

Vomiting

- The act of vomiting and the sensation of nausea that accompanies it are protective reflexes that serve to rid the stomach and intestine of toxic substances and prevent their further ingestion

GI Agents

Vomiting - Antiemetics

- Vomiting = the expulsion of gastric contents Before treating, the cause of the vomiting needs to be identified
- Causes are many: motion sickness, viral & bacterial infection, food intolerance, surgery, PG, pain, shock, effects of some drugs, radiation, & disturbances of the middle ear affecting equilibrium.
- Antiemetics can mask the cause & should not be used until cause is determined, unless vomiting is severe enough to cause dehydration & electrolyte imbalance

Regulation of vomiting

- **medulla oblongata**

- the vomiting centre
- chemoreceptor trigger zone (area postrema)
 - emetogenic substances, apomorphine, morphine, chemotherapy, motion sickness
- Ach, histamine, 5-HT, Dopamine
- For the act of vomiting VC needs to be activated by impulses reaching to it directly or via CTZ

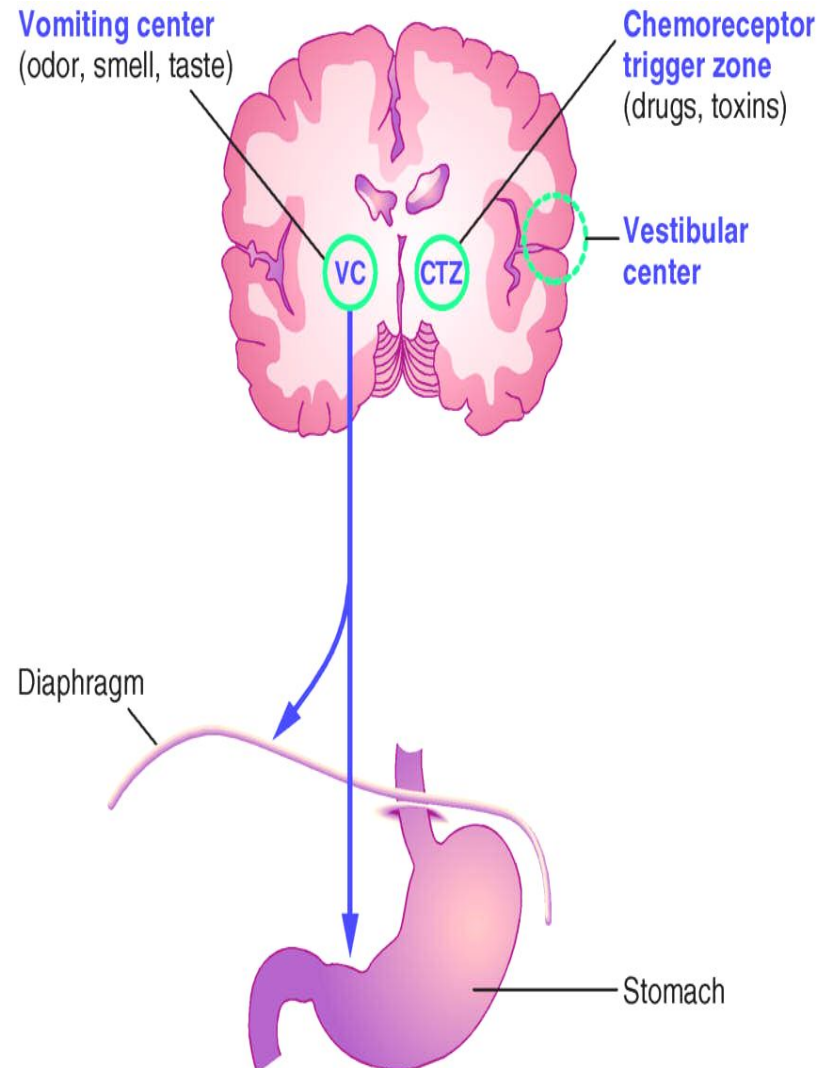
Anti-emetics

- Two centres: Emetic centre (EC) and chemoreceptor trigger zone (CTZ)
- Both near the floor of the fourth ventricle, close to the vital centres
- EC is within the blood brain barrier (BBB)
- CTZ outside in the area postrema
- They are connected together

