GERD, PUD, H-Pylori & Gastroparesis: An update

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• Non financial: No nonfinancial relationship exists
Objectives

• To educate the current treatment guidelines for GERD and peptic ulcer disease

• To learn the treatment of H-pylori infection and its current pharmacologic management

• To understand the treatment of Gastroparesis and its current clinical recommendations
GERD

- “A condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications” (Montreal Consensus)
Pathogenesis

GERD is complex, an imbalance between

- **Defensive factors protecting the esophagus**
  - anti-reflux barriers
  - esophageal acid clearance
  - tissue resistance

- **Aggressive factors from the stomach**
  - gastric acidity
  - Volume
  - duodenal contents

Feldman, Friedman, & Brandt, 2015, pg. 907
Gastric secretion

- Stomach secretes water, electrolytes (H+, K+, Na+, Cl-, HCO3-), Enzymes (pepsins, gastric lipase), and glycoproteins (intrinsic factor, mucins).

<table>
<thead>
<tr>
<th>Product</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloric acid</td>
<td>Provides optimal PH for pepsin and gastric lipase</td>
</tr>
<tr>
<td></td>
<td>Assists duodenal inorganic iron absorption</td>
</tr>
<tr>
<td></td>
<td>Negative feedback of gastrin release</td>
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<tr>
<td></td>
<td>Stimulation of pancreatic HCO3- secretion</td>
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<td></td>
<td>Suppression of ingested microorganisms</td>
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<tr>
<td>Pepsins</td>
<td>Early hydrolysis of dietary proteins</td>
</tr>
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<td></td>
<td>Liberation of vit B12 from dietary protein</td>
</tr>
<tr>
<td>Gastric Lipase</td>
<td>Early hydrolysis of dietary triglyceride</td>
</tr>
<tr>
<td>Intrinsic factor</td>
<td>Binding of Vit B12 for subsequent ileal absorption</td>
</tr>
<tr>
<td>Mucin/HCO3-</td>
<td>Protection against noxious agents including hydrochloric acid and pepsins</td>
</tr>
</tbody>
</table>

Feldman, Friedman, & Brandt, 2015, pg. 1033
The Proton Pump

Gastric hydrogen potassium ATPase (Adenosine triphosphate)

- Is an integral membrane protein capable of moving protons across a biological membrane
- The parietal cells secretes protons H+ and ATP
- ATPase provides the cell the energy necessary for active pumping of protons

Feldman, Friedman, & Brandt, 2015, pg. 1031
The Proton Pump

https://www.youtube.com/watch?v=fa60VhclNo&t=2s
Peptic Ulcer Disease

Peptic ulcerations are excavated defects in the gastrointestinal mucosa that result when epithelial cells damage due to acid and pepsin in the lumen.

Feldman, Friedman, & Brandt, 2015, pg. 1089
Pathogenesis

• Refers to ulceration of stomach, duodenum or both

• **Pre-epithelial defense mechanism**
  – Gastric epithelial cells/Brunner’s Gland secretes mucus and bicarbonate
  – pH is maintained in neutral

• **Epithelial defense mechanism**
  – It minimizes acid-peptic injury, limits the diffusion of hydrogen ion into the mucosa

• **Post-epithelial defense mechanism**
  – Blood flow provides much of the energy and maintain epithelial cell integrity

Feldman, Friedman, & Brandt, 2015, pg. 1089
H-Pylori Infection

- H-pylori is a gram-negative, spiral, flagellated bacterium.
- Unique organism produces urease and protects itself from acid injury and its flagella enable the organism to burrow through the gastric mucus layer.
- Spread: fecal – oral route
- Inflammation (gastritis) found in almost all
- Can lead to gastric atrophy, peptic ulceration (80% Duodenal ulcer and 60% gastric ulcer), intestinal metaplasia, and gastric cancer

