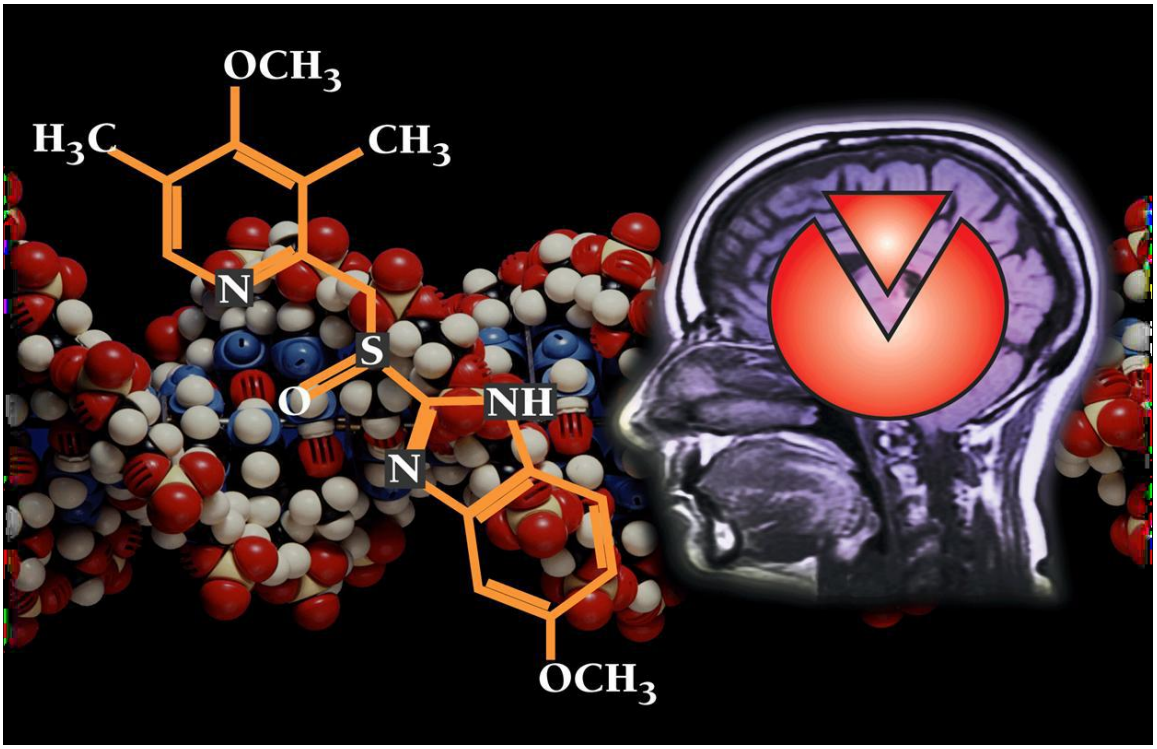
King Saud University
College Of Medicine
Pharmacology Team 430
GIT Block

Antiemetic drugs



Note: First four pages are for explanation, and notes in light green margins are additional information.

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Introduction:

Vomiting

- Is a complex series of integrated events culminating in the forceful expulsion of gastric contents through the mouth.
- Such events are coordinated by the **emetic (vomiting) center (VC)**, lying in reticular formation in medulla.
- Stimulation of this center occurs from peripheral sites, cortex, or **chemoreceptor trigger zone (CTZ)**
- Vomiting can be a valuable, life-saving physiological response to rid stomach & intestine **of toxins** & prevent their further ingestion
- If severe cause **dehydration, acid-base imbalance, electrolyte depletion & aspiration pneumonia**

Note: Aspiration pneumonia is inflammation of the lungs and airways to the lungs (bronchial tubes) from breathing in foreign material. It occurs when foreign materials (**usually food, liquids, vomit, or fluids from the mouth**) are breathed into the lungs or airways leading to the lungs. This may lead to: collection of pus in the lungs (**lung abscess**), Swelling and inflammation in the lung, or lung infection **(pneumonia)**

Causes of Nausea and Vomiting:

Nausea and vomiting may be manifestations of many conditions. However, a useful abbreviation for remembering causes of nausea and vomiting is VOMIT.

