Antiemetics

Dr.Alaa Alanteet
Dr. Mohammed Almutairi

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Classify the main different classes of antiemetic drugs according to their mechanism of action.
- Know the characteristic pharmacokinetics & dynamics of different classes of antiemetic drugs.
- Identify the selective drugs that can be used according to the cause of vomiting.
- Learn the adjuvant antiemetics.
- Describe the major side effects for the different classes of antiemetics.

Dr. Fouda Videos

13:24- 17:00 min

27:37 min

43:24 min

Vomiting

It is the forceful expulsion of gastric movements through the mouth.

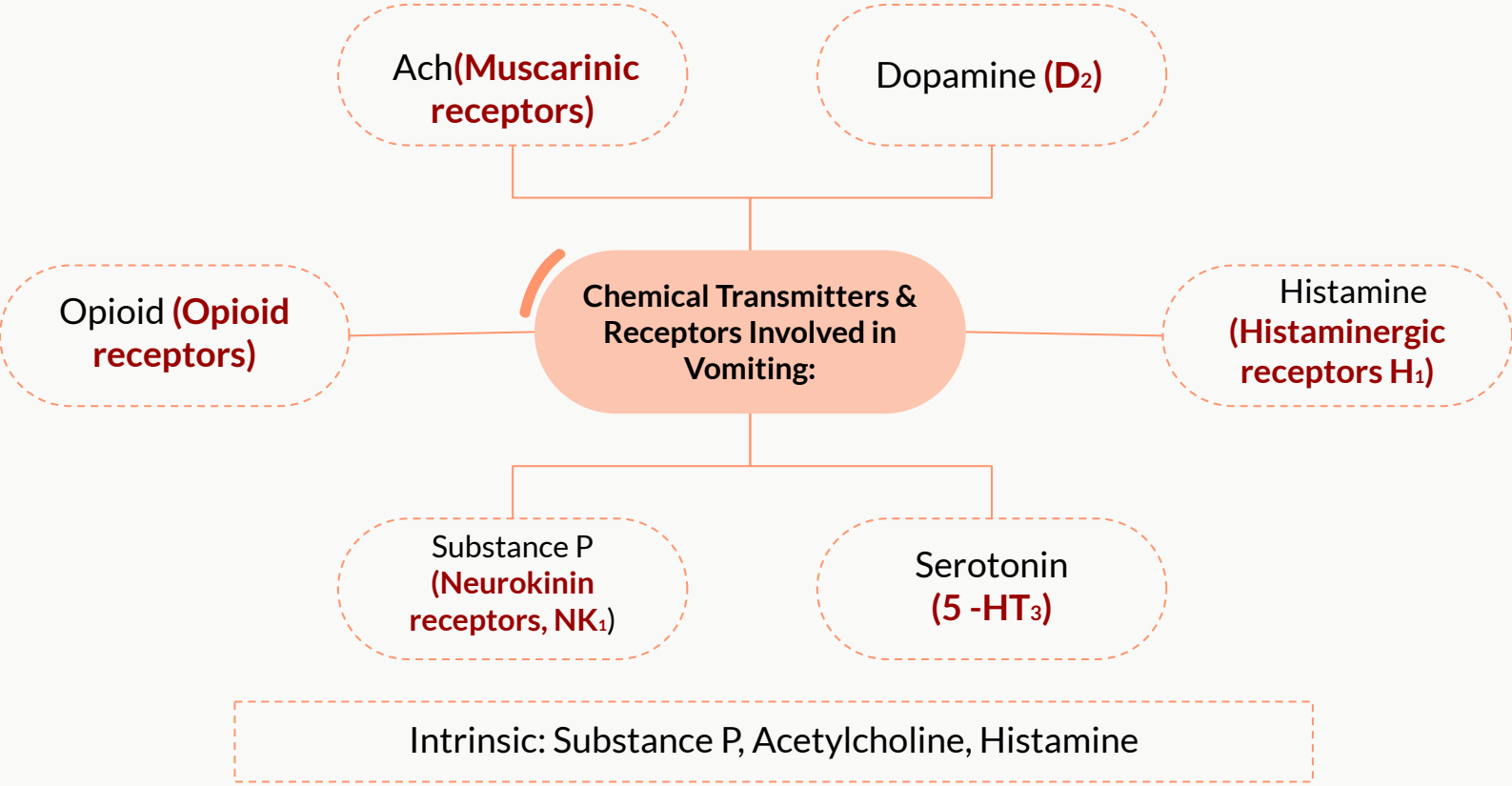
Can vomiting be considered a disease?
It is a **manifestation** of many conditions and diseases.

