Management and Treatment of Chronic Constipation

Initial Management (Patient Education)

- emphasis should be on increasing fluid and fiber intake
- patients are advised to defecate after meals, taking advantage of normal post-prandial increase in colonic activity (highest in the morning)
- bulk-forming laxatives (psyllium or methylcellulose) are safe and effective products for most patients with chronic constipation

Bulk-Forming Laxatives

- Psyllium (Metamucil), Methylcellulose (Citrucel), Calcium Polycarbophil (FiberCon)
  - MOA: bulk-forming laxatives absorb water and increase fecal mass → increase the softening and consistency of fecal mass
- 1st-line agents in the management of constipation → low cost, safe, effective, and easy to use
- Side Effects: may cause distention or flatulence (usually diminishes over several days)

Surfactant Laxatives

- Docusate Sodium (Colace), Docusate Calcium (Surfak), Mineral Oil
  - MOA: lower surface tension of stool → allowing water to easily enter the stool
- generally, less effective than psyllium; therefore, usually combined with stimulant laxatives for greater efficacy → Senokot-S (docusate/senna)
- generally well-tolerated; however, mineral oil may cause lipoid pneumonia if aspirated

Osmotic Laxatives

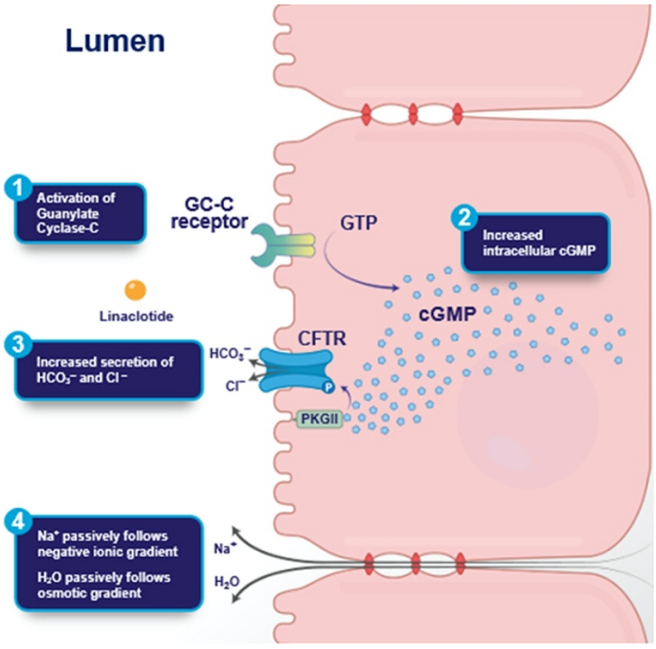
- PEG = Polyethylene Glycol (Miralax), Magnesium Hydroxide (MOM), Lactulose, Sorbitol (70%)
  - MOA: non-absorbable osmotic agents → increase secretion of water into the intestinal lumen → soften stools and promote defecation
- safe and effective for acute and chronic constipation → onset of action: 24 hours
  - Magnesium Citrate (11.6 GM of magnesium) → more rapid response in acute constipation (30 min - 3 hours)
  - Milk of Magnesia (MOM) contains 2.4 GM of magnesium / 30 ml
- magnesium containing laxatives should be avoided in patients with chronic renal insufficiency
  - Magnesium Citrate and MOM may cause hypermagnesemia in chronic renal insufficiency
- Lactulose, Sorbitol are non-digestible carbohydrates → may cause bloating, cramps, flatulence
- PEG (Miralax) is well-tolerated → does not cause flatulence

