Antiemetics:

- **Anti-cholinergics**
  - Hyoscine
  - Dicyclomine
- **H_1 anti-histaminics**
  - Promethazine
  - Diphenhydramine
  - Dimenhydrinate
  - Doxylamine
  - Meclozine
- **Neuroleptics (D_2 blockers)**
  - Chlorpromazine
  - Triflupromazine
  - Prochlorperazine
- **Prokinetic drugs**
  - Metoclopramide
  - Domperidone
  - Cisapride
  - Mosapride
  - Itopride
  - Levosulpiride
  - Cinitapride
- **5-HT_3 antagonists**
  - Ondansetron
  - Granisetron
  - Palonosetron
  - Ramosetron
- **NK_1 receptor antagonists**
  - Aprepitant
  - Fosaprepitant
- **adjuvant antiemetics**
  - Dexamethasone
  - Benzodiazepines
  - Dronabinol

Emesis: vomiting occurs due to stimulation of the emetic (vomiting) centre

→ Most important relay areas for afferent impulses arising in the g.i.t, throat & other viscera – CTZ (chemoreceptor trigger zone) ⇒ unprotected by blood-brain-barrier ∴ it is accesible to blood-borne drugs, mediators, hormones, toxins etc.
– NTS (Nucleus tractus solitarius)

G.I irritants

↓

5-HT released from enterochromaffin cells

↓

acts on 5-HT_3 receptors present on extrinsic primary afferent neurones (PAN) of the enteric nervous system (ENS) → impulses via vagal & spinal visceral afferents

↑

NTS, CTZ

↑ *

→ * CTZ & NTS express receptors:

- histamine H_1
- Dopamine D_2
- Serotonin 5-HT_3
- Cannabinoid CB_1
- cholinergic M
- neurokinin NK_1 (activated by substance P)
- opioid μ

↓

relay of emetic signals

↓

emesis

rotation of body / disturbance of equilibrium / ototoxic drug action

↓

generation of impulse in vestibular apparatus

↓

relay in cerebellum

↓

Impulse reaches vomiting centre

↓

utilization of muscarinic & H_1 receptors

↓

emesis, nausea

} motion sickness

- Nausea is accompanied by reduced gastric tone & peristalsis
- Rhythmic contractions of diaphragm & abdominal muscles compress the stomach & evacuate its contents via the mouth.
- Conditions that inhibit gastric emptying predispose to vomiting.

Emetics: drugs used to evoke vomiting by:

- acting on CTZ: Apomorphine
- acting reflexly & on CTZ: Ipecacuanha

→ vomiting needs to be induced only when an undesirable substance (poison) has been ingested.

Apomorphine: semisynthetic derivative of morphine

→ dopaminergic agonist on CTZ

→ injected i.m/s.c ⇒ dose of 6 mg.

→ should not be used if respiration is depressed (apomorphine has inherent respiratory & CNS depressant action)

→ has therapeutic effect in parkinsonism, but is not used due to side effects.

Ipecacuanha: dried root of Cephaelis ipecacuanha

→ used as syrup ipecac
(15-30 ml in adults, 10-15 ml in children)

→ less dependable than parenteral apomorphine, but safer.

C/I of Emetics:

- Corrosive (acid, alkali) poisoning: risk of perforation & further injury to oesophageal mucosa
- CNS stimulant drug poisoning: may precipitate convulsions
- Kerosine (petroleum) poisoning: risk of aspiration of the liquid & chemical pneumonia.
- Unconscious patient: may aspirate the vomitus ∵ laryngeal reflex is likely to be impaired
- Morphine / phenothiazine poisoning: emetics may fail to act.

Anti-emetics: drugs used to prevent / suppress vomiting

Anticholinergics:

Hyoscine: most effective drug for motion sickness

→ brief duration of action

→ produces – sedation, dry mouth & other anticholinergic side effects

→ acts probably by blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre

→ poor efficacy in vomiting of other etiologies

- transdermal patch of hyoscine 1.5mg delivered over 3 days; applied behind the pinna to suppress motion sickness

Dicyclomine: (10-20 mg oral) – for prophylaxis of motion sickness & morning sickness

↳ cleared of teratogenic potential.

H_1 - Antihistaminics: used mainly in motion sickness & to a lesser extent in morning sickness, postoperative & other forms of vomiting.

Promethazine, Diphenhydramine, Dimenhydrinate: provide protection for 4-6 hrs.

→ side effects: sedation, dry mouth

→ Driving is not advisable after taking these drugs

→ By central anticholinergic action, they block the extrapyramidal side effects of metoclopramide while supporting its anti-emetic action.

