Pharmacologic Palliation of Constipation & Nausea/Vomiting (and Diarrhea)

Summary Drug Tables Are at the End of the Handout

I. A goal of **palliative care** is to relieve the suffering of patients.
Control of pain and other physical symptoms, as well as psychological, social and spiritual problems is paramount.

II. Pharmacologic Palliation of Constipation

A. BULKING AGENTS

Agents

- Dietary fiber (bran)
- Psyllium (Metamucil)

Mechanisms of Action

- Bulk-forming laxatives cause retention of fluid and an increase in fecal mass, resulting in stimulation of peristalsis.
- They usually have an effect within 12 to 24 hours and reach a maximum after several days

Side Effects

Flatulence

Contraindications

In debilitated patients who cannot drink adequate fluid (1.5 – 2 liters/day) could result in fecal impaction, intestinal obstruction

B. OSMOTIC LAXATIVES

These are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid**.**

- **Saline and magnesium salt laxatives**

Agents

- Magnesium citrate
- Magnesium hydroxide (Milk of Magnesia)

Mechanism of Action

- Saline laxatives have an osmotic effect causing increased intraluminal volume that acts as a stimulus for intestinal motility.

- Laxatives that contain magnesium have been shown to release cholecystokinin that causes intraluminal accumulation of fluid and electrolytes and promotes small bowel and possibly even colonic transit.
- Rapid movement of water into distal small bowel and colon leads to high volume of liquid stool.
- High doses produce bowel evacuation in 1-3 hours.

Side Effects/Contraindications
- Contraindicated in any form of bowel obstruction
- Can produce dehydration without adequate fluid replacement
- Because the ions can be partially absorbed, laxatives containing magnesium and phosphorous are contraindicated in patients with impaired renal function
- Rare reports of ischemic colits with magnesium citrate thought secondary to a rapid fluid shift from the intravascular compartment to the gut lumen resulting in transient colonic hypoperfusion and ischemia

Clinical Indications
- Magnesium hydroxide is indicated for relief of constipation
- Magnesium citrate indicated for bowel cleansing in preparing patients for surgery or the colon for x-ray or endoscopy

Polyethylene Glycol

Trade names
Constipation - Miralax, GlycoLax
Bowel Cleanser - Colyte, Golytely

Mechanism of Action:
- Polyethylene glycol is an osmotic agent that causes retention of water in the stool resulting in a softer stool and more frequent bowel movements.
- It appears to have no effect on active absorption or secretion of glucose or electrolytes
- No significant intravascular fluid or electrolyte shifts occur

Side Effects
Minimal

Clinical Indications
- Large volume (ie 4 liters) ingested rapidly causes rapid evacuation for bowel cleansing before endoscopy
- Smaller daily doses can be used for constipation.

Nonabsorbable sugars

Agents
- Lactulose

- Sorbitol

Mechanism of Action
Lactulose is a synthetic disaccharide. Bacteria in the colon degrade lactulose into lactic acid, acetic acid and formic acid resulting in an increase in osmotic pressure and acidification of intestinal contents which in turn, softens the stool by promoting stool water content

Side Effects
- Bloating, cramps, flatulence
- Very sweet – may be difficult for patients to tolerate
- Can worsen dehydration by drawing body water into the bowel lumen

C. STIMULANT LAXATIVES

Agents:
- Senna
- Bisacodyl (Dulcolax)

Mechanism of Action:
- Bisacodyl is a contact laxative that acts on the large intestine to produce strong but brief peristaltic movements. This agent stimulates sensory nerve endings to produce parasympathetic reflexes that results in peristalsis of the colon. Local axon reflexes and segmental reflexes are stimulated, which produces widespread peristalsis of the colon.
- Senna undergoes conversion to active metabolites in the colon that stimulate the myenteric plexus and induce net fluid secretion.
- Response in 6-12 up to 24 hours.

