Chronic Idiopathic Constipation: Therapeutic Options

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Learning Objectives

- Implement individualized treatment plans for patients with chronic idiopathic constipation (CIC) that incorporate data from randomized controlled trials and evidence-based recommendations
- Utilize patient-centric counseling strategies for patients with CIC to support prompt identification of inadequate or poorly tolerated therapy and support long-term therapeutic adherence

Case Study

SK is a 42-year-old female patient with symptoms of nausea, epigastric pain, fullness/bloating after meals, and routine constipation.

- Symptoms began 3 years ago and improved after she initiated a low-carbohydrate, high-fat diet and lost ~25 lb
- She has maintained the weight loss, but constipation symptoms have returned in the past year, tending to worsen each month just before her period
- SK is reluctant to discuss her symptoms but can no longer bear her condition, which now impacts work and social life

Case Study (*cont'd*)

- SK reports having 2 to 3 bowel movements per week, but always feels like she could "go more"
- In addition to dietary changes, she has tried yoga for stress relief, OTC laxatives, fiber supplements, and probiotics, all with limited efficacy
- She takes sertraline for mild depression (~2 years); takes no other medications or supplements and denies any medical comorbidities or history of GI disease

GI, gastrointestinal; OTC, over the counter.

Rome IV Diagnostic Criteria for Functional Constipation

- Must include ≥2 of the following:
  - Straining
  - Lumpy or hard stools (BSFS 1–2)
  - Sensation of incomplete evacuation
  - Sensation of anorectal obstruction/blockage
  - Manual maneuvers to facilitate >25% of defecations
- Criteria should be fulfilled for the previous 3 months, with symptom onset ≥6 months before diagnosis
- Loose stools are rarely present without the use of laxatives

BSFS, Bristol Stool Form Scale; IBS, irritable bowel syndrome.

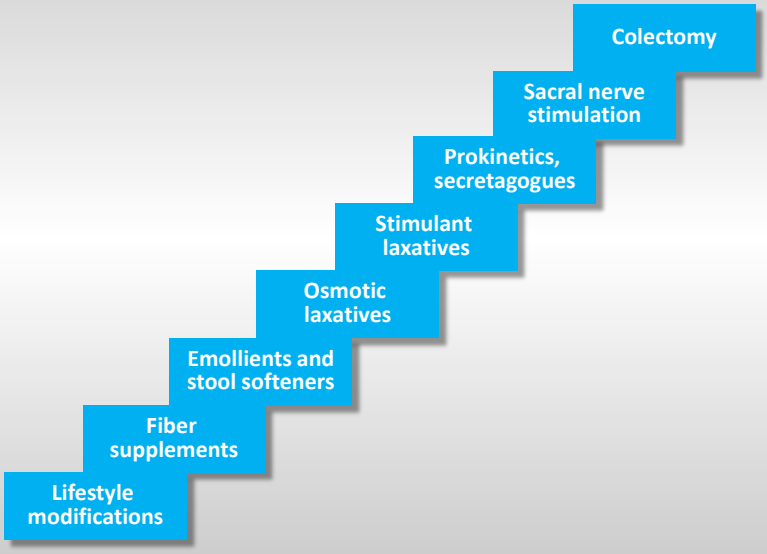
Mearin F, et al. *Gastroenterology*. 2016;150(6):1393-1407.

CIC: Current Treatment Options

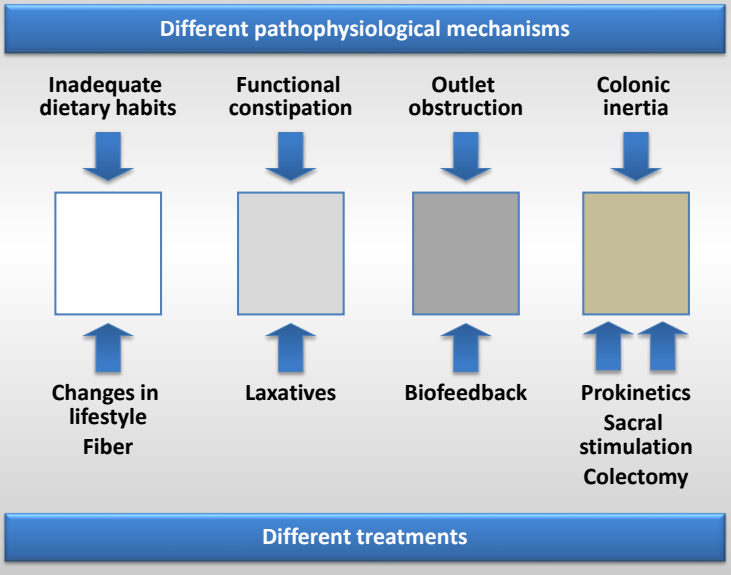
- Education
- Diet, lifestyle modifications, and fiber
- Emollients and stool softeners
- Osmotic agents
- Stimulant laxatives
- Secretagogues (CLC-2 and GC-C agonists)
- 5-HT_4 agonists
- Biofeedback
- Surgery (rarely required)