Severe Vomiting may result in (Consequences of vomiting):

- Dehydration
- Acid-base imbalance (Loss of H+ → Metabolic Alkalosis)
- Electrolyte depletion
- Aspiration, pneumonia

Classification of Antiemetic Drugs:

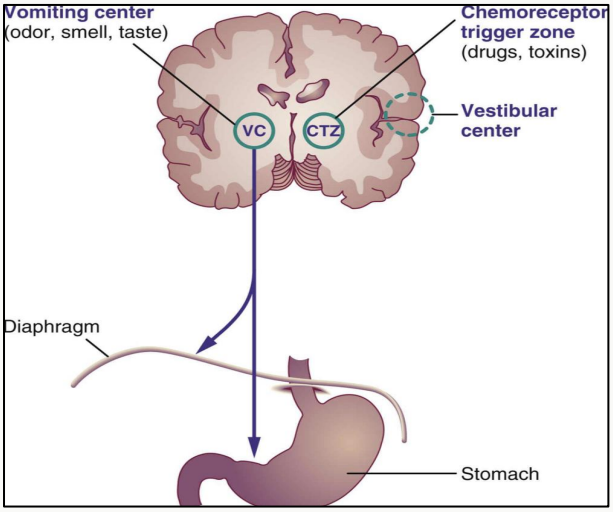
1. 5-HT3 **antagonists**
2. D2 receptor **antagonists**
3. NK1 **antagonists**
4. H1-receptor **antagonists**
5. Muscarinic receptor **antagonists**
6. Cannabinoids (the only agonist drug, not commonly use because of its side effects)
7. Glucocorticoids (treat the inflammation which would suppress substances that causes vomiting and potentiate the effect of antiemetic drugs)

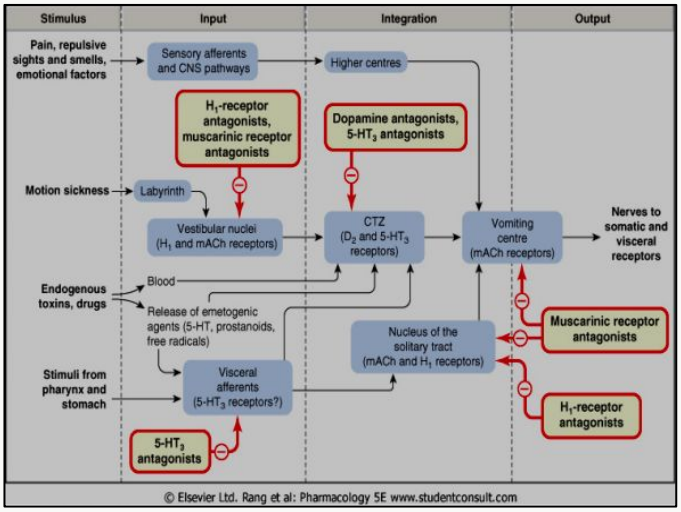


How is Vomiting Induced?

vomiting center (medulla) responds to inputs from:

Area	Information	Receptors	Triggered by
Chemoreceptor trigger zone (CTZ) stimulation	• CTZ is an area of the medulla that communicates with the vomiting center to initiate vomiting. • It is **physiologically outside BBB** (responds to signals from blood)	• **D2** receptors, • **5-HT3** receptors • **Opioid** receptors • **Substance P** receptors	• Emetogenic (causing emesis) drugs: opioids, general anesthetics, digitalis, L-dopa). • Chemicals & toxins (blood, CSF). • Radiation • Chemotherapy • Uremia
Disturbance of the vestibular system	-	• **H1** (Histamine) • **M1** (acetyl-choline)	• Motion Sickness
Higher cortical centers stimulation (CNS)	Anticipatory emesis	-	• Emotional factors • Nauseating smells or sights • thoughts
The periphery stimulation (pharynx, GIT) via sensory nerves	-	• Acetylcholine • Histamine. • **5-HT3**, • Substance P • Mechano receptors	• GIT irritation • Myocardial infarction • Renal or biliary stones • Gastroenteritis • Chemo and radiotherapy Chemotherapy cause irritation of Enterochromaffin cellls of GIT —> Cells injury —> release histamine and 5HT3 —> activate vagal nerve —> activate vomiting center





