Current Pharmacological Treatment Options in Chronic Constipation and IBS with Constipation

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Learning Objectives

- To review the treatments currently available for chronic constipation and IBS-C
- To differentiate treatments based on their mechanism of action
- To discuss how to tailor treatments to the individual patient
Rome III Criteria*: IBS-C

• Recurrent abdominal pain or discomfort at least 3 days/month associated with two or more of the following:
  
  – Improvement with defecation
  
  – Onset associated with a change in the frequency of stool
  
  – Onset associated with a change in the form of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
IBS-C Subtype is Based on Stool Form

**Type 1**
Separate hard lumps, like nuts (hard to pass)

**Type 2**
Sausage-shaped but lumpy

**Type 3**
Like a sausage but with cracks on its surface

**Type 4**
Like a sausage or snake, smooth and soft

**Type 5**
Soft blobs with clear-cut edges (passed easily)

**Type 6**
Fluffy pieces with ragged edges, a mushy stool

**Type 7**
Watery, no solid pieces, entirely liquid

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**IBS-C**
Hard/lumpy stools ≥25%
Loose/watery stools <25%

**IBS-M**
Hard/lumpy stools ≥25%
Loose/watery stools ≥25%

**IBS-D**
Hard/lumpy stools <25%
Loose/watery stools ≥25%

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IBS-C=constipation-predominant IBS; IBS-D=diarrhea-predominant IBS; IBS-M=mixed IBS; IBS-U=unsubtyped IBS.

Rome III: Chronic Constipation (CC)

- ≥2 of the following for ≥12 weeks out of the last 12 months
  - Straining
  - Lumpy or hard stools
  - Sensation of incomplete evacuation
  - Sensation of anorectal obstruction or blockage
  - Manual maneuvers to facilitate defecation
  - < 3 BMs/wk

- Loose stools are rarely present without laxatives. Do not meet criteria for IBS

## Symptoms of Chronic Constipation Overlap with IBS-C

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CC</th>
<th>IBS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 BMs / week</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Hard / lumpy stools</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Straining</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Feeling of incomplete evacuation</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Bloating / abdominal distension</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

- Abdominal pain

Graded Treatment for Patients with IBS-C and CC

- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure
- Multidisciplinary approach
- Psychological treatments
- Improve functioning
- Manage stress
- Pharmacotherapy

Severe
Moderate
Mild
Reasons for Dissatisfaction with Traditional Constipation Treatments

- 557 patients surveyed; 47% not completely satisfied with their constipation relief therapy.

Bar chart showing reasons for dissatisfaction with traditional constipation treatments:

- Ineffective relief of constipation: 44% for OTC laxatives, 50% for prescription laxatives, 50% for fiber.
- Ineffective relief of multiple symptoms: 60% for OTC laxatives, 50% for prescription laxatives, 66% for fiber.
- Lack of predictability: 71% for OTC laxatives, 75% for prescription laxatives, 79% for fiber.
- Ineffective relief of bloating: 67% for OTC laxatives, 52% for prescription laxatives, 80% for fiber.
# ACG Task Force Recommendations: IBS-C

<table>
<thead>
<tr>
<th>Global Symptoms</th>
<th>Pain</th>
<th>Bloating</th>
<th>Stool Frequency</th>
<th>Stool Consistency</th>
<th>Recommendation</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber (psyllium)</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Laxatives</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>2 (PEG)</td>
<td>C</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>Tegaserod†</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>2</td>
<td>A</td>
</tr>
</tbody>
</table>

*Recommendations—based on the balance of benefits, risks, burdens, and sometimes cost: Grade 1=strong, Grade 2=weak; Assessment of Quality of evidence—according to the quality of study design, consistency of results among studies, directness and applicability of study endpoints: Grade A=high, Grade B=moderate, Grade C=low.

†Available only under Emergency IND program; PEG=polyethylene glycol.

