Functional Bowel Disorders: A discussion of IBS, chronic constipation and GERD

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Disclosures

- Speaker Bureau
  - Sanofi-Pasteur, Merck, Pfizer, Moderna and Seqirus: Vaccines
  - AbbVie and Biohaven: Migraines
  - Idorsia: Insomnia
  - AstraZeneca: Asthma
  - Exact Sciences: Colorectal Cancer
- Consultant
  - Sanofi-Pasteur, Merck, Pfizer, Moderna, and Seqirus: Vaccines
  - GlaxoSmithKline: OA and pain
  - Bayer: Chronic kidney disease
  - Idorsia: Insomnia
  - Shield Therapeutics: Iron deficiency anemia

All relevant financial disclosures have been mitigated.

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Slide 1

RK0 Jill, Can you ask Valerie to start checking font sizes of the title. Please make consistent either at 30 or 32 pt. Thanks
Renee Kirshner, 2023-05-31T17:56:47.705

JR0 0 Yes, I will f/u with Valerie. Looking at the slide template, the font is programmed at 30 pt. I wonder if 32 pt is coming from the SME's ppt and the previous FHEA template.
Jill Racicot, 2023-06-05T06:50:34.016

RK0 1 I am not worried about titles at 30 or 32. More concerned about 28 pt and lower :)
Renee Kirshner, 2023-07-27T16:13:15.687

RK1 Sally, not sure how you want to handle. On this second pass, I realized there are sources here from 1980s and 1990s. Larlene mentioned something in the reference section about updating sources more than 10 years old. Guidance is needed regarding how far back can a source be and be relevant. Thanks
Renee Kirshner, 2023-07-27T19:27:09.674

Slide 3

RK0 Jill, I noticed that the disclosure slide between (02) and this one (03) is different. (01) and (03) are the same. Did you want all slides to be unified within this group of presentations? If so, which one should be used?
Renee Kirshner, 2023-05-30T14:25:03.209

JR0 0 I defer to Wendy. Wendy, should the Disclosure slide be the same for all 8 pharm topics? Please advise.
Jill Racicot, 2023-06-05T06:52:17.676

RK0 1 Per WW. Updated
Renee Kirshner, 2023-07-27T16:48:16.804

Objectives

- At the end of this presentation, the participant will be able to:

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

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Tips

- References
  - Listed throughout and at the end of the presentation
- To facilitate your learning
  - Specific tables/images can be viewed full page at the end of your handout.

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Irritable Bowel Syndrome

ACG Clinical Guideline: Management of Irritable Bowel Syndrome

Lacy, B.E., Pimentel, M., Brenner, D.M., Chey, W.D., Keefer, L.A., Long, M.D., Moshiree, B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am J Gastroenterol. 2021,* 116(1):17-44. https://pubmed.ncbi.nlm.nih.gov/33315591/

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Slide 6

RK0 Since entire source info is listed on the slide, I did not include in back. Please let me know if you want it included in back. Thanks
Renee Kirshner, 2023-06-02T16:01:00.649

RK0 0 From WW: It is fine here. I want them to know that this is a big update and the information I am giving them comes from here
Renee Kirshner, 2023-07-27T16:49:28.507

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.

- 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.
  - 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

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RKO

Pathophysiology[1]

- 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.

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The Role of Stress in IBS[2,3]

- 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.

2. Drossman DA. (1999). Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? Am J Med,107:41S-50S. https://pubmed.ncbi.nlm.nih.gov/10588172/

3. Drossman DA. (1997). Irritable bowel syndrome and sexual/physical abuse history. Eur J Gastroenterol Hepatol, 9:327-30. https://pubmed.ncbi.nlm.nih.gov/9160192/

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RKO

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Slide 11

RK0 Note from Larlene: Wendy- is the pink bullet accurate? Smaller amounts of distension causes MORE abdominal distress?
Renee Kirshner, 2023-07-27T16:15:09.432

RK0 0 Per WW: Yes, this is accurate.
Renee Kirshner, 2023-07-27T16:50:37.589

Slide 12

RK0 Wendy, these sources are from 1990s. Too old? Alternatives to consider under the slide. Let me know how you wish to handle. Thanks
Renee Kirshner, 2023-07-27T19:59:00.330

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.

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Irritable Bowel Syndrome (PI-IBS) Four Years after the Outbreak of Waterborne Gastroenteritis (GE) (continued)

- 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.

