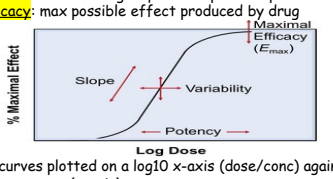
Pharmacology 1 Final Exam Notes

Pharmacology 1 (University of Technology Sydney)

Introduction
- Drugs interact w. specific moles = Drug targets (recep, ion channel, pump, active site on enzyme [sometimes chemicals in body])
- "-azine" = Phenothiazine antipsychotics. "-azepam" = Most antianxiety drugs (Benzodiazepines). "-caine" = Local Anaesthetics. "-pril" = ACE inhibitors. "-olol" = Most beta-recep antagonists
- Potency: Conc. of drug required to produce particular effect, Efficacy: max possible effect produced by drug



- DR-curves plotted on a log10 x-axis (dose/conc) against % of max response (y-axis)
- RCA: Progaressive inhibit, Shift right, ED_{50}↑. Reversible by ↑agonist. ICA: Dissociates slowly or not @ all, E_{max}↓, ED_{50} unchanged. NCA: ED_{50}↓, E_{max}↓
- Desenss & tachyphylaxis: Drug eff grad dimin. - due to change in recep, exhaust of mediators
- Tolerance caused by ↑metabolism degradation, physiological adaptation, translocation of recep
- Therap index = LD_{50}/ED_{50}, Greater ratio = safer, >1.0 therapeutic agent, <2.0 toxicity @ therapeutic dose

Absorption
- Mainly passive diffusion
- pH partitioning: Weak acid = AH <-> A^- + H^+. pH = pKa + $\log_{10}[A^-]/[AH]$. Weak base = BH^- <-> B + H^+. pH = pKa + $\log_{10}[B]/[BH^+]$
- Ionised = unionised if pH = pKa
- Weak acids (pKa >3) or weak bases (pKa <7) pref. absorb
- Alkalinisation of urine: ↑rate of weak acid excretion (+ ionised). Acidification of urine: ↑rate of weak base excretion (+ ionised). ↑Plasma pH: shift weak acidic drugs from CNS to plasma (+ ionised)
- *Routes of admin: Oral, Injection (subcutaneous, intramuscular, intravenous, intrathecal), Sublingual & buccal, Rectal, Vaginal, Ocular, Otic, Nasal, Inhalation, Nebulization, Cutaneous, Transdermal*

Oral
- 1st-pass metab: Via liver before enter system circ.
- Difficulties: Irreg absorb - depend on stomach contents, GI irritation, low pH may inactiv certain drugs, particle size (sml = rapid), requires Pt compliance.

Sublingual
- Under tongue, rapid absorb, avoid gastric exp & 1st-pass

Intravenous
- Precise, accurate, fast eff - Suitable for lrg vol/mixture
- Emergency use - high MW protein & peptide drugs
- Greater risk of ADRs - inject slowly, not suitable for oily/poor soluble sol"/drugs

Intramuscular & Subcutaneous
- Prompt absorb from aqueous sol", but slow & sustained from repository prep.
- Suitable for poor soluble suspensions/SR implants, moderate vols, some irritating substances - Self-admin
- Not suitable for large vols, pain, necrosis @ inject site
- Precluded during anticoagulant therapy
- May interfere w. interpret of certain diagnostic tests

Rectal
- Local/systemic effect
- Unconscious Pt, children (poor IV access), Pt is vomiting
- Easy to terminate - absorb varies, good for drugs aff bowel (laxatives/cathartics/drugs for ulcerative colitis)

Spinal/Epidural
- Delivery of LA/opioids for pain control
- Preferred > GA in lower abdo/limb surgery or childbirth

Topical
- Mucosal Memb/Skin - Dermal/Transdermal - Stable blood lvl, No 1st-pass - must be potent/lipophilic

Distribution
- Depends on: permeab across barriers, binding within compartments, pH partition, lipid solubility
- Strongly protein bound - stay in plasma (~3L), Lipid insoluble stay in plasma/extracellular fluid (~15L), Lipid soluble reach all (may accum. in fat) (~40L)

Plasma Protein Binding
- Albumin: binds slightly to H_2O sol drugs (weak acid/base)
- α_1-acid glycoprotein & β-globulins - binds mainly weak bases
- Free Frctn (% unbound) is <10% slight variations can have important conseq. - potential drug interactions
- Strong+ affinity will displace weak+ - Imp. if also ↓elim.

Volume Distribution
- Vol of fluid required to contain total amt of drug (Q) in body @ conc. present in plasma (C_p)
- Loading dose = target plasma conc.*Vol of distrib" (V_d)
- Assumes drug must be instant distrib", no metab occur, no portion of drug been excreted/sequestered)

Drug Metabolism
- Enz convert of 1 chem entity to another in body
- Termin. drug action, allows for rapid elim of drug, most occur in liver via microsomal & nonmicrosomal enzyme react"
- Lipophilic drugs have polar/charged groups added in liver
- Phase 1 (Bioactivation): REDOX, Hydrolysis, Catabolic reaction, gen. functional/reactive group.
- Products can be + reactive/toxic than precursor
- Phase 2: Conjugation w. hydrophilic groups, anabolic reaction, usual results in inact. compounds

Biliary & Faecal Excretion
- Unabsorbed Orally Administered drugs excreted via faeces
- Low MW (<325 rats, <500-700 humans) drugs poorly excreted in bile, above MW some compounds transferred from plasma > bile > GIT > faeces in appreciable amounts

Enterohepatic Recirculation
- Bile acids allow absorb of fats/fat soluble stuff > deliver to duodenum - 95% of bile acids reabsorbed in ileum > Portal vein delivers back to hepatocytes > extract bile acids
- β-glucuronidase from gut microflora removes glucuronide, reform original drug > re-enter hepatic circulation