- ✓ **V**estibular
- ✓ **O**bstruction or drugs like **o**piates)
- ✓ **M**ind (dysmotility)
- ✓ **I**nfection (irritation of gut)
- ✓ **T**oxins (taste and other senses)

Nausea and vomiting may be manifestations of many conditions and may occur due to stimulation **of vomiting center that respond to inputs from:**

1-Chemoreceptor trigger zone (CTZ) stimulation:

- ✓ CTZ is an area of medulla that communicates with vomiting center to initiate vomiting.
- ✓ CTZ is **physiologically outside BBB**
- ✓ CTZ Contains **D2 & 5 HT_3 receptors ,** opioid receptors and NK1 (substance P) receptors

CTZ can be stimulated by

- Drugs such as **morphine**, apomorphine, L-dopa, bromocryptine, digitalis, estrogen, emetine.
- Chemicals.
- Radiation.
- Uremia.

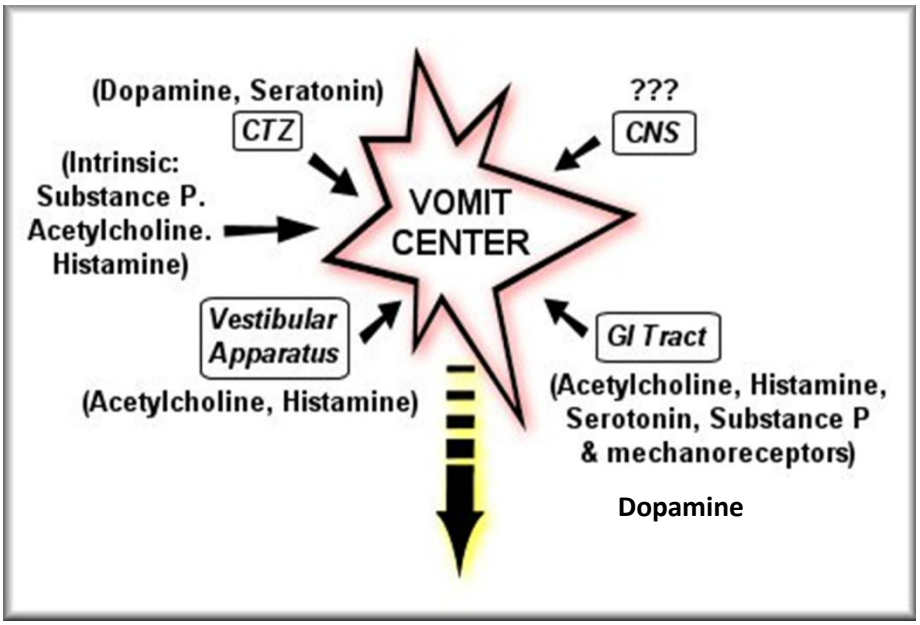
Note: Emetine is a drug used as both an anti-protozoal and to induce vomiting of toxic food, liquids, drugs, etc... **In patients in wakeful state.**