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What about small intestinal bacterial overgrowth (SIBO)?[4,5]

- 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

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Slide 15

RK0 Please see reference 4. at bottom of slide. I tried to find as written. What I found was the title (see source left under slide) and the journal info separate (see right under slide). Not sure which should be used/and or both. Please advise. Thanks.
Renee Kirshner, 2023-06-02T16:16:45.038

RK0 0 Per WW: Can you include both...he s the founder of this concept?
Renee Kirshner, 2023-07-27T16:51:45.384

RK0 1 Included both as requested.
Renee Kirshner, 2023-07-27T16:52:03.342

Pathophysiology of Functional Bowel Disorders [6-8]

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

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Diagnosis of Functional Bowel Disorders

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Rome III Diagnostic Criteria for Irritable Bowel Syndrome (all subtypes)[9]

- 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

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Diagnostic Criteria – Chronic Constipation[10]

- 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

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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

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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 (ages >50 years)
- Fevers
- Oral ulcers
- Bloody stools

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Red Flags (continued)

Evaluate for alarm features. (cont.)

- Abnormal exam (weight loss, arthritis, rashes)
- Fever, oral ulcers
- Anemia
- Leukocytosis

- Abnormal chemistry
  - Abnormal LFTs, 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 of age), flexible sigmoidoscopy, thyroid function tests, etc…is not recommended.
- Routine testing for celiac disease should be done for those with IBS-D.
- Individuals >45 years of age should undergo colorectal cancer screening.

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Laboratory Evaluation

- C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin should be considered for those with IBS-D. RK1
  - CRP and fecal calprotectin – Best
- Fecal lactoferrin[11]
  - During intestinal inflammation, activated leukocytes infiltrate the mucosa and lumen, increasing the level of fecal lactoferrin.[11]
  - 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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Slide 24

RK0 Please see "1" in yellow highlights. Is there a source connected to these statements? There was not a source listed on the original PPT. I was able to find: Chen CC, Chang CJ, Lin TY, Lai MW, Chao HC, Kong MS. Usefulness of fecal lactoferrin in predicting and monitoring the clinical severity of infectious diarrhea. World J Gastroenterol. 2011 Oct 7;17(37):4218-24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3208367/ as a possible source if needed. Let me know how you wish to handle. Thanks
Renee Kirshner, 2023-05-31T19:08:14.081

RK0 0 Per WW: Chen CC, Chang CJ, Lin TY, Lai MW, Chao HC, Kong MS. Usefulness of fecal lactoferrin in predicting and monitoring the clinical severity of infectious diarrhea. World J Gastroenterol. 2011 Oct 7;17(37):4218-24. - use this renee
Renee Kirshner, 2023-07-27T16:53:20.679

RK0 1 From WW: I changed spelling here to reflect the US language -not UK; this is fine now as is
Renee Kirshner, 2023-07-27T16:59:34.431

RK1 Please see first blue bullet: I changed F. Cal and F. Lactoferrin to what is on the slide. Not sure F.Cal and F. Lactoferrin actual abbreviations. If you meant these to be something different. Please advise. Thanks
Renee Kirshner, 2023-05-31T19:14:29.471

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.[12]

- Rectal manometry
  - Catheter inserted into rectum to assess muscle pressure and nerve function
- Defecography
  - Completed 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.

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Consider pelvic floor dysfunction and colonic inertia.[12] (continued)

- Sitz marker study
  - Procedure to assess colonic motility
  - Ingest barium sulfate (Sitzmarks®) capsule. Brought back in for abdominal X-ray on day 1, day 3 and day 5
  - Normal: Complete evacuation by day 5

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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[13] – Soluble Fiber Preferred

- Bulking agents
  - Psyllium (Metamucil®): 15–25 grams per day
    - 1 teaspoon (5 grams) or packet 1–3 times/day
  - Methylcellulose (Citrucel®): 19–57 grams per day
    - 1 heaping tablespoon (15 grams) 1–3 times/day
  - Polycarbophil (Fibercon®)
    - 625 mg tablet
    - 2 tablets 1–4 times daily

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Bulking Agents[13]

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

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Summary of Trials on Bulking Agents[14-16]

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

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RK0

Polyethylene Glycol – Not Recommended by ACG[17]

- Polyethylene glycol (Miralax®)
  - Osmotic agent
- Indication – Constipation
- Adult dosage – 17 g in 8 ounces (236.6 mL) of water
  - FDA indication – Once daily for up to 2 weeks
- Precautions
  - Nausea and vomiting
- Contraindications
  - Bowel obstruction

