

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



جراح

GIS Pharmacology | FINAL 4

IBS Pt.2, Antiemetic, Antiprotozal Drugs



Written by : Mousa Al-Neimat

Reviewed by : Mousa Al-Neimat

Drugs used in Irritable Bowel Syndrome

☐ Serotonin 5-HT₃- Receptor Antagonists:

- **Alosterone:**

- Selective **antagonist of 5-HT₃ receptors.**
- Has **long duration** of action.
- Approved for **women** with severe IBS in whom diarrhea is the prominent symptom.
- Efficacy in men is **not** established.
- Can **cause ischemic colitis**, severe constipation requiring hospitalization and surgery.
- Ischemic colitis occurs **when blood flow to part of the large intestine is temporarily reduced, which will result in severe constipation, and the need of surgical intervention.**

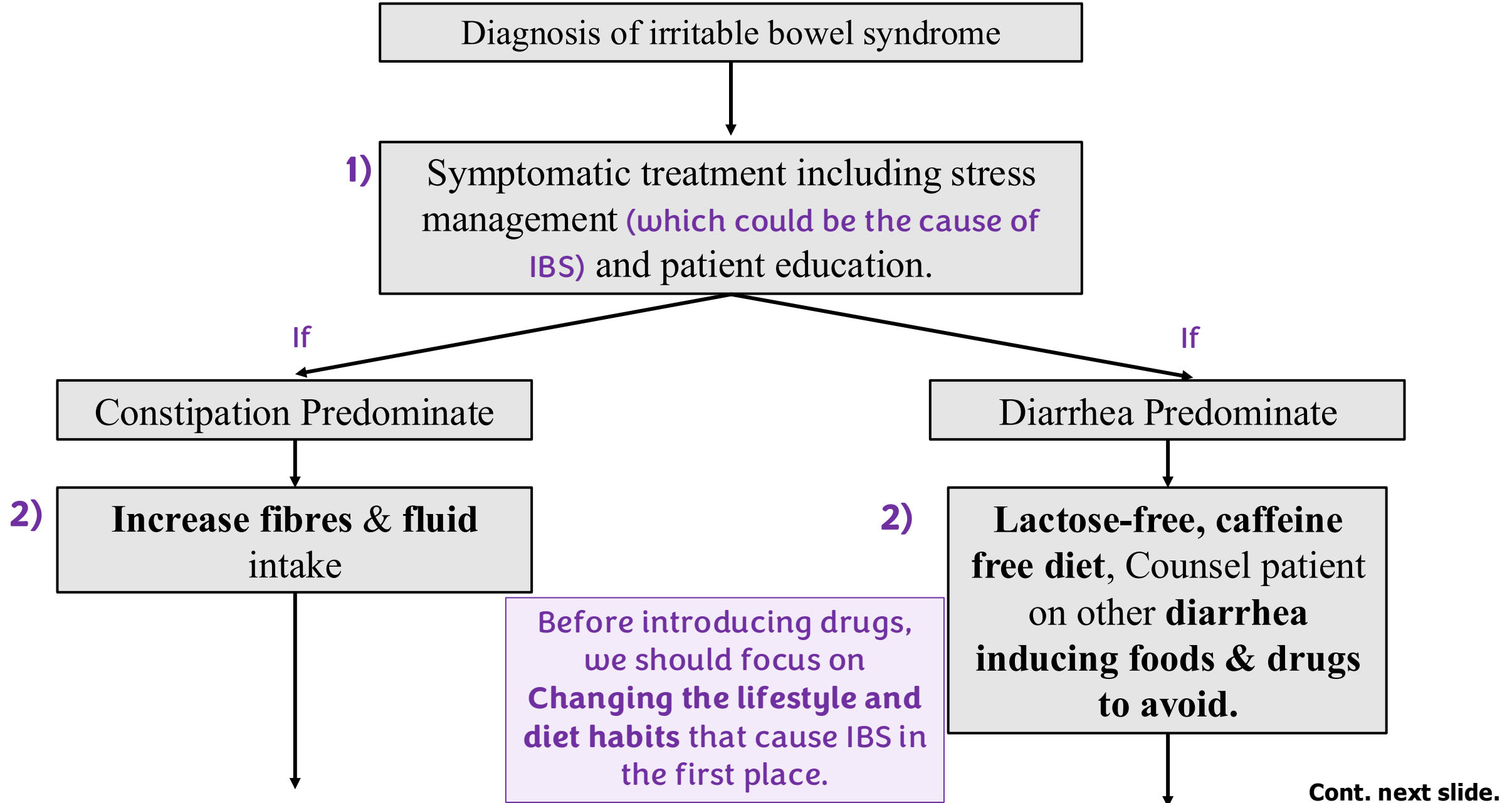
Drugs used in Irritable Bowel Syndrome

☐ Serotonin 5-HT 3- Receptor Agonists:

- **Tagaserod:**

- Approved for **short term** treatment of **women** with IBS who predominantly have constipation.
- **Its side effects are less severe than alosterone.**
- **Reduces pain, bloating and hardness of stool.**
- Expensive.

Drugs used in Irritable Bowel Syndrome



Constipation Predominate

Diarrhea Predominate

Laxatives → soften/push stool out.

If the lifestyle modification & dietary changes weren't enough to resolve the symptoms, we will move to the drugs.

Loperamide → tells the gut slow down.

3) Add **bulk-Forming laxatives** consider **anti-spasmodic agents**.

3) Add **laperamide or other anti-spasmodic**.

If the 1st line therapy doesn't work we will introduce other agents

4) Add **serotonin-4 agonist (e.g, tegaserod)**.

4) Add **serotonin-3 antagonist (eg. Alosetron)**.

Tegaserod → tells the gut "move faster" (5-HT4 signal) For Diarrhea.

Alosetron → blocks the signal that speeds gut up (5-HT3 block).

5)

Add **Psychotherapeutic** behaviour modification, including **stress reduction**, and consider **antidepressants** for **associated pain symptoms**.

