ANTI-EMETIC DRUGS
To describe the pharmacodynamics and pharmacokinetics of dopamine antagonists, anti-cholinergic agents, serotonin antagonists, anti-histamines and steroids.

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:
  - Centrally → basal ganglia, limbic system and anterior pituitary → antipsychotic effect, sedation, agitation, extrapyramidal symptoms, and ↑ PRL
  - 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
  - (iii) Treatment of vertigo
  - (iv) Treatment of hiccups

**Pharmacokinetics of phenothiazines:**

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Well-absorbed from GIT → extensive 1st pass hepatic metabolism (30% oral bioavailability) → thus often given parentally (IM/IV)</th>
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<tbody>
<tr>
<td>Distribution</td>
<td>- Highly lipid soluble → crosses BBB and placenta</td>
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<tr>
<td>Metabolism and elimination</td>
<td>- Highly protein-bound</td>
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<tr>
<td>Metabolism and elimination</td>
<td>- Hepatic metabolism (oxidation/conjugation) → most metabolites inactive (except for chlorpromazine) → excreted in urine (and also bile)</td>
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<tr>
<td>Elimination</td>
<td>- Elimination $t\frac{1}{2}$ 10-20 hrs</td>
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**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, $\alpha$-adrenoceptor)
- Hypotension (due to ↓ vasomotor reflex (central effect), peripheral $\alpha$-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, leukopaenia)
- Obstructive jaundice

(2) Droperidol:

- Type – Butyrephenones (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 $\alpha$1-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:

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Parental route only (IV or IM)</th>
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<tbody>
<tr>
<td>Distribution</td>
<td>- V_D 2 L/kg; protein-binding 90% → minimal BBB/placental transfer</td>
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<td>- Prolonged duration of effect (3-24 hrs) due to strong receptor binding</td>
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<tr>
<td>Metabolism and elimination</td>
<td>- Hepatic metabolism (mainly HBF-dependent) → metabolites inactive excreted in urine</td>
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<td>- Elimination t ½ 2 hrs</td>
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</table>

- Issues:
  
  o Excess sedation, dysphoria, dystonic extrapyramidal symptoms (rare unless ↑ dose)
  o Neuroleptic malignant syndrome (rare)
  o ↓ CBF and ICP (due to cerebral vasoconstriction) but without effect on CMRO₂
  o Hyperprolactinaemia (galactorrhoea, gynaecomastia, menstrual irregularities)
  o Orthostatic hypotension 2° to ↓ SVR (due to central effects and peripheral α-receptor inhibition)
  o Hypertensive crisis if given in patient with phaeochromocytoma
  o Antiarrhythmic effect (a/w α-adrenoceptor inhibition, ↓ MAP and cardiac membrane stabilisation effect)
  o 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
  o 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:
  o Centrally → basal ganglia and anterior pituitary → causes extrapyramidal symptoms, sedation, agitation, and ↑ PRL
  o Peripherally → area postrema of medulla (outside BBB) → inhibits vomiting reflex at CTZ → anti-emetic effect
- (ii) 5-HT₄ agonist peripherally:
  o Causes selective cholinergic stimulation of GIT via → (a) ↑ ACh release from postganglionic cholinergic nerves to GI SM, and (b) Sensitising GI SM to ACh
  o Dependent on background cholinergic activity → thus, effect negated by anti-cholinergics (Eg. atropine)
  o 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 ½ 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 (Ie. renal/biliary colic, uterine cramps, PG-induced TOP)

Pharmacokinetics of metoclopramide:

<table>
<thead>
<tr>
<th>Absorption</th>
<th>PO: Well-absorbed from GIT → extensive 1st 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</th>
</tr>
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<tbody>
<tr>
<td>Distribution</td>
<td>- Crosses BBB, placenta and into breast milk - Protein binding 10-20%; Vd 2-3 L/kg</td>
</tr>
<tr>
<td>Metabolism and elimination</td>
<td>- Hepatic metabolism and renal elimination (both unchanged and inactive metabolites) - Elimination t ½ 2-4 hrs - Nb. Requires dose reduction with renal impairment</td>
</tr>
</tbody>
</table>

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 phaeochromocytoma (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 ½ 7 hrs
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 ½ 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:
  - (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
  - (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

