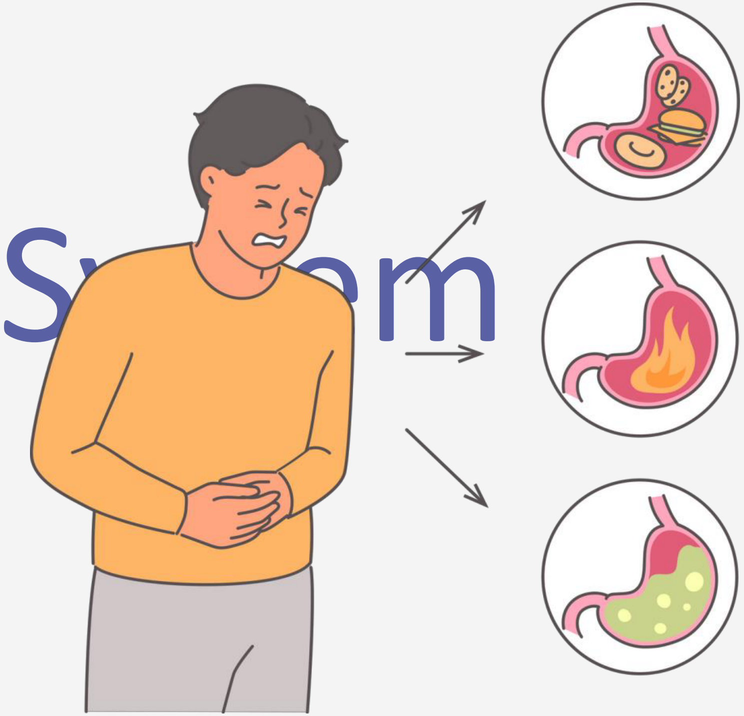
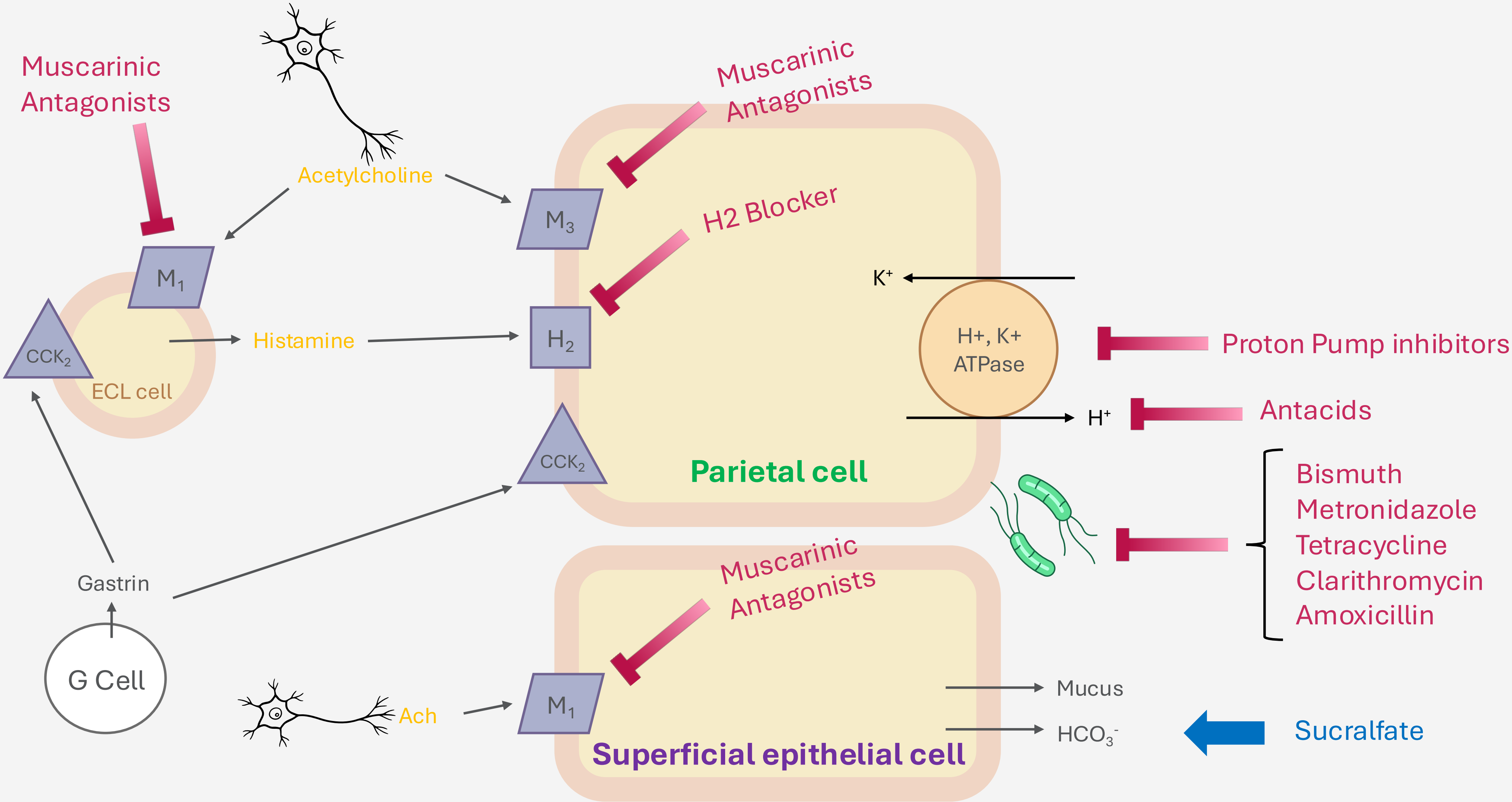
PHARMACOLOGY 201 | DR. MORA

