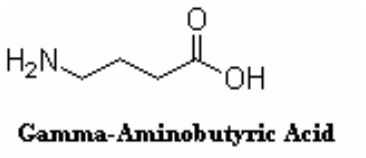
NEUROPHARMACOLOGY

(a) ***To describe the physiology and pharmacology of neurotransmitters and their receptors with particular reference to GABA, excitatory amino acids, acetylcholine, noradrenaline, dopamine and serotonin.***

GABA:

Overview of GABA:

- GABA (γ-aminobutyric acid) is the main inhibitory neurotransmitter in the brain
- Although found in trace amounts, it is ubiquitous in the brain:
  - Concentrated in the nigrostriatal system, and throughout the grey matter
  - Mainly found in short interneurons in the CNS, but also in long-tracts (Ie. to cerebellum and striatum)
  - 30% of synapses involve GABA, and nearly all neurons are sensitive to the inhibitory effects of GABA



Gamma-Aminobutyric Acid

Metabolism of GABA:

- GABA is formed in GABA-synthesising neurons from the decarboxylation of Glutamate by "Glutamic acid decarboxylase":

Glutamate —(Glutamic Acid Decarboxylase)→ γ-aminobutyric acid

- GABA is removed from the synapse via two means:
  - (1) Primarily by the removal of GABA from the synaptic cleft by GABA-ergic neurons and astrocytes (via specific GABA transporters)
  - (2) By transamination of GABA:
    - "GABA transaminase" transfers the amino group from GABA to α-oxoglutaric acid, thus producing glutamate and succinic semialdehyde, respectively
    - Succinic semialdehyde is later converted to succinic acid via the TCA cycle

Types of GABA Receptors:

- (1) GABA-A receptor:
  - Ligand-gated receptor Cl^- ion channel (inotropic receptor)
  - Pentameric (2α, 2β, γ) – Each subunit has 3-6 molecular subtypes, allowing for several permutations
  - Found widespread in the CNS; mainly postsynaptic in location
  - GABA activity at the GABA-A receptor causes "fast" inhibition – GABA binds to an α subunit of the receptor and causes increased membrane conduction to Cl^- (Ie. opening of the Cl^- channel). This causes the membrane potential to approach the equilibrium potential of Cl^- (-60 mV), thereby resulting in hyperpolarisation of the neuron
  - Modulatory sites exist (Bz bind to a Benzodiazepine receptor on the α-subunit distinct from the GABA binding site; barbiturates, propofol, VAs, etomidate and neurosteroids bind to a site on the β subunit) – Activation of these sites cause

increased affinity of the receptor for GABA (Ie. prolonged GABA-A receptor activation when the receptor is bound by GABA), leading to prolonged central Cl^- channel opening, and hyperpolarisation (and inhibition) of the postsynaptic neuron

- (2) GABA-B receptor:
  - G-protein-coupled receptor (metabotropic receptor)
  - Dimeric (two subunits)
  - Found widespread in the CNS; pre-and post-synaptic locations
  - GABA activity at the GABA-B receptor causes inhibition – GABA activates a "Gi" protein that inhibits Adenylate cyclase, thereby reducing intracellular levels of cAMP and thus preventing activation of Protein kinase A. This then causes (i) inhibition of voltage-gated Ca^{2+} channels (Ie. inhibits Ca^{2+} influx) and (ii) opening of K^+ channels (causes K^+ efflux), both of which results in hyperpolarisation of the neuron

Excitatory amino acids:

Types of excitatory amino acids in the CNS:

- (1) Glutamate
  - Main excitatory NT in the CNS (75%) – Uniformly distributed in the brain and spinal cord
  - Formation of glutamate stores in Glutamatergic-neurons occurs 3 ways:
    - (i) Glucose is converted via TCA cycle to α-oxoglutarate, which undergoes reductive amination (via GABA transaminase) into glutamate
    - (ii) Glutamate is recycled from the synapse via Glutamate transporters (Na^+-coupled reuptake transporters)
    - (iii) Glutamine is transferred from neighbouring astrocytes (via Glutamine transporter), which is then converted in the neuron to glutamate (via Glutaminase)
  - Glutamate is then stored in vesicles, and released into the synapse by Ca^{2+}-dependnent exocytosis
  - Synaptic activity of glutamate is terminated by reuptake via Glutamate transporters (Na^+-coupled reuptake transporters) into:
    - (i) Glutamatergic-neurons, whereby the glutamate is recycled
    - (ii) Astrocytes, whereby glutamate is converted to glutamine (via Glutamine synthetase), which is transported back into neurons for reconversion to glutamate
- (2) Aspartate

  - picture of glutamate-glutamine cycle and stuff

Types of Glutamate receptors:

- (1) Metabotropic receptor:
  - Monomeric GPRC (11 subtypes) – Associated with either Gq (increase IC IP_3/DAG) or Gi (decrease IC cAMP)
  - Widely distributed in the brain (neurons and astrocytes); pre- and post-synaptic locations
  - Function – Synaptic plasticity and excito-toxicity
- (2) Ionotropic receptors:
  - (a) Kainite
    - Pentameric ligand-gated ion channel (consists of GluR5-7 subunits plus KA 1-2) that mediates fast-excitatory synaptic transmission – Glutamate

(and kainite) binding causes opening of the ion channel (Na^+ influx/K^+ efflux)
        - Widely distributed in the brain (neurons and glial cells); pre- and post-synaptic locations
    - (b) AMPA (α-amino-3-hydroxy-5-methylisoxazole-4propionate)
        - Pentameric ligand-gated ion channel (consists of GluR1-4 subunits) that mediates fast-excitatory synaptic transmission – Glutamate (and AMPA) binding causes opening of the ion channel (mainly Na^+ influx, but also some Ca^{2+} influx)
        - Widely distributed in the brain (neurons and glial cells); post-synaptic location only
    - (c) NMDA (N-methyl-D-aspartate)
        - Pentameric ligand-gated ion channel (consists of NR1 and NR2 subunits) that mediates slow-excitatory synaptic transmission
        - Function – Excito-toxicity, synaptic plasticity (LT potentiation)
        - Widely distributed in the brain (esp in the hippocampus) only on neurons; found post-synaptically usually paired with an AMPA receptor
        - Features of the NMDA receptor
            - Cation channel is highly permeable to Ca^{2+} (but also Na^+ and K^+)
            - Glutamate (and NMDA) cause receptor activation in combination with Glycine as a co-agonist at low [ ] (Nb. glycine and glutamate bind at separate sites)
            - This channel is blocked by Mg^{2+} at resting potential – This is removed when the neuron is partially depolarised by activation of adjoining AMPA
            - Separate binding site for phencyclidine, ketamine, dextromethophan (all of which inhibit the receptor)

Acetylcholine:

- ACh is an acetyl ester of choline => made from reaction of acetyl CoA with acetate (via choline acetyltransferase in cytoplasm of nerve ending)
    - neurons take up choline via transporter; also syntheised in neurons
    - acetate activated by combination with coenzyme A
- ACh is then stored in synaptic vesicles of cholinergic neurons
- Removal form synapse
    - Hydrolysis to hcoline and acetate by AChE (true or specific cholinesterase => highest affinity fo rACh; found in synaptic cleft)
    - Pseudocholinesterase (nonspecficic) found in plasma => also hydrolyse ACh
- ACh is the NT at NMJ, ANS ganglia, and post-ganglionic PNS nerve target organ junctions; some postgang SNS nerve-target junctions; also in brain (sleep-wake state, learning, memory)

