Functional Bowel Disorders: A Discussion of IBS, Chronic Constipation and GERD

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Disclosures

- Speaker Bureau
  - Sanofi-Pasteur, Merck, Pfizer Seqirus, Moderna: Vaccines
  - Exact Sciences: Colorectal cancer
  - AstraZeneca: Asthma and COPD
- Consultant
  - Sanofi-Pasteur, Merck, Pfizer, Moderna, and Seqirus: Vaccines
  - AstraZeneca: Asthma and COPD
  - GSK: OA/Pain

All relevant financial relationships have been mitigated.

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Objectives

Upon completion, the participant will be able to:

- Discuss latest statistics regarding functional bowel disorders in men and women
- Differentiate functional bowel disorders by clinical presentation
- Discuss pharmacologic treatment options for patients with functional bowel disorders

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Irritable Bowel Syndrome

ACG Clinical Guideline: Management of Irritable Bowel Syndrome

Lacy, Brian E. PhD, MD, FACG1; Pimentel, Mark MD, FACG2; Brenner, Darren M. MD, FACG3; Chey, William D. MD, FACG4; Keefer, Laurie A. PhD5; Long, Millie D. MDMPH, FACG (GRADE Methodologist)6; Moshiree, Baha MD, MSc, FACG7 ACG Clinical Guideline: Management of Irritable Bowel Syndrome, The American Journal of Gastroenterology: January 2021 - Volume 116 - Issue 1 - p 17-44 doi: 10.14309/ajg.0000000000001036

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Dysmotility and Abnormalities in 5-HT (5 Hydroxytryptamine) Contribute to Functional Bowel Disorders?

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Role of 5-HT (5-hydroxytryptamine)

- 5-HT is a neurotransmitter within the enteric nervous system
- Gut contains 95% of all 5-HT in the body
- 14 sub-types of 5-HT
  - 5-HT(3) and 5-HT (4) receptors are proving to be very important in the patient with IBS

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Role of 5-HT(3) Receptors (5-hydroxytryptamine)

- 5-HT(3) receptors are extensively distributed within the gastrointestinal tract
- These receptors have been implicated in the mechanisms controlling colonic motility/ transit time, gastrointestinal secretions and pain.

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Role of 5-HT(3) Receptors (5-hydroxytryptamine)

- Blockade of these receptors has been shown to reduce intestinal distension, reduce bowel frequency, slows colonic transit/motility, and increases jejunal water and sodium absorption.
- Alosetron - works on the 5-HT (3) receptors
  - Is now available

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Role of 5-HT(4) Receptors (5-hydroxytryptamine)

- Blockade of these receptors has been shown to increase motility.
- Two medications on market
  - Prucalopride (Motegrity)
  - Tegaserod (Zelnorm)
    - ** Withdrawn from market 2022

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

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Pathophysiology

- Diarrhea and constipation are explained by the alteration in motor function.
- Abnormal pain experienced by patients with IBS is believed to be caused by excessive sensitivity to colonic distension.
  - Smaller amounts of distension causes more abdominal distress

Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology. 2000;118:842-848.

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The Role of Stress in IBS

- Stress is widely believed to play a significant role in the pathophysiology and clinical presentation of IBS.
- Genetically predisposed individual.
- Sustained stress can result in a permanent increased stress response in the central stress circuits/pathways.

Drossman DA. Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? Am J Med 1999;107:41S-50S.
Drossman DA. Irritable bowel syndrome and sexual/physical abuse history. Eur J Gastroenterol Hepatol 1997;9:327-30.

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Irritable Bowel Syndrome (PI-IBS) Four Years After The Outbreak Of Waterborne Gastroenteritis (GE)

- Purpose: Determine the incidence and natural history of Post Infectious-IBS (PI-IBS) in a population exposed to a municipal water contamination in Canada in 2000
- Methods/ Results:
  - Bowel Disease Questionnaire employed to identify IBS via Rome I criteria (n=1587)
  - 1,012 (63.8%) reported GE in '00, and of those, 273 (17.2%) fulfilled Rome I IBS criteria in '04
    - **Marshall J et al, DDW 2006 abstract 344**

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Irritable Bowel Syndrome (PI-IBS) Four Years After The Outbreak Of Waterborne Gastroenteritis (GE)

- Conclusions:
  - The prognosis of PI-IBS appears favorable, with spontaneous resolution in half of patients.
  - Independent predictors of IBS in '04 were: female gender, weight loss, abdominal pain, and duration of diarrhea at outbreak

- **Marshall J et al, DDW 2006 abstract 344**

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What About SIBO? (Small Intestinal Bacterial Overgrowth)

- Increasing attention to the role of small intestinal bacterial overgrowth in IBS
  - 84% of patients diagnosed with IBS had SIBO compared with 20% of control group
  - 35% of IBS group treated with neomycin had improvement in symptoms vs. 11.4% of placebo group
    - Further research is clearly needed
  - Now available: hydrogen breath test

Pimentel, M, Chow, EJ, Lin HC. Eradication of small intestinal bacterial Overgrowth reduces symptoms of irritable bowel syndrome: a double Blind, randomized controlled study. Am J Gastroenterol. 2003;98:412-19

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Pathophysiology of Functional Bowel Disorders

Altered Serotonin Signaling
SERT, TpH1, 5-HT release, EC cells

↓

Altered GI Physiology
Motility, sensitivity, secretion

↓

Clinical Symptoms and Disorders
Chronic Constipation
IBS- D, C and M

Coates MD et al. *Gastroenterology*. 2004;126:1657-1664.
Crowell M et al. *Curr Opin Investig Drugs*. 2004;5:55-60.
Baig MK et al. *Colorectal Dis*. 2002;4:348-354.