Feldman, Friedman, & Brandt, 2015, pg. 1094
Gastroparesis

- Gastroparesis is defined as a syndrome of delayed gastric emptying in the absence of mechanical obstruction
- Cardinal symptoms: early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain
- Gastroparesis seen in 30-60% of diabetic patients
- Diagnosis typically by history and physical followed by EGD and radiolabeled Scintigraphy

Feldman, Friedman, & Brandt, 2015, pg. 723
Gastroparesis

- https://www.youtube.com/watch?v=veVxI4CeE
Gastric motor and sensory physiology

• Gastric pacemaker
• Motor response to a meal
  – Receptive relaxation and accommodation
  – Abolition of the migrating motor complex
  – Intragastric meal distribution and emptying

Feldman, Friedman, & Brandt, 2015, pg. 1000-06
Antacids

- Antacids are a class of medicines that neutralize acid in the stomach
- Contents: Aluminum, calcium, or magnesium
- Action: the bases counteract the stomach acid and lower PH
- Onset of action: Quick and symptom relief
- Available: liquid or tablets
- Use: short term use for dyspepsia/indigestion/heartburn/reflux
<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Gone</td>
<td>Aluminum hydroxide/magnesium carbonate</td>
</tr>
<tr>
<td>Di-Gel</td>
<td>Aluminum hydroxide/Mg hydroxide/Simethicone</td>
</tr>
<tr>
<td>Mylanta</td>
<td>Aluminum hydroxide/Mg hyd/Simethicone</td>
</tr>
<tr>
<td>Neut</td>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td>Gas-X with Maalox extra streg</td>
<td>Calcium carbonate/Simethicone</td>
</tr>
<tr>
<td>Gaviscon Extra strength</td>
<td>Alum hydroxide/Mg carbonate</td>
</tr>
<tr>
<td>Gaviscon Regular Stregth Liq</td>
<td>Alum hydroxide/Mg carbonate</td>
</tr>
<tr>
<td>Icar Prenatal Chewable Calcium</td>
<td>Calcium carbonate</td>
</tr>
<tr>
<td>Maalox Adv Regul Strength</td>
<td>Alum hydroxide/Mg hydroxide/Simethicone</td>
</tr>
<tr>
<td>Maalox regular strength</td>
<td>Calcium carbonate</td>
</tr>
<tr>
<td>Masanti Supreme</td>
<td>Calcium carbonate/Mg hydroxide</td>
</tr>
<tr>
<td>Mi-Acid</td>
<td>Alum hydroxide/Mg hydroxide/Simethicone</td>
</tr>
<tr>
<td>Mi-Acid Double Strength</td>
<td>Calcium carbonate/Mg hydroxide</td>
</tr>
<tr>
<td>Milantex</td>
<td>Alum hydroxide/Mg hydroxide/Simethicone</td>
</tr>
<tr>
<td>Mintox</td>
<td>Alum hydroxide/Mg hydroxide/Simethicone</td>
</tr>
<tr>
<td>Mintox Plus</td>
<td>Alum hydroxide/Mg hydroxide/Simethicone</td>
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</tbody>
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Maalox
Brand name: Maalox Advanced

Clinical pharmacology

- **Mechanism of Action:** An antacid that reduces gastric acid by binding with phosphate in the intestine, and then is excreted as aluminum carbonate in feces. Aluminum carbonate may increase the absorption of calcium due to decreased serum phosphate levels. The drug also has astringent and adsorbent properties.

- **Therapeutic Effect:** Neutrilizes or increase gastric PH

- **Indications:** Heartburn, indigestion, bloating, sour stomach, upset stomach

- **Dose:** each 5ml (200mg Alum Hyd/200 mg Mg Hyd/20 mg Simethicone)
  - Adults-2-4 tsp QID; Children-under 12 do not use

- **Contraindication:** Kidney disease, Mg restricted diet, intestinal obstruction, hypersensitivity to aluminum

(Maalox, 2017)
Side Effects:

*PO:* Chalky taste, mild constipation, stomach cramps  
*PO:* Nausea, vomiting, speckling or whitish discoloration of stools

**Serious reactions**
- Prolonged constipation may result in intestinal obstruction.
- Excessive or chronic use may produce hypophosphatemia manifested as anorexia, malaise, muscle weakness, or bone pain and resulting in osteomalacia and osteoporosis.
- Prolonged use may produce urinary calculi.

