Keeping Things Moving in the Treatment of Chronic Idiopathic Constipation

Exploring the Evidence and Guidelines Through Case Studies

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Today's Activity Is Eligible for ABIM MOC Credit and as a CME for MIPS Improvement Activity

Actively engage in the activity through polling and asking faculty questions.
Complete your post-test and evaluation at the conclusion of the activity.

ABIM CME MOC ACCREDITED

Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation so we can submit your credit to ABIM

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Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation

- Complete the follow-up survey from CME Outfitters in approximately 3 months
- CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity

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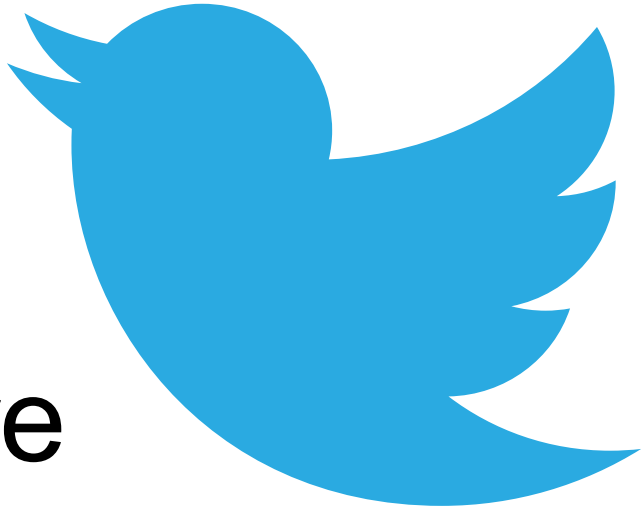

CME OUTFITTERS

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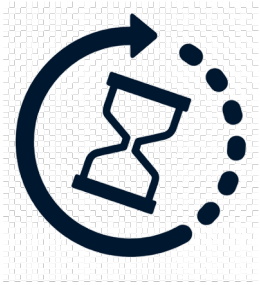
Learning Objectives

- Accurately diagnose chronic idiopathic constipation (CIC), differentiating it from irritable bowel syndrome with predominant constipation (IBS-C).
- Evaluate the characteristics of therapies used in the management of CIC.
- Develop a comprehensive treatment strategy for patients with CIC, constructed from evidence and clinical guidelines.

Personal and Economic Impact of CIC

~ 35 million U.S. adults[1] (1 in 7 people)



~7 in 10 people experienced CIC symptoms for 2+ years[2]

Estimated to affect twice as many women as men (17% vs. 9%)[1]

4th most common GI symptom, prompting outpatient clinic visit resulting in > 3 million outpatient clinic visits[3]

In 2013, direct medical costs for chronic constipation ranged from > $1,900 to > $7,500 per year per patient[4]

In 2011, national costs for ER visits exceeded $1.6 billion[5]

ER = emergency room; GI = gastrointestinal

1. Suares NC, et al. *Am J Gastroenterol*. 2011;106:1582-1591. 2. Johanson JF, Kralstein J. *Aliment Pharmacol Ther*. 2007;25(5):599-608.
3. Peery AF, et al. *Gastroenterology*. 2015;149(7):1731-1741.e1733. 4. Nellesen D, et al. *J Manag Care Pharm*. 2013;19(9):755-764.
5. Sommers T, et al. *Am J Gastroenterol*. 2015;110(4):572-579.

BURDEN CIC Study: Impact on Quality of Life

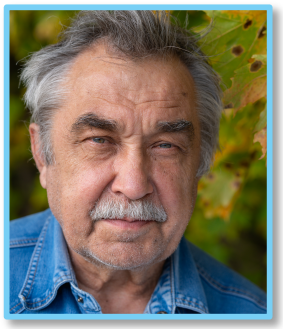
- **60%** of patients indicated that their CIC interfered with personal activities 4 days/month
- **25%** missed an average of 60 days of work or school/year
- Most common emotional symptom is frustration followed by acceptance
- Patients' frustration, obsession, and acceptance greater than clinicians' perception
  - Disconnect about acceptance may be due to patients' lack of knowledge about other alternatives for therapies

Harris LA, et al. *Adv Ther*. 2017;34(12):2661-2673.

Accurately Diagnose CIC, Differentiating It from IBS-C

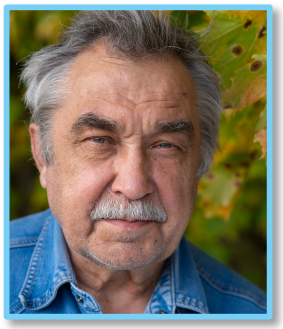
CME OUTFITTERS

Patient Case: Richard



- 69-year-old man with a history of lifelong constipation getting worse over past 2 years
- BMs type 1-3 Bristol Stool Form Scale 2x/wk
- Frequent straining, bloating; no blood per rectum; no weight loss
- Tried multiple OTC laxatives (senna bisacodyl, PEG) with limited success
- No narcotics
- Relates ER visits several times/year for the last 2 year, but because of COVID wants to avoid the ER
- Plans his life around BMs, hesitates to go out to dinner with his wife when he uses a laxative

Patient Case: Richard



Past Medical History

- Robotic prostatectomy 2.5 years ago
- Hypertension treated with thiazide and ACE inhibitor
- Hyperlipidemia
- Colonoscopy 2 years and 4 years ago normal

Family History

- Mother, brother, and wife also have constipation
- No colon cancer

ACE = angiotensin-converting enzyme

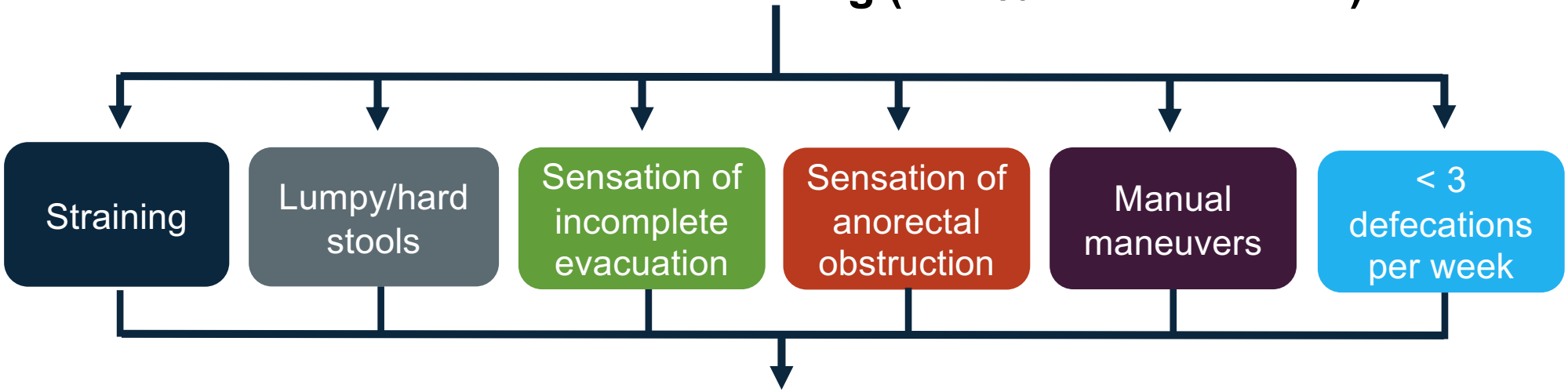
Audience Response

What is your diagnosis for Richard?

A. IBS-C
B. CIC
C. Pelvic floor dyssynergia (PFD)
D. Slow transit constipation
E. I’m not sure; I need more information

Does Richard Have Constipation?
Rome IV Criteria for Functional Constipation

Must include ≥ 2 of the following (> 25% of defecations):



Loose stools rarely present without laxative use insufficient criteria for IBS

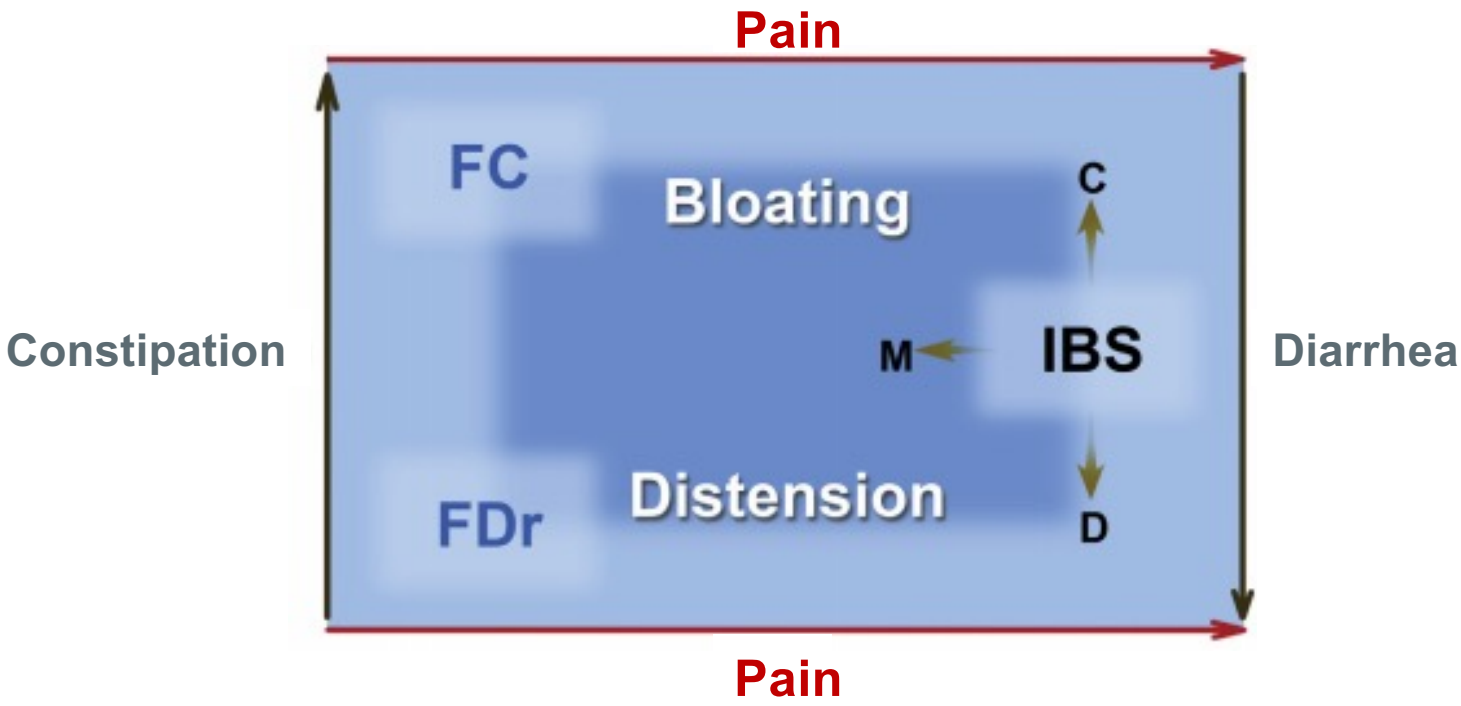
Note: Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Lacy BE, et al. *Gastroenterology*. 2016;150(6):1393-1407.