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Antispasmodics – Not Recommended by ACG[9]

- Anticholinergic agents (antispasmodic)
  - Reduces sigmoid motility in response to fat
  - Decreases postprandial pain and distension by inhibiting postprandial colonic contractions

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Slide 34

RK0 There were 4 sources on this slide. Please see remaining source on slide. I could not find. Please provide additional info so it can be verified. Thank you
Renee Kirshner, 2023-06-02T17:23:50.210

RK0 0 Per WW: This is fine.
Renee Kirshner, 2023-07-27T17:02:20.364

RK0 1 Wendy, I am interpreting your comment as, remove the source that didn't have enough info and leave the other 3 as the sources for this slide. I moved the original source I couldn't find off to the right side incase you wish to include in the future; however I will need additional info to verify or I supplied an alternative source to consider underneath.

Later I realized the sources on this slide are from 1980s, which is probably too old. I did place alternatives under the slide for you to consider. Let me know how you wish to handle. Thanks
Renee Kirshner, 2023-07-27T17:04:52.809

Slide 35

RK0 Please see reference on bottom of slide. Can not verify. Please provide additional info. Thank you
Renee Kirshner, 2023-06-02T17:35:24.239

RK0 0 From WW: Same: Also comes from the guideline - previous slide which says no longer recommended; you can keep reference at bottom
Renee Kirshner, 2023-07-27T17:36:24.159

RK0 1 FYI, Wendy, after a ton of searching I was able to verify the source and added it to the back reference section.
Renee Kirshner, 2023-07-27T17:46:27.463

Anticholinergic Agents[9]

RK0

- Dicyclomine (Bentyl®)
  - 20–40 mg before meals (AC)
- Hyoscyamine sulfate (Levsin®)
  - 0.125 mg 1–2 tabs PO q4hrs PRN
  - Levsin® SL, LevBid® (0.375 mg 1–2 tablets PO BID)

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Prescribing Information

- Precautions
  - Cardiovascular disease, hypertension, elders
- Adverse effects
  - Drowsiness
  - Anticholinergic adverse effects
- Contraindications
  - Glaucoma
  - Unstable CV status

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Lactulose

RK1

- Dosage
  - 10–20 g/day
  - Increase 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

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Slide 37

RK0 Please see first pink bullet. Does the ac after 40 mg mean "before meals" ? If so, will need to be written out. Please advise. Thanks
Renee Kirshner, 2023-05-31T20:17:11.975

RK0 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:18:03.255

Slide 39

RK0 Please see first pink bullet: https://www.drugs.com/pro/constulose.html, Constulose discontinued 6.22? Remove from this list?
Renee Kirshner, 2023-05-31T20:25:28.229

RK0 0 From WW: removed from list and removed all brand names
Renee Kirshner, 2023-07-27T18:09:26.697

RK1 The first blue bullet is a repeat of the title. Did you want to rename as "brand names" ?
Renee Kirshner, 2023-05-31T20:36:52.508

RK1 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:19:12.419

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 those aged 65 years and older

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Lubiprostone (continued)

- Dosage
  - 8 mcg BID with food
  - 24 mcg BID with food
- Mechanism of action
  - Activates ClC-2 (found in the human intestine)
  - Increases intestinal fluid secretion and increases motility in the intestine

- Efficacy
  - Increases BMs by 3 per week on average
  - Significant increase over placebo of spontaneous bowel movements within first 24 hours after taking medication

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Lubiprostone (continued)

- Adverse effects
  - Nausea – 30%
  - Diarrhea – 13%
- Contraindications
  - History of mechanical GI obstruction
  - Diarrhea

- Precautions
  - Not studied in individuals with moderate to severe hepatic ***or*** renal impairment
  - Pregnancy – C

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Slide 41

RK0 Please see left side, 2nd pink bullet, is the "and" needed? Should it read: By increasing intestinal fluid secretion, increases motility in the intestine.
Renee Kirshner, 2023-05-31T20:44:30.182

RK0 0 Changed; see my change
Renee Kirshner, 2023-07-27T18:11:16.853

Additional Approval

- Lubiprostone
  - Opioid-induced constipation
  - Not effective for those on diphenylheptane opioids (e.g., methadone)
  - 24 mcg BID with food

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Linaclotide[18]