**Patient/family education**
- Thoroughly chew tablets, follow with glass of water
- Do not take other drugs within 1 hour before or 4 hrs after
- Stool may appear white
- Maintain adequate fluid intake

(Maalox, 2017)
H2 receptor Blockers

- Mechanism of action: It inhibits the H2 receptors of the parietal cells. The efficacy is identical among all different types.

Common H2 Blockers

- **Nizatidine (Axid)**
  - Adult dose: 75mg, 150 mg, 300 mg
  - Pediatric dose: 10 mg/kg/day

- **Famotidine (Pepcid, Pepcid AC)**
  - 40 mg daily or 20 mg BID
  - 20 mg IV every 12hrs

- **Cimetidine (Tagamet, Tagamet HB)**
  - 300 mg IV or IM q 6-8 hrs
  - 800-1600 mg oral dose per day

- **Ranitidine (Zantac)**
  - 50 mg IM or IV q 6-8 hrs/day
  - 150 mg BID or 300 mg QD
Ranitidine (Zantac)

• Zantac is a reversible inhibitor of the action of histamine at the H2 receptor site on the gastric cells.

Clinical Pharmacology:
• **Absorption** - 50% absorbed after oral administration, decreases with concurrent use of antacids
• **Distribution** - The volume of distribution is 1.4L/kg
• **Metabolism** - Principal metabolite is found in urine, hepatic dysfunction was not significant
• **Excretion** - Urine

(U.S. Food & Drug Administration, 2005)
Pharmacodynamics:

- **Effect on gastric secretion**: Zantac inhibits both nocturnal and daytime basal gastric acid secretion stimulated by food. Do not affect gastrin, pepsin, or intrinsic factor secretion
- **Indications and usage**: Duodenal ulcer, gastric ulcer, erosive esophagitis, Zollinger-Ellison syndrome, and GERD
- **Contraindications**: hypersensitivity to the drug
- **Drug interactions**: concurrent use with Coumadin can change the INR, can affect the bioavailability of drugs which are PH dependent. No carcinogenic effects.
- **Pregnancy**: Category B. It is secreted in human milk.
- **Dose**: adults-150 mg BID for active ulcer, 150 mg daily for maintenance
  - Paediatrics-1-16 years: 2-4mg/kg/twice daily
- **Side Effects**: Dizziness, insomnia, vertigo, rare reports of arrhythmias, gynecomastia, impotence, rare reports of pancytopenia, alopecia

(U.S. Food & Drug Administration, 2005)
Proton Pump Inhibitors (PPIs)

- PPIs suppresses the final step in gastric acid production by covalently binding to the \((H^+ , K^+)\)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the \((H^+ , K^+)\)-ATPase results in a duration of anti-secretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

- Generally used to treat ulcer disease as well as for prophylaxis.
## List of PPIs

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
</tr>
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<tbody>
<tr>
<td>Nexium 24HR</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Aciphex</td>
<td>Rabeprazole</td>
</tr>
<tr>
<td>Protonix</td>
<td>Pantoprazole</td>
</tr>
<tr>
<td>Prevacid</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Zegrid</td>
<td>Omeprazole/Sodium Bicarbonate</td>
</tr>
<tr>
<td>Prilosec</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Dexilant</td>
<td>Dextralansoprazole</td>
</tr>
<tr>
<td>Strontium</td>
<td>Esomeprazole magnesium</td>
</tr>
</tbody>
</table>

**Protonix**
Pharmacokinetics:

- **Absorption** - Peak plasma concentration in 2.5 hrs, 77% bioavailability, concurrent use of antacids has no effect. With food may delay its absorption.
- **Distribution** - mainly in extracellular fluid.
- **Metabolism** - Through liver CYP450.
- **Excretion** - 71% excreted via urine, 18% via feces through biliary excretion.