CME OUTFITTERS

Does Bloating/Discomfort Mean the Patient Has Irritable Bowel Syndrome?

A spectrum of constipation-related disease?



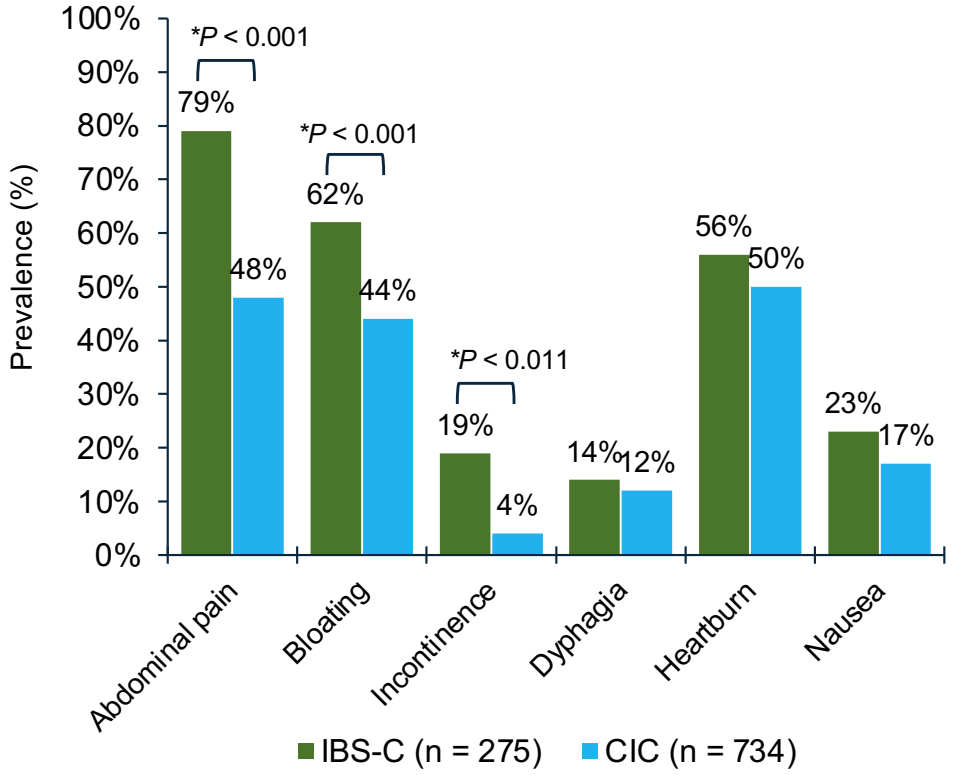
FC = functional constipation; FDr = functional diarrhea; IBS = irritable bowel syndrome; IBS-D = IBS with predominant diarrhea; IBS-M = IBS with mixed bowel habits (C and D)

Lacy BE, et al. *Gastroenterology*. 2016;150(6):1393-1407.

ROME FOUNDATION CME OUTFITTERS

Prevalence of GI Symptoms in IBS-C and CIC

- While symptoms in IBS-C are generally more severe, abdominal pain, bloating, upper GI symptoms are common in CIC
- Painful "subtype" of CIC might be in-between both diseases
- While not meeting Rome criteria for IBS, individuals may experience greater use of healthcare resources and have worse QoL than in individuals with nonpainful CIC

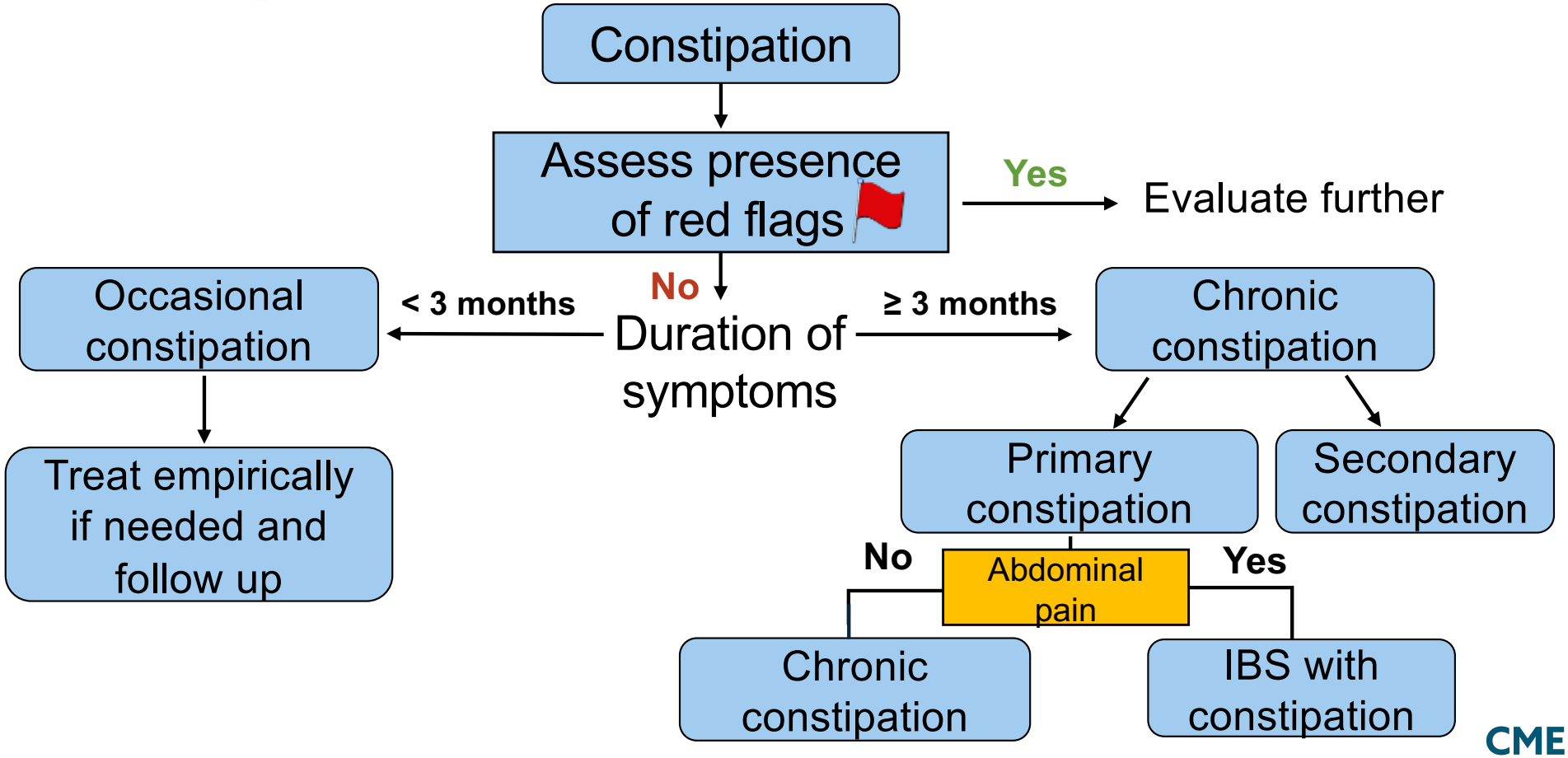


QoL = quality of life

Shah ED, et al. *J Neurogastroenterol Motil*. 2018;24(2):299-306.

