

Drugs

- **Nifedipine**- blocks Ca^{2+} channels for reduced blood vessel constriction and therefore reduced blood pressure
- **Fluoxetine**- blocks serotonin uptake into nerves, prolonging serotonin action and used for major depressive disorder. It is a **selective serotonin reuptake inhibitor**. It has various nuisance side effects such as insomnia, sexual dysfunction (only effect that doesn't wear off while still taking SSRI), GIT disturbances and restlessness. Has a high therapeutic index (minimal toxicity in overdose unless combined with other drugs).
- **Aspirin**- inhibits both types of COX, acting covalently to modify the active site of COX by acetylating the serine, reducing the synthesis of mediators of pain/fever/inflammation. In overdose we administer sodium bicarbonates to make the urine basic (aspirin is acidic) such that the basic solution will cause an increase in the amount of ionised aspirin and thus will reduce absorption and increase excretion. High doses lead to ulcers.
- **L-dopa**- prodrug converted by dopa decarboxylase which increases the synthesis of dopamine for Parkinson's disease
- **Fluorouracil**- false substrate that replaces uracil as an intermediate in purine biosynthesis- inhibiting DNA synthesis
- **Morphine**- μ -Opioid receptor agonist used for pain, is naturally occurring. It acts in the CNS to cause analgesia, euphoria, respiratory depression (reducing sensitivity of medullary respiratory centre for CO_2), nausea and vomiting, pupillary constriction (classical pinhole pupil-stimulation of oculomotor nucleus- important diagnostic feature for overdose) and is antitussive (cough suppression). In the periphery, morphine will act on the GIT to cause constipation (as μ receptors on myenteric neurons decrease acetylcholine release- decreasing motility) and causes histamine release from mast cells (not mediated by opioid receptors) causing bronchoconstriction (triggers asthma), vasodilation (reducing blood pressure) and itching. Morphine is normally administered intravenously or intramuscularly with oral absorption being variable (bioavailability=25%), there have been slow release oral preparation for chronic pain. It undergoes significant hepatic metabolism (metabolised to **morphine 6-glucuronide**- more potent analgesic -4-6 fold but poor CNS entry). Morphine has plasma half-life of 3-6 hours (12-24 in slow release oral tablets). Morphine **tolerance** can occur where higher doses are required for equivalent effect (gradual loss of effectiveness). Level of tolerance is dependent on potency of agonist and the route and frequency of administration, with tolerance impacting morphine's ability to cause analgesia, euphoria, sedation, respiratory depression, nausea and emesis (tolerance has no impact on constipation and miosis), the tolerance occurs to all patients on chronic morphine usage. Morphine dependence can also develop where physical dependence leads to withdrawal or abstinence syndrome when morphine is stopped where the reaction is proportional to the level of tolerance and it lasts for days. In psychological dependence, there is a craving for morphine that lasts for months to years. Morphine can be used to treat burns, chronic pain (cancer) and myocardial infarction as well as just a regular analgesic.
- **Naloxone**- opioid receptor antagonist with an affinity for all opioid receptors. It undergoes rapid hepatic metabolism and is administered intravenously (half-life of 1 hour). It normally has no effect on individuals that doesn't use opioids but will induce withdrawal in opioid tolerant patient. It's used for heroin overdose (to reverse sedation and respiratory depression).
- **Salbutamol/terbutaline**- β_2 partial agonist, SABA (short acting β_2 -adrenoceptor agonist-reliever). Acute bronchodilator therapy, rapid onset of action, duration of 2-4 hours and selective for β_2 -adrenoceptor. Adverse effects include β_1 -receptor activation produces tachycardia and β_2 action causes tremor.