(U.S. Food & Drug Administration, 2017)
Pharmacodynamics:

- **Anti-secretory activity**: Acid secretion returned to normal in one week
  - Decreased gastrin levels to normal in 3 months with 40 mg daily dose

- **Indications and Use**: GERD, erosive esophagitis, Z-E syndrome

- **Contraindications**: allergies

- **Drug interactions**: Rilpivirine containing products, methotrexate

- **Pregnancy**: Category C (use when risk outweighs benefit)

- **Dose**: 20 and 40 mg (oral), 40 mg suspension

- **Warning**: Hypersensitivity, acute interstitial nephritis, C-diff diarrhea, Bone fracture, SLE, B12 deficiency, Hypomagnesemia

- **Side effects**: nausea, diarrhea, headache, abdominal pain, dizziness, arthralgia

(U.S. Food & Drug Administration, 2017)
Sucralfate (carafate)

- Sucralfate is an Alpha-D-glucopyranoside, β-Dfructofuranosyl-, octakis-(hydrogen sulfate), aluminum complex.

Clinical pharmacology:
- Absorption - minimally absorbed from the GI tract
- Excretion - small amount absorbed are excreted through urine
- Mechanism of Action: sucralfate’s antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14 to 16 meq of acid-neutralizing capacity per 1 g dose of sucralfate.

(U.S. Food & Drug Administration, 2013)
• **Indication and usage:** short-term use (up to 8 weeks) for active duodenal ulcer

• **Contraindication:** hypersensitivity to the drug

• **Precaution:** Chronic renal failure and dialysis pts, diabetics,

• **Pregnancy:** category B

• **Drug interaction:** Bioavailability is reduced with cimetidine, digoxin, fluoroquinolone antibiotics, ketoconazole, l-thyroxine, phenytoin, quinidine, ranitidine, tetracycline, and theophylline.

• **Dose:** adults 1 gm (10ml) 4 times per day, Not for pediatrics. Administer in empty stomach

• **Adverse reactions:** diarrhea, dry mouth, indigestion, nausea, vomiting, dizziness, headache, hyperglycemia, delayed gastric emptying

(U.S. Food & Drug Administration, 2013)
Guideline: Medical management of GERD

- 8 week course of PPI
- Delayed release PPI should be administered 30-60 min before meals
- PPI therapy initiate once daily, may increase to BID if night-time symptoms
- Non-responders to PPI should be referred for evaluation
- May switch to different PPI for partial responders
- Maintenance PPI therapy: for pts with symptoms, Barrett’s esophagus, and complications. Use lowest effective dose
- H2RA therapy: used for maintenance option in pts with out erosive esophagitis. It may be added to daytime PPI therapy for night-time relief
- There is no role for sucralfate in GERD
- PPIs are safe in pregnant patients if clinically indicated

(Katz, Gerson & Vela, 2013)
Management of GERD

Symptoms of GERD

Are there alarm symptoms?

yes -> Endoscopy for alarm symptoms/out of guidelines

No -> Initial management (8 weeks)
- PPI/antacids
- Behavior Modification
- Endoscopy for pts>50 and symptoms >10 years

Symptom Relief?

yes -> Encourage single trial step down therapy

No -> Endoscopy

Positive?

yes -> Mgmt for negative endoscopy

No -> Return to PPI Therapy

Symptoms Recur?