Adapted from ACG Task Force on IBS. *Am J Gastroenterol.* 2009;104(suppl 1):S1-S35.
# ACG Task Force Recommendations: CC

<table>
<thead>
<tr>
<th>Type of laxative</th>
<th>Examples</th>
<th>Efficacy</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk laxatives</td>
<td>Psyllium, methylcellulose</td>
<td>Psyllium increases stool frequency and consistency</td>
<td>B (Psyllium)</td>
</tr>
<tr>
<td>Stool softeners</td>
<td>Docusate sodium mineral oil</td>
<td>Less effective than psyllium for increasing BM frequency no evidence to support use in CC</td>
<td>B</td>
</tr>
<tr>
<td>Stimulant laxatives</td>
<td>Senna, bisacodyl</td>
<td>May be effective when given acutely for short periods</td>
<td>B</td>
</tr>
<tr>
<td>Osmotic laxatives</td>
<td>PEG, lactulose, magnesium compounds</td>
<td>PEG effective in constipation Magnesium compounds</td>
<td>A (PEG, lactulose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B (Magnesium)</td>
</tr>
</tbody>
</table>

Lubricants, alternative, herbs, combination all received a C recommendation due to the lack of controlled trials

Note: Lubiprostone was not included in the Task Force’s recommendation

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• Each gram fiber = 2.7 grams of stool

• In non-constipated adults dietary fiber:
  – increases stool weight and frequency of defecation
  – decreases colonic transit time

• Bloating, distention, cramps are common. Over 50% of patients do not continue therapy!

Cummings JH et al Postgrad Med J 1984; 60:811-9
### Systematic Review: Fiber in CC

<table>
<thead>
<tr>
<th>Study</th>
<th>Fiber</th>
<th>Criteria used to define response to therapy</th>
<th>N</th>
<th>Treatment effect in fiber arm</th>
<th>Treatment effect in placebo/no therapy arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenn</td>
<td>Psyllium</td>
<td>Improvement in global symptoms</td>
<td>211</td>
<td>86.5%</td>
<td>47.4%</td>
</tr>
<tr>
<td>Ashraf</td>
<td>Psyllium</td>
<td>Increase in mean stool frequency per week</td>
<td>22</td>
<td>0.9*</td>
<td>0.2*</td>
</tr>
<tr>
<td>Nunes</td>
<td>Psyllium</td>
<td>Normalization of evacuation</td>
<td>60</td>
<td>86.7%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Lopez Roman</td>
<td>Inulin</td>
<td>Straining during defecation</td>
<td>32</td>
<td>35.7%</td>
<td>78.6%</td>
</tr>
<tr>
<td>Badiali</td>
<td>Bran</td>
<td>Straining during defecation</td>
<td>16</td>
<td>55.6%</td>
<td>28.6%</td>
</tr>
</tbody>
</table>

Soluble Fiber improved global symptoms 86% vs. 47% with placebo (n=4 studies)
The results of studies of insoluble fiber conflict (n=2 studies)

* Represents the number of bowel movements per week

Fiber in IBS-C

- Most effective in improving constipation symptoms, not abdominal pain!

- Limited number of studies; small sample size; only 2 studies limited enrollment to IBS-C
  - Psyllium (ispaghula husk) (5 clinical trials)
    - Moderately effective (Grade 2C)
  - Wheat bran:
    - No more effective than placebo in relieving global symptoms of IBS

- Side effects: gas, bloating and discomfort

Soluble vs Insoluble Fiber for IBS

Proportion of patients with adequate relief of symptoms by week

Responders (%)

Psyllium 10 grams
Bran 10 grams
Placebo

N=275

Study duration (weeks)

*P<.05

Responder: Adequate symptom relief

Bijkerk CJ et al. BMJ. 2009;339:b3154
Osmotic Laxatives

- Poorly or non-absorbed substances which result in secretion of water in the intestines. Generally take 1-2 days to work
  - Salts (e.g., magnesium and phosphate)
  - Disaccharides (e.g., lactulose)
  - Sugar alcohols (e.g., sorbitol or mannitol)
  - Polyethylene glycol (e.g. PEG-3350)

- Pts with renal or cardiac insufficiency may experience electrolyte /volume overload to Mg or Phosphorus absorption
# Osmotic Laxatives in CC

<table>
<thead>
<tr>
<th>Osmotic Laxative</th>
<th>Studies</th>
<th>Result</th>
</tr>
</thead>
</table>
| Lactulose        | • 3 RDBPC  
                  • 2 well designed | • All trials lactulose > placebo  
                  • Lactulose improved stool consistency and # BM/day |
| Polyethylene Glycol (PEG) | • 3 RDBPC  
                         • All well designed  
                         • 2 compared PEG and lactulose | • PEG improved stool frequency and consistency, reduced straining  
                         • Overall effectiveness higher vs. lactulose |
| Sorbitol         | • 1 RCT vs lactulose | • Efficacy in the elderly similar to lactulose |
| Magnesium        | • No studies | |