CME OUTFITTERS

Diagnostic Algorithm for Chronic Constipation



CME OUTFITTERS

Red Flags

Red flags

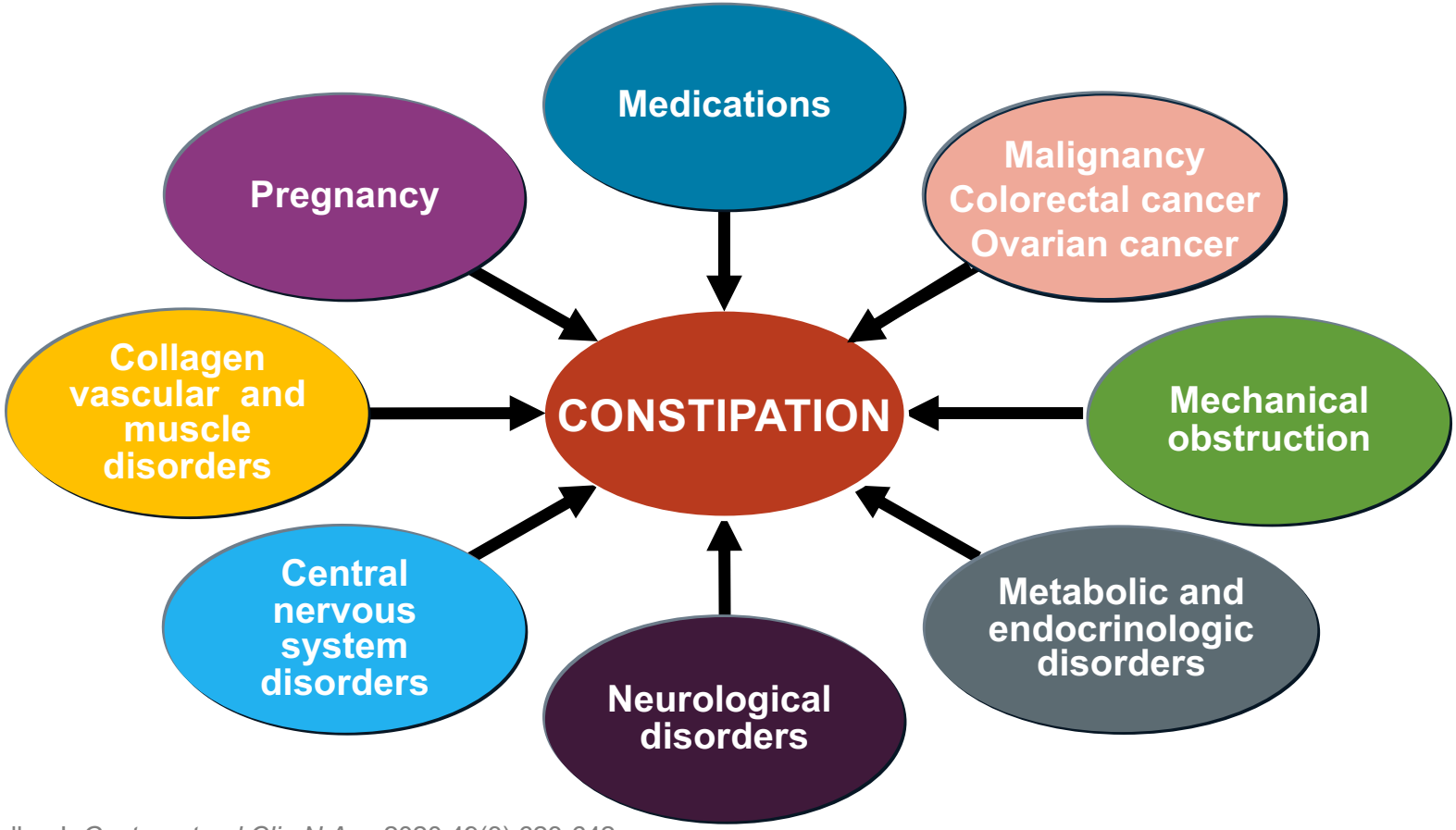
- Unintentional weight loss ≥10 lbs
- Onset in patient > 50 years
- Family history of cancer or IBD/celiac disease
- Rectal bleeding
- Anemia
- Fecal occult blood test
- Abnormal chemistries, thyroid function tests or ↑ CRP

Important elements

- Nature of symptoms, duration and characteristics
- Laxative use/medication
- Dietary history
- Family history of bowel disturbance
- Obstetric history
- Assessment of emotional distress or affective disorders

American College of Gastroenterology Chronic Constipation Task Force. *Am J Gastroenterol*. 2005;100(suppl 1):S1-S4.

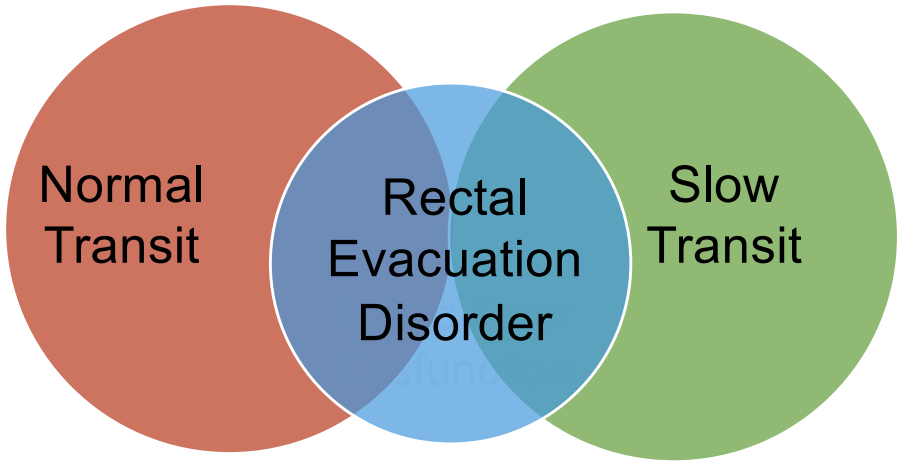
Potential Secondary Causes of Constipation



Camilleri M, Brandler J. *Gastroenterol Clin N Am*. 2020;49(3):623-642.

CME OUTFITTERS

Diagnostic Considerations



In a tertiary referral practice
- 5% Slow transit
- 65% Normal transit
- 30% dyssynergic defecation

- Normal transit (IBS)
- Slow transit
  - Myopathic vs. neuropathic defect
- Rectal evacuation disorder
  - Inability to relax pelvic floor muscle
  - Improper coordination of abdominal and pelvic floor muscles while defecating
  - Inability to produce necessary propulsive forces in the rectum

Nullens S, et al. *Gut.* 2012;61(8):1132-1139.

Audience Response

What diagnostic testing would you order for Richard?

A. Digital rectal exam
B. Balloon expulsion test
C. Anorectal manometry
D. Colon transit study
E. Colonoscopy
F. I'm not sure

Rectal Evacuation Disorders

- Dyssynergic defecation
- Pelvic floor dysfunction
- Pelvic floor dyssynergia
- Obstructed defecation syndrome
- Rectocele/rectal prolapse
- Descending perineum syndrome

Camilleri M, Brandler J. *Gastroenterol Clin North Am.* 2020;49(3):623-642.

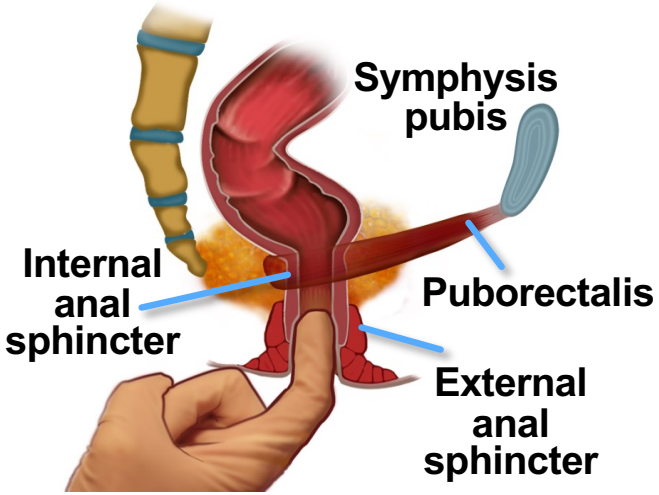
Pelvic Floor Dyssynergia (PFD) Frequently Overlaps with CIC

- PFD is more common in women
- Dyssynergic defecation can usually be identified with a careful digital rectal exam (DRE)
- A balloon expulsion test can easily be performed in the motility lab or office
- High-resolution anorectal manometry (HRAM) can be helpful in some patients

Digital Rectal Exam

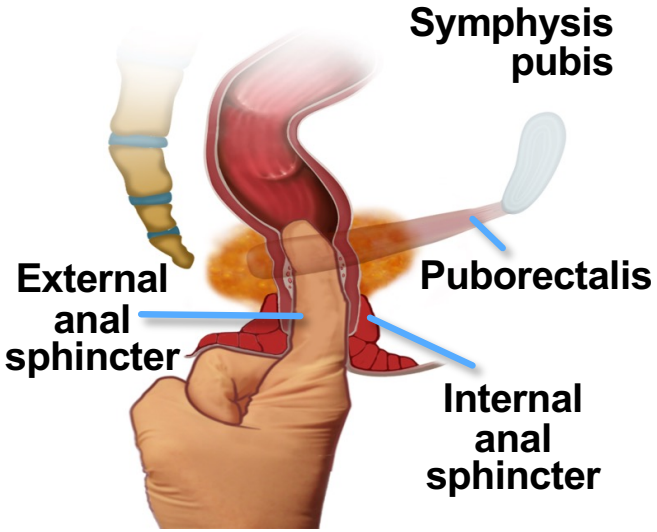
Position 1

- Check anal tone at rest
- Ask patient to squeeze

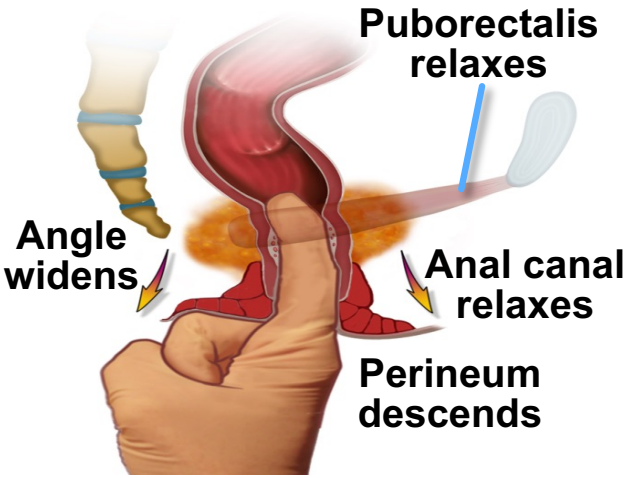


Position 2

- Insert finger deeper and feel puborectalis muscle
- Ask patient to squeeze



Expulsion



Rajab TK, et al. *N Engl J Med.* 2018;378(22):e30.

