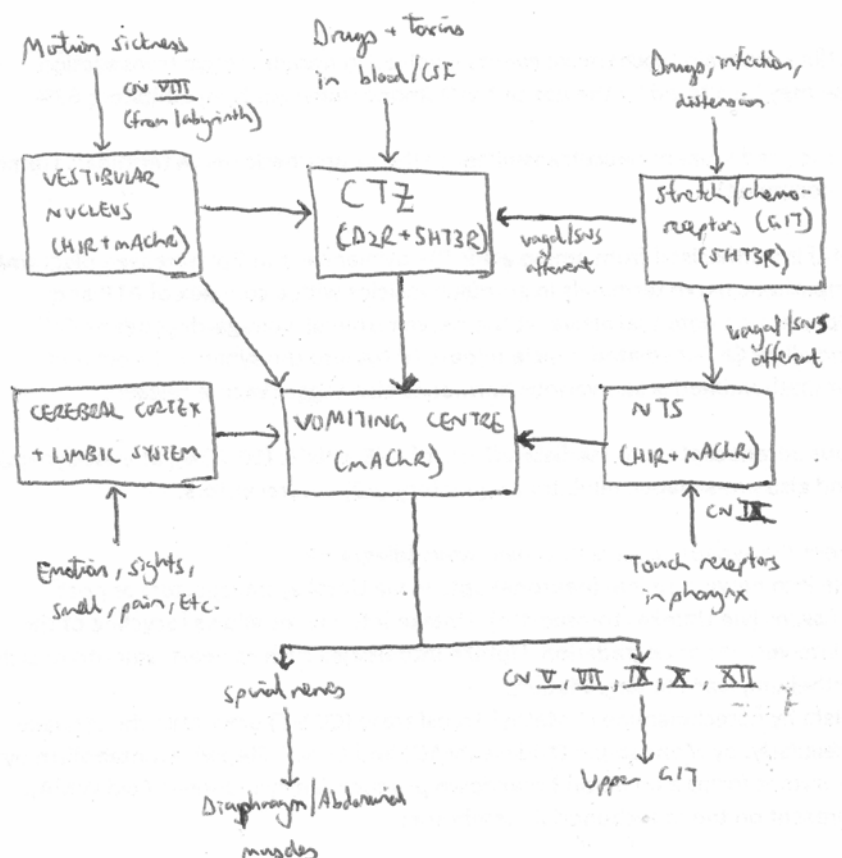


ANTI-EMETIC DRUGS

- (a) *To describe the pharmacodynamics and pharmacokinetics of dopamine antagonists, anti-cholinergic agents, serotonin antagonists, anti-histamines and steroids.*
- (b) *To critically appraise the clinical usage of these drugs.*



(I) Dopamine Antagonists:

(1) Phenothiazines:

Overview of phenothiazines:

- 3-ring structure → 2x benzene rings linked by sulphur and N-atoms
- Two agents used for anti-emesis – Chlorpromazine (propylamine) and Prochlorperazine (piperazine)

Mechanism of action of phenothiazines:

- (i) D2R antagonist:
 - o Centrally → basal ganglia, limbic system and anterior pituitary → antipsychotic effect, sedation, agitation, extrapyramidal symptoms, and ↑ PRL
 - o Peripherally → area postrema of medulla (outside BBB) → inhibits vomiting reflex at CTZ → anti-emetic effect
- (ii) Antagonism of mAChR, α-adrenoceptor, H1R, 5-HT → antiemetic effect, hypotension, sedation, anti-cholinergic effects
- (iii) Membrane stabilising effects
- (iv) Inhibits uptake 1 → ↓ NAD reuptake into SNS nerves

Clinical uses of phenothiazines:

- (i) Treatment of schizophrenia/psychosis → antipsychotic/neuroleptic effect
- (ii) Prevention and treatment of nausea/vomiting

- Reserved for severe N/V (esp a/w vertigo, motion sickness, migraine) and useful in opioid-induced N/V → but limited used due to issue of side-effects
- Inhibits vomiting reflex at multiple sites (due to D2R, H1R, mAChR antagonism)
- (iii) Treatment of vertigo
- (iv) Treatment of hiccups

