 5-HT
- 5-HIAA is the major metabolite of 5-HT
Adverse Drug Reactions

Classification of hypersensitivity reaction

1. Type I:
   - anaphylactic shock
2. Type II, III, or IV:
   - haemolytic anaemia
   - agranulocytosis
   - thrombocytopaenia
3. Allergic liver damage (Type II + III reaction)
4. Skin rashes (Type IV)
5. Generalized autoimmune (Type IV)
   - SLE-type disease

Features of allergic reaction

1. a different time course from the pharmacodynamic action, for example:
   - delayed onset of the adverse drug reaction
   - the ADR manifests only after repeated drug exposure
2. no dose related effect
3. hypersensitivity reaction, unrelated to the pharmacological actions of the drug
**Benzodiazepines**

**Method of action**
- receptors are located in a supramolecular complex with GABA<sub>A</sub> receptors (BZ/GABA) and chloride ion channel
- BZDs bind to the γ<sub>2</sub> subunit
- they enhance GABA neurotransmission, thereby altering indirectly the activity of other systems such as noradrenaline and 5-HT
- BZDs do not work in the absence of GABA

**Pharmacokinetics**
- rapidly absorbed: liquid DIAZEPAM is absorbed quicker than i.m. DIAZEPAM
- strongly bound to plasma proteins but because they are lipophilic, pass readily into the brain
- LORAZEPAM and OXAZEPAM are less lipophilic, and so have a slower absorption
- metabolized to a large number of compounds, many of which are active e.g. TEMAZEPAM and OXAZEPAM are metabolites of diazepam
- excretion is mainly as conjugates in the urine
- BZDs with a short half life (TEMAZEPAM and LORAZEPAM) have a 3-hydroxyl grouping which allows a one-step metabolism to inactive glucuronides
- diazepam is metabolized to long-acting derivatives such as desmethyldiazepam which is therapeutically active

<table>
<thead>
<tr>
<th>Compound</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LORAZEPAM</td>
<td>12</td>
</tr>
<tr>
<td>OXAZEPAM</td>
<td>8</td>
</tr>
<tr>
<td>TEMAZEPAM</td>
<td>8</td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>32</td>
</tr>
<tr>
<td>CHLORDIAZEPoxide</td>
<td>12</td>
</tr>
</tbody>
</table>

**Pharmacodynamics**
- all BZDs have a similar efficacy
- two types of receptor: BZ<sub>1</sub>, BZ<sub>2</sub>
- the BZ<sub>2</sub> receptor may mediate anti-anxiety effects of BZDs
- BZ<sub>2</sub> receptor is concentrated in the amygdala and septo-hippocampal pathways
- action may be to open chloride channel or increase chloride ion movement
  - chloride ion moves into cell and inhibits depolarization
  - makes neurone less reactive
- **tribulin** in human breast milk binds to B<sub>2</sub> receptor
- DBI (diazepam binding inhibitor) - a natural neuropeptide - displaces DIAZEPAM from binding sites, and produces ‘anxiety’ in rats

**Hypnotics**
- tolerance to the effects of BZDs develops in 3-14 days
- withdrawal causes rebound insomnia
• broken sleep with vivid dreams and increased REM sleep may persist for several weeks after stopping a BZD which has been prescribed for a prolong period

  e.g.  LORMETAZEPAM, TEMAZEPAM  - short action, little hangover effect
        NITRAZEPAM, FLURAZEPAM  - prolonged action, hangover effects
        ZOPICLONE, ZOLPIDEM  - acts on BZ₁ receptor; short duration of action with little/no hangover effect
        - side effects include a bitter aftertaste, confusion, amnesia, and depressed mood

Other hypnotics
• CHLORAL HYDRATE
  • gastric irritant
  • fatalities in OD
  • high rate of abuse
• CHLORMETHIAZOLE EDISYLATE
  • dangerous potentiation of alcohol effects and can result in respiratory failure

Anxiolytics
• not appropriate for treating depression, phobic, or obsessional states
• in bereavement, psychological adjustment may be inhibited by BZDs
• dependence is particularly likely in patients with a history of alcohol or drug abuse and in patients with personality disorder

  e.g.  DIAZEPAM, CHLORETOZEPoxide  - have a sustained action
        LORAZEPAM, OXAZEPAM  - may be preferred in patients with a history of hepatic impairment, but carry a greater risk of withdrawal symptoms

Side-effects
• BZDs have a wide spectrum of safety
• sedation with larger doses, which can lead to ataxia and drowsiness and occasionally to confused thinking
• minor degrees of drowsiness and impaired coordination/ataxia and judgement can affect skilled tasks, e.g. driving
• anterograde amnesia due to impaired consolidation (useful in surgical pre-meds)
• a paradoxical increase in hostility and aggression has been reported

Interactions
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCOHOL</td>
<td>decreased clearance of CHLORETOZEPoxide and DIAZEPAM</td>
</tr>
<tr>
<td></td>
<td>additive psychomotor impairment</td>
</tr>
</tbody>
</table>
• antacids • decreased rate of CHLORDIZEPOXIDE and diazepam absorption
• CIMETIDINE • decreased clearance of BZDs and increased elimination half-life
• CLOZAPINE • respiratory suppression, possibly death
• FLUOXETINE • decreased clearance of DIAZEPAM
• ISONIAZID • decreased metabolism of DIAZEPAM
• OMEPRAZOLE • decreased clearance of DIAZEPAM
• oral contraceptive • increased concentrations of free CHLORDIAZEPOXIDE
• • decreased clearance and increased half-life of DIAZEPAM
• RIFAMPICIN • increased metabolism of DIAZEPAM

Withdrawing Benzodiazepines
• 5 - 50% of patients after 6 months develop physical dependence; the usual time is around 4 months
• withdrawal of a BZD suddenly can result in confusion, toxic psychosis, convulsions, or a syndrome similar to the DTs
• the BZD withdrawal syndrome:
  • symptoms usually develop within 2-3 days of stopping a short-acting one (e.g. LORAZEPAM) and within 7 days after stopping a longer acting BZD (e.g. DIAZEPAM)
  • the symptoms last 3-10 days, peak at 7-8 days
  • characterized by anxiety, restlessness, apprehension, insomnia, nausea, tremor, muscle tension, sweating and heightened sensitivity to perceptual stimuli (e.g. hyperacusis)
  • less common: malaise, blurred vision, nightmares, depression, hyperreflexia, ataxia, metallic taste in the mouth
  • rare: tinnitus, perceptual disturbances (illusions, macropsia, micropsia, and occasionally hallucinations)
  • epileptic seizures have been reported
• factors increasing likelihood or risk of BZD withdrawal:
  • > 60 yrs of age
  • passive-dependent personality (Peter Tyrer)
  • short or medium duration BZDs
  • concurrent use of LITHIUM, neuroleptics, some tricyclics, BUPROPION
  • history of withdrawal - seizures, delirium, alcohol
  • long duration of treatment
  • rapid withdrawal from high dose

