<table>
<thead>
<tr>
<th>General Purpose</th>
<th>Name of Drug</th>
<th>Overall Use and Function</th>
<th>Mechanism of Action</th>
</tr>
</thead>
</table>
| Block or modulate ion channel opening that allow passage of ions into cells | Nifedipine (S4) | • Reduced blood vessel constriction,  
• Reduced blood pressure | Blocks Ca2+ channels |
| Block or (utilise) carriers that transport molecules across lipid membrane | Fluoxetine (Vd=35L/kg) | • Prolongs serotonin action  
• Used for depression | Blocks serotonin uptake into nerves |
| Inhibit enzymes that catalyse synthesis/breakdown of molecules | Aspirin | Reduced synthesis of mediators of pain/fever/inflammation  
- Can induce asthma | Inhibits cyclo-oxygenase (COX) |
| Use enzymes (prodrug to produce active drug) | L-dopa | • Increased synthesis of dopamine  
• Used for Parkinson’s disease | Uses dopa decarboxylase |
| Use enzymes (false substrate to produce abnormal metabolites) | Fluorouracil | • DNA synthesis inhibited preventing cell division.  
• Treating tremors/cancers | Replaces uracil as an intermediate in purine biosynthesis |
| Activate or block receptors | Morphone (agonist) (24% bioavailability) Vd=2L/kg (S8) | Used for pain | Activates opioid receptors |
| Kinase-linked receptors agonist | Growth factor receptor agonist | Regulation of cell growth | • Agonist binding causes receptor dimerisation  
• Activation of tyrosine kindase (cytoplasmic domain)  
• Phosphorylates substrates that regulate cell growth (gene transcription) |
| Nuclear receptor agonist | Glucocorticoid receptor agonist (GCs) | • Activates GR complex  
• Up-regulates the expression of anti-inflammatory proteins in the nucleus  
• Or represses the expression of pro-inflammatory proteins in the cytosol (by preventing the translocation of other transcription factors from the cytosol into the nucleus). | Activation inhibits synthesis of cyclo-oxygenase |

Ligand-gated ion channels (ionotropic receptors): milliseconds, eg: nicotinic receptors  
G-protein-coupled receptors (metabotropic receptors): seconds, eg: muscarinic receptors  
Kinase-linked receptors: hours, cytokine receptors  
Nuclear receptors: hours, oestrogen receptors

- Buprenorphin: Opiate receptor agonist  
- Sumatriptan: 5-HT\textsubscript{1} receptor agonist  
- Fexofenadine: Histamine receptor antagonist  
- Hexamethonium: Nicotinic receptor antagonist, both parasympathetic/ sympathetic nerves  
- Direct nerve stimulation on local tissue gives indication of such tissue controlled by PNS or SNS.