Side Effects
- Electrolyte abnormalities depending on volume of stool
- Senna - Melanosis coli – brown pigmentation of the colon
  - Lipofuscin laden macrophages
  - No clinical sequela

Clinical Indication
Relief of constipation

D. DETERGENT LAXATIVES

Agent
Docusate (Colace)

Mechanism of Action

- Docusate is an anionic surfactant that is believed to increase the penetration of fluid into the stool by emulsifying feces, water, and fat
- Soft feces = easier passage
- Minimal effect on peristalsis
- Initial response in 1-3 days

Clinical Indications

Docusate is used to soften or prevent the formation of hard stools.
Increasing body of clinical data that docusate is not meaningfully effective in the management of constipation

E. LUBRICANTS

Agents

- Glycerin suppository/enema
- Mineral oil enema

Mechanism of Action

- Due to its osmotic effect, glycerin softens, lubricates, and facilitates the elimination of inspissated feces. By serving as a bowel irritant it may also stimulate rectal contractions.
- Mineral oil helps soften (by coating fecal material with mineral oil) and lubricate hard stools, easing their passage without irritating the mucosa.
- Lubricants may stimulate a response within 30 minutes.

Side effects/contraindications

Mineral oil should **never be administered orally** to debilitated patients - inhalation/aspiration of the oil can lead to lipoid pneumonitis**.**

Clinical Indications

Usually reserved for treatment of fecal impaction

F. ENEMAS

Agents

Sodium phosphate enema (Fleet's enema)
Tap water

Mechanism of Action

Soften stool by increasing water content
Distend distal colon inducing peristalsis

Clinical Indications

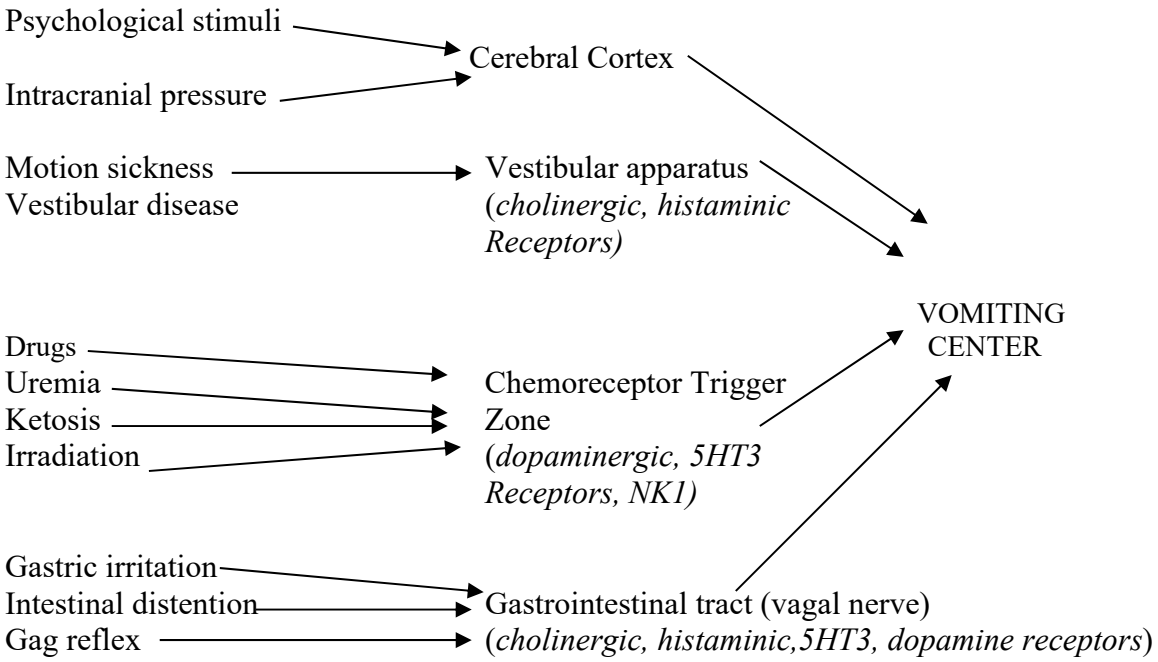
Usually reserved for treatment of fecal impaction