Promethazine theoclate: AVOMINE 25mg tab. ⇒ salt of promethazine.

Doxylamine: sedative H_1 antihistaminic with prominent anticholinergic activity

↳ for morning sickness

→ First line Tx of morning sickness = Doxylamine + pyridoxine (approved by FDA)

→ side effects - drowsiness, dry mouth, vertigo, abdominal upset.

- 10-20 mg at bedtime
- DOXINATE, GRAVIDOX, VOMNEX, NOSIC 10 mg with pyridoxine 10 mg tab.

Meclozine: less sedative, less anticholinergic

↳ longer acting

→ protects against sea sickness for nearly 24 hours

- DILIGAN: meclozine 12.5 mg + nicotinic acid 50 mg tab.
- PREGNIDOXIN: meclozine 25 mg + caffeine 20 mg tab.

Cinnarizine: antivertigo drug having antimotion sickness property

→ probably acts by inhibiting influx of Ca^{2+} from endolymph into the vestibular sensory cells which mediates labyrinthine reflexes.

Motion Sickness: antiemetics with anticholinergic - antihistaminic property ⇒ First choice of drugs

→ act better when taken ½ - 1 hour before commencing journey

Morning Sickness: antihistaminics ⇒ have teratogenic potential; most cases can be managed by reassurance & dietary adjustment; dicyclomine, promethazine, prochlorperazine, metoclopramide may be prescribed in low doses

Neuroleptics: older neuroleptics (phenothiazines, haloperidol) are potent antiemetics & sedatives.

↳ act by blocking D_2 receptors in the CTZ

→ antagonize apomorphine induced vomiting

→ additional antimuscarinic + H_1 antihistaminic property

Broad Spectrum of Antiemetic action in:

- Drug-induced & postoperative nausea & vomiting (PONV)
- Disease-induced vomiting: gastroenteritis, uraemia, liver disease, migraine, etc.
- Malignancy-associated & cancer chemotherapy (mildly emetogenic)-induced vomiting.
- Radiation sickness vomiting (less effective)
- Morning sickness: should not be used except in hyperemesis gravidarum.

→ side effects - significant degree of sedation - muscle dystonia (especially in children & girls)
- hypotension

→ antiemetic dose is generally much lower than antipsychotic doses

Prochlorperazine: D_2 blocking phenothiazine

↳ selective antivertigo + antiemetic actions

→ highly effective when given by injection in vertigo associated vomiting & CINV.

→ limitations - muscle dystonia, other EPS.

→ mouth dissolving tab may be used in vomiting

Dose: 5-10 mg BD/TDS oral, 12.5-25 mg by deep i.m. injection

STEMETIL 5mg tab, 5mg mouth dissolving tab, 12.5mg in 1ml amp.

NAUSETIL 5mg tab, 12.5 mg/ml inj.

Prokinetic Drugs: drugs which promote GI transit & speed gastric emptying by enhancing coordinated propulsive motility [gastric hurrying agents]

Metoclopramide: substituted benzamide

↳ acts in g.i.t & CNS

GIT: more prominent effect on upper g.i.t

- increases gastric peristalsis
- relaxes pylorus & first part of duodenum
- speeds up gastric emptying
- LES tone is increased
- gastroesophageal reflux is opposed
- increases intestinal peristalsis
- no significant action on colonic motility & on gastric secretion

CNS: acts on CTZ ∴ blocks apomorphine induced vomiting

Mechanism of Action: through dopaminergic & seratonergic receptors

- **D_2 Antagonism:** dopamine (inhibitory transmitter) in g.i.t

↓ ⊖ metoclopramide ⇒ blocks D_2 receptors → gastric hurrying

- normally acts to delay gastric emptying when food is present in stomach
- causes gastric dilatation & LES relaxation

∴ central antidopaminergic (D2) action of metoclopramide on CTZ ⇒ antiemetic property

- **5-HT_4 Agonism:** in git ⇒ enhanced release from myenteric motor neurones due to 5-HT_4 receptor activation on primary afferent neurones (PAN) of ENS → activates excitatory interneurones

→ this action of bethanechol is synergised by bethanechol & attenuated by atropine.

- **5-HT_3 Antagonism:** at high concentrations, metoclopramide blocks 5-HT_3 receptors present on inhibitory myenteric interneurons & in NTS/CTZ.

→ rate of absorption of some drugs, e.g., aspirin, diazepam, digoxin may be altered by the gastric hurrying action of metoclopramide.

→ By blocking dopaminergic receptors in basal ganglia, metoclopramide abolishes the therapeutic effect of levodopa. ∴ c/I = parkinsonism = ϕ on long-term use.

