ANTIEMETIC AGENTS

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Nausea and vomiting may be manifestations of a wide variety of conditions, including:

adverse effects from medications;

systemic disorders or infections;

pregnancy; vestibular dysfunction;

central nervous system infection or increased pressure; peritonitis; hepatobiliary

disorders; radiation or chemotherapy; and gastrointestinal obstruction, dysmotility, or infections.

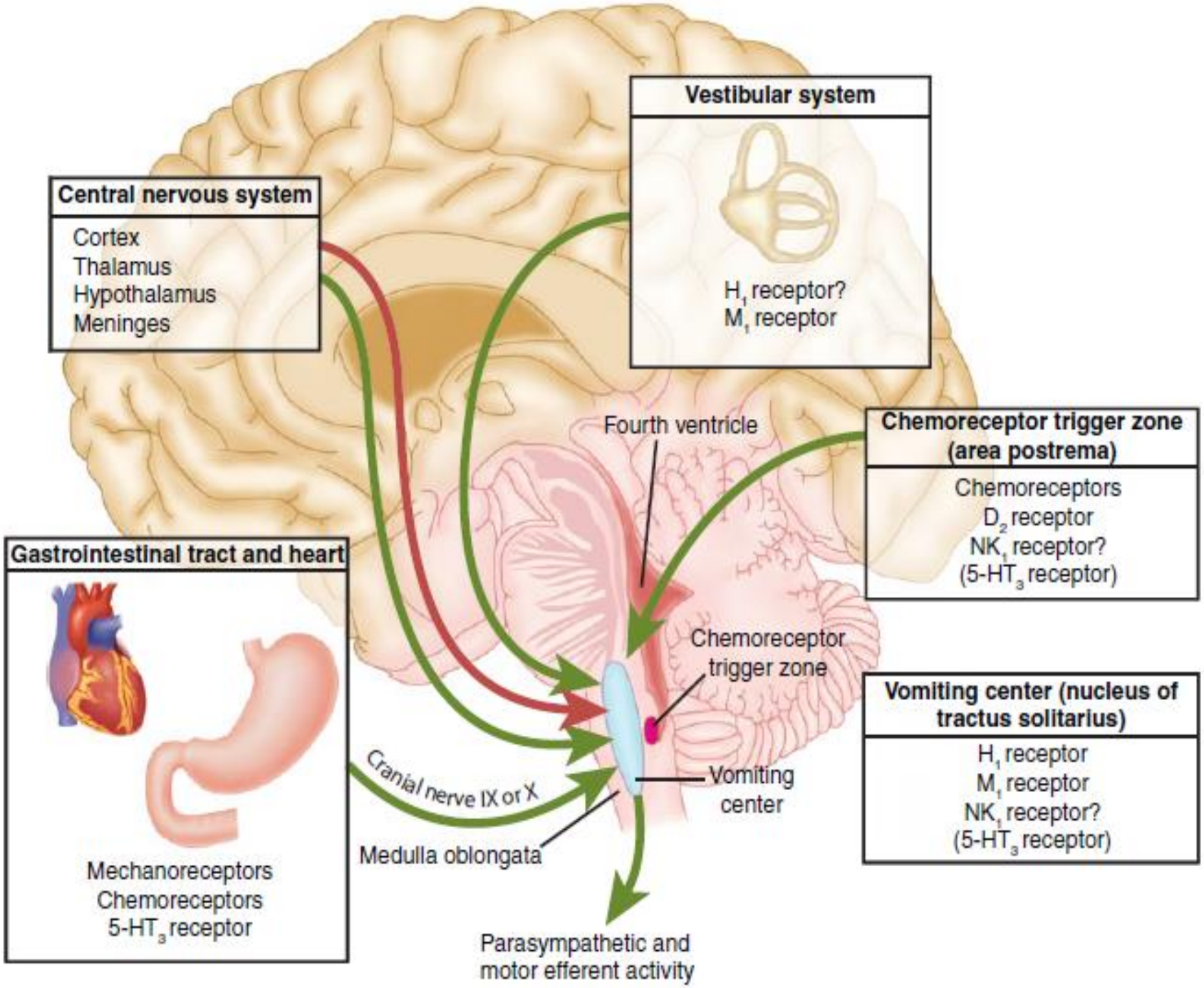
PATHOPHYSIOLOGY

The brainstem "vomiting center" is a loosely organized neuronal region within the lateral medullary reticular formation and coordinates the complex act of vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor centers.