Drugs used in Irritable Bowel Syndrome

Irritable Bowel Syndrome treatment starts with **general measures including stress reduction, patient education, lifestyle modification, and dietary changes** because stress and certain foods can trigger symptoms.

➤ Constipation-predominant IBS (IBS-C)

- Increase fiber and fluid intake.
- If symptoms persist: use bulk-forming laxatives and antispasmodic drugs to relieve constipation and abdominal cramps.
- In resistant cases: use 5-HT₄ agonists such as Tegaserod, which increase intestinal motility and accelerate bowel movement.

➤ Diarrhea-predominant IBS (IBS-D)

- Avoid trigger foods such as lactose and caffeine.
- Use Loperamide to slow intestinal motility and reduce stool frequency, with antispasmodics for pain relief.
- If symptoms continue: use 5-HT₃ antagonists such as Alosetron to decrease gut motility and secretion.
- Psychological therapy, stress management, and sometimes antidepressants may also help because IBS is strongly associated with the brain-gut axis and visceral pain sensitivity.

Antiemetic Agents

- Antiemetic drugs are drugs used for resolving vomiting & nausea.
- Different causes of nausea & vomiting requires different drugs.
- Nausea and vomiting may be manifestations of a wide variety of conditions, including:
 - Adverse effects of medications. systemic disorders or infections.
 - Pregnancy.
 - Vestibular dysfunction.
 - CNS infection or increased pressure.
 - Peritonitis.
 - Hepatobiliary disorders. Radiation or chemotherapy.
 - GIT obstruction, dysmotility, or infections.

Pathophysiology

- The brainstem "**vomiting center**" coordinates vomiting through interactions with cranial nerves **VIII (Vestibulocochlear)** and **X (Vagus)** and neural networks in the **nucleus tractus solitarius** that control respiratory, salivatory, and vasomotor Centers.
- Vomiting center contains high concentrations of:
 - **M1** receptors.
 - **H1** receptors.
 - **Neurokinin 1 (NK1)** receptors.
 - **5-HT3** receptors.

Pathophysiology

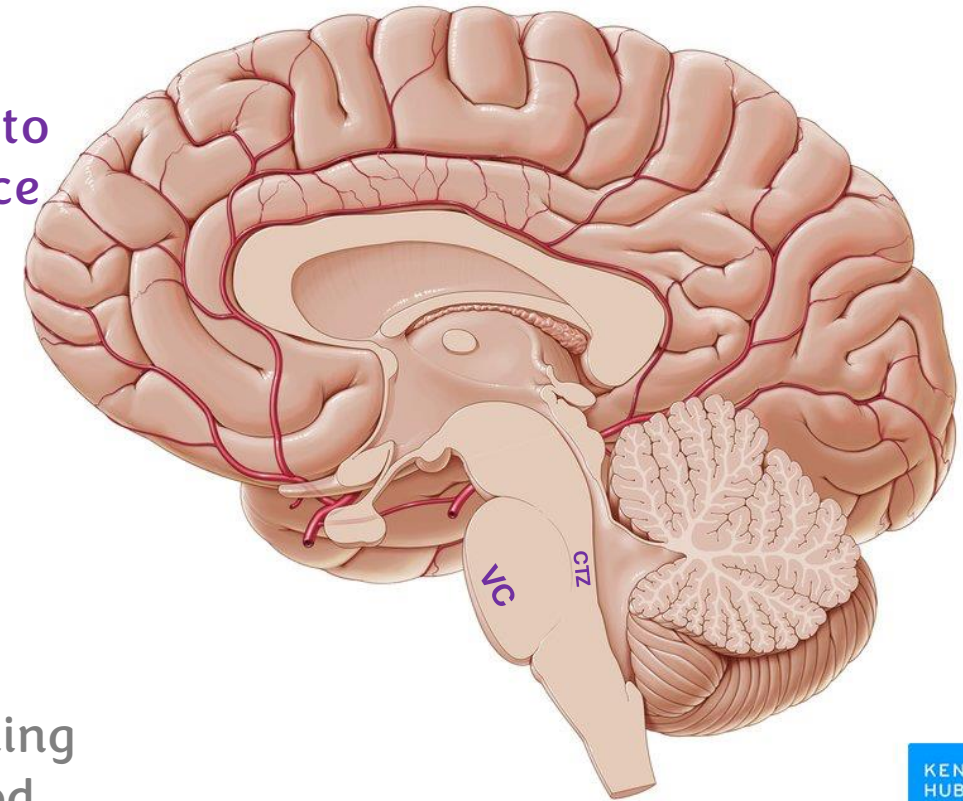
➤ When talking about **nausea & vomiting**, we are interested in the **Brain Stem**, especially 2 centres (collection of neurons) located at the medulla, which are :

➤ **Vomiting Centre (VC) – located anteriorly**

- Responsible for initiating vomiting process in response to different signals coming from different sources (Balance system (inner ear), GIT tissue, Cerebellum).

➤ **Chemoreceptor Triggers Zone (CTZ) – located posteriorly**

- It senses the changes in the chemical state of the CSF & Blood.
- One of its side is facing the CSF at the 4th Ventricle.
- The other side is facing the blood vessels passing through the brain stem.
- It can send signals to the VC to initiate vomiting depending on a speech age in the chemical states of the CSF & Blood.