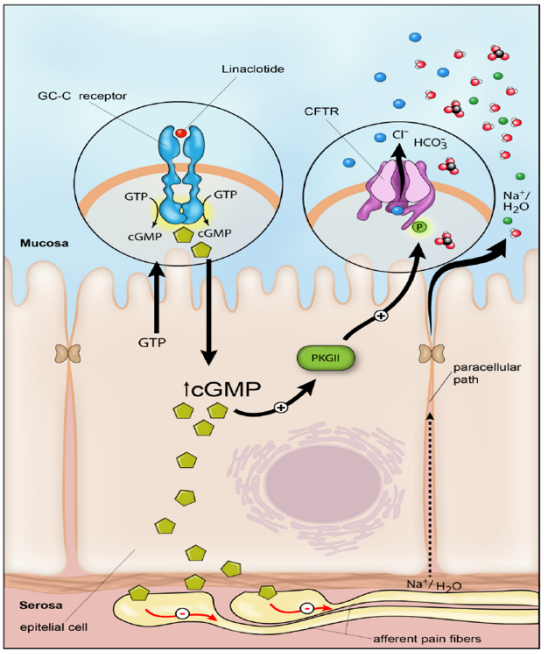
Stimulant Laxatives

- Bisacodyl tablet or suppository (Dulcolax), Senna (ExLax, Senokot), Cascara (Nature's Remedy)
  - MOA: stimulate fluid secretion and colonic contraction → bowel movement
    - onset (PO): 6-12 hours / onset (PR): 15-60 mins
- stimulant laxatives are generally recommended as "PRN" agents for patients with incomplete response to osmotic laxatives
- Side Effects: (1) cramping and (2) "laxative bowel" is a condition characterized by dependence on stimulant laxatives for bowel function

Chloride Secretory Agents

- Linaclotide (Linzess), Lubiprostone (Amitiza)
  - Linaclotide (guanylate cyclase agonist) → activates GC-C receptor → increases cGMP → cGMP stimulates secretion of chloride and bicarbonate into intestinal lumen → increases intestinal fluid by drawing Na^+ / H_2O and accelerates transit
  - Lubiprostone activates chloride channel → stimulates secretion of chloride and bicarbonate into intestinal lumen → increases intestinal fluid by drawing Na^+/H_2O and accelerates transit
- Dosage and Administration
  - Linaclotide (Linzess): 145 mcg PO daily (Onset: 12-24 hours)
  - Lubiprostone (Amitiza): 24 mcg PO BID (Onset: 24-48 hours)
- Side Effects
  - Linaclotide (Linzess) bloating, diarrhea / Lubiprostone (Amitiza): nausea, diarrhea
- Cost: Linzess (30 capsules) - $450 / Amitiza 24 mcg (30 capsules) - $200





Peripherally Acting Mu-Opioid Receptor Antagonists (PAMORA)

- Methylnaltrexone (Relistor) and Naloxegol (Movantik) → block peripheral opioid receptors (GI tract) without affecting central analgesia
- FDA-approved for treatment of opioid-induced constipation in patients taking opioids for chronic non-cancer pain, who have not responded to conventional laxatives
  - severe abdominal pain and bowel perforation may be associated with PAMORA use in cancer and bowel obstruction
- Methylnaltrexone: 8-12 mg SC daily / 450 mg PO daily (dosage adjustment in renal insuff)
- Naloxegol (Movantik): 12.5-25 mg PO daily (dosage adjustment in renal insuff)
- Efficacy: Methylnaltrexone SC formulation is more effective than oral Naloxegol and oral Methylnatrexone.
- Cost: Relistor 150 mg (30 tabs) $680 / Relistor Injectable: 12 mg (14 syringes): $2000
  Movantik 25 mg (30 tabs): $350
- Side Effects: abdominal pain, nausea, diarrhea, flatulence

Antidiarrheals

Antimotility Agents

- Loperamide (Imodium), Diphenoxylate w/Atropine (Lomotil) → opioid analogs of meperidine (Demerol) that have opioid-like action on intestinal motility
    - MOA: activate opioid receptors → inhibit peristalsis, prolong transit time, reduce fecal volume, increase viscosity, and diminish fluid and electrolyte loss
- Loperamide (Imodium) - OTC
    - Dose: 4 mg PO initially, then 2 mg PO after each loose stool (max dose: 16 mg/day)
    - Side Effects: dizziness (1%), constipation (2-5%), abdominal cramps (<3%), nausea (3%)
- Diphenoxylate w/Atropine (Lomotil) – Rx
    - atropine is added to discourage abuse with diphenoxylate
    - Dose: 5 mg PO QID prn diarrhea
    - SE: (1-10%) anticholinergic effects (i.e., blurred vision), sedation, abdominal cramps, nausea

