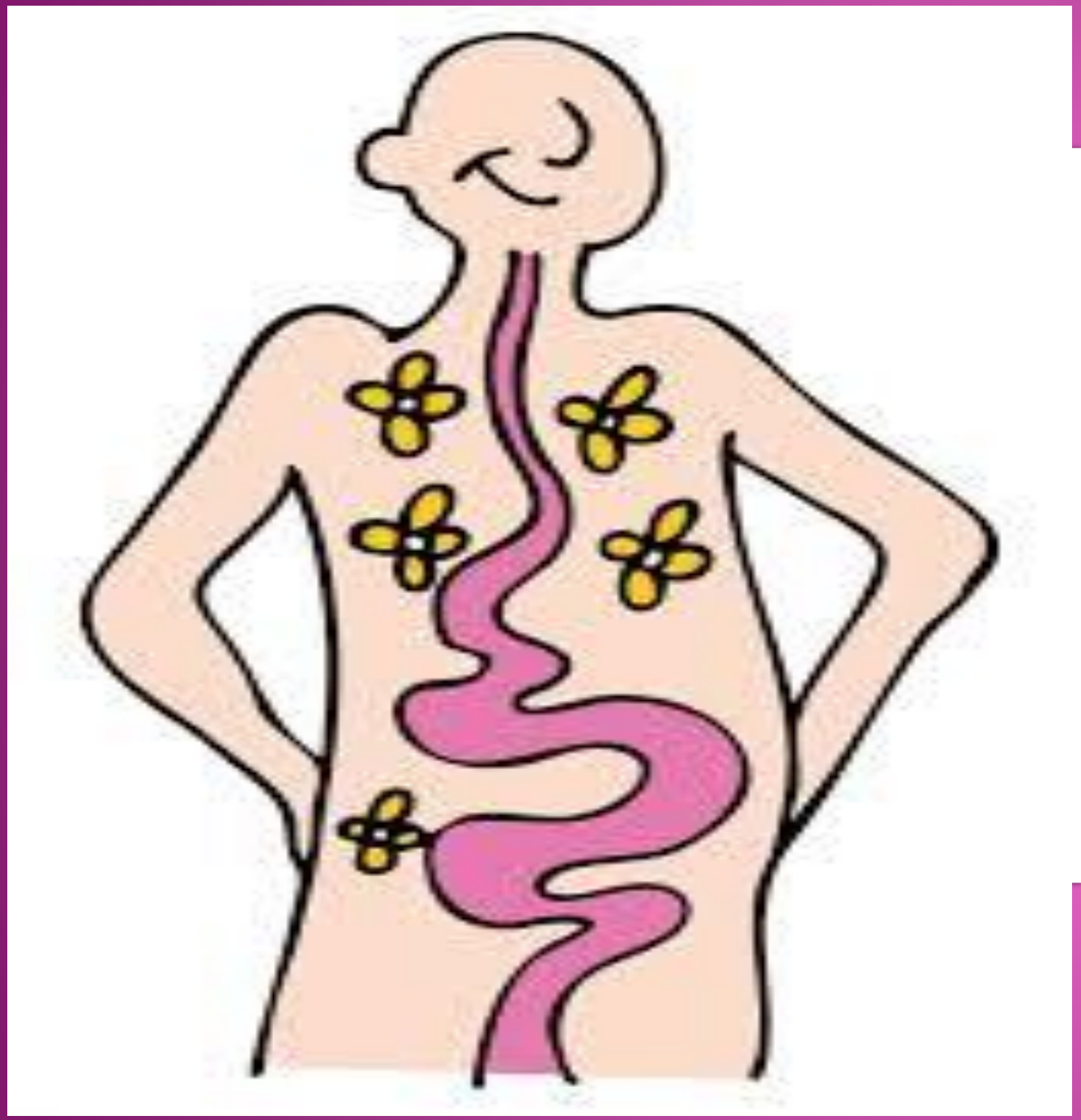


DRUGS AFFECTING GIT MOTILITY

Dr. Heba Ahmed Hassan
Assistant Professor of clinical pharmacology
, Faculty Of Medicine , mutah University