No -> Continue Step Down Therapy

yes -> Mgmt for Refractory Reflux

Institute for Clinical systems Improvement, 2006
Potential PPI complications

- **Vitamin B12 Deficiency**
  - Dharmarajan, T.S. et al, CMAJ, 2010

- **Increased Pneumonia Risk**
  - Eom, C.S. et al, CMAJ, 2010

- **Reduced Gallbladder Motility**

- **Increased Risk of Osteoporosis Fractures**
  - ETargownik, L.E. et al, CMAJ, 2010
  - Yang, Y.X. et al, JAMA, 2006
  - Corley, D et al, Gastroenterology, 2006

- **PPI Interaction With Plavix**
  - Ho, P.M. et al, JAMA, 2009

- **Increased Risk of Fundic Gland Polyps**
  - Jalving, M. et al., Ailment Pharmacol Therapy, 2006

- **Magnesium Deficiency**
  - Cundy, T. et al, Clinical Endocrinology, 2008

- **Increased Risk of Bacterial Gastroenteritis**

- **Increased Risk of Small Intestinal Bacterial Overgrowth**
  - Lombardo, L. et al, Clinical Gastro & Hep, 2010
Pre-procedure Endoscopy to evaluate the valve
H-pylori Infection

- Worldwide prevalence of 50%
- US and Europe-20 to 50%
- H-pylori associated with upper GI disease: functional dyspepsia, Chronic gastritis, peptic ulcer disease, gastric cancer, Lymphoma
- Eradication-Increased rate of peptic ulcer healing and reduced risk of gastric cancer

Therapy
- **Triple:** Amoxicillin or metronidazole, Clarithromycin, and PPI
- **Quadruple:** PPI or H2RA, Bismuth, Metronidazole, Tetracycline

(Xin, et al. 2016)
## H-Pylori Treatment regimens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pylera</td>
<td>Bismuth Subcitrate Potassium/Metronidazole/tetracycline 140 mg-125 mg-125 mg oral capsule: 3 capsules orally 4 times daily, after meals and at bedtime for 10 days. Omeprazole 20 mg orally twice daily after morning meal and after evening meal.</td>
</tr>
<tr>
<td>Omeclamox-Pak</td>
<td>Omeprazole delayed-release capsules 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg, each given twice daily, for 10 days, before eating a meal.</td>
</tr>
<tr>
<td>Prevpac</td>
<td>30 mg PREVACID, 1 g amoxicillin, and 500 mg clarithromycin administered together twice daily for 10 or 14 days</td>
</tr>
</tbody>
</table>
PREVPAC consists of a daily administration card containing two Prevacid 30 mg delayed release capsules, four amoxicillin 500 mg capsules, USP, and two clarithromycin 500 mg tablets, USP, for oral administration

- **Pharmacokinetics:** Coadministered all three are not studied, studies done individually
- **Prevacid:** absorption and onset of action is in 1.7 hrs with a bioavailability of 80%, 97% bound to plasma protein, metabolized in the liver, excreted in urine and feces
- **Amoxicillin:** Rapidly absorbed and peak level in 1-2 hours, diffuses into body tissues and fluids, metabolized and excreted through urine
- **Clarithromycin:** Rapidly absorbed and peak level in 2-2.5hrs, metabolized through liver and excreted in urine

(U.S. Food & Drug Administration, 2013)
Pharmacodynamics:

- **Antisecretory activity:** Acid suppression may enhance the effect of antimicrobials in eradicating Helicobacter pylori (H. pylori).
- **Indications and Usage:** H-pylori eradication, reduce the risk of duodenal ulcer recurrence
- **Contraindications:** Hypersensitivity, co administering with cisapride, pimozide, astemizole, terfenadine, ergotamine or dihydroergotamine can lead to prolonged QT interval, Clarithromycin and statins should not be co administered due to Rhabdo
- **Pregnancy:** category C
- **Dose:** The recommended adult oral dose is 30 mg PREVACID, 1 g amoxicilllin, and 500 mg clarithromycin administered together twice daily (morning and evening) for 10 or 14 days

(U.S. Food & Drug Administration, 2013)
Adverse effects:

- Body as a Whole - abdominal pain
- Digestive System - dark stools, dry mouth/thirst, glossitis, rectal itching, nausea, oral moniliasis, stomatitis, tongue discoloration, tongue disorder, vomiting
- Musculoskeletal System - myalgia
- Nervous System - confusion, dizziness
- Respiratory System - respiratory disorders
- Skin and Appendages - skin reactions
- Urogenital System - vaginitis, vaginal moniliasis