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Diagnosis of Functional Bowel Disorders

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Rome III Diagnostic Criteria for Irritable Bowel Syndrome (all subtypes)

- At least 3 months, with onset at least 6 months previously of recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) associated with 2 or more of the following:
  - Improvement with defecation; and/or
  - Onset associated with a change in frequency or stool; and/or
  - Onset associated with a change in form (appearance) of stool

ROME III *Gastroenterology* 2006:130:1377-1390.

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Diagnostic Criteria: Chronic Constipation

- Characterized by unsatisfactory defecation that results from:
  - Infrequent stools or
  - Difficult stool passage
    - Characterized by: straining, sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool
  - Or, a combination of both

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

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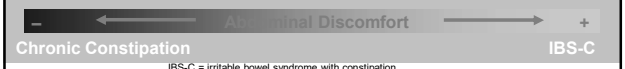
Chronic Constipation and IBS-C Share GI Dysmotility Symptoms

Symptoms >3 months	Chronic Constipation	IBS-C
Straining	+++	+++
Hard/lumpy stools	+++	+++
<3 BM/wk	+++	+++
Feeling of incomplete evacuation	+++	+++
Bloating/abdominal distension	++	+++
Abdominal pain/discomfort	+	+++



Chronic Constipation — IBS-C

IBS-C = irritable bowel syndrome with constipation.

Thompson WG et al. *Gut.* 1999;45(suppl 2):II43-II47.
Drossman DA et al. *Gastroenterology.* 1997;112:2120-2137.

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Red Flags

- Evaluate for alarm features
  - Reported weight loss
  - Nocturnal symptoms
  - Recent travel history
  - Family history of colon cancer or inflammatory bowel disease
  - Family history of Celiac disease
  - Onset in older patients (> 50)
  - Fevers
  - Oral ulcers
  - **B**loody stools

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Red Flags

- Evaluate for alarm features
  - Abnormal exam (weight loss, arthritis, rashes)
  - Fever, oral ulcers
  - Anemia
  - Leukocytosis
  - Abnormal chemistry – abnormal LFT's, Creatinine
  - Elevated sed rate
  - Abnormal TSH
  - Positive fecal occult blood test

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ACG Evidence-Based Guideline: Diagnostic Testing

Chronic Constipation

- Among CC patient without alarm features, there are inadequate data to make a recommendation about the *routine* use of diagnostic tests

Irritable Bowel Syndrome

- Among IBS patients without alarm features, the *routine* use of colonoscopy (<45 years old), flexible sigmoidoscopy, thyroid function tests, etc is not recommended.
- Routine testing for celiac disease should be done for those with IBS-D
- Individuals $\geq$ 45 years should undergo colorectal cancer screening

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Laboratory Evaluation

- CRP, F. calprotectin, F. lactoferrin should be considered for those with IBS-D (CRP and F. Cal: best)
- Fecal lactoferrin[1]
  - During intestinal inflammation, activated leukocytes infiltrate the mucosa and lumen, increasing the level of fecal lactoferrin[1]
  - Lactoferrin is a glycoprotein secreted by mucosal membranes
  - Fecal lactoferrin is elevated in patients suffering from active inflammatory bowel disease (IBD) but not in those with irritable bowel syndrome (IBS)

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Possible Additional Tests

- Celiac Disease Testing
  - 4.6% of individuals with IBS are likely to have this present; Compared with 0.25-0.5% of general population
  - Celiac Panel: Immunoglobin A (IgA), anti-tissue transglutaminase (tTGA), and IgA anti-endomysial antibodies (AEA)
- Colonoscopy: routine age 45 years
  - Positive occult blood test
  - Nocturnal awakenings
  - Colon cancer

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Consider Pelvic Floor Dysfunction and Colonic Inertia

- Rectal manometry
  - Catheter inserted into rectum to assess muscle pressure and nerve function
- Defecography
  - Done on individuals who have had an inconclusive result on rectal manometry or individuals suspected of a structural abnormality of the rectum
  - Barium is instilled into rectum. Patient then sits on radiolucent commode and pictures are taken as the patient defecates
- Sitz Marker Study
  - Procedure to assess colonic motility
  - Ingest Sitz Marker capsule; brought back in for abdominal x-ray on day 1, day 3 and day 5
  - Normal: complete evacuation by day 5

http://www.medscape.com/viewarticle/501075_4
Accessed on September 13, 2006.

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Case Study

- **45 year old woman presents with a 30+ year history of straining, hard/lumpy stools, and a sense of incomplete evacuation. She passes stool approximately 2 times per week.**
- **Upon further questioning, she also notes frequent bloating, minimal abdominal discomfort, and partial relief with defecation.**

What is her diagnosis?

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Treatment Options for Functional Bowel Disorders

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Diet

- Trial of FODMAP diet is recommended to see if symptoms improve
  - Eliminating dietary fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
  - Dietitian referral is important, if able
- Trial of peppermint oil is recommended to see if it provides symptom improvement

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Pharmacologic Options

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Bulking Agents: Soluble Fiber Preferred

- Bulking agents
  - Psyllium (Metamucil): 15-25 grams per day
    - 1 teaspoon or packet 1 – 3 times/day
  - Methylcellulose (Citrucel): 19 – 57 grams per day
    - 1 heaping tablespoon 1 – 3 times/day
  - Polycarbophil (Fibercon)
    - 625 mg tablet
    - 2 tablets 1 – 4 times daily

Bijerk CJ, Muris JWM, Knottnerus JA et al. Systematic review: the role of different types of fiber in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;19:245-251.

