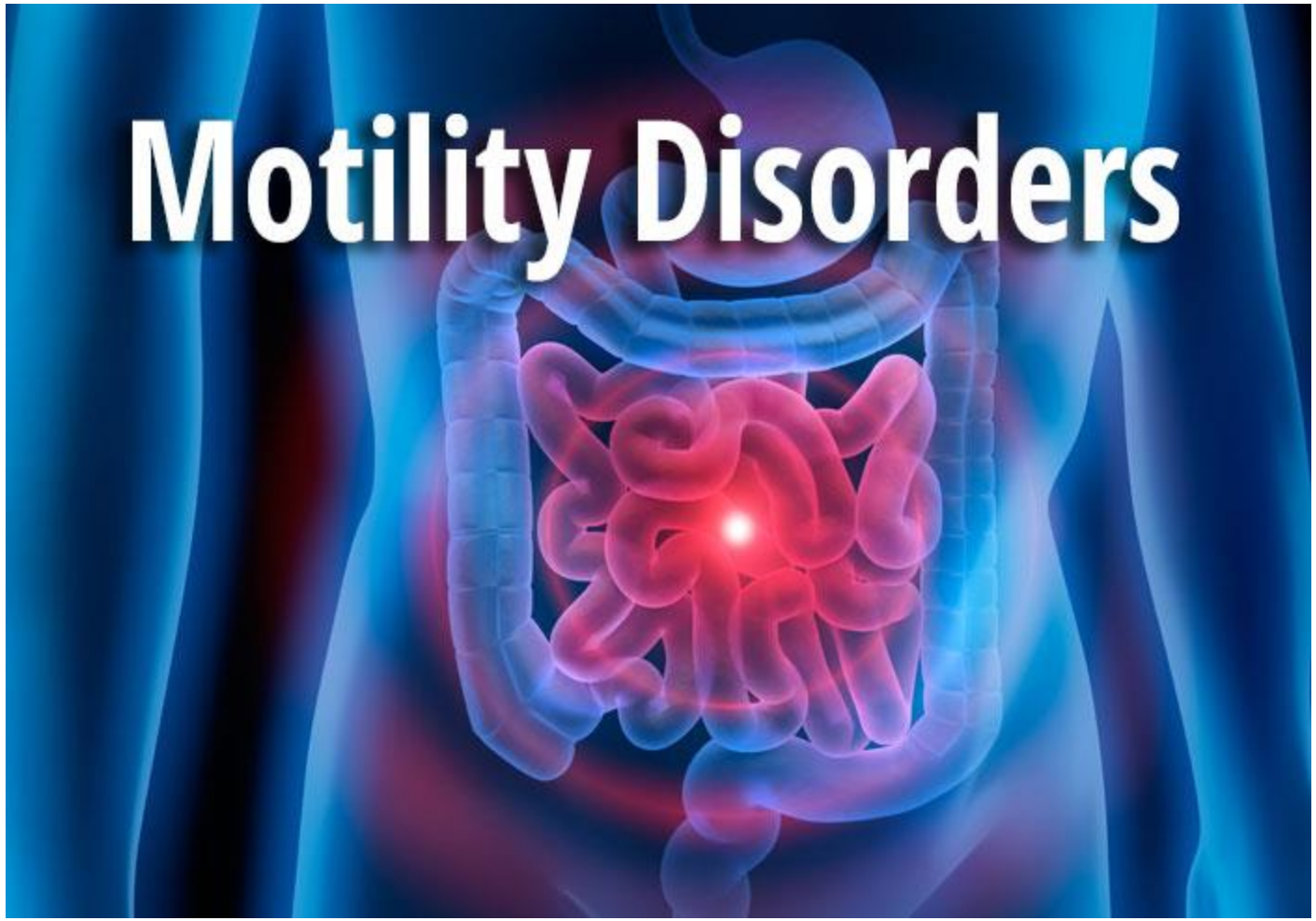
Prokinetic and Antiemetic drugs

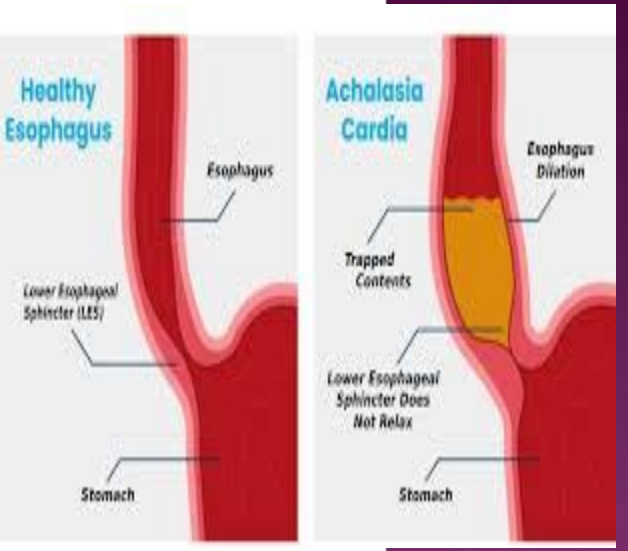
Presented by
Dr. Heba Ahmed Hassan
Assistant Professor of clinical pharmacology