Gastrointestinal System

H2 Blockers, PPIs, Anti-Emetics




Muscarinic Antagonists
Acetylcholine
Muscarinic Antagonists
H2 Blocker
M1
M3
CCK2
ECL cell
Histamine
H2
K+
H+, K+ ATPase
Proton Pump inhibitors
H+
Antacids
CCK2
Parietal cell
Bismuth
Metronidazole
Tetracycline
Clarithromycin
Amoxicillin
Gastrin
Muscarinic Antagonists
G Cell
Ach
M1
Mucus
HCO3-
Sucralfate
Superficial epithelial cell

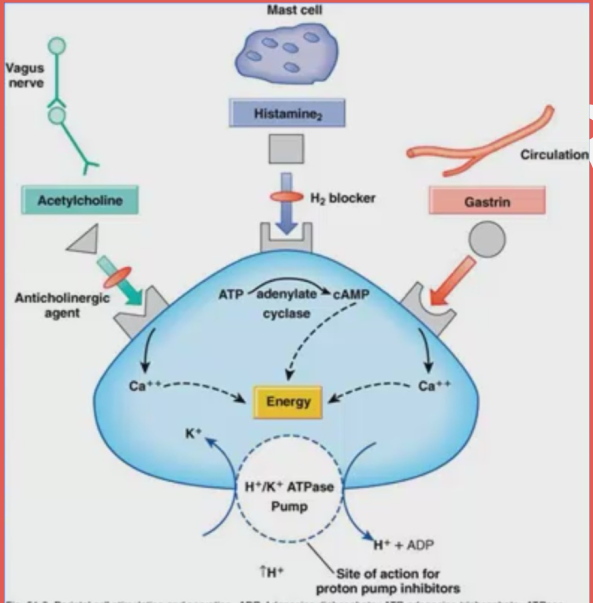
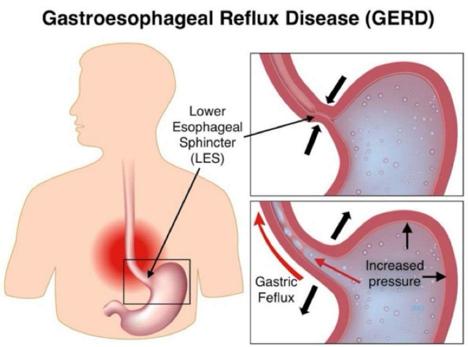
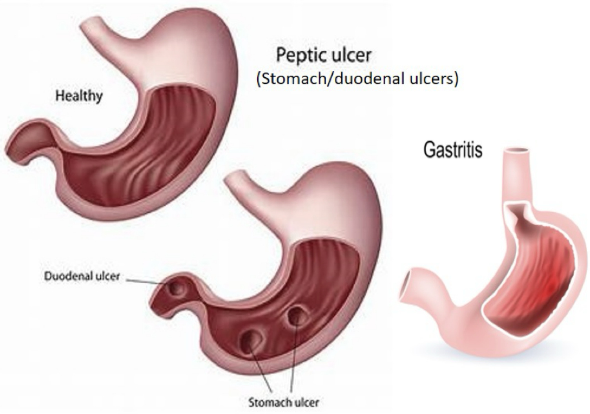
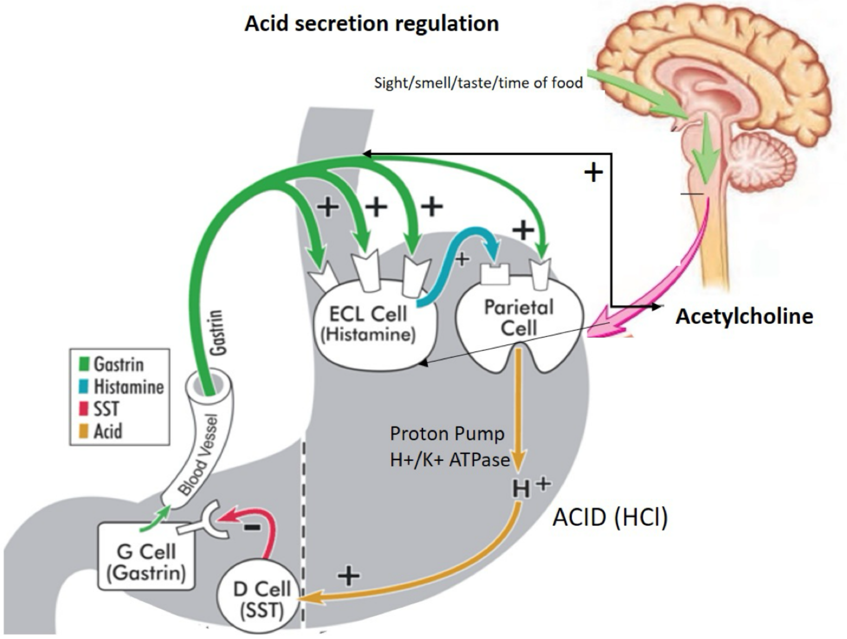