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Bulking Agents

- Begin these agents very slowly
  - Bloating, flatulence and abdominal pain are the side effects frequently encountered
- Advance dosage every 2 – 4 weeks
- Each patient will respond differently to each agent
  - Try various products

Bijerk CJ, Muris JWM, Knottnerus JA et al. Systematic review: the role of different types of fiber in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;19:245-251.

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Summary of Trials on Bulking Agents

- 13 trials; 7 met high quality criteria
  - 3 trials showed a statistically significant benefit
- Supplemental fiber
  - Accelerates colonic and oro-anal transit
  - Improves constipation with sufficient supplementation (20-30g per day)
  - May worsen some IBS symptoms
    - Bloating and pain
  - Limited data suggest equivocal benefits in IBS

Muller-Lissner, *BMJ* 1988;296:615
Cann et al, *Gut* 1984; 25:168
Coot et al, *Gastroenterology* 1990; 998:66
Lucey et al, *Gut* 1987;28:221

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Polyethylene Glycol: Not Recommended by ACG

- Polyethylene glycol (Miralax)
  - Osmotic agent
- Indication: Constipation
- Adult dosage: 17 g in 8 ounces of water
  - FDA indication: once daily for up to 2 weeks
- Precautions
  - Nausea and vomiting
- Contraindications
  - Bowel obstruction

Am J Gastroenterol 2002;97: Suppl Nov. S18-25.

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Antispasmodics: Not Recommended by ACG

- Anticholinergic agents (Antispasmodic)
  - –Reduce sigmoid motility in response to fat
  - –Decrease postprandial pain and distension by inhibiting postprandial colonic contractions

ROME III *Gastroenterology* 2006:130:1377-1390.

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Anticholinergic Agents

- Dicyclomine (Bentyl)
  - –20mg-40mg ac
- Hyoscyamine sulfate (Levsin)
  - –0.125mg 1-2 tabs po q 4 hours prn
  - –Levsin SL, LevBid (0.375mg 1 – 2 tablets po bid)

ROME III *Gastroenterology* 2006:130:1377-1390.

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Prescribing Information

- Precautions:
  - – Cardiovascular disease, Hypertension, Elders
- Side Effects
  - – Drowsiness
  - – Anticholinergic side effects
- Contraindications
  - – Glaucoma
  - – Unstable CV status

Hyoscyamine Product Insert

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Lactulose

- Lactulose:
  - Constulose; Enulose; Generla; Kristalose
- Dosage:
  - 10-20 g/day; increased to bid as needed
- Indication: Chronic Constipation
- Mechanism of Action: Osmotic (draws fluid into colon)
- Precautions: use with caution in those with diabetes; monitor electrolytes
- Adverse Reactions: flatulence, diarrhea, abdominal discomfort, nausea, vomiting

Product insert

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Lubiprostone

- Lubiprostone (Amitiza)
- Class:
  - Locally acting chloride channel activator
- Indications:
  - IBS-C in women 18 years of age and older
  - Chronic idiopathic constipation in the adult population
    - Men and women
    - All adults, including 65 and older

Gastroenterology 2006;130:5.

Product Insert

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Lubiprostone

- Dosage:
  - 8 mcg bid with food
  - 24 mcg bid with food
- Mechanism of Action:
  - Activates CIC-2 (found in the human intestine)
  - By increasing intestinal fluid secretion and increases motility in the intestine
- Efficacy
  - Increases BM's by 3 per week on average
  - Significant increase over placebo of spontaneous bowel movements within first 24 hours after taking medication

Gastroenterology 2006;130:5

Amitiza Product Insert

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Lubiprostone

- Side effects:
  - Nausea - 30%
  - Diarrhea – 13%
- Contraindications
  - History of mechanical GI obstruction
  - Diarrhea
- Precautions:
  - Not studied in individuals with moderate - severe hepatic or renal impairment
  - Pregnancy – C

Gastroenterology 2006;130:5 Amitiza Product Insert

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Additional Approval

- Lubiprostone
  - Opioid-induced constipation
  - Not effective for those on diphenylheptane opioids (e.g., methadone) has not been established
  - 24 mcg two times daily with food

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Linaclotide

- Brand name: Linzess
- Class:
  - Guanylate cyclase-C agonist
  - Activation of the GC-C – results in an increased in intra and extracellular concentrations of cGMP.
  - This stimulates secretion of chloride and bicarbonate into the intestinal lumen; resulting in increased intestinal fluid and accelerated transit
  - Also reduces intestinal visceral pain
- Indications:
  - Irritable bowel syndrome with constipation (IBS-C)
  - Chronic idiopathic constipation (CIC)
- Dosage:
  - IBS –C: 290 mcg once daily
  - CIC: 145 mcg once daily
  - Take on empty stomach; 30 minutes before first meal of the day
  - Taking it WITH foods – increases risk of loose stools/diarrhea
  - *** NOW available in 72 mcg dosage

http://www.frx.com/pi/linzess_pi.pdf accessed 12-20-2012

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Linaclotide

- Boxed warning:
  - Contraindicated in pediatric patients < 2 years of age
  - Safety in children < 18 years has not been established
  - Another contraindication: suspected or known mechanical gastrointestinal obstruction

https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/Final_labeling_text_10-2018-AR-updates-LINZESS-clean.pdf accessed 03-01-2022