Pharmacokinetics of phenothiazines:

Absorption	Well-absorbed from GIT → extensive 1 st pass hepatic metabolism (30% oral bioavailability) → thus often given parentally (IM/IV)
Distribution	- Highly lipid soluble → crosses BBB and placenta - Highly protein-bound
Metabolism and elimination	- Hepatic metabolism (oxidation/conjugation) → most metabolites inactive (except for chlorpromazine) → excreted in urine (and also bile) - Elimination t_{1/2} 10-20 hrs

Issues with phenothiazines:

- Extrapyramidal symptoms (due to central D2R antagonism) → acute dystonia (muscle rigidity and cramping of face, neck, back, tongue), akathisia, tremor, masked facies, and tardive dyskinesia with chronic use (abnormal involuntary movements of face, neck, extremities, trunk)
- Neuroleptic malignant syndrome (<1%) → hyperthermia, generalised hypertonicity of muscles, ANS instability (BP, HR and arrhythmias), and fluctuating LOC
- Hyperprolactinaemia (due to central D2R antagonism) → galactorrhoea, gynaecomastia, menstrual irregularities
- Sedation (due to antagonism of mAChR, H1R, α-adrenoceptor)
- Hypotension (due to ↓ vasomotor reflex (central effect), peripheral α-adrenoceptor blockade), -ve inotropy and direct vascular SM relaxation)
- Prolonged QTc → torsades de pointes
- Anticholinergic side-effects
- Impaired glucose tolerance
- Weight gain (↑ appetite)
- Abnormal thermoregulation (esp hypothermia)
- Haematological disturbances (haemolytic anaemia, agranulocytosis, leukopenia)
- Obstructive jaundice

(2) Droperidol:

- Type – Butyrophenones (structurally related to haloperidol)
- Mechanism of action:
 - (i) D2R antagonism
 - Centrally → basal ganglia, limbic system and anterior pituitary → antipsychotic/neuroleptic effect, sedation, agitation, extrapyramidal symptoms, and ↑ PRL
 - Peripherally → area postrema of medulla (outside BBB) → inhibits vomiting reflex at CTZ → anti-emetic effect
 - (ii) Peripheral α1-adrenoceptor antagonism → hypotension
 - (iii) Interferes with neuronal 5-HT, NAd, ACh, GABA neurotransmission (central) → sedation and tranquiliser effect
- Clinical uses:
 - (i) Prevention and treatment of nausea and vomiting (esp opioid-induced)
 - Safe and cost-effective 1st line therapy for PONV (due to CTZ inhibition) → 0.625-1.25 mg IV → this lower dose allows for ↓ side-effects but risk of prolonged QTc still exists
 - It is NOT effective in motion-induced N/V → due to lack of D2R in vestibular apparatus and vomiting ctr (only possess H1R and mAChR)
 - (ii) Neurolept-analgesia (and -anaesthesia)

- 50:1 droperidol:fentanyl (Innovar) → causes neuroleptic analgesia (cataleptic immobility with dissociation, amnesia and intense analgesia)
- Addition of N₂O or hypnotic agent → causes neuroleptanaesthesia (LOC)
- Due to central effects → inhibition of neuronal GABA-A, nAChR, and 5-HT neurotransmission
- Issues – Prolonged CNS depression, failure to suppress SNS response to pain, orthostatic hypotension and dysphoria
- (iii) Control of mania/psychosis → used as an antipsychotic agent (5-10 mg)

- Pharmacokinetics:

Absorption	Parental route only (IV or IM)
Distribution	- V_D 2 L/kg; protein-binding 90% → minimal BBB/placental transfer - Prolonged duration of effect (3-24 hrs) due to strong receptor binding
Metabolism and elimination	- Hepatic metabolism (mainly HBF-dependent) → metabolites inactive excreted in urine - Elimination t_{1/2} 2 hrs

- Issues:

- Excess sedation, dysphoria, dystonic extrapyramidal symptoms (rare unless ↑ dose)
- Neuroleptic malignant syndrome (rare)
- ↓ CBF and ICP (due to cerebral vasoconstriction) but without effect on CMRO₂
- Hyperprolactinaemia (galactorrhoea, gynaecomastia, menstrual irregularities)
- Orthostatic hypotension 2° to ↓ SVR (due to central effects and peripheral α-receptor inhibition)
- Hypertensive crisis if given in patient with pheochromocytoma
- Antiarrhythmic effect (a/w α-adrenoceptor inhibition, ↓ MAP and cardiac membrane stabilisation effect)
- Prolonged QTc (and polymorphic VT) → due to impaired ventricular repolarisation a/w efflux of IC K⁺ → ↑ risk if pre-existing prolonged QTc, use of drugs that prolong QTc, CCF, bradycardia, elderly, or hypokalaemic
- No respiratory depression → augments ventilatory response to ↓ PaO₂

(3) Metoclopramide:

Overview of metoclopramide:

- Benzamide type DA antagonist
- Structurally related to procainamide (as methoxychloroprocainamide) → BUT without LA activity

Mechanism of action of metoclopramide:

- (i) D2R antagonist:
 - Centrally → basal ganglia and anterior pituitary → causes extrapyramidal symptoms, sedation, agitation, and ↑ PRL
 - Peripherally → area postrema of medulla (outside BBB) → inhibits vomiting reflex at CTZ → anti-emetic effect
- (ii) 5-HT₄ agonist peripherally:
 - Causes selective cholinergic stimulation of GIT via → (a) ↑ ACh release from postganglionic cholinergic nerves to GI SM, and (b) Sensitising GI SM to ACh
 - Dependent on background cholinergic activity → thus, effect negated by anti-cholinergics (Eg. atropine)
 - Prokinetic effect → ↑ LOS tone and ↑ gastric emptying (due to ↑ upper GI motility and relaxation of pylorus) → BUT it does NOT affect gastric secretions!
- (iii) 5-HT₃R antagonist (at high doses) → anti-emetic effect

Clinical uses of metoclopramide:

- (i) Prophylaxis against aspiration prior to GA (given 15-30 mins pre-op.)

- Due to – (a) ↓ gastric fluid volume (a/w ↑ gastric emptying and prokinetic effects), (b) ↑ LOS tone, and (c) anti-emetic effect
- It has no effect on gastric fluid pH → as it does not affect gastric secretions!
- Note – It does not reverse opioid-induced GI stasis, and its effect is offset by atropine
- (ii) Preventing and treating nausea and vomiting (esp chemotherapy-induced)
 - Due to – (a) CTZ inhibition, (b) GI prokinetic effects, and (c) ↑ LOS tone
 - Most effective at high-doses (1-2 mg/kg), but issues with side-effects and need for frequent dosing ($t_{1/2}$ 2-4 hrs) → equivocal effect at lower doses (0.25 mg/kg)
- (iii) Treatment of gastroparesis (esp a/w DM) → due to GI prokinetic effects
- (iv) Symptomatic treatment of GORD → due to ↑ LOS tone
- (v) Analgesia from SM spasm (I.e. renal/biliary colic, uterine cramps, PG-induced TOP)

Pharmacokinetics of metoclopramide:

Absorption	PO: Well-absorbed from GIT → extensive 1 st pass hepatic metabolism (30-90% oral bioavailability) → onset of action within 30-60 mins IM and IV: Slow IVI (over 5 mins due to side-effects) → onset of action within 3-5 mins Dose: 10-20 mg (0.25 mg/kg) PO, IM or IV → 1-2 mg/kg for anti-emetic effect
Distribution	- Crosses BBB, placenta and into breast milk - Protein binding 10-20%; V_D 2-3 L/kg
Metabolism and elimination	- Hepatic metabolism and renal elimination (both unchanged and inactive metabolites) - Elimination $t_{1/2}$ 2-4 hrs - Nb. Requires dose reduction with renal impairment

Issues with metoclopramide:

- Rapid IVI (< 5 mins) → Abdominal cramping (mainly), but also hypotension, tachycardia or bradycardia, arrhythmias
- Sedation, dysphoria, nervousness and dystonic extrapyramidal symptoms → especially in young females, large doses, chronic therapy, underlying Parkinson's disease, or drug interactions (other D2RBs, MAOi, TCA)
- Hyperprolactinaemia (galactorrhoea, gynaecomastia, menstrual irregularities)
- Neuroleptic malignant syndrome (rare)
- Contraindicated in complete bowel obstruction and GI surgery
- Hyperaldosteronism (due to ↓ DA-mediated inhibition of aldosterone secretion) → ↑ Na^+ and ↓ K^+
- Hypertensive crisis in patients with pheochromocytoma (due to ↑ tumour release of catecholamines)
- Drug interactions – (i) ↓ oral bioavailability of drugs (esp cimetidine), (ii) inhibits plasma cholinesterase (issues with SCh, mivacurium, ester LA metabolism), and (iii) anti-muscarinic drugs inhibits its GI prokinetic effects

(4) Domperidone:

- Type – Benzimidazole derivative
- Mechanism of action – Antagonist of peripheral D2R → located:
 - (i) GIT → causes ↑ upper GI motility (and gastric emptying) and ↑ LOS tone
 - (ii) Area postrema in medulla (CTZ) → anti-emetic effect

Note: It does NOT cross BBB → no central D2R antagonism → thus, no sedation, dysphoria, extrapyramidal symptoms or hyperprolactinaemia

- Clinical use – Prevention and treatment of PONV
- Pharmacokinetics – Rapidly absorbed PO or IM (no IV due to issues with arrhythmias) → extensive hepatic metabolism (with biliary excretion of inactive metabolites) → elimination $t_{1/2}$ 7 hrs

(II) **5-HT₃ Receptor Antagonists:**

Types of 5-HT₃R antagonists:

- (1) Ondansetron (carbazolone derivative) → least 5-HT₃R selective (has 5-HT₁R and 5-HT₂R effects also)
- (2) Tropisetron (indoleacetic acid ester of tropine) → more 5-HT₃R selective
- (3) Granisetron → highly 5-HT₃R selective → long $t_{1/2}$ means single dose can last 24 hrs
- (4) Dolasetron → highly 5-HT₃R selective → antiemetic effect due to hydroxydolasetron metabolite (100x ↑ potent)

Mechanism of action of 5-HT₃R antagonists:

- Selective and competitive inhibitors of 5-HT₃R receptors → located:
 - o (i) Peripherally (in vagal afferent fibres within GIT) → inhibits effect of 5-HT released from enterochromaffin cells of GIT (by mechanical and chemical stimuli) → prevents transmission to vomiting centre → inhibits vomiting reflex
 - o (ii) Centrally (in area postrema (CTZ)) → inhibits stimulation of CTZ by drugs/toxins → inhibits vomiting reflex
- Note – They do NOT have any effect on AChR, H₁R, DA or adrenergic receptors

Aside: 5-HT₃ receptor is an excitatory ligand-gated channels (fast Na⁺/K⁺) → pentameric (5x subunits around central pore) → found in GI tract (in ENS) and widely in brain

Clinical uses of 5-HT₃R antagonists:

- (1) Prophylaxis and treatment of nausea and vomiting
 - o Useful for – (i) Chemo- and radiotherapy-induced N/V, and (ii) PONV
 - o It is NOT effective in motion-induced N/V → due to lack of 5-HT₃R in vestibular apparatus and vomiting ctr (only possess H₁R and mAChR)

Note – It is equally effective as other antiemetics (esp at ↓ PONV) and is relatively free from side-effects → BUT very costly!