RK0

- 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.
    - Results in increased intestinal fluid and accelerated transit
  - Also reduces intestinal visceral pain

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Linaclotide (Linzess®)[18] (continued)

- 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

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Slide 43

RK0 Please see second pink bullet: Reword to: The effectiveness for those on diphenylheptane opioids (e.g., methadone) has not been established.
Renee Kirshner, 2023-05-31T20:53:41.700

RK0 0 From WW: removed-and edited
Renee Kirshner, 2023-07-27T18:12:33.091

Slide 44

RK0 Jill this slide was originally 14 pt before I split it. Please ask Valerie to make the smallest font on a slide 24 mainly, but never smaller than 18 pt. Thanks
Renee Kirshner, 2023-05-31T20:56:18.692

JR0 0 Noted, will do.
Jill Racicot, 2023-06-05T06:57:04.944

Linaclotide (Linzess®)[18] (continued)

- Boxed warning
  - Contraindicated in pediatric patients <2 years of age
  - Another contraindication
    - Suspected or known mechanical gastrointestinal obstruction
- Approved 6 - 17 years and older for functional constipation
  - 72 mcg once daily
  - 30 minutes before meal
- Precautions
  - Pregnancy category C
  - Nursing mothers (unknown if excreted in breast milk)

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Linaclotide (Linzess®)[18] (continued)

- 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)

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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

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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®)[19]

- 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
- 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

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Prucalopride (Motegrity®)[19] (continued)

- 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

RKD

- 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 statistically significant.)

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Slide 51

RK0 Please see pink bullet on left. Are there 2 thoughts there?
Renee Kirshner, 2023-06-01T17:43:43.260

RK0 0 From WW: Keep as is please. It is fine.
Renee Kirshner, 2023-07-27T18:13:21.872

Prucalopride (Motegrity®)[19] (continued)

- Drug-drug interactions
  - No significant drug-drug interactions
- Adverse 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
- Competition
  - Tegaserod (Zelnorm®)*: 5-HT4 receptor agonist
    - *Withdrawn in 2022

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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	

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IBS-D

- Loperamide HCl (Imodium®)[20]
  - Initially – 4 mg followed by 2 mg, as needed
  - Maximum –16 mg daily
  - Mechanism of action – Slows colonic motility
  - Adverse effects – Abdominal pain, dry mouth, nausea

- Diphenoxylate hydrochloride and atropine (Lomotil®)
  - Initially – 2.5 mg
  - 1–2 pills up to 4×/day until control achieved
  - Maximum – 8 mg daily
  - MOA – Inhibits excessive GI motility and decreases GI propulsion
  - Adverse effects – Tachycardia, dry mouth, nausea

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IBS-D (continued)

- 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
  - Adverse effects
    - Constipation
    - Impaction
    - Inhibits absorption of other medications

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Alosetron[10]

- Alosetron (Lotronex®)
  - Withdrawn from the market in December of 2000
- Reintroduced in 2002

- Available under Prometheus prescribing program (REMS)
- Indication: IBS-D in women
- Dosage: 0.5–1 mg up to two times daily

56

56

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

57

57

Eluxadoline (Viberzi®)[21]

- 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 individuals:
    - Taking concomitant organic anion transporting polypeptide1B1 (OATP1B1) inhibitor
    - With mild-moderate hepatic impairment

58 RKJ

58

Eluxadoline Efficacy[21]

- 1700 patients with IBS-D have been exposed to eluxadoline.
- Length of exposure: 3–12 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%

59

59

Eluxadoline[21]

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

60

60

Slide 58

RK0 Please see pink bullet. The wording "following individuals" The green bullets that follow are not people...so can this be reworded? Not sure maybe at "with" at end of individuals?
Renee Kirshner, 2023-06-02T00:41:50.565

RK0 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:22:05.704

Eluxadoline Precautions[21]

- NOW contraindicated in individuals without a gallbladder

61

61

Eluxadoline[21]

- Adverse 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.

62

62

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 index

RKO

63

63

Slide 63

RK0 Please see 2nd blue bullet on rt. 01-02-2016 (was in white and blended in...should it be deleted or is something missing?)
Renee Kirshner, 2023-06-01T13:49:40.166

RK0 0 Per WW: deleted date
Renee Kirshner, 2023-07-27T18:14:17.526

Eluxadoline[21]

- 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.

