Evidence-based Treatment Strategies for Chronic Constipation

William D. Chey, MD
Professor of Medicine
University of Michigan

Rome III criteria*: Chronic constipation

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

- Straining
- Lumpy / hard stools
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction
- Manual maneuvers
- <3 defecations per week

Loose stools rarely present without laxative use insufficient criteria for IBS

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

Longstreth et al, Gastroenterology 2006; 130: 1480–91
Overlap of IBS-C and CC:
When the Rome III requirement that FC cannot be diagnosed in a patient meeting criteria for IBS is suspended, 89.5% of IBS-C cases meet criteria for FC and 43.8% of FC patients fulfill criteria for IBS-C

Wong et al. Am J Gastroenterol 2010;105:2888

IBS-C 201
FC 411

180
231
21

Diagnostic Evaluation of Chronic Constipation
**Pathophysiology of constipation**

**Subtypes of constipation**

- **Normal-transit constipation**
  - Defecatory dysfunction
    - Inability to coordinate muscles
    - Can overlap with STC

- **Defecatory constipation**
  - Decreased colonic motility
  - Blunted response to meals
  - Absent pacemaker cells

- **Slow-transit constipation**
  - Dyssynergic defecation
  - Megarectum
  - Rectocele
  - Perineal descent

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**Normal Anorectal Physiology**

- **At Rest**
  - Anorectal Angle ~90°

- **Defecation**
  - Angle more Obtuse
  - Sphincter relaxes
  - Pelvic floor descends

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*Used with permission from Lembo A, Camilleri*

Read in: Sleisinger & Fordtran’s Gastrointestinal and Liver Disease. 7th ed. 2002: 1794
Refractory Constipation and Difficult Defecation

1. Patient meeting criteria for functional constipation with no alarm features and no improvement with high fiber diet and laxatives

2. Physiological testing:
   - anorectal manometry
   - rectal balloon expulsion
   - colonic transit

3. Are anorectal manometry and rectal balloon expulsion both normal?

4. Is colonic transit slow?

5. Slow transit constipation

6. Functional constipation with normal transit

7. Are both tests abnormal?

8. Functional defecation disorder

9. Assess barium or MR defecography

10. Does defecography reveal disordered defecation?

11. Is colonic transit slow?

12. Functional defecation disorder with normal transit

13. Functional defecation disorder with slow transit

14. Does slow colonic transit normalize after correction or functional defecation disorder?

Kellow, JE and Drossman, DA, Rome Foundation 2010
Refractory Constipation and Difficult Defecation

Patient meeting criteria for functional constipation with no alarm features and no improvement with high fiber diet and laxatives

Physiological testing:
- anorectal manometry
- rectal balloon expulsion
- colonic transit

Are both tests abnormal?
- Yes: Functional defecation disorder
- No: Are anorectal manometry and rectal balloon expulsion both normal?
  - Yes: Functional constipation with normal transit
  - No: Slow transit constipation

Is colonic transit slow?
- Yes: Does defecography reveal disordered defecation?
  - Yes: Does slow colonic transit normalize after correction or functional defecation disorder?
  - No: Functional defecation disorder with slow transit
- No: Assessment of barium or MR defecography

Kellow, JE and Drossman, DA, Rome Foundation 2010

Management Options for Chronic Constipation (CC)
Colon Transit Time According to Physical Activity Level

Mean Total Colon Transit Time in 49 Volunteers


Pharmacological Treatments for Chronic Constipation:

- Bulking Agents
  - Psyllium/isphagula

- Osmotic Laxatives
  - PEG 3350
  - Magnesium salts

- Stool Softeners
  - Ducosate sodium

- Stimulant Laxatives
  - Picosulfate
  - Bisacodyl
  - Senna

- Prokinetic Agents
  - Prucalopride
  - Tegaserod

- Prosecretory Agents
  - Lubiprostone
  - Linaclotide, Plecanatide
  - A3309

ACG Functional GI Disorders Task Force. Am J Gastroenterol. 2005;100(suppl 1):S1-21
PEG* for Chronic Constipation

- US multicenter, double-blind, randomized placebo-controlled trial of PEG vs. placebo for 6 months

- Treatment response** ROME Criteria not met BM per week (#)

- *PEG = polyethylene glycol 3350 ***p<0.001 vs placebo
- **treatment response = ≥3 BMs/week and no more than 1 of the remaining 3 Rome symptoms in the absence of rescue medications = ≥ 50% of the time

- Adverse events not different between PEG and placebo


Randomized, Placebo-controlled Trial of Bisacodyl for Chronic Constipation

- RCT, 27 centers in UK
- 368 adults with CC (Rome III), 75% female
- Bisacodyl 10mg/d x 4 wks (n=247) vs. placebo ( n=121)

<table>
<thead>
<tr>
<th></th>
<th>Bisacodyl</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSBM/wk (1.1)</td>
<td>5.2 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBM/wk (4)</td>
<td>12-8</td>
<td>unchanged</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Global assessment*</td>
<td>79.5%</td>
<td>49.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QOL</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Bisacodyl superior to placebo for straining, sense of anorectal blockage and stool form ( p < 0.001)
- AEs 72% vs. 37%, SAEs 6.5% vs. 1.7%