Drugs affecting git motility

INCREASES

- **Prokinetics**

- **laxatives**

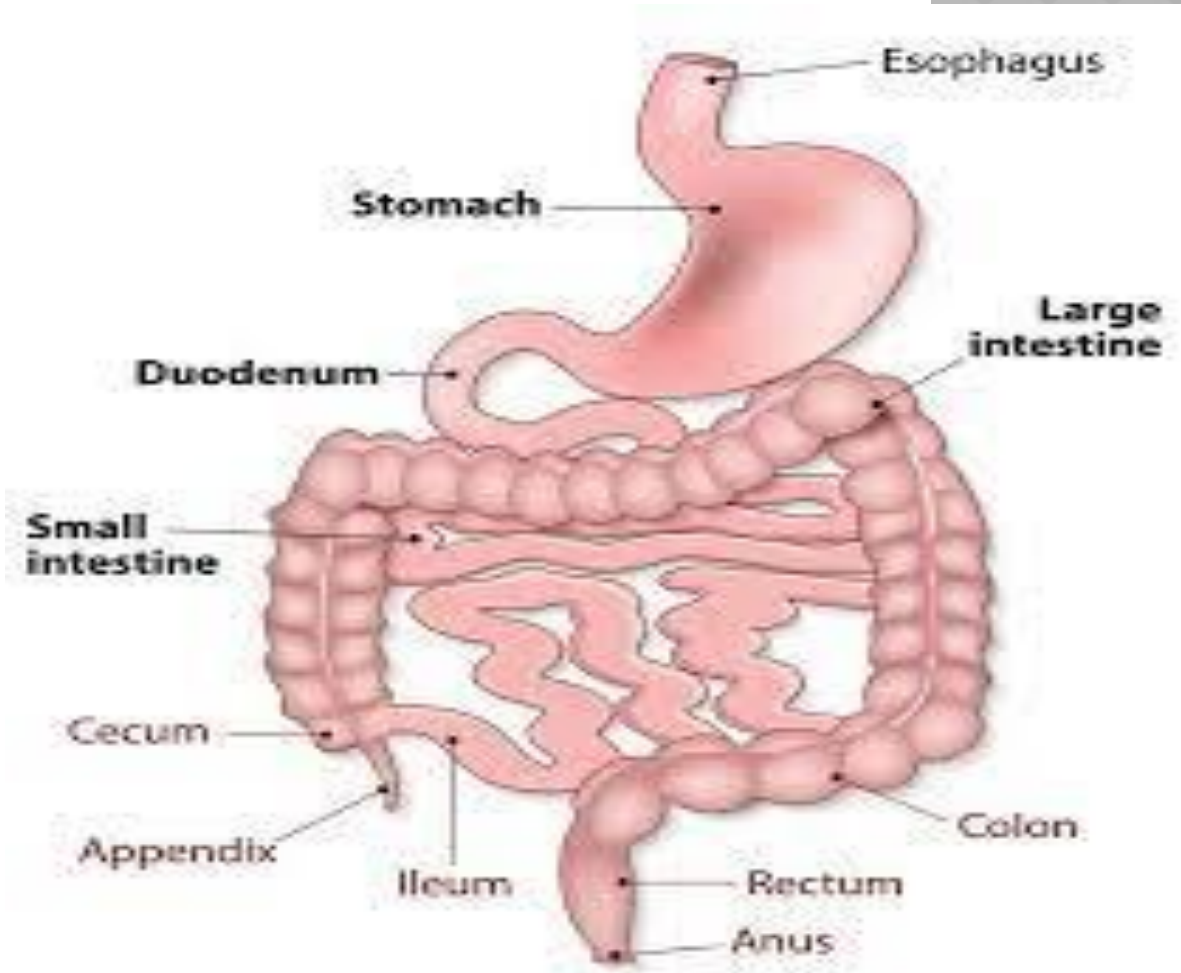
DECREASES

- **antispasmodic**

- **antidiarrheal**

Prokinetic drugs

- **Drugs that selectively stimulate gut motor function.**



1.Dopamine (D_2) antagonists:

- Metoclopramide.
- Domperidone.
- Sulpiride.

2. Serotonin receptor modulators:

- Tegaserod Maleate (Zelnorm), partial 5-HT_4 agonist.
- Cisapride (Proplusid), 5-HT_4 agonist.

3. Muscarinic receptor agonist : Bethanechol

3. Directly stimulate motilin receptors Macrolides

Dopamine (D_2) antagonists: Metoclopramide

Pharmacokinetic:

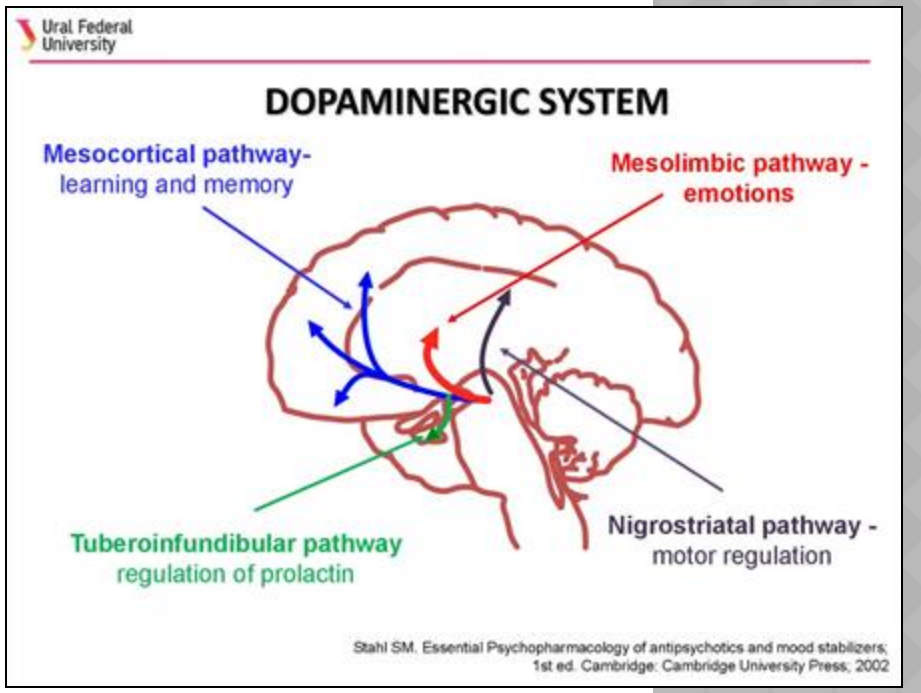
- Rapidly absorbed.
- Half life 4-6 hrs.
- Distributed rapidly to most tissues (bl. brain barrier, placenta, milk).
- Hepatic metabolism (sulfation & glucuronidation).
- Excreted in urine.

➲ Mechanism of action:

- ***D_2 receptor antagonist.***
- Promotes release of Ach from myenteric plexus (***5-HT_4 agonist***)
- ***5-HT3 antagonists.***

Pharmacological effects:

- **1. C.N.S.:** D_2-blocker.
  - Antiemetic. (CTZ)
  - Hyperprolactinemia.
  - Extrapyramidal symptoms. (basal ganglia)
- **2. G.I.T. :** ↑esophageal peristaltic amplitude, ↑ LESP, and enhances gastric emptying (upper digestive tract) but has no effect upon small intestine or colonic motility



➲ Uses:

1. Antiemetic (potent antiemetic).
2. Prokinetic action:

   A. GERD (Gastroesophageal reflux disease) (rarely used).

   B. Gastric hypomotility & postoperative ileus.

   C. To facilitate intubation procedure (nasoenteric feeding tube) and radiological examination of gut.

   D. To empty the stomach before emergency surgery

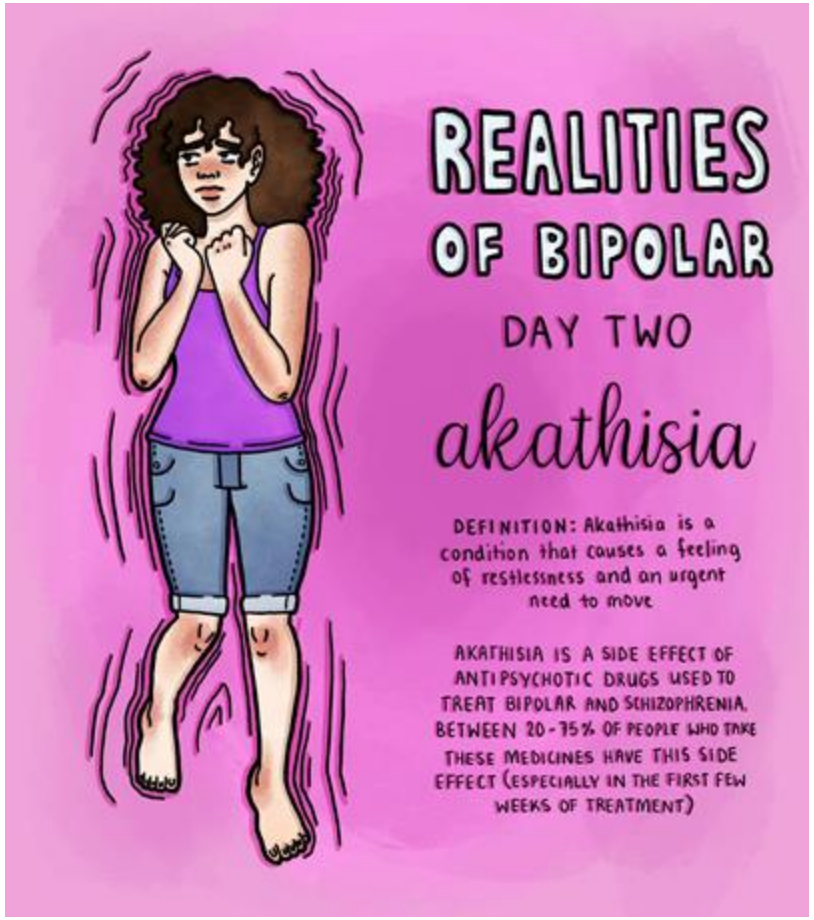
➲ **Side effects:**

1. **Restlessness,** drowsiness, insomnia, anxiety & agitation (10-20%, especially the elderly).
2. **Extrapyramidal effects** (dystonia, akathisia, parkinsonian features).

- 25% in high doses & 5% in long term therapy.
- Tardive dyskinesia, sometimes irreversible (in long term therapy).
- Long term use should be avoided unless absolutely necessary, especially in the elderly.

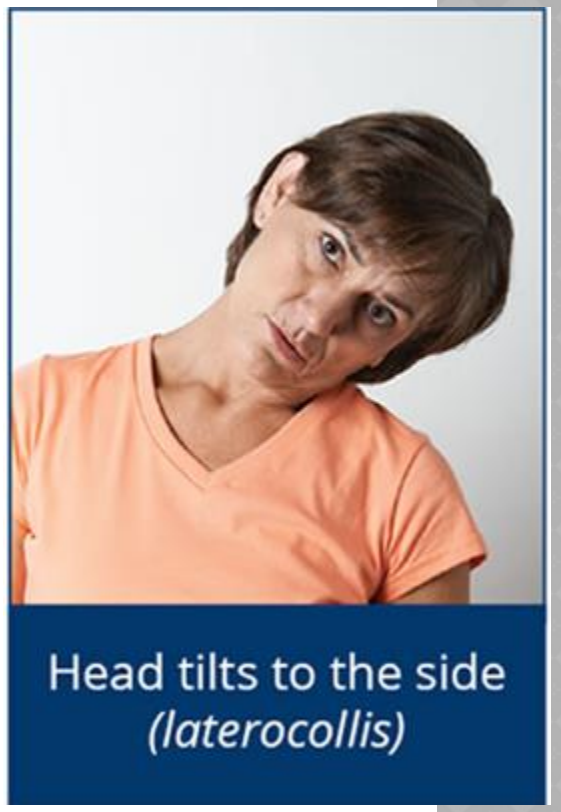
3. Stimulates prolactin release → Galactorrhea, gynecomastia, impotence & menstrual disorders.

Akathisia



Tardive dyskinesia

dystonia



DOMPERIDONE (MOTILIUM)

➲ Pharmacokinetics:

- Rapidly absorbed.
- Half-life 7-8 hrs.
- Excreted in feces.
- ***Rarely crosses bl. brain barrier*** (rare extra-pyramidal reactions).
- Hyperprolactinaemia.

➲ Mechanism of action: D_2-blocker.

➲ Pharmacological effects: As Metoclopramide

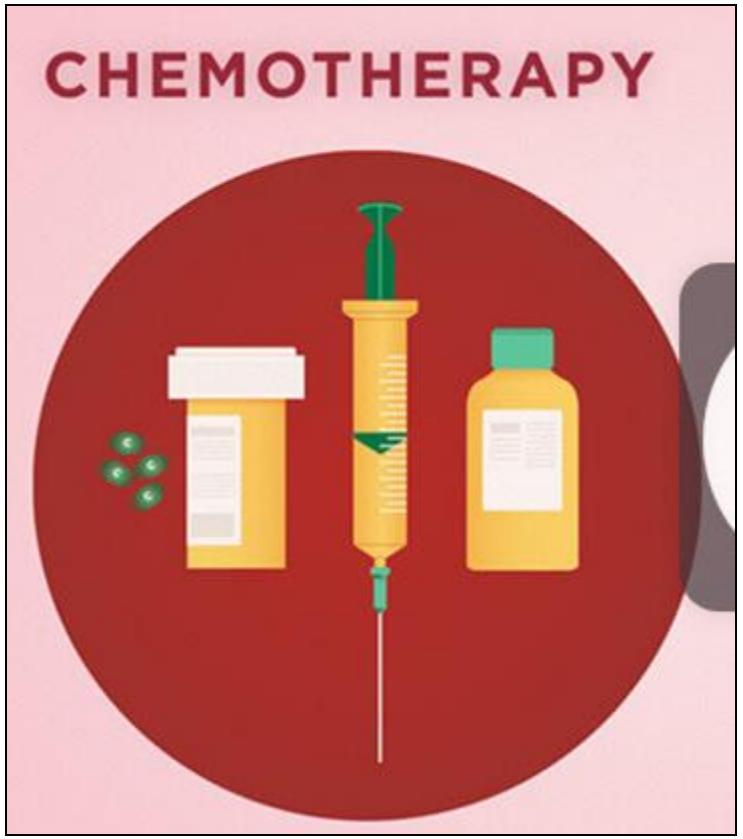
CISAPRIDE (PREPULSIDE)