5-HT_4, 5-hydroxytryptamine receptor 4; CLC-2, chloride ion channel 2; GC-C, guanylate cyclase-C.

Range of Treatment Approaches



Pathophysiologic Treatment Approach



CIC: Diet and Lifestyle Modifications

- Diet: goal of 25 g to 30 g of fiber per day
- Modify risk factors when able
  - Inactivity
  - Reduced caloric intake
  - Medications
    - Opioids, high-dose TCAs, calcium channel blockers
- Routines and positional changes
- Scheduled bathroom time
- Exercise—may stimulate intestinal motility

TCA, tricyclic antidepressant.

CIC: Fiber Supplements

- Mechanism of action (MOA)
  - Hydrophilic, adds bulk, increases intestinal transit
  - Colonic fermentation with local stimulation
- Advantages: cheap, safe, no prescription needed
- Disadvantages: may worsen bloating
- Data
  - Quality of evidence: low
  - 6 trials; 3 analyzed; N=293; NNT=2

NNT, number needed to treat.

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

CIC: Stool Softeners, Stimulant Laxatives

- Stool softeners
  - Add water weight to stool (3%)
  - Act as an emollient
  - No better than placebo in RCT
- Stimulant laxatives
  - Decrease water absorption
  - Stimulate intestinal motility
  - Side effects: abdominal pain
- Data
  - Quality of evidence: moderate
  - 2 trials; N=735; NNT=3

RCT, randomized controlled trial.

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

CIC: Osmotic Laxatives

- MOA: Stimulate electrolyte and water secretion into the lumen of the small intestine and colon
- Advantages: cheap, safe, easy to titrate
- Disadvantages: dosing and timing can be tricky, not always effective, may worsen bloating (notably, lactulose)
- Choices: PEG, lactulose, mannitol, MOM
- Data: PEG
  - Quality of evidence: high
  - 4 trials; N=573; NNT=3

MOM, milk of magnesia; PEG, polyethylene glycol.

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

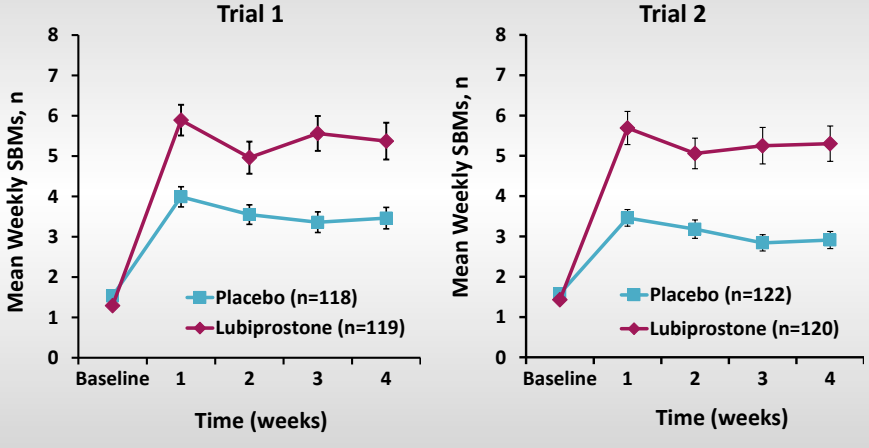
CIC: Secretagogues[1,2]

- CLC-2 agonists
  - Lubiprostone (approved 2006)
- GC-C agonists
  - Linaclotide (approved 2012)
  - Plecanatide (approved 2017)

1. Ford AC, et al. *Am J Gastroenterol.* 2014;109(suppl 1):S2-S26.
2. Rao SSC. *Therap Adv Gastroenterol.* 2018;11:1756284818777945.