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Linaclotide

- Precautions:
  - Pregnancy category C
  - Nursing mothers (unknown if excreted in breast milk)
- Adverse reactions:
  - Diarrhea: 16% - 20% (depending upon indication)
  - Abdominal pain: 7%
  - Approximately 8% - 9%% of patients treated with linaclotide and 3%-4% with placebo discontinued due to adverse reactions
- Drug/drug interactions:
  - NONE; does not use P450 system; nor is it an inhibitor or substrate of the P-gp (P-glycoprotein)

http://www.frx.com/pi/linzess_pi.pdf accessed 12-20-2012

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Plecanatide (Trulance)

- Class:
  - Guanylate cyclase-C agonist
- Indication:
  - Adults for treatment of chronic idiopathic constipation
- Dosage:
  - 3 mg taken orally once daily
  - With or without food; may be crushed and put in applesauce but not cut in 1/2

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208745lbl.pdf
Accessed 12-30-2017

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Other options

- Methylnatrexone bromide (Relistor)
  - Indicated for the treatment of opioid-induced constipation when other therapies are ineffective
  - Subcutaneous injection
  - Used a lot in individuals receiving palliative care
  - One dose every other day
  - Dosage is weight based

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Prucalopride (Motegrity)

- Indication:
  - Treatment of chronic idiopathic constipation (CIC) in adults
- Class:
  - Serotonin-4 (5-HT4) receptor agonist
  - Gastrointestinal prokinetic agent that stimulates colonic peristalsis and increases bowel motility

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

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Prucalopride

- Dosage:
  - 2 mg once daily
  - With or without food
- Warnings and precautions:
  - Renal dosing (CCl < 30 mL/min) : 1 mg once daily
  - Monitor patients for persistent worsening of depression and emergence of suicidal thoughts and behavior
  - Pregnancy, Lactation, and Children
- Contraindications:
  - Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

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Prucalopride

- Efficacy:
  - 2530 patients enrolled in clinical trials
    - 1251 received drug/1279 placebo
  - Responder was defined as a patient with an average of 3 or more CSBMs per week, over the 12-week treatment period
    - 33% vs. 10% and 38% vs. 18% (5 of 6 studies stat. significant)
- Drug – Drug Interactions:
  - No significant drug-drug interactions

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

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Prucalopride

- Side effects (Drug/placebo):
  - Headache (19% vs. 9%)
  - Abdominal pain (16% vs. 11%)
  - Nausea (14% vs. 7%)
  - Diarrhea (13% vs. 5%)
  - Dizziness (4% vs. 2%)
  - Vomiting (3% vs. 2%)
- Advantages:
  - Another option to the market
  - No QT prolongation

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

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Prucalopride

- Competition:
  - Tegaserod (Zelnorm) – 5-HT4 receptor agonist
    - **Withdrawn in 2022

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

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Summary: Traditional Treatment Options for IBS-D

Agent	GI Indication
Anti Diarrheal	IBS-D
Bile Acid Sequestrant	IBS-D
Selective 5 HT3 Receptor Antagonist	IBS -D
Discussion of possible psychological factors. Symptom resolution and reassurance	

Gastroenterology 2006;130:5.

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IBS - D

- Loperamide HCl (Imodium)
  - Initially: 4 mg followed by 2 mg, as needed
  - Maximum: 16 mg daily
  - Mechanism of action: slows colonic motility
  - Side effects: abdominal pain, dry mouth, nausea

Loperamide HCL Product Insert

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IBS-D

- Diphenoxylate hydrochloride and atropine (Lomotil)
  - Initially: 2.5mg
  - 1-2 pills up to 4x/day until control achieved
  - Maximum: 8 mg daily
  - Mechanism of Action: inhibits excessive GI motility and decreases GI propulsion
  - Side Effects: tachycardia, dry mouth, nausea

Lomotil Product Insert

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IBS - D

- Cholestyramine (Questran); Colesevelam (Welchol); Colestipol (Colestid)
  - Off-label usage: Not recommended by ACG
  - Bile acid sequestrant
  - Cholestyramine - Dosage: 1 packet or scoop in fluid bid
    - Maximum: 6 scoops daily
  - Colesevelam: 4 – 7 capsules daily; titrate as needed
  - Side effects:
    - Constipation
    - Impaction
    - Inhibits absorption of other medications

Gastroenterology 2006;130:5.

Product Inserts

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Alosetron

- Alosetron (Lotronex)
  - Withdrawn from the market in December of 2000
- Reintroduced in 2002
- Available under promethius prescribing program (REMS)
- Indication: IBS – D in women
- Dosage: 0.5 – 1 mg up to two times daily

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

Alosetron Product Insert

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Alosetron Post-Marketing Information

- Ischemic colitis
  - Of 275,000 patients given alosetron, ischemic colitis occurred in 80 patients
  - 74% of the cases occurred in the 1st month of alosetron use
  - Of the 80 cases, 48 hospitalizations, 6 surgeries, no deaths

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

Alosetron Product Insert

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Eluxadoline (Viberzi)