- Gaddum’s equation measures the binding of agonist (affinity) in the presence of antagonist.  
- K\textsub{D} (dissociation constant) measures affinity, low K\textsub{D} gives high affinity  
- EC\textsub{50} and pEC\textsub{50} measures potency  
- Antagonists can elicit responses in the body only when endogenous agonist is present, no efficacy in vitro, active in vivo (clinical efficacy) which measure potency  
- Relative shifts (concentration ratios) \( \rightarrow \) antagonist affinity and potency  
- pA\textsub{2}: negative log of concentration of antagonist required to cause a two-fold rightward shift of the agonist concentration-response curve. \( \rightarrow \) antagonist potency. pK\textsub{A} \( \approx \) pK\textsub{B}  
- Pattern of antagonism \( \propto \) association/dissociation constant, relative concentrations, duration of exposure.  
- Competitive/non-competitive, surmountable/insurmountable, reversible/irreversible, direct/indirect, functional? antagonism  
- Antagonist effectively decreases the number of receptors available on the time, receptors slowly regenerating.
<table>
<thead>
<tr>
<th>(catecholamine)</th>
<th>Synthesis: Tyrosine (&amp; Tyrosine hydroxylase) → L-dihydroxyphenylalaine (L-DOPA) in cytosol (&amp; DOPA decarboxylase) → Dopamine (&amp; Dopamine β-hydroxylase) in synaptic vesicles → Noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I. Calcium-dependent NA release across synaptic junction</td>
</tr>
<tr>
<td></td>
<td>II. inactivation (uptake)</td>
</tr>
<tr>
<td></td>
<td>III. Inactivation (metabolism)</td>
</tr>
<tr>
<td>Drugs modulating release and inactivation of NA</td>
<td>Cocaine</td>
</tr>
<tr>
<td></td>
<td>MAO-inhibitor</td>
</tr>
<tr>
<td>Indirectly Acting Sympathomimetics</td>
<td>• Amphetamine (S8)  • ephedrine (pseudoephedrine) S3  • tyramine (dietary product-substrate for MAO)</td>
</tr>
<tr>
<td>Adrenaline (catecholamine)</td>
<td>Synthesis: Noradrenaline (&amp; PNMT) → Adrenaline</td>
</tr>
<tr>
<td></td>
<td>Increase Bronchodilation - also able to treat anaphylactic shock (allergic reaction)</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Phenylephrine (PE)</td>
</tr>
<tr>
<td></td>
<td>Clonidine</td>
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<tr>
<td></td>
<td>Isoprenaline (ISO)</td>
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<tr>
<td></td>
<td>Dobutamine</td>
</tr>
<tr>
<td></td>
<td>Salbutamol S3</td>
</tr>
<tr>
<td>Sympathomimetic Antagonist</td>
<td>Phentolamine</td>
</tr>
<tr>
<td></td>
<td>Prazosin</td>
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<tr>
<td></td>
<td>Propranolol</td>
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<td></td>
<td>Pindolol</td>
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<tr>
<td></td>
<td>Atenolol</td>
</tr>
<tr>
<td>Potency: Blood Vessel (α receptors predominant): PE&gt;NA2ADR&gt;ISO</td>
<td>Heart (β receptors): ISO&gt;ADR≥NA&gt;&gt;PE</td>
</tr>
</tbody>
</table>

**a1 receptors** (→ Gq & GTP → ↑ Phospholipase C → ↑ IP3, DAG from membrane PIP2 → ↑ Ca2+ mobilisation & PKC activation → Vasoconstriction): blood vessels (postjunctional sites),  
**a2 receptors** (→ Gi & GTP → ↓ Adenylate cyclise → ↓ cAMP → ↓ neurotransmitter release): nerve terminals (prejunctional inhibitory action),  
**b1 receptors** (→ Gs → ↑ cAMP): heart & kidney,  
**b2 receptors** (→ Gs → ↑ cAMP): airways & some blood vessels  

