# DRUGS USED IN GIT L 3,4 2022



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# : Nausea and Vomiting

Although nausea and vomiting occur in a variety of **conditions** (like motion sickness, pregnancy, and GI illnesses) and are always unpleasant for the patient, the nausea and vomiting produced by chemotherapeutic agents (CINV = chemotherapy induce nausea and vomiting) demands .especially effective management

Chemotherapeutic agents can **directly** activate the medullary, **CTZ** or **vomiting center**. Several **neuroreceptors**, including **D2** and serotonin type 3 (**5-HT3**), play critical **roles**

uncontrolled vomiting can produce dehydration, profound .metabolic imbalances, and nutrient depletion

# Anti-emetic

is a drugis a drug that is effective .against vomiting and nausea

**Medulla is a center** for vomiting (contain **muscarinic**, **H 1**, and **5HT3** receptors). **Medulla** does **not initiate** but it **coordinates** vomiting on receiving stimuli from many sources including

**CTZ** (Chemoreceptor Trigger Zone): the zone is **outside** the **.1** blood–brain **barrier**. Thus, it can **respond directly** to chemical stimuli in the blood or cerebrospinal fluid. It contains **D2, 5HT, .Neurokinin 1 (NK1) and opioid receptors**

**The vestibular** system: functions mainly in **motion** .2
.sickness, **It contain** :**muscarinic and H1 receptors**

Thus Anticholinergic drugs, especially The muscarinic receptor antagonist *scopolamine* and **H1-receptor antagonists**, such as *dimenhydrinate*, *meclizine*, and *cyclizine*, **are very useful** in motion sickness but are **ineffective** against substances that act **directly** on .the **CTZ**

**The peripheral source: kidney diseases (**renal colic), .3
.angina and GIT biliary disease and pharynx

**Cortical centers and brain stain**: due to stress , unwanted.**4**
odor (bad smell) and gag reflex

# Classification of antiemetics :

## PHENOTHIAZINES

*Prochlorperazine* GENERIC ONLY

## 5-$HT_3$ SEROTONIN RECEPTOR ANTAGONISTS

*Dolasetron* ANZEMET

*Granisetron* SANCUSO, SUSTOL

*Ondansetron* ZOFRAN

*Palonosetron* ALOXI

## SUBSTITUTED BENZAMIDES

*Metoclopramide* REGLAN

## BUTYROPHENONES

*Droperidol* GENERIC ONLY

*Haloperidol* HALDOL

## BENZODIAZEPINES

*Alprazolam* XANAX

*Lorazepam* ATIVAN

## CORTICOSTEROIDS

*Dexamethasone* DECADRON

*Methylprednisolone* MEDROL

## SUBSTANCE P/NEUROKININ-1 RECEPTOR ANTAGONIST

*Aprepitant, Fosaprepitant* EMEND

*Netupitant** AKYNZEO

*Rolapitant* VARUBI

**Phenothiazines:** like **prochlorperazine**, act by **blocking D2** in the CTZ, effective against **low or moderately** emetogenic chemotherapeutic agents (example, *fluorouracil* and *doxorubicin*). Although increasing the dose improves antiemetic activity, **adverse effects** are **dose** limiting. .1

**HT3 receptor blockers** : discussed later-5 .2

3. **Substituted benzamides** : discussed later

**Butyrophenones:** like **Droperidol**, **blocking D2 recep.**, **moderately effective** antiemetics, it may **prolong the QT** interval, and should be used for **patients with inadequate** response to other agents. .4

**Benzodiazepines:** The antiemetic **potency** of **lorazepam** and **alprazolam** is **low**. Their **beneficial** effects may be **due** to their **sedative** , **anxiolytic**,and **amnestic** properties .5

**6. Corticosteroids:** antiemetic mechanism is **not known**, but it may involve blockade of prostaglandins.

**7. Neurokinin 1 ($NK_1$) antagonists: discussed**

# :Prokinetic agents

## .They are drugs stimulating GIT motility

They **enhance** the **release of Ach** from the myenteric plexus :of the gut, they have the following action

.**Increase** lower esophageal **sphinecteric tone** -1

.**Increase** rate of **gastric emptying** -2

**Increase peristalsis** -3

# : Prokinetic agents include

**A- Substituted Benzamide : (**metoclopromide)

**B- Cholinomimetics: bethanechol** (stimulate $M_3$ R), **neostigmine**

**C-Macrolide** Abs: Erythromycin (acts on motilin receptor in antral wall) which enhances **gastric emptying** and **gastric contraction**