- **Glucocorticoid**- steroid hormone that binds to glucocorticoid (nuclear) receptors in the cytoplasm inhibiting synthesis of COX. Useful for asthma treatment (preventer). Three different mechanisms that influence prostaglandin production: reduced induction of COX-2 gene, reduced induction of TNF and IL1 genes (cytokine triggers of AA metabolism) and increased induction of **annexin 1 gene** (protein inhibitor of phospholipase A2). Act by diffusing across membrane, bind to cytosolic receptor, translocates to nucleus to activate and repress some genes. First effect in hours to days and weeks to months to reach maximum therapeutic effect. Used in first-line therapy except in children (disodium cromoglycate used first) and acts to decrease inflammatory cell number and activation. Examples include **budesonide** and **fluticasone propionate** which are used if we need to use β_2 agonist >3 times a week. We start at an effective dose and step down. **Prednisolone** is orally administered (several days) for acute exacerbations (more effective at treating inflammation). Side effects of inhaled glucocorticoids (well tolerated) include changed voice, oral thrush mouthwash while oral glucocorticoids have limiting side effects such as suppression of adrenal/pituitary/hypothalamic axis (lose capacity to produce cortisol), withdrawal, growth suppression and diabetes/hypertension.
- **Yohimbine**- α_2 adrenoceptor antagonist
- **Fexofenadine**- H1 antagonist
- **Verapamil**- inhibits L-type calcium channels. Relaxes smooth muscle (decreasing TPR) and has little effect on veins (no effect on preload) as well as little effect on skeletal muscle (sarcoplasmic reticulum dependent calcium pools).
- **Atropine**- selective inhibitor of acetylcholine- muscarinic antagonist. They reduce secretions (in anaesthesia) to stop bronchoconstriction and used for acetylcholinesterase inhibitor poisoning
- **Mepyramine**- selective inhibitor of Histamine- targets the H1 receptor-antagonist
- **Cocaine**- blocks the high affinity uptake 1 channel (neuronal) stopping reuptake of noradrenaline causing sustained stimulation of the tissue in the periphery. Same action also applies to dopamine, serotonin and adrenaline (biogenic amines) in the CNS (CNS stimulant) with dopamine leading to craving from dopamine acting on reward centre. There are also local anaesthetic properties unrelated to CNS stimulus effects and contributing to convulsions and dysrhythmias. In South American Indians, they ate cocaine which had slow absorption and therefore had more pleasant symptoms and only psychological dependence and minimal tolerance. In western cultures however, cocaine is snorted, smoked or injected and thus leads to higher blood concentration which thus can lead to overdose where there are sympathetic effects of increased heart rate and blood pressure as well as acute fear and psychotic symptoms, tolerance can also develop where higher doses are required for euphoric effects (acute and euphoric) while dependence in cocaine leads to abstinence (withdrawal syndrome) leading to an intense drug-seeking behaviour and depression, anxiety, need for sleep and fatigue.

- **Amphetamine**- indirectly acting sympathomimetic which acts to displace noradrenaline in synaptic vesicles causing the noradrenaline to either be broken down by MAO or pushed into synaptic cleft to act on adrenoceptors. Other drugs that act the same are **ephedrine** and **tyramine**. Same action for that on dopamine, noradrenaline and serotonin in the CNS (CNS stimulant). Effects of it varies with mood, personality and environment with physical and mental performance improving (fatigue postponed with confident, speedy performances but less accuracy). It is an appetite suppressant (as a result of serotonin release inhibiting food intake). Overdose can lead to sympathetic effects such as tachycardia, increased blood pressure as well as anxiety and tremors. Dependence is not as marked as cocaine but it is particularly present in those that are depressive or lonely, leading to withdrawal syndrome (lethargy, sleepy, desire for food and depression)
- **Isoprenaline**- β -selective agonist, may be used for asthma but could cause severe heart palpitations
- **Phenylephrine**- α selective agonist (useful as nasal decongestant)
- **Phentolamine**- α -adrenoceptor antagonist
- **Propranolol**- β -adrenoceptor antagonist, could be used in cardiovascular disease but could worsen asthma (β_2 receptor inhibition)
- **Dobutamine**- β_1 adrenoceptor agonist
- **Atenolol**- β_1 adrenoceptor antagonist (useful in hypertension). There are multiple side effects from **β -adrenoceptor antagonists** where we can get **cold extremities** from a loss of β_2 receptor-mediated dilatation of cutaneous vessels, **fatigue** from β_2 receptor inhibition (skeletal muscle vessels unable to dilate during exercise), **cardiac depression** (particularly in the elderly), **bradycardia** (which is an abnormally slow heart rate and can lead to life threatening blocks in patients with coronary disease) and **bronchoconstriction** from β_2 receptor inhibition which particularly present in asthmatic patients.
