Week 8 Pharmacology – Neuro I VIVA Q:

1. Describe the classification of cholinoreceptors & give examples

Muscarinic = G protein linked
Nicotinic = ion channels

M1 – nerves
M2 – heart, nerves, smooth muscle
M3- Glands, smooth muscle, endothelium
M4- CNS
M5- CNS
Nm- skeletal muscle neuromuscular junction
Nn- CNS, postganglionic cell body, dendrites + adrenal medulla.

Atropine – antimuscarinic

Clinical effects of stimulation (parasympathetic effects)
Eye – miosis (constriction), contraction of ciliary muscle for near vision → "cycloplegia" in antimuscarinic excess = weakened ciliary muscle + loss of near vision 2° cannot accommodate
Heart
- SA node- decreased rate/chronotropy
- Atria – decreased contractile strength, decreased refractory period
- AV node- decreased conduction velocity and increased refractory period
- Ventricles- small decrease in contractile strength

Blood Vessels - Dilation at lower doses and constriction at high doses
Lung
- Muscle- Bronchoconstriction
- Glands- secretion

GIT
- Increased motility
- Relaxation of sphincters
- Stimulation of secretion

Bladder- Detrusor contracts and sphincter relaxes
*Glands (*sweat, salivary, lacrimal) all increase secretion

2. Describe the actions and give examples of cholinesterase inhibitors

VIVA Q:
Target – acetylcholinesterase
MOA: Increase concentration of endogenous acetylcholine at cholinoreceptors by inhibiting AchE.
Group 1: i.e. edrophonium – reversibly bind to active site, short lived
Group 2: i.e. neostigmine/physostigmine – similar process (2 step hydrolysis) but prolonged action 30mins – 6 hours
Group 3: organophosphates. Covalent bond forms, slow hydrolysation (hundreds of hours)
Process of *aging* where bonds are strengthened – varies based on the compound. Clinical relevance because drugs like pralidoxime can break bonds if you get in before aging.

Clinical effects: most pronounced in cardiovascular, GI system, eye, skeletal muscle NMJ.
Uses – for myasthenia gravis, ileus, anticholinergic poisoning antidote, glaucoma

3. Describe the pharmacology of anticholinergics – atropine etc

Antimuscarinic agents – atropine is the prototype (from the bella donna deadly nightshade), also scopolamine (hyoscine), ipratropium, glycopyrrolate,

Atropine – tertiary amine alkaloid ester of tropic acid.
- low dose ↓HR higher dose ↑HR

Well absorbed from the gut and conjunctival membrane
Wide distribution – available in the CNS in 30 minutes
Half-life atropine 2 hours (fast phase) then 13 hours (slow phase)
* 50% excreted unchanged in the urine * → rest is hydrolysed + conjugated
Effects on the eye can persist >72 hours
MOA: reversible/surmountable blockade at muscarinic receptors
Selective for muscarinic receptors – doesn't distinguish M1/M2/M3 subgroups

Anticholinergic drugs acting on the muscarinic receptor giving the classical features of:
- red as a beet (vasodilatation)
- dry as a chip (decreased sweating)
- blind as a bat (pupillary vasodilatation)
- mad as a hater (delirium)

Benztropine
- centrally acting antimuscarinic @ the basal ganglia.
- Clinical: parkinsons disease ↓tremor + rigidity

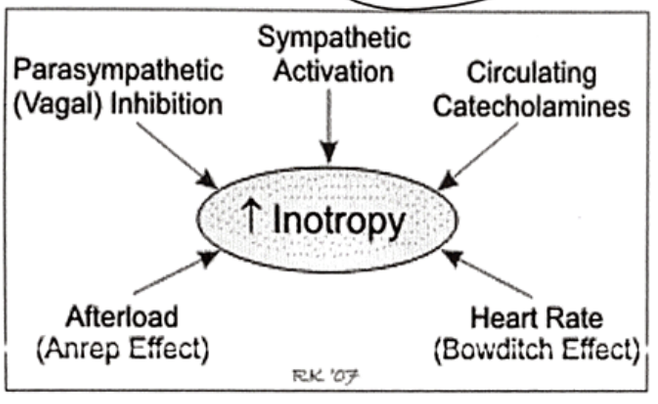
Glycopyrrolate:
rapid onset
↓ airway secretions
NO CNS activity

Note: there are no muscarinic receptors on the blood vessels of the penis. Vasodilation occurs via nitric oxide form the endothelium.

Clinical effects

- *CNS* – minimal in atropine doses typically used. Some parkinsons drugs reduce PSNS activity in CNS.
- *Eye-* pupillary constrictor muscle depends on muscarinic input. Blocking it causes mydriasis due to unopposed sympathetic input. Big eyes considered beautiful – "belladonna"
- *CVS-* SA node sensitive to blockade, can cause tachycardia in an innervated and spontaneously beating heart by blocking the vagal slowing. Can reduce a prolonged PR interval caused by heavy vagal tone.
- *Resp-* Atropine can cause bronchodilation and reduce secretion. Antimuscarinics not AS effective as beta agonists. Use antimuscarinics to reduce airway secretions.
- *GIT-* Cause dry mouth by inhibition of secretions.
- *Urinary-* slows voiding by relaxing tone of bladder BUT can cause retention
- *Sweat glands-* suppression of thermoregulatory sweating → "atropine fever"

4. Can you describe the classification of inotropes



Inotropy = contractility
Contractility = ability of myocardial fibres to shorten, independent of preload and afterload
Ability to contract and the force of which it does so
Force of contraction is determined by concentration of calcium ions in the cells
Increase contractility by flooding the cell with more calcium (beta agonists) or by keeping more calcium in, preventing it escaping

Indications for inotropes

- To increase cardiac output by increasing the force of contraction in patients with cardiogenic and distributive shock

Inotropes: agents that alter the force or strength of myocardial contractility
Vasopressors: sympathomiometic drugs that mimic the effects of the SNS causing vascular smooth muscle vasoconstriction

Bypyridines (Phosphodiasterase inhibitors)

- Increase contractility by increasing calcium influx into myocardial cells
- Some effects on SR
- Milrinone – inhibits phosphodiesterase 3 (PDE-3), t ½ of 3-6 hours, 10-40% excreted in the urine
  ↳ inotropic + vasodilation so good for right heart failure (↑ contractility + ↓ vasc resis)

Beta- Adrenoceptor Agonists

- Most selective for heart β1 = dobutamine
- Increases CO and decreases ventricular filling pressure
- SE- increased O2 consumption, tachycardia (i.e. bad in CAD or arrythmias)
- Can boost BP also

Beta agonists also used for
→ SMC relaxⁿ in airways
→ uterine relaxation
→ ↑skeletal muscle K⁺ uptake

Investigational

- Istaroxime – steroid derivative, inhibits Na/K/ATPase
- Levosimendan- sensitises the troponin system to calcium
- Omecamtiv mecarbil- activates cardiac myosin, prolongs systole without increasing O2 consumption

Sympathomimetic amines (more often classified as vasopressors)

- Adrenaline – high affinity for β1, β2 ans α1, β effects at small dose, α1 effects at high dose
- Noradrenaline – potent effects at α1 receptors

→ adrenalin synthesised from NA in the adrenal medulla. Same NA pathway synthesis + extra enzyme: _phenylethanolamine – N- methyltransferase adds a methyl group to NA to form adrenaline ⇩ released in blood that perfuses the kidneys.