2. The periphery via sensory nerves: GIT irritation, myocardial infarction, renal or biliay stones.

3. Disturbance of vestibular system

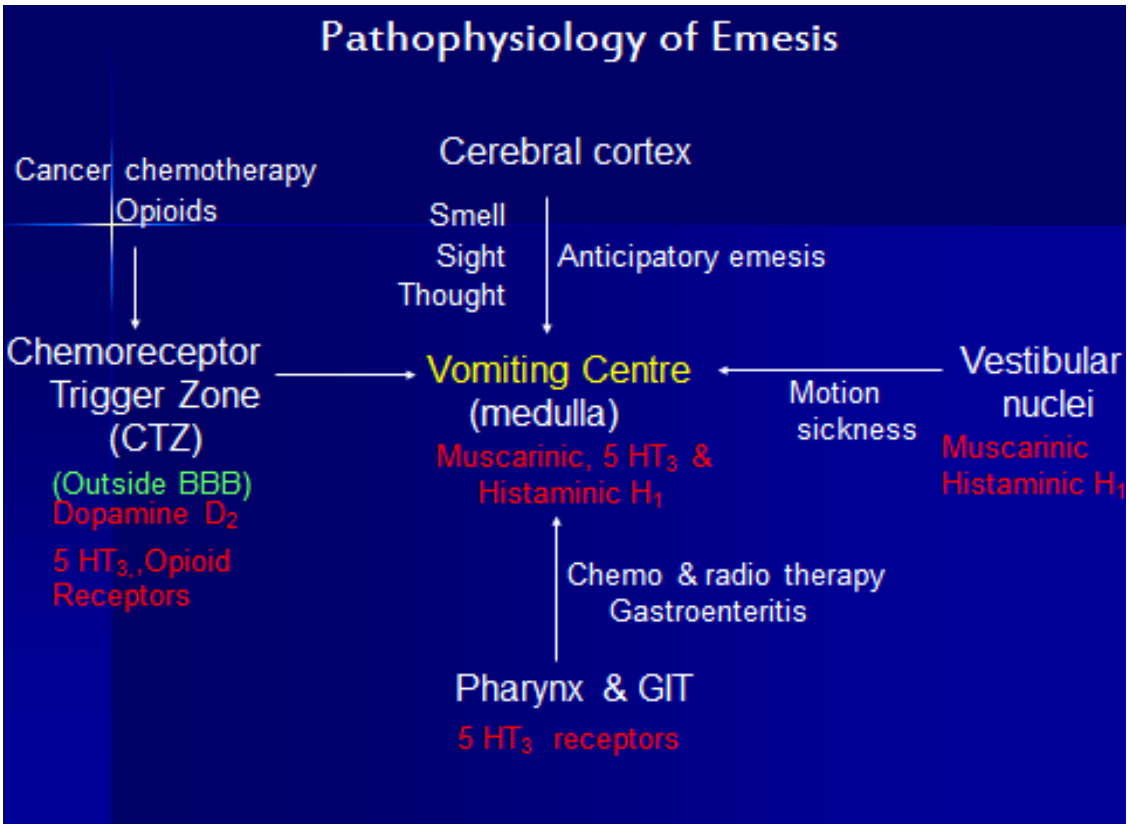
4. Higher cortical centers stimulation: emotional factors, nauseating smells or sights