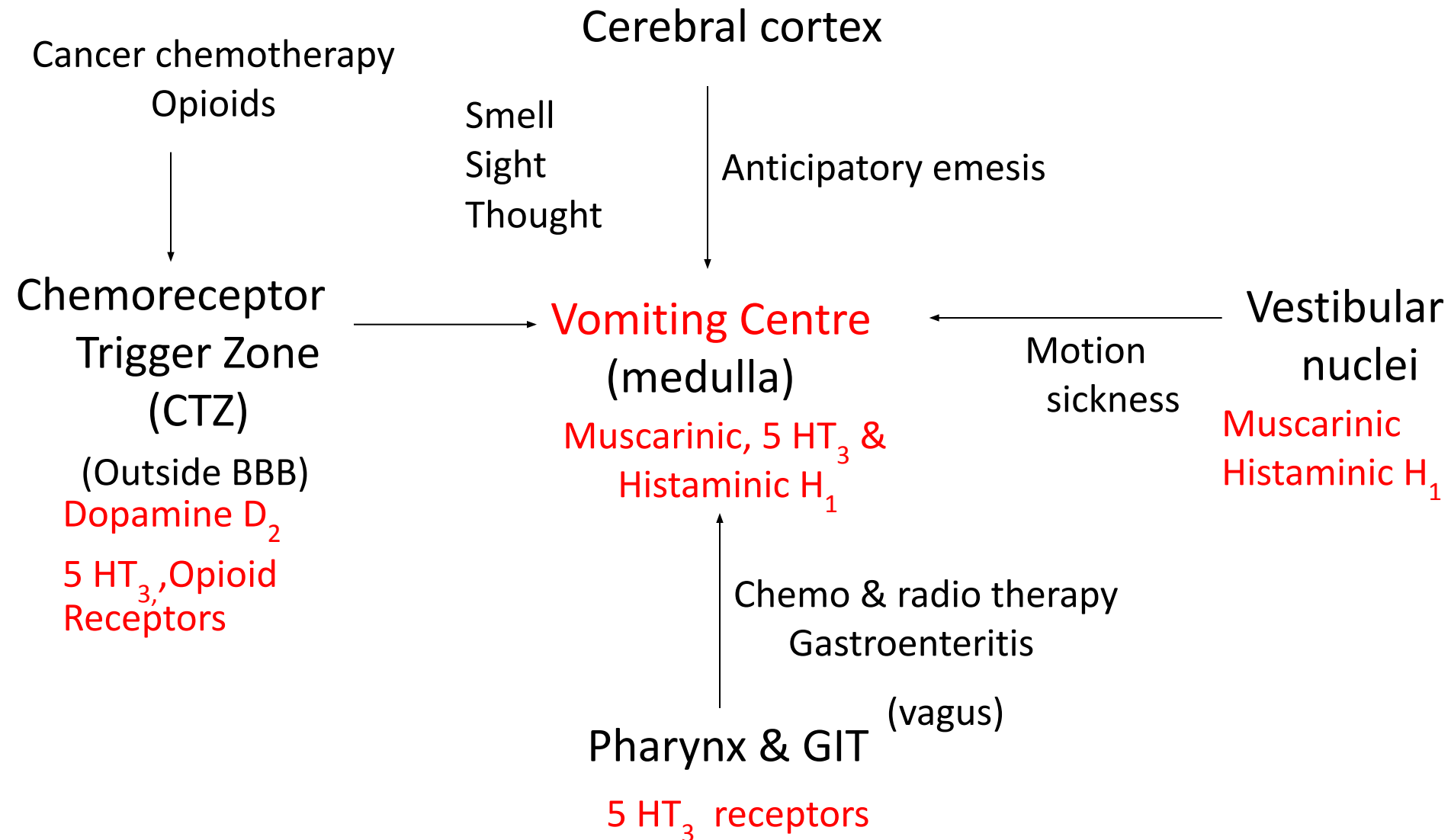
GI Agents

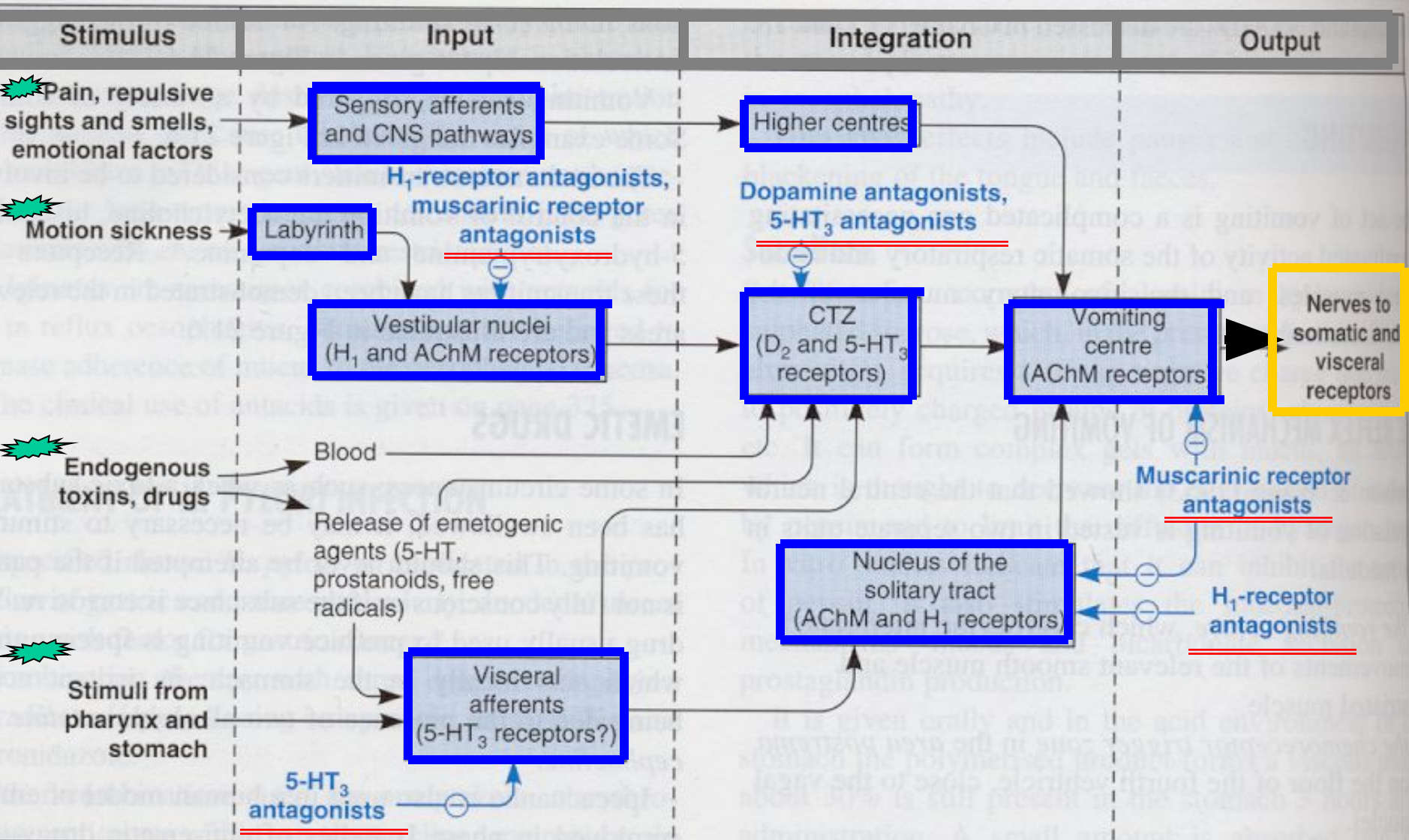
Vomiting - Antiemetics

- the vestibular center.- send impulses directly to VC
- The CTZ receives most of the impulses from drugs, toxins,
- vomiting center, when activated triggered, motor neuron responds □ contraction of diaphragm, anterior abdominal muscles, & the stomach. the glottis closes, the abdominal wall moves, upward & vomiting occurs.



Pathophysiology of Emesis





Group of drugs used as antiemetics

Serotonin 5 HT₃ Antagonists:

Dopamine D₂ Antagonist:

Anticholinergics:

H₁ Antihistaminics

Control of GIT motility

Neurogenic control of GIT motility: the ENS

- ❑ Enteric nervous system (ENS) is a collection of nerves within the wall of the GI tract responsible for the autonomous gastrointestinal activity. It consists of connected networks of neurons:
 1. myenteric (Auerbach's) plexus, found between the circular and longitudinal muscle layers (responsible for motor control)
 2. submucosal (Meissner's) plexus, found below the epithelium (regulates secretion, fluid transport, and vascular flow).