AChR

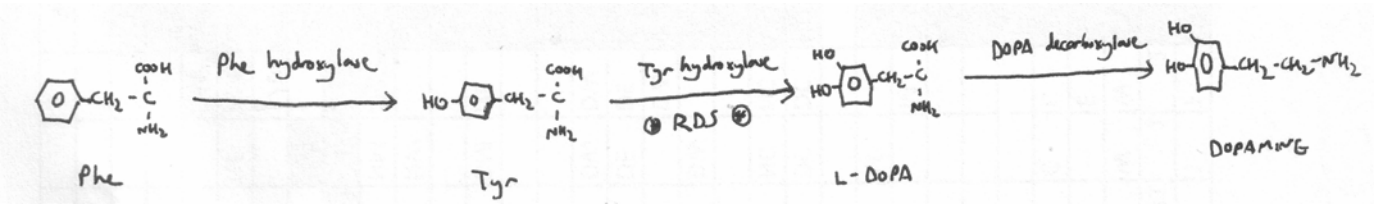
- mAChR
    - bind muscarine => stimulates action of ACh on SM and glands
    - blocked by atropine
    - brain
    - five types: M1-M4; M1 brain; M2 heart; M3/M4 SM; M5 ?
    - G-protein (Gi/Gq)
- nAChR
    - muscle at NMJ
    - ANS galngial
    - CNS
    - Brain

- Ligand-gated ion channels => pentameric (alpha, beta, gamme, delta, episilon); 16 known subunits
  -

Dopamine:

Overview of dopamine:

- Dopamine is a H_2O-soluble amine neurotransmitter
- Synthesis:



> Note: DA neurons lack dopamine β-hydroxylase → thus, NAd/Adr are NOT made!

- After release, it is taken up into nerve terminal via specific "DA transporters" → then metabolised by MAO and COMT into → Dihydroxyphenylacetic acid (DOPAC) and Homovanillic acid (HVA – methoxy-derivative of DOPAAC) → then conjugated (with sulphate) → excreted in urine

> Note – HVA can be used as a measure of DA turnover

Dopamine receptors:

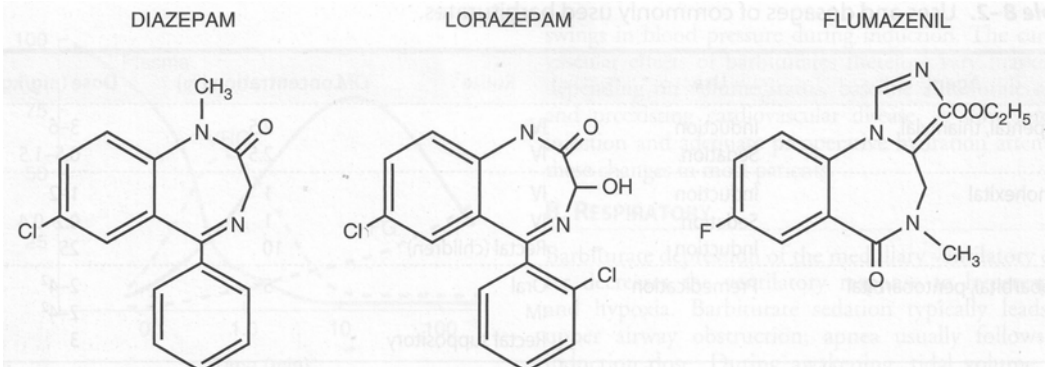
- Two types of DA receptors:
  - D1 receptors
    - GPCR → Gs mechanism (stimulates adenylyl cyclase → ↑ cAMP → activates protein kinase A)
    - Mainly post synaptic inhibition
    - Subgroups → D1 and D5
  - D2 receptors
    - GPCR → Gi mechanism (inhibits adenylyl cyclase → ↓ cAMP → ↓ protein kinase A activity) or Gq mechanism (stimulates PLC → ↑ DAG (activates protein kinase C) and ↑ IP3 (↑ Ca^{2+}))
    - Pre and post synaptic inhibition
    - Subgroups → D2, D3, D4
- Location and function:
  - (1) CNS
    - (a) Nigrostrial pathway (75%) → substantial nigra to corpus striatum → forms extrapyramidal system (motor function)
    - (b) Mesolimbic/mesocortical pathway → midbrain to limbic system (esp nucleus ambiguus and amygdaloid nucleus) and frontal cortex → role in emotion (reward) and behavioural effects (stereotyped behaviour patterns)
    - (c) Tuberohypophyseal pathway → ventral hypothalamus to median eminence and anterior pituitary gland → endocrine effects (inhibits PRL release and stimulates GH release)
    - (d) Medulla → forms chemoreceptor trigger zone (role in emesis)
  - (2) Peripheral
    - (a) Renal vasculature → causes renal vasodilation
    - (b) Cardiac muscle → causes ↑ cardiac contractility

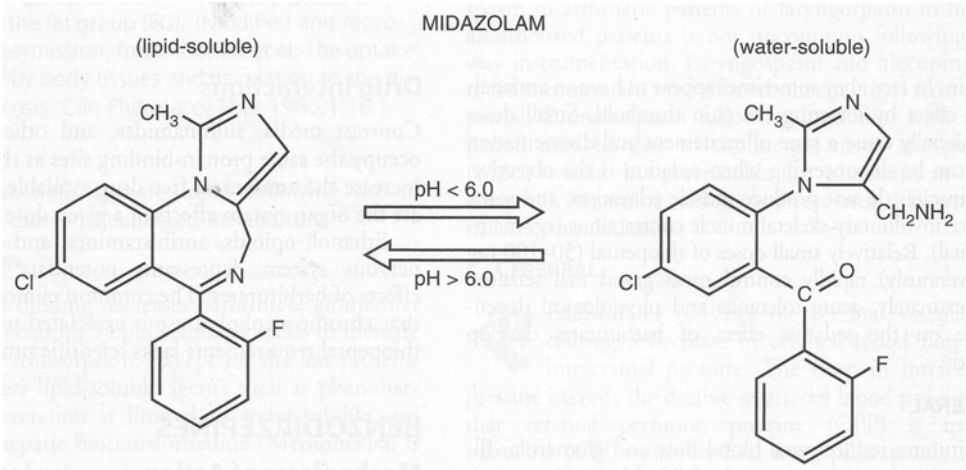
(b) ***To describe the pharmacology of anxiolytic/hypnotic agents with particular reference to benzodiazepenes and barbiturates.***
(c) ***To describe the comparative pharmacology of the benzodiazepines with particular reference to midazolam, diazepam, lorazepam and flumazenil.***

<u>Benzodiazepines</u>:

<u>Chemical structure of benzodiazepines</u>:

- Basic two ring structure – Benzene ring fused to a seven-membered diazepine ring (5 C-atom; 2 N-atom)
- For pharmacological activity, benzodiazepines will generally have:
    - (i) Another benzene ring is added to the diazepine ring at position-5 – This forms 5-aryl-1,4-benzodiazepine
    - (ii) Halogen fused onto the original benzene ring
    - (iii) Carbonyl group on position-2





<u>Mechanism of action of midazolam</u>:

- Benzodiazepines potentiates the inhibitory effects of GABA on GABA-A receptor in the CNS (esp the brain):
    - GABA-A receptor is a pentameric ligand-gated receptor (2α, 2β, γ) that is associated with a central Cl^- channel pore. It is found widespread in the CNS and is mainly postsynaptic in location
    - Benzodiazepines act at the α-subunit of the receptor (similar to GABA, BUT at a separate binding site on the α-subunit):
        - Acts via α1-subunit (most abundant in the brain; 60%) to cause sedation, and α2-subunit to cause anxiolysis

        - They do NOT activate the receptor directly – Instead they enhance the affinity of the receptor for GABA (Ie. prolonged GABA-A receptor activation when the receptor is bound by GABA), leading to prolonged central Cl^- channel opening, increased Cl^- influx, and hyperpolarisation/inhibition of the postsynaptic neuron
- The receptor complex has separate binding sites for other agents (Eg. barbiturates, propofol, etomidate, EtOH):
    - Synergistic effects on GABA-A receptor-mediated CNS inhibition (Ie. risk of OD/life-threatening CNS depression) occur when other GABA-mediated agents are given concurrently
    - Cross-tolerance occurs between different agents acting on the receptor (Ie. benzodiazepines can be used for EtOH detoxification)

Relevant benzodiazepines:

(A) **Midazolam**:

Chemical structure of midazolam:
- Basic two ring structure (benzene and diazepine rings) with an "Imidazole" ring moiety that displays pH-dependent ring opening and closing:
    - At pH < 4 – Ring opens to form an ionised molecule (water-soluble). Thus, the parental solution is buffered at pH 3.5!
    - At pH > 4 – Ring closes to form an unionised molecule (lipid-soluble). This occurs at physiological pH

Formulation of midazolam:
- Prepared as a clear and colourless aqueous solution at pH 3.5 – This favours the ionised open imidazole-ring structure (Ie. this makes it water-soluble so that it does not require a solubilising agent; cf. diazepam and lorazepam)
- Concentrations of 1, 2 and 5 mg/mL

Pharmacokinetics of midazolam:
- Overview:
    - IV midazolam has rapid onset (30-60 seconds) because it can rapidly cross the BBB due to its (i) high lipid solubility, (ii) largely unionised at physiological pH (despite large degree of protein-binding), and (iii) Small V_D
    - However, its requires sufficient time for peak clinical effect (3-5 minutes) due to its slow effect-site equilibrium time
    - IV midazolam has a short duration of action (30 minutes) because:
        - (i) It rapidly redistributes to peripheral tissues ($t_{½\ \alpha}$ ~ 6-15 minutes)
        - (ii) It has rapid clearance by hepatic/intestinal metabolism and renal excretion

Absorption	- PO: Rapid absorption from GI tract with 50% bioavailability (heavy first-pass metabolism) - IM: 80-100% bioavailability - Given as IV bolus or infusion
Distribution	- High lipid solubility - $V_{DISTRIBUTION}$ ~ 1-1.5 L/kg (same as diazepam) - pKa ~ 6.15 (Nb. 90% unionised at physiological pH) - 98% protein-bound - Long effect-site equilibrium time (1-5.5 minutes) - Short "Distribution half life" ($t_{½\ \alpha}$) ~ 6-15 minutes
Metabolism and Excretion	- Clearance rate (6-8 mL/kg/min): - Metabolism – Extensive oxidative metabolism by hepatic and

	small intestinal CYP450 3A4, which produces: o Main metabolite – 1-hydroxymidazolam (50% activity), which is rapidly conjugated to glucuronide-1-hydroxymidazolam (high activity at high concentrations, which occurs with chronic use, prolonged infusions or with renal disease) o Minor metabolite – 4-hydroxymidazolam, which is glucuronidated also o Nb. Metabolism is slowed by liver disease, age, and inhibitors of CYP450 3A4 – Fentanyl, alfentanyl, cimetidine, erythromycin, CCBs, antifungals - Excretion – Both inactive and active metabolites are renally excreted - Shortest "Elimination half-life" (t ½ β) ~ 1-4 hrs due to very high hepatic extraction (metabolism) - Small CSHT (cf. diazepam, lorazepam) – Can be used for infusion - Note – Due to EXTENSIVE hepatic metabolism, elimination half-life, V_D and renal clearance is NOT affected by renal failure

<u>Clinical uses of midazolam</u>:

- (1) Induction of anaesthesia:
  - IV 0.1-0.2 mg/kg provides rapid onset (30-60 seconds) but delayed peak clinical of anaesthesia (3-5 minutes) that lasts for 30 minutes
  - Co-administering other CNS depressants that act synergistically (Eg. fentanyl) help to (i) Hasten the onset of LOC, and (ii) Reduce the dose of midazolam required
  - Causes minimal CVS depression (unless given with other CNS depressants)
- (2) Maintenance of anaesthesia:
  - Given to supplement opioid, propofol and inhaled anaesthetic agents in maintaining GA
  - Benefits – (i) Allows lower doses of midazolam and co-administered agents (Eg. MAC-sparing, reduces opioid requirements), (ii) Minimises PONV, and (iii) Minimises emergence excitement
  - Issues – (i) Prolonged awakening following GA, (ii) Slightly longer CSHT (cf. propofol)
- (3) IV sedation for brief procedures or during regional anaesthesia:
  - IV 1 to 2.5 mg with similar onset/offset profile as induction of GA
  - Benefits – (i) Rapid onset, (ii) Greater amnesic effects (cf. sedation), (iii) Less post-operative sedation, (iv) Minimal CVS depression
  - Issues – (i) Ventilatory depression (esp if other CNS depressants given, elderly or COPD), and (ii) Slightly longer CSHT (cf. propofol)
- (4) IV sedation in ICU
  - IV 0.5-4 mg bolus, then infusion of 1-7 mg/hr
  - Issues of "delayed emergence" after cessation of a prolonged infusion:
    - This is because midazolam has a slightly prolonged CSHT due to:
      - (i) Clearance being dependent more on hepatic clearance/metabolism rather than distribution (as peripheral tissues are saturated)
      - (ii) Presence of pharmacologically active metabolites
    - This is exacerbated if – (i) Larger doses are given, (ii) Longer infusion, (iii) Older patient (less clearance), and (iv) More obese patient (more V_D)
    - This can be prevented by giving concurrent opioids (Eg. morphine), which reduces the doses of midazolam used
- (5) Preoperative medication (esp for children)

    - PO 0.25 mg/kg to 0.5 mg/kg syrup (up to max 1 mg/kg) given 20-30 minutes prior to surgery permits sedation and anxiolysis without respiratory depression, delayed emergence and significant amnesia
- (6) Anticonvulsant (to treat grand-mal seizures and status epilepticus)

Pharmacodynamic effects of midazolam:

CNS effects	
General effects	- (i) Anxiolysis - (ii) Sedation/hypnosis - (iv) Spinal cord-mediated skeletal muscle relaxation (but not adequate for surgery; does not change dose of NMBD) - (v) Anterograde amnesia – Note that amnesic effects more potent than sedative (Ie. awake but remain amnesic of events thereafter) - Absence of analgesic effects
CBF	Dose-dependent decrease due to cerebral vasoconstriction from decreased metabolism
ICP (and IOP and CPP)	- No rise in ICP for patients with IC pathology - Increase in ICP if severe head trauma with ICP < 18 mmHg or if given rapidly - Does not prevent rise in ICP caused by AW instrumentation
$CMRO_2$	Dose-dependent decrease
EEG and seizure activity	- Dose-related decrease in EEG activity – Gradual progression from awake α pattern (high frequency, low voltage) to δ- and θ-waves (synchronised slow frequency, high voltage) BUT unable to produce silent (isoelectric) EEG (even at very high doses) - Potent anticonvulsant used to treat grand-mal seizures and status epilepticus
CVS effects	
HR	Dose-dependent increase in HR (up to 20%; especially if hypovolaemic) due to activation of BRR with the fall in BP
CO	Unchanged
BP	Dose-dependent fall in MAP (up to 5%; especially if hypovolaemic) due to decreases in SVR
SVR	Dose-dependent decrease by 15-30% due to peripheral vasodilation
Haemodynamic sequelae of AW instrumentation	- Hypertensive response to AW instrumentation CANNOT be blunted by the fall in BP caused by midazolam – Thus, opioids must be given concurrently - Hypotensive effects of midazolam can be prevented by the hypertensive response to AW instrumentation
Arrhythmogenicity	Nil. Does not prolong QTc
Coronary BF and CMRO2	Decreased O_2 metabolism and increased O_2 delivery (due to coronary vasodilation)
Respiratory effects	
Minute ventilation and resting $PaCO_2$	- Dose-dependent decrease in MV (TV decreases but RR increases) - Significant ventilatory depression and apnoea can occurs, especially with – (i) COPD, (ii) rapid bolus of large dose (> 0.15 mg/kg IV for induction), (iii) Concurrent opioids - Increased resting $PaCO_2$
Ventilatory response to $PaCO_2$ and PaO_2	Impaired
Effect on AW	- No bronchodilatory effects - Depresses UAW reflexes (risk of aspiration and AW obstruction)

Pulmonary vasculature	Hypoxic pulmonary vasoconstriction intact
GI, GU, metabolic and other effects	
- Decreased HBF - Decreased GFR, RBF and U/O - Decreased PONV - Decreased platelet activity	
Issues with injection	
- None	
Relevant adverse or undesired effects	
- Lower potential for abuse as less tolerance (cf. other benzodiazepines), BUT dependence and withdrawal symptoms still occur - Delayed awakening	
Drug interactions	
- Synergistic effects with other CNS depressants (Eg. volatile agents, other IV induction agents, opioids, EtOH) - Prolonged duration of action by inhibitors of hepatic CYP450 (Eg. cimetidine, erythromycin, Etc.) - Antagonised by flumazenil	

(B) **Diazepam**:

Formulation of diazepam:

- For IV or IM:
  - Highly water insoluble (cf. midazolam) and requires either an:
    - (i) Organic solvent (propylene glycol, sodium benzoate) to produce a clear yellow solution
    - (ii) Oil phase (soybean) to produce a white oil-in-water emulsion
  - Comes as 0.5% (5 mg/mL) at a pH of 6.6 to 6.9
- For PO – Tablets (2, 5 or 10 mg) or syrup
- PR suppositories

Pharmacokinetics of diazepam:

- Rapid onset (either PO or IV/IM) due to its very high lipid solubility (and thus rapid effect-site equilibrium time)
- Offset determined – (i) Mainly by clearance rate (hepatic metabolism and urinary/biliary excretion), which is very SLOW, and (ii) Redistribution to peripheral compartments (rapidly and extensively taken up by fat due to high lipid solubility)
- Cannot be used as an IV infusion due to – (i) High CSHT with prolonged infusions (due to slow clearance, saturation of fat compartments, long t ½ β), and (ii) Accumulation of active metabolites (esp desmethyl-diazepam, which has a elimination half-life 2X longer than diazepam!)

Absorption	- PO: Rapid GI absorption due to high lipid solubility, and minimal first-pass metabolism with 86-100% bioavailability. Effects peak at 1 hr - IM: 86-100% bioavailability - Given as IV bolus only (not as an infusion)
Distribution	- Very high lipid solubility - $V_{DISTRIBUTION}$ ~ 1-1.5 L/kg (same as diazepam) - pKa ~ 3.5 - 96-98% protein-bound - Very rapid effect-site equilibrium time (due to lipid solubility) - "Distribution half life" (t ½ α) ~ 60 minutes
Metabolism and	- Clearance rate (0.2-0.5 mL/kg/min) is the LOWEST of all

Excretion	benzodiazepines: - Metabolism – Hepatic metabolism by CYP450 (via N-demethylation) into active metabolites that cause prolonged Bz effects – (i) Desmethyl-diazepam, (ii) Oxazepam, and (iii) Temazepam (small amounts). They are then glucuronidated into inactive metabolites - Nb. Metabolism is slowed by liver disease, age, and inhibitors of CYP450 3A4 – Fentanyl, alfentanyl, cimetidine, erythromycin, CCBs, antifungals - Excretion – (i) Renal (<1% unchanged; > 99% as inactive and active metabolites), (ii) Bile (enterohepatic circulation "recycles" diazepam and its metabolites causing recurrent effects in 6-12 hrs) - Longest "Elimination half-life" (t ½ β) ~ 21-37 hrs of all Bz – Due to slow hepatic extraction and large V_D - Long CSHT (thus, not suitable for infusion) due to (i) Low clearance rate, and (ii) Significant redistribution (esp into fat stores)

Clinical uses of diazepam:

- (1) Premedication prior to surgery (PO 0.2-0.5 mg/kg)
- (2) IV induction for GA (IV 0.3-0.6 mg/kg) or sedation for brief procedures (IV 0.04-0.2 mg/kg) – NOT used anymore due to midazolam!
- (3) Treatment of seizures (esp status epilepticus or LA-induced seizures)
- (4) Muscle relaxation (esp for use in lumbar-disc disease)
- (5) Anxiety management
- (6) Treat EtOH withdrawal or delirium tremens

Pharmacodynamic effects of diazepam:

CNS effects	
General effects	- (i) Anxiolysis - (ii) Sedation/hypnosis - (iv) Spinal cord-mediated skeletal muscle relaxation (but not adequate for surgery; does not change dose of NMBD) - (v) Anterograde amnesia - Absence of analgesic effects
CBF	Dose-dependent decrease due to cerebral vasoconstriction from decreased metabolism
$CMRO_2$	Dose-dependent decrease
EEG and seizure activity	- Dose-related decrease in EEG activity – Gradual progression from awake α pattern (high frequency, low voltage) to δ- and θ-waves (synchronised slow frequency, high voltage) BUT unable to produce silent (isoelectric) EEG (even at very high doses) - Potent anticonvulsant activity (used to treat seizures)
CVS effects	
HR	- Mildest effects on CVS system cf. other Bz agents - Minimal dose-dependent decrease in CO, SVR and BP at doses of 0.5-1 mg/kg IV (Ie. induction doses) - Decrease in HR due to blunting of BRR
CO	
BP	
SVR	
Coronary BF and CMRO2	Decreased O_2 metabolism and increased O_2 delivery (due to coronary vasodilation)
Respiratory effects	
Minute ventilation and resting $PaCO_2$	- Minimal ventilatory depression of all Bz agents - Rarely produces apnoea (unless high doses given, concurrent CNS depressants or COPD)