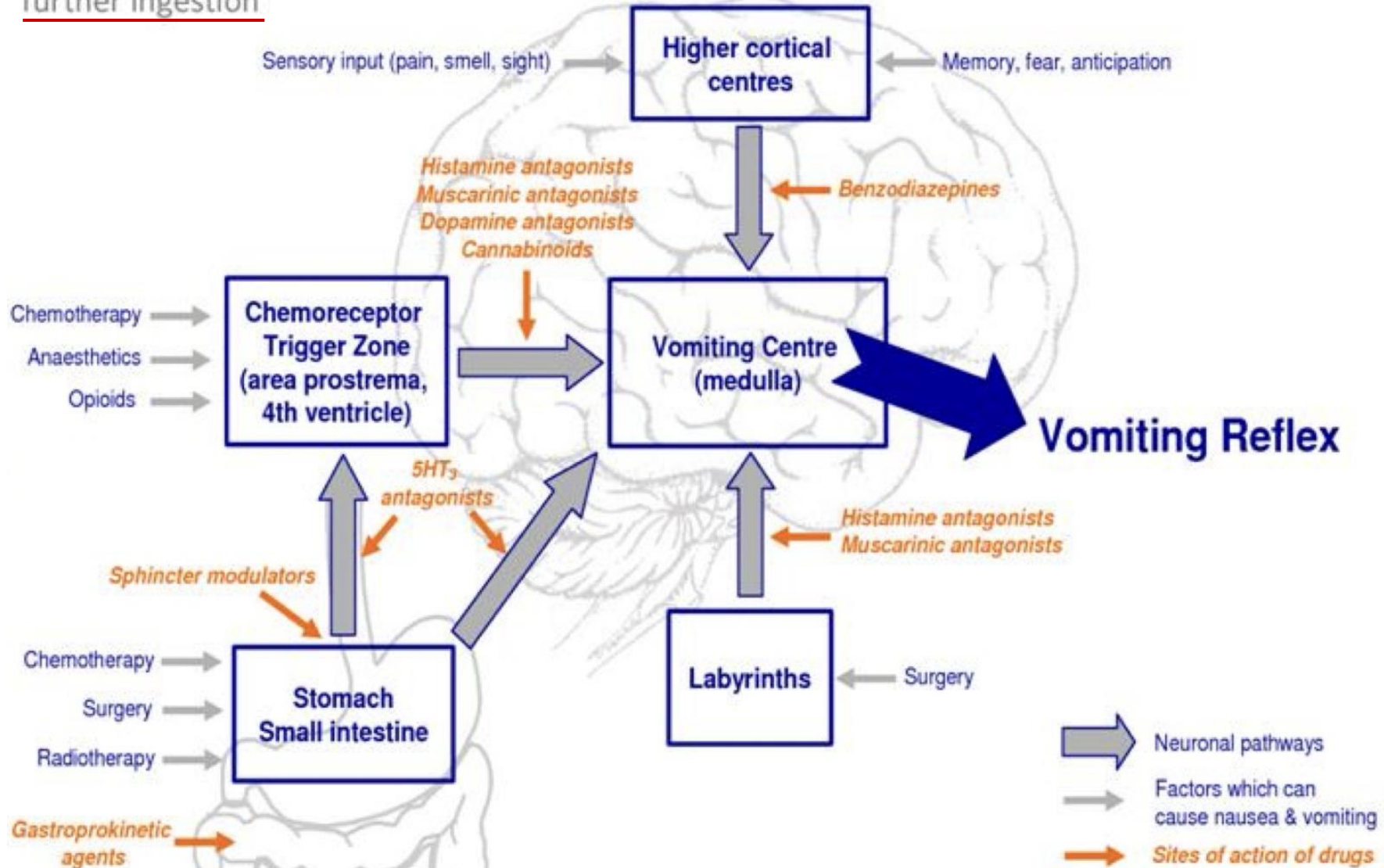
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Extra image

Antiemetic Agents

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



Explanation of the previous Slide

- **Vomiting** is considered a **protective reflex** that prevents toxic substances from entering the intestine and stomach.
- **The main structure responsible for controlling vomiting is the *vomiting center***, and it is influenced by several different pathways and factors, for example :
 - **The higher cortical centers** can stimulate vomiting
 - **The chemoreceptor trigger zone (CTZ)** also contributes to the induction of vomiting (In response to specific change in chemical state of CSF or Blood).
 - **The presence of toxic substances in the stomach and small intestine** can stimulate both the vomiting center and the chemoreceptor trigger zone (CTZ).
 - Different drugs act on different pathways involved in vomiting, and these will be discussed later.
 - From the diagram, it can be seen that **cannabinoids may suppress the pathway extending from the higher cortical centers to the vomiting center.**
 - **Histamine antagonists, muscarinic antagonists, dopamine antagonists, and cannabinoids** can also affect the pathway connecting the chemoreceptor trigger zone to the vomiting center.
 - **Muscarinic antagonists and histamine antagonists** act on the pathway originating from the labyrinth and stimulating the vomiting center.

Serotonin 5-HT₃ Antagonists

Ondansetron, Granisetron

- **Block central 5-HT₃ and peripheral (main effect) 5-HT₃ receptors.**
- Prevent emesis due to vagal stimulation and chemotherapy.
- Other emetic stimuli such as **motion sickness** are poorly controlled.
- **Uses**
- Prevention of **acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting.**
- **Their efficacy is enhanced by combination therapy with dexamethasone and NK₁-receptor antagonist.**
- **Adverse effects:** Headache, dizziness, and constipation.

The doctor only read the slide, further external explanation in the next slides

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Types Of Vomiting

1) Motion Sickness

- Motion sickness occurs because of a mismatch between the information received from the visual system and the balance system.
- For example, when you are sitting in a moving car reading your phone:
 - 1) Your eyes detect that you are relatively stable.
 - 2) At the same time, the vestibular system in the inner ear (vestibule and cochlea) detects movement because the car is moving at high speed.
 - 3) The cochlea sends signals through the cochlear nerves to the cerebellum, while visual information is also sent to the cerebellum.
- ✓ If the cerebellum detects that both sources of information match, vomiting does not occur.
- ✓ If the cerebellum detects a mismatch between the visual and vestibular inputs, it sends signals through the Chemoreceptor Trigger Zone (CTZ) to the Vomiting Center (VC), initiating vomiting.

□ Treatment

- Drugs used for motion sickness mainly act on:
 - **M1 receptors**
 - **H1 receptors**
 - or both
- ✓ These receptors are important in the inner ear pathways involved in motion sickness.
- ✓ This also explains why 5-HT3 receptor antagonists are ineffective in motion sickness, because this type of vomiting occurs through a different pathway.