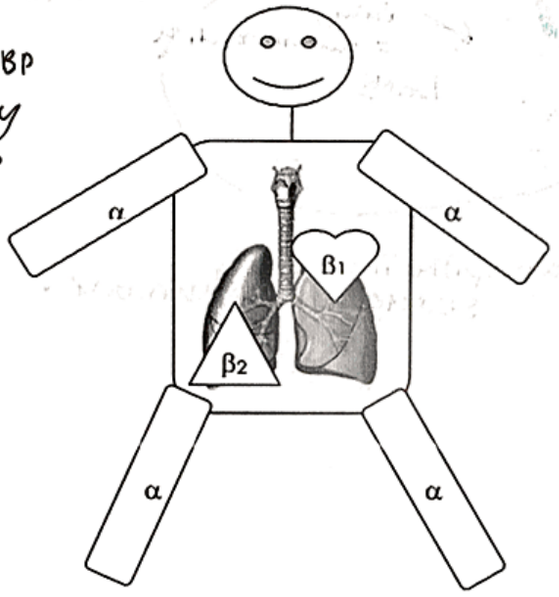
Synthetic Catecholamines

- Dobutamine
  - Strong β1 ~~and β2 effects~~
  - Cardiac effect makes it a strong inotrope
  - Weak chronotropic activity
  - Vascular smooth muscle binding results in combined α1 agonism and antagonism
  - ~~β2 stimulation with a net vascular effect of mild vasodilation~~

5. Describe the effects of adrenoceptors and distribution in the body

Receptor Location: (β1, β2, α)

Norad = peripheral ↑BP
Adrenalin = run away
Isopret = ↑HR – (N) BP



α2 – G_i CNS reuptake, smooth muscle.

Receptor Type	Location	Actions when stimulated
Alpha 1 1 norad 2 adren 3 isopret PLC DAG	Vascular smooth muscle	Vasoconstriction Arterial SMC = contraction = ↑SVR Peripheral vasoconstriction
Beta 1 1. isoprenaline + dobutamine ↓ 2. adrenalin = norad. G_s	Heart and intestinal smooth muscle	Increased contractility via ↑Ca in cells facilitating actin/myosin binding with trop C Increased automaticity Increased AV conduction Increase HR via Ca channel activation
Beta 2 1. isoprenaline 2. adrenalin ~~norad~~ G_s 3. norad.	Bronchial Vascular and uterine smooth muscle	Vasodilation and bronchial dilation B2 on vasc SMC causes ↑Ca uptake by SR and vasodilation Bronshial dilatation and dilation of coronary arteries
Dopaminergic receptors	Renal and mesenteric vessels	Vasodilation Increase blood flow to kidneys and mesentery
V1 and V2 receptors	V1 – vascular smooth muscle V2 – renal collecting duct	V1- constriction V2 – enhanced permeability collecting duct and mediates water reabsorption

Treatments for glaucoma

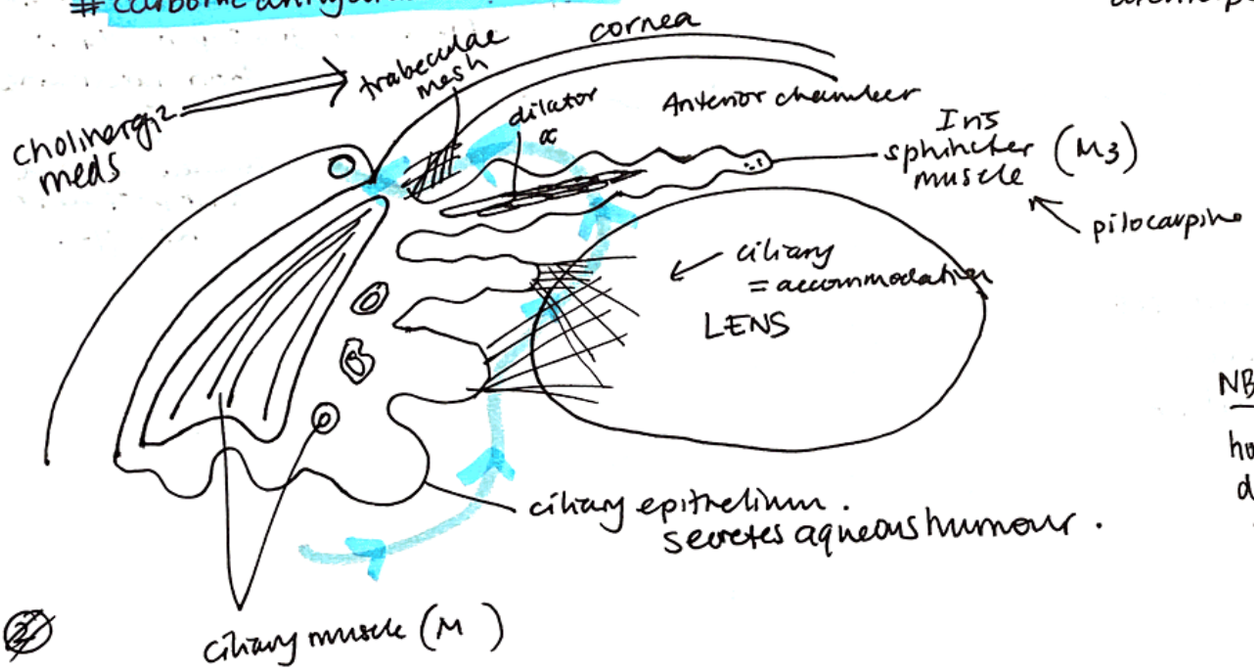
↑IOP = >21mmHg

① ↓ of ~~aceh~~ aqueous humor secretion (ABC)

α_2 agonists – ↓secretion i.e apraclonidine

β blockers – ↓secretion from ciliary epithelium (timolol, carteolol, metipranolol)

carbonic anhydrase inhibitors → ↓secretion 2° ↓HCO_3^- (acetazolamide, dichlorphenamide)



NB:
homatropine dilates pupil + can precipitate glaucoma.

② ↑aqueous outflow

meshwork

cholinomimetics ⇒ ciliary muscle contraction; opening of meshwork, ↑ flow
(i.e. pilocarpine, physostigmine)
direct indirect – ↑ACH via AChE inhibition.

alpha agonists ⇒ ↑outflow – nonselective.
(i.e adrenalin)

prostaglandins ⇒ ↑outflow, relax ciliary muscle, modulate ECF
(i.e latanoprost, bimatoprost)

DURATION OF EFFECT OF ~~THESE~~ DROPS FOR ED Review of eyes

Atropine ⇒ 5-6 days

Scopolamine ⇒ 3-7 days

Homatropine ⇒ 12-24 hrs

Cyclopentolate ⇒ 3-6 hours

Tropicamide ⇒ 15-60mins (BEST)

SYMPATHOMIMETICS = temporising only, time to institute other Rx.

METARAMINOL

MOA: α1 receptor agonist
some indirect effects via ↑NA
minimal/negligent CNS effects.

NORAD

MOA: α1 receptor agonist
α2 receptor (presynaptic - negfeedback)
β1 receptor ↑contractility & ↑SBP.

NOTE: β1 activity ↑HR HOWEVER baroreflex from ↑BP causes reflex bradycardia so minimal overall change in HR.

ADRENALINE - low dose mainly beta, ↑dose ↑alpha.

MOA:
- EQUAL: β1 receptor → ↑HR & ↑force
- EQUAL: β2 receptor → vasodilation in skeletal muscle beds.
- α receptors → peripheral vasoconstriction.

PK: IM/IV/subcut/neb
poor oral bio av.
Ø cross BBB
does cross placenta
50% protein bound.
onset - seconds
duration - 2mins.
metab: COMT & MAO in sympathetic nerves
metabolites excreted via urine.

DOBUTAMINE

MOA: β1 selective.
→ ↑CO w less reflex tachy.