	- Minimal increase on $PaCO_2$ (except at high doses)
Ventilatory response to $PaCO_2$ and PaO_2	Decreased ventilatory response to $PaCO_2$ and PaO_2 at induction doses only
Effect on AW	- No bronchodilatory effects - Depresses UAW reflexes (risk of aspiration and AW obstruction)
Pulmonary vasculature	Hypoxic pulmonary vasoconstriction intact
Issues with injection	
- Pain and thrombophelebitis occur (EXCEPT with soybean formulation)	
Relevant adverse or undesired effects	
- Tolerance - Overdose causes significant CNS depression (coma) if CVS and respiratory functions not supported OR if other CNS depressants present (Eg. opioids, EtOH)	
Drug interactions	
- Synergistic effects with other CNS depressants (Eg. volatile agents, other IV induction agents, opioids, EtOH) - Prolonged duration of action by inhibitors of hepatic CYP450 (Eg. cimetidine, erythromycin, Etc.) - Antagonised by flumazenil	

(C) **Lorazepam**:

Formulation of lorazepam:
- IV/IM: Water insoluble (like diazepam) and thus requiring a solvent (polyethylene glycol or propylene glycol) to produce a clear and colourless solution (4 mg/mL; 0.4%)
- PO: 1 and 2.5 mg tablets

Pharmacokinetics of lorazepam:
- Slow onset (either PO or IV/IM) due to its moderate lipid solubility (and thus delayed effect-site equilibrium time)
- Offset determined mainly by clearance rate (hepatic metabolism and urinary/biliary excretion), which is SLOW
- Cannot be used as an IV infusion due to high CSHT with prolonged infusions (due to slow clearance, long t ½ β)
- Despite shorter t ½ β than diazepam, duration of activity is as prolonged due to very high receptor affinity

Absorption	- PO and IM: Good absorption with 90% bioavailability - Given as IV bolus only (not as an infusion)
Distribution	- Moderate lipid solubility - $V_{DISTRIBUTION}$ ~ 0.8-1.3 L/kg (lower than midazolam/diazepam) - 96-98% protein-bound - Delayed effect-site equilibrium time (due to moderate lipid solubility) - "Distribution half life" (t ½ α) ~ 60 minutes

Metabolism and Excretion	- Clearance rate (0.7-1 mL/kg/min):
	  - Metabolism – Hepatic conjugation with glucuronide into ONLY inactive metabolites (cf. midazolam and diazepam). Unlike other Bz, its rate of metabolism is relatively SLOWER, and is NOT unaffected by cirrhosis, inhibitors of CYP450 function (Eg. cimetidine) or age!
	  - Excretion – Renal (> 80% inactive; < 20% active). Note that as most lorazepam is metabolised by the liver, clearance is NOT affected by renal disease!
	- Long "Elimination half-life" (t ½ β) ~ 10-20 hrs – Due to slow

	hepatic metabolism - Long CSHT (thus, not suitable for infusion) due to low clearance rate and long t ½ β

Clinical uses of lorazepam:

- (1) Premedication (for anxiolytic and amnesic properties)
    - PO 50 μg/kg/day or 1-4 mg/day (in divided doses) with effect in 2-4 hrs and persisting for 24-48 hours
    - Amnesic effects (lasting maximum 6 hours) are greater than sedation; however, higher doses lead to additional sedation without an increase in amnesic effects
    - Main issue is delayed emergence due to its prolonged duration of action
- (2) IV induction or sedation for brief procedures
    - IV 30-40 μg/kg (1-4 mg) with effect in 1-2 minutes, peaking at 20-30 minutes and lasting 6-10 hours
    - Benefits – (i) Significantly more potent sedative and amnesic effects (cf. diazepam and midazolam) but with same degree of CVS and respiratory stability, (ii) Effective in limiting "emergence delirium" with ketamine use, (iii) Prolonged sedative effect ideal for long-term sedation in ICU
    - Issues – (i) Significantly delayed emergence and weaning from mechanical ventilation due to prolonged sedation, (ii) Prolonged amnesic effects
- (3) Short-term treatment of anxiety
- (4) Treatment of status epilepticus

Pharmcodynamic effects of lorazepam:

- Similar effects to diazepam EXCEPT:
    - (i) No direct CVS effects
    - (ii) Less pain on injection and thrombophlebitis

(D) **Flumazenil**:

Overview of flumazenil:

- 1,4-imidazobenzodiazepine derivative
- Available as a clear and colourless solution (100 mcg/mL)

Mechanism of action of flumazenil:

- Has a high affinity for the benzodiazepine receptor-binding site on the GABA-A receptor where it has the following effects:
    - (1) Competitive antagonist activity (Main effect) – Prevents or reverses any agonist effect of a Bz at the receptor in a dose-dependent manner
    - (2) Minimal agonist activity
    - (3) May possess inverse agonist activity (as it can cause seizures)

Pharmacokinetics of flumazenil:

- Good absorption in the GI tract But significant first-pass hepatic metabolism (25% oral bioavailability)
- 50% plasma protein bound with a V_D of 0.9 L/kg
- Significant hepatic metabolism by CYP450 into inactive metabolites (carboxylic acid and glucuronide)
- Inactive metabolites undergo renal excretion (only < 0.1% excreted unchanged)
- Clearance of 0.7-1.1 L/min
- Elimination half-life (t ½ β) ~ 60 minutes

Clinical uses of flumazenil:

- (1) Reverse effects of Bz (esp excessive sedation or OD)

    - IV 0.1-0.2 mg IV given with effect evident within 1-2 minutes (Eg. reverse CNS effects of Bz). Further 0.1 mg IV can be given minutely (to a max of 1 mg IV)
    - Usually 0.3-0.6 mg is needed to reverse sedation with Bz (while up to 1 mg may be needed to completely abolish the effects of Bz). Unconsciousness due to OD of Bz may need up to 5 mg!
    - Short t ½ β means that the duration of action is only 30-60 minutes – Thus, repeated doses or continuous infusion (0.1-0.4 mg/hr) is needed to maintain level of consciousness
- (2) Part of "wake up test" for scoilosis surgery
- (3) Treatment of EtOH intoxication

Pharmacodynamic effects of flumazenil:
- Flumazenil has no intrinsic effects (although it may posses anticonvulsant properties)
- Side-effects include – N/V, hypotension, facial flushing, anxiety, headaches
- Withdrawal effects not seen (Eg. anxiety, increased CVS response, increased neuroendocrine outflow, increased anaesthetic requirements such as with MAC)
- However, withdrawal effects are seen in epileptic patients on anti-epileptic drugs and patients with mixed drug ODs – Thus, do NOT give these patients flumazenil due to risk of acute withdrawal seizures!