Agents not first line for management of constipation

Drug	Mechanism of Action	Indications
Lubiprostone	Chloride Channel Activator; Promotes secretion of chloride-rich fluid, improved stool consistency and transit	Constipation predominant IBS Opioid Induced Constipation Chronic Constipation
Linaclotide Plecanatide	Increased synthesis of cyclic GMP → enhanced chloride, bicarbonate secretion into intestinal lumen→water secretion and enhanced motility	Chronic idiopathic constipation in adults
Tenapanor	Inhibitor of an Na+H+ exchanger most abundantly expressed in GI tract. Reduces absorption of Na+→ enhances intestinal fluid volume and transit	Constipation predominant IBS
Methylnaltrexone	Peripherally acing μ receptor antagonist	**Refractory** opioid induced constipation

III. Pharmacologic Palliation of Nausea and Vomiting

A. Pathophysiology of nausea and vomiting



Chemoreceptor trigger zone is located in the area postrema outside the blood brain barrier
Vomiting Center is located in the lateral reticular formation of the medulla and coordinates the motor mechanisms of vomiting

B. Antiemetic Drugs

Dopamine receptor antagonists
Phenothiazines - **Prochlorperazine (Compazine)**
Butyrophenones - Haloperidol (Haldol)
Benzamides – Metoclopramide (Reglan)

Serotonin (5HT3) antagonists
Ondansetron (Zofran)
Granisetron (Kytril)
Dolasetron
Polansetron

Neurokinin (NK1) receptor antagonist
Aprepitant

Antihistamines
Promethazine (Phergan)
Diphenhydramine

Anticholinergics
Scopolamine

Corticosteroids
Dexamethasone

Benzodiazepenes
Lorazepam
Alprazolam

Cannabinoids
Dronabinol (Marinol)
Nabilone

B. Select Antiemetics

- **Agent -** Prochlorperazine (Compazine)

  Mechanisms of Action
  - Prochlorperazine acts centrally by inhibiting the dopamine receptors in the medullary chemoreceptor trigger zone

  Adverse Effects
  Extrapyramidal effects, dystonic reactions

  Clinical Indications
  - Opioid related nausea and vomiting
  - Moderately effective for nausea caused by various GI disorders (ie gastroenteritis)

- **Agent -** Metoclopramide (Reglan)

  Mechanism of Action
  - Antiemetic properties are due to central and peripheral dopamine receptor inhibition

- Prokinetic - Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of metoclopramide. Metoclopramide increases esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but has no effect on small intestine or colonic motility

Adverse Effects

- Extrapyramidal effects, such as dystonia, akathisia, parkinsonism, may develop due to central dopamine receptor blockade.
  - Acute dystonic reactions, such as trismus, torticollis, facial spasms, can be treated with an anticholinergic agent (benztropine or diphenhydramine)
- Tardive dyskinesia – black box warning – risk increases with total cumulative dose. Avoid use for greater than 12 weeks
- Cautious use in patients with Parkinson's Disease
- Contraindicated in patients with complete bowel obstruction

Clinical Indications

- Chemotherapy induced nausea and vomiting
- Vomiting due to dysmotility of the upper GI tract - gastric stasis and diabetic gastroparesis

Agent - Ondansetron (Zofran); Granisetron (Kytril)

Mechanism of Action

- Ondansetron is a competitive, highly selective antagonist of 5-hydroxytryptamine (serotonin) subtype 3 (5-HT 3) receptors. 5-HT 3 receptors are present peripherally on vagal nerve terminals and centrally in the area postrema of the brain. Cytotoxic drugs and radiation appear to damage gastrointestinal mucosa, causing the release of serotonin from the enterochromaffin cells of the gastrointestinal tract. Stimulation of 5-HT 3 receptors causes transmission of sensory signals to the vomiting center via vagal afferent fibers to induce vomiting. By binding to 5-HT 3 receptors, ondansetron blocks vomiting mediated by serotonin release.

Side Effects

Most common side effect is headache
Small but statistically significant prolongation of the QT interval
Serotonin syndrome

Clinical Indications

- Chemotherapy induced nausea and vomiting and its prophylaxis
- Radiation induced nausea and vomiting and its prophylaxis

- Agent – Aprepitant

Mechanism of Action

- Aprepitant inhibits the neurokinin 1 (NK_1) receptor in the chemoreceptor trigger zone

Side Effects

Fatigue, dizziness, diarrhea

Clinical indications

- Prevention of nausea/vomiting from highly emetogenic chemotherapy
  Augments activity of 5-HT3 receptor antagonist + glucocorticoids