Drug Clearance (CL)
- Plasma vol cleared of drug per unit time (L/hr)
- Relates rate of drug elim to plasma conc. (C_p) (mg/L)
- Rate of drug elim = C_p x CL (mg/hr)
- CL is same @ diff. therap doses (Q) - not in overdose
- $CL_{total} = CL_{renal} + CL_{non\text{-}renal}$
- $CL_{renal} = CL_{filtrn} + CL_{secretn} - CL_{reabsorb}$

Half-Life
- 1st-order kinetic - direct proportional to V_d & inv proportional to CL
- Initial plasma conc. (C_0) = Q/V_d

Repeat Dosing
- Dosing interval <4.5 x $t_{1/2}$ = drug accum.
- <4.5 x t1/2 rate of drug elim = rate of drug absorp/supply = max accum. = steady state (C_{ss})
- Infusion rate = C_{ss} x CL
- Less often a drug is given, greater fluctuations in C_p
- Elim = Excret" + metab

Two Compartment Model
- Fast & slow phase of drug loss from plasma noted
- Fast characterised as distrib" from plasma to tissue, slow equates to elim from plasma

Zero-order Elimination
- Theoretic all drugs could saturate their metab pathways
- For most drugs: occurs above therapeutic conc
- Rate of elim independent of drug start conc
- $t_{1/2}$ dependent on drug starting conc
- *Ex: Aspirin, Ethanol, Quinidine, Heparin, Phenytoin*

ADR
- Related costs exceed cost of meds: surgery, lost productivity, hospitalization
- Causes:
  - 2/3 patient visits result in prescription
  - ADR ↑exponentially w. 4 (or +) meds
  - Drugs w. rare toxicity >100,000 patients must be exposed to gen a signal (after drug marketed)

Individual Variation to Drugs
- Idiosyncratic - qualitative diff.
- Cause: Age, pharmacogenetics, disease, idiosyncratic reaction, drug interaction

Age & Drugs
- Changes in drug action in elderly due to degrad of func in heart, liver, kidney, low enz activity, CYP450, glucuronyltransferase, acetyltransferase, plasma ChE
- Slow hepatic conjugation of: Morphine during labour, Chloramphenicol in babies
- Cardiac output decline = ↓blood flow proportional to liver/kidney
- ↓GFR w. age w. ↓d creatinine clearance rate
- ↓Albumin = less plasma protein binding & + free drug
- Same plasma drug conc. cause diff. eff in young & old
  - BDZ = + confusion & less sedation in old
  - Hypotensive drugs = postural hypotension + common in old than young
- Abacavir: rev. transcriptase inhibitor, highly eff in treating HIV - use limited by severe rashes
- Trastuzumab: Monoclonal antibody > antagonist epidermal grow fact > bind to recep HER2 (occur in tumor tissue) - Used in patients w. breast cancer whose tumour tissue overexpress this recep. No benefit for other patients
- CYP2D6: Extensive metabolizer (EM-normal), Codeine to morphine, rapid relief - many drugs inactivated
- CYP2D6: Poor metabolizer (PM), Codeine to less morphine - many drugs inactivated slowly (+ toxicity)

Effects of Disease
- Liver & kidney: Prolonged drug effects
- Migraine & diabetic neuropathy: Slow drug absorb due to gastric stasis
- <3 fail: ↓Liver perfusion (toxic) - mucosal oedema (↓absorb)
- Hyperthyroidism: ↑Sensitivity to pethidine
- Hypothermia: ↓CL

Drug Interactions
- 3-5% in hospital preventable ADRs
- >6 meds = >80% chance of interaction
- Therap Margin = max. $dose_{non\text{-}toxic}$/ min. $dose_{eff}$
- Drug absorb into system. Circ. > distrib" to site of action & tissue > metab to polar intermediates > elim from body
- Drug interaction nearly always @ Phase 1 metab
- Drugs can be substrate to inducers & inhibitor concurrently; & to multiple enzymes
- *CYP3A4: Inhibited by grapefruit juice*
- Drug can affect renal excret" of another by: inhib of tubular secretion, altered protein binding & filtration altering urine flow or urine pH

Ligand-Gated Ion Channels
- "Ionotropic recep": mainly in fast synaptic transmission
- Several structural families exist- Most common: heteromeric assemblies of 4 or 5 subunits w. transmembrane helices arranged around central aqueous channel
- Ligand binding & channel opening occur in msec
- *Ex: NACh, $GABA_A$ & 5-hydroxytryptamine 3 recep.*

G-Protein Coupled Receptors (GPCRs)
- GPCRs/Metabotropic recep
- Effector: Channel/enzyme, couples w. G-protein - affinity for guanyl nucelotides (GDP/GTP)
- Slow cell activation in secs
- *Ex: Muscarinic ACh, Adrenoceptors*
- Amp of signal: 1 recep can activ many G-proteins > cause effector enz to prod many intracellular 2nd messengers
- Principal 2nd messengers: cAMP, Ca^{2+}, phosphoinositides (IP_3 & DAG)
- Inv intermed G-proteins present in recep-memb complex
- Exists in 2 forms: Active - GTP, Inactive GDP
- Bind guanosine triphosphate (GTP) & GDP, provides link between ligand-activated recep & effector, have intrinsic GTPase activity which spontaneously hydrolyses bound GTP to bound BDP (switch themselves off)
- Targets: adenylate cyclase/cAMP sys., phospholipase C/inositol phosphate sys., Regulation of ion channels