1. Transfer patient to an equivalent dose of diazepam, taken at night
  • Diazepam 5 mg =
    • Chlordiazepoxide 15 mg
    • Lorazepam 500 micrograms
    • Nitrazepam 5 mg
    • Temazepam 10 mg

2. Reduce Diazepam in fortnightly steps of 2.5 mg. Maintain this dose if withdrawal symptoms occur
3. Stop completely; time needed for withdrawal can vary from 4 weeks to a year
Azapirones

- BUSPIRONE

Method of action
- partial agonist at post-synaptic $5HT_{1A}$ receptors and full agonist at pre-synaptic $5HT_{1A}$ receptors, which are found in high concentration in the raphe nuclei in the brainstem where it regulates the firing of $5HT$ cell bodies
- administration of BUSPIRONE lowers the firing rate of $5HT$ neurones and thereby decreases $5HT$ neurotransmission in certain brain areas
- also affects DA systems, where it acts as an agonist and indirect antagonist

Pharmacokinetics
- poor systemic availability because of extensive first-pass metabolism
- 95 % protein-bound
- half-life is 2.5 hours
- anxiolytic effects may take several days to develop, and can take up to 4 weeks

Side effects
- less sedating than BZDs
- side-effects worse early in treatment
- light-headedness
- nervousness
- headache
- dysphoria
- galactorrhoea due to post-synaptic DA blockade

Interactions
- avoid with HALOPERIDOL, as it can alter the pharmacokinetics
- in combination with MAOIs it can raise blood pressure

Cautions
- poor clearance in cirrhosis and renal failure

Efficacy
- claimed to be as effective as BZDs in generalized anxiety disorder after 4 weeks
- low abuse potential

Beta-Blockers

Pharmacological properties
- anxiolytic effects are due to antagonism at peripheral beta-adrenoceptors
- most effective when physical symptoms are prominent
- usually well tolerated
- response within one week
- may affect cognitive aspects of anxiety
- non-sedating
• half life of PROPANOLOL is 2-6 hours, but beta-blockade lasts for 8-12 hours

Side effects
• delayed ejaculation
• nocturnal enuresis
• induce myocardial depression and precipitate heart failure
• precipitation of asthma
• fatigue
• coldness of the extremities
• sleep disturbances with nightmares
• deterioration of glucose tolerance in diabetics
• exacerbation of psoriasis

Disulfiram (Antabuse)

Method of action
• inhibits aldehyde dehydrogenase, thus increasing the hangover effects produced by acetaldehyde
• alcohol is metabolised to acetaldehyde, and then on to acetic acid
• the reaction can occur within 10 minutes, and last several hours
• alcohol should be avoided for at least 1 week after stopping

The acetaldehyde reaction
• Small amounts of alcohol:
  • facial flushing
  • headache
  • palpitations
  • tachycardia
  • nausea
  • vomiting
• Large amounts of alcohol:
  • ‘air hunger’
  • arrhythmias
  • severe hypotension

Side effects
• drowsiness and fatigue
• nausea, vomiting
• halitosis
• reduced libido
• psychotic reactions (rare)
• allergic dermatitis
• peripheral neuritis
Cautions

- hepatic impairment
- cardiac failure
- coronary artery disease, hypertension, CVA

**Cyproterone Acetate**

Pharmacological actions

- acts as an anti-androgen
- can take 8 weeks for full benefit

Side effects

- inhibition of spermatogenesis
- tiredness
- gynaecomastia
- female pattern of pubic hair growth
- weight gain
- improvement of existing acne vulgaris
- increased scalp hair growth
- abnormal liver function
- dyspnoea can result from high-dose treatment
Antidepressants

1) inhibit the *presynaptic* reuptake of noradrenaline and/or 5-HT
   - tricyclic antidepressants
   - SSRIs
2) inhibit *synaptic* monoamine oxidase
   - MAOIs
3) complex effects on monoamine mechanisms – blockade of *presynaptic*
   reuptake of noradrenaline
   - MIANSERIN
   - TRAZODONE

Mechanism of action
- acute effect of MAOIs and re-uptake inhibitors is to enhance the functional activity of noradrenaline and/or 5-HT
- half life of most antidepressants is around 24 hrs and therefore steady state in plasma levels will be reached only after 5-7 days
- facilitation of NA and 5-HT neurotransmission results in adaptive changes:
  - activation of inhibitory autoreceptors in the cell bodies of cells in the midbrain, which reduces cell body firing and attenuates the increase in neurotransmission caused by the drug
  - after several days the autoreceptors on NA and 5-HT cell bodies become *subsensitive* > this frees NA and 5-HT neurones from inhibitory feedback control, and restores the firing rate to normal levels despite the presence of increased synaptic levels of NA and 5-HT
- the antidepressant effects are probably due to long-term potentiation of NA and 5-HT neurotransmission

Tricyclic Antidepressants

Structure and pharmacological properties
- three-ringed structure with side-chain
- *tertiary amines* have a terminal methyl group on the side-chain; *secondary amines* do not
- tertiary amines have a higher affinity for the 5-HT uptake site and are more potent antagonists of $\alpha_1$-adrenoceptors and muscarinic cholinergic receptors
- tertiary amines are more sedating and cause more anticholinergic effects than secondary amines
- also have quinidine-like membrane stabilizing effects, and can impair cardiac conduction

Method of action
- inhibit the re-uptake of both 5-HT and NA
Pharmacokinetics
• well absorbed from the GI tract
• peak plasma levels occur 2-4 hours after ingestion
• subject to high first-pass metabolism in the liver
  • metabolized by hydroxylation and demethylation
  • tertiary amines are metabolized to secondary amines
• highly protein bound
• in the elderly:
  • increased plasma half-life
  • increased steady state levels
  • increased volume of distribution

Pharmacodynamics
• blockade of Ach muscarinic receptors
• blockade of histamine H$_1$ receptors
• blockade of alpha-1 adrenoceptors
• blockade of 5-HT$_{2/1C}$ serotonergic receptors
• membrane stabilization

