Vomiting

- **Vomiting** (synonyms: **emesis)** is the involuntary, forceful expulsion of the contents of stomach through the mouth and sometimes the nose.
- Vomiting can be caused by a wide variety of conditions

✓ gastritis or poisoing.

✓ clinically useful drugs: – cancer chemotherapy & radiation ; opioids; general anesthetics

✓ Migraines

✓ pregnancy

- The feeling that one is about to vomit is called nausea, which often precedes, but does not always lead to, vomiting.
- Antiemetics are sometimes necessary to suppress nausea and vomiting.

Physiology of Nausea & Vomiting

Initiation of nausea and vomiting revolves around two emetic centers located within the medulla oblongata; the vomiting center and chemoreceptor trigger zone (CTZ). Both of these centers are located outside of the normal blood-brain barrier and are comprised of a nucleus of neurons that receive direct and indirect input to stimulate the nausea and vomiting reflex. Signal input is facilitated by four main neurotransmitters; histamine, acetylcholine, serotonin and dopamine. Substance-P and opioid receptors also play a role.

The vomiting center carries the primary function of inducing the mechanical act of vomiting. This occurs when it is directly stimulated by afferent pathways from the cerebral cortex, sensory organs and the vestibular apparatus. The vomiting center may also be stimulated directly as a result of irritation or injury (ie head injury, increased ICP) which results in projectile vomiting. Indirect stimulation of the vomiting center occurs from signals sent from the neighboring CTZ.

Physiology of Nausea & Vomiting

The CTZ is activated directly as a result of emetogenic substances which includes endogenous hormones in the blood and CSF. Substances that stimulate the CTZ include drugs, toxins, viruses, bacteria, and hormones of pregnancy. Indirect CTZ stimulation occurs by afferent pathways from the GI tract. It is through CTZ detection that opioid induced nausea and vomiting occurs.

Primary Locations for Stimulation

GI Tract:

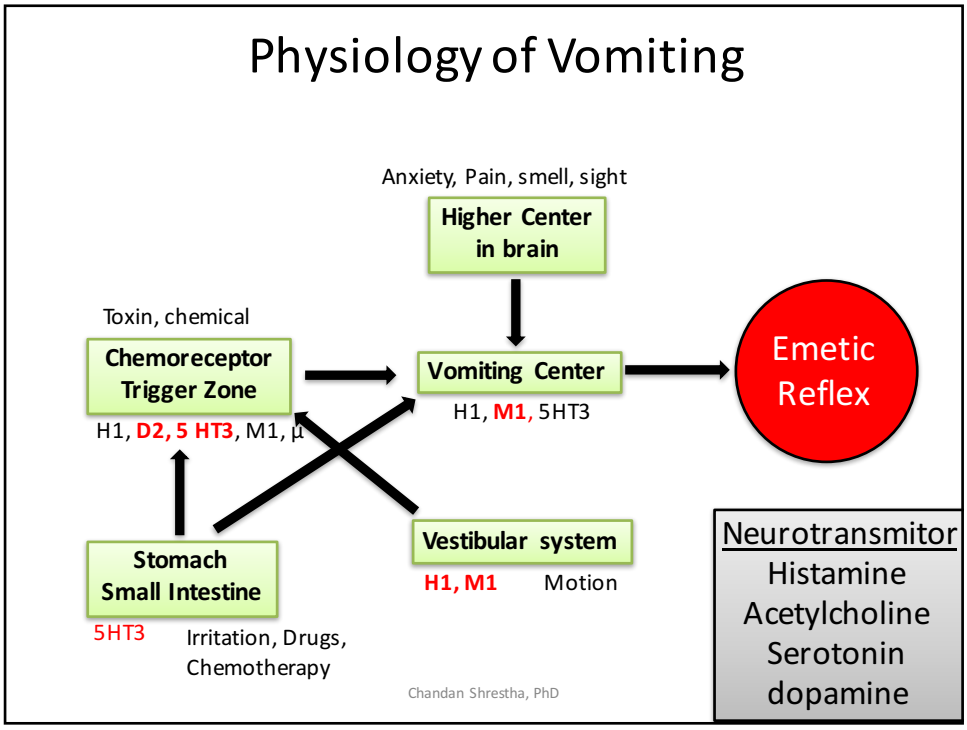
Chemoreceptors and mechanoreceptors in the gut sense changes that result from many pathologies including visceral distention and inflammation, decreased gastric emptying from opioids and other causes, cytotoxins from chemotherapy, and gastroenteritis. Changes in the GI system cause a release of serotonin which is the main neurotransmitter responsible for communicating nausea to the CTZ.