Kinase-linked Receptors
- Effects protein kinases w. direct coupling.
- *Ex: Insulin, Growth Factors, Cytokine Recep*
- Cell activation w. time scale of minutes to hours
- Consist of extracellular hormone binding domain & cytoplasmic enzyme domain
- Enzyme usually protein tyrosine kinase - can be protein serine kinase/threonine kinase/guanyl cyclase
- Ligand binding: conform change in recep causes inactive monomeric recep moles to bind (noncovalently) to one another to form active dimer > Brings together intracellular protein tyrosine kinase domains that become enzyme active > Tyrosine (Y) residues in cytoplasmic domains becomes phosphorylated (by each other) > Enzymatic activity activated to catalyse phosphorylation of substrate proteins > Cross phosphorylation intensifies/prolongs allosteric action of hormone

Nuclear Receptors
- Intracel location, eff gene transcript" & couples via DNA
- *Ex: Sex steroids, glucocorticoids, mineralocorticoids, hormones & vitamins*
- Activation w. time scale of hou
- Agonist-recep complex acting on DNA = transcript" & translat" of mediator proteins/repress" of express" of certain genes w. inhibit" of product" of specific proteins

Receptor Classification
- Based on eff of select antag/representative agonists - diff. in nucleotide sequence - presence of orphan recep

Muscarinic ACh
- Family A: Monoamine, neuropeptide & chemokine recep
- Family B: Calcitonin & glucagon recep
- Family C: Glutamate & GABA recep

Drugs in Pregnancy
- Cat A: Taken by lrg # of women with no proven ↑in frequency of malform or direct/indirect harmful eff. Cat B: (50%): 3 groups (B1, B2, B3)-taken by limited number of women - no ↑incidence of malform or eff on fetus(Differences range from no effects in animals (B1) to evidence of fetal damage in animals (B3)) Cat C: Cause (or sus) harmful eff without causing malform - may be reversible OR No data available. Cat D: Cause (or susp) ↑incidence of fetal malform or irrev damage - benefits may be acceptable despite risk. Cat X:Drugs with high risk - not to be used in pregnancy (or possibility of pregnancy)
- Changes: ↑plasma, ↓maternal plasma albumin conc. to 70-80%, ↓protein bind (fetus albumin conc.↑), ↑cardiac output (↑eGFR, liver perfusion), ↑GFR (↑CL of free drug), estrogen & progesterone alter enzyme lvl (variable), ↑body fat (↑Vd lipid soluble drugs), ↑gastric pH
- Placental transfer: mainly by diff", sml mole = faster transfer, lipophilic drugs cross fast+, fetal pH + acidic - weak bases become + ionised & tend to accumulate
- 40% Drugs taken during preg. are taken during critical period & associated w. teratogenicity
- Majority birth defects (70%) occur w. no recognisable causative factor
- Teratogens: Toxic agent ↑occurrence of structural defect/abnorm./death in embryo/fetus after admin to: female during preg. or directly to developing organism
  - Eff varies depend on: amt & lgth of exp., time of exp., genetic factors, additive effects of other teratogens
  - Teratogenicity confined to agent eff on somatic ©
  - Most potent teratogens lack toxicity in mother but produce malform in fetus - cause death @ high doses (fetal/maternal)
  - Diff teratogens may give sim abnormalities during same critical periods - @diff. times may prod diff. eff
  - ↓d © or © products @ partic site due to excessive © death, ↓d biosynth of DNA, RNA/protein
  - Fetal liver: 20-40% adult activity for phase 1 reaction
- 66% All drugs w. preg. cat. now Cat. C
- 40% Aus women report chr. health prob. during preg. 60% Women on med for chr. prob. report non-adherence to med due to some concerns
- 30% Used complementary/alt. Therapies
- ↑Avg. age of women having babies - + likely to have issues w. chronic med condition. E.g.hypertension
- Probability of structural defect is great++ during organogenesis (Days 17-60)
- Thalidomide: Causes birth defects, Smoking: Lrg risk factor for preg. related morbidity, higher risk of SIDS
- Antidepressants & preg.: 18.4% Preg. women depressed - approx.2x ↑ risk of cardiac malform. (mainly VSD/ASD) in infants exposed to paroxetine
- (SSRI) compared w. general population (~2% vs. 1%, respectively)

Effect of Ethanol on CNS
- Agonist of GABA recep - inhibit glutamate - releases dopamine & serotonin
- Enhance of action of GABA on $GABA_A$ recep - Classical BDZ are + allosteric modulators of response to GABA
- EtOH enhance CNA inhib. GABA release, glycine recep
- Interacts w.: antihist, antidep, BDZ, opiates, antipsych, cannabis, amphetamines.

Chronic Effects
- Irrev. neurological abnorm., loss/damage to neurons & glia, tissue shrink, ↑CSF, ↓glucose metab, ↓blood flow & neuronal viability
- Peripheral neuropathies, cerebellar degen, dementia, Wernicke-Korsakoff's syndrome

Effect of Ethanol on CVS
- Vasodil due to central vasomotor depression. - + assoc w. Hypertension - Myocardial problems
- Neg. assoc btwn chr. use of low amt. of alcohol & CAD

Effects of Ethanol on lipids, platelets & blood ves
- ↓atheroma formation, clotting, platelet aggregation
- Protect eff is offset by ↑d risk of haemorrhagic stroke

Effects of Ethanol on Liver
- ↑Fat accum. due to ↑synth. of lipids & ↓synth. of lipoproteins
- Release of fatty acids & impaired fatty acid oxidation
- Hepatitis > irrev. liver necrosis & fibrosis
- Liver failure (High intake)
- Direct cellular toxicity of EtOH metabolites - also malnutrition - vit. deficiencies