Lubiprostone Increased Weekly SBMs

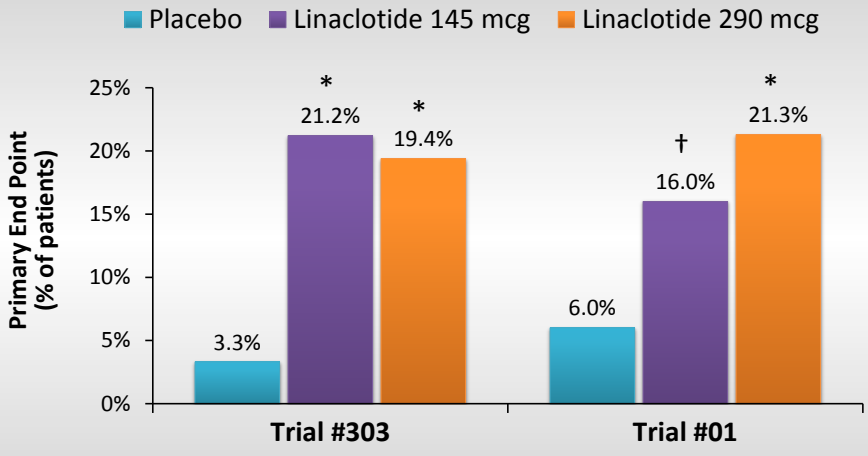
Mean Weekly SBMs in 2 clinical trials[1,2]



SBMs, spontaneous bowel movements.

1. Barish CF, et al. *Dig Dis Sci*. 2010;55(4):1090-1097.
2. Johanson JF, et al. *Am J Gastroenterol.* 2008;103(1):170-177.

Linaclotide Increases CSBMs



*P≤.001 vs placebo.
†P≤.01 vs placebo.

CSBMs, complete spontaneous bowel movement.

Lembo A, et al. *N Engl J Med*. 2011;365(6):527-536.

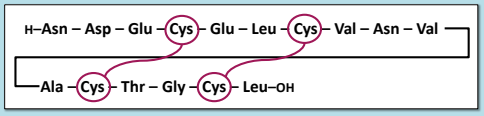
72 mcg Linaclotide: New Dose for CIC

- Based on a double-blind, randomized, placebo-controlled trial using Rome III criteria; N=1223
- Mean age of patients: 46 yrs; 77% women
- Primary end point: ≥3 CSBMs and increase of ≥1 CSBM per week for ≥9 of 12 weeks
- 13.4% of linaclotide vs 4.7% of placebo patients met the primary end point (P<.001)
- Diarrhea: 0% in placebo group vs 2.4% in linaclotide group

Schoenfeld P, et al. *Am J Gastroenterol*. 2018;113(1):105-114.

Plecanatide in CIC

- 16 amino acid analogue of the natural peptide uroguanylin
- Activates GC-C receptors in a pH-dependent manner

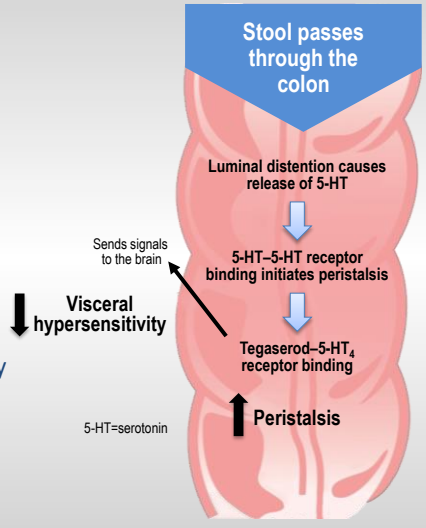


- Double-blind, placebo-controlled, multicenter trial in patients meeting Rome III criteria for functional constipation (N=1394)
- Randomized to 3 mg or 6 mg plecanatide vs placebo for 12 weeks
- Primary end point: durable overall CSBMs
  - Met by 21% of 3-mg group and 19.5% of 6-mg group vs 10.2% for placebo (*P*<.001 for both)
- Adverse events: diarrhea in 1.3% of placebo group vs 5.9% (3 mg) and 5.7% (6 mg) in group treated with plecanatide

Miner PB, et al. *Am J Gastroenterol*. 2017;112(4):613-621.