64

64

Rifaximin (Xifaxan®)[22]

- Indication: IBS-D; targeting SIBO
- Dosage: 550 mg three times daily × 2 weeks
  - May repeat dose up to 2 times if helpful or patient has recurrent symptoms
- With or without food
- Precautions/contraindications
  - Avoid use in 1st trimester (increased risk of congenital abnormalities based upon animal data).

- Adverse effects
  - Diarrhea
  - Peripheral edema
  - Nausea
  - Risks of *C. difficile*
- Drug-drug interactions
  - P-glycoprotein inhibitors (cyclosporine): Increased rifaximin exposure

65

65

TCAs

- 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
- Adverse effects
  - Sedation
  - Anticholinergic effects

66

66

SSRIs

- Although no conclusive evidence exists to document efficacy…
  - SSRIs 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.

67

67

Studies to Date on SSRIs[23]

- 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.

68

68

Studies to Date on SSRIs[23] (continued)

- Paroxetine (Paxil®) has also been looked at in patients with IBS. RKO
  - 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
    - Lower number of pain days at 3 months; not statistically significant at 1-year

69

69

Slide 69

RK0 Please review format structure of last pink bullet. Should this line be as is or green as subbullet under 257 patients, etc...
Renee Kirshner, 2023-06-01T14:35:49.289

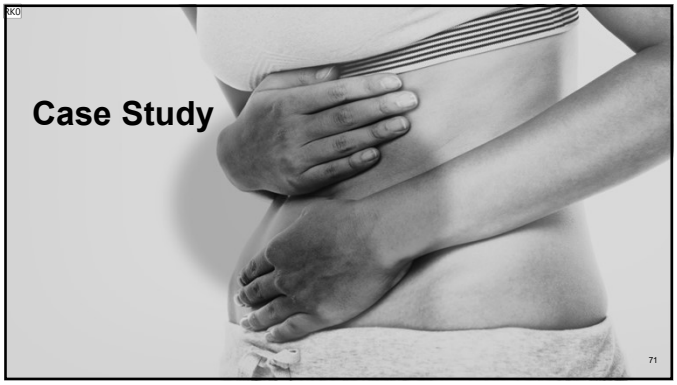
RK0 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:26:20.597

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

70

70



71

71

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?

72

72

Slide 71

RK0 I am assuming the image on the left is NOT a Shutterstock or microsoft stock image so it will need to be switched out. However, the Case study that follows remarks on a 45 yo woman (not man) with a GI issue; Not sure why he is on the phone either. The image on the slide on the right is from Shutterstock. If it works, let me know and I'll official download it. Thanks.
Renee Kirshner, 2023-06-02T00:44:05.348

RK0 0 Per WW: Remove any image you need to: can go without it.
Renee Kirshner, 2023-07-27T18:17:11.540

What would you recommend?

- Nonpharmacologic therapies?
- Pharmacologic therapies?

73

73

GERD

74

74

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

75

75

EE (continued)

- Aggravating factors
  - Foods – Fatty meals, spicy meals
- Alleviating factors
  - None
- Medications
  - Escitalopram 5 mg once daily

76

76

EE (continued)

- PMH
  - Anxiety disorder
  - Postmenopausal
  - Overweight
  - L5-S1 disc surgery

77

77

EE (continued)

- No previous work-up for symptoms
- Physical examination
  - Unremarkable except for 1+ tenderness epigastric region
  - 12-lead ECG: No abnormalities
  - Hemoccult: Negative

78

78

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

79

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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.

80

80

EE (continued)

- Most likely diagnosis is…
  - GERD
  - Consider cardiac etiology given age.
  - Negative nuclear stress test

81

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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

82

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Etiology of Heartburn and GERD

RK1
RK0

- Relaxation of the lower esophageal sphincter (LES)
  - 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.

83

83

RK0

Cause of Lower Esophageal Sphincter (LES) 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
  - Pregnancy
    - Progesterone relaxes LES; slows peristalsis and increases retention of partially digested food and acid

84

84

Slide 83

RK0 Please see first blue bullet. I think it should be worded differently...not sure how. But Relaxation relaxes seems not quite right.
Renee Kirshner, 2023-06-01T15:02:52.605

RK0 0 WW: changed
Renee Kirshner, 2023-07-27T18:34:02.917

RK1 Please see second pink bullet. Should "and" be switched to "then"
Renee Kirshner, 2023-06-01T15:04:36.809