NB: comes as a mixture of isomers w equal α agonist/antagonist.

Local Anaesthetics

Lipophilic group (aromatic ring) — ? — ionizable group (hydrophilic) esters/amines (shorter duration)

Aminoamides

A
ii

- Lignocaine
- bupivicaine (↑ cvs tox)
- mepivicaine
- prilocaine.

⇒ Hydrolysed by P450 in the liver so longer $t_{1/2}$.
Prilocaine metabolised fastest (but MetHb)
protein bound

Aminoesters

E

- Procaine
- Benzocaine
- Tetracaine (amethocaine)
- Cocaine

⇒ Hydrolysed rapidly by pseudocholinesterase to inactive metabolites so shorter $t_{1/2}$
Allergies more common

LA's = weak bases → made as salts
Exist as uncharged base or cation depending on pKa + pH
Most LA pKas are 7.5–9 i.e above physiological pH ⇒ mostly cationic form

This is why they dont work in infected tissues (acidic) b/c ↓pH means more charged form.

Most effective at the receptor site.
BUT
needs unionized form to get in through the membrane

pKa 8-9.0 positively charged at physiologic pH → charged = active @ receptor
needs to be uncharged to get to receptor.

Week 9 Pharmacology- Neuro II: Local Anaesthetic, General Anaethetic, Muscle Relaxants

1. Describe pharmacological properties of lignocaine and prilocaine

Lignocaine
T ½ distribution 10 mins
T ½ elimination 1.6 hours
Vd 91
CL 0.95 L/min

TRANSIENT NEUROLOGICAL SYMPTOMS
post spinal anaesthesia w lignocaine/LA
pain in buttocks + thighs + legs
few hours post spinal → days post (≤10)
no other neurology

Local Anaesthetic Blocks
1. sympathetic
2. pain
3. temp
4. motor
5. proprioception

Prilocaine
T ½ distribution 5 mins
T ½ elimination 1.5 hours
Vd 261
CL 2.84 L/min

can cause methaemaglobinaemia 2° to accumulation of metabolite O-toluidine → Ferrous ions of haem Fe^{2+} oxidised to Fe^{3+} + cannot bind O_2.

Eliminated via conversion to water soluble metabolites in the liver or plasma
MOA of local anaesthetics: voltage gated sodium channel blockade without altering the resting membrane potential. Prevents the generation of action potential. Channels in the resting state have lower affinity, where active channels bind better. The recovery from a drug induced block is 10 – 1000 times slower than recovery from normal activation.

NB: high extracellular calcium antagonizes LA, high extracelluiar K enhances LA. → promotes depol.
Basic = better
Acidic = inhibits action. (abscess)
LA also interact with other channels K/Ca, enzymes adenylyl cyclase and receptors i.e. NMDA/g proteins effect is poorly understood but seems to be important.
↑risk of toxic effects in vascular areas i.e intercostal block.

myelinated nerves blocked 1st (same size)
pain > proprioception
small > large
fast > slow
proximal > distal (due to inner fibres from distal areas)

2. What is anaesthesia?
Unconsciousness, amnesia and immobility.
See also: inhibition of autonomic reflexes and skeletal muscle relaxation + analgesia

3. Describe the pharmacological properties of common anaesthetic agents – NO, Isoflurane

NO – MOA ↑dynorphin release → kappa receptors; modulates GABA A; NMDA agonist
Incomplete anaesthetic
Rapid onset and recovery → excreted in lungs.
MAC >100
Blood : gas = 1 : 2
↑SNS tone, mild CVS depression, ↑PVR (beware pul HTN)
Low solubility in blood so more rapid onset (blood gas partition coefficient 0.47 = at equilibrium between alveolar space and blood, the concentration in the blood is less than half the concentration in the inspired air)
Brain:Blood partition coefficient = 1.1
1-4 x RR PONV
Expands airspace → ears, bowel → PTX

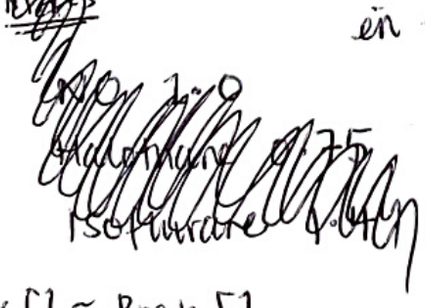
prolonged use > 6hrs
= prevents DNA synth
= megaloblastic anaemia
< periph neuropathy
= agranulocytosis.

Isoflurane – ↓ myocardial O_2 requirement so good for IHD pts.
Medium rate of onset and recovery
MAC 1.4
Higher solubility so longer time to onset because more gas dissolves in the blood before the tension changes.
Blood:gas partition 1.40
Brain:Blood partition coefficient = 2.6

4. What is the MAC?
The minimum alveolar concentration, a measure of potency of an anaesthetic
MAC is the partial pressure of an inhalational anaesthetic in the alveoli of the lungs at which 50% of a population of non-relaxed patients remained immobile at the time of surgical skin incision

only valid at sea level.
sex/wt/duration doesn't Δ MAC

measured as a percentage at 1 atmosphere of gas in the mixture required to achieve this effect.



Alveolar [] ≈ Brain []

MACs of drugs
NO >100%
Halothane 0.75%
Isoflurane 1.4%
methoxyflurane 0.16%
Sevo 2%
desflurane 6.6%

FACTORS THAT ↓ MAC
- Hypoxia
- Hypothermia
- Old age
- circadian rhythm (10%)
- opioids (ceiling effect)

General Anaesthetic Inhaled agents:

BASICS: Clinical effect of inhaled/volatile agent depends on partial pressure in CNS

@ equilibrium; partial pressure in CNS = P_a (blood) = P_A (alveolus)

NB: not done in practice — can take hours.

Rate of onset + offset depends on transfer of gas

1. Into alveoli
2. from alveoli to blood
3. from blood to CNS.

MACS OF DRUGS
NO >100%.
desflurane 6.6%.
sevoflurane 2%.
Isoflurane 1.4%.
Halothane 0.75%.
Methoxy 0.16%.

MAC = minimum alveolar [] @ steady state to prevent movement to surgical incision in 50% of subjects. A measure of POTENCY.

But doesnt reflect lack of awareness or other agents so 1 MAC usually ok.

MAC-AWAKE = End tidal [] of agent that prevents response to verbal command in 50%.

Usually 1/3 of the MAC.

These are only valid @ sea level given they are partial pressures & conc.

PARTITION COEFFICIENT:

Relative affinity for 2 phases when equal volume

Blood:gas ⇒ solubility in blood relative to air.

low blood:gas = rapid offset/onset b/c poorly soluble agents generate high P_a ⇒ steep concentration gradient b/w P_a + P_B (brain)

high blood:gas = dissolves readily in blood w/out Δ P_a. Doesnt have the oomph to generate gradients = slow onset

Blood:gas coefficients for agents:

Methoxyflurane = 12!! → green whistle fast.

Halothane 2.3

desflurane lowest 0.42.

Inhaled agents ↓ MAP in proportion to inhaled alveolar [].

~~N2O does not cause~~

Halogenated agents have a higher brain:blood coefficient.

Clinical Effects

↓ GFR + urine flow — filtration fraction ↑

Bronchodilation

↓ cardiac output

∴ ↓ portal blood flow

desflurane + isoflurane cause tachycardia.