Pharmacology Department, Faculty Of Medicine , Mutah University

Prokinetic drugs

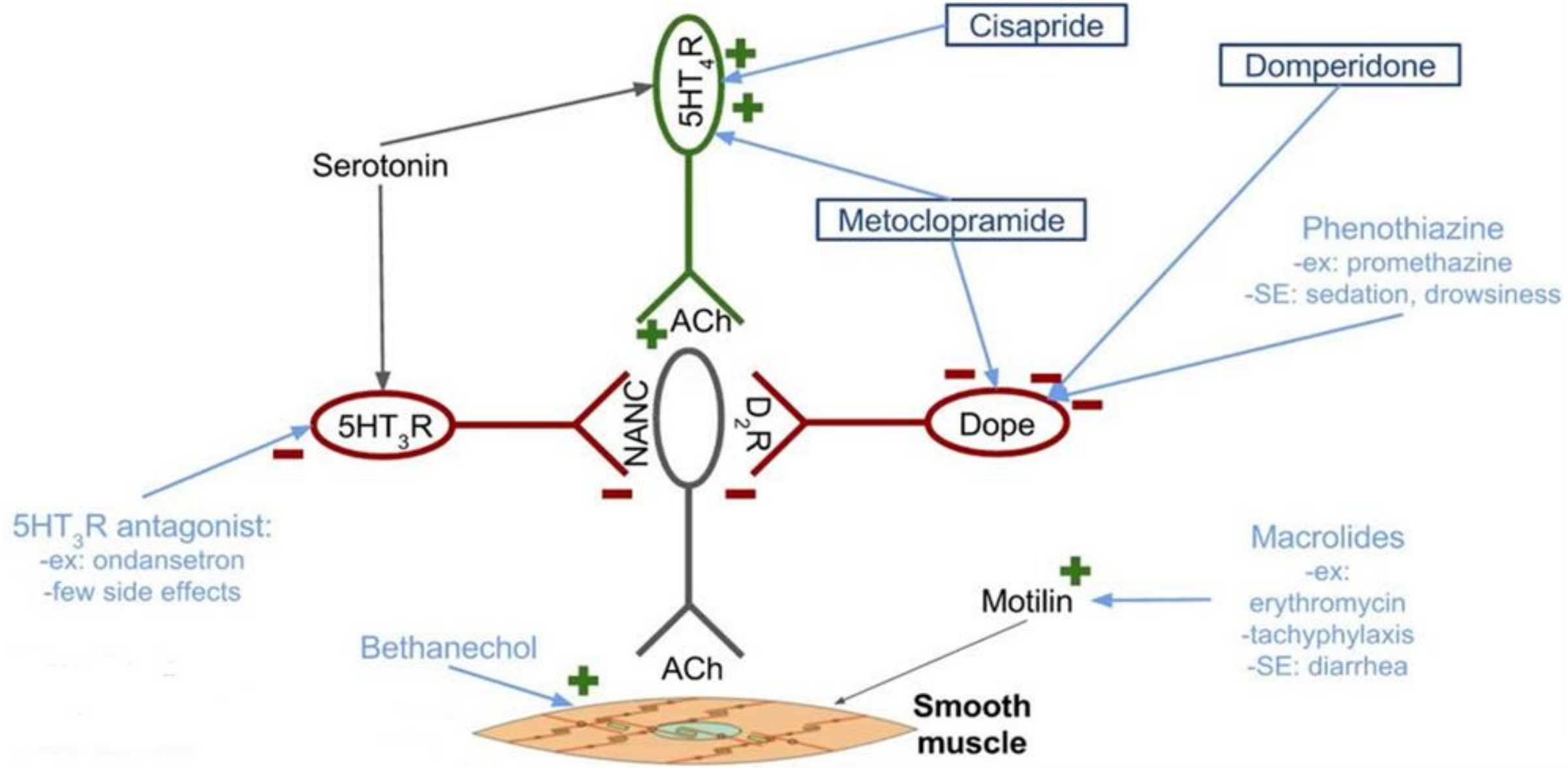


PROKINETIC AGENTS



- Drugs that selectively stimulate gut motor function.
- **Motility disorders of the GIT:**
  - Achalasia of the esophagus
  - Drugs that improve gastric emptying may be helpful for gastroparesis and postsurgical gastric emptying delay.
  - Agents that stimulate the small intestine may be beneficial for postoperative ileus or chronic intestinal pseudo-obstruction.
  - Agents that enhance colonic transit may be useful in treatment of constipation

ANTIEMETICS and PROKINETICS



Dopamine (D_2) antagonists:

Metoclopramide Domperidone Sulpiride.

Serotonin receptor modulators:

Tegaserod Cisapride Prucalopride

Cholinomimetic agents:

Bethanechol stimulates M_3 (now seldom used). Neostigmine I.V. 2 mg. drug of choice (Acute Colonic Pseudo-obstruction).

Directly stimulate motilin receptors

Macrolides

METOCLOPRAMIDE (PRIMPERAN)

❑ Pharmacokinetic:

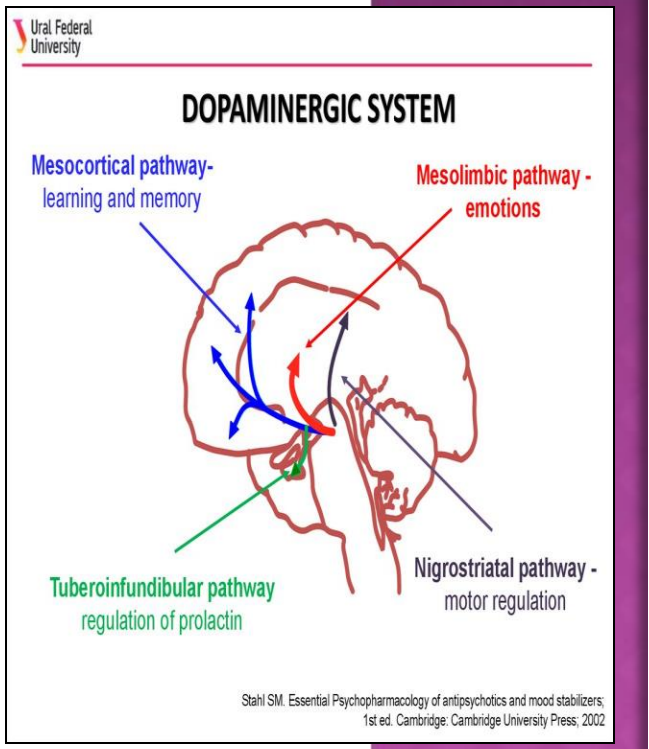
- Rapidly absorbed.
- Half life 4-6 hrs.
- Distributed rapidly to most tissues (bl. brain barrier, placenta, milk).
- Hepatic metabolism (sulfation & glucuronidation).
- Excreted in urine.

❑ 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
   E. Hiccough.