High concentrations of muscarinic **M 1** , histamine **H 1** , neurokinin 1 (**NK 1**), and serotonin 5-HT 3 receptors have been identified in the vomiting center

Mechanisms that trigger vomiting

Two brainstem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone (CTZ) is located in the area postrema (a circumventricular structure at the caudal end of the fourth ventricle). It is outside the blood–brain barrier. Thus, it can respond directly to chemical stimuli in the blood or cerebrospinal fluid. The second important site, the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting. The vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and GI tract), and higher brainstem and cortical structures. The vestibular system functions mainly in motion sickness


Vestibular system
H1 receptor?
M1 receptor
Central nervous system
Cortex
Thalamus
Hypothalamus
Meninges
Fourth ventricle
Chemoreceptor trigger zone (area postrema)
Chemoreceptors
D2 receptor
NK1 receptor?
(5-HT3 receptor)
Chemoreceptor trigger zone
Vomiting center (nucleus of tractus solitarius)
H1 receptor
M1 receptor
NK1 receptor?
(5-HT3 receptor)
Gastrointestinal tract and heart
Mechanoreceptors
Chemoreceptors
5-HT3 receptor
Cranial nerve IX or X
Vomiting center
Medulla oblongata
Parasympathetic and motor efferent activity

There are four important sources of afferent input to the vomiting center:

1. The "chemoreceptor trigger zone" or area postrema is located at the caudal end of the fourth ventricle. This is outside the blood-brain barrier but is accessible to emetogenic stimuli in the blood or cerebrospinal fluid. The chemoreceptor trigger zone is rich in dopamine D 2 receptors and opioid receptors,

and possibly serotonin 5-HT 3 receptors and NK 1 receptors.

2. The vestibular system is important in motion sickness via cranial nerve VIII. It is rich in muscarinic M 1 and histamine H 1 receptors.

3. Vagal and spinal afferent nerves from the gastrointestinal tract are rich in 5-HT 3 receptors. Irritation of the gastrointestinal mucosa by chemotherapy, radiation therapy, distention, or acute infectious gastroenteritis leads to release of mucosal serotonin and activation of these receptors, which stimulate vagal afferent input to the vomiting center and chemoreceptor trigger zone.

4. The central nervous system plays a role in vomiting due to psychiatric disorders, stress, and anticipatory vomiting prior to cancer chemotherapy

Classification

1. **Dopamine D_2 antagonists (prokinetics)**
   Metoclopramide, domperidone,
   trimethobenzamide
2. **5-HT_3 antagonists**
   Ondansetron, granisetron, dolasetron
   Tropisetron, palanosetron
3. **Antimuscarinics**
   Hyoscine, promethazine
   Cyclizine, diphenhydramine
4. **Neuroleptics**
   Chlorpromazine, prochlorperazine
   Haloperidol
5. **Neurokinin receptor antagonists**
   Aprepitant
   Fosaprepitant
6. **Other agents**
   Glucocorticoids
   Cannabinoids—dronabinol, nabilone

Dopamine D2 Antagonists

Metoclopramide and domperidone act centrally by blocking dopamine D2 receptors in the CTZ and thereby prevent vomiting.

They enhance the tone of the lower oesophageal sphincter and increase gastric peristalsis—they are prokinetics.

The principal adverse effects of these central dopamine antagonists are extrapyramidal: restlessness, dystonias, and parkinsonian symptoms.

domperidone It blocks the dopamine receptors in the CTZ and thereby acts as an antiemetic. Advantages over metoclopramide are— domperidone does not cross the blood–brain barrier and hence extrapyramidal and neuropsychiatric side effects are rare.