Common Things

- All inhaled agents undergo liver metabolism except halothane (reduced)
- All halogenated agents ↓ Tidal vol + ↑ RR = ↑ CO_2 via ↓ MV.
  also ↓ central chemoreceptor sensitivity to CO_2
- ↓ MAP ⇒ ∴ ↓ GFR.
- Muscle relaxation via Ca^{2+} channel blockade (may precipitate MH

Week 10 Pharmacology – Neuro III

Thiopental / Thiopentone

barbiturate → hypnosis, anaesthesia but NOT analgesia. sedation,

- Rapidly crosses BBB
  - Plasma: Brain equilibrium < 1 min 2° ↑ lipid solubility
- Rapidly diffuses out of brain & vascular tissues → redistributed to muscle + fat
- Metabolism 12-15% per hour — 5-10 mins of action
- < 1% excreted unchanged in kidneys

Advantages: Rapid, controllable, amnesic, ↓ICP, anticonvulsant

Disadvantages: Hypotension, myocardial depression, venous irritant, minimal muscle relaxation & analgesia, hepatic metabolism. Rare: porphyric crisis.

↑ GABA & ↓ glutamate

Propofol

- IV administration → procedural sedation – 0.5-1.0 mg/kg bolus or 10-20 mg aliquots
  - → induction dose – 1-2.5 mg/kg & 2.5-3.5 mg/kg in kids
- Rapid onset/recovery due to redistribution from brain → skeletal muscle → fat rather than metabolism
- Distribution t½ 2-4 mins
- Duration of action 3-8 mins
- Elimination t½ 4-23 mins
- Metabolism in liver (rapidly) & lung
- Excreted as glucuronides & sulphates, < 1% unchanged in urine (↑ water soluble metabolites)

Indicated for: – Induction
– Maintenance of anaesthesia
– procedural sedation.

CNS/Resp/CVS effects.

Advantages: Antiemetic, anaesthesia + sedation; rapid onset/offset (for procedures)

Disadvantages/SE's: Hypotension – vaso/venodilation + -ve inotropic effect
Apnoea – dose related central depression, ↓TV, ↓ airway reflexes.
Pain on injection, egg allergy, not analgesic, metabolic acidosis (infusion)

Limit SE's → caution w/ simultaneous opiates/benzos (↓ resp, ↑ sedation)
→ titrate small doses
→ ↓ doses in elderly or poor cardiac reserve
→ caution in haemodynamically unstable pts.

↳ propofol infusion syndrome (tachycardia)

Related to phenylcyclidine

Ketamine → IV / IM / oral / rectal / epidural

- "dissociative ~~analgesia~~ anaesthesia" + also analgesia + sedation + amnesia.
- MOA: inhibition of NMDA receptor complex (antagonist)
  OR / ALSO blockade of the membrane effects of the excitatory action of glutamate at the NMDA receptor complex.
- Rapid onset from high lipid solubility; offset from redistribution (quick)
- metabolised in liver (P450) → norketamine (1/3 as potent) → water soluble products excreted in urine.
- Low protein binding (12%)
- Reflexes preserved (but not able to maintain airway)

CNS effects → cerebral vasodilator that increases cerebral blood flow, so caution / avoid in ↑ICP or open globe.
→ anticonvulsant effects
→ unpleasant emergent effects: hallucinations, distortion, fear, euphoria. (can combine w/ benzo to ↓)
→ anaesthesia (dissociative) + profound analgesia

CVS effects → haemodynamically stable
→ transient ↑ SBP / HR / CO via central SNS stimulation.
→ can be myocardial depressant

Resp effects → intact airway reflexes.
→ single drug: resp response to ↑CO_2 preserved.
→ Risk of laryngospasm from ↗ salivation (especially in kids)
→ Relaxes bronchial smooth muscle: good for asthma pts
* inhibits histamine release *

Induction dose: 1-2 mg/kg IV / 4-6 mg/kg IM

Analgesia dose: 0.2-0.8 mg/kg for a block / epidural.

Other SE's: vomiting, seizures.
Main indications → analgesia, procedural sedation, bronchodilator effect in severe asthma, ?behavioural disturbance, emergence agitation
Avoid in: allergy, ↑IOP, ↑ICP, recent / current URTI, shock

Contraindications: Previous laryngospasm with ketamine
Documented allergy to ketamine
↑HR ↑BP i.e methamphetamine OD
Theoretical risk w/ ↑ICP ↑IOP.

Benzodiazepines (midazolam, lorazepam, diazepam) (intersects usually α or γ)

MOA: Binds to molecular components of **GABA$_A$ receptor** in neuronal membranes in CNS. This receptor is a **chloride ion** channel (i.e. ↑ hyperpolarization membrane)

NB: BZD dont substitute for GABA (inhibitory NT) but enhance effects without directly activating or opening the channel, causes ↑ freq of channel opening.

diazepam ↑ lipid soluble than lorazepam

Organ level effects of diazepam:

CNS
- sedation
- anxiolysis
- amnesia
- hypnosis (↑ stage 2 NREM, ↓ REM)
- adjuntor (high dose) anaesthesia
- anticonvulsant (clonazepam/diaz)
- muscle relaxation

CVS/Resp.
- depression @ high doses (↑CCF/hypovol/CHD) especially resp disease
- midaz ↓BP > diaz 2° peripheral vasodilation.

Clinical uses:
anticonvulsant, sedation of agitated pt, EtOH/Benzo withdrawal, various toxidromes.

Lipid soluble → rapid onset, redistribution effects

Indications:
- anxiety disorders/panic disorder
- preop medication
- insomnia/sleep disturbance
- seizure disorders
- alcohol withdrawal
- muscle spasm
- to induce amnesia during cardioversion/endoscopy.

DIAZEPAM
t½ 20-40hrs
no effect on hepatic metab.
Binds GABA-A to ↑ transmission.
metabolised to oxazepam & desmethyldiazepam

*** All hepatic metabolism * to active metabolites**

BZDs in ETOH withdrawal.

ETOH excess → down regulation of neuro-inhibitory GABA receptors in alcohol dependent person; leads to GABA deficiency in withdrawal.

BZD's act on a modulatory site on $GABA_A$ receptor to facilitate binding of GABA, enhance chloride channel opening & overcome neuroexcitory symptoms of GABA deficiency.

Flumanzil: selective BZD antagonist.

causes vomiting / seizures / unmasking withdrawal

Dont forget re-sedation once effects wear off.

MIDAZOLAM

- Water soluble — so oral / IM / intranasal ok → IV / buccal / PR also.
- poor oral bioavailability
- Highly protein bound
- crosses BBB easily
- Elimination t½ short: 1.5 - 2.5 hours ✿ active metabolites
- Hepatic metabolism + renal excretion (56% renal excretion)

Pharmacodynamics (MOA) — anticonvulsant, sedative-hypnotic, anxiolytic, amnesia.

dose: **Seizures**

paediatric IM/IV 0.1 mg/kg

buccal / IN 0.3 mg/kg

adult: IV 5mg IV/IN/buccal

>70yrs 2.5mg IM

Etomidate

GABA receptors

conscious sedation + RSI

Alcohol Mech: enhances GABA-mediated inhibition, inhibits Ca^{2+} entry, inhibits NMDA receptors, inhibits adenosine transport.

PK: Absorption: Rapid, from GIT, peak levels in 30mins
Distribution: Rapid, volume is TBW 0.5-0.7 L/kg
Metabolised in the Liver by alcohol dehydrogenase (& small amounts by microsomal ethanol oxidising system (MEOS) 1 unit per hour
zero order kinetics (elimination @ constant rate no matter [])
Excretion in the lungs & small amounts in urine (10% unchanged)

→ Other zero order drugs: phenytoin, theophylline, warfarin, heparin, paracetamol.

PD:
CNS - sedation, disinhibition, impaired judgement, impaired motor skills, ataxia, slurred speech, coma, respiratory ↓ central mechanism.
CVS - ↓ contractility, vasodilation → hypothermia.