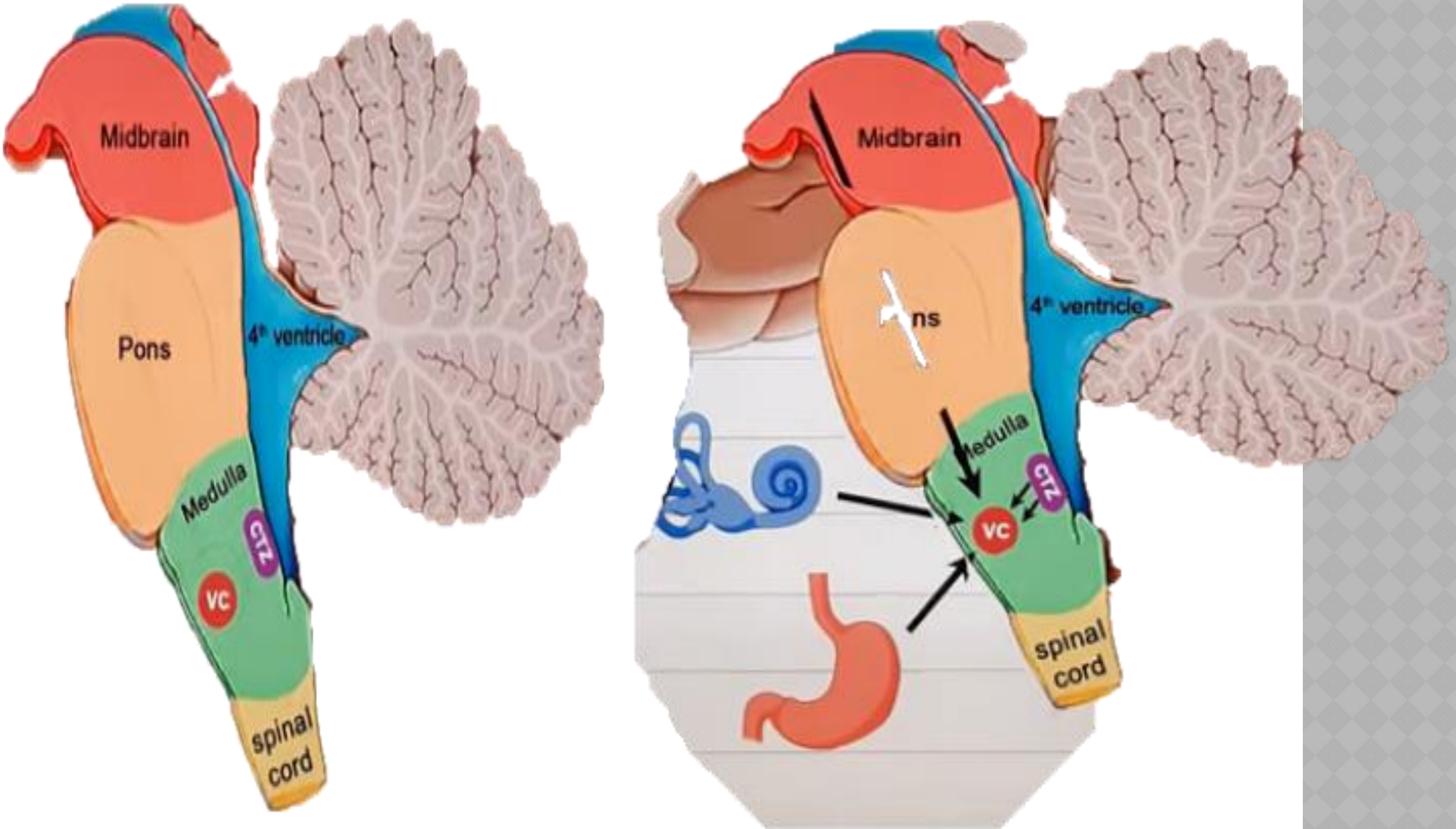
- **Mechanism of action**: Release of myenteric Ach ($5HT_4$ agonist).
- **Pharmacological effect:** Acts on both upper and lower gut.
- **Uses:**
  - Prokinetic.
  - Chronic idiopathic constipation and colonic hypomotility.
- **Side effects:**
  - Diarrhea.
  - Arrhythmia (due to inhibition of cardiac hERG K^+ channels, which results in QT prolongation in some patients).