Bismuth Subsalicylate (Pepto Bismol) - OTC

- MOA: exerts antisecretory, antimicrobial, and some anti-inflammatory actions
    - Salicylate moiety → produces antisecretory effect
    - Bismuth → exerts antimicrobial effect against gastrointestinal bacteria and viral pathogens
- Side Effects: tongue and fecal discoloration (grayish black)
- Caution: Avoid use in patients allergic to salicylates (aspirin) and pediatrics (Reyes Syndrome)

Treatment Regimens for *Helicobacter Pylori*

General Considerations

- In the US, we generally assume clarithromycin resistance rates are greater than 15%, unless local data indicate otherwise.
- Data suggests that H. pylori resistance rates are high worldwide (>15%).

Bismuth Quadruple Therapy

- Preferred regimen in patients allergic to penicillin (PCN)
- Bismuth Subsalicylate (Pepto Bismol) + Metronidazole (Flagyl) + Tetracycline + PPI → 14 days
    - PPI (standard dose) PO BID → e.g., Lansoprazole (Prevacid) 30 mg PO BID
    - Bismuth Subsalicylate (300 or 524 mg) PO QID
    - Tetracycline (TCN) 500 mg PO QID
    - Metronidazole: 250 mg PO QID or 500 mg PO TID

- Pylera[R]: combination capsule which contains bismuth subcitrate, metronidazole, and tetracycline
    - Pylera: 3 capsules PO QID after meals and at bedtime (PC & HS)

Treatment Regimens for Helicobacter Pylori (cont.)

Clarithromycin-Based Therapy

- Clarithromycin (Biaxin) + Amoxicillin (Amoxil) + Metronidazole (Flagyl) + PPI → 10-14 days
  - PPI (standard dose) PO BID → e.g., Lansoprazole (Prevacid) 30 mg PO BID
  - Clarithromycin 500 mg PO BID
  - Amoxicillin 1000 mg PO BID
  - Metronidazole 500 mg PO BID

Testing: H. pylori Eradication

- confirm eradication with urea breath test, fecal antigen test, upper endoscopy
  - 4 wks or more after completion of antibiotic therapy and/or 2 wks after PPI discontinuation

Antiemetic Agents

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

(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…

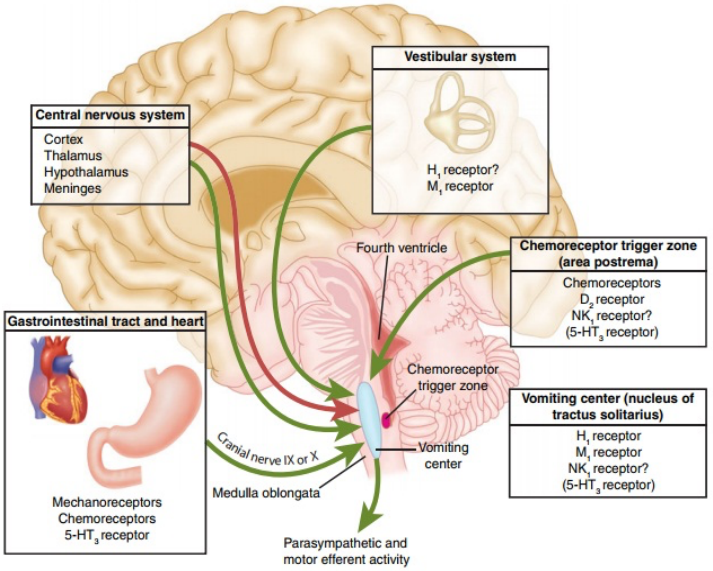
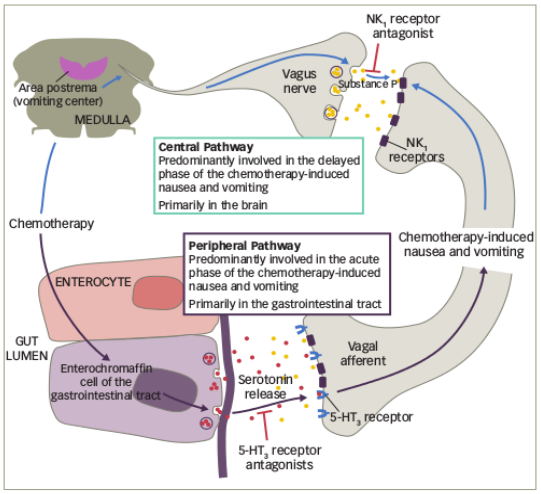


FIGURE 62–6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Modified and reproduced, with permission, from Krakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817.)