- **Prazosin**- α_1 antagonist (useful in hypertension), vasoconstriction inhibitor, decreases noradrenaline mediated vasoconstriction and therefore decreases TPR and blood pressure. Side effects include 1st dose hypotension, initial reflex tachycardia, postural hypotension and nasal congestion.
- **Clonidine**- α_2 adrenoceptor agonist (useful in hypertension- CNS effect)
- **Botulinum Toxin**- blocks exocytosis of acetylcholine out of the nerve terminal. Mechanism of action is that it endocytosed into nerve terminal and breaks into light chain and heavy chain with light chain cleaving SNARE proteins and therefore stopping formation of SNARE complex and therefore no exocytosis.
- **Physostigmine**- selective anticholinesterase for parasympathetic junctions (used to treat glaucoma)
- **Neostigmine**- selective anticholinesterase for NMJ where it reverses effect of (non-depolarising) neuromuscular blockers and treats Myasthenia gravis. Medium duration anticholinesterase drug.
- **Carbachol**- cholinergic agonist not hydrolysed by acetylcholinesterase
- **Methacholine**- muscarinic agonist hydrolysed by acetylcholinesterase
- **Pilocarpine**- muscarinic agonists
- **Hyoscine**- muscarinic antagonist used for motion sickness
- **Ipratropium**- muscarinic antagonist for chronic obstructive pulmonary disease
- **d-Tubocurarine**- nicotinic antagonist- a neuromuscular blocking agent for surgical paralysis and a competitive reversible antagonist (block reversed with neostigmine)-surmountable and less effective at autonomic ganglia as nicotinic receptor at autonomic ganglia is different to that at skeletal muscle. Is used as a non-depolarising muscle relaxant.
- **Hexamethonium**- ganglion blocking drug (nicotinic receptors) that blocks both parasympathetic and sympathetic nervous system causing large drop in blood pressure. Antagonist of nicotinic receptors
- **Tetrodotoxin**- voltage-operated Na^+ channel blocker derived from marine bacterium (not synthesised by organism but rather is bio-sequestered). Potent neuronal sodium channel blocker that stops the propagation of an action potential. It is useful for dissecting various organ systems. Tetrodotoxin doesn't have an antidote.
- **α -bungarotoxin**- tool for purifying nicotinic receptor for structural analysis and for understanding nicotinic receptor, is a diagnostic tool for myasthenia gravis. Binds with high affinity and blocks nicotinic receptors, irreversible antagonistic.
- **Suxamethonium**- depolarizing muscle relaxant (neuromuscular blocking drug) and agonist to nicotinic receptors. Has short-lived actions that are useful for quick surgical procedures. It has differing efficacy-dosage ratios on different individuals due to polymorphic forms of **plasma cholinesterase** which metabolises it (inactivating it). These polymorphic forms alter the enzyme's expression/activity, where an increased activity of plasma cholinesterase will decrease the efficacy of suxamethonium. It has a very high affinity to nicotinic receptors such that it repetitively stimulates the nicotinic receptor such that it can't repolarise and therefore affects the voltage gated sodium channels (as can't repolarise) thus stopping the muscles ability to contract.
- **Celecoxib**- selective for inhibition of COX-2, NSAID. Effective against pain and swelling but can increase risk of myocardial infarction by interfering with production of prostacyclin in coronary artery endothelium.