Compounds available
• AMOXAPINE
  • fairly selective inhibitor of NA uptake
  • also produces blockade of dopamine D$_2$ receptors
  • useful in depressive psychosis but also results in EPSEs
• CLOMIPRAMINE
  • most potent inhibitor of 5-HT uptake
  • its secondary amine metabolite, methylclomipramine, is an effective NA re-uptake inhibitor
  • also of use in OCD
• LOFEPRAMINE
  • tertiary amine, metabolized to desipramine
  • fairly selective inhibitor of NA uptake, and has fewer anticholinergic and antihistaminic properties than amitriptyline
  • not sedating
  • not cardiotoxic in overdose
• MAPROTILINE
  • tetracyclic antidepressant because the tricyclic nucleus is supplemented by an ethylene bridge across the middle ring
  • most selective NA uptake inhibitor of the tricyclics
  • high doses are associated with seizures

Side effects
1) Autonomic:
• Anticholinergic effects
dry mouth
constipation
impaired visual accommodation/ blurred vision
difficulty in micturition & urinary retention
worsening of glaucoma
confusion
• \( \alpha_1 \)-adrenoceptor blocking effects
drowsiness
postural hypotension (especially in the elderly)
sexual dysfunction
cognitive impairment
• Histamine \( H_1 \)-receptor blockade
drowsiness
weight gain

2) Cardiovascular effects
• tachycardia
• hypotension
• prolongation of PR and QT segments
• ST depression and flattened T waves
• negatively inotropic
• cardiac conduction defect; heart block
• cardiac arrythmia

3) Neurological:
• fine tremor
• incoordination
• headache
• muscle twitching
• epileptic seizures (tricyclics lower the seizure threshold)

4) Haematological
• agranulocytosis (rare)
• leucopenia
• eosinophilia
• thrombocytopenia

5) Dermatological
• rashes (more common than with SSRIs and MAOIs)
• photosensitization

6) Other
• mild cholestatic jaundice (rare)
• hyponatraemia (can occur with all antidepressants)
• testicular enlargement
• black tongue

Interactions with other drugs
• phenothiazines (metabolism reduced competetively)
• barbiturates (metabolism increased competetively)
• MAOIs
• Phenotoin (increased levels)
• Adrenaline, Noradrenaline (pressor effects potentiated)
• Warfarin (anticoagulant effects possibly increased)
Contraindications

- agranulocytosis
- severe liver damage
- narrow angle glaucoma
- prostatic hypertrophy
- post MI
- heart block
- caution in:
  - epilepsy (TCAs lower seizure threshold)
  - elderly
  - coronary thrombosis
  - ECT (cardiac events)

Withdrawal of TCAs

- symptoms are due to cholinergic hyperfunction:
  - malaise
  - headache
  - nausea
  - abdominal pain
  - diarrhoea
  - restlessness
  - insomnia
  - anxiety
Selective Serotonin Reuptake Inhibitors (SSRIs)

Pharmacological properties
- all inhibit the reuptake of 5-HT with high potency and selectivity
- low affinity for NA uptake site
- very low affinity for monoamine transmitter receptors

Pharmacokinetics
- absorbed slowly - reach peak levels after 4-8 hours
- \( t_{1/2} \) for PAROXETINE and SETRALINE is about 24 hrs; \( t_{1/2} \) for FLUOXETINE is 48-72 hrs
- eliminated by hepatic metabolism
- FLUOXETINE is metabolized to norfluoxetine, which is also a potent 5-HT uptake blocker and has a half-life of 7-9 days
- SERTRALINE is metabolized to desmethylsertraline which has a half-life of 2-3 days and is 5-10 times less potent than the parent compound

Pharmacodynamics
- long term administration results in:
  - ↓ 5-HT\(_2\) receptor function
  - ↑ 5-HT\(_1\) receptor function post-synaptically
  - ↓ 5-HT\(_{1A}\) receptors presynaptically

Efficacy
- as effective as tricyclics in the treatment of major depression

Side effects
1) Gastrointestinal:
   - common -
     - nausea & diarrhoea 27 %
     - loss of appetite
     - dry mouth 5-18 %
     - constipation
     - dyspepsia
   - uncommon -
     - vomiting
     - weight loss
2) CNS:
   - common -
     - headache
     - insomnia 15 %
     - dizziness
     - anxiety and agitation 5 - 15 % (FLUOXETINE)
• fatigue
• tremor
• sedation/ somnolence 7% (PROZAC) - 21% (SEROXAT)
• uncommon -
• seizures
• mania

3) Cardiovascular:
• reduction in pulse rate
• postural hypotension

4) Other:
• common -
  • sweating
  • delayed orgasm/ anorgasmia
  • withdrawal reactions (insomnia, nausea, agitation, dizziness)
    especially with paroxetine due to short half-life
• uncommon -
  • rash
  • alopecia
  • hyponatraemia

Interactions
• an SSRI should not be started until 2 weeks after a MAOI and a MAOI should not
  be started until at least a week after an SSRI (2 weeks in the case of PAROXETINE,
  and 5 weeks in the case of FLUOXETINE)
• caution when using other drugs that increase brain 5-HT function:
  • LITHIUM
  • TRYPTOPHAN
• inhibition of the hepatic metabolism of some other drugs:
  • tricyclic antidepressants
  • antipsychotic drugs
  • anti-convulsants
  • PROPAANOLOL (enhanced effects)
  • WARFARIN (increase in anticoagulant effect)

Indications for SSRI treatment
1. concomitant cardiac disease
2. intolerance of anticholinergic side effects
3. significant risk of overdose
4. sedation is undesirable
5. depression and OCD
6. bulimia nervosa

The Serotonin Syndrome
• thought to result from overstimulation of 5-HT$_{1A}$ and possibly 5-HT$_{2A}$ receptors
  in the CNS, and was initially seen with MAOIs and L-TRYPTOPHAN
• symptoms fall into three main groups:
  1. altered mental state
2. autonomic dysfunction
3. neuromuscular hyperactivity
   • common symptoms include:
     • agitation
     • delirium
     • mydriasis
     • hyperpyrexia
     • tremor
     • myoclonus
     • rigidity
     • unstable blood pressure
Monoamine Oxidase Inhibitors (MAOIs)

Pharmacological effects

- In the CNS, MAO-A acts on:
  - noradrenaline
  - serotonin
  - dopamine
  - tyramine
- MAO-B acts on:
  - dopamine
  - tyramine
  - phenylethylamine
- benzylamine