* "good or "satisfactory"  
Kamm et al, 2011, CGH; 9:557
Chloride Channels in Intestinal Transport

Enterocytes

H₂O  Na⁺  Cl⁻  Cr

CFTR Channel
Linaclotide
Plecanitide

Lubiprostone

Tight Junction

H₂O  Na⁺  Cl₂

K⁺  Na⁺  K⁺  2Cl⁻

Lubiprostone for CC:
Results from Phase III
Lubiprostone 24 mcg bid vs. placebo x 4 weeks
242 adults with CC (Modified Rome II)

Johanson et al. 2008; Am J Gastroenterol; 103:170
Incidence of Nausea with Lubiprostone in Clinical Trials

- Chronic idiopathic constipation: 24 mcg bid with food
- Irritable bowel syndrome with constipation: 8 mcg bid with food


Emerging Therapies for IBS-C and Chronic Constipation (CC)

Prosecretory Drugs:
- Linaclotide
- Plecanitide
- RDX5791
Linaclotide for CC & IBS-C: MOA

- Minimally absorbed, 14-amino acid investigational peptide
- Guanylate cyclase-C (GC-C) agonist, results in generation of cyclic guanosine monophosphate (cGMP)
- Based upon available preclinical data, cGMP is proposed to have two activities:
  - *Intracellular*: activation of CFTR leads to increased luminal fluid secretion and intestinal transit
  - *Extracellular*: inhibition of pain fiber activity, which is thought to result in reduced visceral pain

CCEYCCNPACTGCY

Linaclotide for Chronic Constipation:
Primary Results from 2 Phase III Clinical Trials

Responders = ≥3 CSBM/wk & increase of ≥1 CSBM/wk for ≥ 9/12 wks

<table>
<thead>
<tr>
<th></th>
<th>Study 01</th>
<th>Study 303</th>
</tr>
</thead>
<tbody>
<tr>
<td>L 145 mcg, n=430</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>L 290 mcg, n=418</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Placebo, n=424</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

* p ≤ 0.0012

Most common AE diarrhea (14-16% vs. 4.7%)
Discontinuation (4% vs. 0.5%)

CSMB, complete spontaneous bowel movement
Linaclotide for IBS-C: Adequate Relief of IBS Symptoms for ≥ 13/26 weeks

% Adequate Relief: IBS Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Lin 290 mcg (N = 401)</th>
<th>Placebo (N = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate Relief</td>
<td>49.1 * p&lt;0.0001 NNT = 4.2</td>
<td>25.1</td>
</tr>
</tbody>
</table>

Most common AE: diarrhea (19.7% vs 2.5%)

Chey WD, et al. DDW 2012

Emerging Therapies for Chronic Constipation (CC)

Prokinetic Drugs: Prucalopride
Prucalopride for CC

Post-hoc analysis of phase III data from patients who had failed previous laxative therapies

% ≥ 3 SCBM for weeks 1-12

<table>
<thead>
<tr>
<th></th>
<th>Pru 2 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>458</td>
<td>478</td>
</tr>
<tr>
<td>NNT</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>24.7</td>
<td></td>
<td>9.2</td>
</tr>
</tbody>
</table>

Quigley E, et al. *DDW* 2012

Phase III Studies of Prucalopride for Chronic Constipation: Adverse Events

<table>
<thead>
<tr>
<th>AE</th>
<th>% Reported</th>
<th>Prucalopride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>25-30%</td>
<td>12-17%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12-24%</td>
<td>8-14%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12-19%</td>
<td>3-5%</td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>2.7%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>4-15%</td>
<td>2-7%</td>
<td></td>
</tr>
</tbody>
</table>

Prucalopride 2 or 4 mg QD
No effect on vital signs or ECG parameters.

Emerging Therapies for Chronic Constipation (CC)

Bile Acid Modulators: Elobixibat

**Elobixibat: Mechanism of Action**

*Increasing Delivery of Bile Acids to Colon Induces Secretion and Motility*

- A3309 partially blocks the ileal bile acid transporter from the luminal side, increasing delivery of bile acids to the colon inducing secretion and motility.
- A3309 only affects the delivery of bile acids to the colon: No effect on the uptake of fat soluble nutrients.
- As synthesis of bile acids from cholesterol requires increased uptake of cholesterol, IBAT inhibition by A3309 leads to decreases in plasma LDL cholesterol.