Fig. 51-2. Parietal cell stimulation and secretion. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; *ATPase*, adenosine triphosphatase; *cAMP*, cyclic adenosine monophosphate.







G-cells (antrum) → produce gastrin. D-cells protect stomach from overproduction of gastric acid by releasing somatostatin (SST) → inhibits production of gastrin. ACh and gastrin → increase release of histamine-2 from enterochromaffin-like (ECL) cells. Gastrin, Histamine-2, ACh (acetylcholine) → bind to receptors on parietal cells → gastric acid secretion

Antacids


DI-GEL
antacid/anti-gas
Extra Strength
Maalox
ANTACID/ANTI-GAS
Riopan
PLUS
ANTACID & ANTI-GAS
MYLANTA
ANTACID/ANTI-GAS
DOCTOR RECOMMENDED
ANTACID LIQUIDS
IN CHEWABLE FORM
Tempo
Great Tasting Antacid
Relieves Indigestion
On Contact With
The Speed of Liquids
Tagamet HB
Acid Reducer / Cimetidine Tablets 100 mg
JUST 1 TABLET PER DOSE
Relieves & Prevents
Pepcid
AC Acid Controller
ACID REDUCER / FAMOTIDINE TABLETS 10 mg
Now Available Without a Prescription
Gelusil
Antacid/Anti-Gas
Sodium Free*
Get fast relief with the smoother creamier
100 tablets
GENUINE
Phillips'
Milk of Magnesia
LAXATIVE • ANTACID
• Dependable Overnight Relief
• Sugar Free, Low Sodium
ORIGINAL
4 FL OZ (118 mL)
EffeCal
CALCIUM
PEPPERMINT
TUMS
REGULAR STRENGTH
ANTACID
36 TABLETS/ 3 ROLLS
Rolaids
CALCIUM RICH • ANTACID
Alka-Seltzer
ORIGINAL
FAST RELIEF

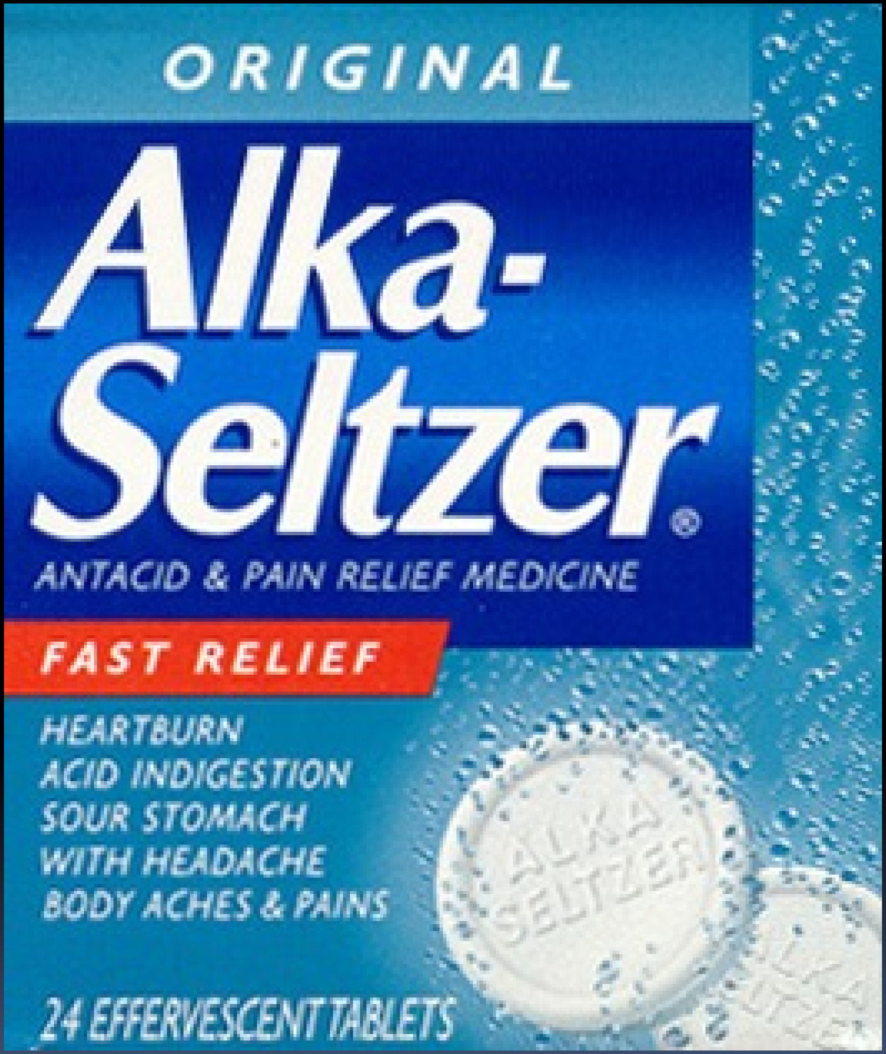
Antacids (Maalox, Mylanta)