Acetylcholine | Decrease cardiac rate  
Synthesis: Choline (from ECF to ICF through choline carrier) → & AcetylCoA (from mitochondria) & Choline-acetyltransferase
<table>
<thead>
<tr>
<th>Drugs modulating release and inactivation of ACh</th>
<th>Botulinum Toxin (BoTox)</th>
<th>Inhibit release of ACh vesicle into synaptic junction • Treat Blepharospasm</th>
<th>BoTox endocytosed→light chain cleaves specific SNARE protein→SNARE complex doesn’t form→no membrane fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinesterase</td>
<td>Inhibit inactivation of ACh, prolong ACh effect • Variable selectivity: btn neuromuscular junctions and postganglionic parasympathetic junctions • Variable CNS access • Variable duration of action (short→irreversible) Irreversible: oranophosphates : can be reversed by Pralidoxime</td>
<td>Inhibit Acetylcholine Esterase (AChE)</td>
<td></td>
</tr>
<tr>
<td>Anticholinesterase</td>
<td>Physostigmine</td>
<td>Selective for parasympathetic junction, used to treat glaucoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neostigmine</td>
<td>Selective for neuromuscular junction • Reverse effect of non-depolarising neuromuscular blockers Treat Myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>Cholinceptor Agonist</td>
<td>Carbachol</td>
<td>Non selective for both Mus/Nic activity , NO hydrolysis by AChE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methacholine</td>
<td>Major Mus, minor Nic activity, YES hydrolysis by AChE</td>
<td></td>
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<tr>
<td></td>
<td>Bethanechol</td>
<td>GIT or Bladder paralysis Only Mus activity, NO hydrolysis by AChE</td>
<td></td>
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<tr>
<td></td>
<td>Pilocarpine</td>
<td>Glaucoma</td>
<td></td>
</tr>
<tr>
<td>Cholinceptor Antagonist</td>
<td>Atropine (Mus antagonist)</td>
<td>From Atropa Belladonna (Deadly Nightshade), • local installation: dilated pupils attractive, • greater quantity (systemically): dry mouth, photophobia • Anti-SLUD • Ocular: dilation of pupil and loss of accommodation • Tachycardia (small) • CNS effects: agitation, restlessness, disorientation, coma • Reduce secretion (in anaesthesia) • AChE-inhibitor poisoning</td>
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<tr>
<td></td>
<td>Hyoscine</td>
<td>Mus antagonist, Helps motion sickness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ipratropium</td>
<td>Mus antagonist, Treat Chronic Obstructive Pulmonary disease (COPD)</td>
<td></td>
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<tr>
<td></td>
<td>d-tubocurarine (Curare)</td>
<td>Nic Antagonist • Neuromuscular blocking agent: treat surgical paralysis, replaced by Vecuronium • Competitive reversible antagonist: block reversed with neostigmine • Less effective at ganglia, need high concentration • Receptor differ skeletal muscle vs Autonomic Ganglia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hexamethonium (S4)</td>
<td>• Nicotinic receptor antagonist, both parasympathetic/sympathetic ganglia • Ganglion Blocking drug • Can cause large drop in Blood Pressure • Direct nerve stimulation on local tissue gives indication of such tissue controlled by PNS or SNS.</td>
<td>If addition of HEX has no impact on response to direct nerve stimulation (tissue), there is the absence of nicotinic receptor, which means the stimulation is on SNS.</td>
</tr>
</tbody>
</table>

Nicotinic receptor signalling: agonist binds to receptor allow influx of Na+→skeletal muscle contraction (NMJ)/AP initiation/propagation (Ganglia)

M3 receptor (smooth muscle, glands): →Gq &GTP→↑Phospholipase C→↑IP₃,DAG from membrane PIP₂→↑Ca²⁺ mobilisation & PKC activation→↑GIT contraction secretion
M2 receptor (cardiac): →GI & GTP→↓Adenylate cyclise→↓cAMP→↓Cardiac Rate/Force

Co-transmission: Rapid response: Ach (PNS) or ATP (SNS), intermediate response: NO (nitric oxide, PNS) or NA (SNS), slow response: VIP (vasoactive intestinal polypeptide, PNS) or NPY (neuropeptide Y, SNS, enhance NA)

Cholinceptors: muscarinic: post-ganglionic PNS & sweat gland (SNS)

Acetylcholine (&CoA) → Ach in vesicle (through Ach carrier)

I. Ca²⁺ dependent ACh release from synaptic junction

Influx of Ca²⁺ trigger release of synaptic vesicles to synaptic junction

II. ACh inactivation

Breakdown by Acetylcholine Esterase (AChE) into Choline (&acetate)

Drugs modulating release and inactivation of ACh

Botulinum Toxin (BoTox)

Anticholinesterase

Physostigmine

Neostigmine

Cholinceptor Agonist

Carbachol

Methacholine

Bethanechol

Pilocarpine

Muscarine: only Mus activity, Nicotine: only Nic activity. BOTH no hydrolysis by AChE

Atropine (Mus antagonist)

From Atropa Belladonna (Deadly Nightshade), local installation: dilated pupils attractive, greater quantity (systemically): dry mouth, photophobia Anti-SLUD Ocular: dilation of pupil and loss of accommodation Tachycardia (small) CNS effects: agitation, restlessness, disorientation, coma Reduce secretion (in anaesthesia) AChE-inhibitor poisoning

Hyoscine

Ipratropium

d-tubocurarine (Curare)

Nic Antagonist

Hexamethonium (S4)