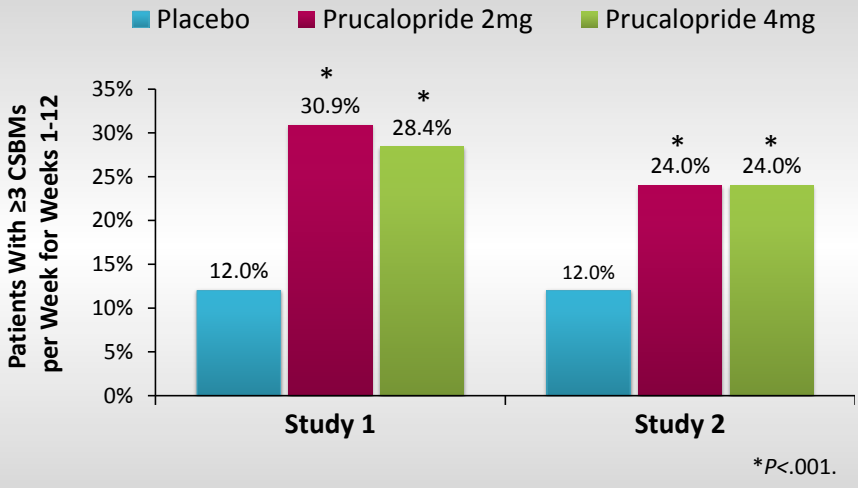
CIC: Serotonin Agonists (5-HT_4 agonists)

- Prucalopride
  - 4 large RCTs demonstrating efficacy
  - Available in EU since 2012
  - Approved 2018
- Tegaserod
  - Previously approved by the FDA for the treatment of both CIC and IBS
    - Voluntarily withdrawn from the US market in 2007
  - Several large RCTs demonstrating efficacy
  - OK'd for reintroduction for IBS-C in women age <65 years (low CV risk)



CV, cardiovascular; EU, European Union; FDA, US Food and Drug Administration; IBS-C, constipation-predominant irritable bowel syndrome.

Prucalopride Improves CSBMs in Patients With CIC*



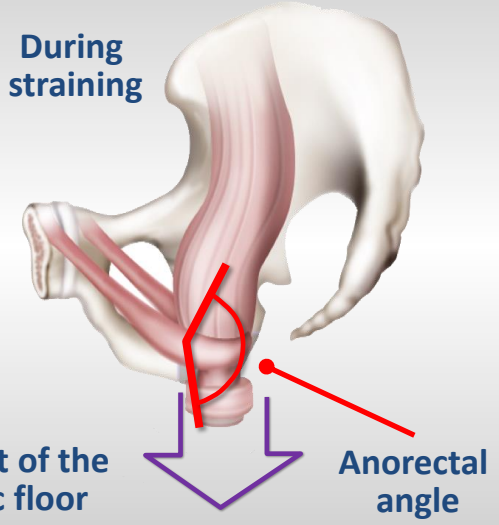
*Entrance criteria: ≤2 CSBMs per week.

Camilleri M, et al. *N Engl J Med*. 2008;358(22):2344-2354; Quigley EM, et al. *Aliment Pharmacol Ther*. 2009;29(3):315-328.

Pelvic Floor and Anorectal Function: Defecation

Defecation requires:

- Relaxation of puborectalis
- Straightening of anorectal angle
- Relaxation of sphincter



Lembo A, Camilleri M. *N Engl J Med*. 2003;349(14):1360-1368.

CIC: Enemas and Suppositories

- Make sense physiologically in patients with obstructed defecation
- No large RCTs
- For suppositories, the technique may be more important than the substance
- Enemas: Warn your patients about high-volume enemas and the risks of hyponatremia, perforation, and hematomas

CIC and Biofeedback

Cochrane Database Systematic Review

- 17 randomized trials in adults; N=931
- 16 of 17 at high risk for bias due to blinding
- Meta-analysis not possible due to significant heterogeneity (different techniques; different comparators)
- Conclusion: Insufficient evidence due to low-quality, heterogeneous studies

Woodward S, et al. *Cochrane Database Syst Rev*. 2014;(3):CD008486.

Conclusions

- CIC is common
- Treatment can be challenging
- Multiple treatment options are available—but one size does not fit all
- Combination therapy may be required
- Don’t forget pelvic floor disorders
- Even more treatment options will be available in the next few years