- Onset: immediate (minutes)
- Duration: 30 minutes on an empty stomach, but 3 hours when taken within 1 hour of meals
- Alginic acid may be added to antacids → forms a viscous solution that floats on top of gastric contents → protects the esophageal mucosa from acid reflux
- Simethicone (surfactant) may be added to antacids → ”breaks up” gas bubbles → relieves gas
- Caution: small amounts of aluminum and magnesium are absorbed and can accumulate in renal insufficiency → toxicity
  - Magnesium: avoid in patients with CrCl < 30 ml/min
  - Aluminum: avoid in patients with renal failure (CrCl < 15 ml/min)

Antacids (cont.)

Sodium Bicarbonate
(Alka-Seltzer)

High sodium content (567 mg per tablet) → Na^+/H_2O retention → exacerbates hypertension, heart failure, chronic kidney disease



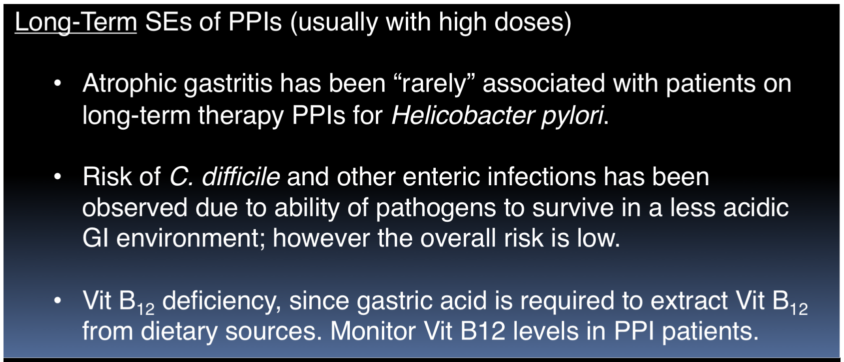
Proton Pump Inhibitors (PPIs)


Prilosec OTC
omeprazole delayed-release tablets 20 mg / acid reducer
42 TABLETS
Three 14-day courses of treatment
Treats FREQUENT Heartburn! Occurring 2 Or More Days A Week
PREVACID 24 HR
Lansoprazole delayed-release capsules 15 mg / acid reducer
TREATS FREQUENT HEARTBURN
14 CAPSULES
ONE 14-DAY COURSE OF TREATMENT
• MAY TAKE 1 TO 4 DAYS FOR FULL EFFECT
• SODIUM FREE
Nexium 24HR
Clear Minis
See new warning information
Treats Frequent Heartburn
esomeprazole magnesium delayed-release capsules 20 mg/acid reducer
AcipHex
rabeprazole sodium
20 mg
Delayed-Release Tablets
PROTONIX
(pantoprazole sodium)
Delayed-Release Tablets
40 mg