- **Agent -** Promethazine (Phenergan)

Mechanism of Action

Antiemetic effects come from its H(1) receptor blocking properties.
-Has antidopaminergic properties though primary anti-emetic action is through H1 receptor blocking

Adverse Effects

Sedation

Clinical Indications

Promethazine is effective in the active and prophylactic treatment of motion sickness

- **Agent** Scopolamine

Mechanism of Action

Pure anticholinergic agent

Adverse Effects

- *Dry mouth (xerostomia)
- Acute narrow angle glaucoma (contraindicated in patients with known glaucoma)
- Urinary retention
- Confusion

Clinical Indications
- Treatment of motion sickne

Agent Dronabinol (Marinol)

Mechanism of Action
Synthetic delta-9-tetrahydrocannibinol
Cannabinoid 1 (CB1) central receptor agonist

Adverse Effects
- Euphoria
- Dysphoria
- Paranoid delusions
- Cognitive clouding
- Somnolence, sedation
- Hypotension

Clinical Indications
- Breakthrough chemotherapy induced nausea/vomiting
  - AIDs-related anorexia and wasting

IV. Drugs Used for the Management of Diarrhea

Drug	Mechanism	Side Effects/ Precautions
Loperamide (Imodium)	Opiate; passes poorly to CNS Acts directly on circular and longitudinal intestinal muscles through μ receptor; Inhibits peristalsis, reduces fecal volume, antisecretory; Increases tone on anal sphincter	Do not use with *C. difficile* diarrhea, dysentery (fever, bloody or mucoid stools) FDA black box warning: In excess– prolonged QTc, torsades
Diphenoxylate and atropine (Lomotil)	Opioid + subtherapeutic *atropine (to decrease risk of abuse) Decreases Motility *if taken in excess: nausea, dry mouth, blurred vision	Do not use with C. difficile diarrhea, dysentery (fever, bloody or mucoid stools)
Bismuth-Salicylate (Peptobismol)	Bismuth and salicylate suspended in mixture of magnesium aluminum silicate clay. Bismuth: antisecretory, anti-inflammatory, antimicrobial effects Salicylate: Inhibits prostaglandin synthesis reducing hypermotility	

Drug Table:
Drugs used to palliate CONSTIPATION

Drug Class	Medications	Mechanism	Indications	Side Effects	Contraindications	Comments
Bulking Agent	Dietary Fiber Psyllium	Increases stool weight Fluid retention in stool	Constipation	Flatulence	-Debilitated -End of life [Inability to intake appropriate amount liquid (1.5-2 liters/day)]	Must have adequate fluid intake
Osmotic Laxatives: Nonabsorbable sugars	Lactulose Sorbitol	osmotic load into the colonic lumen stimulates movement	Constipation	Bloating Cramps Flatulence		Very sweet taste Require prescription
Osmotic laxatives: Saline and Magnesium salts	Magnesium hydroxide (Milk of Magnesia)	osmotic load into the colonic lumen stimulates movement	Constipation		Renal Failure (can cause hypermagnesemia if used regularly)	Ions can be partially absorbed
Osmotic Laxatives: Saline and Magnesium Salts	Magnesium Citrate	osmotic load into the colonic lumen stimulates movement High doses - RAPID bowel evacuation	Bowel prep for endoscopy, surgery	Dehydration Electrolyte abnormalities	Bowel obstruction Fecal impaction Renal Failure Very cautious use in CHF	Ions can be partially absorbed High doses - Rapid bowel evacuation Ischemic colitis – rare side effect
Low dose Polyethylene Glycol	“Miralax”, Glycolax”	osmotic load into the colonic lumen stimulates movement	Constipation			“taste-less” no absorption of ions
High dose Polyethylene Glycol	Colyte Golytely	osmotic load into the colonic lumen stimulates movement	Bowel prep for colonoscopy, colon surgery			1-4 liters of volume of prep! no absorption of