Chronic alcohol exposure: arrhythmias, HTN, CAD chronic pancreatitis
Alcoholic cardiomyopathy, fatty liver disease → cirrhosis (varices)
obesity 2° ↑ energy content, Wernickes ataxia, Korsakoffs syndrome
neurotoxicity. FASD.
folic acid related anaemia.

Tolerance – upregulation of NMDA receptors
– downregulation of GABA response

VIGABATRIN
GABA analogue that inhibits 4-aminobutyrate-transaminase (enzyme that usually breaks down GABA) ↑GABA availability
(off-label use for cocaine dependence)
Renal elimination unchanged drug, no liver metabolism.

ETHOSUXIMIDE: for absence seizures. Nausea/vom
blocks Ca^{2+} channels. CNS dep.

NK10.

ANTIEPILEPTICS

Carbamazepine – Antipsychotic for bipolar "mood stabiliser"
- Antiepileptic (focal & focal to full)
- Trigeminal neuralgia (great!)

dont have a seizure in the car eating salty chips

MOA: Sodium channel blockade
Binds to inactive state to stabilise there
High frequency trains of AP preferentially inhibited
so interfere less in normal / baseline activity

Pharmacokinetics:
100% bioavailability
peak levels 6-8 hours post ingestion
slower after meals = more well tolerated
* 70% protein bound
Vd 1 L/kg
Low clearance – t½ 36 hrs (↓ over time)
Induces its own metabolism
Liver converts to active metabolite
P450 enzymes ↑↑
- Valproate can inhibit clearance. (+ phenytoin)
- carbamazepine induces enzymes.

SE:
GI symptoms
diplopia, ataxia
sedation @ high doses
agranulocytosis
? Seizures. OD: manage as per TCAs
benign leukopaenia.

NB oxycarbazepine – analog, less potent, no active metabolite

Antiepileptics

Sodium Valproate.

- protects against many seizure types
- also bipolar mood stabiliser
- migraine prophylaxis.

↓ LIVER TOXICITY

MOA: unknown, effective on diverse epilepsy models.
∅ = ↓ drug level so ? active part.

VIVA Q: What could it be?
could be: Na+ channels
GABA transmission
NMDA.

used for all kinds of seizures.

PK
oral bioavailability 80%.
Peak level 2hrs → food delays absorption
Highly protein bound = low Vd 0.15L/kg.
$t_{1/2}$ 9 - 18 hours
20% excreted as a conjugate

Interactions
Inhibits the metabolism of several drugs
Displaces phenytoin from plasma proteins
↑ levels of carbamazepine
↓ clearance of lamotrigine
Inhibits its own metabolism
* P450 enzyme inhibitor *

Toxicity
Nausea / vomiting / abdo pain / heartburn
Fine tremor
* Hepatic toxicity (<2yrs) *
Thrombocytopaenia + bruising
↑ ammonia → tiredness to coma.
Neural tube defects in 1st trimester.
CNS: coma, cerebral oedema

Antiepileptics

PHENYTOIN

MOA: Sodium channel blockade (similar to carbamazepine)
Inhibits the generation of repetitive APs. Plus GABA ↑ activity.

Used for: focal, tonic clonic seizures, status
NOT FOR absence, Dravets, juvenile myoclonic (worsens)

PK

PO/IV - highly variable absorption
90% albumin bound = low Vd 0.6 L/kg
ENZYME INDUCING
Metabolised in liver to inactive metabolites → urine
First order → saturated → variable t½ 12-36hrs
takes 5-7 days to reach steady state

Toxicity

Nystagmus, loss of smooth pursuit is NORMAL + OK
Diplopia + ataxia = needs dose ↓
Gingival hyperplasia + hirsutism
Long term use = ↓vit D & osteomalacia
IV administration = purple glove syndrome. Black discolouration distal to IV site. Can cause local necrosis 2° extravasation
IV administration can cause ~~tachy~~ bradycardia & ↓BP → CVS collapse.

Status epilepticus dose → 20mg/kg IV/IO
over 20 mins, 50mg per min.

Why is the dose dependent elimination important?
Small, frequent ↑ in dose can lead to overdose + toxicity
Low doses = first order kinetics, higher doses = ~~1st~~ zero order.

Antiepileptics

LEVETIRACETAM

Liked because of: favourable SE profile
broad therapeutic window
lack of drug interactions

MOA: Binds to SV2A – synaptic vesicle protein (? related to exocytosis)
Endocytosis → binds in the vesicle +
prevents release of glutamate during ↑ frequency activity

Uses: focal seizures, generalised T/C, status.

PK: Rapid oral absorption – peak 1-3 hours
Linear kinetics.
Low protein binding (<10%)
t½ 6-8 hours (BD dosing)
2/3 excreted unchanged in the urine
1/3 deaminated in the BLOOD
NO LIVER METABOLISM, MINIMAL INTERACTIONS.

SEs:
mild: somnolence, ataxia, infection, dizziness
worse: behavioural + mood changes (aggression, anxiety)

Status dose → paediatrics: 40mg/kg IV/IO (max 3g)
→ adults: 60mg/kg IV/IO (max 4.5g)

Antiepileptics

LAMOTRIGINE – well tolerated, ↓ foetal risk.

MOA: Sodium channel blockade

clinical: almost all seizures exc. absence.

PK:
- 50% protein bound
- t½ 24hrs – daily dosing to 2nd daily
- usually dosed in valproate (which ↑ its metabolism)
- glucuronidated in the liver

GABAPENTIN + PREGABALIN

MOA: Binds to α2δ on voltage gated Ca^{++} channels
?↓ glutamate release

used for – focal seizures (NOT generalised or absence)
– neuropathic pain

PK: Eliminated unchanged in urine
Absorbed in upper small intestine
variable absorption.
Pregab ↑ bioavailability ~90%.
t½ ~5-8 hours BD/TDS

SES somnolence
ataxia
dizziness
weight gain + peripheral oedema

Skeletal Muscle Relaxants

receptor occupation.

NON depolarising

- smaller muscles affected first.
- occupies receptor sites + prevents channel opening
- NB: can enter pore @ very high doses.

STEROIDAL ≠ metabolised in liver ± renal excretion

↑DURATION IN:
- hypothermia
- renal failure (steroids)
- acidosis
- hypokalaemia
- hyper mag

Intermediate acting 5-30mins

Rocuronium
- Hepatic metabolism (<5%) biliary elim (60%)
- Lasts 30mins, onset 45-90sec
- 40% urinary excretion.
- ↑HR @ high doses ↑anaphylaxis

Vecuronium (Potent)
- Has least effect on CVS
- Hepatic metabolism (70-90%)
- Lasts 45mins – 1hr

→ can be reversed with sugammadex which binds roc + vec.

Pipecuronium – ✗

Pancuronium (Potent)
- LONG ACTING. >35mins, onset 90-150sec.
- 80% renal elimination of unchanged product
- small ↑HR via M. block @ heart
- no histamine release

ISOQUINOLINE

Tubocarine
- >50mins action duration.
- 40% renal elimination.

Atracurium
- lasts 25-30mins
- histamine release ⇒ hypotension / bronchospasm
- Hoffmann elimination (spontaneous breakdown)
  - ↳ by products: laudanosine ⇒ seizures.

Cisatracurium
- less histamine
- less laudanosine.
- Still mostly spontaneous elimination.
- lasts slightly longer.

Other

Gantacurium (new)

Depolarising

~~Suxamethonium~~ (suxamethonium)

Succinylcholine – occupies receptor sites & blocks channel.

Looks like 2 Ach molecules together.