Compounds available

- Hydrazine compounds:
  - PHENELZINE
  - ISOCARBOXACID
    - fewer side effects than phenelzine
- Non-hydrazine compounds:
  - TRANYLCYPRAMINE
    - partly metabolized to amphetamine and has a stimulating effect
    - higher incidence of dependence
    - more likely to cause hypertensive crisis
- Reversible inhibitors:
  - MOCLOBAMIDE (Manerix™)
    - reversible inhibitor of MAO-A (RIMA)
    - less potentiation of the pressor effects of tyramine
    - no treatment-free period is required because of its short action

Pharmacokinetics

- rapidly absorbed and widely distributed
- short half-lives (2-4 hours)
- metabolized in the liver by acetylation, oxidation, and deamination (60 % of people are ‘fast acetylators’ and metabolize hydrazine MAOIs quicker
- MAOIs (except MOCLOBEMIDE) bind irreversibly to both MAO-A and MAO-B by covalent linkage > the enzyme is permanently inhibited

Efficacy

- similar to TCAs
- particularly useful in atypical depression
- more effective than TCAs for bipolar depression
- hypochondriacal, or hysterical features are said to respond best to MAOIs
Side effects

1) CNS:
   - insomnia
   - drowsiness
   - agitation
   - headache
   - fatigue
   - weakness
   - tremor
   - mania
   - confusion
   - seizures (rare)

2) Autonomic:
   - blurred vision
   - difficulty with micturition
   - sweating
   - dry mouth
   - postural hypotension
   - constipation

3) Other:
   - sexual dysfunction
   - weight gain
   - peripheral neuropathy (pyridoxine deficiency)
   - oedema
   - rashes (uncommon)
   - SLE-type syndrome
   - jaundice (uncommon)

Interactions
- MAOIs result in the accumulation of amine neurotransmitters
- danger of interaction persists for 2 weeks after treatment has stopped

1. Food and Drink containing tyramine
   - cheeses
   - extracts with meat and yeast (Bovril®, Oxo®, Marmite®)
   - smoked/ pickled fish
   - hung poultry and game
   - some red wines (e.g. chianti)

2. Drugs
   - adrenaline, noradrenaline
   - indirect-acting sympathomimetics e.g. ephedrine (found in cough medicines)
   - L-Dopa
   - opiates (esp. Pethidine)
   - Alcohol
   - Barbiturates
   - Insulin and oral hypoglycaemics (risk of hypoglycaemia increased)
• Antidepressants (esp. SSRIs) - have a drug free period of 2 weeks when changing from MAOIs to other antidepressants

Contraindications
• liver disease
• phaeochromocytoma
• congestive cardiac failure

Combination of MAOIs with TCAs
• safe if:
  1. CLOMIPRAMINE and IMIPRAMINE are not used - the most favoured are amitriptyline and trimipramine
  2. the MAOI and TCA are started together, or the MAOI is added to the TCA (adding TCAs to MAOIs is more likely to cause dizziness and postural hypotension)
Other Antidepressant Drugs

Mianserin

Pharmacological actions
- weak NA reuptake inhibitor
- potent antagonist at several 5-HT receptor subtypes, esp. 5-HT$_2$
- competitive antagonist at histamine H$_1$ receptors and $\alpha_1$ and $\alpha_2$-adrenoceptors
- not a muscarinic cholinergic antagonist
- not cardiotoxic
- has a sedating profile but is not anticholinergic and is relatively safe in overdose

Pharmacokinetics
- rapidly absorbed
- peak plasma concentrations in 2-3 hrs
- half-life of 10-20 hrs

Efficacy and use
- similar to TCAs

Side effects
- drowsiness
- dizziness
- cognitive impairment
- weight gain
- lowers seizure threshold
- lowers white cell count; fatal agranulocytosis has been reported > initial FBC and monthly for 3/12 afterwards
- arthritis
- hepatitis

Interactions
- potentiates the effect of other central sedatives

Mirtazepine

Pharmacological actions
- noradrenergic and specific serotonin antidepressant (NaSSA)
- antagonist at $\alpha_2$ auto- and heteroreceptors
- increased serotonin release stimulates 5-HT$_{1A}$ receptors
- blocks presynaptic $\alpha_2$ autoreceptors and enhances NA transmission
- high affinity for 5-HT$_1$
- blocks 5-HT$_{2A/C}$ and 5-HT$_3$ receptors – therefore prevents side effects such as anxiety, agitation, nausea, and sexual side effects
- weak affinity for muscarinic receptors
• potent H₁ receptor antagonist

• at higher doses, the increased NA transmission partially offsets the sedating antihistamine activity that predominates at lower doses

Side effects
• increased appetite and weight gain (H₁ blockade)
• drowsiness and sedation

Interactions
• potentiates effects of other sedatives

Cautions
• risk of neutropenia and agranulocytosis
• cardiac disease

Trazodone

Pharmacological actions
• weak 5-HT re-uptake inhibitor
• antagonist at 5-HT₂ receptors but its active metabolite is a 5-HT receptor agonist
• blocks post-synaptic α₁-adrenoceptors
• sedating profile

Pharmacokinetics
• short half-life (4-14 hrs) but once daily dosing usually adequate
• metabolized by hydroxylation and oxidation

Efficacy
• superior to placebo
• similar to TCAs

Side effects
• excessive sedation
• cognitive impairment
• nausea (should take with food)
• dizziness
• postural hypotension
• priapism (1 in 6000 patients)

Interactions
• may potentiate the effects of alcohol and other CNS depressants
Nefazodone

Pharmacological actions
• related to trazodone but lacks $\alpha_1$-adrenoceptor antagonist properties and is therefore not sedating

Pharmacokinetics
• rapidly absorbed
• extensive 1$^{st}$ pass metabolism
• highly protein bound
• short half-life (2-4 hrs) therefore twice daily dosing

Efficacy
• superior to placebo
• similar to TCAs

Side effects
• headache
• loss of energy
• dizziness
• dry mouth
• nausea
• somnolence

Interactions
• coadministration of propanolol can increase levels of active metabolites
• nefazodone can increase haloperidol levels and plasma BZD concentrations

Venlafaxine

Pharmacological actions
• is a Serotonin and Noradrenaline Reuptake Inhibitor (SNRI)
• phenylethylamine derivative
• potent blockade of both 5-HT and NA re-uptake
• negligible affinity for other sites and so lacks sedative and anticholinergic effects

Pharmacokinetics
• well absorbed
• peak plasma levels in 1½ -2 hrs
• half life of 5 hrs but the metabolite has same pharmacological actions and has a half-life of 8-13 hrs