(U.S. Food & Drug Administration, 2013)
H-pylori Treatment-Clinical Guidelines

- Ask about any previous antibiotic exposure(s)
- All three options can be used as first line therapy

- Sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5–7 days is a suggested first-line treatment option

- Hybrid therapy consisting of a PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 days is a suggested first-line treatment option

- Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5–7 days is a suggested first-line treatment option

(Chey, et al. 2017)
The main determinants of successful H. pylori eradication are:

- the choice of regimen
- the patient’s adherence
- the sensitivity of the H. pylori strain to the combination of antibiotics administered

H. pylori antimicrobial resistance can be determined by culture and/or molecular testing - not in U.S

Confirm eradication using

- urea breath test
- fecal antigen test or biopsy based testing at least 4 weeks post therapy
- PPI therapy has been withheld for 1–2 weeks.

(Chey, et al. 2017)
Metoclopramide hydrochloride, the active ingredient of Reglan, is a dopamine-2 receptor antagonist.

**Clinical Pharmacology:**
- **Mechanism of Action** - increases the tone and amplitude of gastric contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum. It do not stimulate gastric, biliary, or pancreatic secretions
- **Pharmacokinetics** - for IV dose 80% bioavailability with peak of 1-2 hrs, bound to plasma protein, enzymatic metabolism, and excreted through urine.
- **Indication and usage** -
  - 4-12 weeks treatment for patients who failed conventional therapy for GERD
  - Acute and recurrent diabetic gastroparesis
  - Not recommended for pediatric use

(U.S. Food & Drug Administration, 2017)
• **Dose**- Adult dose is 10-15 mg QID for 4-12 weeks.
  – Administer 30 minutes before the meal
  – Maximum dose is 60 mg/day.
  – Elderly-5 mg QID
  – Dose adjustments-severe hepatic impairment, creatinine clearance <60ml/min, concomitant use of strong CYP2D6 inhibitors (5mg QID)
  – Avoid reglan >12 weeks

• **Contraindications**- h/o tardive dyskinesia, GI bleed, mechanical obstruction, or perforation, pheochromocytoma, epilepsy, hypersensitivity

• **Warning**- Tardive Dyskinesia, extrapyramidal symptoms, Neuroleptic malignant syndrome, Depression, HTN, Fluid retention, Hyperprolactinemia

(U.S. Food & Drug Administration, 2017)
• **Adverse reactions:** Restless, drowsiness, fatigue, lassitude, insomnia, headache, confusion, nausea, diarrhoea, urinary frequency, hepatic toxicity with certain drugs, visual disturbances

• **Drug interactions**—antipsychotics, strong CYP2D6 inhibitors, MAO inhibitors, CNS depressants, drugs that impair GI motility, Dopaminergic agonists,

• **Pregnancy**—no increased risk

• **Lactation**—Crosses placenta barrier and present in human milk, watch for extrapyramidal symptoms in neonates

(U.S. Food & Drug Administration, 2017)
Gastroparesis-Treatment Guideline

• In addition to dietary therapy, prokinetic therapy should be considered

• **Metoclopramide** is the first line of prokinetic therapy, should be administered at the lowest effective dose in a liquid form to facilitate absorption

• Discontinue therapy if any side effects

• **Domperidone** is the second choice (a baseline EKG is recommended due to prolonged QT)

• **Erythromycin** can be used to improve symptoms. IV should be considered in hospital patients. Long-term effectiveness of oral therapy is not available.

• **Antiemetics** should be used to improve nausea and vomiting

• **Tricyclic antidepressants** can be considered for nausea and vomiting, however will not improve gastric emptying

(Camilleri, et al. 2013)
References:

- U. S. Food and Drug Administration (2004). Zantac: Prescription information. FDA Public health Advisory, MD
- U. S. Food and Drug Administration (2017). Protonix: Prescription information. FDA Public health Advisory, MD
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- U. S. Food and Drug Administration (2017). Reglan: Prescription information. FDA Public health Advisory, MD
Thank you

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