						ions Requires prescription
Stimulant Laxatives	Senna Bisacodyl	Stimulate intestinal motility via myenteric plexus	Constipation Prevention of constipation with opiate therapy	Cramping		Melanosis coli with long-term use Bisacodyl can be given rectally in suppository form
Detergent "laxative" – stool softener	Docusate (colase)	Surfactant Increases penetration of fluid into stool	Prevention of hard stool			Recent studies have brought its utility into question
Lubricants	Glycerin	Administered rectally: -Osmotic -Irritant -Stimulates rectal contractions	Fecal Impaction			
Lubricants	Mineral Oil	Administered rectally: Coats feces Softens and lubricates feces	Fecal Impaction			NEVER use oral mineral oil in patients at risk of aspiration – Lipoid Pneumonitis
Large volume enemas	Tap water enema Sodium phosphate "soap suds" - historical	Increase water content of stool Distend distal colon Induce peristalsis	Fecal impaction		Sodium phosphate – cautious use in advanced CKD (phosphorous absorption)	
Increase Bowel Secretions	Locally acting chloride channel	Chloride Channel Activator; Promotes	Constipation predominant IBS			Not currently a first line agent for opioid induced or

	activator	secretion of chloride-rich fluid, improved stool consistency and transit	Opioid Induced Constipation Chronic Constipation			chronic constipation
Agonist of the guanylate cyclase-C receptor	Linaclotide Plecanatide	Increased synthesis of cyclic GMP→ enhanced chloride, bicarbonate secretion into intestinal lumen, water secretion	Chronic idiopathic constipation in adults (not currently a first line agent)			
Sodium/hydrogen exchanger inhibitor	Tenapanor	Inhibitor of an Na+-H+ exchanger absorption of Na and enhances intestinal fluid volume and transit	Constipation predominant IBS			
μ receptor antagonist		Peripherally acting μ receptor antagonist	Opioid induced constipation refractory to other laxatives			

Drug Table:
Drugs used to palliate NAUSEA/VOMITING

Drug Class	Medications	Mechanism	Indications	Side Effects	Contraindications	Comments
Dopamine Receptor Antagonist	Prochlorperazine (Compazine)	Central: Blocks dopamine receptors in CTZ Peripheral: Blocks GI vagus nerve projections to the vomiting center	Opioid induced nausea & vomiting Primary GI disorders (ie gastroentritis)	Extrapyramidal effects Acute dystonic reactions		
Dopamine receptor antagonist	Metoclopramide (Reglan)	Central and peripheral dopamine inhibition Prokinetic on upper GI tract (stomach)	Moderately emetogenic chemotherapy induced nausea & vomiting Postoperative N/V Dysmotility of upper GI tract – gastroparesis and gastric stasis	Tardive dyskinesia Extrapyramidal side effects Acute dystonic reaction	Cautious use in patients with Parkinson disease	Black box warning – avoid use greater than 12 weeks – risk of Tardive Dyskinesia
5HT-3 Receptor Antagonist	Ondansetron (Zofran)	Central inhibition of	Highly emetogenic	QT prolongation	Prolonged QT	Potent antiemetic

		dopamine receptors in CTZ Peripheral block of 5HT-3 induced transmission of vagal stimulation of vomiting center	chemotherapy induced N/V Radiation induced N/V Postoperative N/V	Headache		
Neurokinin 1 (NK1) Receptor Antagonist	Aprepitant	Central inhibition of NK1 receptors in chemoreceptor trigger zone	Prevention of nausea/vomiting with highly emetogenic chemotherapy			Augments activity of 5HT3 antagonist + glucocorticoid
Histamine 1 receptor antagonist	Promethazine (Phenergan)	Blocks H1 receptors of vestibular apparatus	Motion Sickness	Sedation		
Anticholinergic	Scopolamine	Blocks cholinergic receptors of vestibular apparatus	Motion sickness	Delirium Dry mouth Urinary retention	Glaucoma	
Steroids	Dexamethasone	Blocks CNS projections to the vomiting center	Increased intracranial pressure In combination with 5HT3 antagonist, NK1 antagonist for chemotherapy associated nausea/vomiting			

Benzodiazepine	Lorazepam	Blocks CNS projections to the vomiting center	Anxiety induced nausea/vomiting			
Cannabinoid	Dronabinol	Synthetic delta-9-THC, Central CB1 agonist	Breakthrough chemotherapy associated nausea/vomiting	Euphoria Dysphoria Sedation Paranoid delusions Hypotension		Very narrow therapeutic window