- Eluxadoline
- Class: mu-opioid receptor agonist
- Indications: IBS-diarrhea predominant
- Dosage: 100 mg two times daily with food
  - Start lower dosage (75 mg two time daily) in the following individuals
    - Concomitant OATP1B1 inhibitor (Organic Anion Transporting Polypeptide1B1) inhibitor
    - Mild-moderate hepatic impairment

www.viberzi.com accessed 01-02-2016

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Eluxadoline Efficacy

- 1700 patients with IBS-D have been exposed to eluxadoline
- Length of exposure: 3 months – 12 months
- ROME III criteria for IBS-D
- Efficacy in Study 1 (improvement in worst abdominal pain by 30% AND reduction in the BSS to < 5 on at least 50% of days):
  - 12 weeks: 24% – 25% vs. 17% placebo
  - 26 weeks: 23% – 29% vs. 19%
  - Abdominal pain improvement ≥ 30%: 42% – 43% vs. 40%

www.viberzi.com accessed 01-02-2016

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Eluxadoline

- Contraindications:
  - Biliary duct obstruction
  - Alcoholism or individuals drinking more than 3 drinks per day
  - History of pancreatitis
  - Severe hepatic impairment
  - Severe constipation

www.viberzi.com accessed 01-02-2016

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Eluxadoline Precautions

- NOW contraindicated in individuals without a gallbladder

www.viberzi.com accessed 01-02-2016

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Eluxadoline

- Side effects:
  - Constipation (8% vs. 2%)
  - Nausea (7% vs. 5%)
  - Abdominal pain (7% vs. 4%)
  - Vomiting (4% vs. 1%)
- Drug/drug interactions
  - OATP1B1 Inhibitors: cyclosporine, gemfibrozil, antiretrovirals, rifampin
    - Use 75 mg two times daily

www.viberzi.com accessed 01-02-2016

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Additional drug/drug interactions

- Strong CYP inhibitors
  - Ciprofloxacin, gemfibrozil, fluconazole, clarithromycin, paroxetine and bupropion
  - Use 75 mg two times daily
- Rosuvastatin
  - Increase exposure to rosuvastatin
  - Use lowest dosages of rosuvastatin
- Caution in drugs with narrow therapeutic index01-02-2016

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Eluxadoline

- Avoid in pregnancy and lactation
- Do not use in children < 18 years of age
- Do not take other medications such as alosetron or loperamide on a regular basis while using this medication

www.viberzi.com accessed 01-02-2016

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Rifaximin (Xifaxan)

- Indication: IBS-D; targeting SIBO
- Dosage: 550 mg three times daily x 2 weeks
  - May repeat dose up to 2 times if helpful or patient has recurrent symptoms
- With or without food

www.xifaxan.com accessed 01-03-2016

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Rifaximin

- Precautions/Contraindications:
  - Avoid use in 1st trimester (increased risk of congenital abnormalities based upon animal data)
- Side effects:
  - Diarrhea
  - Peripheral edema
  - Nausea
  - Risks of *C. difficile*
- Drug/drug interactions:
  - P-glycoprotein inhibitors (cyclosporine): increased rifaximin exposure

www.xifaxan.com accessed 01-03-2016

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TCA's

- Numerous products:
  - Examples: Amitriptyline and nortriptyline
- Mechanism of action
  - Low dose at bedtime may reduce abdominal pain
  - May decrease diarrhea, therefore helping those with IBS-D
  - May worsen IBS-C
- Side effects:
  - Sedation
  - Anticholinergic effects

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SSRI's

- Although no conclusive evidence exists to document efficacy…
  - SSRI's work on the 5-HT (2) receptors in the body
  - Majority are in the brain but some are in the bowels
  - Some patients report significant improvement in anxiety, frequency, and urgency of stools

Gastroenterology 2006;130:5.

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Studies to Date on SSRI's

- Broekaert and colleagues reported that Citalopram (Celexa) reduced the number of abdominal pain days as well as the severity of the pain
  - Also reduced bloating and severity
  - Only 14 patients studied
- Paroxetine (Paxil) has also been looked at in patients with ibs
  - 257 patients; 78% women; randomized to 1 or 3 treatment arms: routine care by GI provider; 8 weeks of psychotherapy or 20 mg of paroxetine
  - Paroxetine: lower number of pain days at 3 months; not statistically significant at 1 year

Gastroenterology 2006;130:5.

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ACG: Probiotics Not Recommended

- Bifidobacterium infantis
  - Only one shown in multiple clinical trials to be effective
  - Has been shown to reduce gas, bloating, abdominal pain
  - ? May help to reduce inflammatory cytokines in IBD
  - Decreased straining and hard stools
  - Note: symptoms may worsen before better

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Case Study

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Case Study

- **45-year old woman presents with a 30+-year history of straining, hard/lumpy stools, and a sense of incomplete evacuation. She passes stool approximately 3 times per week**

- **Previously, she tried bulking agents and anticholinergic agents with minimal improvement in her symptoms, and she experienced bloating with lactulose**

What treatment would you consider?

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What Would You Recommend?

- Nonpharmacologic therapies??
- Pharmacologic therapies??

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GERD

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EE

- 52 year old female presents with anterior chest pain; non-radiating and not associated with any exertion. Occurs daily unless she avoids most foods. Has tried OTC antacids without much effect.
- Aggravating factors:
  - Foods – fatty meals, spicy meals
- Alleviating factors:
  - None
- Medications:
  - Escitalopram 5 mg one daily

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EE (Continued)

- PMH
  - Anxiety disorder
  - Postmenopausal
  - Overweight
  - L5-S1 disc surgery
- No previous work-up for symptoms
- Physical Examination
  - Unremarkable except for 1+ tenderness epigastric region
  - 12-lead ECG: No abnormalities
  - Hemoccult: negative

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What is GERD?