→ less adverse effects (generally well-tolerated) — sedation, dizziness, loose stools, muscle dystonias (especially in children)

- Long term use ⇒ parkinsonism, galactorrhoea, gynaecomastia (but should not be used to augment lactation)

Dose: 10 mg (children 0·2–0·5 mg/kg) TDS oral or i.m.

For CINV: 0·3–2 mg/kg slow i.v./i.m.

PERINORM, MAXERON, REGLAN, SIGMET, 10 mg tab, 5mg/5ml syringe, 10 mg/2 ml inj., 50 mg/10 mL inj.

Uses:

- Antiemetic: used for many types of vomiting — postoperative, drug-induced, disease associated, radiation sickness, etc.

→ less effective in motion sickness

→ used for prophylaxis & treatment of vomiting induced by emetogenic anticancer drugs (cisplatin)

→ dexamethasone i.v. augments efficacy of metoclopramide

- Gastrokinetic: to accelerate gastric emptying:
  - when emergency general anaesthesia has to be given & the patient has taken food less than 4 hours before
  - to relieve postvagotomy or diabetic gastroparesis associated gastric stasis.

→ clinical efficacy is moderate

- Dyspepsia: for symptomatic relief; metoclopramide may stop persistent hiccups
- Gastroesophageal Reflux Disease: used in milder cases of GERD; much less effective than PPIs / H_2 blockers.

Domperidone: D_2 receptor antagonist

→ antiemetic & prokinetic action have a lower ceiling

→ prokinetic action is only based on D2 receptor blockade & is not attenuated by atropine

→ crosses blood-brain-barrier poorly ∴ EPS are rare but hyperprolactinemia can occur

→ antiemetic action is exerted mainly through CTz which is unprotected by blood-brain-barrier

→ does not block the therapeutic effect of levodopa in parkinsonism (due to poor CNS penetration)

→ side effects – dry mouth, loose stools, headaches, rashes, galactorrhoea

[cardiac arrhythmias on rapid i.v. injection]

→ not effective in severe cases

→ not useful in motion sickness & not advisable for morning sickness

→ efficacy in CINV is low

Dose: 10-40 mg (children 0.3-0.6 mg/kg) TDS.

DOMSTAL, DOMPERON, NORMETIC 10 mg tab., 1mg/ml suspension

MOTINORM 10 mg tab, 10 mg/ml drops.

Cisapride: prokinetic with little antiemetic property

↳ lacks D_2 receptor antagonism

→ prokinetic action is exerted mainly through 5-HT_4 agonism

Mosapride: gastrokinetic & LES tonic action due to 5-HT_4 agonistic & 5-HT_3 antagonistic action in the myenteric plexus

→ no clinically useful antiemetic action

→ no EPS or hyperprolactinemia (due to absence of D_2 blockade)

→ side effects – loose motions, abdominal pain, headache, dizziness, insomnia

→ its plasma concentration is elevated by erythromycin & other CYP3A4 inhibitors which increases the risk of Q-T prolongation

Indications: – nonulcer dyspepsia, diabetic gastroparesis, GERD (as adjuvant to PPIs), some cases of chronic constipation

Dose: 5mg (elderly 2·5mg) TDS

KINETIX 5mg tab, MOZA, MOZASEF, MOPRIDE 2·5mg, 5mg tabs;

MOZAMPS 5mg + methylpolysiloxane 125 mg tab.

Itopride: D_2 antidopaminergic & anti-ChE activity

→ very low affinity for 5-HT_4 receptors

→ metabolized mainly by flavin monooxygenases

→ side effects – diarrhoea, abdominal pain, headache (galactorrhoea & gynaecomastia ⇒ infrequent)

→ no EPS

→ Indications: similar to other prokinetic drugs

Dose: 50 mg TDS before meals

GANATON, ITOFLUX, ITOKINE, ITOPRD 50 mg tab.

Levosulpiride: blocks central as well as peripheral D_2 receptors

→ atypical antipsychotic, prokinetic & antiemetic properties

→ used mainly for symptomatic relief of several functional g.i. disorders – dyspepsia, nausea, bloating, GERD, irritable bowel syndrome, etc.

Dose: 25 mg TDS to 75 mg BD as SR tab.

LESURIDE, NEXIPRIDE 25mg tab, 75 mg tab, 25 mg/2ml inj.

Cinitapride: gastrokinetic drug

↳ acts by inhibiting 5-HT_2 & D_2 receptors & stimulating 5-HT_4 receptors in myenteric plexus.

→ Indications: functional g.i. disorders like non-ulcer dyspepsia, delayed gastric emptying & GERD.