Neurons in both plexuses release acetylcholine at their terminals.

- ❑ Autonomic nervous system:

Parasympathetic : act by releasing acetylcholine at nerve terminals. It causes contraction of muscles in the wall of the intestine and relaxation of the sphincters and increases gland secretion

Sympathetic: act by releasing norepinephrine at nerve terminals. It causes relaxation of muscles in the wall of the intestine and contraction of the sphincters

Types of cholinergic receptors are M_2 and M_3 (present in the GIT in a 4:1 ratio). M_3 receptor is more important in muscle contraction.

Agents that increase GIT motility

1- Cholinergic agents

Stimulate cholinergic receptors. Enhance contractions in an uncoordinated manner that produces no net propulsive activity. Not useful for treating motility disorders

2- Prokinetic agents

enhance coordinated GIT propulsive motility. Prokinetic agents act at receptor sites on the motor neuron itself increasing the release of acetylcholine at the motor nerve terminal without interfering with the normal physiological pattern and rhythm of motility. Useful for treating motility disorders

Anti-emetic agents

Chemoreceptor trigger zone

- Anti-dopaminergic agents
 - phenothiazines e.g. chlorpromazine
 - butyrophenones e.g. droperidol
 - procainamide derivs. e.g. metoclopramide
 - benzimidazole derivs. e.g. domperidone

Antidopaminergics as antiemetics

- D2 receptors are preset at CTZ in pathway of vomiting
- Older neuroleptics have D2, H1, M3 antagonism therefore more broad spectrum action
- Most of these drugs have high sedation, though their antiemetic dose is much lower than antipsychotic dose muscle dystonia may occur
- Prochlorperazine is the only antipsychotic which is used as antiemetic
- It is also useful in labyrinthitis induced vomiting as it suppresses labyrinthine apparatus

Antidopaminergics as prokinetic

- Some of antidopaminergic agents have prokinetic action also. Eg. Metoclopramide-
- It increases upper GI peristalsis. No effect on gastric secretion
- Increase gastric emptying- stronger in intact Vegas
- LES tone is increased , opposes esophageal reflex
- Lesser effect on intestinal peristalsis movement
- No effect on colonic motility
- Prokinetic action is due to D2 antagonism as Dopamine is inhibitory neurotransmitter in GIT

Antidopaminergics as prokinetic

- 5HT4 agonism- 5HT4 receptors at primary afferent neurons of ENS when gets excited cause Ach release from motor neurons adds to prokinetic action
- 5HT3 antagonism –only at high doses these receptors present on inhibitory myenteric interneurons are blocked causing Ach release in gut.
- Minor effect

Antidopaminergics as antiemetics

metoclopramide

- Effective D2 blocking effect on CTZ
- Inhibits 5HT3 receptors at NTS/ CTZ-minor action
- Inhibits 5HT3 receptors at vagal afferent in GIT
- Other drug Domperidone- d2 antagonist
- Poor BBB penetration, CTZ mediated antiemetic action and D2 mediated prokinetic action

1- Metoclopramide

Adverse Effects:

1- **Extrapyramidal effects** (more commonly in children and young adults and at higher doses).

- Tardive dyskinesia=repulsive, involuntary, purposeless movements (usually involve the face) like tongue protrusion, lip smacking, pursing of the lips and rapid eye blinking. It occurs with chronic treatment (months to years) and may be irreversible
- Akathisia = restlessness and inability to sit still or remain motionless
- Dystonias = muscular spasms of neck usually occurring acutely after intravenous administration
- parkinsonian-like symptoms that may occur several weeks after initiation of therapy generally respond to treatment with anticholinergic or antihistaminic drugs and are reversible upon discontinuation of metoclopramide.

2-Galactorrhea by blocking the inhibitory effect of dopamine on prolactin release (infrequent)- as the pituitary lacks blood-brain barrier domperidone also can produce this ADR

Anti-emetic agents at CTZ

Anti-dopaminergic agents... uses

- Chemotherapy
- Drug induced N and V e.g. opioids and chemotherapy
- Parkinson's disease (domperidone)
- Postoperative N and V
- Motion sickness ?