• Nicotinic receptor antagonist, both parasympathetic/sympathetic ganglia • Ganglion Blocking drug • Can cause large drop in Blood Pressure • Direct nerve stimulation on local tissue gives indication of such tissue controlled by PNS or SNS. If addition of HEX has no impact on response to direct nerve stimulation (tissue), there is the absence of nicotinic receptor, which means the stimulation is on SNS. |
### Nicotinic: Skeletal Muscle Response & Ganglionic Transmission & Stimulation of Adrenal Gland

- Adrenocceptor: A & B: SNS (except sweat gland) & circulating adrenaline

Nicotinic receptors belong to PNS usually in local tissue (long preganglion), belong to SNS usually NOT in local tissue (short preganglion near spinal cord).

### Benzodiazepines
- Non-competitive Allosteric modulation
  - Increase the affinity of the receptor for GABA

### Bioactive Lipids

#### Arachidonic Acid (Eicosatetraenoic Acid, C20:4)
- A precursor for biologically active lipids
- Source: poly-unsaturated fatty acids (PUFAs), diet: usually dominated by omega-6 PUFAs
- Directly as C20:4
- Indirectly as C18:2 → elongation to C20:2 → desaturation to C20:4
- Transport bound to plasma proteins
- Very little "free" either extracellularly or intracellularly
- Deep sea fish enriched in Omega-3: C18:3 & C20:5, ↓production of active arachidonic acid metabolites
- Storage: esterified in membrane phospholipids
- Release: by Phospholipase A2 (may contain in snake venoms): activated by increase in intracellular calcium

#### Eicosanoids (metabolised from arachidonic acid)
- Biologically active metabolites of arachidonic acids
  1. **Cyclooxygenase** expressed in all cells
     - Constitutive (COX-1) → physiological prostaglandins (PGs)
     - Inducible (COX-2) → gene induced by inflammatory stimuli (e.g. interleukin-1)
     - Patho(physiological) PG overproduction
  2. **Lipoxygenase** expressed in inflammatory cells: eosinophils and mast cells
     - Production associated with inflammation

#### Arachidonic acid

- → Cyclooxygenase (COX-1 & COX-2) → Cyclic Endoperoxides (unstable) (& Isomerases)
  - PGD_2, PGE, PGF (stable prostaglandins) & PGI_2 (Prostacyclin) & TXA (Thromboxane A_2)
- → 5-lipoxygenase → SHPETE → LTZ, LTD, LTE

#### Prostacyclin
- Chemically unstable, half-life ~3mins
- Produced by endothelial cells
- Reduces platelet activation
- Vasodilator
- Protects against coronary artery disease

#### Thromboxane A_2 (there is corresponding antagonist)
- Chemically unstable, half life ~ 30sec
- Produced by platelets
- Increases platelet activation
- Vasoconstrictor
- Promotes coronary artery disease
- **OPPOSE to PGI_2**

#### 5-lipoxygenase (can be inhibited by 5-LOX and LT-receptor inhibitors)
- Restricted in distribution to inflammatory cells
- No known physiological role
- Activated by increase in intracellular calcium by stimuli produced in infection, allergic responses and other forms of inflammation

#### Aspirin (68% bioavailability)
- Vd=0.1L/kg
- Inhibits both types of COX
- Aspirin overdose: administer NaHCO_3 → makes urine basic → ↑amount of ionised aspirin (negatively charged), ↓reabsorption, ↑excretion

#### "Coxib" drugs (e.g. celecoxib)
- Selective for inhibition of COX-2

#### Glucocorticoids (& NSAIDS)
- Influence PG production
  - I. reduced induction of the COX-2 gene
  - II. reduced induction of TNF & IL1 genes (these cytokines are triggers of AA metabolism)
  - III. increased induction of annexin-1 gene (annexin-1 is a protein inhibitor of PLA_2)
  - IV. suppress inflammatory cytokines (ie. Interleukins)

#### Cysteinyl leukotrienes (LTC/D/E)
- Slow reacting substance of anaphylaxis (SRS-A)
- Bronchoconstrictor
- Vasoactive
- Leaky vessels → tissue oedema
- Implicated in asthma