Vestibular Apparatus:

The vestibular system plays a major role in motion induced nausea and vomiting. Opioids can also naturally stimulate this system. Histamine and acetylcholine are the primary neurotransmitters responsible for communicating nausea from the vestibular system.

Cerebral Cortex:

Nausea originating from this region is often from unpleasant tastes, smells, sights, memories and emotion. This is also known as anticipatory nausea. The mechanism for nausea in this system is less understood. Benzodiazepines are sometimes effective in treating anticipatory nausea.


Physiology of Vomiting
Anxiety, Pain, smell, sight
Higher Center in brain
Toxin, chemical
Chemoreceptor Trigger Zone
H1, D2, 5 HT3, M1, μ
Vomiting Center
H1, M1, 5HT3
Emetic Reflex
Vestibular system
H1, M1
Motion
Stomach Small Intestine
5HT3
Irritation, Drugs, Chemotherapy
Neurotransmitor
Histamine
Acetylcholine
Serotonin
dopamine
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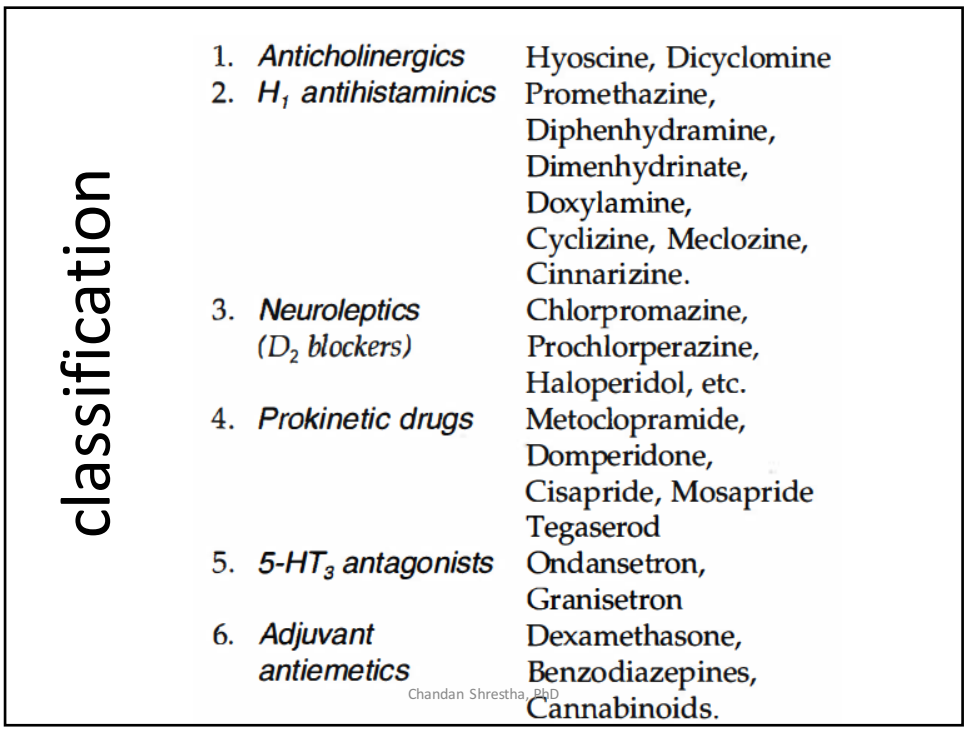
classification
1. Anticholinergics Hyoscine, Dicyclomine
2. H1 antihistaminics Promethazine, Diphenhydramine, Dimenhydrinate, Doxylamine, Cyclizine, Meclozine, Cinnarizine.
3. Neuroleptics (D2 blockers) Chlorpromazine, Prochlorperazine, Haloperidol, etc.
4. Prokinetic drugs Metoclopramide, Domperidone, Cisapride, Mosapride Tegaserod
5. 5-HT3 antagonists Ondansetron, Granisetron
6. Adjuvant antiemetics Dexamethasone, Benzodiazepines, Cannabinoids.
Chandan Shrestha, PhD

Anticholinergic

Hyoscine

- 0.2 – 0.4 mg oral, i.m
- Effective drug for motion sickness
- Blocks conductive impulses across a cholinergic link in the pathway leading from the vestibular apparatus to vomiting center
- Not effective in vomiting due to other causes
- Transdermal patch containing 1.5 mg of hyoscine to be delivered over 3 days have been developed.
- Adverse effect: sedation and other anticholinergic side effects

Dicyclomine

- 10 – 20 mg oral
- Used for prophylaxis of motion and morning sickness

H1 Antihistaminics

- Some antihistaminics are antiemetic.
- Mainly useful in motion sickness and to a lesser extent in morning sickness, postoperative.