Efficacy
• superior to placebo
• equal to other antidepressants
• possible faster onset of action
Side effects
• headache
• dizziness
• dry mouth
• nausea
• somnolence
• anxiety
• sexual dysfunction
• postural hypotension, but in high doses can increase blood pressure
• discontinuation syndrome reported

Interactions
• little effect on hepatic drug metabolism
• should not be given with MAOIs

Reboxetine
Pharmacological actions
• selective noradrenaline reuptake inhibitor (NARI)

Pharmacokinetics

Efficacy and use

Side effects
• dry mouth
• constipation
• insomnia
• impotence and decreased libido at higher doses

Interactions

L-Tryptophan
Pharmacological properties
• naturally occurring amino acid, present in the normal diet
• used for protein synthesis; 1 % is synthesized to 5-HT via 5-Hydroxytryptophan
• tryptophan hydroxylase, the enzyme that catalyses the formation of 5-HTP from L-tryptophan is normally unsaturated with tryptophan so increasing tryptophan availability to the brain increases 5-HT synthesis

Pharmacokinetics
• rapidly absorbed
• peak levels 1-2 hrs after ingestion
• extensively bound to albumin
Efficacy

- little evidence for efficacy by itself
- combined with MAOIs, it can increase the antidepressant effects of MAOIs
- evidence is less strong with TCAs

Side effects

- nausea
- drowsiness
- eosinophilia-myalgia syndrome:
  - high levels of circulating eosinophils
  - muscle pain
  - oedema
  - skin sclerosis
  - peripheral neuropathy
  - due to a contaminant in the manufacturing process

Interactions

- interactions with drugs that increase brain 5-HT function e.g. SSRIs
Antipsychotics

Classification of Phenothiazines

<table>
<thead>
<tr>
<th>Group</th>
<th>Sedation</th>
<th>Antimuscarinic Side-effects</th>
<th>Extrapyramidal Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 – aliphatic</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CHLORPROMAZINE, PROMAZINE, METHOTRIMEMAPRIZINE</td>
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<tr>
<td>Group 2 – piperidine</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>THIORIDAZINE, PIPOTHIAZINE, PERICYAZINE</td>
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</tr>
<tr>
<td>Group 3 – piperazine</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>FLUPHENAZINE, TRIFLUOPERAZINE, PERPHENAZINE</td>
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</tr>
</tbody>
</table>

Other (non-atypical) drugs tend to resemble the phenothiazines of group 3

- **BUTYROPHENONES:** DROPERIDOL, HALOPERIDOL
- **DIPHENYLIBUTYLPIPERIDINES:** PIMOZIDE
- **THIOXANTHENES:** FLUPENTHIXOL, ZUCLOPENTHIXOL
- **SUBSTITUTED BENZAMIDES:** SULPIRIDE
- **DIBENZODIAZEPINES:** CLOZAPINE
- **THIENOBENZODIAZEPINE:** OLANZAPINE
- **DIBENZOTHIAZEPINE:** QUETIAPINE
- **BENZIXASOLES:** RISPERIDONE
- **IMIDAZOLIDINNONE:** SERTINDOLE

Miscellaneous neuroleptics include:

- Loxapine
- Fluspirilene
- Pericyazine

**Pharmacokinetics**

- well absorbed, mainly from jejunum
- extensive 1st pass metabolism (75% for CHLORPROMAZINE, more with FLUPHENAZINE)
- combinations of active and inactive metabolites may occur
- CHLORPROMAZINE induces its own metabolism

**Contraindications**

- myasthenia gravis
- Addison’s disease
- glaucoma
- evidence of past/present bone marrow depression
- liver disease (CHLORPROMAZINE)
Movement Disorders and their pharmacology

Acute Dystonia
- fixed muscle postures with spasm e.g. opisthotonus, torticollis, oculogyric crisis
- appears within hours to days
- young males are most at risk

Extrapyramidal symptoms (EPS)/ Parkinsonism
- mask-like facies, tremor, rigidity, festinant gait, akathisia
- appears within days to weeks
- occur in up to 90 % of patients taking conventional neuroleptic medication
- due to blockade of D2 receptors in the basal ganglia; EPS does not occur until D2 occupancy by antipsychotic is > 70%
- treatment:
  1. anticholinergic drug (PROCYCLIDINE, ORPHENADRINE)
  2. reducing dose
  3. switching to an ‘atypical’

Tardive Dyskinesia (TD)
- orofacial dyskinesia, lip smacking, tongue rotating, choreoathetoid movements of head, neck, and trunk
- appears after months or years
- ? due to supersensitivity of D2 receptors (see Neuropathology for other theories)
- increased risk in:
  - elderly
  - female (especially post-menopausal)
  - organic brain damage
  - affective disorders
  - intermittent treatment may be a risk factor - the syndrome often appears when the drug is stopped
- 5-60 % will develop TD, with increased risk of 3-5 % per year
- treatment:
  - increasing the dose may temporarily alleviate symptoms
  - use of anticholinergics may increase risk of TD
  - switch to CLOZAPINE (up to 70 % of patients may improve)

Akathisia
- subjective and objective (i.e. motor) restlessness
- treatment:
  - reduce dose
  - PROPAANOLOL or BZD rather than anticholinergic
Other side effects

1) CNS:
   • sedation - due to $\alpha_1$ adrenergic and $H_1$ blockade
   • toxic confusional state - due to muscarinic blockade

2) Autonomic:
   • muscarinic blockade
     - dry mouth
     - urinary hesitancy
     - constipation
     - blurred vision and worsening of glaucoma
   • $\alpha_1$ adrenergic blockade
     - postural hypotension
     - impotence
     - ejaculatory failure
     - nasal congestion

3) Endocrine:
   • dopamine receptor blockade in H-P-A axis > increased prolactin
     - amenorrhoea
     - galactorrhoea
     - impotence
     - infertility

4) Skin:
   • urticaria
   • dermatitis
   • rashes
   • photosensitivity (probably autoimmune, commonly seen with phenothiazines, especially CHLORPROMAZINE)
   • purplish pigmentation

5) Eye:
   • purplish pigmentation of:
     - conjunctiva
     - cornea
     - retina
   • opacity of:
     - lens
     - cornea
   • retinal degeneration can occur with higher doses of THIORIDAZINE (or CHLORPROMAZINE)

6) Increased body weight

7) Blood:
   • agranulocytosis
   • neutropenia, especially with CLOZAPINE

8) Cardiovascular:
   • prolongation of QT and PR interval
   • T-wave blurring
   • torsades de pointes (THIORIDAZINE)
   • long QT interval and sudden cardiac death with PIMOZIDE