- **Codeine**- prodrug- active form is morphine, is a naturally occurring opiate. It is also known as methyl-morphine and is less potent than morphine. It's orally active (10% is metabolised in the liver to morphine) with 10% of Caucasians lacking the enzyme leading to no analgesic effect of the drug. Codeine gives little or no euphoria, little respiratory depression, causes constipation and is antitussive (cough suppression) at sub-analgesic doses leading to it being useful in cough mixtures.
- **Paracetamol**- liver damage with high doses
- **Probenecid**- competes with other drugs for tubular secretion, it reduces the renal excretion of acidic drugs and masks the appearance of other banned substances in urine (not performance enhancing but banned in sport)
- **Sodium bicarbonates**- administered to patients in aspirin overdose to make urine basic such that we increase amount of ionised aspirin (as it's acidic) and thus reduce reabsorption and increase excretion.
- **Buprenorphine**- partial agonist at opiate receptor
- **Sumatriptan**- 5-HT₁ receptor partial agonist
- **Tensilon (edrophonium)**- used as part of diagnosis of myasthenia gravis and is a short-acting anticholinesterase

- **Glyceryl trinitrate (GTN)**- prodrug that's converted to nitric oxide and stimulates guanylate cyclase causing a rise in cGMP and vasodilation. It dilates veins (reducing preload on heart and therefore myocardial O₂ demand-consumption- as not pushing blood to the heart), dilates arterioles (reducing afterload- less TPR as less systemic vascular resistance, also reduces cardiac work) and it dilates coronary collateral vessels (increasing blood delivery to ischemic myocardium) and relieving vasospasm. Administered sublingually, non-ionic and very high lipid solubility, absorbed rapidly and very potent, surpasses hepatic first-pass metabolism as goes from mouth to SVC. Side effect that it may cause reflex tachycardia and an increased vascular tone (increasing TPR)
- **Captopril and enalapril**- ACE inhibitors- help to relieve hypertension and cardiovascular structural changes. Side effects of 1st dose hypotension, hyperkalaemia (K⁺ retention), acute renal failure, dry cough.
- **Losartan**- AT1 receptor antagonist- side effects of 1st dose hypotension, hyperkalaemia, renal problems but no dry cough (as no rise in bradykinin)
- **Dihydropyridines**- L-type Ca²⁺ antagonists and include **nifedipine**, felodipine and amlodipine. Cause arterial smooth muscle to relax and therefore decrease TPR, are vascular selective. Have adverse effects of reflex tachycardia, palpitations, nausea, flushing and headache.
- **Salmeterol and Formoterol**- Long-acting β_2 -adrenoceptor agonists (LABA-controllers). Salmeterol has slow onset and formoterol has rapid onset with both having 12 hours duration. Indicated for preventing the disease and are used only in combination with inhaled glucocorticoids.
- **Zafirlukast and Montelukast**- Cysteinyl leukotriene receptor antagonists which are orally active and cause modest bronchodilation and used in combined therapy with glucocorticoid/ β_2 agonists (thus lesser dose of individual ingredients for same effect). Useful in patients with aspirin-induced asthma due to them overproducing leukotrienes resulting from aspirin inhibiting COX thus taking lipoxygenase pathway. Few side effects with liver function may be impaired.
- **Disodium cromoglycate**- Non-steroidal anti-allergic drugs (preventers). Administered by inhalation as not orally active and reduce mediator release (diminished mast cell and sensory nerve activation). Modest anti-inflammatory activity (preferential use in children), side effects include some irritation following inhalation (bronchospasm possible).
- **Omalizumab**- targets B lymphocyte which makes IgE, thus reducing sensitisation of mast cells by IgE reducing the airway of mast cells. It is a humanised murine monoclonal antibody that is administered subcutaneously. It will bind to the Fc portion of IgE reducing the serum IgE, preventing it from binding to the Fc ϵ R1 receptor on mast cells and therefore reducing asthma and allergic symptoms. Not orally active as protein (antibody) will be broken down in stomach and adverse effects are few and mild.