Performance of DRE for Dyssynergic Defecation in Chronic Constipation

Chronic Constipation by Rome III, N = 209	Estimated Value	95% CI	
		Lower Limit	Upper Limit
Sensitivity	0.75	0.68	0.81
Specificity	0.87	0.68	0.96
Positive predictive value	0.97	0.92	0.90
Negative predictive value	0.37	N/A	N/A

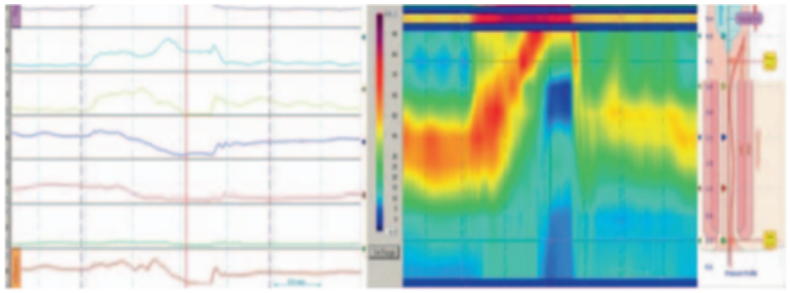
Take-home points: DRE reliably identifies patients with dyssynergic defecation and facilitates selection of patients for further physiologic testing

CI = confidence interval; DRE = digital rectal examination

Tantiphlachiva K, et al. *Clin Gastroenterol Hepatol*. 2010;8:955-960.

Anorectal Function Testing

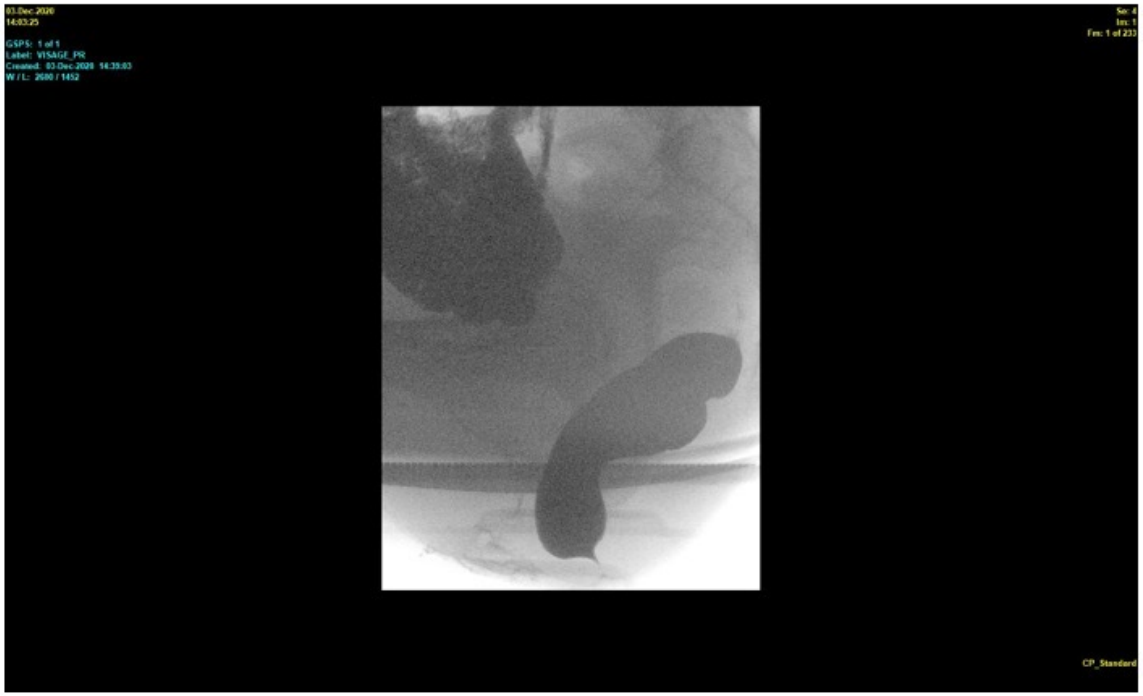
- Balloon attached to pressure sensing catheter to assess strength, tone, and sensation in the anus and rectum
- Balloon expulsion test
  - 4-cm balloon in rectum filled with 50 mL of warm water or silicon-filled stool-like device (fecom)
  - Patient attempts to expel balloon
  - Normal balloon expulsion < 1 min
  - Abnormal expulsion > 1 min
- Testing techniques, body position, and types of balloons highly variable



Camilleri M, Brandler J. *Gastroenterol Clin N Am*. 2020;49(3):623-642.

Pelvic Floor Evaluation

- Barium defecating proctogram
- MRR dynamic defecography



CME OUTFITTERS

Colon Transit Study

Hinton Technique: Qualitative

- Capsule containing 24 radiopaque markers high-fiber diet for 5 days (no laxatives, enemas, or meds that affect bowel function)
- Day 5: abdominal plain film
  - Slow-transit constipation is confirmed if > 20% of the radiopaque markers are retained
  - PFD–markers cluster in left colon?

Metcalf Technique: Quantitative

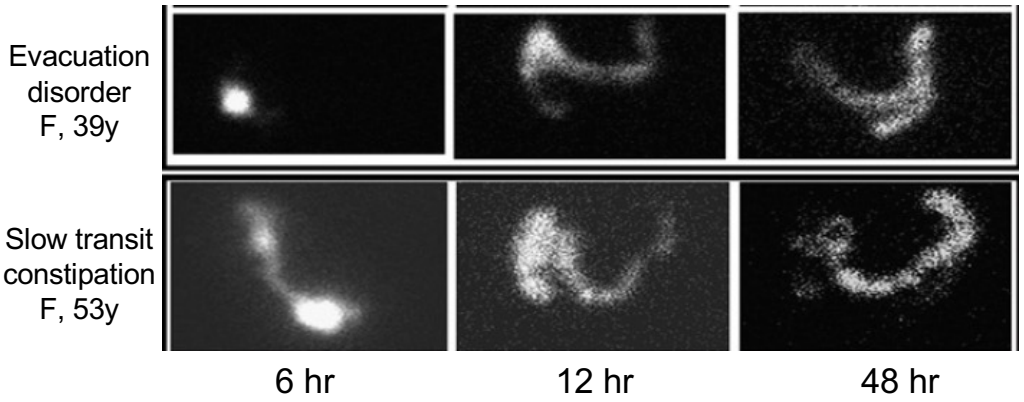
- 24 capsules/day for 3 days
- Picture on Day 4 and 7 (< 68 capsules)

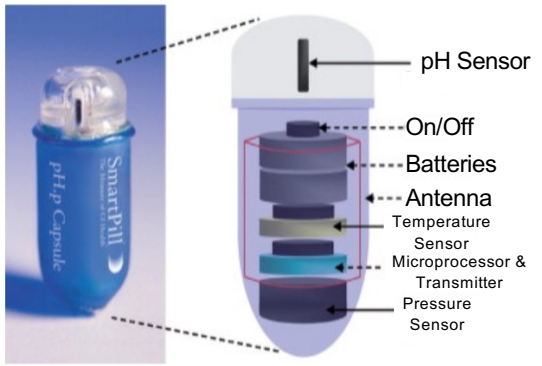
Lembo A, et al. *N Engl J Med.* 2003;349:1360. [Evidence Level C]

Other Colon Transit Studies

Whole Gut Transit Study

- Radio-isotope-labelled meal with timed measurements of residual radioactivity
- Wireless motility capsule: (Smart Pill®)
  - After standard meal, transit measured utilizing changes in pH along the GI tract
  - Takes 3-5 days

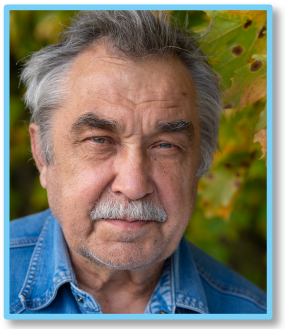




Nullens S, et al. *Gut.* 2012;61:1132-1139.