Uses as prokinetics

- Prokinetics agents can be used in
- To accelerate gastric emptying in emergency general anaesthesia
- Postvagotomy and diabetes induced gastric stasis
- To facilitate duodenal intubation
- Dyspepsia
- Gastroesophageal reflux disease
- Persistent hiccups

Serotonin 5 HT₃ Antagonist

ondansetron Potent antiemetics

Antiemetic action is mainly against: chemotherapy induced N/V which is caused by cellular damage

causing release of mediators including 5HT from intestinal mucosa which activates vagal afferent in gut which in turn sends emetogenic impulses to NTS & CTZ

Mechanism of action:

- 1- Peripheral 5-HT₃ receptor blockade on intestinal vagal afferents.
- 2- Central 5-HT₃ receptor blockade in the vomiting center and chemoreceptor trigger zone

High first pass metabolism

Excreted by liver & kidney

No dose reduction in renal insufficiency but needed in hepatic insufficiency

Drugs Available

1. Ondansetron
2. Granisetron
3. Dolasetron
4. **Palonosetron**

Indications

- 1) Chemotherapy induced nausea and vomiting
- 2) postradiation nausea & vomiting
- 3) Vomiting of pregnancy
- 4) Postoperative vomiting

Adverse Effects

The most common adverse effects are:

- 1- Headache and dizziness
- 2- Constipation or diarrhoea

Granisetron-more potent than ondansetron long $t_{1/2}$

So twice daily dose is enough

Anti-emetic agents at EC

Anticholinergics

- Atropine and hyoscine, dicyclomine
- Glycopyrrolate ?
- Hyocine is more effective but shorter duration so give transdermal
- Blocks impulses travelling from vestibule to VC
- Dicyclomine is also tried in morning sickness- as it has shown free of teratogenicity

Uses

- Travel sickness

Anti-emetic agents at EC**Anti-histamines**

- Cyclizine, maclizine
- Promethazine (other actions?), diphenhydramine

Uses

Motion sickness & to small extent morning sickness

- Postoperative N and V- lesser effect
- Main mechanism is by anticholinergic antihistaminic and sedative action

H1 receptor antagonists and Anticholinergics

Use:

prevention or treatment of motion sickness.

Adverse effects: sedation, dizziness, confusion, dry mouth, cycloplegia, and urinary retention.

Diphenhydramine dimenhydrinate	First generation H1 receptor blockers that have anticholinergic and sedating properties
Meclizine	First generation H1 receptor blockers that have lesser anticholinergic and sedating properties
Hyoscine	Muscarinic receptor blocker

cinnarizine

- Used as antivertigo agent also protective to motion sickness
- Act by inhibiting influx of Ca from endolymph into vestibular sensory cells which mediate labyrinth reflexes
- Antihistaminics are not free from teretogenicity

Corticosteroids

Corticosteroids have antiemetic properties

Mechanism of action: possibly by suppressing peritumoral inflammation and prostaglandin production.

Use: to enhance efficacy of 5HT₃ receptor antagonists in the treatment of chemotherapy-induced vomiting.

Benzodiazepines

- **Uses:**
- Benzodiazepines such as diazepam are used prior to the initiation of chemotherapy to reduce anticipatory vomiting or vomiting caused by anxiety

Cannabinoids (Dronabinol)

- **The mechanisms for the antiemetic effects** is not known.
- **Pharmacokinetics.**

readily absorbed after oral administration

It undergoes extensive first-pass metabolism with limited systemic bioavailability after single doses. Metabolites are excreted primarily *via* the biliary-fecal route.

- **Adverse effects include:**
 1. Euphoria or dysphoria, sedation and hallucinations
 2. Abrupt withdrawal leads to withdrawal syndrome (restless, insomnia and irritability)
 3. Autonomic effects (sympathetic) in the form of tachycardia, palpitation, conjunctival injection, and orthostatic hypotension.