Types Of Vomiting

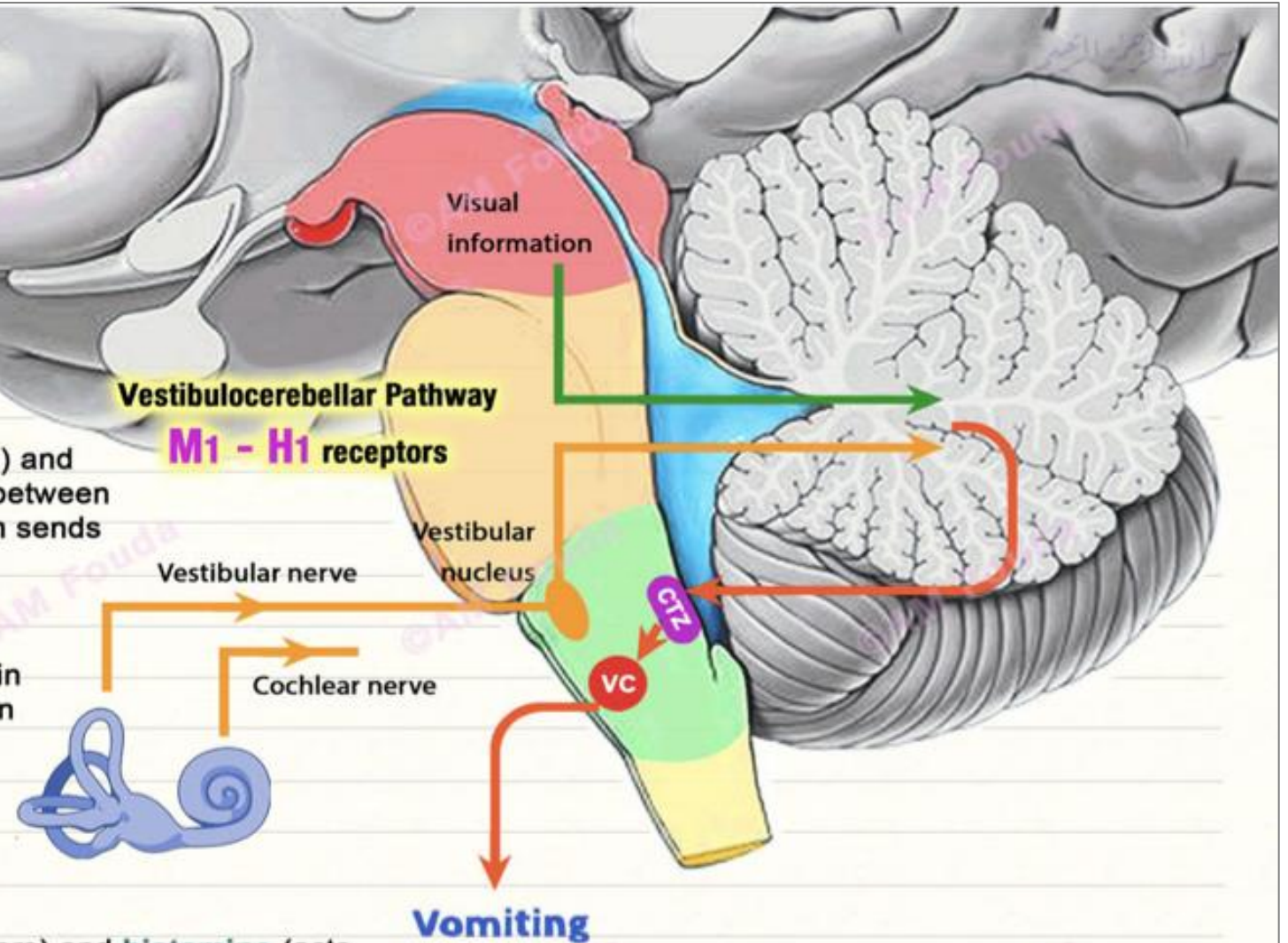
Extra slide, extra picture, extra explanation

Motion Sickness

Motion sickness is a complex condition that occurs as a result of conflicting sensory information received by the brain. It is caused by a mismatch between what the inner ear senses (motion) and what the eyes see (stillness). This conflict between the vestibular system and the visual system sends conflicting signals to the brain, leading to feelings of nausea and vomiting.

The mechanism for this phenomenon is as following: The motion stimulates receptors in the vestibular labyrinth of the inner ear, then to the vestibular nuclei in the medulla through the vestibular branch of the 8th cranial nerve. The cerebellum receives information from the vestibular nuclei and sends impulses to the CTZ, and finally to the VC to cause vomiting.

Acetylcholine (acts on **muscarinic** receptors) and **histamine** (acts on **H1 receptors**) are the primary transmitters involved in this arc.



Just look at the picture for more understanding, text was explained previously.

Types Of Vomiting

2) Chemotherapy-Induced Nausea and Vomiting (CINV)

- Chemotherapy and radiotherapy can damage the gastrointestinal mucosa, especially the enterochromaffin-like cells.
 - When these cells are injured, they release:
 - **Serotonin (5-HT)**
 - **Dopamine**
 - **Substance P.**
 - **Mechanism**
 - Serotonin acts on nerve terminals in the gut, sending signals through the vagus nerve to the Vomiting Center (VC).
 - In addition, serotonin, dopamine, and substance P act centrally on receptors in the VC:
 - **5-HT₃ receptors**
 - **Dopamine (D₁) receptors**
 - **NK₁ receptors**
- ✓ Activation of these receptors initiates vomiting.