Anti-Emetics

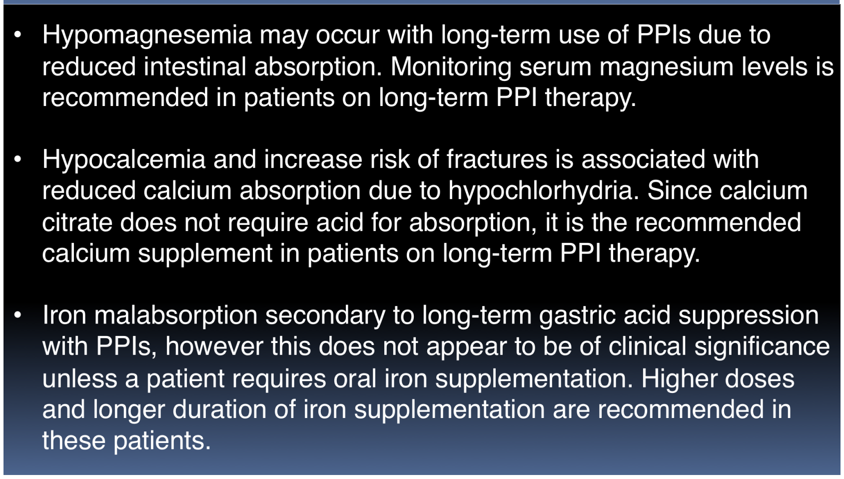
Study Checks

- What are the serious adverse drug reactions of PPIs?



Long-Term SEs of PPIs (usually with high doses)

- Atrophic gastritis has been “rarely” associated with patients on long-term therapy PPIs for *Helicobacter pylori*.
- Risk of *C. difficile* and other enteric infections has been observed due to ability of pathogens to survive in a less acidic GI environment; however the overall risk is low.
- Vit B_{12} deficiency, since gastric acid is required to extract Vit B_{12} from dietary sources. Monitor Vit B12 levels in PPI patients.



- Hypomagnesemia may occur with long-term use of PPIs due to reduced intestinal absorption. Monitoring serum magnesium levels is recommended in patients on long-term PPI therapy.
- Hypocalcemia and increase risk of fractures is associated with reduced calcium absorption due to hypochlorhydria. Since calcium citrate does not require acid for absorption, it is the recommended calcium supplement in patients on long-term PPI therapy.
- Iron malabsorption secondary to long-term gastric acid suppression with PPIs, however this does not appear to be of clinical significance unless a patient requires oral iron supplementation. Higher doses and longer duration of iron supplementation are recommended in these patients.