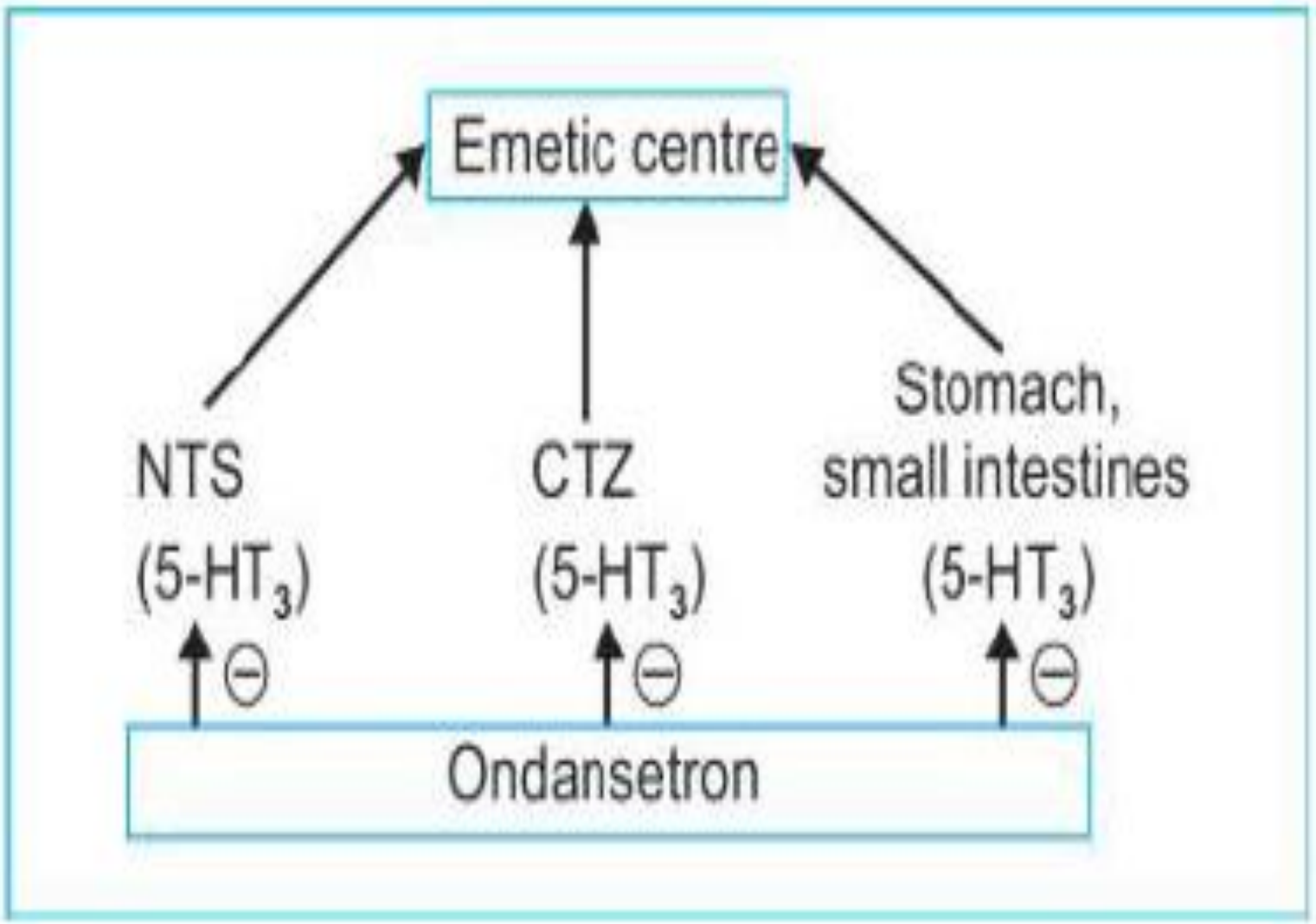
SEROTONIN 5-HT 3 ANTAGONISTS

5-HT3 Antagonists

Ondansetron: 5-Hydroxytryptamine released in the gut is an important inducer of emesis and the nerve endings including vagal affarents in the gut are rich in 5-HT3 receptors. It is believed that anticancer drugs, radiation therapy and infection of the gastrointestinal mucosa induce the release of 5-HT in the gut which initiates emetic reflex through 5-HT3 receptors present in the gut, nucleus tractus solitarius (NTS) and area postrema in the brain.

Ondansetron blocks 5-HT3 receptors in the GI tract, CTZ and nucleus tractus solitarius and prevents vomiting. It is a

powerful antiemetic and can be given orally or intravenously (4–8 mg).


Emetic centre
NTS
(5-HT3)
CTZ
(5-HT3)
Stomach,
small intestines
(5-HT3)
Ondansetron

The first three agents (ondansetron, granisetron, and dolasetron, have a serum half life of 4–9 hours and may be administered once daily by oral or intravenous routes.