**Leukotriene receptor antagonists** block cysteinyl-leukotrienes (eg. Montelukast)
**Leukotriene B<sub>4</sub>**
- No direct actions on smooth muscle
- Promotes inflammation by attracting leukocytes

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Action of drugs: local vs systemic</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>First-pass hepatic metabolism</th>
<th>Following oral administration only, directly enters hepatic portal vein, transferred directly to liver (can be extensively metabolised or rendered inactive during metabolism) $\downarrow$ amount of blood circulation</th>
<th>Pathway to avoid: skin, lungs, nose, rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic administration</td>
<td>Injectable: subcutaneous (sc), intramuscular (im), intravenous (iv)</td>
<td>Avoids first-pass hepatic metabolism</td>
</tr>
<tr>
<td>Absorption → lipid diffusion</td>
<td>Factors affecting: aqueous solubility (drug must be in solution) and lipid solubility (cross cell membrane)</td>
<td></td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Proportion of active drug which enters systemic circulation Oral: e.g. diazepam 100%</td>
<td>Factors: amount absorbed, amount undergoes first pass hepatic metabolism</td>
</tr>
<tr>
<td>Drug distribution</td>
<td>Uneven distribution across body, distribution faster than elimination (simultaneously, distribution equilibrium)</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution: (apparent) volume of body water which drug appears to be dissolved in after distribution in body ($V_d = X/C$)</td>
<td>Steps: blood (all drugs) (some limited to here as it’s protein/bound to protein) $\rightarrow$ ECF (only those able to escape vasculature: small and not protein bound, evenly distributed) $\rightarrow$ bind to cells/uptake into cells (lipid solubility, able to cross cell membrane) $\rightarrow$ some may bind extensively to tissues, $V_d$=total body water volume</td>
<td>Vd: plasma volume (0.06L/kg) ECF volume (0.2L/kg) Total body water volume (0.6L/kg) e.g. mannitol: 0.2L/kg, ethanol: 0.6L/kg digoxin: 6L/kg $V_d$ can tell you how much drug will give (intravenous) a particular concentration of drug in plasma ($X=V_dX/C$)</td>
</tr>
<tr>
<td>Drug elimination:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excretion (kidney) or/and metabolism (liver)</td>
<td>Renal excretion: passive removal from blood, NOT for drugs bound to plasma protein Tubular secretion: removal uses active carrier, able to remove protein-bound drug, can be competitively inhibited Tubular reabsorption: passive reuptake, pH dependent, principles developed for absorption apply, can be manipulated clinically in overdose (aspirin overdose)</td>
<td></td>
</tr>
<tr>
<td>Renal clearance (ml/min): $CL_{renal} = GF + TS - TR$</td>
<td>Drug metabolism (biotransformation): chemical change to drug, enzyme-catalysed, mainly in liver (occurs in most tissues), $\uparrow$ water solubility ($\downarrow$ lipid solubility, harder to cross membrane) $\rightarrow$ $\uparrow$ excretion</td>
<td>Metabolites can be inactive, active, have a new activity, or can be toxic</td>
</tr>
<tr>
<td>Stages of metabolism: phase I: creates chemical functional group (e.g. –OH, NH$_2$, -SH, -COOH) on drug. Phase II: conjugation of water soluble molecules to functional group on drug. e.g. glucuronidation, sulphation, acetylation, glutathione conjugation (major detoxification process).</td>
<td>Drug elimination process: drug can be: 1) directly excreted 2) phase I metabolite $\rightarrow$ excreted 3) phase II metabolite $\rightarrow$ excreted 4) phase I metabolite $\rightarrow$ phase II metabolite $\rightarrow$ excreted</td>
<td></td>
</tr>
<tr>
<td>Cytochrome P450</td>
<td>Superfamily of enzymes, responsible for many phase I drug metabolism reactions (oxidation), action can be inhibited or enhanced by drugs leading to a drug-drug interactions.</td>
<td></td>
</tr>
<tr>
<td>One compartment model (distribution)</td>
<td>Dugs distribute rapidly, behave as if in a single compartment.</td>
<td></td>
</tr>
<tr>
<td>First-order kinetics</td>
<td>Absorption/elimination of drugs proportional to the amount of drug present in blood.</td>
<td></td>
</tr>
</tbody>
</table>
| Measure drug concentration in plasma (first order elimination) | • rapid intravenous administration (amount administrated → amount of drug in body → amount of drug eliminated)  
• rapid rise (concentration in blood vs time graph) → display an exponential decay curve  
• drug has half life (quantifies its persistence in the bloodstream)  
• peak concentration can be determined from Vd (X=Vd X C)  
• oral administration  