9) Cholestatic jaundice:
   • seen rarely with CHLORPROMAZINE - possibly due to impurity
10) **Hypothermia:**
   - interference with temperature is a dose-related side-effect

**Neuroleptic malignant syndrome (NMS)**

- is an idiosyncratic response to neuroleptics, thought to be due to complete dopamine blockade, although exact mechanism unclear
- incidence is 0.5-1% of patients
- onset is often within first 10 days of treatment
- combined LITHIUM and antipsychotic drug may be a risk factor

**Risk factors**
- organic brain disease
- hypermetabolic states (e.g. hyperthyroidism)
- agitation
- dehydration
- recent dose increase

**Signs and symptoms**
- rapid onset (24-72 hrs)
- **motor symptoms:**
  - generalized muscle hypertonicity (but may be confined to head and neck)
  - dysphagia, dyspnoea
- **mental symptoms:**
  - akinetic mutism
  - stupor
  - fluctuating consciousness
- **autonomic symptoms:**
  - unstable blood pressure
  - tachycardia
  - excessive sweating
  - hyperthermia
  - hypersalivation
  - urinary incontinence

**Investigations**
- increased CPK (>1000 iu/L)
- increased white cell count (neutrophilia)
- abnormal LFTs

**Treatment**
1. stop antipsychotics immediately
2. BROMOCRIPTINE to reverse dopamine blockade
3. DANTROLENE for muscle rigidity
4. general supportive treatment on a medical ward
5. rehydration
6. sedation with short-acting BENZODIAZEPINES
7. other treatments include: antimuscarinic agents; propanolol; ECT; plasmaphoresis

Complications
- pneumonia
- pulmonary embolism
- rhabdomyolysis leading to renal failure
- arrhythmias, cardiac arrest, stroke, cardiogenic shock
- hepatic failure
- E. coli fasciitis
- mortality is 20% - due to renal failure and rhabdomyolysis

Antipsychotic rechallenge
- success not related to gender or age
- wait at least 5-14 days
- use structurally dissimilar agents
- start at low dose and titrate slowly
- avoid depot preparations
- ? use agents with lower D₂ receptor blockage

Compliance
- 40-60% of schizophrenic patients are non-compliant with prescribed oral medication

Depot medication
- no trial comparing long-term relapse rates on daily tablets vs. depot has demonstrated that depots are more effective
Atypical Antipsychotics

Risperidone

Pharmacological properties
- serotonin-dopamine atypical antipsychotic (SDA)
- high affinity for the 5-HT\textsubscript{2A} receptor
- antagonist at Histamine and NA receptors

Efficacy
- at least as effective as conventional antipsychotics in reducing total symptom scores
- as effective as CLOZAPINE in reducing +ve symptoms in patients who were intolerant to typical drugs
- greater response rate for negative symptoms than conventional treatment

Side effects
- incidence of EPS is no greater than placebo
- at higher doses (> 8 mg), RISPERIDONE can cause EPS at a similar rate to typical drugs
- dose-related hyperprolactinaemia (and sexual side effects) may be a problem
- insomnia
- headache
- anxiety
- weight gain

Sertindole

Pharmacological properties
- serotonin-dopamine atypical antipsychotic (SDA)
- high affinity for the 5-HT\textsubscript{2A} receptor
- specifically targets D\textsubscript{2} receptors in the limbic region

Efficacy
- trials conclude that SERTINDOLE is as effective as conventional treatment

Side effects
- incidence of EPS is no greater than placebo
- nasal congestion - due to α\textsubscript{1} adrenoceptor blockade
- orthostatic hypotension
- prolongs QT interval in 4% of patients (16 deaths among 2194 patients)

Interactions
- caution with local and general anaesthetics
Clozapine

Pharmacological properties
- low affinity for \(D_2\) receptors
- higher affinity for \(D_1\) and \(D_4\) receptors
- antagonistic at \(5-HT_{1A}\), \(5-HT_{2A}\), \(5-HT_{2C}\), and \(5-HT_3\) receptors
- antagonistic at \(\alpha_1\) and \(\alpha_2\) receptor
- higher potency of action than do typical antipsychotics on the following receptors:
  - \(5-HT_2\)
  - \(D_4\)
  - \(D_1\)
  - muscarinic
  - \(\alpha\)-adrenergic

Efficacy
- superior efficacy for negative symptoms
- only used, on a named patient basis, for patients unresponsive to 2 other conventional antipsychotics, or those with TD or severe EPS

Side effects
- hypersalivation
- weight gain (up to 2 stone)
- tachycardia
- hypotension
- sedation is the most common side-effect
- does not cause EPS or hyperprolactinaemia
- neutropenia occurs in one in 43 patients - blood monitoring essential
  - 83% of cases occur within the first 20 weeks of treatment
- 0.8% risk of agranulocytosis
  - risk factors are older age, female
  - risk of agranulocytosis decreases to 0.07% after the first year
- 5% risk of seizures at doses above 600 mg – dose related (add in VALPROATE)

Interactions
- caution with other drugs that cause blood dyscrasias (e.g. CARBAMAZEPINE, sulphonamides)
- with drugs that are strongly protein bound > increased levels of WARFARIN and DIGOXIN
- with drugs that use cytochrome \(P_{450}\) enzyme system (e.g. phenothiazines, antidepressants)
Olanzapine

Pharmacological properties
- structurally similar to CLOZAPINE
- higher affinity for D₂ and 5-HT₂A receptors than CLOZAPINE, with a lower affinity at the D₁ receptor

Efficacy
- as effective as HALOPERIDOL for positive symptoms and ? superior for negative symptoms (some evidence)

Side effects
- EPS no greater than placebo
- sedation
- significant weight gain

Interactions

Quetiapine

Pharmacological properties
- similar binding profile to CLOZAPINE
- lower affinity for all receptors than CLOZAPINE
- little affinity for muscarinic receptors
- tends to target cortical receptors rather than basal ganglia

Efficacy
- as effective as HALOPERIDOL for both positive symptoms and negative symptoms
- superior to HALOPERIDOL in the treatment of hostility and aggression

Side effects
- EPS no greater than placebo across the whole dose range
- no significant prolactin elevation
- somnolence
- dry mouth
- lower propensity to cause weight gain than CLOZAPINE and OLANZAPINE
- constipation
- most common SE’s are mild and transient

Interactions
Amisulpride

Pharmacological properties
- D2/ D3 antagonist
- at low doses it blocks autoreceptors thus increasing synaptic dopamine levels - improvement in negative symptoms

Efficacy
- equivalent to conventional drugs for treating positive symptoms
- no extra benefit for negative symptoms on low doses compared to HALOPERIDOL