Serotonin 5-HT_3 Antagonists

- Ondansetron (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

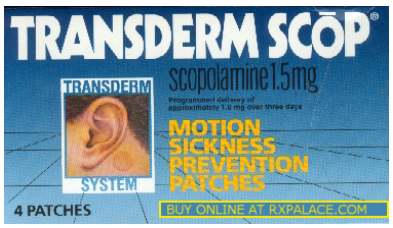
- Metoclopramide (Reglan) and Trimethobenzamide (Tigan)
  → block D_2 receptors
  → stimulate cholinergic receptors on GI smooth muscle → increases GI motility (Prokinetic)
  → increases lower esophageal sphincter (LES) tone (tx: GERD)
- Side Effects: anxiety, restlessness, EPS (due to CNS dopamine blocking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

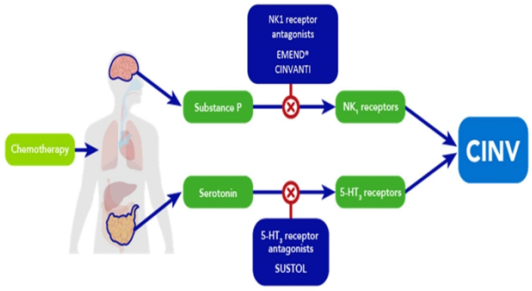
Anticholinergic Drugs

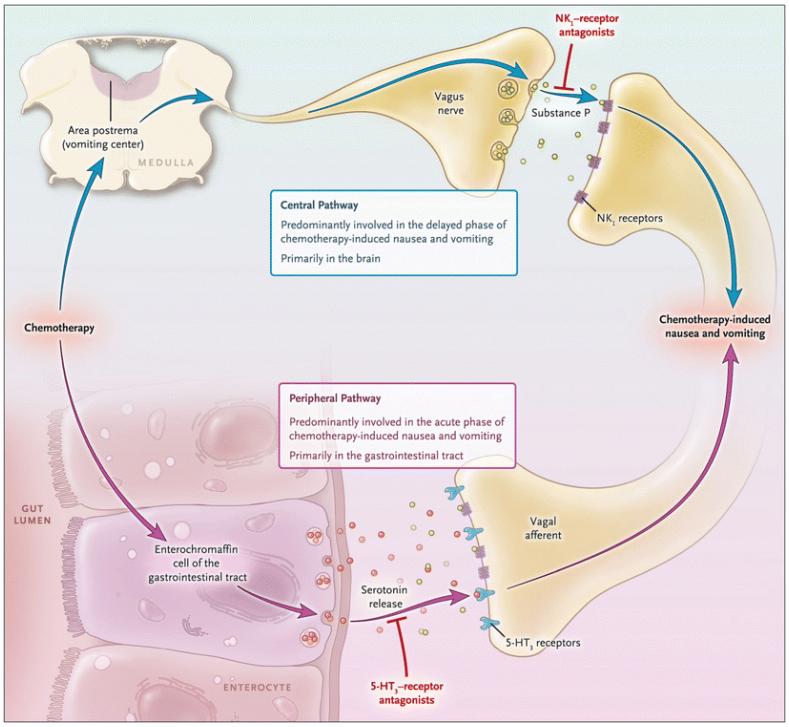
- Scopolamine (Transderm Scop) → highly effective M_1 receptor antagonist for the prevention of motion sickness (vestibular dysfunction)
- Scopolamine Patch: Apply to clear area behind the ear every 72 hours (1.5 mg Q72H)
- Side Effects: anticholinergic adverse effects are minimized d/t localized effects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