Effects of Ethanol on Kidney & GIT
- Diuretic = ↓Release of ADH = ↓Reabsorb of H_2O in renal tubules = diuresis
- 15-20% Mucosal irritation - 30% of alcoholics have chr gastritis, inflamed pancreas/gallbladder - duodenal/esophageal varices

Foetal Alcohol Syndrome
- From placental transfer - 1:3 in alcoholic mothers
- Microcephaly, abnormal facial structure, growth deficit, cardiac defects, mental retardation, impaired immune system
- Risk when consump >4drinks/day or binge

Alcohol Consumption Pharmacokinetics
- Rapidly absorbed primarily from duodenum (peak @30-90 mins)
- Peak BAC depends on: rate of drinking, gastric/hepatic 1st pass metab, amt & alcohol conc, carbonation, food consump & composition, gender, weight.
- Acute Metabolism
  - EtOH > acetaldehyde > acetic acid
  - 1st step oxidation by alcohol dehydrogenase - rate limiting, zero-order
  - Availability of cofactor NAD step
  - Slightly enhanced by fructose & amino acids (TPN) - ↑ supply of NAD+
  - 5-10% excreted unchanged
  - @ ↑d metabolism (mixed function oxidase) = + sensitive to barbiturates, warfarin, steroids - competition for enzymes
  - H_2 histamine recep blockers inhibit gastric ADH to ↑ peak BAC
- Chronic Metabolism
  - ↑d oxidative metabolism - inducer

- 50% of asians express inactive genetic variant of aldehyde dehydrogenase (low alcoholism)
- Low expression of ADH2*2 isoform of alcohol dehydrogenase w. ↓d activity see in asians
- Women = higher blood EtOH than men - less 1st-pass metab - V_d smaller
- Very little excreted by kidney - constant % of plasma alcohol via lungs

Alcoholism Acute Overdose
- Potentially fatal - avg lethal BAC 0.3% - resp. failure
- Gen. self-limiting - overcome w. rapid consump of lrg amt

Alcoholism Tolerance & Dependance
- Tolerance develops over 1-3 weeks
- Dependence: 4-5% of population - strong physical & psychological dependence

Alcoholism Withdrawal
- Stage 1 (6-48hrs): Tremor, sweats, nausea, vomiting, anxiety, agitation, headache, perceptual disturbances
- Stage 2 (48-72hrs): "Rum Fits" – ↑Stage I symptoms & seizures can be observed (50% have 1 fit)
- Stage 3 (72-96hrs): "Delirium Tremens" – gross tremors, agitation, hallucinations, disorientation, confusion, fever, tachycardia, dehydration – high mortality rate if untreated
- Stage 4 (>7days): Protracted withdrawal

Alcoholism treatment
- BDZ – 1st line agents – best efficacy, safety, cost – ↑ $GABA_AR$ function
- For Wernicke-Korsakoff Syndrome give thiamine
- Psychiatric: haloperidol or droperidol

Insect Toxicology Basics
- CNS neurotransmitters: Acetylcholine (ACh) excitatory, GABA inhibitory, Glutamate inhibitory
- PNS neurotransmitters: Glutamate (excitatory), GABA (inhibitory)
- Neuroactive insecticides target synapse: Organophosphates, Carbamates, Neonicotinoids
- Neuroactive insecticides target axons/neurons: organochlorides (DDT), pyrethrins & pyrethroids

Insecticides
- OP: Anticholinesterases - Atropine & oxime enzyme reactivator for poisoning treatment (dichlorvos, malathion, parathion)
- Carbamates: Contain carbamic acid group, relatively low mammal toxicity, broad spec (aldicarb, carbaryl)
- Safety Factor = LD_{50} Rats/LD_{50} Houseflies

Pyrethrum
- Extracted from chrysanthemum flower (1-2%)
- Fast knockdown - household sprays
- Natural pyrethrins: broad spec, low mammal toxicity, photo-stable, costly

Pyrethroids
- Synth mod pyrethrum
- 1st gen: eff on flies/mosquitos - photo unstable
- 2nd gen: ↑d knockdown
- 3rd gen: Methyl group replaced by chlorines - eff agricultural pyrethroids - photostable
- 4th gen: alpha cyano group introduced, dichloro group replaced by dibromo - 10x more active
- Slows closing of Na, channel inactivation (h) gate/activation (m) gate
- Key effect is overall depolar > produce activation > block of synaptic transmission > paralysis

Mammalian Pyrethroid Toxicity
- Esters, hydrolyse easily.
- Mammal blood has ChE & carboxylesterase, low toxicity, no bioaccum, no persistence in soil
- Cause: allergic rhinitis, asthma, paraesthesia in face, pruritus w. blotch erythema, lachrymation

Organochlorides
- DDT, Dieldrin, Lindane
- Broad-spec - control insect disease vectors

DDT
- control malaria, lice, insects in crops
- Contact poison - potent against insect NS
- Interferes w. Na channel in activation of nerves - rapid, repetitive firing
- Low mammalian toxicity - high conc may cause CNS stim, low dose induce hepatic enzymes
- Chemically stable, persistent (potential for bioaccum/biomagn)

Insecticide Resistance
- Long-term appl^n, sml armament of insecticides, restricted # of identified invertebrate nervous system targets
- Metabolic Resistance: most common, detoxification enzymes, ↑d levels/activity of enzymes, piperonyl butoxide – oxidase inhibitor that prevents resistance
- Target site insensitivity: altered AChE, knockdown-type resistance, alteration in nap regulatory gene locus that controls Na, channel density, Resistance to cyclodienes (OC) arises from point mutation in GABA recep channel pore
- Penetration resistance: Thickening of insect cuticle, normally only 3x ↑ in resistance level