Clinical uses of 5-HT3R antagonists:
- (1) Prophylaxis and treatment of nausea and vomiting
  - Useful for – (i) Chemo- and radiotherapy-induced N/V, and (ii) PONV
  - 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)
- (2) Treat pruritis 2° to opioids and cholestasis
- Note – It does NOT affect GI motility or LOS tone

Pharmacokinetics of 5-HT3R antagonists:

<table>
<thead>
<tr>
<th>Absorption</th>
<th>PO:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Well-absorbed from GIT → 60% oral bioavailability</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4-8 mg, Granisetron 2 mg, Dolasetron 100 mg (nil PO tropisetron)</td>
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<td></td>
<td>IV:</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4-8 mg, Granisetron 2 mg, Dolasetron 12.5 mg, Tropisetron 2 mg</td>
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<thead>
<tr>
<th>Distribution</th>
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<tr>
<td></td>
<td>Crosses BBB → therapeutic brain [ ] → 30-60 mins (PO) vs. few minutes (IV)</td>
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<tr>
<td></td>
<td>Protein binding 60-75%; Vd 2 L/kg</td>
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<thead>
<tr>
<th>Metabolism and elimination</th>
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<tbody>
<tr>
<td></td>
<td>Hepatic metabolism (CYP450) via hydroxylation/conjugation → metabolites renally excreted</td>
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<tr>
<td></td>
<td>Note – Dolasetron is rapidly metabolised to hydrodolasetron → 100x more potent → exerts antiemetic effects</td>
</tr>
<tr>
<td></td>
<td>Elimination t ½ ~ 3 hrs (ondansetron); ~ 7 hrs (tropisetron), ~ 8 hrs (metabolite of dolasetron); ~ 9 hrs (granisetron)</td>
</tr>
</tbody>
</table>

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)

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

Note – It is equally effective as other antiemetics (esp at ↓ PONV) and is relatively free from side-effects → BUT very costly!
- 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, antisympathetic) 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
  - Ideal for N/V ²° to motion-sickness, GI irritants or PONV → best used as a transdermal patch and on prophylactic basis
  - 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
  - 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 |
| Distribution | Oral bioavailability 10-50% only (despite lipid solubility) |
| Metabolism and elimination | Lipid-soluble → readily crosses BBB, eyes, placenta |
| | Protein binding 10 %; Vₐ 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 ½ > 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, \( \alpha \)-adrenoceptors → causes sedating effect, antiemetic and anticholinergic effects

<table>
<thead>
<tr>
<th>Note – 2nd generation H1RBs selectively block H1R only (cannot cross BBB and activate mAChR, 5-HT, ( \alpha )-receptors) → non-sedating and without antiemetic or anticholinergic effects</th>
</tr>
</thead>
</table>

- Clinical uses:
  o (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)
  o (ii) Treat vertigo and Meniere’s disease
  o (iii) Treat symptoms of allergic rhinoconjunctivitis
  o (iv) Treat pruritis and chronic urticarial lesions
  o (v) Sedation
  o (vi) Protection against bronchospasm induced by histamine, exercise, cold/dry air
  o (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 angiooedema

- Pharmacokinetics:

| Absorption | PO: Well-absorbed but ↓ bioavailability due to extensive 1st pass metabolism IV → 1st 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 ½ ~ 3-6 hrs |

- Issues:
  o 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
  o CVS side-effects – Tachycardia, prolonged QTc, heart block, arrhythmias (esp if concurrent liver disease, prolonged QTc, ↓ K\(^+\), ↓ Mg\(^{2+}\))
  o ↑ respiratory depression when used concurrently with opioids (Ie. to treat PONV/pruritis), barbiturates or Bz’s
  o 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)
  o Mechanism → effect via CTZ (? opioid-mediated)
- (ii) Neurokinin-1 antagonist (E.g. aprepitant)
  o Issues → drowsiness, dizziness, dry mouth, orthostatic hypotension, hallucinations, psychosis, mood changes
  o Mechanism → highly selective NK1 antagonism (central)
  o Issues → fatigue, dizziness, diarrhoea, ↑ warfarin metabolism

- (iii) Benzodiazepines (E.g. Midazolam)
  o Mechanism → ↓ anxiety, ↓ DA input to CTZ, ↑ adenosine levels (which inhibits DA synthesis/release), GABA-A inhibition
  o Used for chemotherapy-induced nausea/vomiting