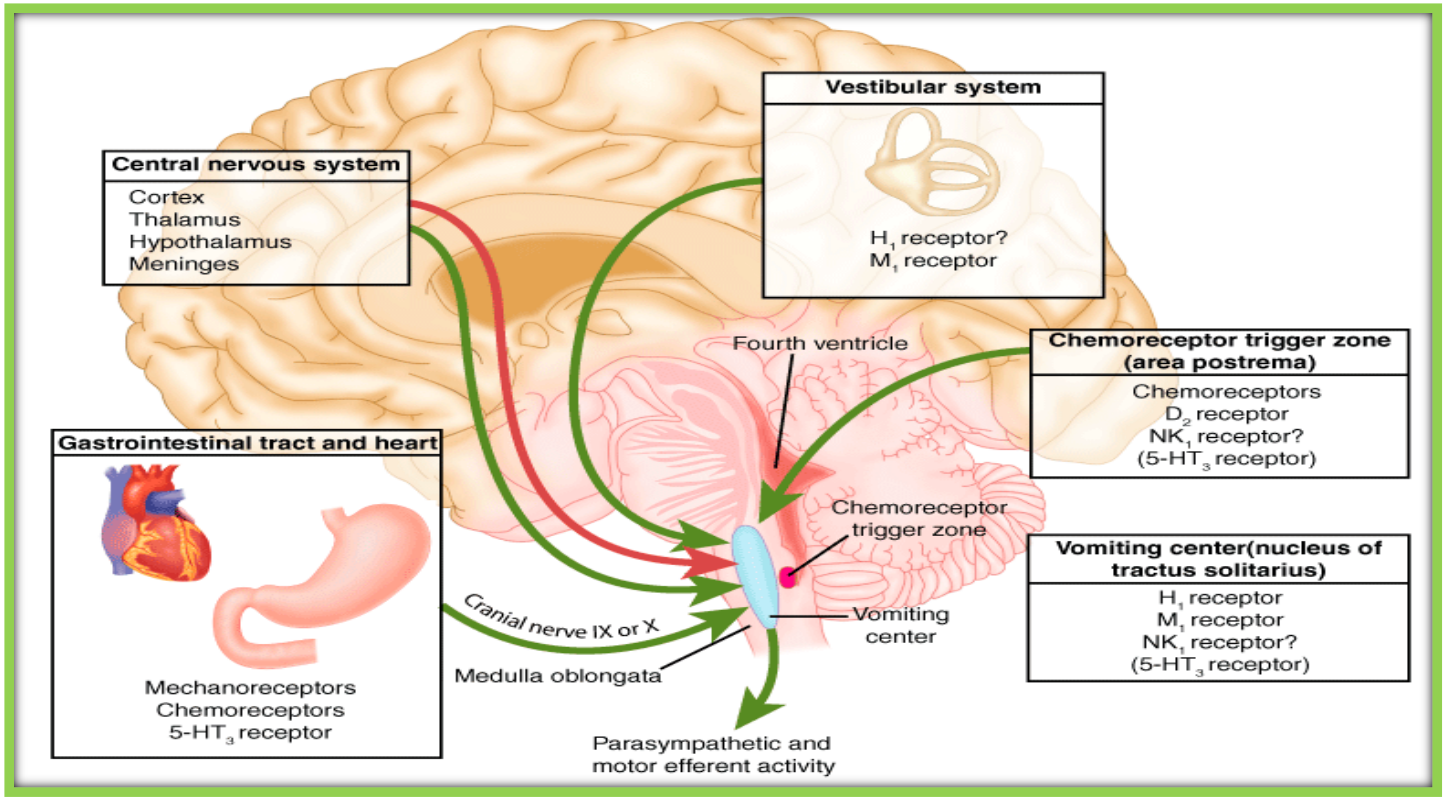
Receptors Associated with Nausea and Vomiting



Note:

- GIT tract is especially rich with **5HT-3** receptors. So the most effective antiemetic in this region is 5HT3 antagonists.
- Vestibular apparatus has **only Histamine and Muscarinic** receptors, thus the only effective Antiemetics in this region are **Anti-Muscarinic and Anti-Histamines.**





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

1-The chemoreceptor trigger zone 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 **D2 receptors and opioid receptors** (Mu, Kappa, etc...) and possibly **5-HT3** receptors and **NK1** receptors.

2-The vestibular system is important in motion sickness via cranial nerve VIII. It is rich **in muscarinic M1 and histamine H1** receptors.

3-Vagal and spinal afferent nerves from the gastrointestinal tract are rich **in 5-HT3 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.

What are the neurotransmitters & receptors involved in vomiting?

- ✓ Histamine (Histaminergic receptors H 1)
- ✓ Serotonin (5 -HT3)
- ✓ Ach (Muscarinic)
- ✓ Dopamine (D2)
- ✓ Substance P (Neurokinin receptors)
- ✓ Opioid Receptors

Classification of Antiemetic Drugs:

1. **5-HT3** antagonists
2. **D2** receptor antagonists
3. **NK1** antagonists
4. **H1**-receptor antagonists
5. **Muscarinic** receptor antagonists
6. **Cannabinoids**
7. **Glucocorticoids**

Indications of antiemetics

1- Chemotherapy-induced vomiting
2- Post-irradiation vomiting
3- Postoperative vomiting
4- Vomiting of pregnancy
5- Motion (travel) sickness