Very short duration → 5 - 10 mins

hydrolysed by butyrylcholinesterase in liver & pseudocholinesterase in plasma (Main elimination)

→ genetic deficiency can cause prolonged blockade

NB: Sux is hydrolysed enroute to NMJ so, circulating cholinesterase determines how much gets there to begin with + ∴ duration of action.

∴ action can be prolonged if pt has genetic abnormality ("pseudocholinesterase deficiency") (abnormal cholinesterase number)

Phase I block (depolarising) Tense phase

Activation ⇒ transient contraction

paralysis 2° to inability of nerve to repolarise + depolarise again (which is req'd for maintenance of muscle tension)

Phase I augmented by cholinesterase inhibitors.

Phase II (desensitising) relaxed phase

With prolonged exposure the membrane is able to repolarise.

BUT does not depolarise again ⇒ it is now desensitised.

Behaves like a non-depol block.

Can be antagonised by anticholinesterase inhibitors (controversial)

Other effects 2nd dose causes bradycardia. (nobody knows why)

Stimulates cardiac muscarinic receptors ⇒ attenuated by atropine/glycopyrrolate.

negative inotropic + chronotropic effects

Hyperkalaemia – K released from muscles 2° fasciculations. If extrajunctional receptor proliferation (burns) ∴ ↑K can → arrhythmias.

↑IOP – not for open globe trauma.

↑intragastric pressure –

Myalgias –

Interactions – malignant hyperthermia → abnormal Ca^{2+} release from skeletal muscle → give dantrolene (over next page)

– Aminoglycosides enhance blockade

Neuromuscular MCQs

Sugammadex:

- modified gamma cyclodextrin
- selectively reverses effects of rocuronium + vecuronium
- maybe pancuronium
- MOA: forms a complex w these drugs so they can't bind to nicotinic receptors in NMJ.
- IV administration – elimination $t_{1/2}$ 2.2 hours (↑ elderly, ↓ in kids)
- mostly excreted unchanged in urine so not for renal pts
- immediate reversal = 16mg/kg 3 mins post roc
- 4mg/kg for reversal of deep block
- 2mg/kg for shallow block.
- More effective than neostigmine for reversal (quicker)
- Recurrence of blockade can occur.

SUX does not cause urinary retention.

Pancuronium / Rocuronium / Vecuronium rely on liver or kidney metabolism to clear a drug. BC they are STEROIDAL

Atracurium is cleared via Hoffman elimination (i.e enzymatic & non-enzymatic hydrolysis of ester bonds). Better for liver / renal disease pts. Cisatracurium is better b/c all the advantages w less histamine.

Pseudocholinesterase deficiency: (1 in 3k-5000 people)
Usually drugs are rapidly metabolized by plasma cholinesterase. In individuals w this, the paralysis can be prolonged (hours)
Eg succinylcholine, mivacurium.
procaine + pesticides + cocaine
Iatrogenic causes: ACHE inhibitors, esmolol, steroids, contraceptives.

Causes of prolonged neuromuscular blockade (vecuronium)
- hypothermia (↓ clearance) & hyperthermia (↑ activity)
- ~~severe burns / burn disease~~ ← acidosis (↑ activity)
- abx / steroids / narcotics (gentamicin potentiates) by ↓ ACh release

Shortened in burns – resistant 2° to proliferation of extrajunctional receptors

Week 11 Pharmacology: Neuro IV.

1. Biogenic amine theory of depression

→ Noradrenaline + serotonin

→ "depression is a result of ↓ functional activity of these"

→ ∴ ↑ availability by blocking reuptake → more at binding sites.

Now more evidence for neurotrophic + endocrine factors / neuroplastic hypothesis

Involves BDNF.

Hormones — abnormal HPA axis in major depression, ↑cortisol, Δ TFTs.

• SSRIs •

flu — 70%. ↑ bioav, protein bound.

Act on SERT, serotonin only, block reuptake

Used for: GAD, PTSD, OCD, Panic disorder, PMDD, Bulimia.

Highly lipophilic

Fluoxetine — inhibits CYP2D6, metabolised to active product, longest t½, wait 4 wks b4 MAOI. 3 days

Sertraline

Citalopram

Paroxetine — Inhibits CYP2D6.

Fluvoxamine — Inhibits CYP3A4

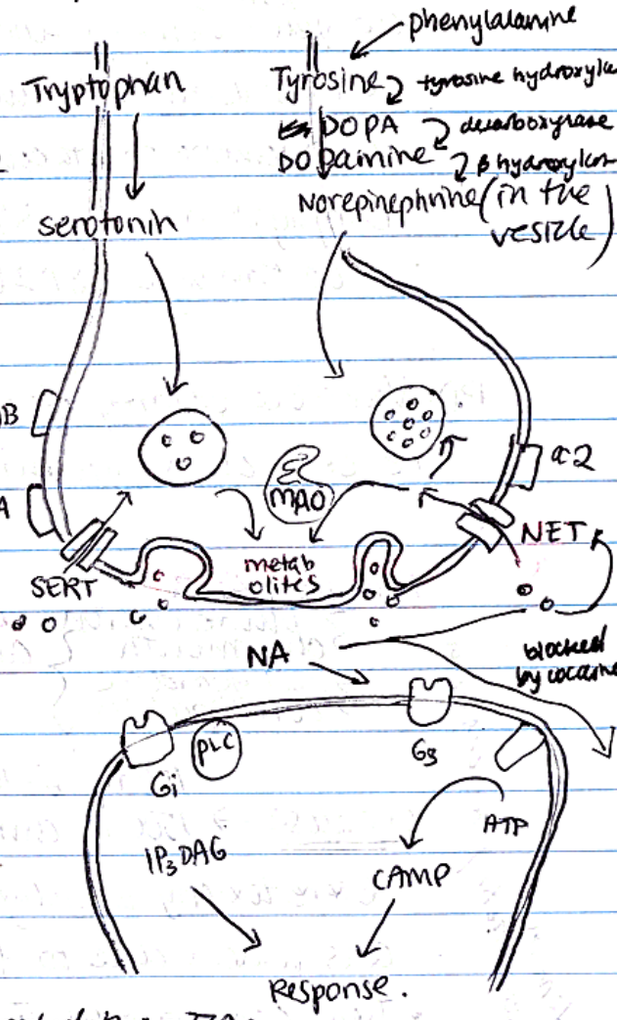
Escitalopram

Relatively safe in overdose

SE → nausea / diarrhoea, ↓ libido, headaches

Risk of serotonin syndrome

TRAZODONE



SNRIs

Act at both SERT & NET, better tolerated than TCAs.

All different structures.

Venlafaxine — weak inhibitor of NET, 45% bioav, liver metabolism CYP2D6 to desvenlafaxine, t½ of both = 10 hours, 45% des is excreted unchanged in urine (4% ven)

Des = better for liver disease

Duloxetine → 3 RINGS → 50% bioav, t½ 12-15 hrs, protein bound, hepatic impairment significantly Δ levels.

Also milnacipran + levomilnacipran.

SE: norad effects → HTN, ↑HR, CNS = insomnia, agitation, anxiety.

10mg/kg lethal

Nortriptyline.

TCAs (old school) iminodibenzyle core → used if SS & SNRIs fail.

Imipramine → highly anticholinergic.
→ strong SSRI/SNRI
→ OD = VF arrest

Amitriptyline
BioAv 45%, t½ 31-46hrs (active metabolite 96hrs)
90% protein bound.