Barbiturates:
- See "Barbiturates" in "IV anaesthetic agents"
- Use of barbiturates as anxiolytic and sedative-hypnotic agents declining and have been largely replaced by Bz due to:
    - (1) Lack of specificity of effect in CNS (and more side-effect profile)
    - (2) Lower therapeutic index
    - (3) Higher tolerance and risk of abuse
    - (4) Higher incidence of drug interactions due to hepatic CYP450 induction
    - (5) Issues with "hangover" effect (residual CNS effect lasting several hours), paradoxical excitement, antanalgesia at low doses, and absence of skeletal muscle relaxation

(d) ***To outline the pharmacology of the antidepressant medications and their adverse effects. To describe the potential adverse drug interactions with these agents.***

(1) Tricyclic antidepressants (TCAs):
- Types: Amitriptyline, imipramine, nortriptyline, clomipramine, doxepin
- Mechanism of action:
    - Mainly competitive inhibition of neural reuptake of amines (esp NAd and 5-HT; less effect on DA), thereby increasing their concentrations within the synapse
    - Also antagonise mAChR, 5-HT receptors, histamine receptors, α2-adrenoceptors (thus, causing side-effects)
- Clinical effects (and adverse effects):
    - Generally long-acting drugs due to long-elimination half-life (10-20 hrs), presence of active metabolites, and high $V_{DISTRIBUTION}$
    - Antidepressant effect is delayed and takes up to 2-4 weeks for effect
    - Sedation (due to antihistamine effect)
    - Anticholinergic effects (dry mouth, constipation, confusion, urinary retention, blurred vision)
    - Postural hypotension (due to adrenoceptor blockade)
    - Overdose of a TCA can be lethal – Causes delirium, seizures, coma, respiratory depression, cardiac arrhythmias (prolonged QTc, leading to VT/VF), and hyperthermia
- Drug interactions:
    - MAOi – Enhance hypertensive response to dietary tyramine (thus, do NOT give TCA and MAOi together)
    - SSRI – TCA metabolism is inhibited by SSRIs, thereby leading to TCA toxicity (thus, do NOT give TCA and SSRI together)
    - Effects enhanced by drugs that compete for protein-binding (Eg. antifungals, NSAIDs, aspirin)
    - Effects enhanced by drugs that inhibit CYP450 (Eg. antipsychotic drugs, steroids)

(2) Selective 5-HT reuptake inhibitors (SSRIs):
- Types: Fluoxetine (most commonly prescribed), paroxetine, citalopram, sertraline
- Mechanism of action – Selectively inhibit neural reuptake of 5-HT (significantly more than NAd)
- Clinical effects (and adverse effects):
    - Antidepressant effect similar to other agents and effect only seen after 2-4 weeks also – BUT side-effect profile is much better (less sedation, fewer anticholinergic effects, less cardio-toxic with overdose)
    - Long-acting drugs due to long elimination half-life (15-24 hrs; up to 96 hrs with fluoxetine)
    - Main side-effects include – Constipation, N/V, anorexia, insomnia, loss of libido, and failure of orgasm
- Drug interactions
    - "5-HT syndrome" occur when serotinergic drugs are combined (SSRI with MAOi, TCA, amphetamines, pethidine, tramadol) – Causes tremor, hyperreflexia, clonus, agitation, hyperthermia, and CVS collapse
    - MAOi – Enhance hypertensive response to dietary tyramine (thus, do NOT give SSRI and MAOi together)
    - TCA – TCA metabolism is inhibited by SSRIs, thereby leading to TCA toxicity (thus, do NOT give TCA and SSRI together)
    - NSAIDs – Inhibit coagulation by platelet inhibition

(3) Other monoamine uptake inhibitors:
- Selective NAd reuptake inhibitor (Eg. reboxetine) – Only inhibit NAd reuptake

- Selective 5-HT/NAd reuptake inhibitor (Eg. venlafaxine, duloxetine) – Inhibit 5-HT reuptake at lower doses, but have increasing inhibitory effect on NAdr reuptake at higher doses
- Both these types of agents have far fewer adverse effects cf. TCA and SSRIs (esp to cardiac effects), and thus safer with accidental OD

(4) Monoamine oxidase inhibitor (MAOi):
- Mechanism of action:
    - MAO-A and –B are present within presynaptic neurons and play a role in deamination of amine NTs – MAO-A deaminates 5-HT/NAd; MAO-B deaminates phenylethamine/benzylamine
    - 5-HT/NAd can leak from pre-synaptic vesicles but are usually metabolised by MAO-A. Inhibition of MAO-A prevents this, thereby leading to enhanced synaptic transmission of 5-HT/NAd
- Types:
    - (i) Irreversible and non-selective MAOi (Eg. phenelzine, tranylcypromine) – Very long-acting (weeks) and associated with significant side-effects
    - (ii) Reversible and selective MAO-Ai (RIMA; Eg. moclobemide) – Shorter duration of action and fewer side-effects (esp lower risk of "cheese reaction")
    - Nb. Due to significant side-effects and drug interactions, MAOi are NOT 1st line antidepressant agents
- Side-effects:
    - Sedation
    - Orthostatic hypotension
    - CNS stimulation (tremor, excitement, insomnia and seizure)
    - Weight gain
    - Anticholinergic symptoms
    - Hepatotoxicity (rarely)
- Drug interactions:
    - "Cheese reaction" – Hypertensive crisis (with CVA and arrhythmias) occur when indirect acting sympathomimetics (Ephedrine and Tyramine-rich food such as cheese, chocolate, red wine) are given. This is because MAO normally metabolises these substances, thus inhibition of MAO will lead to their accumulation in the body
    - Direct acting sympathomimetic agents (phenylephrine, NAd, Adr) should be used cautiously due to risk of hypertensive crisis also
    - Drugs that potentially stimulate NAd release (Eg. ketamine, pancuronium) should be avoided also
    - Should not be given with TCA or SSRI (enhances hypertensive response to dietary tyramine)
    - Should not be given with pethidine and fentanyl (due to opioid metabolite inhibiting metabolism of MAOi) – May cause cerebral irritability, hyperpyrexia, CVS instability, coma
    - 5-HT syndrome – MAOi and opioids with 5-HT activity (tramadol, pethidine)
    - Nb. MAOi may be withdrawn 2-3 weeks pre-operatively to minimise these drug interactions, BUT there is risk of relapsed depression

(5) NAd/Selective 5-HT antagonists (Eg. Mianserin and mirtazapine):
- Act by antagonising pre-synaptic α2-adrenoceptors and 5-HT receptors, thereby indirectly causing release of NAd and 5-HT into the synapse
- Side-effects:
    - Agranulocytosis and aplastic anaemia
    - Very little anticholinergic and hypotensive effects (due to minimal mAChR and peripheral α-adrenoceptor antagonism)

(6) Lithium carbonate:

- Mechanism of action – In excitable cells, it imitates Na^+ and thereby decreases the release of NTs. It may also interfere with formation of IC 2nd messengers (cAMP and IP3)
- Long-plasma half-life and narrow therapeutic index require careful monitoring of plasma levels (esp with renal disease or diuretic usage) – Maintain levels at 0.5-1.5 mmol/L to avoid adverse effects
- Side-effects:
    - N/V
    - Polyuria and polydipsia (due to ADH antagonism)
    - Thyroid enlargement with hypothyroidism
    - Mental confusion
    - Tremor, increased muscle tone and weakness
    - Weight gain
    - With acute OD – Confusion, ataxia, coma, convulsions, cardiac arrhythmias
- Drug interactions:
    - Can prolong action of muscle relaxants
    - Decreases GA requirements (esp reducing MAC of VAs)

(e) ***To outline the pharmacology of antipsychotic medication.***

Typical antipsychotic agents:

- Includes:
  - (1) Phenothiazines (Eg. Chlorpromazine)
  - (2) Butyrophenone (Eg. Haloperidol)
  - (3) Thioxanthenes (Eg. Flupenthixole)
- Mechanism of action:
  - (i) Primarily potent D2R antagonists (> 80% of receptors must be antagonised for therapeutic effect)
  - (ii) Moderate antagonism of 5-HT2 receptors and α-adrenoceptor
  - (iii) Weakly inhibit mAChR and H1R
- Effect – Ameliorate +ve symptoms only (little effect on –ve symptoms)
- Very narrow TI – Substantial side-effects at therapeutic doses:
  - (i) Movement disorders:
    - Extrapyramidal symptoms, such as dystonias, akathisias, pseudoparkinsonism – These are acute and reversible
    - Tardive dyskinesia (involuntary movements of tongue, lips, face, trunk and extremities) – Gradual onset and irreversible
  - (ii) Endocrine – Sexual dysfunction, gynaecomastia (due to PRL release), menstrual disorders, weight gain
  - (iii) Hypotension (α-adrenoceptor-related)
  - (iv) Sedation (H1R related)
  - (v) Seizures
  - (vi) Jaundice and agranulocytosis (esp with phenothiazines)
  - (vii) Anticholinergic symptoms
  - (viii) Neuroleptic malignant syndrome

Atypical antipsychotic agents:

- Includes:
  - (1) Diazepines (Eg. Clozapine, Olanzapine)
  - (2) Dibenzothiazepines (Eg. Quetiapine)
  - (3) Benzamides (Eg. Sulpiride)
  - (4) Benzisoxazols (Eg. Respirdone)
- Mechanism of action:
  - (i) Highly selective D2R antagonists (> 80% of receptors must be antagonised for therapeutic effect)
  - (ii) High affinity for 5-HT2R and moderate affinity for α-adrenoceptors (Except benzamides)
  - (iii) Diazepines have D4R antagonistic effect also
- Indicated for treatment resistance or side-effects with typical agents (esp extrapyramidal symptoms)
- Have greater therapeutic efficacy (ameliorate both +ve and –ve symptoms) and fewer side effects than typical agents (esp movement disorders and gynaecomastia)
- Relevant side-effects include – Cardiac arrhythmias, seizures, clozapine-induced agranulocytosis (requires blood screening), myocarditis and cardiomyopathy (requires cardiac enzyme and TTE monitoring)

(f) ***To outline the mechanisms of action and pharmacology of the anticonvulsants drugs.***

<u>Conventional anticonvulsant drugs</u>:

- (1) Phenytoin:
  - Hydantoin derivative used to treat:
    - (i) Epilepsy – Stabilises neuronal membrane and preventing spread of seizure activity (Nb. does not abolish primary epileptic focus as it does not increase seizure threshold)
    - (ii) Arrhythmias (esp with digoxin toxicity and TCA OD) as it is a class I antiarrhythmic agent
    - (iii) Pain management (esp trigeminal neuralgia)
  - Mechanism of action:
    - (i) Inhibit neuronal membrane VG-Na^+ channels:
      - Maintains channel in an "inactivated" state (Ie. prevents them returning to "resting" state), thus reducing ability to further generate AP's
      - This selectively inhibits neurons that have repetitive AP's (Ie. higher the frequency of APs's, the greater the block)
      - Does NOT inhibit "normal" neuronal activity (which involves low frequency AP activity)
    - (ii) Enhance action of GABA
    - (iii) Reduce glutamate release and thus attenuating Ca^{2+} entry
  - Pharmacokinetics:
    - PO (90% bioavailability), IM or IV (incompatible in 5% dextrose)
    - 90% protein-bound
    - Hepatic CYP450 metabolism
      - Follows "first-order" kinetics but changes to "zero-order" (saturation) kinetics with doses above its therapeutic range of 10-20 μg/mL – This causes it to have a low TI (Ie. dose required to produce therapeutic range is close to toxic dose) and warrants close drug level monitoring
      - Phenytoin can induces its own CYP450, thereby inducing its own metabolism
      - Reduced clearance with liver disease
    - Renal excretion as glucuronidated metabolite (< 5% unchanged)
    - Elimination t ½ ~ 9-24 hrs with first order kinetics (but t ½ increases with dosage due to saturation kinetics)
  - Dosing:
    - Oral: 200-600 mg/day (start with small doses and increase thereafter)
    - IM: 100-200 mg q4h for 2-3 days, then reduce to 300 mg/day
    - IV: Loading dose of 10 mg/kg (given slowly), then maintenance dose of 100 mg q6h
  - Adverse effects:
    - (i) Idiosyncratic – Acne, hirsutism, coarsening of facial features, gum hyperplasia, folate-dependent megaloblastic anaemia, aplastic anaemia, peripheral neuropathy, skin rashes
    - (ii) Dose-dependent – Ataxia, nystagmus, vertigo, slurred speech, paraesthesia, and if given too rapidly, hypotension and complete heart block (and possible asystole)
    - (iii) Teratogenicity
  - Drug interactions:
    - Induces hepatic CYP450 – Increases metabolism of many drugs (Eg. warfarin, Bz, OCP, pethidine, Etc.)
    - Reduced protein binding in presence of aspirin, valproate, Etc.

        - Metabolism inhibited by drugs that block CYP450 function (Eg. metronidazole, isoniazid, aspirin, antifungal)
        - Metabolism increased by drugs that enhance CYP450 function (Eg. EtOH and carbamazepine)
        - MAC-sparing and reduces doses of muscle relaxants
- (2) Carbamezapine (and Oxcarbazepine):
    - Mechanism of action – Similar to phenytoin
    - Pharmacokinetics:
        - PO (high bioavailability) or PR
        - 75% protein-bound
        - Hepatic metabolism – Produces an active metabolite that is renally excreted unconjugated. Very powerful inducer of CYP450, and induces its own metabolism
        - t ½ ~ 10-12 hrs
    - Adverse effects:
        - CNS – Headache, diplopia, ataxis, sedation
        - GI upset
        - Anti-diuresis (causing water retention)
        - Drug-induced hepatitis
        - Skin rashes
        - Agranulocytosis (rarely)
        - Teratogenicity
    - Drug interactions – Similar to phenytoin but it is a more powerful inducer of hepatic CYP450
    - Oxcarbazepine is a pro-drug of carbaezapine – It is metabolised to an active drug. It has a better side-effect profile
- (3) Sodium valproate:
    - Mechanism of action:
        - (i) Attenuates GABA transaminase
        - (ii) Enhances activity at GABA receptors
        - (iii) Inhibit VG-Na^+ channels by maintaining them in "inactivated" state (similar to phenytoin)
    - Pharmacokinetics:
        - Good oral absorption
        - 90% protein bound.
        - t ½ ~ 12-15 hrs – Hepatic metabolism produces active and inactive metabolites that are renally excreted
    - Fewer side-effects than other agents – But issues with GI upset, weight gain, hair loss, thrombocytopaenia, fatal hepatotoxicity, and teratogenicity
- (4) Ethosuximide:
    - Blocks T-type Ca^{2+} channels
    - Very long t ½ ~ 60 hrs
    - Very few side-effects (Eg. N/V, headaches, mood changes)
- (5) Barbiturates (Eg. Phenobarbitone)
    - Works by potentiating effects of GABA at GABA-A receptors, directly activating GABA-A receptors, inhibiting VG-Na^+/Ca^{2+} channel, reducing glutamate release
    - Effective anticonvulsant but significant issues limit its long-term use – (i) Sedation, (ii) Long duration of action, (iii) Induction of hepatic enzymes, (iv) Drug interactions (several)
- (6) Benzodiazepines (Eg. Diazepam, Midazolam, Lorazepam)
    - Works by potentiating effects of GABA at GABA-A receptors
    - Used to treat status epilepticus; sedation limits long-term use