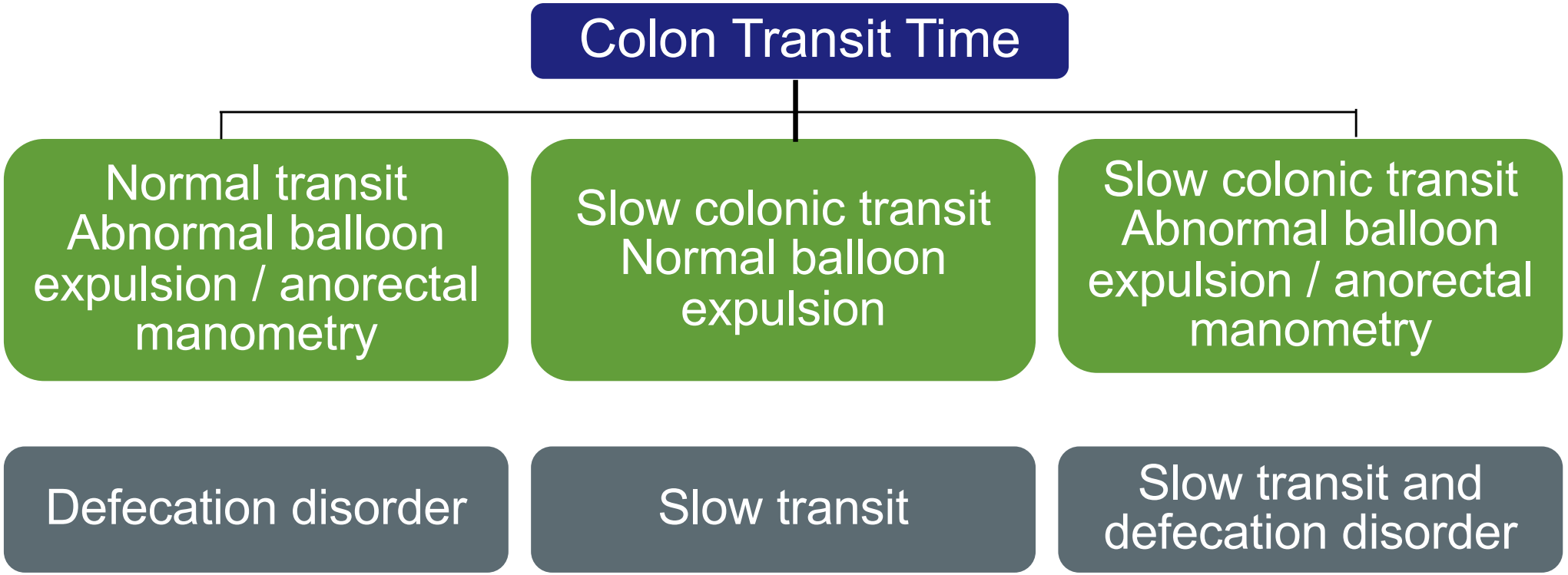
CME OUTFITTERS

Anorectal Manometry and Balloon Expulsion Test Results



- Mean resting anal sphincter pressure 72mmHg (normal 60-90mmHg)
- Maximum squeeze sphincter pressure 180mmHg (normal > 150mmHg)
- Residual anal pressure 60mmHg (normal 30-95mmHg)
- Anal sphincter relaxation 15% (normal 5-75%)
- Rectoanal pressure differential: -10mmHg (normal 7 to -35mmHg)
- Intra-rectal pressure during straining 55mmHg (normal 30-90mmHg)
- Balloon expulsion time 15 seconds (normal < 60 seconds)

Other Tests for Chronic Constipation



Lacy BE, Brunton SA. *MedGenMed*. 2005;7(2):19. Cash BD, et al. *Rev Gastroenterol Disord*. 2007;7:116-133.

Other Diagnostic Tools: Breath Testing

- Breath testing represents an important, simple, safe test to diagnose small intestinal bacterial overgrowth (SIBO)
- Useful in the diagnosis of methane-associated constipation, but not in the assessment of oro-cecal transit
- Methane levels $\geq$ 10 ppm are considered methane positive

Ppm = parts per million

Rezaie A, et al. *Am J Gastroenterol*. 2017;112(5):775-784.

Audience Response

Results indicate that Richard does not have an anorectal disorder. He exercises regularly, is well-hydrated, and consumes an average of 25g of fiber daily.

What approach would you recommend for Richard?

A. Conduct a colon transit study
B. Different over-the-counter (OTC) agent (fiber supplements, stool softeners, laxatives)
C. Prescribe a therapeutic agent (lubiprostone, linaclotide, plecanatide, prucalopride)
D. I'm not sure

Treatments for CIC

Osmotic and Stimulant Laxatives

Osmotic Agents

Contain poorly absorbed ions or molecules that increase water in intestinal lumen

- Polyethylene glycol
- Lactulose
- Magnesium hydroxide
- Magnesium citrate
- Magnesium sulfate
- Sodium phosphate

Strongly recommended for CIC, based on varying levels of evidence

Stimulant Agents

Peristalsis in the colon

- Bisacodyl
- Sodium picosulfate*
- Senna
- Cascara
- Rhubarb
- Aloe

*Not approved by the FDA.

Ford AC, et al. *Am J Gastroenterol.* 2014;109(Suppl 1):S2-S26.

Patient Experiences with OTC Medication for CIC (N = 1,423)

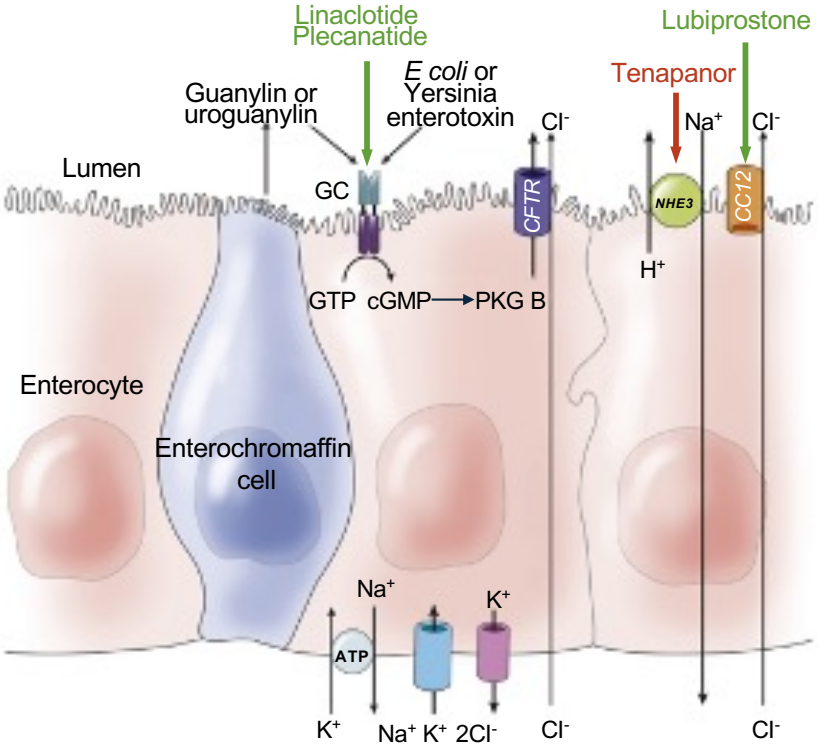
- **70%** reported trying ≥ 1 OTC medication during past 6 mon
- **19%** reported trying ≥ 1 OTC medication
- **44%** had tried and stopped 1 or more medications
- **30%** had tried and stopped 1 or more medications due to insufficient relief of symptoms

- Very few patients were very confident they could predict the timing of their BMs after taking an OTC medication
  - 49%-81% were not confidence at all
- High proportion of patients who report stopping OTC medication due to insufficient relief of symptoms suggests patients may be cycling through medications

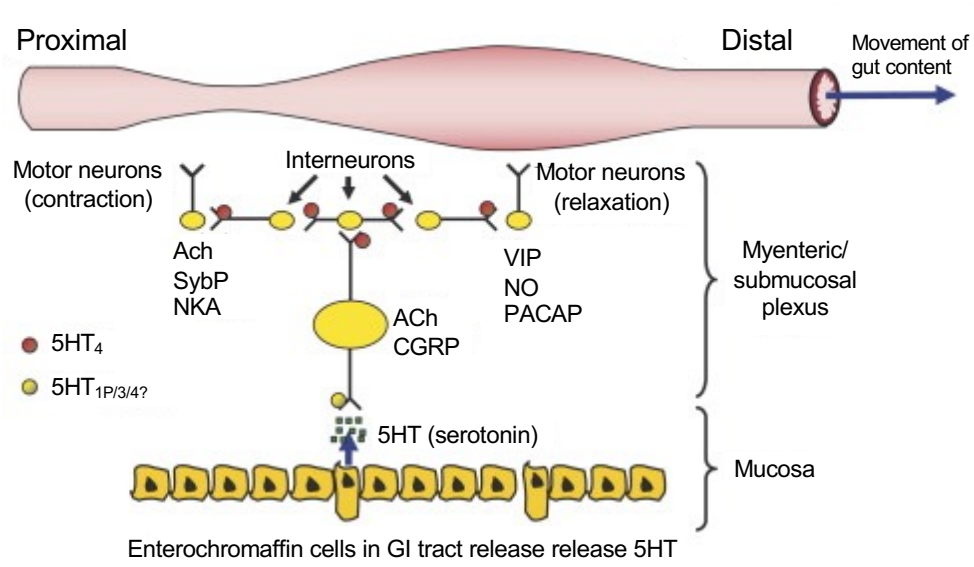
Lacy BE, et al. *PLoS ONE*. 2021;16(1):e0243318.

Mechanism of Action of Prescription Agents for CIC

Secretagogues[1]



Serotonin (5-HT$_4$) agonists[2] (prucalopride)



1. Pannemans J, Tack J. *Gastroenterology.* 2018;155(6):1677-1679. 2. Baker DE. *Am J Health Syst Pharm.* 2005;62(7):700-711;quiz 712-703.