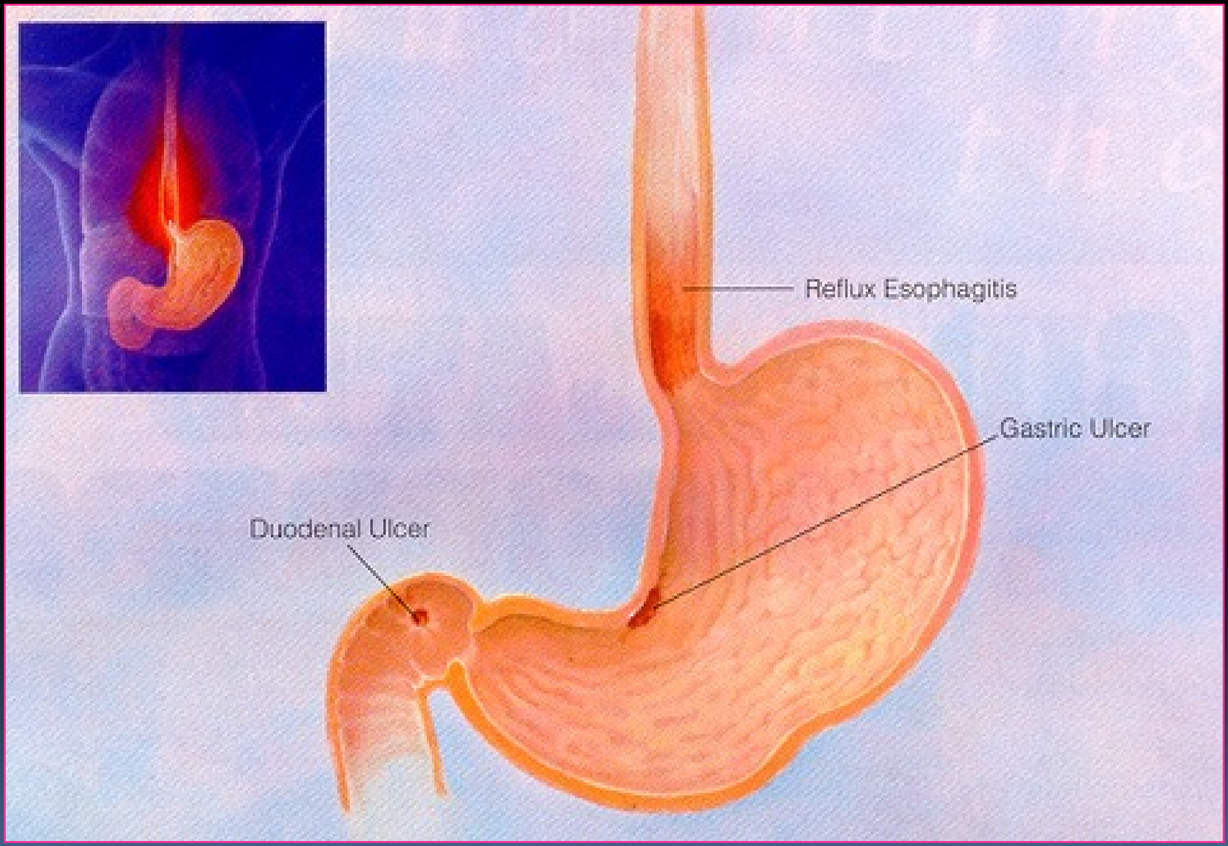
References

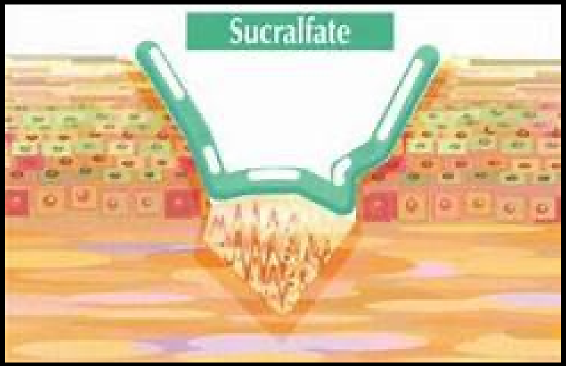
1. Brunton LL, Knollmann BC, eds. Goodman & Gilman’s the Pharmacological Basis of Therapeutics. Fourteenth edition. McGraw Hill; 2023.
2. Golan DE, Armstrong EJ, Armstrong AW, eds. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. 4. Edition. Wolters Kluwer; 2017.
3. Papadakis, M., Rabow, M., McQuaid, K., & Gandhi, M. (2024). CURRENT medical diagnosis and treatment 2025 (64th ed.). Columbus, OH: McGraw-Hill Education.
4. Whalen K, Lerchenfeldt S, Giordano CR, eds. Pharmacology. Eighth edition. Wolters Kluwer Health; 2023.

Sucralfate (Carafate)

(cytoprotective agent)

MOA: binds to gastric ulcer forming a protective barrier





Sucralfate (Carafate)

- Sucralfate may also have protective affect by stimulating release of mucosal prostaglandins (PGE)
- SE: constipation (1-3%) due to aluminum content
- Caution: aluminum content may accumulate in patients with renal insufficiency → “aluminum encephalopathy” (i.e., dementia), and anemia
- Aluminum binds dietary phosphate (GI tract) → hypophosphatemia

- Sucralfate tablets are large and may be difficult for geriatrics to swallow → use liquid formulation

Misoprostol (Cytotec)

MOA: synthetic prostaglandin (PG) analog

- stimulates the production of mucus and bicarbonate (“mucoprotective shield”)
- improves mucosal blood flow
- reduces mucosal cell turnover
- mildly inhibits gastric acid secretion (less than H_2RAs)

SE: diarrhea (up to 30%), abdominal cramping

- take with food and reduce daily dose to minimize incidence of diarrhea

Caution: misoprostol is contraindicated in pregnancy.

- use in women in childbearing years requires negative serum pregnancy test and adequate contraception

Antiemetic Agents

There are 4 major sources of afferent input to the vomiting center.

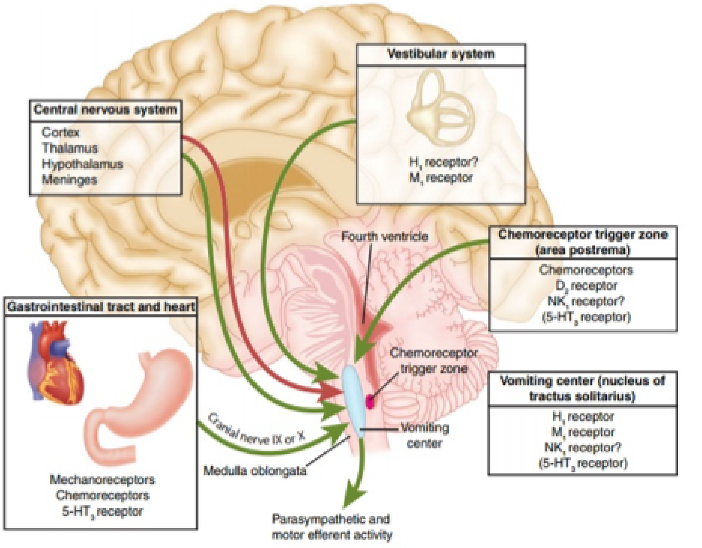


FIGURE 62–6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Modified and reproduced, with permission, from Krakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817.)