<u>Newer anticonvulsant drugs</u>:

- (1) Gabapentin (and Pregabalin):

    - GABA analogue that promotes GABA release (does not activate GABA receptor directly)
    - Very few side-effects, safe with OD (due to saturation of transporter in GIT), and does not interact with hepatic enzymes (Ie. minimal drug interactions)
    - Pregabalin is a pro-drug that is more potent
- (2) Vigabatrin:
    - Irreversibly inhibits GABA transaminase
    - Side-effects include mood changes, sedation, headaches
- (3) Tiagabine:
    - GABA analogue that inhibits GABA reuptake
    - Relatively short half-life
    - Side-effects include sedation and confusion
- (4) Topiramate:
    - Works by inhibiting VG-Na^+ channels, blocking AMPA receptor, and enhancing GABA activity
    - Similar to phenytoin but with fewer side-effects and more favourable pharmacokinetic profile
    - Main issue is teratogenesis
- (5) Lamotrigine:
    - Works by inhibiting VG-Na^+ channels and attenuating glutamate release
    - Metabolism rate increased by enzyme-inducing drugs (Eg. phenytoin)
    - Long half-life (t ½ ~ 24-36 hrs)
    - Side-effects – Headache, N/V, diplopia, ataxia, Steven-Johnson syndrome

(g) ***To outline the pharmacology of the antiparkinsonian drugs.***

Levodopa:

- Oral L-DOPA is readily absorbed in intestines into plasma
- 99% of L-DOPA is converted to DA peripherally in the liver, GIT and vasculature by peripheral DOPA decarboxylase such that only 1% reach the CNS – This can be prevented by giving Carbidopa or Benserazide (peripheral DOPA decarboxylase inhibitors that cannot cross the BBB)
- L-DOPA is transported across the BBB via aromatic a.a transporters into dopaminergic neurons, where it is converted by DOPA decarboxylase to DA, which is then stored in vesicles for release
- Issues with L-DOPA:
    - (i) Short plasma t ½ ~ 2 hrs requires frequent dosing
    - (ii) Reduced efficacy with time – Due to receptor downregulation and continued dopaminergic neuronal degeneration
    - (iii) Acute peripheral effects (due to peripheral conversion to DA) – N/V and hypotension. This can be prevented using either a peripheral DOPA decarboxylase inhibitor (Eg. carbidopa) or peripheral D2R antagonist (Eg. domperidone)
    - (iv) Dyskinesia (involuntary writhing movements in face and limbs can occur in the first few years of therapy)
    - (v) On-Off effect (with disease progression, rapid fluctuation in symptoms whereby hypokinesia and rigidity suddenly worsen, but improves in minutes or hours)
    - (vi) Psychiatric effects (schizophrenic-like hallucinations, paranoia, psychosis, delusions, depression)

Inhibitors of DA metabolism:

- (1) MAO-B inhibitors (Eg. Selegiline)
    - Prevent breakdown of DA by MAO-B concentrated in dopaminergic neurons in CNS – Selective MAO-B inhibition means lack of (i) undesired peripheral effects of non-selective MAOi, and (ii) "cheese reactions" associated with MAO-Ai
    - Increases efficacy of L-DOPA if given concurrently
    - Neuroprotective effect (slows progression of neuronal degeneration by attenuating formation of toxic metabolites by MAO-B)
- (2) Catechol-O-Methyl Transferase inhibitors (Eg. Tolcapone, Entacapone)
    - Reduce metabolism of DA

D2 receptor agonists:

- Bromocriptine, Apomorphine, Pergolide all interact directly with agonist effects at D2R (although at different subtypes)
- ?neuroprotective
- Has a longer t ½ than L-DOPA (~ 6-8 hrs), has fewer side-effects, may have a neuroprotective role, BUT is less efficacious

Amantidine:

- Antiviral drug with an unknown mechanism for treating PD – (i) ?Enhanced DA release, (ii) ?Attenuates DA reuptake, (iii) ?direct DA receptor effect, (iv) ?NMDA activity
- Not as effective as L-DOPA or D2R agonists, but less side-effects than L-DOPA
- Contraindicated in renal failure as it is renally excreted

ACh Antagonists:

- Stimulation of mAChR opposes effects of DA in CNS
- Atropine or Benzatropine (fewer peripheral effects) can be used, BUT issues with anticholinergic symptoms

(h) ***To outline the pharmacology of drugs used to treat migraine.***

Drugs used to treat acute migraine:

- (1) Ergot-derivatives (Eg. Ergotamine, dihydroergotamine)
    - They are partial agonists for 5-HT 1D receptor and agonists on α-adrenoceptors – This causes (i) selective cranial vasoconstriction, and (ii) inhibition of trigeminal nerve transmission (by inhibiting release of neurogenic inflammatory peptides)
    - Poor absorbed orally (can be given PR or inhaled) but effective with effects lasting 12-24 hours
    - Use limited by side-effects – Causes peripheral vasoconstriction (Ie. precipitates cardiac ischaemic, gangrene of extremities, gut ischaemia), N/V, and uterine contraction
- (2) 5-HT 1B/D agonists (Eg. Sumitriptan, zolmitriptan)
    - They are highly selective agonist for 5-HT 1 B/D receptors – This causes (i) selective intracranial large artery vasoconstriction, (ii) inhibition of trigeminal nerve transmission (by inhibiting release of neurogenic inflammatory peptides), and (iii) neuroinhibition of the trigeminocervical nuclei (ONLY zolmitriptan as it can cross the BBB)
    - Sumatriptan is poorly absorbed orally (but can be given S/C), has a delayed onset of effect and short duration of action (2 hrs). It cannot cross the BBB and has more systemic side-effects (esp cardiac ischaemia, fatigue and dizziness)
    - Zolmitriptan has better oral bioavailability, has a faster onset, is able to cross the BBB and has fewer side-effects (esp cardiac ischaemia)
- (3) Simple analgesia (paracetamol/aspirin/NSAID) with metoclopramide to enhance absorption

Drugs used to prophylactically treat migraine:

- (1) Methysergide
    - Oral agent that acts as a partial agonist/antagonist of the 5-HT 2 receptor – Inhibits cerebral arteriolar vasoconstriction
    - Use limited by its side-effects – N/V, diarrhoea, and more seriously risk of retroperitoneal or mediastinal fibrosis (rare)
- (2) Pizotifen
    - Oral antagonist of 5-HT 2 A-C receptor and mAChR – This (i) blocks cerebral arteriolar vasoconstriction, (ii) impairs platelet aggregation, and (iii) increases capillary permeability
    - Side-effects include weight gain and anticholinergic effects
- (3) Cyproheptadine
    - Oral antagonist of 5-HT 2 receptor and H1 receptor (and weakly mAChR)
    - Side-effects include weight gain, sedation and anticholinergic effects
- (4) Beta-blockers (propranolol, metoprolol)
- (5) TCA (amitriptyline only)
- (6) Anticonvulsant (sodium valproate)