General rules on use of antiemetics

- Should only be used when the cause of nausea or vomiting is **known** i**.e cause of vomiting should be diagnosed.**
- Otherwise, the symptomatic relief produced could delay diagnosis of a remediable and serious cause.
- **Treat the cause** (e.g. diabetic ketoacidosis, intestinal obstruction, intracerebral space-occupying lesion) usually cures the vomiting.
- **The choice of drug depends on the etiology**

1-5-HT3 antagonists

e.g. Ondansetron, Granisetron

- The **most Potent antiemetic**, mediated through central (vomiting center, chemoreceptor trigger zone) and peripheral (intestinal and spinal)act by **5-HT3** receptor blockade
- Taken **Orally or i.v.,** long duration of action.
- Has high first pass metabolism **(undergo extensive hepatic metabolism)**
- Very effective in nausea & vomiting due to :
  Cytotoxic drugs (cisplatin)
  Post-radiation and Post-operative

Note: **Cisplatin** is a chemotherapy drug. It is used to treat various types of cancers.

2- Dopamine (D2) receptor antagonists

Note: metoclopramide has also a **5HT-3** blocking effect (not as potent as **Ondansetron**), and it was the first drug discovered to have this action

- Antagonize **D2** receptors in **CTZ**
- Drugs such as **metoclopramide**(PlasilR), **domperidone**
- Both drugs are also **prokinetic** agents due to their **5 HT4** agonist activity
- **Domperidone**- oral; **Metoclopramide**-oral, i.v .
- **Metoclopramide crosses BBB** but **domperidone** cannot .

Note: **5HT-4 agonistic** action indirectly facilitate muscarinic **Acetylcholine activity** which would then increase the gastric motility.(Gastroprokinetic)

- Effective against vomiting due to **drugs, gastroenteritis, surgery, toxins, uremia, radiation**
- Can be used in **reflux esophagitis** and **gastroparesis(**delayed gastric emptying). **(**Due to their prokinetic effect)

Which is a better antiemetic, metoclopramide or domperidone?

- As **CTZ** is outside **BBB** both have **antiemetic effects**.
- But as **metoclopramide crosses BBB** it has adverse effects **like extrapyramidal side effects**.
- **Side effects**: dyskinesia, galactorrhea, menstruation disorders, sedation and postural hypotension **(only for metoclopramide).**

Other uses of Metoclopramide

- **Facilitate duodenal intubation & endoscopy**
- **↓ Regurgitation & reflux esophagitis**
- **Diagnostic radiology of gut → ↓ time required for barium to reach caecum → ↓ No. of films required**
- **Clears gastric contents in emergency anesthesia**

Other D2 receptor antagonists:

Neuroleptics :

- Antipsychotics with potent antiemetic property due to **D2 antagonism**
- **Chlorpromazine, droperidol**
- Taken orally, parentrally, suppository
- **Used** for vomiting due to **chemotherapy- induced emesis** and and post-operative nausea and vomiting (**Not commonly used nowadays**)
- **Side effects**: **extrapyramidal symptoms**, **hypotension**(due to alpha blocking effect), **sedation(** due to Antihistaminic effect), **restlessness**

3-Neurokinin1 (NK1) receptor antagonists e.g.: Aprepitant

- ✓ Is a **substance P** antagonist that acts by blocking **neurokinin 1 receptors** .
- ✓ Used in **prevention of acute and delayed *chemotherapy-induced nausea and vomiting (CINV)*** and for **prevention of postoperative nausea and vomiting.**

4-H1-receptor antagonists (Antihistamines):

- ✓ Effective for motion sickness, morning sickness in pregnancy, and to **combat opioid nausea**.
- ✓ Drugs as:
  - **Diphenhydramine**
  - **Cyclizine**
  - **Meclizine**
  - **Promethazine:** severe morning sickness of pregnancy **(if only essential)** because there is no risk of teratogenic effect.