Palonosetron is a newer intravenous agent that has greater affinity for the 5-HT 3 receptor and a long serum half-life of 40 hours.

Clinical Uses

1-5-HT3 antagonists are used to control vomiting induced by anticancer drugs or radiotherapy.

They should be given intravenously 30 min before (ondensetron 8 mg infusion over 15 min) or orally 1 hr before starting chemotherapy.

2_They are also useful in postoperative vomiting and other drug-induced vomiting (but not in motion sickness).

Antimuscarinics:

Hyoscine is a very effective in motion sickness. Motion sickness or travelling sickness is due to over stimulation

of the vestibular apparatus along with psychological and environmental factors.

Hyoscine also relaxes the gastrointestinal smooth muscle. Taken 30 minutes before journey, hyoscine (0.4–0.6 mg oral) acts for 6 hours and the dose should be repeated, if the journey is longer than that. A transdermal patch delivers hyoscine constantly over 3 days and is to be applied behind the ear.

Sedationand dry mouth

are common side effects.

Dicyclomine is used to control vomiting in morning sickness and motion sickness—orally in the dose of 10–20 mg H1 antihistamines like promethazine, diphenhydramine, doxylamine, cyclizine and cinnarizine have anticholinergic properties.

Antihistamines block H1 receptors in the area postrema as well as muscarinic receptors in the CNS. They probably also act on the GI tract. Some of them are useful in motion sickness and postoperative vomiting.

Doxylamine is available in combination with pyridoxine for ‘morning sickness’ in some countries.

Adverse Effects

The 5-HT 3 -receptor antagonists are well-tolerated agents with excellent safety profiles. The most commonly reported adverse effects are headache, dizziness, and constipation prolongation of the QT interval(dolasetron)

CORTICOSTEROIDS

Corticosteroids

(dexamethasone,methylprednisolone) have antiemetic properties, but the basis for these effects is unknown These agents appear to enhance the efficacy of 5-HT 3 -receptor antagonists for prevention of acute and delayed nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy regimens.

NEUROKININ RECEPTOR ANTAGONISTS

Aprepitant , *netupitant*, and *rolapitant* target the neurokinin receptor in the vomiting center and block the actions of **substance P**.

Neurokinin 1 (NK 1)-receptor antagonists have antiemetic properties **Aprepitant** (an oral formulation) is a highly selective NK 1 -receptor antagonist that crosses the blood-brain barrier and occupies brain NK 1 receptors **Fosaprepitant** is an intravenous formulation that is converted within 30 minutes after infusion to aprepitant.

Clinical Uses

Aprepitant is used in combination with 5-HT 3 - receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from highly emetogenic chemotherapeutic

Regimens

Adverse Effects

Aprepitant may be associated with fatigue, dizziness, and diarrhea.

The drug is metabolized by CYP3A4 and may inhibit the metabolism of other drugs metabolized by the CYP3A4 pathway..

PHENOTHIAZINES & BUTYROPHENONES

Neuroleptics

Neuroleptics also block D2- receptors in the CTZ and are useful in vomiting due to most causes except motion sickness. Sedation and extrapyramidal symptoms are the common side effects.

Prochlorperazine

is mainly used as an antiemetic in vomiting and is also effective in vertigo associated with vomiting.

Prochlorperazine Dose: 5–25 mg. , 12.5 mg/ml inj.

H 1 ANTIHISTAMINES & ANTICHOLINERGIC DRUGS

As single agents, these drugs have weak antiemetic activity, although they are particularly useful for the prevention or treatment of motion sickness. Their use may be limited by dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention.

Diphenhydramine and one of its salts, **dimenhydrinate,** are first generation histamine H 1 antagonists that also have significant anticholinergic properties. Because of its sedating properties, diphenhydramine is commonly used in conjunction with other antiemetics for treatment of emesis due to chemotherapy

Meclizine is an H 1 antihistaminic agent with minimal anticholinergic properties that also causes less sedation. It is used for the prevention of motion sickness and the treatment of vertigo due to labyrinth dysfunction.

Hyoscine (scopolamine), a prototypic muscarinic receptor antagonist, is one of the best agents for the prevention of motion sickness. However, it has a very high incidence of anticholinergic effects when given orally or parenterally. It is better tolerated as a transdermal patch.