Venom
- Made of: pain producing agents, neurotoxins, myotoxins, haemotoxins, cytotoxins, cardiotoxins, nephrotoxins, enzymes

Snake Neurotoxins
- Classic venom components, flaccid paralysis, usually act on NMJ - Asphyxia
- Postsynaptic NMJ neurotoxins are widely distributed in elapid snake venom
- Some venoms have both pre- & postsynaptic neurotoxins

Snake Postsynaptic Neurotoxins
- a-neurotoxins - block nicotinic ACh recep - asphyxia due to respiratory muscle paralysis
- All bind w. high affinity to a-subunit of nAChR @ NMJ - long-chain neurotoxins also bind to a7 nAChR in CNS

Snake Presynaptic neurotoxins
- Monomers or multimers of PLA_2 subunits (110-135 residues) - affect terminal axon, block release of ACh from terminal > flaccid paralysis
- Unlikely to manifest in less than 1-2 hrs postbite
- AKA: β-nurotox, SPANS, snake $sPLA_2$ nurotox

Bite Symptoms
- Neurotox paralysis: progressive flaccid paralysis - Intraocular muscles (blurred vision) > dysarthria, Ptosis > diaphragm (cessation of respiration) - Tiger, taipan, death, rough-scaled, copperheads, rarely brown
- Coagulopathy: defibrination, procoagulant action w. fibrinogen depletion (initial coag in sml vessel > rapid dissol^n of microscopic clots & blood is unable to clot), deplete clotting factors, fibrinogen degrad products are detected (gen by intrinsic fibrinolysis)
- Bite site continues to ooze - spont internal bleed
- Anticoagulants: no fibrinogen depletion, inhibit platelet aggression - death, copperhead, mulga
- Myopathy: gen muscle pain/weakness + dark urine - mainly tiger, mulga, black, rough-scaled, broad-headed, small-eyed snakes - Myotoxic PLA_2 enzymes
- FIRST AID: Venom transported via lymphatic, Sutherland Pressure-Immobilisation Technique - do not wash, ELISA VDK

Antivenoms
- Created from horses - 1 vial neutralises av. yield of snake
- 1U neutralises 0.01mg dry snake ven. - PT size irrelevant
- Only given if systemic envenomation is present
- Eff against postsynaptic neurotoxin, poorly against presynaptic - unlikely to rev. paralysis & myotox, rev. coag/bleeding

Funnel-web Spider
- Only toxic to primates - pain, hypertension, dyspnoea, muscle fasciculations, salivation & lachrymation - death due to cardioresp collapse
- FIRST AID: S.P.I.T - AV avail
- Slowing of Na_v channel inactivation > spont repetitive nerve firing > uncontrolled transmitter release = muscle fasciculation/autonomic effects

Box Jellyfish
- Nematocysts trig by chemical/physical recep, thin layer of clothing can be protective
- Extruded thread 200 µm long (>1500 nematocysts/mm2)

Autonomic Nervous System
- Reg homeostat activity of smooth muscle, exocrine gland, cardiac muscle, intermediary metab

Parasympathetic Nervous System
- Long preganglionic fibers release ACh onto nicotinic recep, close to end-organ, short postgang fibr release ACh onto muscarinic recep
- controls rest & digest

Sympathetic Nervous System
- Short pregang release ACh onto N - located in paravertebral chain close to spinal cord - innervates adrenal medulla where adrenaline is released - long postgang release NAd onto a/β adrenorecep
- controls fight or flight

Cholinergic transmission
- Cholinergic neurons release ACh - Transmitter at all autonomic ganglia (para & sympathetic; N), parasymp nuroeffector junctions (visceral organs), neuromuscular junction

Anticholinesterases
- Short-acting: Edrophonium, Donepezil, Tacrine
- Medium-acting: Neostigmine, Physostigmine
- Irreversible: Organophosphates
- Poisoning = bradycardia, hypermotility, bronchoconstriction, muscle fasciculation, ↓d intraocular pressure
- Pralidoxime: cholinesterase reactivation

Noradrenergic transmission
- Postgang sympathetic neurons - release NAd - nurotrans at symptoms neuroeffector junction

Adrenergic transmission
- NAd & Ad terminated by uptake (blocked by TCA) & enzymatic degradation (blocked by amphetamine)
- Cholinergic ≠ parasympathetic & adrenergic ≠ sympathetic.

Types of postsynaptic receptors

Cholinergic
- Nicotinic recep - skeletal muscle, ganglionic, CNS
- Muscarinic recep - G protein-coupled recep - M1 (neural), M2(cardiac), M3 (Glandular/smooth muscle), M4/5 (confined to CNS, unknown func), Atropine (non-selective M antagonist - inhibit ACh on M recep only)

Adrenergic
- a_1 recep: CVS & lower UT - NAd released > smooth muscle contract^n in blood ves, GIT & bladder, sphincters, uterus, iris
- Glycogenolysis in liver - Specifically blocked by prazosin
- a_2 recep: neuronal (inhib of transmitter release) - NAd released > inhib of transmitter release from adrenergic nerves terminal > Vasoconstriction of veins, platelet aggregation > Inhib of insulin secretion in pancreas & leptin production in adipose tissue
- NAd released onto $β_1$ recep in <3 = Increase rate/force of contract > blocked by atenolol & metoprolol
- NAd released onto $β_2$ recep = smooth muscle relax in blood ves, bronchi, uterus, GIT,
- Bladder, & ciliary muscle > tremor of skeletal muscle, hypokalœmia > Glycogenolysis (inhibition of glycogen synthase, activation of phosphorylase) > inhib of histamine release from mast © - Activated by salbutamol & terbutaline
- NAd released onto $β_3$ recep = Lipolysis (activation of lipase)
- β recep agonists: inhib of lymphocyte prolif & activity
- a = contraction, β = relaxation (except cardiac contract)