- (2) Treat pruritis 2° to → opioids and cholestasis
- Note – It does NOT affect GI motility or LOS tone

Pharmacokinetics of 5-HT₃R antagonists:

Absorption	PO: - Well-absorbed from GIT → 60% oral bioavailability - Ondansetron 4-8 mg, Granisetron 2 mg, Dolasetron 100 mg (nil PO tropisetron) IV: - Ondansetron 4-8 mg, Granisetron 2 mg, Dolasetron 12.5 mg, Tropisetron 2 mg
Distribution	- Crosses BBB → therapeutic brain [] → 30-60 mins (PO) vs. few minutes (IV) - Protein binding 60-75%; V_D 2 L/kg
Metabolism and elimination	- Hepatic metabolism (CYP450) via hydroxylation/conjugation → metabolites renally excreted - Note – Dolasetron is rapidly metabolised to hydrodolasetron → 100x more potent → exerts antiemetic effects - Elimination $t_{1/2}$ ~ 3 hrs (ondansetron); ~ 7 hrs (tropisetron), ~ 8 hrs (metabolite of dolasetron); ~ 9 hrs (granisetron)

Issues with 5-HT₃R antagonists:

- Nil major issues with side-effects → mainly headache, constipation, transient LFT derangements, dizziness/flushing, and slightly QTc prolongation (esp dolasetron)

Note – It lacks sedation, hypotension, extrapyramidal symptoms and dysphoria a/w other antiemetics → due to selective 5-HT₃R antagonism only

- Requires dose reduction with liver disease
- Drug interactions – Tropisetron → antagonises analgesic effect of paracetamol;
Ondansetron → antagonises analgesic effect of tramadol

(III) **Anti-Cholinergic Agents:**

Hyoscine (scopolamine) is the only anti-cholinergic agent used to prevent and treat nausea and vomiting → because (i) atropine has too many CVS side-effects, and (ii) glycopyrrolate cannot cross BBB (devoid of anti-emetic effect)

Overview of hyoscine:

- Naturally-occurring alkaloid of belladonna plant, a lipid-soluble tertiary amine, and exists as a racemic mixture with only the L-isomer being active
- Ester of tropic acid (aromatic acid) and scopine (organic base)

Mechanism of action of hyoscine:

- Selectively and competitively inhibit ACh binding to and activating mAChR at postganglionic cholinergic sites (I.e. parasympatholytic or antimuscarinic activity) – Note that it affects all types of mAChR indiscriminately

Clinical uses of hyoscine:

Most clinical effects of hyoscine are derived from its CNS effects (sedation, amnesia, antiemetic, antisialogogue) as it is highly lipid-soluble and crosses the BBB → it has far less peripheral effects (cardiac and respiratory) cf. atropine

- (i) Prevents and treats nausea and vomiting
 - o Ideal for N/V 2° to motion-sickness, GI irritants or PONV → best used as a transdermal patch and on prophylactic basis
 - o NOT effective on N/V caused by CTZ stimulation by drugs/toxins → due to lack of mAChR at CTZ
- (ii) Ideal premedication for sedation and ↓ salivation/respiratory secretions
 - o More CNS effects (esp sedation and amnesia) and antisialagogue effects/anti-respiratory secretions, and far less CVS side-effects (↑ HR) → cf. atropine
- (iii) Potent antispasmodic of GIT/biliary tree

Pharmacokinetics of hyoscine:

Absorption	- Transdermal patch (0.5 mg) or 10 mg tablet of hyoscine HCl - Oral bioavailability 10-50% only (despite lipid solubility)
Distribution	- Lipid-soluble → readily crosses BBB, eyes, placenta - Protein binding 10 %; V_D 2 L/kg
Metabolism and elimination	- Extensive hepatic esterase metabolism to scopine/scopic acid (99%) → minimal renal excretion unchanged (1%) - Clearance 45 L/hr and t_{1/2} 2.5 hrs

Issues with hyoscine:

- CVS issues → tachycardia, ↑ atrial arrhythmias and nodal (junctional) rhythms
- CNS issues → stimulatory (excitation, restlessness, hallucinations) or depressive effects (sedation, amnesia) → central-cholinergic syndrome or delayed awakening from GA
- Ocular issues → mydriasis (pupil dilation) and cycloplegia (inability to accommodate to near-vision) → closed-angle glaucoma
- Respiratory issues → bronchodilation → ↑ anatomic DS
- GIT issues → ↓ salivary secretions and gastric secretions, ↓ GI motility (delayed gastric emptying, reduced intestinal motility) and ↓ LOS tone (↑ aspiration risk)
- GUT issues → ↓ ureteric/bladder tone → risk of urinary retention