Cinnarizine

- Used for nausea and vomiting associated with vestibular disorders, such as vertigo, tinnitus, motion sickness
- side effects: Allergic skin reactions, fatigue, extrapyramidal side effects.

H1 Antihistaminics

Cyclizine

- Used for nausea, vomiting, vertigo, motion sickness
- Side effects: drowsiness, occasional dry mouth and blurred vision,

Promethazine

- Used for nausea, vertigo, motion sickness
- Side effects: drowsiness, dry mouth, blurred vision, sedation.

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Dopamine antagonists (Prochlorperazine)

- Antiemetic action of these compounds is due to inhibition of dopamine receptors in the CTZ.
- has selective antivertigo and antiemetic actions.
- It is highly effective when given by injection in vertigo associated with vomiting and to some extent in cancer chemotherapy associated vomiting.
- Prochlorperazine is used as an antiemetic rather than as antipsychotic.
- Adverse effect: Muscle dystonia and other extrapyramidal side effects

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Prokinetic Drugs

- These are drugs which promote gastrointestinal transit and speed gastric emptying by enhancing coordinated propulsive motility.

Metoclopramide

- Act through both *dopanergic (D2 antagonist) and serotonergic receptors* (5-HT_3 antagonist)
- **D2 antagonism**: Increase gastric peristalsis→ speeds gastric emptying. Gastrokinetic action may contribute to the antiemetic effect.
- **Uses**: Antiemetic, gastrokinetic, GERD, dyspepsis and other GI disorders. Hiccups.
- **Side effects:** Extra-pyramidal effects (dystonia, akathisia, parkinsonism and tardive dyskinesia)
- Hypoprolactinaemia (galactorrhoea, gynaecomastia)
- Drowsiness, dizziness, restlessness, diarrhea, headache

Prokinetic Drugs

Domperidone

- Prokinetic, D2 antagonist
- Poorly enters to BBB (less extra-pyramidal side effects)
- Efficacy lower than metoclopramide.
- Advantages over metochlopramide : less likely to cause central effects such as sedation because it does not readily cross BBB.
- Side effect: dry mouth, loose stools headache, rashes, galactorrhoea

Cisapride

- Prokinetic drug with little antiemetic property because it lacks D2 receptor antagonism,
- Increase gastric emptying
- Side effect: abdominal cramps, diarrhoea, dizziness.

Serotonin 5-HT3 receptor antagonists (Ondansetron, Granisetron)

- New class of antiemetic drugs developed to control cancer chemotherapy induced vomiting and also found to be highly effective in **postoperative** nausea and vomiting as well.
- **Cytotoxic drugs/radiations** produces nausea and vomiting by causing cellular damage --> release of mediators including 5-HT from intestinal mucosa --> activation of vagal afferents in the gut and CNS --> Emetogenic impulses to CTZ
- Ondansetron blocks emetogenic impulse both at their peripheral origin and their relay centre.
- Side effects: Generally well tolerated. Headache (common);
  mild constipation or diarrhoea and abdominal discomfort (few)
  Rashes and allergic reactions following i.v. administration.

Table 1: Antiemetics suitable for use in pregnancy (in order of preference)[3,4,10]

Medication	Dose	Adverse effects
Metoclopramide	10 mg three times daily	Extrapyramidal symptoms Tardive dyskinesia especially if used for more than 12 weeks
Prochlorperazine	5 mg three times daily	Extrapyramidal symptoms Sedation
Cyclizine	50 mg three times daily	Sedation
Promethazine	25 mg at bedtime, increased to maximum 100 mg daily in divided doses	Extrapyramidal symptoms Sedation
Ondansetron (hyperemesis gravidarum)	4 – 8 mg two to three times daily	Constipation