- **Use:**

For the prevention of chemotherapy-induced nausea and vomiting

Anti-emetic agents: Choice

- Postoperative
- Chemotherapy
- Travel sickness
- Parkinson's disease (especially apomorphine)
- Pregnancy

Area	Type of receptors	Stimulus
Chemoreceptor trigger zone (CTZ)	a) Dopamine D2 b) 5HT3 c) Opioid	1) Cancer chemotherapy 2) Opioids
Vestibular nuclei	a) Mscarinic b) Histamine H1	1) Motion sickness
Pharynx and GIT	a) 5HT3	1) Cancer chemotherapy 2) Radio therapy 3) Gastroenteritis
Cerebral cortex		1) Smell 2) Sight 3) Thought 4) Anticipatory emesis

Serotonin 5HT3 receptor antagonists	5HT3 receptor
Phenothiazines	Dopamine D2 receptors Antihistaminic Anticholinergic
Substituted benzamides	Dopamine D2 receptors
Anticholinergic drugs	Muscarinic receptors
Antihistaminic drugs	Histamine H1 receptors

Other prokinetic agents

- Cisapride-action is only prokinetic
- It facilitates GI motility through out gut including colon
- Act as 5HT₄ agonistic which promotes Ach release from myenteric neurons, in addition same mechanism promot cAMP dpendent Cl secretion in colon, increses water content of stool
- + weak 5HT₃ antagonist inhibits inhibitory myentreric neurotransmitter
- Primary indication is GERD, nonulcer dyspepsia, impaired gastric emptying, chronic constipation

Cisapride

- High conc of cisapride has blocks delayed rectifying K channel of heart- causing prolong qtc
- Avoid inpt taking CYP3A4 inhibitor
- Mosapride- not shown QTc prolongation
- Tegaserod- partial 5HT4 agonistic no 5HT3 effect
- Currently tegserod is only indicated in constipation

Cholinergic Agents

- **Direct cholinergic agents**

- Stimulate cholinergic receptors in the wall of the GIT.

1- ACh is not used pharmacologically because:

- ☐ it affects both nicotinic and muscarinic receptors
- ☐ It is degraded rapidly by acetylcholinesterase.

2- Bethanechol

- ☐ Muscarinic receptor agonist
- ☐ Resists enzymatic hydrolysis.
- ☐ In addition, it lacks real prokinetic efficacy,

Indirect cholinergic agents:

Acetylcholinesterase Inhibitors. These drugs inhibit the degradation of ACh , allowing ACh to accumulate at sites of release.

- Neostigmine has been used to treat paralytic ileus.

Clinical use of anti-emetic drugs:

H₁-receptor antagonists:

□ **cylizine** - motion sickness

□ **cinnarizine** - motion sickness, vestibular disorders (e.g. Menière's disease)

□ **promethazine** - severe morning sickness of pregnancy (only if absolutely essential)

D₂-receptor antagonists:

□ **phenothiazines (e.g. thiethylperazine)** - vomiting caused by uraemia, radiation, viral gastroenteritis (drugs of choice); severe morning sickness of pregnancy (if absolutely essential)

□ **metoclopramide** - vomiting caused by uraemia, radiation, gastrointestinal disorders, cytotoxic drugs

Muscarinic-receptor antagonists:

□ **hyoscine - motion sickness (drug of choice)**

5-HT₃ receptor antagonists:

□ **ondansetron - vomiting caused by cytotoxic anticancer drugs (drug of choice), postoperative vomiting; radiation-induced vomiting**

Cannabinoids:

□ **nabilone - for vomiting caused by cytotoxic anticancer drugs**

Motility of GIT

laxatives

antidiarrhoeal drugs

GI Agents - Emetics

- **Emetics** - for when an individual has consumed certain toxic substances and must be expelled before absorption -- Don't induce vomiting if caustic substances have been ingested, □ ammonia, chlorine bleach, lye, toilet cleaners, or battery acid. Activated charcoal is given when emesis is CI
- **Ipecac** - stimulates the CTZ in the medulla & acts directly on the gastric mucosa - take w/ water (not milk or carbonation) - onset in 15 to 30 min. Repeat tx if needed. Toxic if absorbed □ give charcoal.
 - s/s toxicity □ hypotension, tachycardia, chest pain
 - SE: diarrhea, sedation, lethargy
- **Apomorphine** is a morphine derive emetic, SQ/IM, Onset 15 min