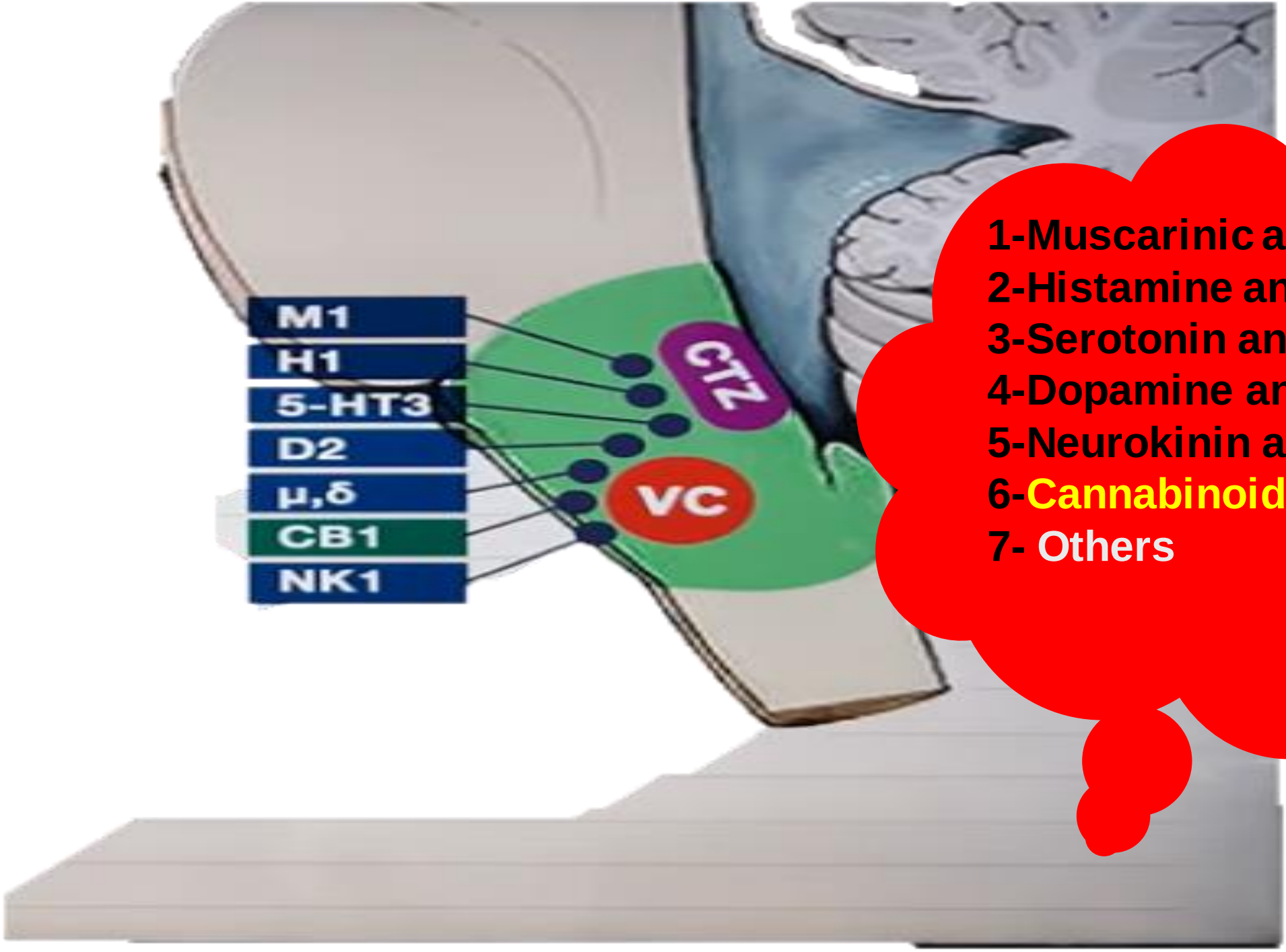
MACROLIDES

- ➲ Directly stimulate **motilin** receptors on G.I.T. smooth muscle and promote the onset of a migrating motor complex.
- ➲ **Uses**:
  - 1. IV erythromycin in gastroparesis, however tolerance rapidly develops.
  - 2. Acute upper GIT hemorrhage to promote gastric emptying of blood prior to endoscopy.

Antiemetics




Midbrain
Pons
4th ventricle
Medulla
CTZ
VC
spinal cord
Midbrain
ns
4th ventricle
Medulla
CTZ
VC
spinal cord



1-Muscarinic antagonist
2-Histamine antagonist
3-Serotonin antagonist
4-Dopamine antagonist
5-Neurokinin antagonist
6-Cannabinoid agonist
7- Others

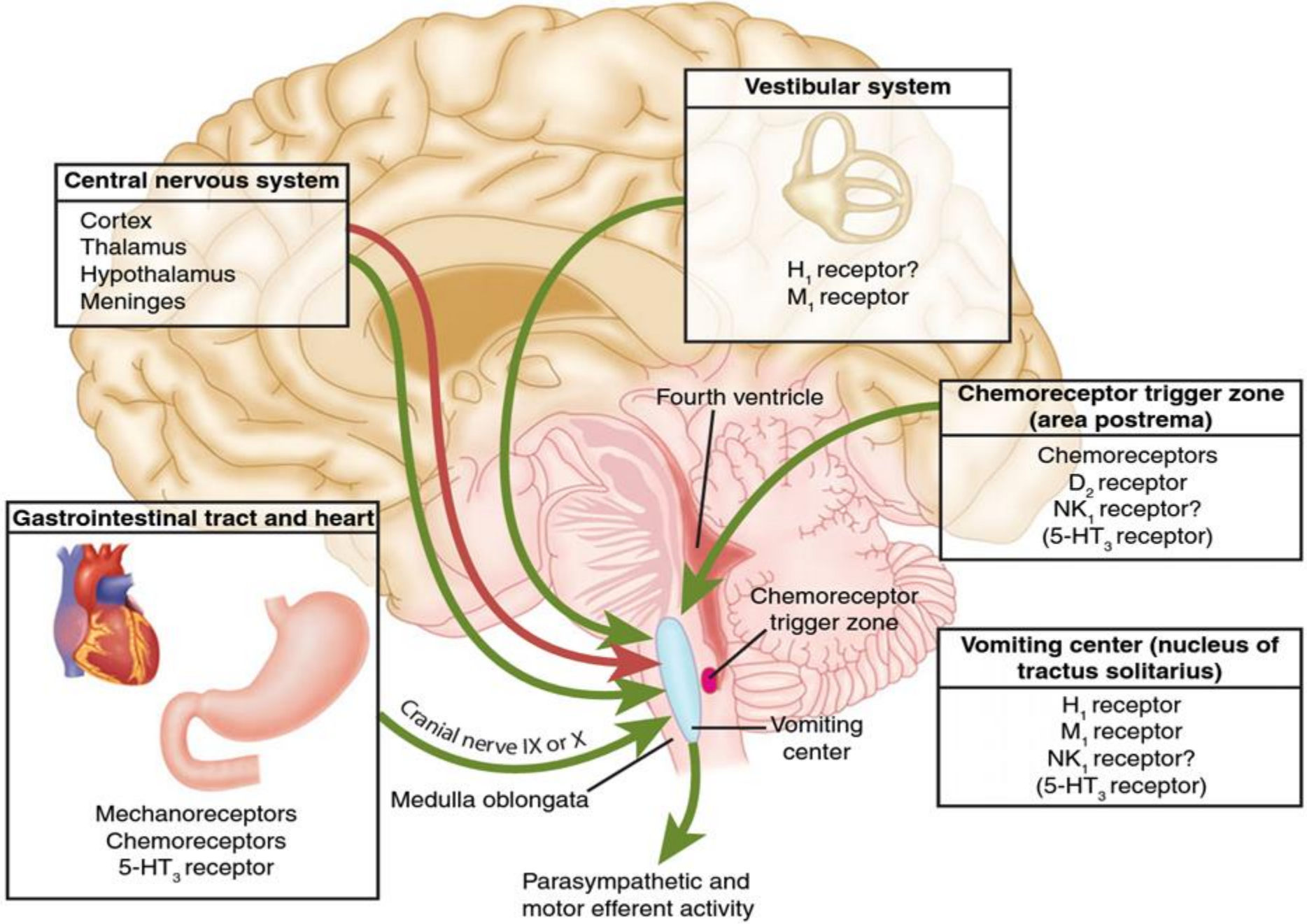
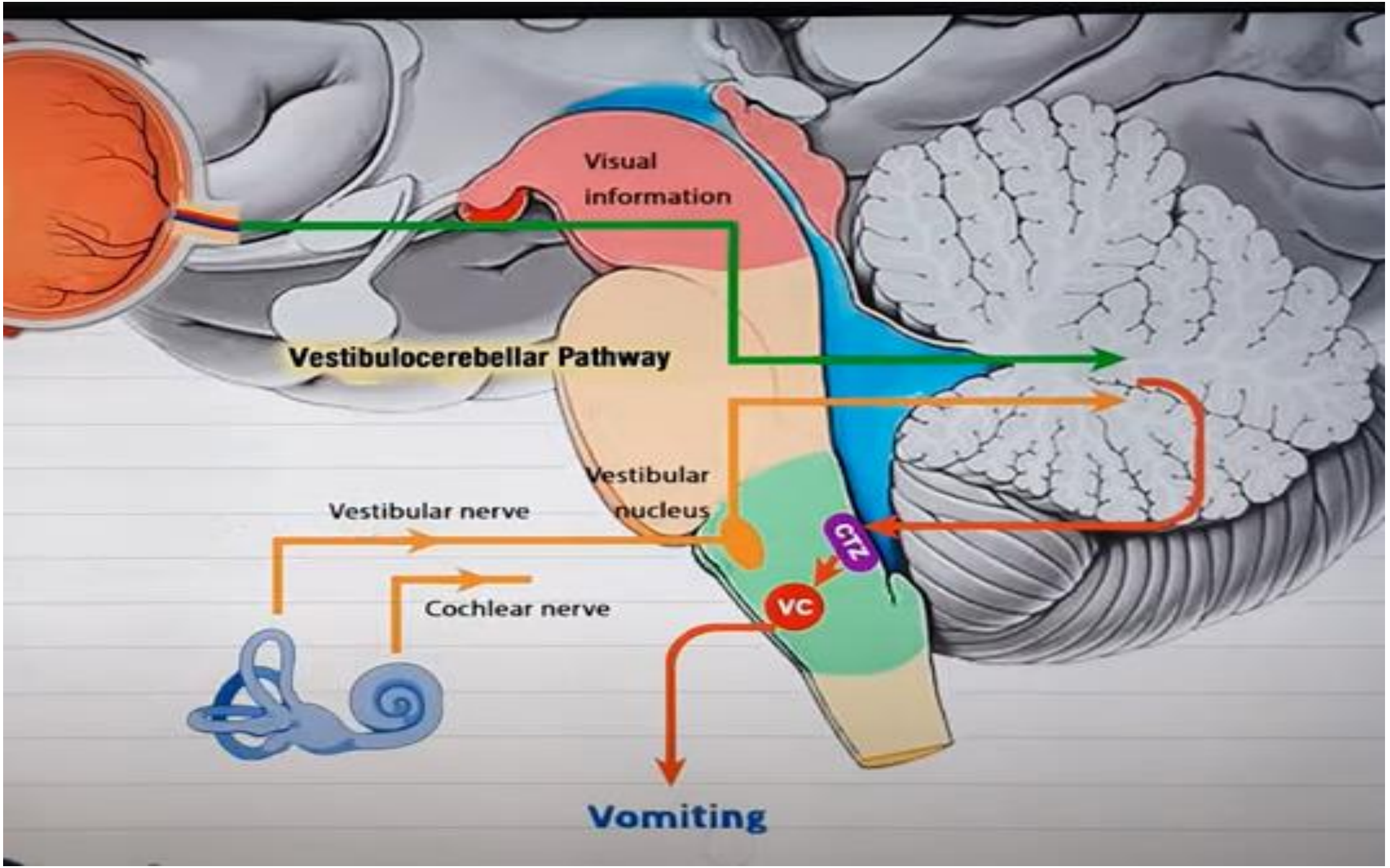