**D-Others : dompridone peripherally** selective $D_2$ Receptor antagonist

**Cisapride** (**5HT4 agonists act only peripherally**)

**Renzapride** ($5HT_4$ full agonist and $5HT_3$ antagonist.

# :Metoclopramide-1

This drug acts by 2 mechanisms including

. **Centrally** by **blocking D2-** receptor in CTZ **-1**

**Peripherally** by **enhancing** the action of **Ach** on myenteric plexus in **-2**
.the gut


,**Kinetics**: 1- It its metabolized by the liver

.t**1/2** = 4 hrs -2

# :Clinical uses

Gastroesophageal Reflux Disease -1

Impaired Gastric Emptying like vagotomy -2

Prevention of Vomiting **in 30% to 40%** of patients(GIT disorders, -3
.Chemotherapy, radiotherapy, Migraine, After surgery

Postpartum Lactation Stimulation -4

.To empty the stomach before emergency surgery -5

# : Side Effects

**A-Extra-pyramidal side effects:** [(bs antagonist at D2-R) that can be abolished by **benzotropine** I.V.(antimuscarinic)]
: , and these side effects are

.Torticollis, facial spasm, and oculogyric crises.1

.parkinson like features (if Long use) .2

**B- Increase prolactine release : (dopamine vs prolactine)**

**bs** The hormone prolactin The hormone prolactin stimulates lactation . Dopamine The hormone prolactin stimulates lactation . Dopamine, released by the hypothalamus The hormone prolactin stimulates lactation . Dopamine, released by the hypothalamus stops the release of prolactin .from the pituitary gland

# : Dompridone -2

a **peripherally selective** dopamine $D_2$ receptor antagonist -1

**Centrally : it blocks D2-receptor in CTZ -2**

**Has some gastric emptying effect -3**

## :Kinetics

**t1/2 = 7hrs -1**

**Poorly crosses BBB -2**

## :Side effects

**diarrhea, abdominal Cramp -**

**headache, drowsiness, galactorrhea and gyencomastia - may occur (It has little central side effects (bs it is .peripheraly selective))**

# :Contraindicated in

Severe hepatic impairment -1

Cardiac conduction impairment -2

.Congestive heart failure -3

.Co-adminstration with QT prolonging drugs -4

Potent CYP 450 inhibitors -5

**Cisapride**: (**5HT4 agonist effect** and some **5HT3** antagonistic **-3**
.action)

It acts only **peripherally** by increase Ach. in the gut (only prokinetic
.action) and It has no effect on D2 receptors

**Kinetics**

t1/2 =10 hrs -1

Undergoes **lst pass** metabolism-2

.orally -3

Structurally related to metoclopromidie -4

**:Uses**

.Reflex esophagitis

**Gastroparesis (**In diabetes mellitus (When the gastric motility is
.impaired )

## : Drug interactions

C**ardiac arrhythmia** may occur when taken with **Macrolides** antibiotics as erythromycin and clarithromycin, and **-1**

**,Antifungal** drugs as **ketoconazole** and **miconazole** **-2**

.Thus, this drug is **no more used**

## cts

.Abdominal cramping

Diarrhea

**Renzapride** is a gastroprokinetic agent is **-4**

a gastroprokinetic agent and antiemetic , acts as $5\text{-}HT_4$ full agonist full

.agonist and $5\text{-}HT_3$ antagonist

## :5HT3 RECEPTOR ANTAGONIST -5

Several **factors** influence the **incidence** and severity of chemotherapy-induced **nausea** and vomiting (CINV), including the **specific** chemotherapeutic drug , **dose**, **route**, .and **schedule** of administration; and patient **variables**

The **selective** **5HT3** receptor antagonists, **highly effective** for treatment of nausea & vomiting induced by **chemotherapy** :and **radiotherapy**. **They are**

