Chronic Idiopathic Constipation: Therapeutic Options

Brian E. Lacy, PhD, MD, FACG
Professor of Medicine
Senior Associate Consultant
Mayo Clinic, Jacksonville, FL

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.

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-HT₄ agonists
- Biofeedback
- Surgery (rarely required)

5-HT₄, 5-hydroxytryptamine receptor 4; CLC-2, chloride ion channel 2; GC-C, guanylate cyclase-C.
Range of Treatment Approaches

- Colectomy
- Sacral nerve stimulation
- Prokinetics, secretagogues
- Stimulant laxatives
- Osmotic laxatives
- Emollients and stool softeners
- Fiber supplements
- Lifestyle modifications

Pathophysiologic Treatment Approach

Different pathophysiological mechanisms:

- Inadequate dietary habits
- Functional constipation
- Outlet obstruction
- Colonic inertia

Different treatments:

- Changes in lifestyle: Fiber
- Laxatives
- Biofeedback
- Prokinetics Sacral stimulation Colectomy
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.
**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.

**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.
CIC: Secretagogues\textsuperscript{1,2}

- CLC-2 agonists
  - Lubiprostone (approved 2006)

- GC-C agonists
  - Linaclotide (approved 2012)
  - Plecanatide (approved 2017)


Lubiprostone Increased Weekly SBMs

Mean Weekly SBMs in 2 clinical trials\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Placebo (n=118)</th>
<th>Lubiprostone (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

SBMs, spontaneous bowel movements.

Linaclotide Increases CSBMs

- Placebo
- Linaclotide 145 mcg
- Linaclotide 290 mcg

CSBMs, complete spontaneous bowel movement.


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

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


CIC: Serotonin Agonists (5-HT₄ 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.


Pelvic Floor and Anorectal Function: Defecation

Defecation requires:
- Relaxation of puborectalis
- Straightening of anorectal angle
- Relaxation of sphincter
- Descent of the pelvic floor

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

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