• delay until peak is reached (concentration in blood vs time graph) → complex concentration vs time profile (the changing rates of drug in and out of the blood)  
• peak lower than iv: some elimination during absorption  
PLUS: might not completely absorption, part might undergo first pass hepatic metabolism (reduced bioavailability) |
| --- | --- |
| Probenecid | Banned  
• Competes with other drugs for tubular secretion  
• Reduces renal excretion of acidic drugs  
• Masks appearance of other banned substances in urine |
| Evolution of Medical therapies |  
| Hippocrates (460BC-370BC): disease is production of environment, diet and lifestyle Humorism  
| Galen (129AD-200AD): Humours produces personality (dominant for 1300-1700)  
| Vesalius (1514-1564): Human dissection (anatomy); Disprove Galen, great influences |
| Drug Discovery to Clinical Used |  
| Scientific Development: Drug candidate | Target selection (in vitro): lead finding & optimisation, pharmacological profiling  
Animal testing: pharmacokinetics, formulation synthesis.  
& monitor short term safety, long term safety (extended to clinical development) |
| Clinical Development: development compound | Human Testing:  
Phase I: clinical pharmacology: safety?, 20-50 healthy  
Phase II: clinical investigation: appropriate dose?, 50-300 healthy/small number of diseased  
Phase III: formal therapeutic trials: effective? 250-1000+ diseased  
Accelerated development: straight from Phase I to clinical use.  
Long term safety monitoring |
| Clinical use: approved drug | Post marketing surveillance  
Phase IV: post-marketing studies: safety? efficacy?, 2000-10000+, licensed for use, reporting adverse events in individuals, side effects (inc. long term & rare) |
| Reality and validity of testing result |  
| Eliminate/minimise:  
• Biased: single blind vs double-blind experiment  
• Variability: randomisation  
• Confounding issues:  
controls (no treatment/current treatment): cross-over experiment (patient acts as own control, washout between treatments)  
• Ethics: denial of effective treatment (no treatment/placebo) unethical, must aim to improve existing clinical outcome,  
• Informed consent: respect, trust, mutual responsibility, ethical equality, voluntary, based on sufficient information, understanding of benefits and possible risks, achievable for all? |
| Placebo effect | Influencing effect  
- Natural history of the disease (diabetics vs sugar pills)  
- Patient factor difficult to predict: positive vs anxious, compliant vs non-compliant  
- provider factors: knowledge of treatment, empathy  
Explanation  
- decreased anxiety  
- patient expectations  
- learning (past experience)  
- endorphin effects  
- unknown physiological effects |
| Homeopathy | Like cures like, serial dilution >12C, no original substance left, theory of water memory, theory of potentiation, serial dilution: 2C=1:10^4, nC=1:10^n |
| Drug control schedule |  
2: therapeutic use, labelled as PHARMACY MEDICINE, from pharmacies and licensed retailers, able publicly advertised  
e.g. Nurofen (ibuprofen) (unscheduled if <25 packs)  
3: therapeutic use, labelled as PHARMACIST ONLY MEDICINE, supplied by a pharmacist personally, pharmacist advice, no public advertised  
e.g.: sedating antihistamine, β-agonist asthma sprays, codeine - combination analgesics, pseudoephedrine, Nurofen Plus (S3) (ipuprofen & codeine phosphate)  
Panadeine Extra (S3) (paracetamol & codeine phosphate)  
Codial Day & Night (New formula S2, old formula S3)  
4: Prescription from medical professionals, labelled as PRESCRIPTION ONLY MEDICINE or PRESCRIPTION ANIMAL REMEDY, strictly NO publicly advertised, possession without authority is illegal  
e.g. antibiotics, psychotropics, blood pressure drugs, “statins”, diabetes drugs, Diaformin (metformin) (S4) |
5: Hazardous household substances, labelled as **CAUTION**, available everywhere, sold in original pack, eg: liquid hydrocarbons, weak mineral acids, garden chemicals
6: More toxic substances for agricultural or industrial use, labelled as **POISON**, available everywhere, sold in original pack, eg: stronger acids and alkalis, eucalyptus oil
7: Very dangerous poisons with specialised non-therapeutic uses, labelled as **DANGEROUS POISON**, special controls on handling, some obtain only with permit, e.g. some organophosphorus compounds, cyanide, strychnine, arsenic
8: drugs of **addiction**, labelled as **CONTROLLED DRUG**, prescription only, possession without authority is illegal, high security and detailed records, e.g. morphine, pethidine, oxycodone (ENDONE), amphetamine
9: **prohibited** substances, high likehood of abuse, not for therapeutic use, permitted for research or analytical use, approved use only, e.g. heroin, cannabis, hallucinogens