→ claimed to afford partial to complete relief of symptoms like epigastric pain, belching, reflux, early satiety, dysphagia, nausea & vomiting in patients of dyspepsia

→ side effects – drowsiness, diarrhoea, muscle dystonias of head, neck & tongue, mental confusion, allergic reactions

→ driving is not advised after taking cinitapride.

→ no Q-T prolongation or risk of arrhythmia

→ atropinic drugs may reduce its efficacy

Dose: 1mg TDS 15 min before meals, or 3mg OD as ER tablet

CINTAPRO, KINPRIDE, CIN MOVE 1mg tab, 3mg ER tab.

5-HT_3 Antagonists:

Ondansetron: prototype drug

→ mainly used to control cancer chemotherapy / radiotherapy induced vomiting

→ highly effective in PONV & disease / drug associated vomiting as well.

→ blocks the depolarizing action of 5-HT exerted through 5-HT_3 receptors on vagal afferents in g.i.t & NTS, CTZ

Cytotoxic drugs / radiation

↓

cellular damage

↓

release of mediators including 5-HT from intestinal mucosa

↓

activation of vagal afferents in gut

↓

transmission of emetogenic impulse to NTS & CTZ

ondansetron ⇒ blocks emetogenic impulses mainly at their peripheral origin in git & at their central relay

- vomiting induced by apomorphine or motion sickness is not suppressed
- oral bioavailability of ondansetron is 60-70%

Dose:

- For cisplatin & other highly emetogenic drugs: 8 mg i.v. by slow injection over 15 min, 30 min before chemotherapeutic infusion; followed by 2 similar doses 4 hrs apart. **or** single 24 mg i.v. dose on first day
- To prevent delayed emesis: 8 mg oral BD for 3-5 days
- For PONV: 4-8 mg i.v. given before induction; repeated 8 hourly
- For less emetogenic drugs & for radiotherapy: oral dose of 8 mg given 1-2 hr prior to procedure; repeated twice 8 hourly.

EMESET, VOMIZ, OSETRON, EMSETRON 4, 8 mg tabs, 2 mg/mL inj. in 2mL & 4 mL amps.

ONDY, EMESET 2mg/5ml syrup.

→ in patients who do not obtain optimum protection from ondansetron alone, addition of dexamethasone, promethazine/diazepam or both enhances antiemetic efficacy

→ ondansetron alone is less effective in delayed emesis.

→ efficacy of 5-HT_3 antagonists in prevention & Tx of PONV is not well established.

→ vomiting due to drugs or drug overdosage, g.i. disorders, uraemia, neurological injuries is also suppressed.

→ odansetron to be avoided in pregnancy (except in hyperemesis gravidarum)

→ side effects: (generally well-tolerated) – headache, dizziness, mild constipation & abdominal discomfort (hypotension, bradycardia, chest pain, allergic reactions after i.v. injection)

Granisetron: 10 times more potent than ondansetron

↳ weak 5-HT_4 blockade also seen.

Dose: 1-3 mg diluted in 20-50 mL saline & infused i.v. over 5 min before chemotherapy; repeated after 12 hrs

- For less emetogenic regimen: 2mg oral 1 hr before chemotherapy or 1mg before & 1mg 12 hrs after it.
- For PONV: 1mg diluted in 5ml & injected i.v. over 30s before starting anaesthesia or 1mg orally every 12 hours

GRANICIP, GRANISET 1mg, 2mg tabs; 1mg/ml inj. in 1ml & 3ml amps.

Palonosetron: longest acting 5-HT_3 blocker (highest affinity for 5-HT_3 receptor)

→ more effective in suppressing delayed vomiting occurring between 2nd to 5th days.

→ side effects – headache, fatigue, dizziness, abdominal pain (additive Q-T prolongation can occur when given with moxifloxacin, erythromycin, antipsychotics)

→ rapid i.v. injection causes blurring of vision

Dose: 250 µg by slow i.v. injection 30 min. before chemotherapy [do not repeat before 7 days]

- For PONV: 75 µg i.v. as single injection just before induction

PALONOX 0.25 mg/ml inj., PALZEN 0.25 mg / 50 ml inj.

Ramosetron: potent 5-HT_3 antagonist

↳ general properties are similar to ondansetron

Dose:

- For CINV: 0.3 mg i.v. injected before chemotherapy; repeated once daily
- For low emetogenic chemotherapy: can be given orally in a dose of 0.1 mg OD
- For PONV: ramosetron 0.3 mg i.v ≈ ondansetron 8 mg i.v.

NOZIA 0.1 mg tab, 0.3 mg in 2ml amp.