Stimulant Laxatives in CC

- Increase contractions of the bowel through effects on the nerves and/or muscles.
- Three major classes:
  - Senna, Bisacodyl, Cascara
- Two recent randomized trials with stimulants

<table>
<thead>
<tr>
<th>1.1.2 Stimulant laxatives</th>
<th>Laxative</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamm 2010</td>
<td>86</td>
<td>247</td>
<td>89</td>
<td>121</td>
</tr>
<tr>
<td>Mueller-Lissner 2010</td>
<td>116</td>
<td>233</td>
<td>110</td>
<td>134</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>480</td>
<td>255</td>
<td>49.8%</td>
<td></td>
</tr>
</tbody>
</table>

Total events 202 199

Favors Drug Favors Placebo

Heterogeneity: Tau² = 0.02; Chi² = 3.80, df = 1 (P = 0.05); I² = 74%
Test for overall effect; Z = 4.92 (p < 0.00001)

Bisacodyl for Chronic Constipation

Rome III Functional Constipation

- Bisacodyl 10 mg (n=247)
- Placebo (n=121)

Dose titration down was allowed

Adverse Events

- Diarrhea = 53%
- Abdominal pain = 25%
- AE leading to discontinuation = 18%
Laxatives in IBS-C

- No well conducted randomized controlled trials in adults with IBS-C
- One study in adolescents with PEG (n=27)

Lubiprostone: Chloride Channel Activator

- Locally-acting GI-targeted bicyclic functional fatty acid

- Selectively activates ClC-2 channels, enhancing intestinal fluid secretion

- Accelerates small bowel and colonic transit

Effects of Lubiprostone on Number of Spontaneous Bowel Movements in CC

Adverse Events: Nausea (31%) Diarrhea (13%) and Headaches (13%)

Treatment of Chronic Constipation: Lubiprostone

Symptom score at week 4 (mean)

- **Stool Consistency**
  - Placebo (n=122): 2.5
  - Lubiprostone 24 mcg bid (n=120): 2.09

- **Straining**
  - Placebo (n=122): 1.81
  - Lubiprostone 24 mcg bid (n=120): 1.5

- **Constipation severity**
  - Placebo (n=122): 2.52
  - Lubiprostone 24 mcg bid (n=120): 1.94

*** p≤0.0003 vs placebo

- Stool consistency, straining and constipation severity improved significantly with lubiprostone vs placebo throughout the 4 week period

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M.H, Random, 95% CI</th>
<th>Year</th>
<th>M.H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johanson 2007</td>
<td>52</td>
<td>96</td>
<td>22</td>
<td>33</td>
<td>27.2%</td>
<td>0.81 [0.60, 1.10]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Johanson 2008</td>
<td>51</td>
<td>120</td>
<td>90</td>
<td>124</td>
<td>39.1%</td>
<td>0.59 [0.46, 0.74]</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>Barish 2010</td>
<td>48</td>
<td>119</td>
<td>72</td>
<td>118</td>
<td>33.7%</td>
<td>0.66 [0.51, 0.86]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>335</strong></td>
<td><strong>275</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.67 [0.56, 0.80]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>151</td>
<td>184</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.01; \chi^2 = 2.84, df = 2 (P = 0.24); I^2 = 30%$

Test for overall effect: $Z = 4.37 (P < 0.0001)$
Lubiprostone for IBS-C

- Pooled data from 2 Phase III studies

Patients achieving overall response (%)

- Placebo (n=387)
- Lubiprostone 8 mcg bid (n=780)

Overall responder = monthly responder for ≥2 of 3 months
Monthly responder = at least moderate relief 4 out of 4 weeks or significant relief 2 out of 4 weeks

*** p=0.001 vs placebo

Lubiprostone: IBS with Constipation

Change in Abdominal Pain/Discomfort (0-4)

Mean Change From Baseline

Month 1  Month 2  Month 3

Placebo  Lubiprostone

Pooled ITT Population
‡ - Significant
p< 0.05

## Lubiprostone in IBS-C: Adverse Events

|                            | Placebo  
|                            | N=387 | Lubiprostone  
|                            |       | 8 mcg BID  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N=779</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious Adverse Events</strong></td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Treatment-related Adverse Events</strong></td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Cardiovascular-related Events</strong> (Mild tachycardia reported in 1 patient)</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>6%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Antidepressants in IBS