□ Treatment

- Vomiting can be controlled using:
 - **5-HT₃ receptor blockers.**
 - **Dopamine blockers.**
 - **NK₁ receptor blockers.**
- Additional potentiation may occur with:
 - **Corticosteroids**
 - **CB₁ agonists** (recently discovered, but generally preferable to avoid)

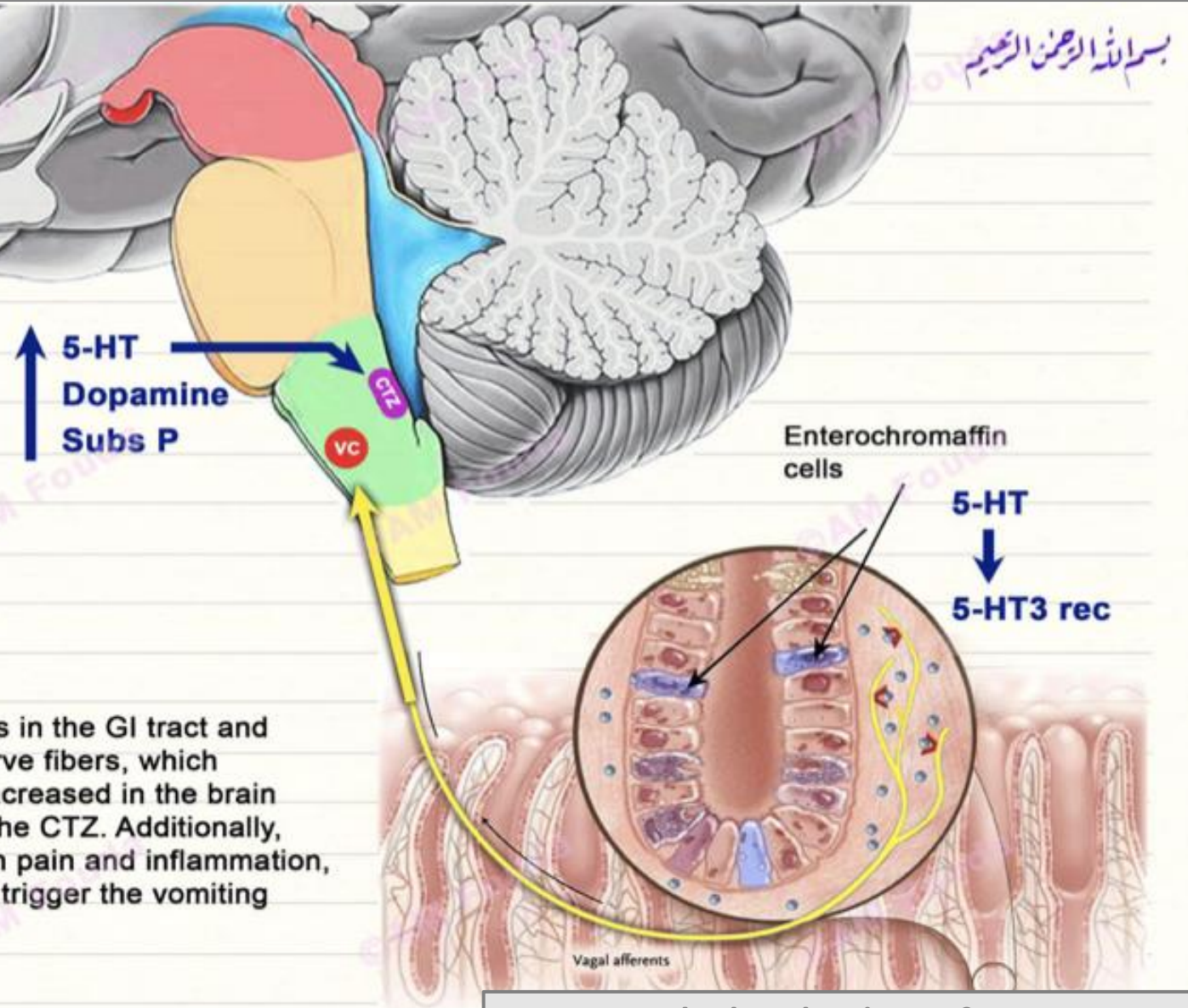
Types Of Vomiting

Extra slide, extra picture, extra explanation

Chemotherapy-Induced Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing side effect of cancer treatment. Chemotherapy agents cause damage to the cells lining the GI tract, leading to the release of various neurotransmitters, including serotonin, dopamine, and substance P.

Serotonin is released by enterochromaffin cells in the GI tract and activates **5-HT₃** receptors on vagal afferent nerve fibers, which transmit signals to the VC. Also, dopamine is increased in the brain and stimulates the **dopamine D₂** receptors in the CTZ. Additionally, **substance P**, a neuropeptide that is involved in pain and inflammation, can activate the **NK₁** receptors in the CTZ and trigger the vomiting reflex.



Just look at the picture for more understanding, text was explained previously.

Types Of Vomiting

3) Nausea and Vomiting in Early Pregnancy

- This usually occurs during weeks **4-16** of pregnancy.

☐ Physiology

- During early placental development:
 - The placenta releases **hCG**
 - Levels of **progesterone** and **estrogen** increase
- These hormonal changes alter blood chemistry, which is detected by the CTZ. **Signals are then sent to the Vomiting Center (VC), initiating nausea and vomiting.**

☐ Treatment

- Blocking hCG, progesterone, or estrogen is contraindicated because these hormones are essential for maintaining pregnancy.
- Instead, treatment commonly includes:
- **Vitamin B6 (Pyridoxine)**
Vitamin B6 is effective, although its exact mechanism of action is still not fully understood.