- ↓ sweating → ↑ body temp and “atropine fever”

(IV) **Histamine 1 Receptor Antagonists (H1RBs):**

- 1st generation H1RBs (promethazine, diphenhydramine, cyclizine) → used for anti-emesis
- Mechanism of action – Competitively and reversibly inhibit histamine activity at H1R → also blocks mAChR, 5-HT, α- adrenoceptors → causes sedating effect, antiemetic and anticholinergic effects

Note – 2nd generation H1RBs selectively block H1R only (cannot cross BBB and activate mAChR, 5-HT, α-receptors) → non-sedating and without antiemetic or anticholinergic effects

- Clinical uses:
 - (i) Treat nausea/vomiting → esp due to motion sickness, post-operative, opioid-induced, and radiotherapy-induced → due to multiple receptor effects in vomiting reflex (esp at vomiting centre and vestibular apparatus)
 - (ii) Treat vertigo and Meniere’s disease
 - (iii) Treat symptoms of allergic rhinoconjunctivitis
 - (iv) Treat pruritis and chronic urticarial lesions
 - (v) Sedation
 - (vi) Protection against bronchospasm induced by histamine, exercise, cold/dry air
 - (vii) Prevent and treat anaphylactic/anaphylactoid reactions → block histamine-mediated vascular effects (causing haemodynamic instability) and airway effects. Also used to treat pruritis, urticaria and angioedema

- Pharmacokinetics:

Absorption	PO: Well-absorbed but ↓ bioavailability due to extensive 1 st pass metabolism IV → 1 st generation H1RBs only (as H2RBs have ↓ H ₂ O solubility)
Distribution	- Protein binding 80-99% - 1st generation H1RBs can cross BBB
Metabolism and elimination	- Hepatic metabolism (CYP450) - Elimination t_{1/2} ~ 3-6 hrs

- Issues:
 - 1st generation H1RBs (cf. 2nd generation agents) have a ↑ incidence of:
 - CNS side-effects – Somnolence, diminished alertness, slowed reaction time, impaired cognitive function
 - Anticholinergic effects – Dry mouth, blurred vision, urinary retention, impotence
 - CVS side-effects – Tachycardia, prolonged QTc, heart block, arrhythmias (esp if concurrent liver disease, prolonged QTc, ↓ K⁺, ↓ Mg²⁺)
 - ↑ respiratory depression when used concurrently with opioids (I.e. to treat PONV/pruritis), barbiturates or Bz’s
 - Antihistamine OD → seizures and cardiac arrhythmias

(V) **Steroids:**

- Dexamethasone (2.5-10 mg) → useful for chemotherapy-induced and post-operative nausea and vomiting
- Mechanism of action – Unknown (?involve PG synthesis)
- Nil significant adverse effects with single dose therapy (cf. long-term steroids use) → caution with DM (↑ BGL), immunosuppression, delayed wound healing, and intense perineal skin burning sensation (esp with rapid IV bolus)

(VI) **Other anti-emetics:**

- (i) Cannabinoids (Eg. nabilone)
 - Mechanism → effect via CTZ (? opioid-mediated)

- Issues → drowsiness, dizziness, dry mouth, orthostatic hypotension, hallucinations, psychosis, mood changes
- (ii) Neurokinin-1 antagonist (Eg. aprepitant)
 - Mechanism → highly selective NK1 antagonism (central)
 - Issues → fatigue, dizziness, diarrhoea, ↑ warfarin metabolism
- (iii) Benzodiazepines (Eg. Midazolam)
 - Mechanism → ↓ anxiety, ↓ DA input to CTZ, ↑ adenosine levels (which inhibits DA synthesis/release), GABA-A inhibition
 - Used for chemotherapy-induced nausea/vomiting