5-HT3 Antagonists

Drugs	Granisetron	Ondansetron
M.O.A	• Act by **blocking 5-HT3** receptor: 1. **centrally** (in vomiting center, **CTZ**) 2. **peripherally** (5-HT3 receptors on **GI** vagal afferents). • It is the most **potent** antiemetic drug blocks 5-HT3 in 3 areas: 1. vomiting center 2. peripheral (GI) 3. central (CTZ)	
P.K	• Orally or parenterally. • Have a long duration of action,first pass effect.	
Uses	• **First choice** for prevention of **moderate to severe** emesis(except motion sickness vomiting: Ondansetron → Oncology • **Chemotherapy**-induced nausea and vomiting **(CINV)** especially **cisplatin** • **Post-radiation** NV & **Post-operative** NV (nausea and vomiting) • Their effects are augmented by combination with corticosteroids and NK1 antagonists (Aprepitant). " if the patient is still not responding, we combine other medications"	
ADRs	Minimal as they are **well tolerated** in general • Headache, • Dizziness • Constipation. • **Minor** ECG abnormalities: **(QT prolongation)**	

Glucocorticoids

Potentiate the effect of antiemetic drugs

Drug	Dexamethasone	methylprednisolone
Uses	• Used in chemotherapy-induced vomiting. • combined with 5-HT_3 antagonists or NK_1 receptor antagonists.	
ADRs	• Hypertension • Hyperglycemia • Cataract • Osteoporosis • Increased intraocular pressure • Increased susceptibility to infection • Increased appetite & obesity	↑ 3 **B**s : 1- **B**lood pressure 2- **B**lood glucose 3- **B**ody weight

D2 Receptor Antagonists

1- Prokinetics

Drug	Domperidone	Metoclopramide
M.O.A	**Blocks D2** Dopamine receptors in the **CTZ**→ Both drugs have antiemetic effects as CTZ is outside the blood brain barrier They are prokinetic agents: Increases upper GI motility and gastric emptying —> ↓Stimulation of vomiting center Increase GI motility is achieved by stimulating: 1- parasympathetic system , 2- **5-HT4** receptor agonist	
P.K	• Given orally • **Does not cross BBB**	• Given orally or IV • **Crosses BBB**
Uses	• **Prokinetic action (5-HT4 agonist activity):** - Gastroesophageal reflux disease (GERD) - Gastroparesis (stomach paralysis) (impaired gastric emptying after surgery, or as a complication of diabetes) • **Antiemetic action (due to blocking D2 receptor in CTZ):** - Effective against vomiting due to cytotoxic drugs, gastroenteritis, surgery, toxins,uremia, radiation.	
ADRs	**Only for Metoclopramide**: "as it crosses the BBB (ADRs Similar to antipsychotics)" • Dyskinesia (extrapyramidal side effects). • Galactorrhea (↓ dopamine → ↑ prolactin), menstrual disorders, impotence. • Postural hypotension (α- blocking action). • Sedation, drowsiness. **Can <u>domperidone</u> produce these side effects?** - Metoclopramide crosses BBB but domperidone can not cross in a significant amount. - both have antiemetic effects as CTZ has incomplete blood brain barrier located outside BBB, we prefer to use drugs than don't cross BBB to avoid CNS side effects).	

2- Neuroleptics (Antipsychotics)

Drug	Chlorpromazine (CPZ)	Droperidol
Uses	• Postoperative vomiting • Chemotherapy-induced emesis	
ADRs	• Extrapyramidal symptoms • Sedation • Postural hypotension (alpha blocking effect)	

Neurokinin-1 Receptor Antagonist

Drug	Aprepitant
M.O.A	Acts centrally as **substance P**(Stimulate NK1) **antagonist** by blocking **neurokinin 1 receptors** in vagal afferent fibers in Solitary Tract Nucleus (STN) and area postrema. (The CTZ is located within the area postrema, which is on the floor of the fourth ventricle and is outside of the blood–brain barrier)(441)
P.K	• Given orally
Uses	usually combined with 5-HT_3 antagonists and corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post-operative NV. (add-on therapy if the patient is not responding to 5-HT3 antagonist)