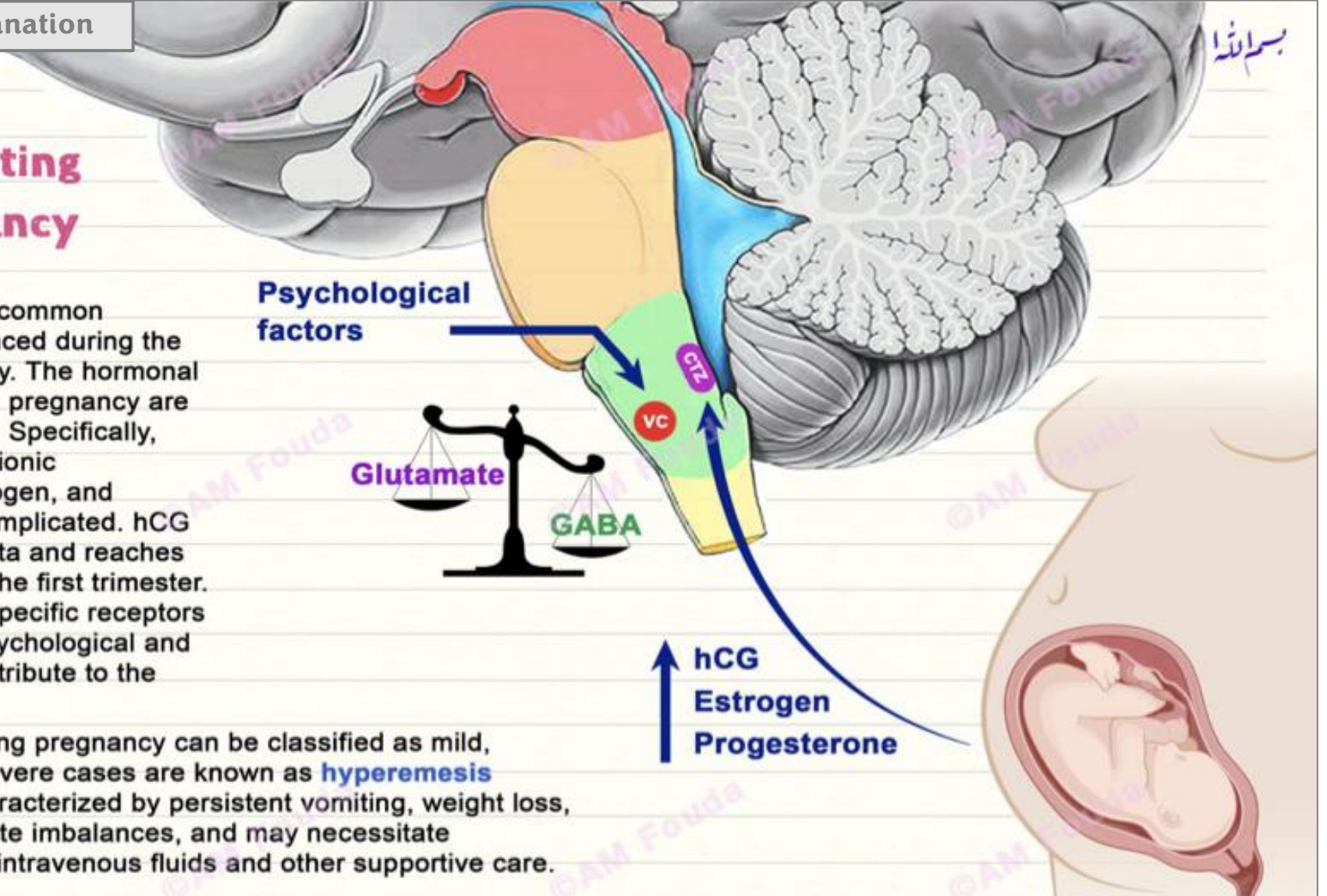
Types Of Vomiting

Extra slide, extra picture, extra explanation

Nausea & Vomiting in Early Pregnancy

Nausea and vomiting are common symptoms (**50%**) experienced during the first trimester of pregnancy. The hormonal changes that occur during pregnancy are thought to play a key role. Specifically, high levels of human chorionic gonadotropin (hCG), estrogen, and progesterone have been implicated. hCG is produced by the placenta and reaches its peak concentration in the first trimester. It is thought to stimulate specific receptors in the VC. Additionally, psychological and emotional factors can contribute to the condition.

Nausea and vomiting during pregnancy can be classified as mild, moderate, and severe. Severe cases are known as **hyperemesis gravidarum**, which is characterized by persistent vomiting, weight loss, dehydration, and electrolyte imbalances, and may necessitate hospitalization to provide intravenous fluids and other supportive care.



Just look at the picture for more understanding, text was explained previously.

Neurokinin 1 Receptor (NK1) Antagonists

- Block central **NK1receptors** in the area postrema.
- **Aprepitant**
- Used in combination with **5-HT3-receptor antagonists** and **corticosteroids** for the prevention of acute and delayed nausea and vomiting from chemotherapy.

➤ **Cannabinoids** Dronabinol, Nabilone

- Psychoactive agents.
- Used for **chemotherapy-induced vomiting**. Mechanisms for these effects are not understood.
- **Adverse effects:**
 - Euphoria, dysphoria, sedation, hallucinations, drymouth, and increased appetite.

Antipsychotic drugs

➤ Prochlorperazine

➤ Promethazine

➤ Droperidol

- Antiemetics due to blocking **dopamine and muscarinic receptors**.
- Sedative effects due to **antihistamine activity**.

➤ Benzodiazepines

- **Lorazepam**
- **Diazepam**

✓ Reduce vomiting caused by anxiety.

ANTIEMETIC AGENTS

Drugs used for the prevention and treatment of nausea & vomiting

Summary Of

Antiemetic Drugs

1 CAUSES OF NAUSEA & VOMITING

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

- Adverse effects of medications, systemic disorders or infections.
- Pregnancy.
- Vestibular dysfunction.
- CNS infection or increased pressure.
- Peritonitis.
- Hepatobiliary disorders.
- Radiation or chemotherapy.
- GIT obstruction, dysmotility, or infections.

↳ Different causes of nausea & vomiting require different drugs.

2 NEURAL CONTROL OF VOMITING

→ The brainstem "vomiting center" coordinates vomiting through interactions with:

- Cranial nerves VIII (Vestibulocochlear) and X (Vagus) and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor centers.