Predominant Autonomic Tone
- Symp predom: Veins/Arterioles, Sweat Glands
- Parasymp predom: Eye, <3, GIT/GU, GIT glands, Bronchi

Blocking Neuromuscular Transmission
- Act presyn to inhibit ACh synth/release - act postsynaptic by blocking ACh recep, activating ACh recep > persistent depolar of motor endplate
- Non-depolar vs depolar Neuromuscular blockers: Both target NACh recep, cause muscle relax, affect ACH ability to cause endplate depolar

Non-depolarising Blockers
- Similar to ACh, contains quaternary nitrogen group > attach to a-subunit of postsynaptic N recep
- Potency: Bisquaternary > monoquaternary amines
- Bulky & rigid head groups
- Bind to anionic & H bond donor sites on one a-subunit
- Bind to anionic site on both a-subunits
- Leptocurare: have a long, thin, flexible structure
- Side effects: Resp. paralysis, hypotension, histamine release from mast ©, tachycardia, suxamethonium, bradycardia/arrhythmia, potassium release, ↑intraocular pressure, prolonged paralysis
- Mechanism of action: competitive antagonists of postsynaptic nicotinic recep; block facilitatory presynaptic nicotinic autorecep; bind tight to desensitized recep & trap them in this state; exhibit desensitization block

Depolarising Blockers
- Bind to anionic subsites of both a-subunits
- Thin & flexible
- Side effects: muscle pain, malignant hyperthermia, hypersensitivity, ↑intragastric pressure
- Mechanism of action: Phase I block - accommodation block, Phase II block- mimics non-depolar block

Pharmacokinetics of Neuromuscular Blockers
- Absorption: Poor oral because all have amine groups, only given parenterally, @ physiologic & acidotic pH, tertiary amines become protonated = ↑potency
- Distribution: High blood flow to NMJ, don't cross BloodBrainBarrier/placenta
- Factors affecting activity of NMBs
  - Age related changes– reduction in total body water, lean body mass & serum albumin conc. lead to ↓vol of distribution of NMBs
  - Hypothermia & acidosis – ↑duration of action of non depolar NMBs

Sedative-Hypnotics-Anxiolytics
- BDZ prod dose-related CNS depression.
- Tranquilization > Sedative > Hypnotic > Gen Anaesth

Benzodiazepines
- BDZs enhance affinity of GABA for recep, increase Cl^- influx, decrease neuronal excitability
- Well absorbed via oral, peak plasma conc within 1 hr, bind strongly to plasma protein, high lipid solubility, manv active metabolites, action duration may not be related to $t_{1/2}$ of elim of parent compound
- Metab direct by conjug w. glucuronide = short-acting
- Renal insufficiency may lead to accum of inactive glucuronide metab,
- Short-acting BDZ: Hypnotics, Long-acting BDZ: Anxiolytic & anticonvulsant
- Inverse agonist: bind to BDZ recep - exert opp effect - increase anxiety & convulsions
- Competitive antagonists: bind to bdz recep - flumazenil

Z-Drugs
- High affinity for a_1-subunit of $GABA_AR$, BDZ non-selective bind a_1-a_3 & a_5
- Reversed by flumazenil - zolpidem associated w. dangerous sleep related behaviours, zopiclone associated w. hangover effects - dependence forming like BDZ

Barbiturates
- Treat anxiety - superseded by BDZ - Death from resp & CV dep (very dangerous in O.D)
- Thiopentone = IV anaesthetic induction agent, Phenobarbitone = selective anticonvulsant
- Similar mech to BDZ - bind to diff site
- Enzyme Induction: Repeat exp = induct of CP450 hepatic enzyme - drugs compete for same metab path broken down faster > lower plasma concs
- High degree of tolerance/dependance

BDZ Clinical Use
- Anxiolytic, hypnotic, muscle relaxant & anticonvulsant, can cause amnesia

BDZ Adverse Effects
- Acute toxicity: Suicide - cause prolonged sleep without serious dep of resp or CV func - co-injestion of CNS dep > life threatening resp failure
- Drowsiness, confusion, amnesia, impaired coord, enhance of dep eff of other drugs, long & unpredictable duration of action
- Withdrawal: Anxiety, tremors, dizziness, tinnitus, weight loss, disturbed sleep
- Flumazenil used to reverse effects of BDZ & activated charcoal given to treat overdose in acute setting

Opioid Analgesics
- Nociceptive neurons
  - Respond to: thermal, mechanical, chemical stimuli
  - Although mechanical & thermal stimuli can trigger nociceptors, in most instances stimulation in periphery is due to chemicals - pain mediators
- Nociceptive afferent neurons terminate in dorsal horn
- Descending inhibitory pathway = main pathway to control impulse transmission in dorsal horn
- Pain mechanisms - gate control theory
  - Neurons in substantia gelatinosa inhibit transmission pathway
  - Inhibitory neurons
  - Substantia gelatinosa rich in opioid recep & opioid peptides