Decreased bile acid synthesis & bile acid concentration may contribute to the pathogenesis of slow transit constipation (Hofmann, Camilleri)

Chey WD et al. *Am J Gastroenterol*. 2011; 106:1803-12
Camilleri M. *Am J Gastroenterol*. 2011;106(5):835-42
Elobixibat: Mean Change from Baseline in Weekly Stool Frequency over 8 weeks

**SBM Frequency**

- Overall
  - 5 mg vs. placebo p=0.113
  - 10 mg vs. placebo p=0.017
  - 15 mg vs. placebo p<0.001

![Graph showing Elobixibat: Mean Change from Baseline in Weekly Stool Frequency over 8 weeks](image)

Chey WD et al. *Am J Gastroenterol.* 2011;106:1803-12

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Elobixibat: Adverse Events and Discontinuations

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=46</th>
<th>A3309 5 mg n=48</th>
<th>A3309 10 mg n=47</th>
<th>A3309 15 mg n=48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE, n (%)</td>
<td>20 (44)</td>
<td>22 (46)</td>
<td>29 (62)</td>
<td>31 (65)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1 (2.2)</td>
<td>1 (2.1)</td>
<td>1 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment discontinuations</td>
<td>6 (12.8)</td>
<td>6 (12.5)</td>
<td>6 (12.8)</td>
<td>11 (22.9)</td>
</tr>
</tbody>
</table>

**Gastrointestinal Adverse Events**

- Total
  - Placebo: 5 (10.9)
  - A3309 5 mg: 12 (25.0)
  - A3309 10 mg: 11 (23.4)
  - A3309 15 mg: 19 (39.6)
- Mild
  - Placebo: 2 (4.3)
  - A3309 5 mg: 6 (12.5)
  - A3309 10 mg: 5 (10.6)
  - A3309 15 mg: 6 (12.5)
- Moderate
  - Placebo: 2 (4.3)
  - A3309 5 mg: 5 (10.4)
  - A3309 10 mg: 4 (8.5)
  - A3309 15 mg: 8 (16.7)
- Severe
  - Placebo: 1 (2.2)
  - A3309 5 mg: 1 (2.1)
  - A3309 10 mg: 2 (4.3)
  - A3309 15 mg: 5 (10.4)
- Abdominal Pain
  - Placebo: 0
  - A3309 5 mg: 5 (10.4)
  - A3309 10 mg: 5 (10.6)
  - A3309 15 mg: 13 (27.1)
- Diarrhoea
  - Placebo: 1 (2.2)
  - A3309 5 mg: 4 (8.3)
  - A3309 10 mg: 3 (6.4)
  - A3309 15 mg: 6 (12.5)
- Abdominal Distension
  - Placebo: 1 (2.2)
  - A3309 5 mg: 4 (8.3)
  - A3309 10 mg: 2 (4.3)
  - A3309 15 mg: 3 (6.3)
- Flatulence
  - Placebo: 3 (6.5)
  - A3309 5 mg: 4 (8.3)
  - A3309 10 mg: 3 (6.4)
  - A3309 15 mg: 2 (4.2)
- Nausea
  - Placebo: 2 (4.3)
  - A3309 5 mg: 2 (4.2)
  - A3309 10 mg: 2 (4.3)
  - A3309 15 mg: 3 (6.3)

TEAE, treatment emergent adverse event; AE, adverse event

Chey WD et al. *Am J Gastroenterol.* 2011;106:803-12
Probiotics and Constipation

- **B. lactis** DN shortens colonic transit in healthy women and in the elderly\(^1\)-\(^3\)
  - Observed only if live organisms used
  - Most obvious if slow baseline colon transit
- **L. rhamnosus**, **B. lactis**, and inulin stimulate bowel motility\(^4\)
- Data from 5 RCTs (n=377) suggest a favorable effect of treatment on defecation and stool consistency\(^3\),\(^5\)
- Use should be considered investigational until further data are available

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**Probiotics Studied in Constipation\(^1\),\(^2\)**

- **B. lactis** DN-173 010
- **L. casei** Shirota
- **E. coli** Nissle 1917

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**Lactobacillus paracasei** enriched artichokes for Chronic Constipation

A double-blind, randomized, crossover trial

- **P = 0.011**
- **P = 0.009**

20 CC pts randomized to 180 g ordinary artichokes vs. artichokes with **L. paracasei** (2x1\(^{10}\) CFU) x 15 days

Improvements also reported for frequency, hard stools, and feeling of incomplete evacuation

Biofeedback for Dyssynergic Defecation

- **Biofeedback**: a process in which a person learns to reliably influence body responses through the use of feedback cues, ultimately leading to the correction of maladaptive behaviors

- **Types of biofeedback**:
  - Pressure (perineometry)
  - Electromyography (EMG)
  - Sensory (rectal balloon retraining)
  - Pelvic floor muscle contraction indicator devices
  - Real time ultrasound

Meta-analysis Results: Global Satisfaction

- Three studies reported data on global patient satisfaction
- No other constipation-related outcomes were consistently reported amongst the included trials

![Proportion of Patients Reporting Satisfaction](image)

RR: 2.15, 95% CI: 1.64-2.81, I²=81%

Maneerattanaporn DDW 11
Summary

• Constipation is a multi-symptom disorder
• There is high quality evidence to support the use of PEG & stimulant laxatives in CC
• Novel therapies for CC:
  – Chloride secretion: Lubiprostone, Linaclotide, Plecanitide
  – Serotonin/Prokinetic: Prucalopride
  – Modulation of Bile Acids: A3309
  – Sodium secretion: RDX5791
• Further studies with probiotics are needed
• PT and biofeedback are preferred in patients with dyssynergic defecation