FIGURE 62–6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Modified and reproduced, with permission, from Krakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817.)

motion sickness



MUSCARINIC-RECEPTOR ANTAGONISTS (HYOSCINE)

- Depresses vomiting center.
- Its anti-emetic action peaks 1-2 hrs after ingestion.
- **Duration:** 4-6 hrs.
- **Uses:** Prophylaxis against motion sickness (short duration of action → used in air sickness).
- **Side effects:** Blurred vision and dry mouth.
- **Doses:** 0.6 mg oral or parenteral 30 min before journey.

  Transdermal patch can be used.

Anti-histaminics (H1 antagonists)

- **Diphenhydramine, Doxylamine, Meclizine and Cyclizine**
- **Peak anti-emetic effect:** 4 hrs.

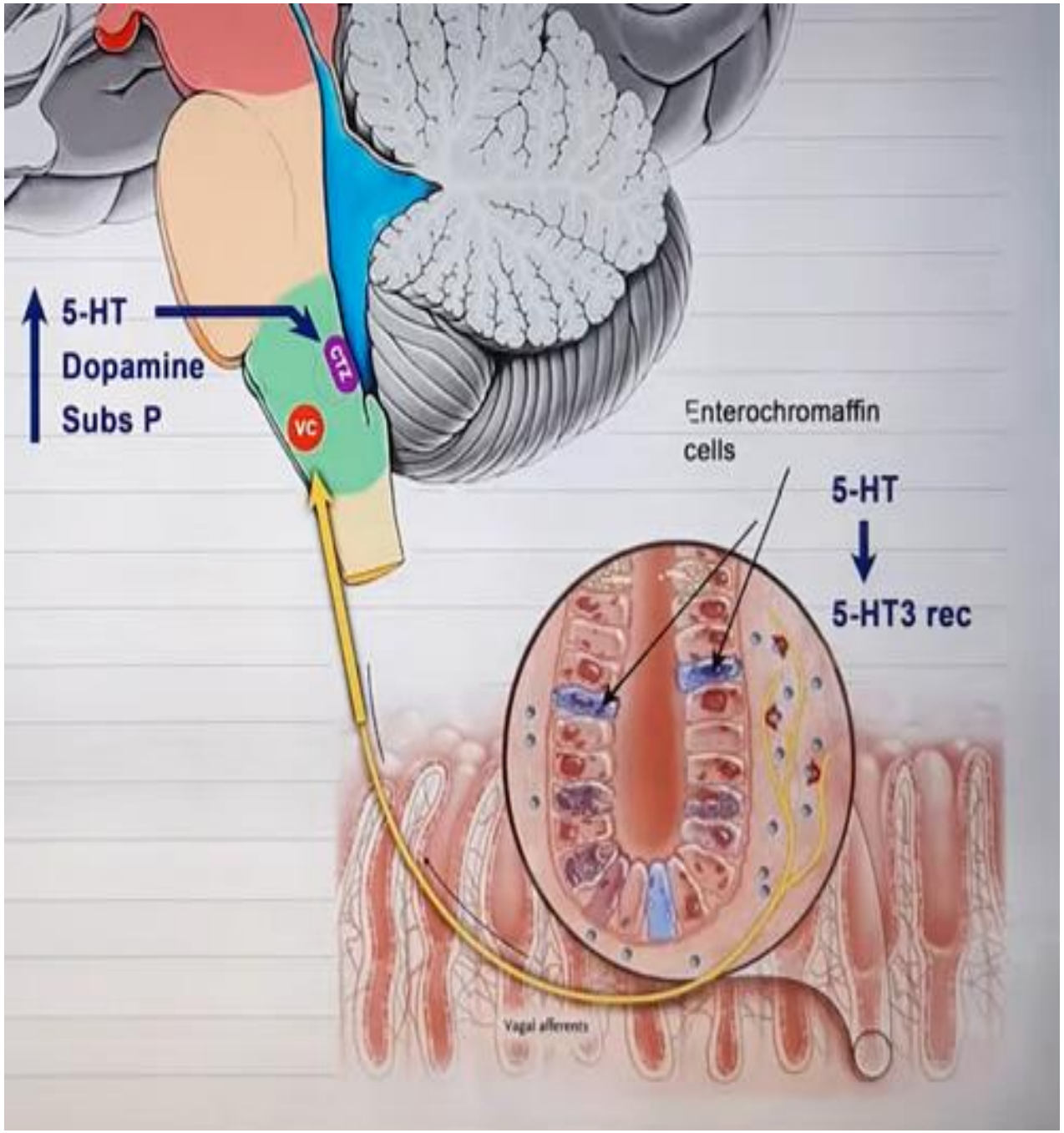
Duration: 24 hrs.