**Ondanosetron**. **Granisetron**, **Tropisetron, palosetron**. Ramosetron **and Dolasetron**

**Palosteron has longer t1/2**

**Ramosetron has** higher affinity for the 5-$HT_3$ receptor

: **Note :** Serotonin receptors of the 5-HT3 type are present

**Peripherally** on **vagal** nerve terminals -1

**Centrally** in **CTZ** (the chemoreceptor trigger zone) -2

## :Mechanism of action

: 5HT3 receptor blocking effect on

.intestinal vagal afferents-1

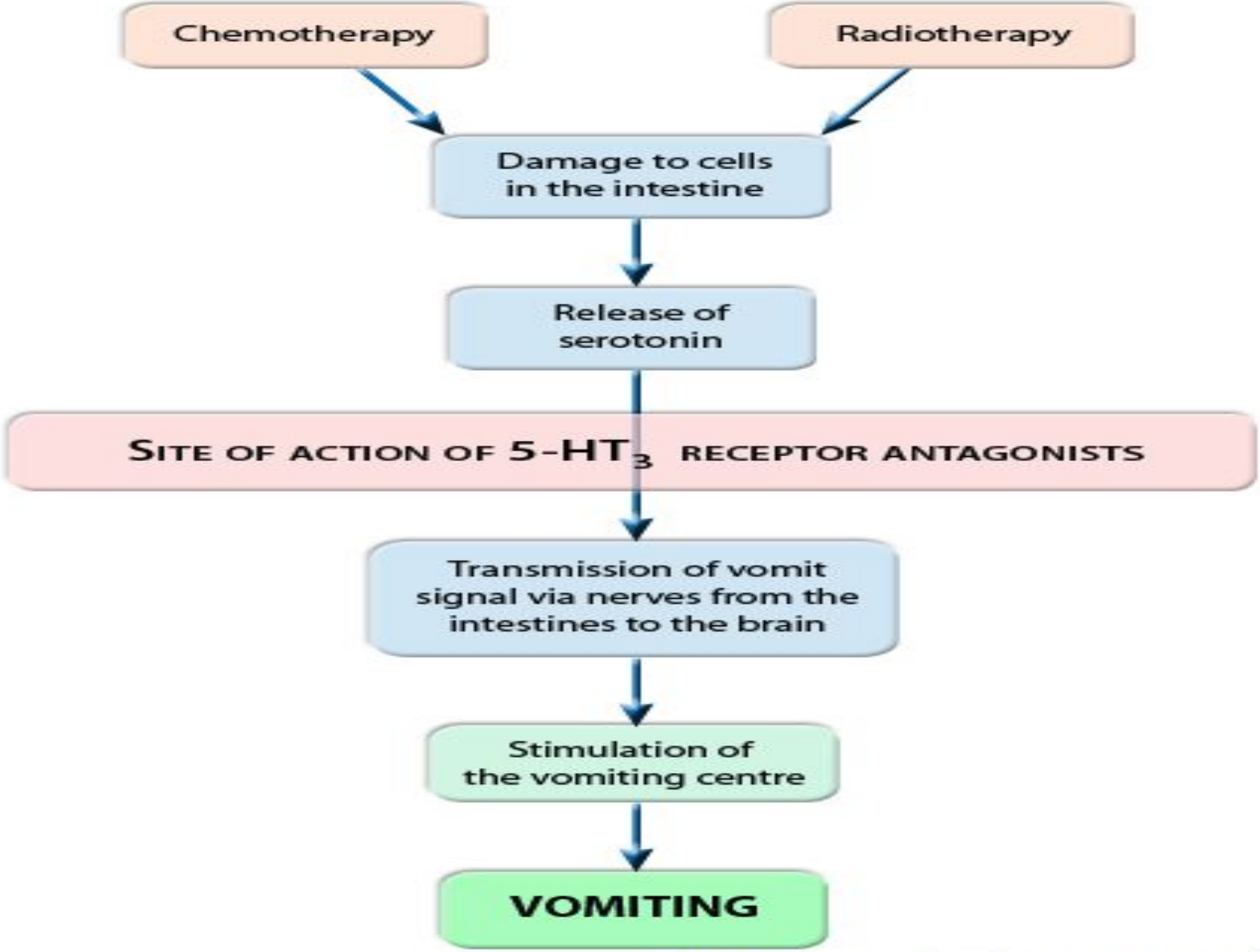
central **5HT3 at the vomiting center , CTZ**-2

Anti cancer (Cytotoxic drug) releases **Serotonin** from the enterochromaffin cells in small intestine and this serotonin activates ,specific receptors in small intestine and CNS to initiate vomiting

Thus blocking 5HT3 receptor will control vomiting by **inhibiting ,serotonin binding to the 5-$HT_3$ receptors**

**So** these drugs are given **before** the chemotherapeutic agents to control .Vomiting

**Side effects:** minimal:including headache, constipation bradycardia


Chemotherapy
Radiotherapy
Damage to cells in the intestine
Release of serotonin
SITE OF ACTION OF 5-HT3 RECEPTOR ANTAGONISTS
Transmission of vomit signal via nerves from the intestines to the brain
Stimulation of the vomiting centre
VOMITING
virtualmedicalcentre.com©