(1) CTZ (chemoreceptor trigger zone)
  - located outside the BBB and is subject to stimuli in blood
  - receptors: D_2, opioid, 5-HT_3, NK_1

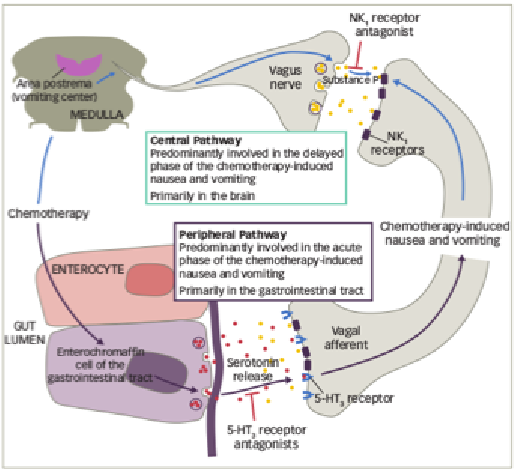
(2) Vestibular System
  - important in motion sickness
  - receptors: M_1 and H_1

(3) Vagal and Spinal Afferent Nerves from the GI tract
  - receptors: 5-HT_3
  - GI irritates (chemotherapy, distention, infection)
    → release of mucosal serotonin
    → activate 5-HT_3 receptors
    → propagate vagal afferent impulses to vomiting center and CTZ

(4) Central Nervous System (CNS)
  - stress, psychiatric disorders, anticipatory vomiting, etc…

<u>Serotonin 5-HT_3 Antagonists</u>

- <u>Ondansetron</u> (Zofran) → mainly blocks 5-HT_3 receptors on intestinal vagal and spinal afferent nerves; also blocks 5-HT_3 receptors in the vomiting center and CTZ.
  - Effective in treating emesis mediated through vagal stimulation (e.g., chemotherapy and postoperative nausea/vomiting)
  - May be combined with corticosteroid (i.e., dexamethasone) for enhanced effects in chemotherapy
  - Side Effects: headache, dizziness, prolongation of QT-interval



Phenothiazines

- Prochlorperazine (Compazine) and Promethazine (Phenergan)
  → block D_2, M_1, and H_1 receptors in CTZ and vomiting center
- Side Effects: extrapyramidal symptoms (EPS), hypotension, sedation (d/t antihistaminic property)
  - EPS is treated with diphenhydramine (Benadryl) 25 mg IV or IM

Benzamides

- Metoclopramide (Reglan) and Trimethobenzamide (Tigan)
  → block D_2 receptors
  → stimulate cholinergic receptors on GI smooth muscle → increases GI motility (Prokinetic)
  → increases lower esophageal sphincter (LES) tone (tx: GERD)
- Side Effects: anxiety, restlessness, EPS (due to CNS dopamine blocking effects)

Antihistamines

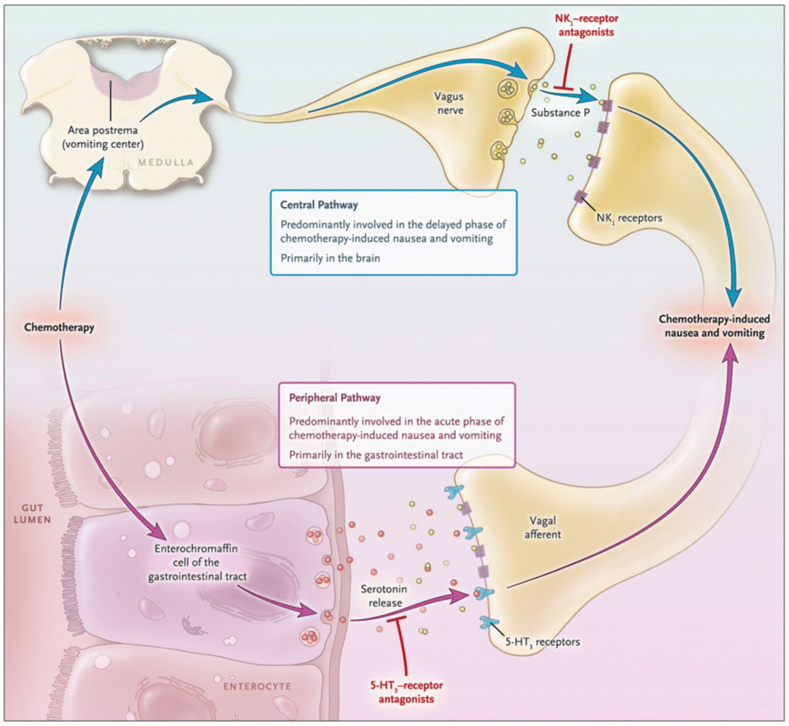
- Diphenhydramine (Benadryl) 25-50 mg PO/IV/IM Q6H and Dimenhydrinate (Dramamine) 50 mg PO Q4H → 1st generation antihistamines → block H_1 receptors with potent anticholinergic properties (SE: dizziness, sedation, dry mouth, blurred vision, urinary retention, etc…)
  - H_1 blocking effect → prevents motion sickness and vertigo (d/t vestibular dysfunction)
- Meclizine (Antivert) 25-50 mg PO Q24H → blocks H_1 receptors with minimal anticholinergic properties (less sedation) → prevents motion sickness and vertigo