Uses: weak antiemetic.

1. Prophylaxis against motion sickness (Meclizine).

➢ Long duration of action → used in **sea sickness**

2. Diphenhydramine is used in conjunction with other anti-emetics for treatment of vomiting due to chemotherapy



Chemotherapy drugs

↓

Damage to cells that line the intestines

↓

Release of serotonin

↓

Activation of nerves which transmit impulses to the brain

↓

Vomiting centre

↓

Vomiting reflex

chemotherapy or radiotherapy induced vomiting

SEROTONIN ($5HT_3$) ANTAGONISTS

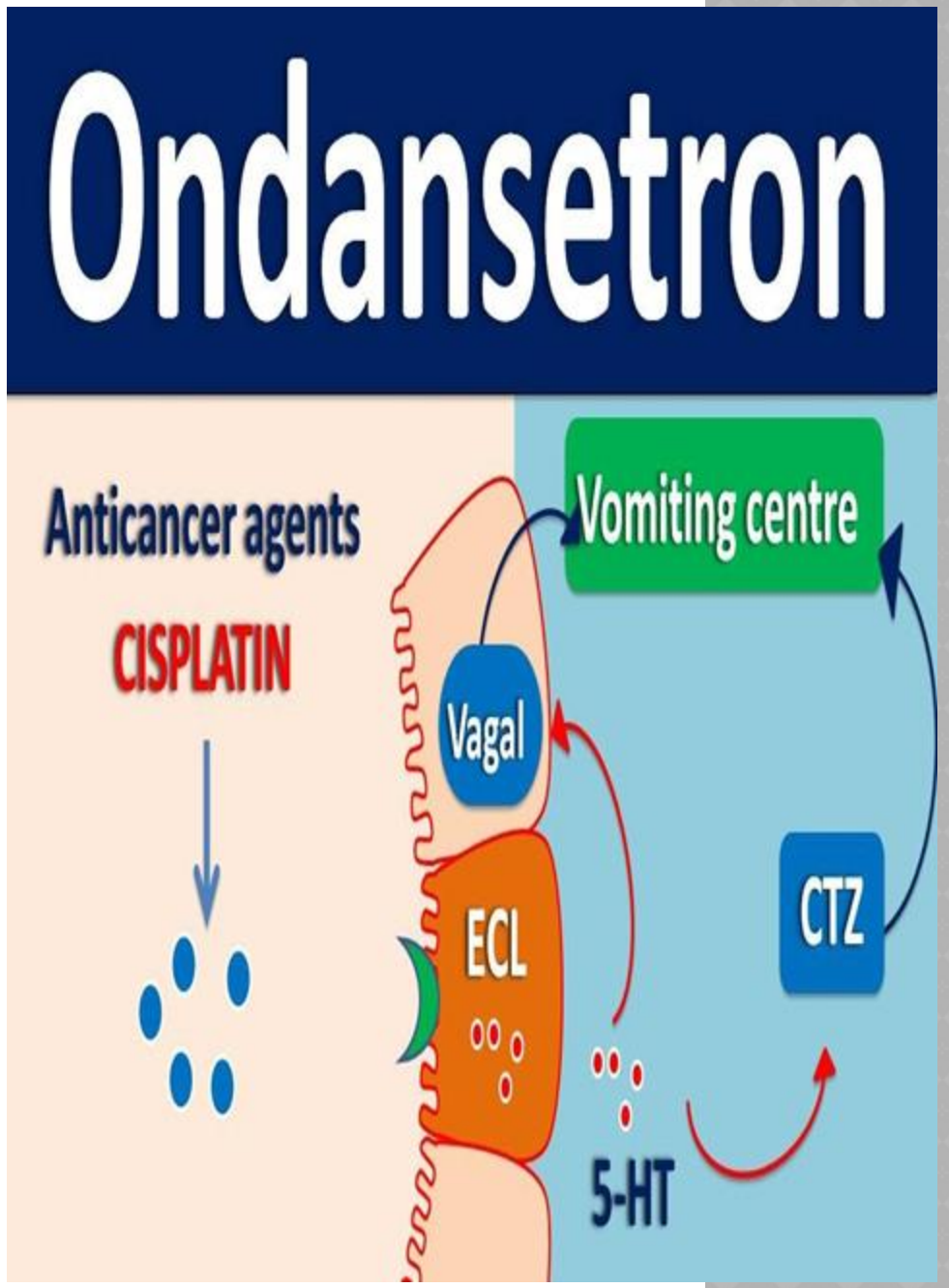
- Ondansetron• Granisetron • Dolasetron Palonosetron

Pharmacokinetics :

- **A:Ondansetron, granisetron & dolasetron** have a serum half-life of 4-9 hours and may be administered once daily by oral or IV routes.
- **Palonosetron (IV)** has greater affinity for 5-HT_3receptors & long $t_{1/2}$ (40hrs).
- **M:**All four drugs undergo extensive hepatic metabolism.
- **E:**They are eliminated by renal and hepatic excretion. However, ***dose reduction is not required*** in geriatric or renal insufficiency.
- ***Dose reduction may be required*** with ondansetron in patients with hepatic insufficiency.