H1 Receptor Antagonists

M1 , H1 receptors located in Vestibular system

Drug	Diphenhydramine	Promethazine	Meclizine	Cyclizine
Uses	• Motion sickness • Morning sickness in pregnancy • Promethazine: severe morning sickness of pregnancy **(if only essential).**			
ADRs	• Prominent sedation (1st generation antihistamines → cross BBB) • Hypotension "α-blocking effect" • Anticholinergic effects or atropine like actions: Dry mouth, dilated pupils, urinary retention, constipation			

Muscarinic Receptor Antagonists

Drug	Hyoscine (Scopolamine)
M.O.A	Reduces impulses from vestibular apparatus by blocking muscarinic receptors
P.K	Orally, injection, patches
Uses	• Used as transdermal patches in **motion sickness** (should be taken before motion exposure as a prophylactic therapy) (applied to the postauricular area "behind the external ear"). • **Not in chemotherapy-induced vomiting**
ADRs	• Sedation • **Atropine like actions** (Blurred vision, tachycardia, dry mouth, constipation, and urinary retention).

Summary From slide

Important

The choice of antiemetic depends on the etiology	
Motion sickness	• Muscarinic antagonists • Antihistamines
Vomiting with pregnancy (morning sickness)	• Avoid all drugs in the first trimester • **P**yridoxine (B6) (unknown mechanism) • **P**romethazine (late pregnancy).
Drug- induced vomiting (CTZ), uremia, gastritis	• Dopamine antagonists (Metoclopramide, Domperidone)
Post-operative nausea & vomiting	• Dopamine antagonists
Vomiting due to cytotoxic drugs.	• 5-HT3 antagonists (Ondansetron) • NK1 antagonists (Aprepitant) • D2- antagonists • Glucocorticoids

MCQ

1 .Galactorrhea is considered a side effect of which of the following drugs?			
A. Promethazine	B.Hyoscine	C.Meclizine	D.Metoclopramide
2.which of the following would be useful for promoting gastric emptying in a patient with a gastrostomy tube?			
A.Diphenhydramine	B.Metoclopramide	C.Ondansetron	D.Aprepitant
3.Applied to the skin in a transdermal patch (transdermal therapeutic delivery system), this drug is used to prevent or reduce the occurrence of nausea and vomiting that are associated with motion sickness.			
A.Scopolamine	B.Ondansetron	C.Diphenhydramine	D.Chlorpromazine
4.Which receptor is found in the vestibular system?			
A. 5-HT3	B . D2	C. H1	D. M3
5.A pregnant woman has early morning sickness what is the drug of choice for her condition?			
A-Dexamethasone	B-Aprepitant	C-Diphenhydramine	D-Metoclopramide
6.Glucocorticoids have proved useful in the treatment of which of the following medical conditions?			
A.Chemotherapy-induced vomiting	B.Essential hypertension	C.Hyperprolactinemia	D.Parkinson's disease

1:D ,2:B ,3:A ,4:C ,5:C ,6:A

SAQ

01

List the ADRs of the 5-HT3 antagonists?

Headache, dizziness, constipation,
Minor ECG abnormalities

02

A 58 years old patient on chemotherapy came to the hospital due to having nausea and vomiting. The doctor gave him ondansetron and Aprepitant . what is the MOA & ADRs for Ondansetron?

MOA: blocking 5-HT3 receptor: 1. centrally (in vomiting center, CTZ)
2. peripherally (5-HT3 receptors on GI vagal afferents).
ADRs: Headache,constipation,Minor ECG abnormalities

03

write two drugs from two different classes can be used in motion sickness?

H1- receptor antagonists: Meclizine
Muscarinic receptor antagonists: Hyoscine(scopolamine)

Team Leaders

Muhnnad Al-Otaibi

Reema Almotairi

Sarah Alajaji

Team members

Maryam Alghannam

Aroub Almahmoud

Layan Sulaiman

Aishah Boureggah

Areej Alquarini

Lama Alotaibi

Jana alshiban

Layan Alruwaili

Sara Alharbi

Fatimah Alghamdi

Alanoud Abdullah

Nourah alarifi

Renad Alotaibi

Wafa Alakeel

Wasan Alanazi

Ayedh Alqantash

Nazmi A Alqutub

Yousef badgesh

Mohammed Alqutub

Fahad Aldhafian

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