BENZODIAZEPINES

Benzodiazepines such as lorazepam or diazepam are used before the initiation of chemotherapy to reduce anticipatory vomiting or vomiting caused by anxiety

CANNABINOIDS

Dronabinol is Δ 9 -tetrahydrocannabinol (THC), the major psychoactive chemical in marijuana

Nabilone is a closely related THC analog

Pyridoxine (vitamin B6) is used in the prevention of vomiting in pregnancy without any known pharmacological basis. The proposed rationale is that pyridoxine serves as a cofactor in GABA synthesis and GABA acting as the inhibitory neurotransmitter at CTZ may suppress vomiting. Dose: 20–60 mg.

Part 3: Antiemetic Drugs

Several classes of antiemetic drugs are available that antagonize the neurotransmitter receptors known to be involved in the physiology of nausea and vomiting. The antiemetic drugs are classified according to their primary action; some agents affect multiple receptors.

Drug	Antiemetic mechanism	Uses as antiemetic	Adverse effects
1. Muscarinic blockers: ▪ Atropine ▪ Hyoscine	They block **M_1** receptors in the vestibulocerebellar pathway, solitary tract nucleus, and chemoreceptor trigger zone (CTZ).	Prevention and treatment of vomiting due to **motion sickness** (0.3-0.6 mg/8 hrs orally).	– Blurred vision – Dry mouth – Urine retention – Glaucoma – Tachycardia
2. H1-blockers: ▪ Diphenhydramine ▪ Cyproheptadine ▪ Cyclizine ▪ Meclizine	– They block H_1 (also M_1) receptors in the vestibulo-cerebellar pathway and CTZ. – They have sedative action.	– Vomiting due to **motion sickness** (diphenhydramine) – Vomiting of **pregnancy** (cyclizine and meclizine) – **True vertigo**: combined with VDs to improve labyrinthine blood flow.	– Sedation (excitation may occur in children). – Atropine-like actions (dry mouth, blurred vision, urine retention). – Hypotension
3. 5-HT3 blockers: ▪ Ondansetron ▪ Granisetron ▪ Tropisetron	They block $5HT_3$ receptors in the GIT, solitary tract nucleus and CTZ.	– Vomiting due to **cancer chemotherapy** or **radio-therapy.** – **Postoperative** nausea and vomiting.	– Dizziness, headache, and constipation.
4. Dopamine blockers ▪ Metoclopramide	– They block D2 receptors in the CTZ.	– Vomiting due to **drugs** or fevers.	– Sedation – Extrapyramidal effects e.g.

▪ Domperidone ▪ Phenothiazines e.g. chlorpromazine	– They inhibit peripheral transmission to VC.	– Vomiting due to **cancer chemotherapy**. – **Postoperative** nausea and vomiting.	dystonia and dyskinesia. – Hyperprolactinemia – Postural hypotension
5. Cannabinoid derivatives: ▪ Nabilone and Dronabinol	– It is a partial agonist at central and peripheral cannabinoid receptors (CB1). The exact mechanism is unclear.	– Vomiting due to **cancer chemotherapy** – Patients refractory to other antiemetics.	– Sedation – Hallucinations – Psychotropic effects – Postural hypotension – Drug abuse.
6. Vitamin B6 (pyridoxin)	May be related to the balance between GABA (CNS *inhibitory* transmitter) and glutamate (CNS *excitatory* transmitter).	– Vomiting in **pregnancy** (50 mg at bedtime). – Vomiting in **children**	-
7. Corticosteroids ▪ Dexamethasone ▪ Prednisolone	The exact mechanism is unclear.	– Combined with Vit B6 to treat vomiting in **pregnancy**. – Vomiting due to **cancer chemotherapy**.	– See endocrine chapter
8. Benzodiazepines ▪ Lorazepam ▪ Diazepam	Allosteric facilitation of central GABA inhibitory transmission	– **Stress-related** vomiting – To controls symptoms in **Ménière disease**	– See CNS chapter
9. Neurokinin-1 receptor blockers: ▪ Aprepitant	Substance-P induces vomiting through stimulation of NK-1 receptors. Aprepitant blocks this receptor.	– In combination with 5-HT3 blockers to treat vomiting due to **cancer chemotherapy**	– Diarrhea and fatigue

Antispasmodic Drugs (smooth ms relaxants)

Classification

- **Anticholinergic drugs:** atropine, hyoscine, propantheline, oxyphenonium.
- **Direct smooth muscle relaxants:** papaverine, mebeverine, alverine, drotaverine.
- **Mixtures:** Librax (clidinium + chlordiazepoxide), Donnatal (hyoscine + phenobarbital)