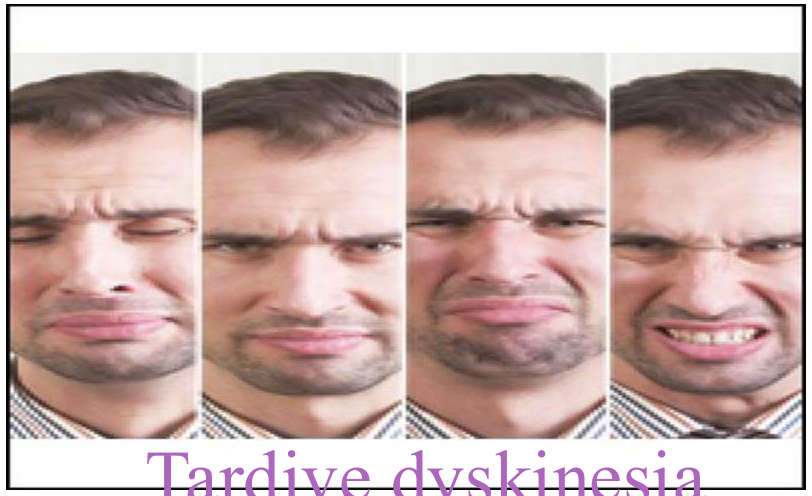
➲ Side effects:

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.



Tardive dyskinesia

➲ **Doses**: 10-20 mg orally or I.V. every 6hrs.

➲ **Drug interactions**:

1. Short transit time in the stomach →↑ absorption of paracetamol & ↓ absorption of digoxin.
2. Potentiates action of neuroleptics (Antipsychotics)
3. Antagonizes action of antiparkinsonian drugs.

DOMPERIDONE (MOTILIUM)

- ➲ **Pharmacokinetics:**
  - Rapidly absorbed.
  - Excreted in feces.
  - Half-life 7-8 hrs.
- ➲ **Mechanism of action**: D_2-blocker.
- ➲ **Pharmacological effects:** As Metoclopramide.
- ***Rarely crosses bl. brain barrier*** (rare extra-pyramidal reactions).
- Hyperprolactinaemia.

CISAPRIDE AND PRUCALOPRIDE

- ➲ **Mechanism of action:** ($5HT_4$ agonist)➥Release of myenteric Ach.
- ➲ **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).

N.B:

Prucalopride: Does NOT significantly block hERG K^+ channels, Very low risk of QT prolongation.

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.

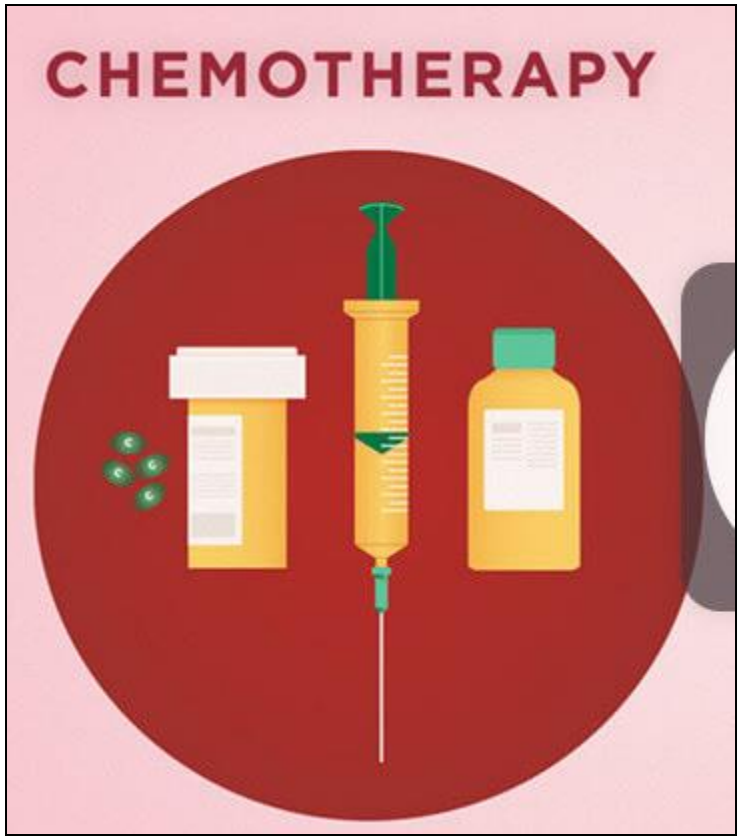
(LUBIPROSTONE)