→ The vomiting center contains high concentrations of:

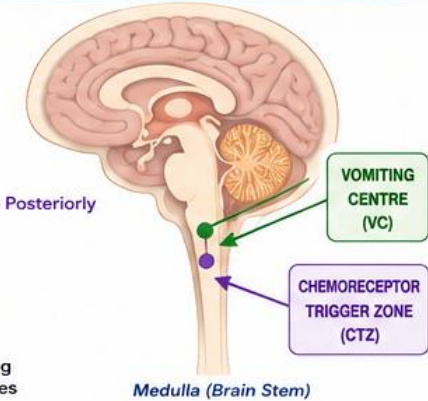


5-HT₃ Receptor = Serotonin Receptor Type
(Further explanation in subsequent slides)

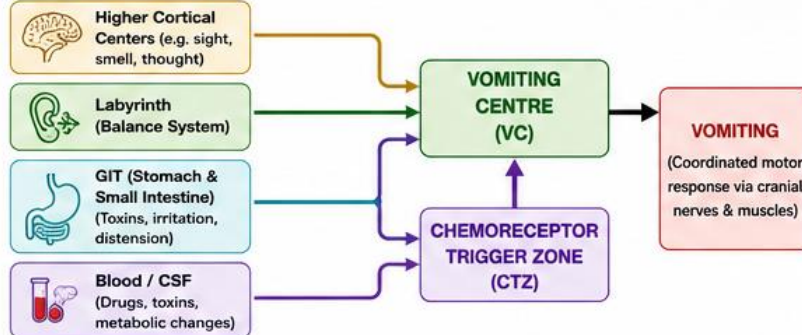
3 PATHOPHYSIOLOGY – KEY CENTERS IN BRAIN STEM

Two key centers in the medulla:

- **VOMITING CENTRE (VC)** – Anteriorly
 - Responsible for initiating vomiting process in response to different signals coming from different sources (Balance system (inner ear), GIT tissue, Cerebellum).
- **CHEMORECEPTOR TRIGGER ZONE (CTZ)** – Posteriorly
 - Senses changes in the chemical state of CSF & Blood.
 - One side faces the CSF at the 4th Ventricle.
 - The other side faces blood vessels passing through the brain stem.
 - Can send signals to the VC to initiate vomiting depending on a change in the chemical states of the CSF & Blood.



4 PATHWAYS INVOLVED IN VOMITING



MODULATION BY DRUGS

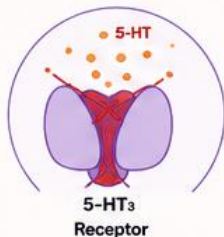
- Cannabinoids may suppress the pathway from higher cortical centers to VC.
- Histamine antagonists, muscarinic antagonists, dopamine antagonists, and cannabinoids affect the pathway from CTZ to VC.
- Muscarinic antagonists and histamine antagonists act on the pathway from labyrinth to VC.
- Dopamine antagonists (e.g. prochlorperazine) act on the pathway from GIT to CTZ & VC.
- Dopamine antagonists and cannabinoids act on the pathway from blood/CSF to CTZ.

5 EXPLANATION OF PATHWAYS

- ✓ Vomiting is a protective reflex that prevents toxic substances from entering the stomach and intestine.
- ✓ The vomiting center (VC) is influenced by multiple pathways & factors.
- ✓ The chemoreceptor trigger zone (CTZ) is activated by specific changes in the chemical state of CSF or blood.
- ✓ Toxins in the stomach and small intestine can stimulate both the VC and CTZ.
- ✓ Different drugs act on different pathways involved in vomiting.
- ✓ Cannabinoids may suppress the pathway from higher cortical centers to the VC.
- ✓ Histamine antagonists, muscarinic antagonists, dopamine antagonists, and cannabinoids affect the pathway from CTZ to the VC.
- ✓ Muscarinic antagonists and histamine antagonists act on the pathway from the labyrinth (vestibular system) to the VC.

6 SEROTONIN 5-HT₃ ANTAGONISTS

Examples: Ondansetron, Granisetron



- Block central 5-HT₃ and peripheral (main effect) 5-HT₃ receptors.
- Prevent emesis due to vagal stimulation and chemotherapy.
- Other emetic stimuli such as motion sickness are poorly controlled.

USES

- Prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting.
- Their efficacy is enhanced by combination therapy with dexamethasone and NK1-receptor antagonist.

ADVERSE EFFECTS: Headache, dizziness, and constipation.

7 OTHER ANTIEMETIC DRUGS

ANTIPSYCHOTIC DRUGS

Antiemetics due to blocking dopamine and muscarinic receptors.

Sedative effects due to antihistamine activity.

- Prochlorperazine
- Promethazine
- Droperidol



BENZODIAZEPINES

- Lorazepam
- Diazepam



Reduce vomiting caused by anxiety.

CANNABINOIDS



Can suppress the pathway from higher cortical centers to the vomiting center.

(Useful in chemotherapy-induced nausea & in refractory cases).

Antiprotozoal drugs

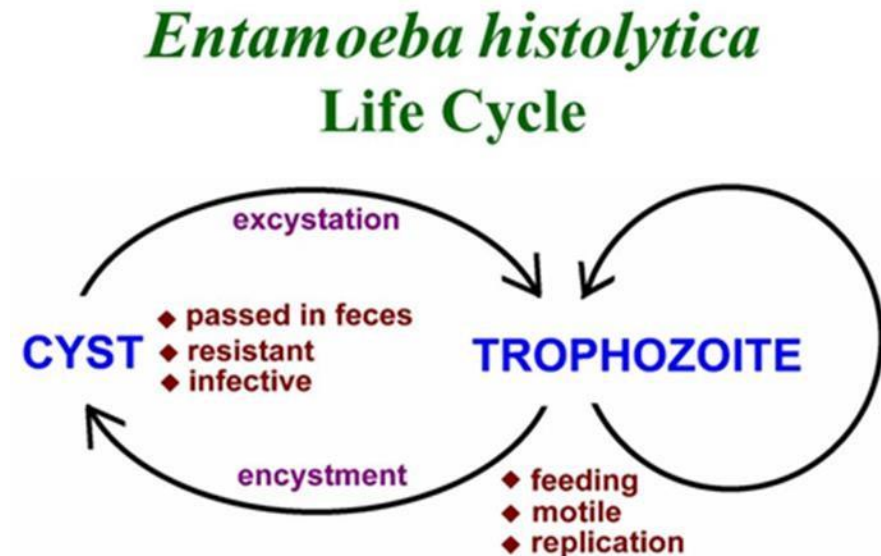
Antiprotozoal drugs

- Protozoal and helminthic infections are a major cause of disease in many parts of the world.
- **Some of these diseases :**
 - In migrant workers.
 - Or individuals returning from an endemic area.