NK_1 Receptor Antagonists: activation of neurokinin (NK_1) receptor in NTS & CTZ by substance P released due to emetogenic chemotherapy & other stimuli plays a role in causation of vomiting.

Aprepitant: selective, high affinity NK_1 receptor antagonist that blocks emetic action of substance P

→ G.I. motility is not affected

Dose: 125 mg + 80 mg + 80 mg over 3 days combined with i.v. ondansetron + dexamethasone regimen ⇒ for patients against high emetogenic cisplatin based chemotherapy.

→ particularly useful in patients undergoing multiple cycles of chemotherapy

- In PONV: single 40 mg oral dose

→ aprepitant is well-absorbed, penetrates blood-brain-barrier to act on central NK_1 receptors

→ well-tolerated (side effects - weakness, fatigue, flatulence, infrequent rise in liver enzymes)

APRECAP, APRESET, APRELIFE, EMPOV 125 mg (one cap.) + 80 mg (2 cap.) kit.

Fosaprepitant: parenterally administered prodrug of aprepitant.

Adjuvant Antiemetics:

Corticosteroids: [dexamethasone 8-20 mg i.v. before chemotherapy]

→ partly alleviates nausea & vomiting due to moderately emetogenic chemotherapy

→ MoA: (not known) appears to be due to anti-inflammatory action.

Benzodiazepines: weak antiemetic property due to sedative action

Cannabinoids: antiemetic activity against moderately emetogenic chemotherapy

↳ probably acts through CB_1 receptors located on neurons in CTZ & / or vomiting centre itself.

Dronabinol: 5-10 mg / m^2 of BSA orally ⇒ alternative antiemetic for moderately emetogenic chemotherapy in patients who cannot tolerate other antiemetics or are unresponsive to them

→ side effects — hallucinations, disorientation, other central sympathomimetic effects; addiction

→ stimulates the appetite ∴ used in lower doses to improve feeding in cachectic / AIDS patients.

Digestants: substances intended to promote digestion of food
↳ used for dyspeptic symptoms, as appetite stimulants & health tonics

- **Pepsin:** may be used along with HCl in gastric achylia due to atrophic gastritis, gastric carcinoma, pernicious anemia, etc.
- **Papain:** proteolytic enzyme obtained from raw papaya
  ↳ efficacy after oral ingestion is doubtful.
- **Pancreatin:** mixture of pancreatic enzymes obtained from hog & pig pancreas
  ↳ indicated in chronic pancreatitis or other exocrine pancreatic deficiency states.
  → fat & nitrogen content of stools may be reduced & diarrhoea/steatorrhoea may be prevented.
- **Diastase & Takadiastase:** amylolytic enzymes obtained from fungus Aspergillus oryzae
  → used in pancreatic insufficiency.

- **Methyl Polysiloxane:** silicone polymer, viscous amphiphilic liquid
  → reduces surface tension & collapses froth (antifoaming agent)
  → not absorbed from g.i.t, pharmacologically inert
  → added to antacid, digestant, antireflux preparations
  → briskly promoted as a remedy for gas
  → also claimed to coat & protect ulcer surface, to aid dispersion of antacids in gastric contents & to prevent gastroesophageal reflux

Dose: 40 - 120 mg, 3-4 times / day
DIMOL 40 mg tab.

Gallstone Dissolving Drugs:

→ laproscopic cholecystectomy is the treatment of choice for gallstones

→ medical therapy is an option with small cholesterol (CH) stones who are unwilling or unfit for surgery.

→ CH remains dissolved in bile with the help of bile salts (salts of cholic acid & chenodeoxycholic acid conjugated with glycine & taurine) because bile salts are highly ampliphilic.

→ high CH:bile salts ratio favours crystallisation of CH in bile; these crystals serve as nidi for stone formation

→ Chenodeoxycholic acid (chenodiol) & ursodeoxycholic acid (ursodiol) decrease CH content of bile which enables solubilisation of CH from the stone surface.

Ursodiol: it gets conjugated in the liver with glycine & taurine & is excreted in bile

→ it promptly reduces CH secretion into bile & promotes solubilization of biliary CH by liquid crystal formation.

→ plasma LDL-CH level is not raised

→ more likely to succeed in patients who have a functioning gallbladder with multiple small floating gall stones

→ much better tolerated than chenodiol

Dose: 450 – 600 mg daily in 2-3 divided doses after meals

UDIHEP 150 mg tab, URSOCOL 150, 300 mg tabs, 450 mg SR cap.

→ dissolution of gall stones is a very slow process

→ once treatment is discontinued after stone dissolution, recurrences are common because bile returns to its CH supersaturated state. Repeat courses may have to given.