Desipramine → more selective NA inhibitor
→ less anticholinergic.
→

Blocks reuptake of:
- serotonin
- noradrenaline

Blocks muscarinic, sympath α_1, $GABA_A$, Na^+ channel + Histamine

PK: RAPID
- Well absorbed + long t½'s 20-40hours, highly lipophilic + high volume of dist. (so cannot dialyse)
- Most dosed nocte due to sedation
- Extensive metabolism - demethylation, hydroxylation, glucoronide conjugation. Only 5% excreted unchanged in the urine.
- Go through CYP2D6 system - interact w fluoxetine

PD: Variable affinity for receptors - SERT vs NET
i.e ~~etopi~~ clomipramine more SERT → good for OCD.

Adverse effects
- → blurred vision
- → dry mouth
- → tachycardia
- → constipation

} anticholinergic/antimuscarinic effects

- seizures (CNS)
- sedation (anti histamine)
- Hypotension (anti alpha)
- wide QRS (Na^+ channel)

100mg in kids. >10mg/kg potentially life threatening

Overdose → 1500mg amitriptyline can kill you (7/7 supply)

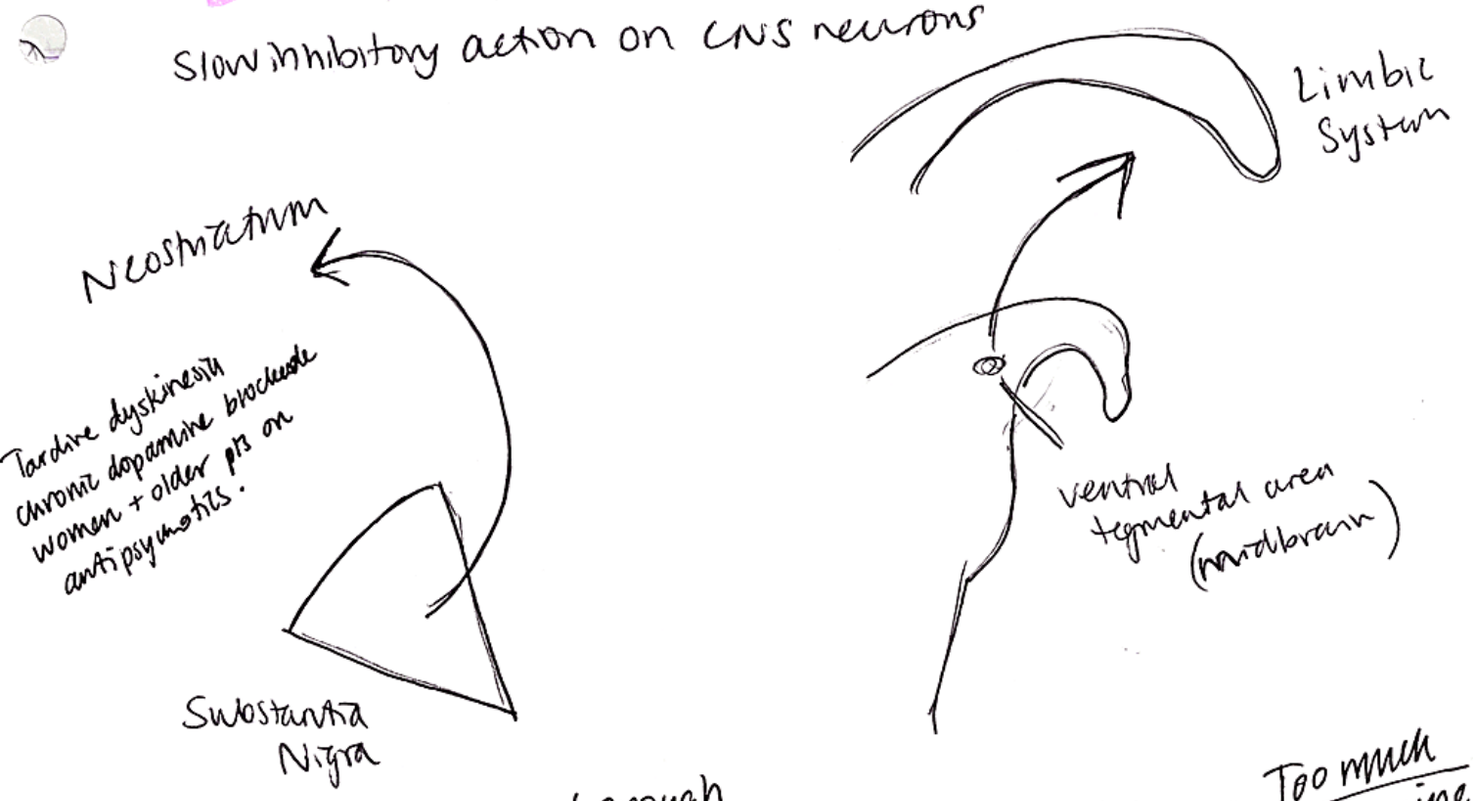
Severe toxicity usually manifests in 2hrs, can block GABA → seizures
QRS widens due to fast Na channel blockade → arrhythmias.

- Treat aggressively w sodium bicarb & hyperventilation.
  - ↳ plasma alkalinisation promotes protein binding to sequester TCA away & reduce free drug available.
  - ↳ sodium load ↑ Na to compete at receptor site.
  - ↳ ameliorate shock → replace volume to dilute + spread TCA.

Similar pattern in propranolol/local anaesthetic/carbamazepine overdose.

DOPAMINE

Slow inhibitory action on CNS neurons



PATHWAY #1 — Not enough dopamine

MOVEMENT

PATHWAY #2 — Too much dopamine

PSYCHOSIS

D2: inhibitory g protein.

D2 blockade (antipsychotics)

⇒ EPSEs

⇒ lactation.

⇒ dystonic rxn to metoclopramide.

D2 agonists (parkinsons Rx)

relief of akathesia.

Bromocriptine

⇒ hallucinations.

Inactivated in solution by Na Bicarb

Also precursor for norepi/adrenalin

used in shock. via adrenergic action

?systemically

Causes renal vasodilation,

↑GFR & natriuresis.

via D1 receptors

D1 = D2 >> β >> α

Pharm II

Antipsychotics → Highly protein bound → Lipid soluble ie get to the brain → Large Vd

"first generation" "typical" ⇒ lots of side effects

"neuroleptic" ↑ large action"

Phenothiazines (+ Thioxanthene) chlorpromazine / Fluphenazine / ~~Thioridazine~~ (LARGACTIL) hypotension promethazine → bad CVS effects

worst antimuscarinic symptoms

MOA: Blockade of D_2 receptors >> 5-HT_{2A} receptors

Effects:
- α-receptor blockade → hypotension
- muscarinic blockade (esp chlorpromazine)
- H_1 receptor blockade
- CNS depression → sedation
- ↓ seizure threshold
- QT prolongation (thioridazine)
- D_2 blockade → EPS, dystonic rxn, lactation.

Used for: schizophrenia (alleviate +ve symptoms)
bipolar mania
antiemesis
pruritis (antihistamine)

PO / parenteral — extensive 1st pass metabolism → PO = 25-30% BioAv.
long t½, metabolism dependent elimination (found in urine for weeks)
Tox: parkinsonian features from D_2 blockade. also α & muscarinic effects.
chlorpromazine can cause cholestasis.

Haloperidol (first generation) "BUTYROPHENONES" ↓ 1st pass = bioav ~ 65%
worst for EPSES
D_2 blockade > 5HT2
causes ++ extrapyramidal SE's.
→ used for tourettes.

Note: D_2 receptors in caudate, putamen, nucleus accumbens & olfactory tubercle.

"Atypicals"

Second Generation = complex pharmacology

Act more on 5HT2 than D_2 (also partial 5HT1A)

Clozapine "the prototype"

- agranulocytosis
- metabolic issues ↑ T2DM, ↑ lipids, ↑ wt gain
- ↓ seizure threshold
- less EPS.