Selected PROTOZOAL DISEASES

Amebiasis

- **Caused by :** The protozoan **Entamoeba histolytica** causes amebiasis, an infection that is endemic in parts of the United States.
- The parasite can be present in the host as either an **encysted** or a **trophozoite** form.
 - **Encysted :** It is easily transmitted (**highly infectious**), **resistant to drugs**, and **harder to be detected**.
 - **Trophozoite :** **active** form of parasite that performs biological processes like **feeding, motile & replication**.



Selected PROTOZOAL DISEASES – *Amebiasis*

- Initial ingestion of the cyst may result either in **no symptoms or in severe amebic dysentery** (**depending on the situation**) characterized by the frequent passage of blood stained stools.
- **Symptoms** occurs after **invasion of the intestinal mucosa by the actively motile and phagocytic trophozoite** form of the protozoan.

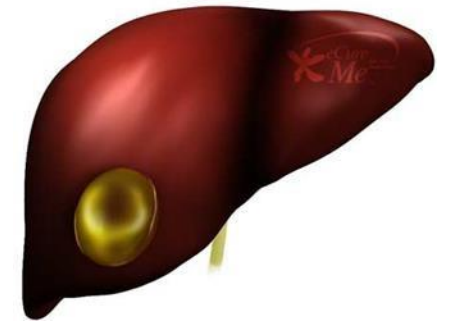
Selected PROTOZOAL DISEASES – *Amebiasis*

- Trophozoites may spread to the liver through the portal vein and produce **acute amebic hepatitis**.
- Many patients **continue to excrete cysts for several years after recovery** from the acute disease and therefore **are a hazard to themselves and other persons**.

☐ *Entamoeba histolytica*.

• This organism can cause:

- **Asymptomatic intestinal infection.**
- Mild to moderate colitis.
- Severe intestinal infection (dysentery).
- **Ameboma (a tumor-like mass in the intestines in amebiasis which results in a large local lesion of the bowel).**
- **Liver abscess and other extraintestinal infection.**

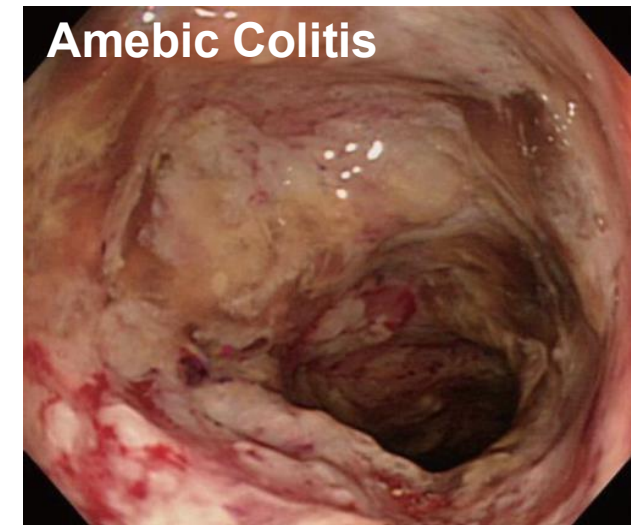


Treatment of Specific Forms of Amebiasis

- **Asymptomatic Intestinal Infection:** Asymptomatic carriers are treated with a **luminal amebicide**.
- **Standard luminal amebicides are:**
 - **Diloxanide furoate,**
 - **Iodoquinol, and**
 - **Paromomycin.**
- Therapy with a **luminal amebicide is also required in the treatment of all other forms of amebiasis.**

□ Amebic Colitis

- **Metronidazole + a luminal amebicide** is the treatment of choice.
- **Tetracyclines** and **erythromycin** are alternative drugs for moderate colitis but are not effective against extraintestinal disease.
- **Dehydroemetine or emetine** can also be used, but are best avoided because of toxicity.



Selected PROTOZOAL DISEASES — *Balantidium coli*

- The **largest** of the protozoans that infect humans.
- **Trophozoite form is covered with cilia, which impart mobility.**
- Infection is acquired through the **ingestion of cyst-contaminated soil, food, or water.**

Selected PROTOZOAL DISEASES — *Balantidium coli*

Symptoms

- The trophozoite causes **superficial necrosis** or *deep ulceration* in the **mucosa and submucosa of the large intestine**.
- Healthy persons commonly exhibit nausea, vomiting, abdominal pain, and diarrhea.
- Nutritionally stressed patients (**patients having nutritional problems**) **may develop severe dysentery**.

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

(numbered in order as cited in the text)

1. Dr. Manar Zraikat's Lecture
2. Dr.Fouda's Lecture
3. Dr.Fouda's Book

Extra References for the Reader to Use:

1. [Antiemetic Drugs by Dr.Fouda](#)
2. [Antiemetic Drugs by Abdelrahman Froukh](#)
3. [Antiprotozoal Drugs by Abdelrahman Froukh](#)

يَا رَبِّ...

هذا قلبي الصَّغِير، مُضغتي التي تُولمُني،

أبسْطُهُ بين يديكَ، وأسألُكَ أن ترأفَ به إذا أحبَّ فاكْتوى،
وإذا تجمَّع فتفرَّق، وإذا أزرَ فحُذِل، وإذا مالَ فانتكَّس، وإذا
شابَ فضَعُف، وإذا ماتَ فتَلجَّج،

فإنَّهُ يُحبُّكَ وإن ضلَّ صاحِبُهُ.

For any feedback, scan the code or click on it.



Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|----------|----------------------------|--|---|
| V0 → V1 | Slide 5; Right corner | Constipation Predominate | Diarrhea Predominate |
| V1 → V2 | Slide 3 Slide 5 | Its side effects are less severe than aldosterone Add serotonin-3 antagonist (eg. Atosetron) | Its side effects are less severe than alosterone Add serotonin-3 antagonist (eg. Alosetron) |