• Reduce abdominal pain/discomfort

• Studies generally include all subtypes of IBS
  – Tricyclic antidepressants
    • anti-cholinergic effects
  – SSRIs
    • increase serotonin in the GI tract
Tricyclic Antidepressants in IBS

- **Tricyclic Antidepressants**
  - reduces pain/global sxs
  - target dose (50 mg/day)
  - AEs are common

### Study (Year, Drug, Dose) | Treatment n/N | Control n/N | RR (Random) 95% CI
---|---|---|---
Heefner (1978, desipramine 150 mg daily) | 10/22 | 12/22 | 
Myren (1982, trimipramine 50 mg daily) | 5/30 | 10/31 | 
Nigam (1984, amitriptyline 12.5 mg daily) | 14/21 | 21/21 | 
Boerner (1988, doxepin 50 mg daily) | 16/42 | 19/41 | 
Bergmann (1991, trimipramine 50 mg daily) | 5/19 | 14/16 | 
Vij (1991, doxepin 75 mg daily) | 14/25 | 20/25 | 
Drossman (2003, desipramine 50-150 mg daily) | 60/115 | 36/57 | 
Talley (2008, imipramine 50 mg daily) | 0/18 | 5/16 | 
Vahedi (2008, amitriptyline 10 mg daily) | 8/27 | 16/27 | 
**Subtotal (95% CI)** | 319 | 256 | 

RR=0.68  
(95% CI=0.56-0.83)  
NNT=4
Low-dose Amitriptyline vs Placebo for IBS-D

No significant difference in AEs between groups

### SSRIs in IBS

<table>
<thead>
<tr>
<th>Study (Year, Drug, Dose)</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuiken (2003, fluoxetine 20 mcg daily)</td>
<td>9/19</td>
<td>12/21</td>
<td>[image of RR and 95% CI]</td>
</tr>
<tr>
<td>Tabas (2004, paroxetine 10-40 mcg daily)</td>
<td>25/44</td>
<td>36/46</td>
<td>[image of RR and 95% CI]</td>
</tr>
<tr>
<td>Vahedi (2005, fluoxetine 20 mcg daily)</td>
<td>6/22</td>
<td>19/22</td>
<td>[image of RR and 95% CI]</td>
</tr>
<tr>
<td>Tack (2006, citalopram 20-40 mcg daily)</td>
<td>5/11</td>
<td>11/12</td>
<td>[image of RR and 95% CI]</td>
</tr>
<tr>
<td>Talley (2008, citalopram 40 mcg daily)</td>
<td>5/17</td>
<td>5/16</td>
<td>[image of RR and 95% CI]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>113</strong></td>
<td><strong>117</strong></td>
<td>[image of RR and 95% CI]</td>
</tr>
</tbody>
</table>

- Most patients note improvement in overall well-being
  - no studies show any benefit regarding bowel habits
  - abdominal pain generally not improved

Chronic Constipation

- Reassurance, General Measures, Increase Dietary Fiber
- No Response
- Bulking Agents: Psyllium, Methylcellulose, Ca polycarbophil

Osmotic Laxatives: Unabsorbed anions Unabsorbed CHO\textsubscript{s} PEG Saline laxatives

Stimulant Laxatives: Bisacodyl, Senna Cascara

Chloride Channels Activators: Lubiprostone

Prokinetics: Prucalopride* Tegaserod**

- Consider: Switching Agent, Combining Therapies Further Investigations

Exclude Red Flags, r/o secondary causes

*Not available in the U.S.
**Available through the FDA with an IND
Pharmacologic Management of IBS

Bloating
- Probiotics
- Antibiotics

Abdominal pain/discomfort
- Antidepressants

Constipation
- Ispagula/psyllium
- Lubiprostone
- Osmotic laxatives

Brandt LJ et al. *Am J Gastroenterol.* 2002;97:S7-26;
Conclusions

• There remains a need to safe and effective therapies in both CC and IBS-C

• Improving bowel function is performed with fiber, laxatives and lubiprostone

• IBS-C treatment is generally aimed at the predominant symptom