- Acts by stimulating **chloride channel** opening in the intestine → ↑ liquid secretion into the intestine & shortens intestinal transit time.
- Used in **chronic constipation**
- **USED IN IBS WITH CONSTIPATION**

LINACLOTIDE

- ❑ **Activates guanylate cyclase-C (GC-C) receptors** on intestinal epithelial cells, ↑ intracellular cGMP↑ secretion of Cl^- and HCO_3^- into intestinal lumen with **Reducing Visceral pain sensation**
- ❑ Uses: 1. Chronic Idiopathic Constipation (CIC)
- ❑ 2. Irritable Bowel Syndrome with Constipation (IBS-C), **Especially useful because it Relieves both constipation + abdominal pain**

Antiemetics



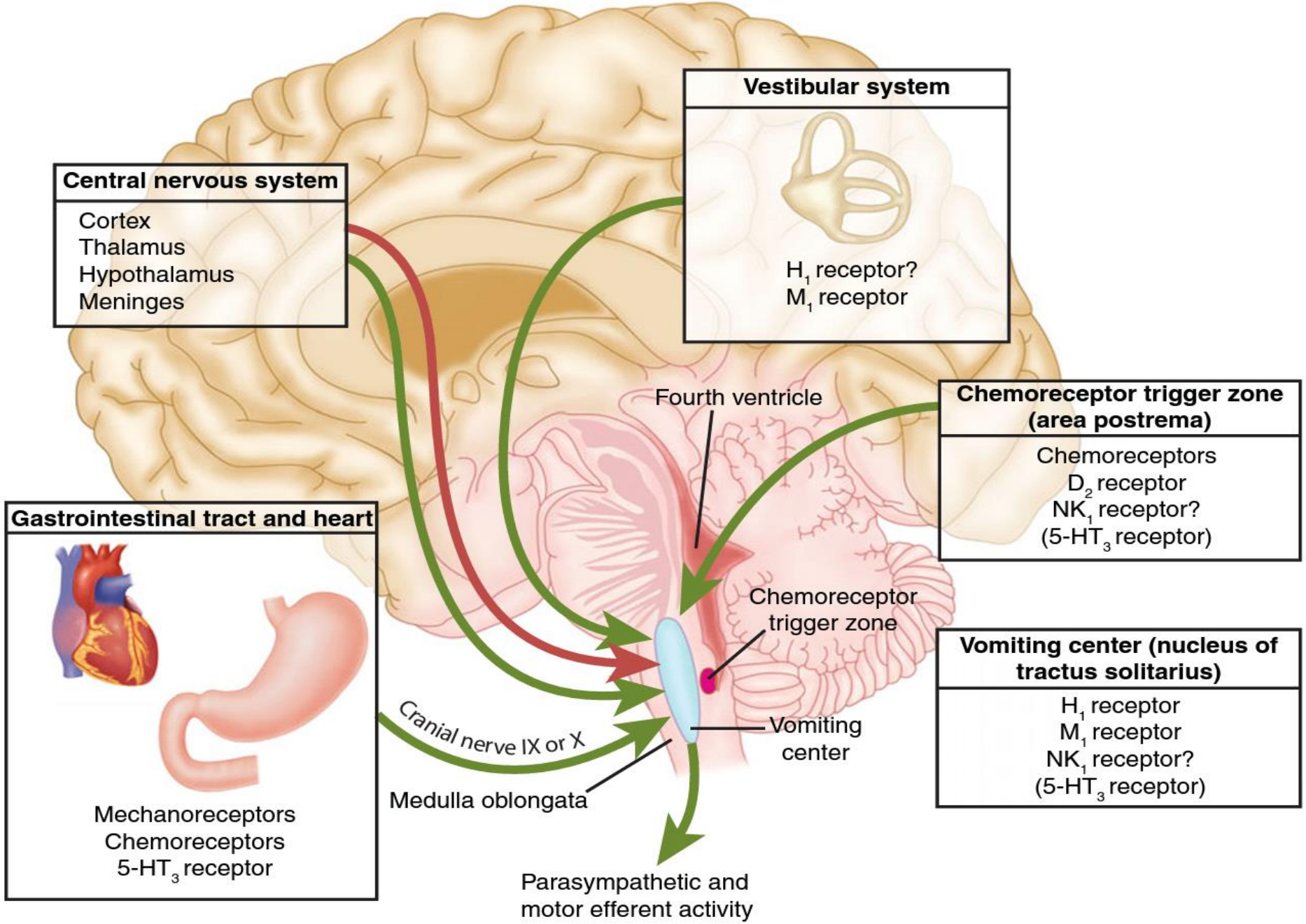
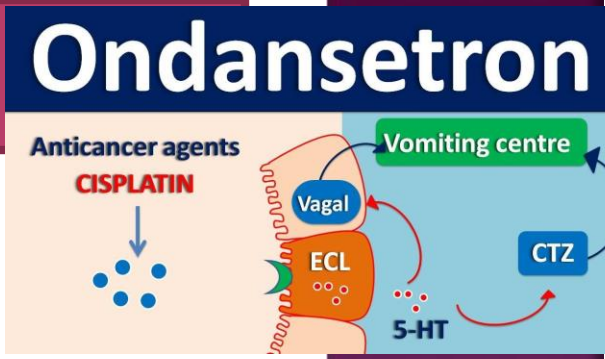