Note: Other uses of diphenhydramine: Cough, Urticaria,Sleeping Aid, and in Motion Sickness

- ✓ **Not in chemotherapy-induced vomiting.**

5-Muscarinic receptor antagonists:

- ✓ **Hyoscine (scopolamine)**
- ✓ Used as **trans-dermal patches** in motion sickness (applied behind the external ear)
- ✓ **Not in chemotherapy-induced vomiting.**
- ✓ Side effects: tachycardia, blurred vision, constipation, urinary retention. So, it's contraindicated in glaucoma, and prostatic hypertrophy.

6-Cannabinoids

- ✓ **Nabilone, dronabinol (psychoactive drugs)**
- ✓ **Used as adjuvant in chemotherapy induced vomiting .**
- ✓ **Side effects:** Sedation, hallucination and dysphoria.

Note: dronabinol is the major psychoactive chemical in marijuana. **Nabilone** closely related to it. They are both used medically as an appetite stimulant and as an antiemetic, but the mechanisms for these effects are not understood.

7-Glucocorticoids

- ✓ **Dexamethasone** and **methylprednisolone**
- ✓ Highly effective **in acute emesis alone** or combined with **ondansetron.**
- ✓ **Used for vomiting by cytotoxic drugs .**
- ✓ **Side effects:**
  - × Hyperglycemia
  - × Hypertension (Due to increased Aldosterone)
  - × Cataract
  - × Osteoporosis
  - × Increased intraocular pressure
  - × Increased susceptibility to infection
  - × Increased appetite & obesity

Note: these side effects usually occur in chronic use.

Summary for Therapeutic Choice of Antiemetics

Motion sickness:

- **Hyoscine:** For short Journey.
- **Diphenhydramine:** For Long Journey.

Vomiting with pregnancy (morning sickness):

- **avoid all drugs in the first trimester**
- **Pyridoxine (B6)**
- **Promethazine (late pregnancy)**

Note: Pyridoxine (B6) and Promethazine are mixed together

Drug- induced vomiting (CTZ) uremia –Gastroenteritis:

- **domperidone & metoclopramide**

Vomiting due to cytotoxic drugs:

- **Ondansetron** (1st choice)
- **D2- antagonists.**
- **Dexamethazone**
- **Nabilone.**

Post-operative vomiting:

- **Dopamine antagonists (Metoclopromide or Domperidone)**

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- ✓ **Ondansetron, Granisetron are** the **most Potent antiemetics**, mediated through central (vomiting center, chemoreceptor trigger zone) and peripheral (intestinal and spinal)act by **5-HT3** receptor blockade
- ✓ They have long duration of action.
- ✓ They are Very effective in nausea & vomiting due to **Cytotoxic drugs** (**cisplatin**)+ Post-radiation and Post-operative.
- ✓ Drugs such as **metoclopramide**, and **domperidone** Antagonize **D2** receptors in **CTZ**
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- ✓ Aprepitant Is a **substance P** antagonist that acts by blocking **neurokinin 1 receptors**
- ✓ Used in **prevention of acute and delayed *chemotherapy-induced nausea and vomiting (CINV)*** and for **prevention of postoperative nausea and vomiting.**
- ✓ **Diphenhydramine,Cyclizine,Meclizine,Promethazine are** Effective for motion sickness, morning sickness in pregnancy, and to **combat opioid nausea**
- ✓ **Promethazine:** severe morning sickness of pregnancy **(if only essential)** because there is no risk of teratogenic effect; however, in the first trimester it's not used
- ✓ **Both antihistamines and Hyoscine are not used in chemotherapy-induced vomiting.**
- ✓ **Nabilone, dronabinol are psychoactive drugs Used as adjuvant in chemotherapy induced vomiting .**
- ✓ **Dexamethasone** and **methylprednisolone are**Highly effective **in acute emesis alone** or combined with **ondansetron.**
- ✓ **Used for vomiting by cytotoxic drugs and their side effects** usually occur in chronic use.