### safety
- Balance between risks vs benefits,
- suitable labelling and packaging,
- limitations on purpose of use,
- limitations on dose/frequency/duration,
- distribution controls through scheduling

### Efficacy
- Reasonable expectation that medicine will performed as claimed
- Advertising limitations
- Individual produce evaluation
- Product registration
- labelling

### Registered goods (DEFAULT)
- Evaluated for safety, quality and efficacy,
- Manufacturers are licensed by the TGA
- Rigorously evaluated by separate independent expert committees

### Listed goods
- Individual ingredients are generally recognised as safe, no evaluation for efficacy
- Presumed to meet quality standards
- Manufacturers licensed by TGA,
- product is NOT evaluated by TGA
- most herbas, vitamins, minerals etc eligible for listing, SUNSCREEN must meet performance standards
- Designated AUST L.... on label

### Orphan Drugs
- Drug, vaccine or in vivo diagnostic agent must be intended to treat, prevent or diagnose a RARE disease (<2000 individuals in AUS) and NOT be commercially available to treat another disease
- “designated Orphan Drugs”
- Included in the Australia Register of Therapeutic Goods

---

### Drug Discovery

**THEN**

**Observation**

Tradition: knowledge of medical properties of plants (e.g. morphine from opium poppies)
In the laboratory: combination of good fortune and good science (e.g. penicillin from Penicillium mould)
In the clinic: sulphonamide (antibacterial drugs) seen to lower blood glucose
→Gave rise to tolbutamide (S4) and other orally-acting hypoglycaemics drugs (S4), treatment of non-insulin dependent diabetes

**Serendipity**

Luck, accidents, wrong hypotheses

**Screening**

- Take a naturally occurring source of compounds: e.g. plants, microorganisms
  →(partially) purify →assay for activity
- Bacteria, yeasts grown in fermentation vats
  →subjected to stress →extracts tested for activity

**Synthetic chemistry**

Major focus of pharmaceutical companies:
- synthetic version of natural product,
- modified natural product, entirely new drug,
- realised could be a way to improve in nature

**Discovery of Penicillin** (observation in lab)

**Before B.C.:** moulds used to treat skin infections

**Late 1800s:**

Louis Pasteur: mould inhibited anthrax growth
Joseph Lister: mouldy urine prevented bacterial growth

**1926:** Alexander Fleming: mould on petri dish prevented grown of streptococcus
  →Penicillium notatum

**1938:** Howard Florey assembles team at Oxford University
Ernst Chain reads of Fleming’s discovery

**1940:** Penicillin used successfully to treat 4 mice infected with streptococcus
**1941:** First human patient treated
**1943:** Mass production begins in US
**1945:** Nobel Prize awarded to Florey, Fleming and Chain

Structure unknown, mechanism unknown, toxicity not well understood