FIGURE 62–6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Modified and reproduced, with permission, from Krakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817.)

1. Anti-histaminics (H1) antagonists)
2. Muscarinic-receptor (M1)antagonists
3. Neurokinin (NK1) receptors antagonists
4. DOPAMINREHGIC (D2) ANTAGONIST
5. Serotonin ($5HT_3$) antagonists
6. Cannabinoids
7. CORTICOSTEROIDES
8. Benzodiazepines
9. VOMITING WITH PREGNANCY

1- SEROTONIN ($5HT_3$) ANTAGONISTS



- Ondansetron, Granisetron, Dolasetron, Palonosetron

Pharmacokinetics :

- **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).
- All four drugs undergo extensive hepatic metabolism.
- 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 wi
  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.

Clinical uses:

1- Chemotherapy-induced nausea & vomiting:

- ***Primary agents*** for the prevention of **acute** nausea and vomiting < 24 hrs**???**.
- When used alone, these drugs have little or no efficacy for the prevention of **delayed** nausea and vomiting (occurring > 24 hrs. after chemotherapy)**???**.
- These drugs are most effective when given as a single dose by I.V. injection 30-60 minutes prior to administration of chemotherapy in the following doses: ondansetron (8mg), granisetron (1mg), dolasetron (100 mg) or palonosetron (0.25 mg).
- A single oral dose given 1 hr. before chemotherapy may be equally effective in the following regimens: ondansetron (8 mg twice daily or 24 mg once), granisetron (2mg), dolasetron (100mg).
- Although effective as single agents, their efficacy is enhanced by combination therapy with a corticosteroid (dexamethasone) and Neurokinin (NK1) receptors antagonists (delayed nausea and vomiting).

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 (block cardiac potassium channels, hERG (IKr) K^+ channels), 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).

2- DOPAMINERGIC (D2) ANTAGONISTS

a. Phenothiazines
b. metoclopramide (Primperan).
c. Domperidone (Motilium).
d. 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

3- 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.

4- ANTI-HISTAMINICS (H1) ANTAGONISTS)

A- Ethanolamine	**Marked sedation & Anti-muscarinic effects.** • **Diphenhydramine.** • **Dimenhydrinate (Dramamine).** • **Doxylamine (in Bendectin).**
B- Phenothiazines	Marked sedation & Anti-muscarinic effects. • promethazine
C- Piperazine	Slight sedation. • Cyclizine (Maxine). • Meclizine (Bonamine). • Cinnarizine.

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

5- CANNABINOIDS

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

6- 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.

7- BENZODIAZEPINES

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

8- 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).

9. Vomiting of pregnancy

- ❑ Treated with vitamin B6 (Pyridoxine) + Doxylamine. 1st line (safe)
- ❑ Ondansetron → effective but cautious use
- ❑ Steroids → only severe cases
- ❑ Supportive treatment


Thank you