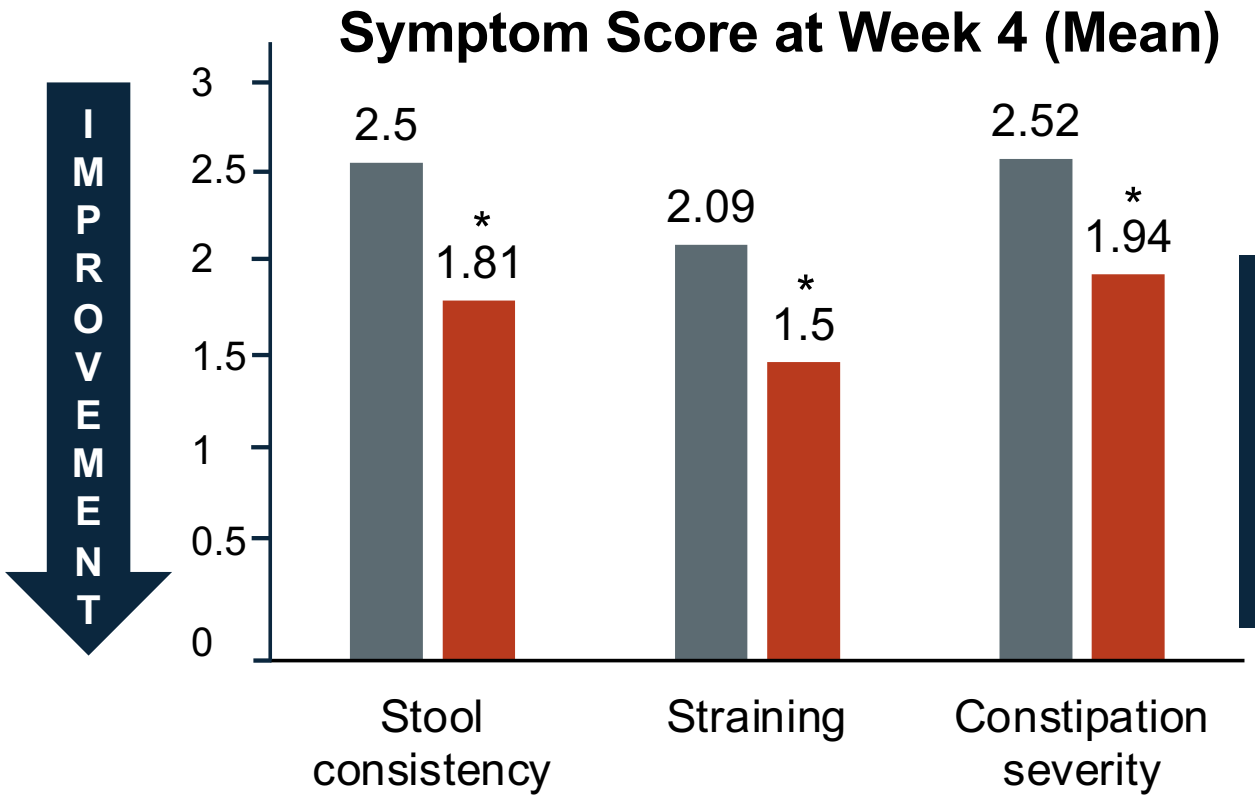
CME OUTFITTERS

Lubiprostone

- Non-absorbable GI-targeted bicyclic functional fatty acid
- Selectively activates type 2 chloride channels, enhancing intestinal fluid secretion
  - Restoration of mucosal barrier function (*ex vivo* studies)
- Dosing:
  - 24 µg twice a day (BID) for adults with CIC
  - 8 µg BID for IBS-C with food and water
- Side effects: nausea, diarrhea, headache

Cuppoletti J, et al. *Am J Physiol Cell Physiol*. 2004;287(5):C1173-1183. Lubiprostone package insert. Revised November 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021908s010lbl.pdf.

Lubiprostone for CIC



Straining
0 = absent
1 = mild
2 = moderate
3 = severe
4 = very severe

Consistency
0 = very loose
1 = loose
2 = normal
3 = hard
4 = very hard

*$p \leq .0003$ vs. placebo

Johanson JF, et al. *Am J Gastroenterol*. 2008;103:170-177.

Linaclotide

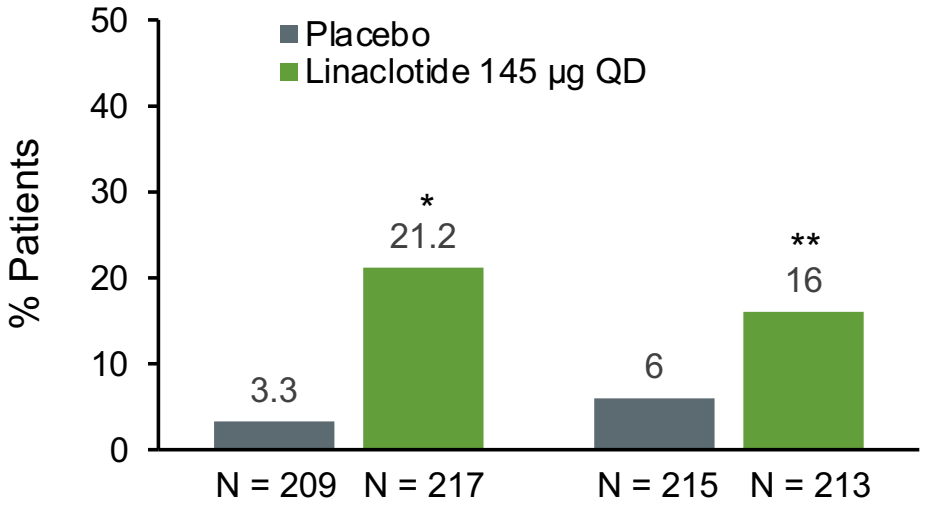
- Guanylate cyclase-C (GC-C) agonist
- Stimulates secretion of intestinal fluid; may also reduce intestinal pain (animal models)
- Dosing:
  - 72 µg/day and 145 µg/day for adults with CIC
- Side effects: diarrhea, abdominal pain

Linaclotide package insert. Revised March 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202811s013lbl.pdf.

Linaclotide for CIC

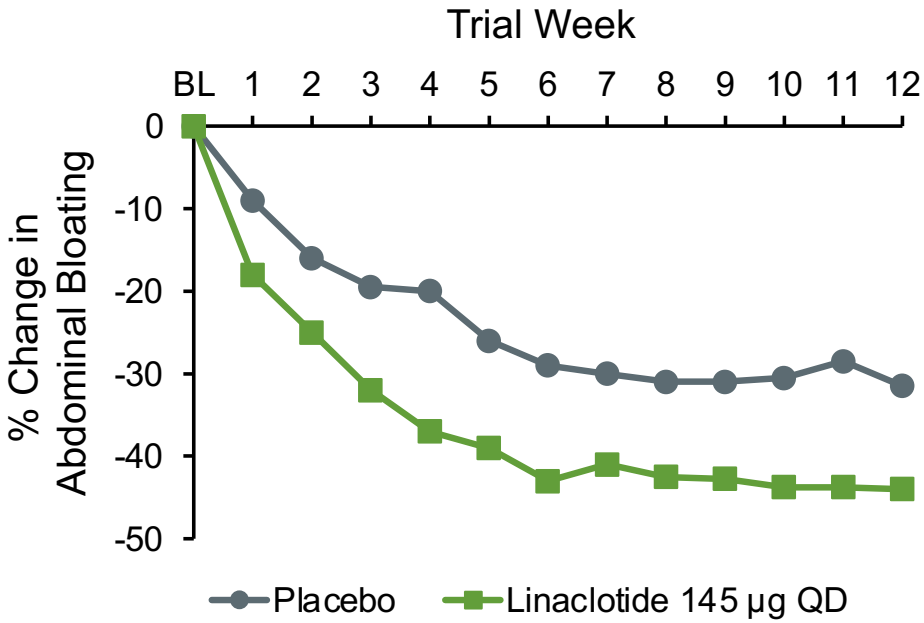
Primary Endpoint[1]

(≥ 3 CSBMs/week and increase of ≥ 1 CSBM/week for ≥ 9/12 weeks)



Abdominal Bloating by Week[2]

(N = 483)