RK1 0 WW: No leave 2nd bullet as is
Renee Kirshner, 2023-07-27T18:34:18.632

Slide 84

RK0 Please dbl check formatting structure here:
In original PPT, the current blue bullet was a purple dash, which means it's a subbullet under: Relaxation of the lower esophageal sphincter (LES) temporarily relaxes (from the earlier slide) If that is the case, I will need to change the formatting for slide 84-86. Please advise to leave as is or change. Also, please note titles are different in both slides, please advise if should stay as is or should one or more titles change. Thanks
Renee Kirshner, 2023-06-01T20:46:46.434

RK0 0 WW: This looks fine here; accept your changes
Renee Kirshner, 2023-07-27T18:36:52.255

RK0 1 Wendy, not quite answered my question; however, I believe your intent is to leave as is currently. :)
Renee Kirshner, 2023-07-27T18:37:45.607

Cause of Lower Esophageal Sphincter (LES) Relaxation (continued)

RKO

- Relaxation or weakening of the LES can be caused by… (cont.)
  - Medications also can decrease LES pressure.
    - Calcium channel blockers (CCBs), hormone replacement therapy, muscle relaxants, beta blockers
    - Alpha-blockers
    - Nitrates
  - Pathophysiologic mechanisms
    - Hiatal hernia and gastric acid hypersecretion
    - Zenker's diverticulum

85

85

RKO

Etiology

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

86

86

Diagnosis of Heartburn and GERD

RKO

- 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.
- Esophagogastroduodenoscopy (EGD) is not needed to make diagnosis.

87

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Slide 85

RK0 FYI wrote out CCBs in 1st green bullet. Please dbl check correct abbrev. Defined. Thanks
Renee Kirshner, 2023-06-01T15:28:45.428

RK0 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:28:08.842

Slide 86

RK0 Per Larlene: Wondering if you want to add eosinophilic esophagitis as a possible etiology?
Renee Kirshner, 2023-07-27T16:29:31.861

RK0 0 Per WW: added
Renee Kirshner, 2023-07-27T18:39:35.127

Slide 87

RK0 FYI, please see third blue bullet, wrote out EGD. Please dbl check for correct abbrev defined. Thanks
Renee Kirshner, 2023-06-01T15:31:32.305

RK0 0 Per LD resolved
Renee Kirshner, 2023-07-27T16:30:38.865

Diagnosis

- Multiple tests available to make this diagnosis.
  - Often, patient is **treated with medication first** to see how he/she responds.
  - If inadequate response, testing performed ***or*** if any worrisome signs present
    - Upper GI series (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.

RK0

88 RK1

88

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, a biopsy is conducted.

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Intraesophageal Acid Perfusion

- Also called Bernstein test
- This is a test where the patient's 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

90

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Slide 88

RK0 FYI, wrote out UGI, please dbl check correct abbrev defined. Thanks
Renee Kirshner, 2023-06-01T15:35:11.195

RK0 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:34:34.027

RK1 Please see last gray bullet. I think the wording is off. Maybe reword to: Barium swallow test reveals normal findings for 40-60% of all individuals with GERD. ?
Renee Kirshner, 2023-06-01T15:39:22.591

RK1 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:34:41.416

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 patient's 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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American College of Gastroenterology (ACG)

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

93

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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
  - Laser (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.

95

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EE (continued)

- 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.

96

96

Treatment Options

97

97

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

Katz, P.O., Dunbar, K.B., Schnoll-Sussman, F.H., Greer, K.B., Yadlapati, R., Spechler, S.J. (2022).

Am J Gastroenterol., 117(1):27-56. https://doi.org/10.14309/ajg.0000000000001538

98

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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 (5–7.6 cm)
  - Weight loss in overweight or obese individuals

99

99

Slide 98

RK0 I did not include this reference in the back since all info is on this slide. Please let me know If you want to be moved to the back as well. Thanks
Renee Kirshner, 2023-06-02T18:38:36.519

RK0 0 WW: Perfect, it is fine here. Same concept as previous
Renee Kirshner, 2023-07-27T18:41:23.622

ACG Guidelines

- PPI therapy is now first-line.
  - For those without alarm findings, PPI × 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 × 8 weeks.