## :Kinetics

These are **important** in treating CINV, because of their superior -1
.**efficacy** and **longer duration** of action

These drugs can be **administered** as a **single** dose **prior** to -2
chemotherapy (**intravenously** or **orally**)

.**Effective** against **all grades** of emetogenic therapy– 3

**Ondansetron** and **granisetron prevent** emesis in **50% to 60%** of -4
.cisplatin-treated patients

They are useful in the **management** of **postoperative nausea** and-5
.vomiting

they are extensively **metabolized by the liver**; however, only – 6
.**ondansetron** requires **dosage adjustments** in **hepatic insufficiency**

.**Excretion** is via the **urine** -7

**QT prolongation** can occur with **high** doses of **ondansetron** and -8
.**dolasetron**

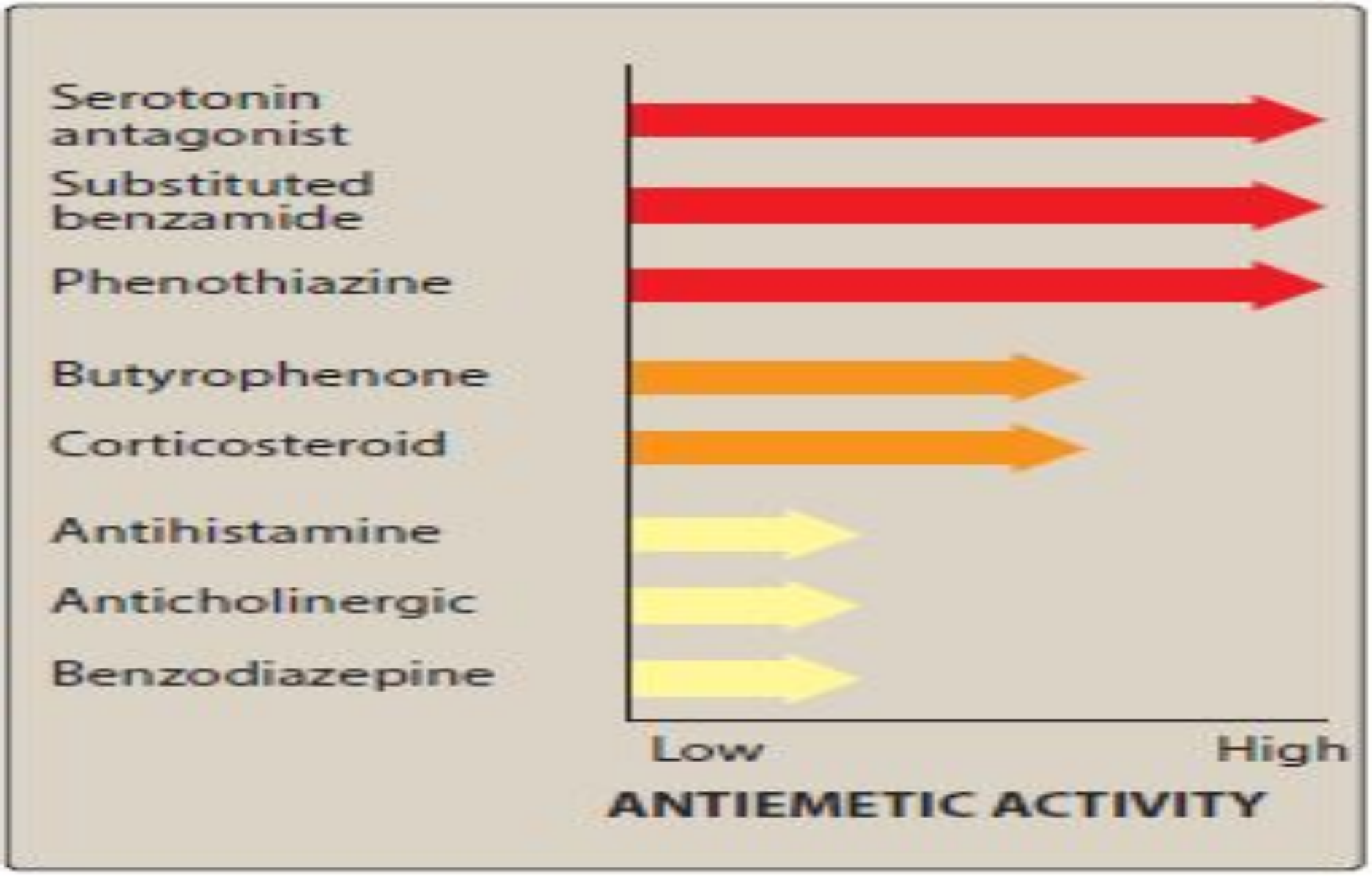



**Figure 31.10**
Efficacy of antiemetic drugs.

**Neurokinin 1 ($NK_1$) antagonists:** Novel class of medications that have antidepressant, anxiolytic, and antiemetic properties. They act by blocking the tachykinin receptor 1 in enteric nervous system, so antagonize the emetic effect of (substance P) peripherally.