- Heartburn is one symptom of GERD
- This is characterized by:
  - Reflux of food and acid from stomach into esophagus
  - Often associated with esophageal inflammation
  - May be associated with mucosal injury or even cancer
    - Erosive esophagitis and/or Barrett's

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Frequency of Heartburn

- Frequency and severity of heartburn does not necessarily correlate with development of esophageal damage or erosions
- Individuals with severe and frequent heartburn may have no esophageal damage whereas individuals with little heartburn may have significant damage
- Therefore…response to standard OTC medications by the patient is likely to be a predictor of more serious or less serious pathology

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EE (Continued)

- Most likely diagnosis is:
  - GERD
  - Consider cardiac etiology given age; Negative nuclear stress test

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GERD

- Heartburn and regurgitation are the most common symptoms of GERD
- GERD is a complex of different abnormalities
  - To simplify, reflux of gastric contents into the esophagus resulting in symptoms and / or complications

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Etiology of Heartburn and GERD

- Relaxation of the lower esophageal sphincter (LES) temporarily relaxes
  - Allows reflux of stomach acid into the esophagus
  - Normally, gravity and peristalsis clear material from the esophagus and the saliva that we swallow neutralizes the remaining esophageal acid
  - Heartburn occurs when any one of these mechanisms are impaired

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Cause of Lower Esophageal Sphincter Relaxation

- Relaxation or weakening of the LES can be caused by:
  - Eating certain foods
    - Onions, garlic, black pepper
  - Pressure on the stomach because of an individual's weight
  - Frequent bending and lifting, particularly after eating
  - Vigorous exercise

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Cause of Lower Esophageal Sphincter Relaxation

- Relaxation or weakening of the LES can be caused by:
  - Pregnancy
    - Progesterone relaxes LES; slows peristalsis and increases retention of partially digested food and acid
  - Medications also can decrease LES pressure
    - CCB's, hormone replacement therapy, muscle relaxants, beta blockers
    - Alpha-blockers
    - Nitrates
  - Pathophysiologic mechanisms
    - Hiatal hernia and gastric acid hypersecretion
    - Zenker's diverticulum

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Etiology

- Several other defects thought to contribute to heartburn and GERD
  - Abnormal esophageal epithelial resistance
  - Abnormalities of gastric emptying
  - Gastric distention
  - Abnormal acid production

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Diagnosis of Heartburn and GERD

- Diagnosis of heartburn is usually made with history and physical examination
  - Usually, this is all that is needed
- Many clinicians will try routine treatments first and assess for response prior to ordering a variety of tests
- EGD – is not needed to make diagnosis

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Diagnosis

- Multiple tests available to make this diagnosis
  - Often times, patient is treated with medication 1st to see how he/she responds
  - If inadequate response, testing performed or…if any worrisome signs present
    - UGI: easiest, least expensive test
      - Hiatal hernia: present in 40-60% of population
      - Mild reflux seen in 30% of general population
      - Looking for esophageal irregularities, ulcers
      - Normal barium swallow may be seen in 40-60% of all individuals with GERD

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Endoscopy

- Endoscopy (Esophagoscopy)
  - Best study for the evaluation and treatment of GERD
  - Allows for direct visualization of the mucosa of the esophagus and the lining of the stomach
  - Essential when suspecting Barrett's esophagitis
  - If abnormalities are seen, biopsy is conducted

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Intraesophageal Acid Perfusion

- Also called Bernstein test
- This is a test where the patients symptoms are reproduced or eliminated with this procedure
- NG tube placed 30-35 cm from the tip of the nares into the esophagus
  - Saline is infused followed by HCL
  - Looking for reproduction of symptoms with HCL and relief of symptoms with saline infusion

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24-hour pH Monitoring

- 2 mm flexible probe is placed transnasally to about 5 cm above the LES
- Probe is connected to a box similar to a Holter monitor
- Wireless: transmits signals to box regarding pH
- Monitoring of pH is conducted in addition to the patients symptoms

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Esophageal Motility Studies

- Conducted to measure the pressure of the LES
- Thin, pressure sensitive tube is passed through mouth or nose and into stomach
- Once in place, the tube is pulled back slowly into the esophagus while the patient is asked to swallow
- The pressure of the muscle contractions is then measured along several sections of the tube

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ACG

- Routine testing for *H. Pylori* is not necessary for GERD

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Barrett's Esophagitis

- Occurs in < 1% of heartburn sufferers
- Occurs when the esophageal lining is replaced by tissue normally found in the intestines (metaplasia)
- Increased risk of adenocarcinoma of the esophagus
  - 30 – 125 times higher in the patient with Barrett's
- Treatment:
  - PPI
  - Halo procedure: thermal ablation of tissue

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The Good News IS…

- 53 – 71% of all heartburn sufferers have endoscopically normal esophageal mucosa

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EE

- History and physical examination were consistent with GERD
- No additional testing performed
- Cardiac pathology ruled-out
- No additional red flags
- Patient started on lifestyle modification and a proton pump inhibitor

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Treatment Options

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ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD, MACG1 , Kerry B. Dunbar, MD, PhD, Felice H. Schnoll-Sussman, MD, FACG , Katarina B. Greer, MD, MS, FACG, Rena Yadlapati, MD, MSHS and Stuart Jon Spechler, MD, FACG

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Nonpharmacologic Treatment Options

- Dietary Modification
  - Avoidance of meals within 2-3 hours of bedtime
  - Avoidance of tobacco/cigarette related products
  - Avoidance of trigger foods
  - Elevate the head of the bed by 2-3 inches
  - Weight loss in overweight or obese individuals