	Papaverine	Mebeverine, Alverine, Drotaverine	Librax
Chemistry & mechanism of action	It is opium alkaloid but chemically different from morphine	They are synthetic drugs	It is a combination of: ▪ **Chlordiazepoxide:** benzodiazepine that has antianxiety effect. ▪ **Clidinium:** anticholinergic drug which ↓ GIT motility and spasm
	The exact mechanism is unclear but may be due to inhibition of **PDE** enzyme →↑ cAMP → smooth muscle relaxation.		
Use	▪ Spasms of the GIT, bile duct and genitourinary tract. ▪ Librax is used for treatment of irritable bowel syndrome (IBS).		
Side effects	– Cardiac **arrhythmia**. – **Abnormal liver functions** in the form of elevated serum transaminases and alkaline phosphatase. – Headache and dizziness		– **Atropine-like actions** e.g, dry mouth, urine retention, etc. – Sedation, drowsiness, confusion, etc.
C/I	– Paralytic ileus. – Constipation for more than one week		

Therapy of Constipation

Non-drug therapy: It is the **first line** in all cases of constipation

- **Diet rich in fibers** e.g. fruits, vegetables, whole meal bread, etc. to be increased to 30 g/day.
- Increase **fluid intake**
- Minimize **tea** and coffee.
- Physical **exercise** to activate abdominal muscles and intestinal peristalsis. This help food move more efficiently through the gut.

Drug therapy: LAXATIVES:

1. Bulk-forming agents:

[Dietary fibers – Methylcellulose – Bran]

Mechanism of action

They are non-digestible fibers; they retain water in the gut and distend the large intestine → activation of stretch receptors → stimulation of peristalsis.

Drug causes of constipation:

- Atropine and related drugs.
- Aluminum containing antacids
- Adsorbents (kaolin & pectin).
- **CCBs:** e.g. **V**erapamil
- **Opioids:** morphine & loperamide

Adverse effects: they are **safe** laxatives but may cause:

– Bloating and abdominal distension.

– ↓ absorption of some drugs e.g. digoxin.

– They may form masses in the gut leading to intestinal obstruction.

2. Osmotic laxatives:

[Mg sulfate & Na salts – Lactulose – Polyethylene glycol]

Mechanism of action

They are retained in the gut lumen and retain water by their osmotic effect → activation of stretch receptors → stimulation of peristalsis.

Adverse effects

– Mg & Na salts (saline laxatives) may be absorbed systemically and produce *hypermagnesemia* and *hypernatremia* especially in patients with renal failure.

– Lactulose may produce abdominal discomfort.

– Polyethylene glycol may produce electrolyte disturbance (hypokalemia).

3. **Irritant (or stimulant) laxatives**:

[Castor oil – Senna – Bisacodyl]

Mechanism of action

They produce inflammation (irritation) of the intestinal mucosa and inhibit *Na+/K+*

ATPase enzyme leading to:

– Accumulation of water and electrolytes in the gut lumen.

– Direct stimulation of peristalsis by their irritant effect.

Adverse effects

Castor oil

- Bad taste.
- Stimulation of uterine contraction and **abortion**

Senna

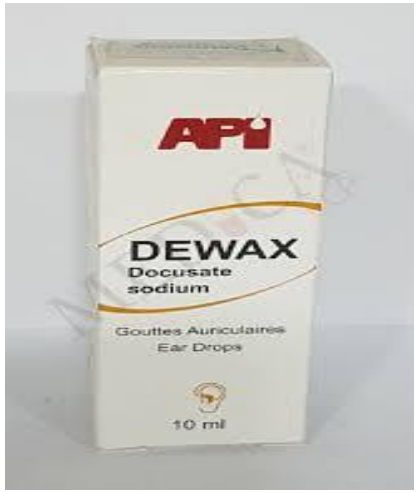
- It passes in urine and cause **urine discoloration**
- It passes in breast milk and cause **cathartic** effect in the baby.
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon.
- Increase menstrual blood flow and **abortion** in pregnancy.
- **Laxative dependence:** Irritant laxatives cause complete evacuation of the colon. The colon requires 2-5 days before the normal fecal mass can be reestablished. The patient becomes worry regarding the lack of bowel movement during this period and may use the laxative again and a vicious cycle is established leading to partial or complete loss of normal bowel function.