Side effects
- placebo-level EPS at low doses
- increase in EPS at higher doses, but still less than with conventional antipsychotics
- prolactin elevation is similar to conventional drugs

Interactions

Evidence for atypicals
- very little evidence for efficacy of atypicals in treatment-resistant cases with the exception of CLOzapine
- best time to use an atypical is 1st episode
- however, do not come in depot medication
- most obvious reason to switch to an atypical is EPS
- some studies have shown better response to OLANZAPINE against RISPERIDONE; adverse effects were less frequent on OLANZAPINE
- a poor response to an atypical (except CLOzapine) is unlikely to improve after a trial of eight weeks

Antiparkinsonian Drugs
- procyclidine
- benzhexol
- benztropine
- orphenadrine
- biperiden
- methixene
Mood stabilizing drugs

Lithium

Pharmacological properties
- mechanism unclear
- appears to reduce the neurotransmitter-induced activation of second messenger systems
- the effect may be via G proteins

- increased:
  - intracellular sodium
  - intracellular calcium in erythrocytes in mania and depression
  - erythrocyte choline
  - erythrocyte phospholipid catabolism (cAMP)
  - serotonergic transmission
  - GABAergic transmission
  - dopamine turnover in hypothalamic-tuberoinfundibular dopaminergic neurones
  - dynorphin in the corpus striatum

- reduced:
  - Na,K-ATPase pump activity
  - Calcium in platelets in bipolar disorder
  - central 5-HT_1 and 5-HT_2 receptor density (demonstrated in the hippocampus)
  - central dopamine synthesis
  - low affinity GABA receptors in the corpus striatum and hypothalamus

Pharmacokinetics
- rapidly absorbed from the gut – absorption is complete in 6-8 hours
- $C_{\text{max}}$ serum after immediate release preparation = 1.5 – 2 hours
- $C_{\text{max}}$ serum after MR preparation = 4 – 4.5 hours
- bioavailabilty = 100%
- volume of distribution = 0.7-0.9 L/kg
- half-life between 14 and 30 hours
- time to steady state is between 5 and 7 days
- moves out of cells more rapidly than sodium
  - results in rapid excretion of lithium from the plasma, with a slower phase reflecting its removal from the whole body pool – a third is excreted within 12 hours
- excreted by the kidney, with 80% reabsorbed in the proximal renal tubules
  - when the proximal tubule absorbs more water, lithium absorption increases
  - therefore dehydration causes plasma levels to increase
- because lithium is transported in competition with sodium, more is reabsorbed when sodium concentrations fall

Indications
- lithium can reduce the number of relapses in bipolar illness
• patients with rapid-cycling B.A.D. generally do not respond

Side effects
• GI upset is due to direct effects on the stomach, therefore SE’s are greater with MR preparations
• A dose reduction of 0.8 down to 0.68 reduces SE’s by 35%

1) Neurological
• fine tremor
• weakness
• dysarthria
• ataxia
• impaired memory
• seizures (rare)
• neurotoxicity with neuroleptics or CARBAMAZEPINE

2) Renal/ Fluid balance
• increased urine output with decreased urine-concentrating ability (10 % of patients)
  - less polyuria with MR preparations
  - reducing total daily protein intake can reduce polyuria
  - if problematic, use a thiazide diuretic and reduce dose of Lithium by 50%; alternatively, use Amiloride 5mg with no need to reduce lithium dose
• thirst
• oedema
• diabetes insipidus (rare)
  - distal tubule becomes resistant to influence of ADH, possibly due to blockage of ADH-sensitive adenylate cyclase
• reports of tubular damage in patients on prolonged treatment

3) Gastrointestinal
• altered taste (commonly metallic taste)
• anorexia
• nausea
• diarrhoea
• weight gain (esp. in women)

4) Endocrine
• Thyroid gland enlargement
  - occurs in 5%
  - shrinks if THYROXINE is given
  - returns to normal after 1-2 months after LITHIUM is stopped
• Hypothyroidism
  - in 3-4 %
  - females > males
  - due to interference with thyroid production
• Hyperparathyroidism (rare)

5) Haematological
• leucocytosis

6) Dermatological
• acne
• exacerbation of psoriasis
• alopecia

7) **Cardiovascular**
• due to displacement of $K^+$ in the myocardium by LITHIUM
• T-wave flattening
• inversion or widening of QRS

**Toxicity**

| Early         | plasma levels 1.5-2 mEq/L | • anorexia  
|               |                           | • vomiting  
|               |                           | • diarrhoea  
|               |                           | • coarse tremor  
|               |                           | • ataxia  
|               |                           | • dysarthria  
|               |                           | • confusion  
|               |                           | • sleepiness  
| Later         | plasma levels > 2 mEq/L   | • impaired consciousness  
|               |                           | • neurological signs:  
|               |                           | • nystagmus  
|               |                           | • muscle twitching  
|               |                           | • hyperreflexia  
|               |                           | • convulsions  
| Severe overdose|                          | • toxic psychosis  
|               |                           | • convulsions  
|               |                           | • syncope  
|               |                           | • oliguria  
|               |                           | • circulatory failure  
|               |                           | • coma and death occur at higher levels

**Long term effects on the kidney**
• Schou (1988) concluded that long-term LITHIUM treatment does not result in a lowering of GFR
• renal failure is rare - only two cases reported

**Lithium and the thyroid**
• LITHIUM inhibits the release of iodine, T3 and T4
• induces thyroid autoantibodies

**Contraindications**
• thyroid disease
• hypopituitarism
• Addison’s disease
• pregnancy  
  • LITHIUM crosses the placenta
• increased incidence of birth defects (esp. cardiac abnormalities)
• LITHIUM is secreted in breast milk
• caution in compromised renal function

Interactions
• increased LITHIUM levels with:
  • thiazide diuretics increase sodium excretion without increasing that of lithium
  • NSAIDs (except ASPIRIN)
  • antibiotics (METRONIDAZOLE)
  • antihypertensives (ACE-inhibitors and METHYLDOPA)
  • salt deficiency
• increased potentiation of antipsychotics in producing EPS (esp. HALOPERIDOL)
• continuation of LITHIUM therapy with ECT may lead to neurotoxicity
• cardioactive drugs:
  • DIGOXIN (increased effects on myocardium)
  • DILTIAZEM
  • VERAPAMIL
  • ACE inhibitors
• LITHIUM increases brain 5-HT levels, and in combination with SSRIs has led to neurotoxicity (myoclonus, seizures, hyperthermia)