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ACG Guidelines

- PPI therapy is now first line
  - For those without alarm findings, PPI x 8 weeks is the recommended treatment
  - Discontinue after 8 weeks if patient has responded to the PPI
- No diagnostic testing needed
- No need for repeat endoscopy, unless patient does not respond adequately to PPI x 8 weeks

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Alarm Findings

- Weight loss
- Dysphagia
- Iron deficiency anemia
- Black/bloody stools
- Chest pain
- Failure to respond to PPI therapy

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Proton Pump Inhibitors

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Mechanism of Action

- PPIs
  - Suppress gastric acid production by blocking parietal cell hydrogen/potassium ion adenosine triphosphatase
  - Known as the proton pump
  - This is the final pathway involved in acid secretion
  - Remember…PPI's affect only those pumps which are active
    - Not all pumps are active at the same time
  - 25% of new proton pumps are synthesized daily

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Proton Pump Inhibitors

- Omeprazole (Prilosec)
- Lansoprazole (Prevacid)
- Esomeprazole (Nexium)
- Rabeprazole (AcipHex)
- Pantoprazole (Protonix)
- Dexlansoprazole (Dexilant)

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PPIs

- Best efficacy when taken in the morning
  - PPIs only bind to proton pumps that are actively secreting acid
  - Ideally, 30–60 minutes before breakfast for once-daily dosing and 30–60 minutes before breakfast and dinner for twice-daily dosing
- If an endoscopy is needed, stopping PPIs 2-4 weeks before endoscopy is beneficial for optimal findings/results

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Switching PPIs

- There is a wide variation in individual intragastric pH
- Sometimes, very helpful to try changing a PPI for an individual having suboptimal response
  - In one study, patients taking lansoprazole and having suboptimal response were changed to bid lansoprazole vs. once daily esomeprazole with equal efficacy

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Refractory GERD

- Considered refractory when individual is on two times daily PPI for 8 weeks and is continuing to have symptoms

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Proton Pump Inhibitors

- Recent studies have shown an increased risk of:
  - Osteoporosis
    - Should take calcium citrate NOT carbonate
    - Carbonate – i.e. Tums needs an acidic environment
  - Pneumonia
    - Diminished acid protection
  - B12 deficiency
  - C. difficile related infections
  - ? Link with dementia
  - Chronic kidney disease
  - Hypomagnesemia

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What Does ACG Say?

- "PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. "
- "Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions."
- "High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections."

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Combination Therapy

- Omeprazole/sodium bicarbonate (Zegerid)
  - Indications
    - Gastric and duodenal ulcer
    - Erosive esophagitis
    - Symptomatic GERD

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Interaction with Clopidogrel

- Interaction has been documented in a few studies but larger studies do not confirm true interaction
- Does not necessarily seem to be a class effect
- Most interaction to least interaction
  - Omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid)
  - Lowest interaction: pantoprazole (Protonix) and dexlansoprazole (Dexilant)

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Stopping PPIs

- Try tapering rather than abruptly stopping
- Try replacing PPI dose with H2RA; as needed antacids
- Lowest dose of PPIs possible to control symptoms, if unable to discontinue

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Heartburn and GERD in Pregnancy

- Heartburn and GERD are very common in pregnancy with 2/3's of pregnant women reporting symptoms
- Lifestyle modifications are the mainstay of treatment
- Medications:
  - Antacids and sucralfate are first line agents
  - All H2RAs are category B in pregnancy
  - All PPIs are category B in pregnancy except omeprazole (C)

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Medications

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ACG

- It is appropriate to start with PPI for patients with GERD
- Two week trial may be all that is needed
- 8 weeks necessary to heal erosive esophagitis unless patient has Barrett's

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Newer Option:
Potassium-Competitive Acid Blocker

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Vonoprazan (Voquezna)

- Approval: first approved 2022
- Indication:
  - for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults
  - to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults
  - for the relief of heartburn associated with non-erosive gastroesophageal reflux disease in adults.
  - in combination with amoxicillin and clarithromycin for the treatment of Helicobacter pylori (H. pylori) infection in adults
  - in combination with amoxicillin for the treatment of H. pylori infection in adults

https://www.phathompharma.com/wp-content/uploads/VOQUEZNA-tablets-Prescriber-Information.pdf accessed 08-30-2024

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Vonoprazan

- Class:
  - Potassium-competitive acid blocker
- MOA:
  - Suppresses basal and stimulated gastric acid secretion at the secretory surface of the gastric parietal cell through inhibition of the H+, K+-ATPase enzyme system in a potassium-competitive manner.
  - This enzyme is regarded as the acid (proton) pump within the parietal cell and as such, vonoprazan has been characterized as a type of gastric proton-pump inhibitor, in that it blocks the final step of acid production.
  - Vonoprazan does not require activation by acid.

https://www.phathompharma.com/wp-content/uploads/VOQUEZNA-tablets-Prescriber-Information.pdf **accessed 08-30-2024**

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Vonoprazan

- Dosage:
  - Heartburn associated with NERD: 10 mg once daily for 4 weeks
  - Take with or without food
  - Take whole
- Warnings and precautions:
  - Carries same warnings as PPIs (Cdiff, bone fracture, B12 deficiencies, SJS, hypomagnesemia)
  - Fundic gland polyps (reported with vonoprazan and PPIs)
  - Avoid in pregnancy and lactation

https://www.phathompharma.com/wp-content/uploads/VOQUEZNA-tablets-Prescriber-Information.pdf **accessed 08-30-2024**