Opioid Drugs
- 4 Opioid recep - mu (µ); delta (δ); kappa (κ); ORL1
- Opioid recep linked through G-proteins, to inhibit^n of adenylate cyclase (leading to ↓cAMP formation) & to MAP kinase (ERK) activation
- Direct membrane action to facilitate opening of K+ channels (causing hyperpolarization).
- Inhibiting opening of Ca2+ channels (inhibiting transmitter release) Main effect to inhibit neuronal excitability, however can also stimulate some pathways by suppressing
- Opioids inactivated via glucuronidation & excreted in kidney/biliary system
- Bc opioids can cross placenta, effects can also be observed in foetus
- Pharmacological effects:
  - Analgesia (strong agonists): Morphine, heroin, methadone, oxycodone, fentanyl
  - Analgesia (mild to moderate antagonists): Codeine, dextropropoxyphene, tramadol
  - Antitussive actions: Suppression of cough reflex by unknown (central?) mechanisms, Codeine suppresses cough in subanalgesic doses but causes constipat^n, Dextromethorphan (isomer of levorphanol)
  - Euphoria & Sedation: Euphoria mediated by micro recep, dysphoria & hallucination mediated by κ recep, @ higher doses, mental clouding & stuporous state called 'narcosis'
  - Respiratory Depression: Mediated by micro recep, occurs @ therapeutic doses; ↓Sensitivity of resp. centres to arterial Pco2 & inhibit^n of resp. rhythm generation; ↓Hypercapnic response; ↑Pco2 may cause cerebrovascular dilation, resulting in ↑blood flow & ↑intracranial pressure; commonest cause of death in acute opiate poisoning (eg. heroin OD)
  - Nausea & vomiting; pupillary constriction; cardiovascular; histamine release
- Tolerance: Rapid ↑12-24 hours; addicts take 50x normal dose; drug rotation to overcome loss efficacy; due to desensitisation of micro-opioid recep
- Dependance can be physical/psychological

Drugs and Diabetes
- Type 1 Diabetes - Results from ß-cell destruction due to autoimmune process usually leading to insulin deficiency
- Type 2 Diabetes - Results from progressive insulin secretory defect on background of insulin resistance
- Gestational Diabetes - 1st Discovered during gestation-insulin resistance due to preg. hormone change & excessive weight gain
- Insulin should be subcutaneous

Oral Hypoglycemic Drugs
- Biguanides - metformin- Type 2
  - ↑Muscle glucose uptake by ↑© membrane GLUT 4 activity
  - ↓Hepatic gluconeogenesis,
  - ↓Glucose absorption from intestine

- ↓Appetite
- ↓Blood lipid levels, cardioprotective effect
- Glitazones - rosiglitazone, pioglitazone
  - Bind to peroxisome proliferator-activated recep γ
  - Requires presence of insulin
  - ↑Insulin sensitivity in muscle & fat
  - ↓Liver glucose production

Asthma

- β2 - agonists
  - Major therapeutic effect is bronchodilation
  - Inhibit mediator release from mast cells
  - ↑Mucus action clearance by its action on cilia
  - Inhalation via metered dose inhaler
  - Powder/Nebulised solution
  - Oral tablets/injections
- β2 - agonists Side Effects
  - Skeletal muscle tremors (common++) due to ↑contraction of muscle fibres
  - Tachycardia that may lead to tachyarrhythmias due to hypokalemia, caused by ↑K intake by skeletal muscles
  - Others: Headaches, muscle cramps, insomnia, anxiety & restlessness, hyperglycaemia due to glycogenolysis in liver & skeletal muscles, tolerance (b2 desensitisation)
- Corticosteroids
  - Inhaled corticosteroids: beclomethasone, budesonide, fluticasone, mometasone, ciclesonide
  - Not bronchodilators - Prevent progress^n^ of chr. asthma; effective in acute severe asthma
  - Given as metered-dose/dry powder inhaler
  - Long term eff: hypertension, osteoporosis, adrenal suppression, hyperglycaemia

Local Anaesthetics

- Consists of aromatic ring w. an ester/amide bond to basic side-chain. Except: Benzocaine – no basic group
- Weak bases, pKa 8 – 9 (ionised @ physiologic pH)
- A higher pKa relative to the local pH favours ionised, hydrophilic state
- Ester-containing compounds: rapidly inactivated in plasma & tissues (mainly liver) by non-specific esterases
- Amide-containing compounds: more stable, longer plasma $t_{1/2}$, biotransformed in liver
- LAs block neuronal voltage-gated sodium (NaV) channels – physically occluding pore
  - Most LAs bind strong++ to active
  - In presence of LAs, equilibrium shifted in favour of inactivated site
- Use-dependent block
  - LAs block neuronal voltage- gated sodium (NaV) channels –physically occluding pore
  - + Open channels = greater block
- Vascular absorb & distribution away from inject site can lead > CNS & cardiac toxicity
- Arteriolar dilatation common
- Frequently given w. adrenaline (vasoconstrictor)
- Ester-type LAs rapidly hydrolyzed in plasma & liver by Pseudocholinesterase (butyrylcholinesterase)
- Adverse effects usually arise from inadvertent intravascular injection, rapid systemic absorb, excess dose, impared CL
- Can cause: AV block, ventricular arrhythmia, depressed cardiac contractility, arteriolar vasodilation, & hypotension
- Uses: Topical anesthesia, local infiltration, peripheral nerve block, IV (Bier) block, epidural block, intrathecal/spinal block
- Local anesthetics, esters & amides, are weak bases, & activities are pH dependent.