..Neurokinin is a natural substance in the brain that causes nausea and vomiting

**examples**

aprepitant

Casopitant

netupitant

Rolapitant

**: Properties**

.aprepitant taken **once** daily, **with or without food** -1

Aprepitant and rolapitant **undergo hepatic metabolism**, by **CYP3A4**. 3- available -2

.as a **capsule** and as an oral **suspension**

used for more than 6 months age -4

**Aprepitant** (**inducer** of **CYP3A4** and CYP2C9). **Rolapitant** (inhibitor of CYP2D6) -5

Fosaprepitant is a **prodrug** of aprepitant, **administered i.v** -6

# Side effects

.tiredness

fatigue

.hiccups

.heartburn

.stomach pain

.diarrhea

.constipation

## :Note

Chemotherapy-induced emesis appears to consist of .acute and delayed phases

he acute phase emesis responds to **5-$HT_3$ antagonists** while **$NK_1$ receptor antagonists** have antiemetic effect in .both **acute** and especially in **delayed** phases of emesis

# Combination regimens

Antiemetic drugs are often **combined to** **increase efficacy** or **decrease toxicity**.

**Corticosteroids**, most commonly **dexamethasone**, **increase antiemetic** activity when given with high-dose **metoclopramide**, a 5-HT3 antagonist, phenothiazine, butyrophenone, or a benzodiazepine.

**Antihistamines**, such as **diphenhydramine**, are often administered in combination with

high-dose **metoclopramide** to **reduce extrapyramidal** reactions **OR** 1- 2. **corticosteroids** to counter **metoclopramide-induced diarrhea**

Addition of a **neurokinin-1** receptor antagonist to a **5-HT3 antagonist** and **dexamethasone** is beneficial in **highly** emetogenic regimens.

# Constipation

**Being constipation** means your bowel **movements are difficult** or happen **less** often than normal. Almost everyone has it at some point .in life, and it's usually not serious

The normal **length** of time **between** bowel movements **varies** widely from person to other

Some people have bowel movements three times a day. Others have .them only once or twice a week

.Going **longer than three** or more days without one is usually **too long**

.**After three days**, the stool or **feces** become **harder** and difficult to pass

## : Drug used in treatment of constipation

Purgative, laxative and evacuant are synonymous, **there are medicines that promote defecation**: including

.**Stool bulking agent (like brane , methylcellulose,psyllium)-1**

**. .....Faecal softeners :like docusate used in hemorrhoid-2**

**:Saline and Osmotic laxative-3**

**A-inorganic salts** this **return** water in the intestinal lumen or it gives as **hypertonic** solution that **draw** water from the .body. Like MgOH and Mg sulphate

**B-Lactulose** **C-Manitol** **D-sorbitol**

**E-**Polyethylglycol(the choice for pediatric)

**Irritant and Stimulant laxative**:cause sensory N**-4**

:stimulation,contra.i in pregnancy & i.obstruction including

**a-Bisacodyl**

**b-Glycerol**

**c-Anthraquinone group include** :Senna , danthron

**.d-Castor oil (induce labour in pregnant women)**

**lubricant laxative**: EX: **Liquid paraffin, glycerin.** It is **inert** **-5**
.mineral oil, **not digested** , promotes the passage of softer feces

**chlorid channel activator**: increases chloride and fluid secretion**-6**
into intestine (EX: lubiprostone)

**Opiod receptor antagonist** (EX: methylnaltrexone)**-7**

**8-5HT4 agonist like tegaserode** ( bs serotonin ↑peristalsis )

**Probiotics are** living microorganisms that improving the balance of **-9**
.bacteria in the body

**Vitamins like vit. C, B5, B9 .-10**

## :Abuse of laxatives

may occur in an illness or in pregnancy or in an individual .who **think** that daily bowel motion is essential for health

**Cessation** of use of laxative may follow by few days constipation **while sufficient material collects to restore .the normal state**

This may **mislead** the patient that constipation return again .and start treatment again