- **Natalizumab**- humanised monoclonal antibody against $\alpha_4\beta_1$ co-ligand for vascular cell adhesion molecule and fibronectin. Used in treatment of multiple sclerosis by preventing leukocyte entry into the CNS and increases the risk of PML.
- **Antihistamines**- decrease actions of mast cell products- H1 receptor antagonists or leukotriene receptor antagonists.
- **Cyclosporin**- fungus derived cyclic peptide and first specific immunosuppressant (acting on subset of lymphocytes). Has variable pharmacokinetics and significant adverse effects (particularly renal failure), cyclic shape allows it to be used as a drug as it persists for long periods of time (not easily metabolised). Acts by binding to **immunophilin** in lymphocytes which inhibits **calcineurin** and therefore the proliferation of T cells and therefore stopping graft rejection.
- **Azathioprine**- non-selective cytotoxic for cancer chemotherapy by reducing cell division in bone marrow leading to neutropaenia (low level of neutrophils) and thus an increase in likelihood of infection.
- **GCSF**- granulocyte colony stimulating factor, boosts immune response after chemotherapy by expanding number of precursors for neutrophils, allowing us to overcome mechanism based toxicity of chemotherapeutic agents.
- **Cimetidine**- H2 receptor antagonist used to treat gastric ulcers.
- **Zanamivir**- anti-influenza drug that targets the neuraminidase surface proteins by acting to inhibit it and therefore stop newly-formed viruses to escape cells and their movement through the mucous in the respiratory tract. It is a potent inhibitor of neuraminidase. Must be administered by puffer and needs to be given early in infection
- **Imatinib**- anti-tumour agent and selective tyrosine kinase inhibitor. Approved for use for chronic myeloid leukemia. Lead compound was PKC inhibitor and converted into selective tyrosine kinase inhibitor that is aqueous soluble and has an improved oral bioavailability. Binds to the active site of ABL kinase to slow CML, but resistance is common.
- **Biological**- drug derived from antibody or protein, including EPO or GCSF. Can cause a receptor blockade, ligand blockade, depletion, receptor downregulation or signalling induction. Problems with biologicals not being optimal (often rapidly hydrolysed, don't readily cross cell membrane, not orally bioavailable). Also problems with immunogenicity of how to humanise antibodies derived from other species.
- **Loratadine**- is an anti-histamine drug
- **Ethinylestradiol**- synthetic oestrogen oral contraceptive that is used in most oral contraceptives that contain oestrogen and is used in hormone replacement therapy. As an oestrogen it can cause nausea, weight gain from fluid retention and mild anabolic activity. Acts to reduce release of FSH.
- **Levonorgestrel**- an old synthetic progestogen oral contraceptive. It is prominent in morning after pill to be bought over counter within 72 hours of sex, containing a high dose of levonorgestrel with an 84% efficacy- earlier taken the better. Disrupts uterine lining to stop implantation from occurring. They thicken cervical mucus making it more difficult for sperm to pass through, change properties of endometrium making it unfavourable for implantation of an embryo and they can interfere with the coordinated contractions of the cervix and fallopian tubes that facilitate fertilisation and implantation.
- **Cyproterone**- new synthetic progestogen oral contraceptive. Is a derivative of progesterone, has anti-androgen activity for PCOS, was used in the past as a chemical castrator and has no diuretic effect and thus may cause weight gain. Useful when combined with oestrogen in the oral contraceptive pill for women suffering from acne and excess hair. Derivative of progesterone. They thicken cervical mucus making it more difficult for sperm to pass through, change properties of endometrium making it unfavourable for implantation of an embryo and they can interfere with the coordinated contractions of the cervix and fallopian tubes that facilitate fertilisation and implantation.