General Anaesthetics

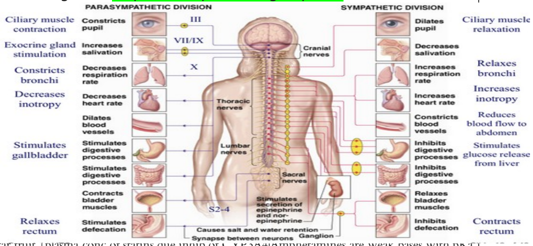
- *Inhaled anesthetics in clinical use: nitrous oxide, halothane, isoflurane, desflurane, sevoflurane*
- Minimum Alveolar Concentration (MAC): Dose of anaesthetic when 50% of humans have no response to surgical stimulus - lower MAC = more potent - addictive, altered by other drugs, ↓with ↓body temp, age, patient's medical condition deteriorates, ↑ with ↑pressure
- Meyer–Overton Rule: anaesthetic potency is directly related to lipid solubility
- Inhaled anesthetics stabilize open state of $GABA_A$ receptor & closed/desens state of nicotinic ACh recep
- Induction > Excitement > Surgical Anaesthesia > Medullary Depression
- GA rare used alone - progress thru stage seldom observed
- Induction & recovery kinetics depends on following parameters: blood solubility (low solubility means less likely to stay in blood), ventilation rate, partial pressure (higher partial pressure = higher induction), increased alveolar blood flow, transfer of anesthetics between blood & tissues.
- Termination of activity through exhalation through lungs - minimal biotransformation.
- Effects on CVS: Halogenated GAs decrease mean arterial pressure, arrhythmia, coronary steal, increase sympathetic discharge/NAd, increased HR/BP
- Effects on Resp: decrease resp rate (increase $PaCO_2$), Halogenated GA blunt ventilatory response to hypoxia & hypercarbia, act as bronchodilators, respiratory irritation
- *Intravenous anesthetics in clinical use: thiopental, propofol, ketamine*
- Intravenous anesthetics used for rapid induction but not used as maintenance.
- 3 IV anesthetic agents have diff time of onset, duration of eff & associated pharmacologic side effects.

Antiepileptic Drugs

- Seizures & epilepsy (>1 episode/24hr) caused by uncontrolled discharges from neurons. - simple or complex & partial or generalized.
- Due to electrical patterns in cortex and thalamus
- Followed by violent, synchronous jerks (duration 2- 4 minutes) then remains unconscious for a few minutes before awakening confused
- Partial: arise in one cerebral hemisphere - discharge being in local area, does not spread - Focal abnormalities in EEG
- Generalised: *Tonic-Clonic (grand mal)*- Initial strong contraction of whole musculature (duration: 1 minute) – rigid extensor spasm & involves cry; resp stops; defaecation, micturition & salivation occur; ashen pale face - *Absence seizures (petit mal.)* - mainly kids; maintenance of body tone & posture, stares vacantly, recover abruptly with no after effect
- Status Epilepticus: Continuous uninterrupted seizures - usually tonic-clonic - when base-line consciousness is not regained between seizures or seizure > 30 min - potentially fatal
- Most common: Complex partial seizures - absence for pediatric
- New antiepileptic drugs less sedating compared to older
- Demo various mech of action. Some could have multiple means of preventing seizures.
- Inhibit gen of repetitive action potentials in epileptic foci
- Use-dependent block of Na+ channels - Enhance inhibitory action of GABA - Block of Ca2+ channels - Inhibit excitatory neurotransmitter action - Open K+ channels - Direct actions on synaptic vesicle release
- Metabolised in liver, excreted as glucuronide
- Gen side effects: sedation, GI upset, Hypersensitivity
- OD: resp depression
- Significant drug interactions can occur due to effect of antiepileptic drugs on liver - potentially teratogenic.

Clinical Use:

- Partial (focal) seizures: carbamazepine (or valproic acid)
- Absence (petit mal) seizures: ethosuximide, valproic acid
- Generalised tonic-clonic (grand mal): valproic acid (or carbamazepine)
- Neonatal Seizures: Pyridoxine, phenobarbitone, phenytoin or clonazepam
- To stabilise mood in mono- or bipolar affective disorders: Carbamazepine, valproic acid, lamotrigine
- Neuropathic pain: Gabapentin, Carbamazepine
- Migraine: Valproate, topiramate, gabapentin


PARASYMPATHETIC DIVISION
SYMPATHETIC DIVISION
Ciliary muscle contraction
Constricts pupil
III
VII/IX
X
Exocrine gland stimulation
Increases salivation
Constricts bronchi
Decreases respiration rate
Decreases inotropy
Decreases heart rate
Dilates blood vessels
Stimulates gallbladder
Stimulates digestive processes
Stimulates digestive processes
Contracts bladder muscles
Relaxes rectum
Stimulates defecation
Cranial nerves
Thoracic nerves
Lumbar nerves
Sacral nerves
S2-4
Stimulates secretion of epinephrine and nor-epinephrine
Causes salt and water retention
Synapse between neurons
Ganglion
Dilates pupil
Ciliary muscle relaxation
Decreases salivation
Increases respiration rate
Relaxes bronchi
Increases inotropy
Increases heart rate
Constricts blood vessels
Reduces blood flow to abdomen
Inhibits digestive processes
Stimulates glucose release from liver
Inhibits digestive processes
Relaxes bladder muscles
Inhibits defecation
Contracts rectum

Starfruit ↑plasma conc of statins due inhib of CYP3A4|Amphetamines are weak bases with pKa of ~9.8. Their elim from body can be ↑ by acidification of urine using ammonium chloride| Antagonist for specific recep possess affinity only|In the adult human liver, paracetamol normally undergoes mainly phase II glucuronidation|salicylates are weak acids and sodium bicarbonate will increase their ionisation|In the liver, aspirin normally undergoes both phase I hydrolysis and phase II glucuronidation|Terbutaline: can only be given prior to an asthma attack acts mainly by decreasing the release of inflammatory mediators from mast cells| Acetylcholine is not the predominant neurotransmitter in sympathetic neuroeffector junctions|a partial agonist at mu receptors and a kappa receptor antagonist:buprenorphine|Intravenous naloxone injection can reverse the severe respiratory depression induced by heroin poisoning| Atracurium can cause hypotension at paralytic doses|