*p < .001 vs. placebo; **p ≤ .01 vs. placebo

CSBM = complete spontaneous bowel movement; QD = every day; BL = baseline

1. Lembo AJ, et al. *N Engl J Med*. 2011;365:527-536. 2. Lacy BE, et al. *PLoS One.* 2015;10(7):e0134349.

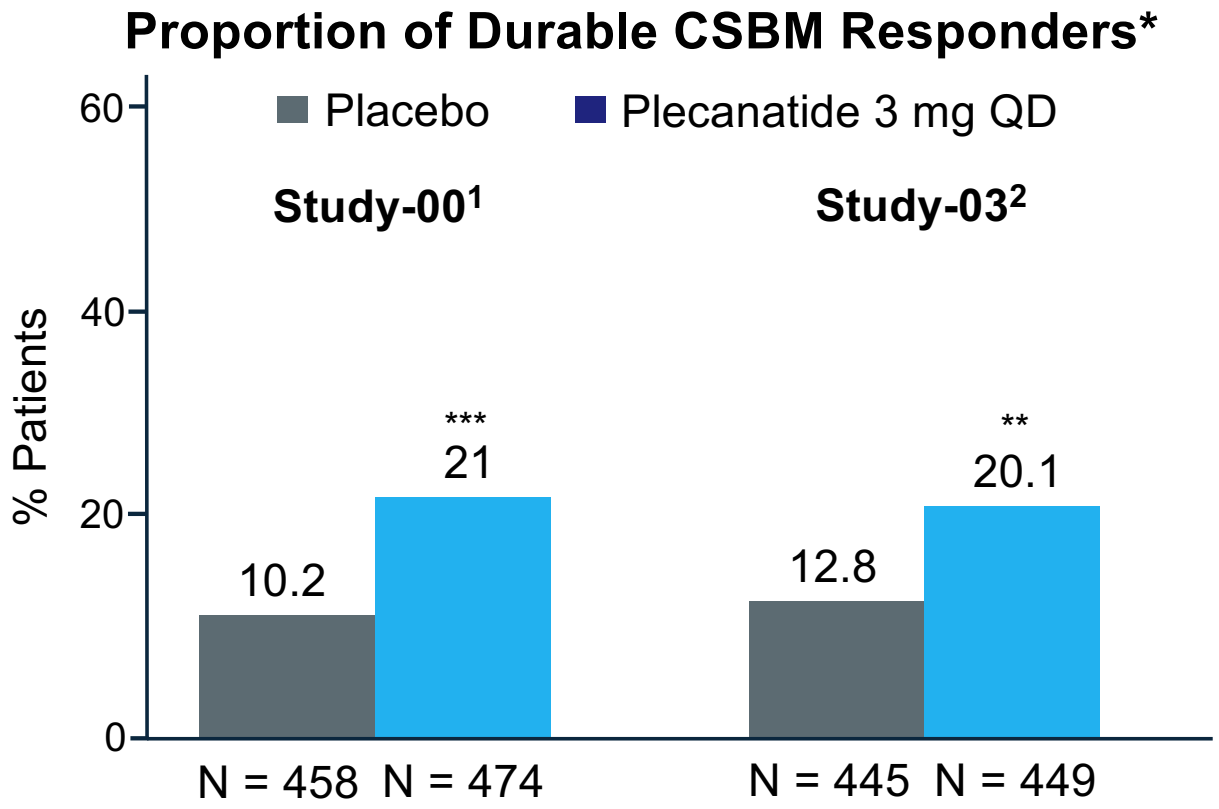
CME OUTFITTERS

Plecanatide

- Uroguanylin analogue (guanylate cyclase-C agonist) with pH selective receptor activity
  - Maximum binding efficiency at lower pH; minimal binding at high pH
- Dosing
  - 3 mg daily for adults with CIC
- Side effects: diarrhea, abdominal pain

Plecanatide package insert. Revised January 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208745s001lbl.pdf.

Plecanatide for CIC



*Defined as weekly responders for at least 9 of 12 treatment weeks, for at least 3 of the last 4 weeks; **p = .004; ***p < .001
Weekly responders had ≥ 3 CSBMs and an increase of ≥ 1 CSBM from baseline

1. Miner PB, et al. *Am J Gastroenterol*. 2017;112:613-621. 2. DeMicco M, et al. *Therap Adv Gastroenterol.* 2017;10(11):837-851.

CME OUTFITTERS

Prucalopride

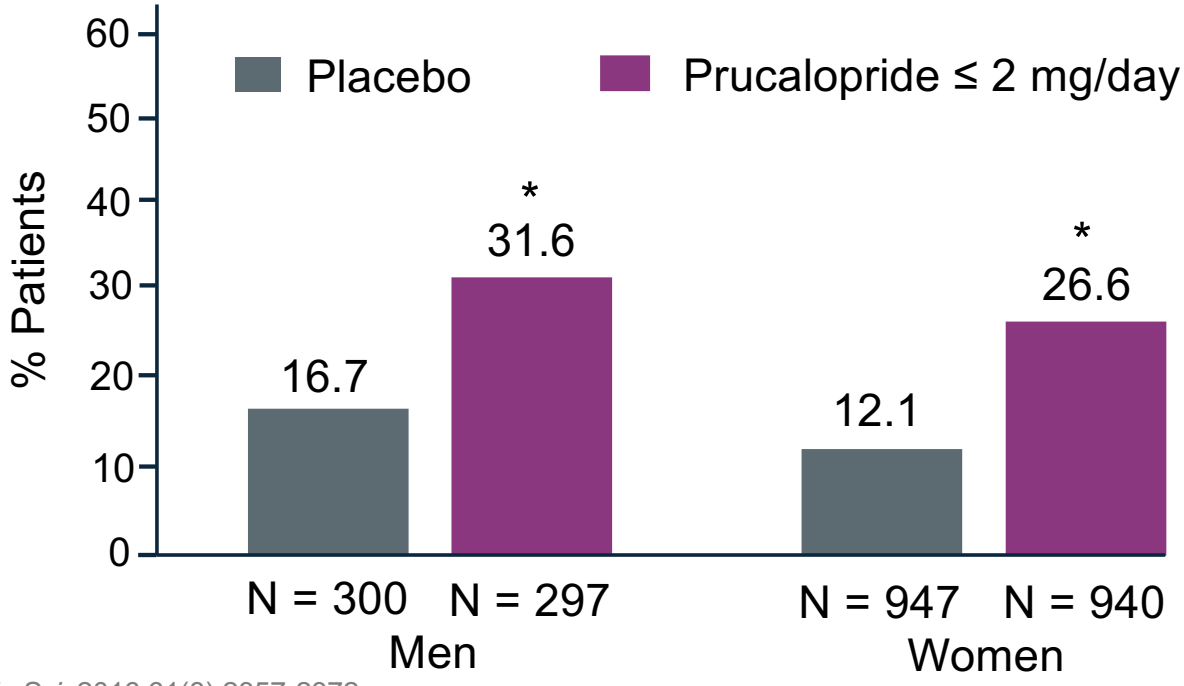
- Selective serotonin-4 (5-HT_4) receptor agonist with colonic prokinetic activity
  - Improves colonic motility, decreases colonic transit time, increases CSBMs
  - Does not interact with serotonergic receptors in blood vessels
- Dosing
  - 2 mg daily for adults with CIC
  - 1 mg daily for patients with severe renal impairment (CrCL < 30 mL/min)
- Side effects: headaches, diarrhea

Vijayvargiya P, Camilleri M. *Expert Rev Clin Pharmacol.* 2019;12(7):579-589. Plecanatide package insert. Revised December 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf.

Prucalopride for CIC

Meta-analysis of six phase III trials (n = 2,484)

Proportion of Patients in a Pooled Population with a Mean Frequency of ≥ 3 CSBM/Week Over 12-Week Treatment Period



*p < .001 vs. placebo

Camilleri M, et al. *Dig Dis Sci*. 2016;61(8):2357-2372.

CME OUTFITTERS

Prucalopride Cardiovascular Safety

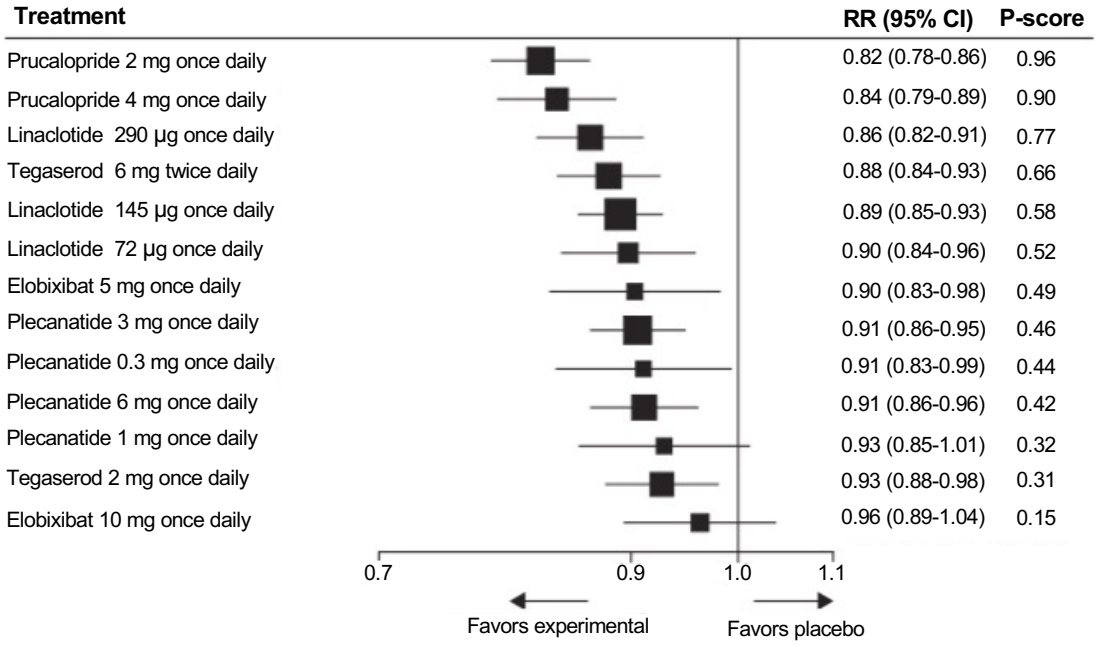
- First-generation 5-HT_4 receptor agonists cisapride and tegaserod were withdrawn from the U.S. market because of cardiovascular risk concerns
- Prucalopride is a selective 5-HT_4 agonist and does not interact with the cardiac hERG potassium channels or other serotonergic receptors in blood vessels
- **No increased risk of major cardiovascular events identified in patients with CIC taking prucalopride**

Gilsenan A, et al. *Drug Safety.* 2019;42(10):1179-1190.

Data Supporting Clinical Decisions in CIC: Network Meta-Analysis of RCTs

- 17 trials + 1 RCT reported data for failure to achieve 3 or more CSBMs/wk at 8-12 wks
- 8827 patients randomized to treatment, 4650 to PBO
- All treatments were significantly more effective than PBO, but prucalopride ranked 1st

Forest Plot for Failure to Achieve 3 or More CSBMs/Week at 8-12 Weeks



RCT = randomized controlled trial

Luthra P, Camilleri M, et al. *Lancet Gastroenterol Hepatol*. 2019;4(11):831-844.

CME OUTFITTERS

What if Richard had a positive ARM?