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Vonoprazan

- Efficacy:
  - Percentage of 24-Hour Heartburn-Free Days in Patients with Non-Erosive Gastroesophageal Reflux Disease Through Week 4
  - 10 mg Once Daily (drug vs. placebo)
    - 45% vs. 28%
  - Drug interaction:
    - rilpivirine used to treat HIV-1 (decreased efficacy)
  - Cost: 694.00 per month

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Antacids

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Antacids

- Examples:
  - Maalox
    - Aluminum hydroxide, magnesium hydroxide
  - Mylanta
    - Same as above
  - Rolaids
    - Calcium carbonate, magnesium hydroxide
  - Surpass
    - Calcium carbonate
  - Tums
    - Calcium carbonate

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Antacids

- Although antacids have long been thought to work in the gastric lumen to decrease gastric acidity, they actually work in the esophageal lumen
- Rapidly increase esophageal pH
- Neutralize esophageal acid for 90 minutes after dosing
- Little change in gastric pH
- Indication: intermittent or episodic heartburn

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Antacids

- Advantages
  - Multiple products available
  - Many different preparations: liquid, swallowable tablets, chewable tablets, effervescent solutions and gum
  - Gum and chewed tablet antacids seem to be more effective (per patients) than liquid products
  - Fast onset of action
  - Ease of dosing – take when patient has symptoms

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Disadvantages of Antacids

- Frequent dosing required
  - Short duration of action
- Few studies done with antacids
- No role with prevention

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H2RA's

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H2RA's

- Axid
  - 75 mg nizatidine
- Pepcid AC
  - 10 mg famotidine
- Maximum Strength Pepcid AC
  - 20 mg famotidine
- Pepcid Complete
  - 10 mg famotidine, 800 mg of $CaCO_3$ (Tums) and 165 mg of MG $(OH)_2$
- Tagamet HB
  - 200 mg cimetidine
- Zantac 75/150
  - 75 mg ranitidine

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Mechanism of Action

- Drugs bind to histamine-2 receptors on parietal cells to decrease gastric acid secretion
- Begin to work by decreasing gastric acid secretion within 1 – 2 hours of dosing
- Seem to work best on nocturnal acid secretion vs. daytime (i.e. after meal secretion)
- Antacids vs. H2RA
  - Antacids: Onset: 30 minutes, Last: 60 minutes
  - H2RA: Onset: 90 minutes, Last: 9 hours

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H2RA's

- Numerous studies conducted at both OTC and prescription strength dosages
- Clearly surpass placebo in onset of action and sustained efficacy

Wright, 2025

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H2RA's

- Indication: episodic heartburn
- All products can be taken daily
- Not indicated for frequent heartburn

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Combination of Antacid and H2RA

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Low Dose H2RA and Antacid

- H2RA and antacid combination
- Speed of an antacid + duration of H2RA
- Indication: intermittent or episodic heartburn
  - Not cost effective or indicated for individuals with frequent heartburn

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Surgical Options

- Nissen fundoplication
  - The upper curve of the stomach (the fundus) is wrapped around the esophagus and sewn into place so that the lower portion of the esophagus passes through a small tunnel of stomach muscle
  - This surgery strengthens the LES between the esophagus and stomach
  - In one study, 62% of people who had surgery were still taking medications to control GERD symptoms.
    - However, they were less likely to need to take medications regularly; and, when they did not take medications, their remaining symptoms were likely to be less severe.

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Additional Surgical Option

- EsophyX
  - Transoral Incisionless Fundoplication
  - Treatment of GERD
    - Reconstruction of the antireflux barrier
    - Restores GE junction back to normal anatomy
    - Same concept as the Nissen without incisions
    - Now FDA approved and cleared for US market

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Magnetic sphincter augmentation (MSA)

- Necklace of titanium beads with magnetic cores that encircle the distal esophagus to prevent the LES relaxation and prevent reflux
- Compared with fundoplication, MSA has shorter operative times and shorter durations of hospital stays.
- No significant differences between MSA and fundoplication in rates of GERD symptom control, postoperative PPI usage, major complications including dysphagia, and rates of reoperation

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EE

- Patient returns 1 month after initiating treatment with a PPI; no improvement in symptoms
- Referred for endoscopy given lack of response to traditional methods
  - Endoscopy shows mild esophagitis; negative biopsy
- PPI – increased by GI to 2 daily
  - No improvement at 1 month

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What Now??

- 24 hour pH probe
- Esophageal motility studies
- Bernstein test

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EE

- 24-hour probe shows NO significant correlation between pH and symptoms
- Esophageal motility studies showed decreased motility
  - Started on metoclopramide (Reglan) 5 mg 1 po tid – 30 minutes prior to meals with significant improvement in symptoms
  - Black box warning re: tardive dyskinesia

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Other Options

- Prucalopride, a 5 HT agonist US Food and Drug Administration (FDA)-approved for treatment of constipation, was shown in 1 off-label use study to improve gastric emptying and reduce esophageal acid exposure in patients with GERD

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Other Options

- Baclofen reduces the transient LES relaxations that enable reflux episodes.
- Baclofen decreases the number of postprandial acid and nonacid reflux events, nocturnal reflux activity, and belching episodes
- A trial of baclofen at a dosage of 5–20 mg 3 times a day can be considered in patients with continued symptomatic reflux despite optimal PPI therapy
- Sedation, dizziness, and constipation are most common side effects

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Sucralfate

- Mucosal protective agent
- Limited evidence to support use
- No real systemic absorption
- Primary use: pregnancy

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Questions?

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Thank You For Your Time and Attention!!!

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