100

100

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**, PPIs 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 (PPIs)

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

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PPIs (continued)

- 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 (BID) and having suboptimal response were changed to esomeprazole (daily) with equal efficacy.[RKO]

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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** calcium carbonate
    - Calcium carbonate (i.e., Tums®) needs an acidic environment.
  - Pneumonia
    - Diminished acid protection
  - B_{12} deficiency
  - *C. difficile* related infections
  - ? Link with dementia
  - Chronic kidney disease
  - Hypomagnesemia

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Slide 106

RK0 FYI, pink bullet original read: In one study, patients taking lansoprazole and having suboptimal response were changed to BID lansoprazole vs. once daily esomeprazole with equal efficacy. I switched to what is on the slide. Let me know if you would like to have it switched back. Thanks
Renee Kirshner, 2023-06-01T16:04:13.372

RK0 0 WW: This is fine.
Renee Kirshner, 2023-07-27T18:42:05.813

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."

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What does ACG say? (continued)

- "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

111

111

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 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).

114

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Medications

115

115

ACG

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

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Antacids

117

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Antacids Examples

- Maalox®
  - Aluminum hydroxide, magnesium hydroxide
- Mylanta®
  - Aluminum hydroxide, magnesium hydroxide
- Rolaids®
  - Calcium carbonate, magnesium hydroxide
- Surpass®
  - Calcium carbonate
- Tums®
  - Calcium carbonate

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Antacids (continued)

- 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 (continued)

- 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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H2RAs

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H2RAs

- 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 360°™
  - Famotidine 20 mg (ingredient)

123

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Slide 123

RK0 Please see last blue/pink bullet on right: Zantac ranitidine taken off market. But Zantac 360 relaunch with famotidine. Did you want to switch out info?
Renee Kirshner, 2023-06-01T16:46:54.260

RK0 0 WW: Changed, thank you
Renee Kirshner, 2023-07-27T18:43:08.896

Mechanism of Action

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

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H2RAs

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

- 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 U.S. 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 reflux. RK0
- Compared with fundoplication, MSA has shorter operative time and shorter durations of hospital stays.
- No significant differences between MSA and fundoplication in rates of GERD symptom control, postoperative PPI usage RK1
- Major complications include dysphagia, and increased rates of re-operation.

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EE (continued)

- Patient returns 1-month after initiating treatment with a PPI. No improvement in symptoms RK0
- Referred for endoscopy given lack of response to traditional methods
  - Endoscopy shows mild esophagitis. Negative biopsy
- PPI – Increased by GI to 1-pill two times daily
  - No improvement at 1-month

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What Now?

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

132

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Slide 130

RK0 Please see first blue bullet. Is "prevent" needed twice in this sentence?
Renee Kirshner, 2023-06-01T17:06:09.136

RK0 0 Resolved per LD
Renee Kirshner, 2023-07-27T16:41:54.179

RK1 Please see last blue bullet. Sentence a bit confusing... Is it "AND" major complications including dysphagia, and rates of reoperation OR is major complications including dysphagia, and rates of reoperation a second thought? Please advise. Thanks
Renee Kirshner, 2023-06-01T17:08:53.824

RK1 0 WW: See my change
Renee Kirshner, 2023-07-27T18:48:50.357

Slide 131

RK0 Please see last blue bullet. Does 2 daily mean BID?
Renee Kirshner, 2023-06-01T17:12:57.697

RK0 0 WW: see change
Renee Kirshner, 2023-07-27T18:50:18.645

EE (continued)

- 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 U.S. Food and Drug Administration (FDA)-approved for treatment of constipation, was shown in **one** off-label use study to improve gastric emptying and reduce esophageal acid exposure in patients with GERD.

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Other Options (continued)

- 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 adverse effects.

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RK0 Please see first pink bullet: 5 mg 1 PO TID...should that be: 5 mg PO TID or took 5 mg daily and titrated up to 5 mg PO TID ? Please advise. Thanks
Renee Kirshner, 2023-06-02T19:23:04.462

RK0 0 WW: It is just as it is here. Please do not change.
Renee Kirshner, 2023-07-27T18:50:51.144

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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RK0 References may need to be renumbered once all issues regarding them have been resolved. Will do on next pass.
Renee Kirshner, 2023-06-02T19:24:44.742

RK1 Per Larlene: References are more than 10 years old. Can we find newer sources?

Update sources for 1990s?
Renee Kirshner, 2023-07-27T16:43:17.774

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RK0 Update sources from 1980s?
Renee Kirshner, 2023-07-27T20:22:09.107

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RK0 Update source from 1980s?
Renee Kirshner, 2023-07-27T20:22:20.582