Bisacodyl

- It is prepared as enteric coated tablets to avoid gastric irritation. If it is given with milk or with other drugs that change gastric pH, the enteric coating may dissolve in the stomach and cause gastric irritation and pain
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon *(should not be used more than 10 days).*

4. Stool softeners: Docusate sodium

Mechanism: they are anionic surfactants that enable additional water and fats to be incorporated in the stool, making it easier to move through the GIT.



5. Lubricant laxatives:

[Liquid paraffin – Glycerin suppositories – Evacuant enema]

Mechanism of action

- **Paraffin oil** it coats the fecal matter and retards water absorption by the colon.
- **Glycerin** has hygroscopic effect. It draws water from rectal mucosa and lubricates the anal canal. It also stimulates reflex rectal contractions and promotes stool evacuation in 15-20 min.

6. **Chloride channel activators**: **Lubiprostone**

Mechanism of action

It acts by activating chloride channels to increase fluid secretion in the intestinal lumen.

This eases the passage of stool and causes little change in electrolyte balance.

General indications of laxatives

 Constipation: laxatives should not be used for prolonged duration to avoid

laxative dependence.

 To fasten excretion of **toxic** substances from the GIT.

 To prepare the bowel before **X-ray** or colonoscopy.

 Hepatic encephalopathy (lactulose): to kill ammonia producing bacteria.

 Painful anal conditions e.g. anal fissure or piles.

 Postoperative: e.g. after hemorrhoids (piles) to avoid strain.

Antidiarrheals

Increased motility of the GI tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport

ANTIMOTILITY AGENTS

Diphenoxylate + atropine LOMOTIL

Loperamide IMODIUM A-D

ADSORBENTS

Aluminum hydroxide GENERIC ONLY

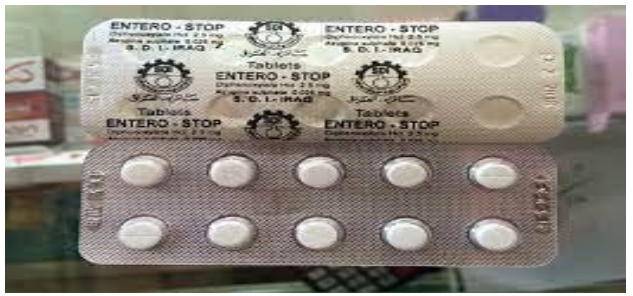
Methylcellulose CITRUCEL

AGENTS THAT MODIFY FLUID AND ELECTROLYTE TRANSPORT

Bismuth subsalicylate PEPTO-BISMOL

A. Antimotility agents

Two drugs that are widely used to control diarrhea are ***diphenoxylate* and *loperamide***. Both are analogs of *meperidine* and have opioid-like actions on the gut. They activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. At the usual doses, they lack analgesic effects. *Loperamide* is used for the general treatment of acute diarrhea, including traveler's diarrhea. Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.



- Loperamide **cannot cross BBB** while diphenoxylate can **cross BBB in very small amount** (no CNS effects in **usual** therapeutic doses) but it can cause addiction if used in large doses and for prolonged duration.

- They are commonly **combined with atropine** (e.g. **Lomotil®** is a combination of diphenoxylate 2.5 mg + atropine 0.25 mg) to produce more ↓↓ in intestinal motility and decrease liability for abuse.

B. Adsorbents

Adsorbent agents, such as aluminum hydroxide and methylcellulose , are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. They are much less effective than antimotility agents, and they can interfere with the absorption of other drugs.

C. Agents that modify fluid and electrolyte transport

Bismuth subsalicylate, used for prevention and treatment of traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. Adverse effects may include **black tongue and black stools**.

Racecadotril: Enkephalins are opioids produced in the body and degraded by enkephalinase. Racecadotril, a prodrug is converted in the body to the active compound thiorphan which is a selective inhibitor of enkephalinase. Thiorphan inhibits enkephalinase in the gut and peripheral tissues and thereby increase enkephaelin levels. Enkephalins are neurotransmitters in the gut—they have antisecretory activity on the intestines (act on opioid receptors)—thus correct the hypersecretion of water and electrolytes seen in diarrhoea without reducing intestinal motility

It has the advantage over loperamide that it is not contraindicated in children.

THANKS