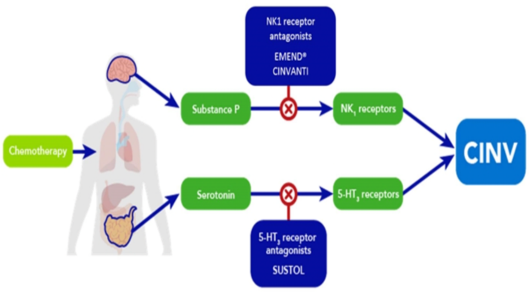
Anticholinergic Drugs

- Scopolamine (Transderm Scop) → highly effective M_1 receptor antagonist for the prevention of motion sickness (vestibular dysfunction)
- Scopolamine Patch: Apply to clear area behind the ear every 72 hours (1.5 mg Q72H)
- Side Effects: anticholinergic adverse effects are minimized d/t localized effects with transdermal application

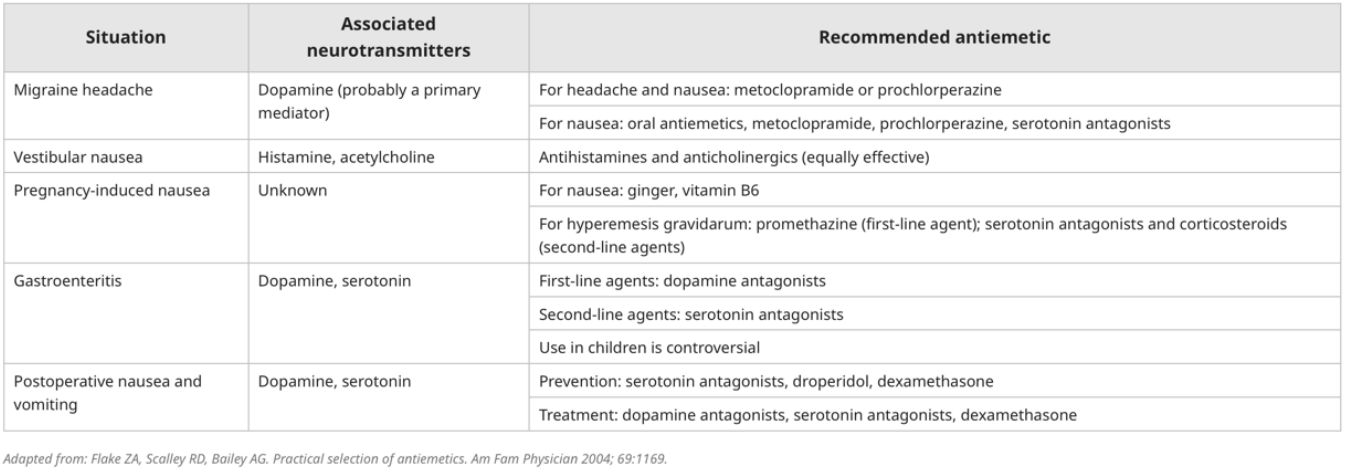
Neurokinin-1 (NK_1) Receptor Antagonists

- Aprepitant (Cinvanti) - PO/IV
  → blocks substance P from binding to NK_1 receptors in vomiting center and CTZ
- Indicated for combination therapy with 5-HT_3 receptor antagonists and corticosteroids for prevention acute and delayed emesis in patients treated with highly-emetogenic chemotherapy agents





Selection of Antiemetics by Clinical Situation



Situation	Associated neurotransmitters	Recommended antiemetic
Migraine headache	Dopamine (probably a primary mediator)	For headache and nausea: metoclopramide or prochlorperazine
		For nausea: oral antiemetics, metoclopramide, prochlorperazine, serotonin antagonists
Vestibular nausea	Histamine, acetylcholine	Antihistamines and anticholinergics (equally effective)
Pregnancy-induced nausea	Unknown	For nausea: ginger, vitamin B6
		For hyperemesis gravidarum: promethazine (first-line agent); serotonin antagonists and corticosteroids (second-line agents)
Gastroenteritis	Dopamine, serotonin	First-line agents: dopamine antagonists
		Second-line agents: serotonin antagonists
		Use in children is controversial
Postoperative nausea and vomiting	Dopamine, serotonin	Prevention: serotonin antagonists, droperidol, dexamethasone
		Treatment: dopamine antagonists, serotonin antagonists, dexamethasone

Adapted from: Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician 2004; 69:1169.