Mechanism of action:

- Potent antiemetic.
  - ***Central*** 5-HT_3 receptors blockade.
  - ***Peripheral*** 5-HT_3 receptors blockade on extrinsic intestinal vagal and spinal afferent nerves → inhibit unpleasant visceral afferent sensation including nausea, bloating and pain.



THERAPUTIC USES:

1- Chemotherapy-induced nausea & vomiting:

- ***Primary agents*** for the prevention of acute nausea and vomiting.
- These drugs are most effective when given as a single dose by I.V. injection 30 minutes prior to administration of chemotherapy.
- Although effective as single agents, their efficacy is enhanced by combination therapy with a corticosteroid (dexamethasone) and Neurokinin (NK1) receptors antagonists.
- when used alone, these drugs have little or no efficacy for the prevention of delayed nausea and vomiting (occurring > 24 hrs. after chemotherapy).

2.Postoperative & postradiation nausea & vomiting

SIDE EFFECTS: WELL-TOLERATED AGENTS

- 1.Headache, dizziness & constipation.
- 2.All four agents cause a small but statistically significant prolongation of the QT interval, but this is most pronounced with dolasetron (Dolasetron should not be administered to patients with prolonged QT or with other medication that may prolong the QT interval).

Dopaminergic (D2) antagonists

Metoclopramide (Primperan). Domperidone (Motilium). Sulpiride (Dogmatil).

Mechanism of action: D_2-blocker; centrally in CTZ & Peripherally in stomach.

Uses: Vomiting due to uremia, radiation sickness, acute viral gastroenteritis, cancer chemotherapy, narcotic analgesics & estrogens

CANNABINOIDS

- Nabilone
- Dronabinol

- The major psychoactive chemical in marijuana.
- **Side effects:** euphoria, dysphoria, sedation, hallucination, dry mouth and increased appetite.

CORTICOSTEROIDS

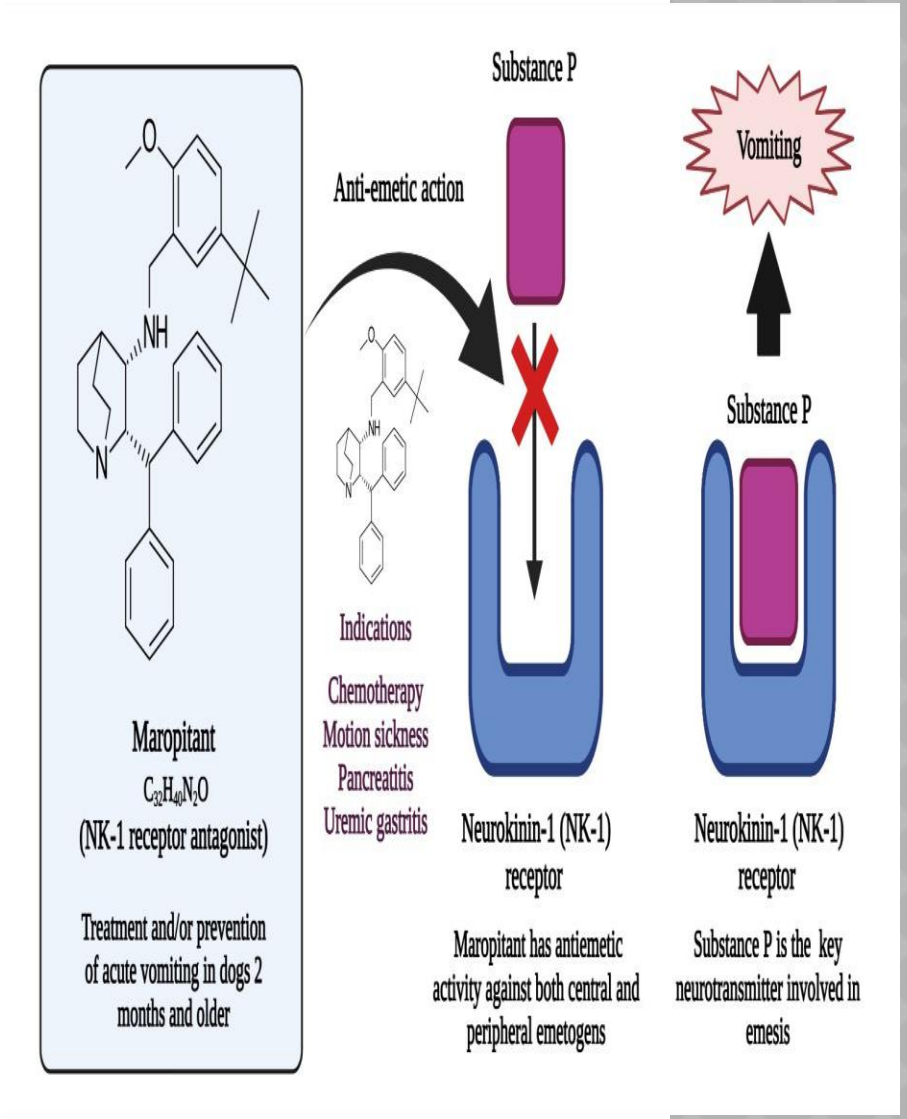
- **Dexamethazone**
- **Methylprednisolone**

- These agents enhance the efficacy of 5-HT_3 receptor antagonists for prevention of acute & delayed nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy.
- **Dose**: Dexamethasone (8-20 mg I.V.) before chemotherapy, followed by 8mg/d orally for 2-4 days.

NEUROKININ (NK1) RECEPTORS ANTAGONISTS

- **Aprepitant (oral)**
- **Fosaprepitant (I.V.)**

- Central blockade NK_1 receptor in CTZ.
- **Pharmacokinetics:**
- Bioavailability 65%
- Half-life: 12 hrs.
- Metabolized by the liver, primarily by the CYP3A4



Clinical uses:

- Combined with 5-HT_3 antagonists & corticosteroids for the prevention of acute & delayed nausea and vomiting from highly emetogenic chemotherapeutic regimen.

Side effects: Fatigue, dizziness & diarrhea.

Drug interactions:

- Inhibit the metabolism of other drugs metabolized by CYP3A4 (e.g. ketoconazole, ciprofloxacin, clarithromycin, verapamil, quinidine).

BENZODIAZEPINES

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

- Used prior to the initiation of chemotherapy to **reduce anticipatory vomiting** or vomiting **caused by anxiety.**

Vomiting of pregnancy:

Treated with vitamin B6 (Pyridoxine).


Thank you