Lithium Drug Monitoring
• Blood samples taken 12 hours post dose
• Serum levels of 0.6 – 1.0 are generally effective:
  • Aim for 0.8 – 1.0 during manic phase; 0.4 – 0.8 during maintenance phase
  • Closer monitoring required with rapid-cycling patients
• Levels generally increase after 5-6 weeks of treatment, typically from 0.8 – 1.0
• Regular levels every 3 months
• Thyroid and renal function every 6 months

Carbamazepine
Pharmacological Properties
• GABA agonist
• blocks neuronal sodium channels and also affects calcium channels
• facilitates some aspects of brain 5-HT function

Pharmacokinetics
• slowly, but completely absorbed
• widely distributed
• extensively metabolized, with at least one metabolite being active
• half-life is 20 hrs
• at the start of therapy, CARBAMAZEPINE induces its own catabolic enzymes

Side effects
• drowsiness
• dizziness
• ataxia
• diplopia
• nausea
• headache
• rash (5 %)
• elevation of liver enzymes

• **agranulocytosis**
  • rare (1 in 10,000 - 1 in 125,000)
  • patients should be warned about fever and infection
  • monitor FBC fortnightly for first 2 months

• **leucopenia**
  • usually in the first few weeks of treatment

• SIADH
• disturbances in cardiac conduction

Interactions
• increased metabolism of:
  • TCAs
  • BZDs
  • HALOPERIDOL
  • Oral contraceptives
  • THYROXINE
  • WARFARIN
  • anticonvulsants

• carbamazepine levels increased by:
  • SSRIs
  • ERYTHROMYCIN
  • ISONIAZID
  • some MAOIs

• decreased effect of other Ca$^{2+}$ channel blockers:
  • FELODIPINE
  • NICARDIPINE

• neurotoxicity with LITHIUM

**Sodium Valproate**

Pharmacological properties
• mechanism unclear – GABA transaminase inhibitor
• increased:
  • GABA release
- GABA-B receptor density
- neuronal responsiveness to GABA
- potassium conductance
- reduced:
  - GABA breakdown
  - GABA turnover
  - sodium influx

Pharmacokinetics
- rapidly absorbed; peak concentrations 2 hrs after dose
- widely and rapidly distributed
- half-life of 8-18 hrs
- metabolized in the liver - many metabolites are active

Side effects
1. Gastrointestinal:
   - nausea
   - vomiting
   - diarrhoea
   - weight gain
2. CNS:
   - tremor
   - sedation
   - ataxia
   - dysarthria
3. Haematological:
   - thrombocytopenia
   - inhibition of platelet aggregation
4. acute pancreatitis (rare)
5. elevation in hepatic transaminases
   - several reports of fatal hepatic toxicity
- VALPROATE must be stopped if vomiting, anorexia, jaundice, or sudden drowsiness occur

Interactions
- potentiates the effects of central sedatives
- increases side-effects of other anticoagulants
- increases plasma levels of:
  - benzodiazepines
  - barbiturates
  - PHENYTOIN
- increased tremor with LITHIUM
- increases effects of:
  - WARFARIN
  - ASPIRIN
- VALPROATE levels increased by:
  - AMITRIPTYLINE
  - FLUOXETINE
- VALPROATE levels decreased by CARBAMAZEPINE

Contraindications
- pre-existing liver disease
- pregnant or nursing mothers

**Gabapentin**

Pharmacological properties
- mechanism unclear, but may act by binding to a cerebral calcium channel

Clinical indications
- adjunctive treatment of partial seizures, with or without secondary generalization

Side effects
- sedation
- dizziness
- ataxia
- nystagmus
- tremor
- diplopia
- weight gain
- nervousness
- pancreatitis (rare)

**Vigabatrin**

Pharmacological properties
- irreversible inhibitor of GABA transaminase

Clinical indications
- tonic-clonic and partial seizures not controlled by other antiepileptics
- monotherapy for infantile spasms (West’s syndrome)

Side effects
- drowsiness
- depression
- ataxia, tremor
- confusion
- aggression
- psychosis
- behavioural disturbance
**Lamotrigine**

**Pharmacological properties**
- inhibition of glutamate release
- prolongs the slow inactivated state of voltage-dependent sodium ion channels

**Indications**
- partial seizures and secondary generalized tonic-clonic seizures
- can be used as a sole treatment or adjunctive therapy

**Side effects**
- rashes, and Stevens-Johnson syndrome
- drowsiness
- hepatic dysfunction (monitor liver and renal function)
- visual disturbance – diplopia, blurred vision
- GI upset
- confusion

**Tiagabine**

**Pharmacological properties**
- inhibition of neuronal and glial uptake of GABA

**Donepezil (Aricept)**

**Mode of action**
- piperidine-based reversible inhibitor of acetylcholinesterase
- increases concentrations of acetylcholine available for synaptic transmission
- relatively selective for cholinesterase in the brain, but peripheral butyrylcholinesterase is also affected to some extent

**Pharmacokinetics**
- absorption is complete with peak plasma concentrations in 3 to 4 hours
- elimination half-life is long (70 hours)
- steady-state plasma concentrations in 15 days
- not affected by food, or time of ingestion
- strongly bound to plasma proteins (mainly albumin and alpha₁-acid glycoprotein)
- metabolised in the liver by CYP-450 isoenzymes 2D6 and 3A4

**Interactions**
- no important interactions recognized
- potential for interference with medications having anticholinergic activity and synergistic activity with SUCCINYLCHOLINE

**Side effects**
- nausea and vomiting
• diarrhoea
• fatigue
• dizziness
• dyspepsia
• insomnia
• muscle cramps
• bradycardia
• occasional syncope
• minor increases in muscle creatine kinase

Cautions
• co-existing cardiac arrhythmias
• peptic ulcer
• asthma
• reversible obstructive airways disease

Relative Contra-indications
• supraventricular cardiac conduction disorders
• bladder outflow disorders
• seizures
• asthma
• reversible obstructive airways disease
Relative safety of drugs in pregnancy and breast feeding

Safe in breast feeding
- most TCAs
- Carbamazepine
- Chlormethiazole
- Valproate
- Beta-blockers

Avoid in breast feeding
- Sulpiride
- Lithium
- Benzodiazepines
- Barbiturates
- Bromocriptine
- Most antipsychotics
- Clozapine
- SSRIs
- Phenytoin
- Reboxetine

Safe during pregnancy
- TCAs
- Trifluoperazine
- Chlorpromazine

Avoid in pregnancy
- SSRIs
- MAOIs
- Depot antipsychotics
- Lithium