Excessive use of laxatives, especially in old patient, may lead to **sever water and electrolyte depletion and malabsorption**

**Diarrhea:** is having more stools than is normal for that .person

## :Antidiarrheal drugs

:There are 3 types of drugs

## Antimotility drugs-1

act on **bowel muscle** to **delay passage** of the gut contents so allowing time for more water to be absorbed. They are analogs of **meperidine** and have opioid-like actions on the gut, they inhibit Ach and decrease :peristalsis. **EX**

Codeine-1

Diphenoxylate: Side effect: nausea, vomiting, and CNS depression-2 (Diphenoxylate + atropine)

Loperamide (used also for inflam.Bowel dis., short bowel syndrome)-3

These drugs **antagonized** by **Nalaxon**).** Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis

**2-Adsorbant drugs. directly** increase the **viscosity** of the gut contents, they **adsorbing intestinal toxins** or microorganisms and/or by **coating** or protecting the intestinal mucosa. **EX**:

1-Kaolin and Chalk

2- Aluminuim hydroxide

3- Methylcellelose

*they are less effective than antimotility agents. *they can **interfere** with the **absorption** of other **drugs**.

**3-Agents that modify fluid and electrolyte transport** : Bismuth subsalicylate, used for traveler's diarrhea. **decreases fluid secretion** in the bowel. Its action may be due to its salicylate component as well as its **coating action .**

****Octreotide** inhibit the release of certain mediator that increased in certain diarrhea associated with carcinoid tumors

# Inflammatory bowel disease

**Aminosalicylates-1**
**Corticosteroids-2**
**immunosuppressive(6MP,cyclosporine)-3**
**Antibiotics (metronidazole)-4**
**biological agents (infliximab-5)**
**6-Gene therapy**
**7- Alicaforsen (antisense )**

**Note(for your information) :** antisense is a single stranded RNA that is complementary to a protein coding messenger RNA with which it hybridizes, and thereby blocks its translation into protein

| Pharmacological class | Drug examples | Pharmacological effect |
|---|---|---|
| Spasmolytics | Mebeverine, Scopolamine, Dicycloverine, Cymetropium, Pinaverynе | Smooth muscle relaxation through anticholinergic effect or calcium channels blockade |
| Antidiarrhoeal agents | Loperamide<br>Diphenoxylate | Opioid μ and K peripheral receptors agonists<br>-decreasing of gastrointestinal motility<br>-sphincter tone increasing,<br>-additionally antinociception |
| Laxative agents | Lactulosum<br>PEG<br>Lubiprostone | Increasing intestinal osmotic load, decreasing water reabsorption, peristaltic movement acceleration |
| 5-HT4 receptor agonists | Tegaserod<br>Prucalopride<br>Metoclopramide | Increase of intestinal motility, - prokinetic effect in IBS – C, increase gastric emptying, decrease oesophageal reflux. |
| 5-HT3 receptor antagonists | Ondansetron<br>Granisetron<br>Alosetron<br>Tropisetron | Decrease the visceral pain associated with IBS, retard small intestinal and colonic transit, antiemetic and antidiarrhoeic |
| Antidepressive agents | SSRIs,TCA'S, 5HT1A receptor agonists (buspirone) | Improvement in abdominal pain and reduction in other IBS symptoms, like nausea diarrhea, constipation, bloating, or urgency. |
| Anxiolytics | | |

## TREATMENT STRATEGIES FOR IBS

| Non Pharmacologic | Pharmacologic |
| --- | --- |
| ❖Patient education/ Therapeutic relationships<br>❖Lactose restriction<br>❖Gluten restriction<br>❖Fiber supplementation<br>❖Low-FODMAP diet ( FODMAP- Fermentable Oligosaccharides Disaccharides,Monosaccharides And Polyols)<br>❖Regular exercise<br>❖Cognitive behavioural therapy | ❖Antispasmodics<br>❖Probiotics<br>❖Antidepressants ( SSRIs ,TCAs)<br>❖Loperamide ( IBS-D or IBS-M)<br>❖Polyethylene glycol (IBS-C)<br>❖Alosetron (Women, IBS D, IBS-M)<br>❖Lubiprostone (IBS-C)<br>❖Rifamixin (IBS-D)<br>❖Linaclotide (IBS-C) |

# Thank you


Ethics
Doxylamine Succinate, Pyridoxine Hydrochloride
& Folic Acid Gastro-Resistant Tablets
DOXLINE


Domperidone Dispersible Tablets 5 mg