CME OUTFITTERS

Anorectal Biofeedback for Dyssynergia

- Overall, 70% of patients with dyssynergia will respond to biofeedback therapy[1]
- Methodological quality of trials of biofeedback has been generally poor and further research is required[2]
- Most centers include the following steps in their protocol:
  - Patient education
  - Training on how to relax the puborectalis muscle with abdominal pushing effort
  - Practice of simulated defecation by use of the balloon expulsion test

1. Camilleri M, et al. *Nat Rev Dis Primers*. 2017;3:17095. 2. Woodward S, et al. *Cochrane Database Syst Rev*. 2014(3).

Audience Response

What would be your treatment choice for Richard?

A. Lubiprostone
B. Linaclotide
C. Plecanatide
D. Prucalopride
E. Anorectal biofeedback
F. I’m not sure

Developing an Evidence-Based Treatment Strategy for Patients with CIC

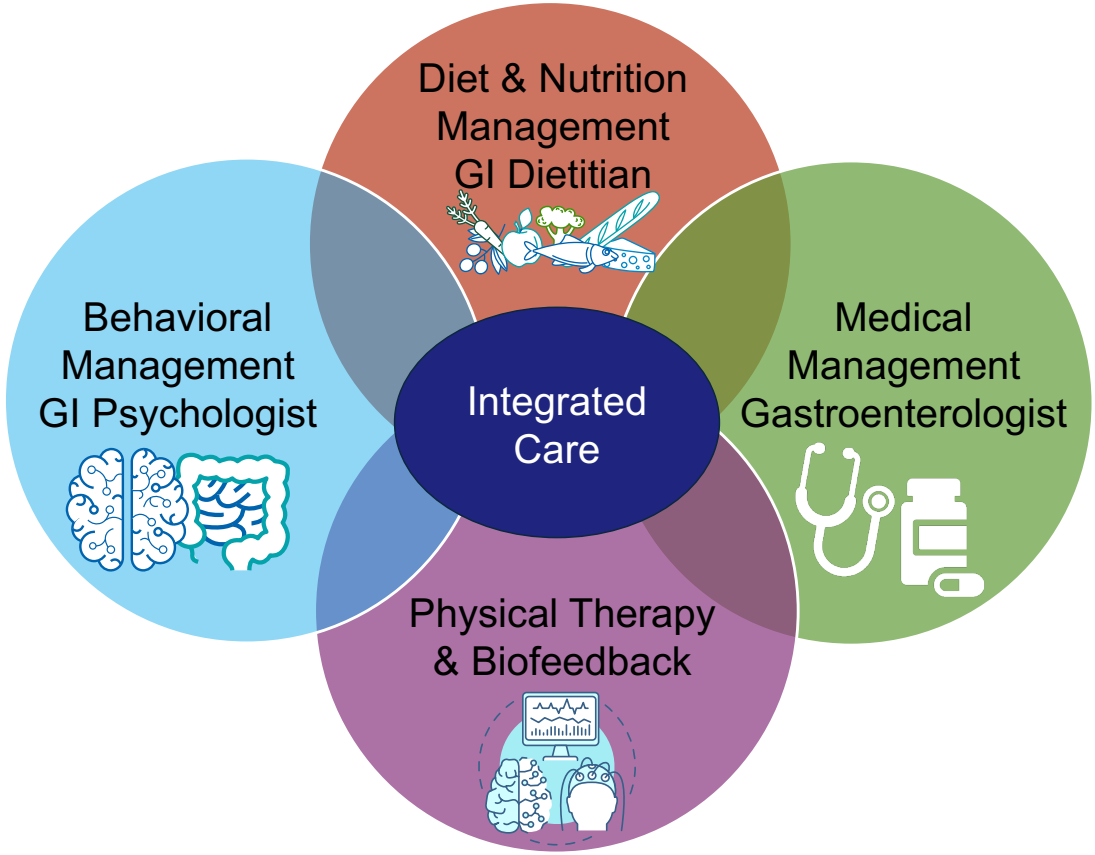
CME OUTFITTERS

Audience Response

How would you describe your interdisciplinary integrative care network for patients with CIC?

A. Challenging for my community-based practice
B. Improving, but still has a ways to go
C. I need strategies for building my network
D. I am fortunate to have a strong network
E. What's an interdisciplinary integrative care network?

Integrated Care in CIC



Chey WD, et al. *Gastroenterol* 2021;160:47-62.

CME OUTFITTERS

The Evolution of Care Models for Disorders of Gut-Brain Interaction

Gastroenterologist only

Gastroenterologist dietitian, behavioral therapist working independently

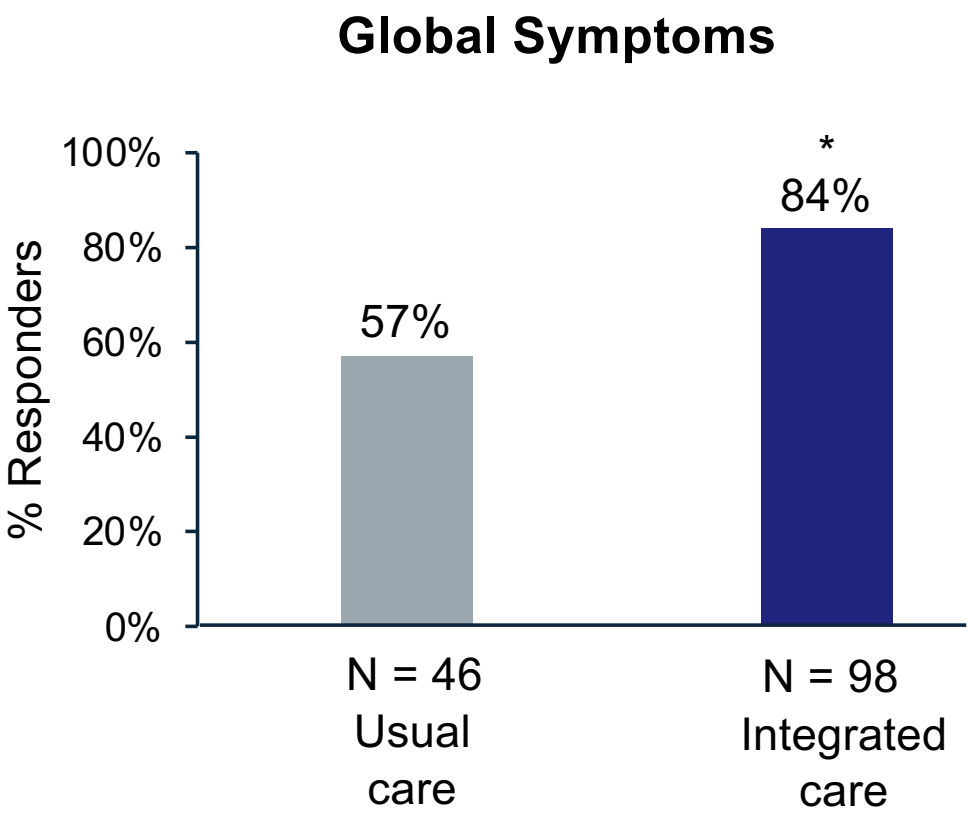
Team-based, collaborative, multi-disciplinary care

Chey WD. *Lancet Gastroenterol Hepatol*. 2020;5(10):876-877.

Integrated Care for FGBIs: Prospective RCT

188 patients with functional GI disorders (FGIDs) randomized to usual GI care vs. team-based care model

- In **usual care** GIs could obtain a nutrition or behavioral therapy consult from a provider outside of their hospital
- **Integrated care** consisted of GI, dietitians, gut-focused hypnotherapists, psychiatrists, and biofeedback therapists working as a team



*p = .001

Basnayake C, et al. *Lancet Gastroenterol Hepatol*. 2020;5(10):890-899.

Improving the Patient-Provider Relationship (PPR)

CME OUTFITTERS

Difficulties with the PPR in Present Health Care Environment

- Clinicians spend less time with patients
  - From 45 minutes in 1970s to 12 minutes in 2019
- The “art of medicine” has all but disappeared
  - Nonverbal engagement, proxemics, and touch improve patient satisfaction and lead to acquiring more meaningful information
- Technology may be replacing clinical observation and reasoning
  - “Why talk with and examine the patient when I can get a CT?”
  - Abnormal structure and physiology correlate poorly with symptoms
- More and more time spent on documenting and certification
  - EMR, MOC, OSHA, HIPPA, training for fire/environment, pathogens, tuberculosis, etc.
- Patients are becoming increasingly dissatisfied with the care that providers are delivering

CT = computed tomography; EMR = electronic medical record; HIPPA = Health Insurance Portability and Accountability Act; MOC = Maintenance of Certification; OSHA = Occupational Safety and Health Administration

Drossman DA, Ruddy J. *Clin Gastroenterol Hepatol.* 2020;18(7):1417-1426.

Effective Provider-Patient Communication

- Provide a clear and confident diagnosis
- Set up mutually agreed-upon goals and expectations for the outcome
- Assess the patient's understanding and respond with clear information
- Encourage collaboration by promoting the patient's active role in decision-making
- Provide positive regard and empathy, and engage with the patient to achieve satisfaction

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Make a confident diagnosis of CIC using Rome IV criteria, and appropriate diagnostic testing and interpretation
- Initiate evidence-based treatment in order to address symptoms that persist despite initial dietary and OTC approaches
- Promote interdisciplinary, integrative care strategies that facilitate comprehensive management of CIC
- Establish a relationship with each patient by educating, providing empathy, and empowering to take an active role in the decision-making process

To Ask a Question

Please click on the *Ask Question* tab and type your question. Please include the faculty member's name if the question is specifically for them.

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Participants will be able to download and print their certificate immediately upon completion.

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