$D_4 = \alpha_1 > 5HT_2 > D_2 = D_1$

Risperidone → to paliperidone (rapid)

- 10% pts poor metabolisers
- ↑ prolactin, weight gain

Olanzapine "the wafer" (oral tab/wafer, IM depot)

$5HT_{2A} > H_1 > D_4 > D_2 = D_1$

- expensive $$

Aripiprazole "the depot"

Partial agonist @ D_2

$D_2 = 5HT_{2A} > D_4 > \alpha_1 = H_1 > D_1$

Adverse effects:

- Extrapyramidal reactions (less common than in typicals)
- Tardive dyskinesia
- Antimuscarinic effects – dry mouth, retention, blurred vision
- Orthostatic hypotension (α_1 block)
- Metabolic – weight gain, ↑BGL, ↑ lipids
- ↑ prolactin (from dopamine)
- Agranulocytosis (clozapine)
- Neuroleptic malignant syndrome

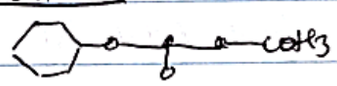
MORE UNCLASSIFIED ANTIDEPRESSANTS.

Pharm 11

5HT2 antagonists – trazodone + nefazodone + vortioxetine
Block negative feedback mechanisms
Highly sedating
sedation + GIT upset.

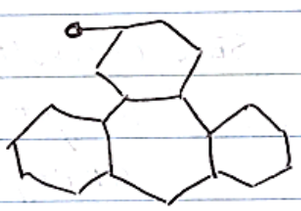
↓
also other 5HTs
also SERT

Tetracyclics –



Bupropion → Rapidly absorbed
unicyclic. → Protein binding 85%
→ significant first pass effect + hepatic metabolism.
→ Biphasic metabolism – 2hr then 14hrs
→ unique SE profile.
→ Resembles amphetamine structure & has CNS activating properties (agitation, insomnia, anorexia)
→

Mirtazapine.



→ no sexual side effects.(?)
→ $t_{1/2}$ 20-40hours
→ sedating = dose in the evening
→ hydroxylation + glucoronide conjugation.

Amoxapine
→ D_2 blocking → parkinson syndrome.

Antiparkinsons Medications

Dopamine replacement

L-DOPA ⟶ via jejunal tube w/ carbidopa.

- precursor for dopamine
- can cross the BBB (dopamine cannot)
- 1-3% enters the brain (↑ if also using dopa decarboxylase inhibitor) i.e carbidopa.

PK: t½ 1-3 hours (longer w/ carbidopa)
causes a +ve coombs test
Rapidly absorbed from small intestine but depends on the rate of stomach emptying and pH of gut (food competes w/ drug for absorption).

GIVEN W/ CARBIDOPA – ↓ side effects (n/v/anorexia)
– ↓ daily requirement by 75%

SE Sudden cessation causes tremor
Abrupt change = neuroleptic malignant syndrome.
80% develop dyskinesia after 10 yrs
DRUG HOLIDAY not recommended
→ slight ↑ responsiveness
→ risk of aspiration, PE, VTE, depression from ↓ mobility
carries it out.

Vomiting in parkinsons patient → use domperidone

Contraindicated in psychosis, Acute angle closure glaucoma, malignant melanoma.

Amantadine

Antiviral w antiparkinsons effects
MOA unclear
Also NMDA antagonist.

Ach blockers

— Improves the imbalance b/w Dopamine & cholinergic systems
— centrally acting antimuscarinic drugs.
i.e. benztropine, biperiden, orphenadrine, procyclidine, trihexyphenidyl.

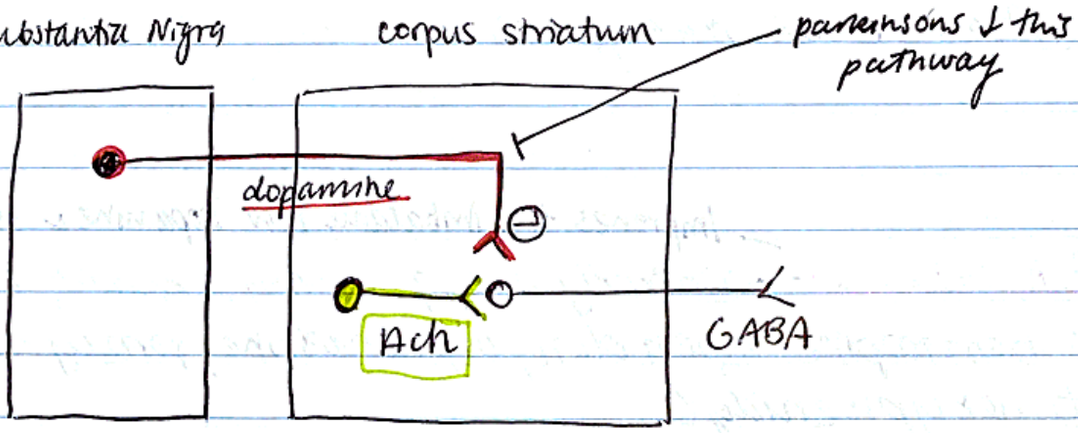
improves tremor + rigidity but little effect on bradykinesia

SI anticholinergic syndromes.
not tolerated in cognitively impaired
Acute suppurative parotitis 2° dry mouth.

VIVA Q:
NB: Benztropine also used as the antidote for acute dystonic rxns 2° to dopamine antagonists i.e Metoclopramide.
↳ acute dystonic rxns occur due to imbalance of dopaminergic + cholinergic neurotransmission.
Mech: nigrostriatal D2 receptor blockade → excess striatal cholinergic output

Antiparkinsons Medications

Basically



Options either ↑ dopamine OR ↓ Ach.

Dopamine agonists

Bromocriptine: D_2 agonist (full) + D_1 (partial)

Pergolide: $D_2 + D_1$

Pramipexole: D_3 > others
excreted unchanged in urine (x if renal failure)

Ropinirole: D2 agonist

Rotigotine: patch – for early disease

Adverse effects: anorexia/nausea/vomiting/heartburn
postural hypotension
cardiac arrhythmias
dyskinesia
mental disturbance – confusion / hallucinations

CI: Psychotic illness
Recent MI
peptic ulcer.

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LITHIUM 0.5mEq/kg/day.

Absorption: absorbs in 6-8hours
peak plasma levels 30mins - 2hours

Acts like Na+ in the tubules.

Distribution Total body water Vd 0.7L/kg
Slow to move into cells
some sequestration to bone
No protein binding.

Narrow therapeutic window: needs monitoring
→ levels 10-12hrs after dose
>2mmol/L toxic
Supportive Rx ± haemodialysis

Not metabolised

Excretion: Almost entirely in urine.
Clearance = 20% of creatinine clearance.
Plasma $t_{1/2}$ ~20hours.

MoA uncertain – supresses inositol signalling + inhibits glycogen synthase kinase-3 (GSK-3) a multifunctional kinase.
No significant effects on autonomic / CNS receptors. Not sedating.

clinically → prophylaxis against moods wings in bipolar. (nephrogenic diabetes insipidus)

Toxicity → Tremor, oedema, hypothyroidism (reversible), renal dysfunction → polyuria → polydipsia, dysrhythmias, pregnancy category D, Ataxia, confusion, Ebsteins anomaly.

Interactions – clearance reduced by thiazide diuretics + NSAIDS + ACEi's.
other antipsychotics can ↑ risk of EPS.
Slowing down of GFR rate = more time in PCT for resorption.
≈80% is filtered + reabsorbed
± Needs dialysis in overdose.

NB Osmotic diuretics or loop diuretics get rid of lithium