Pharmacologic Management of IBS

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IBS Care Varies Widely

Lacy et al. Am College of Gastroenterology October 2014
Rome IV Criteria for IBS

Recurrent abdominal pain at least 1 day/week (on average) in the last 3 months associated with ≥2 of the following:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form of stool

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


IBS: Patient Centered Care
(What do your patients really want from you?)

- They want answers
- They want you to listen
- Education
- Reassurance
- A positive diagnosis
- Symptom improvement
Treatment Depends on Severity of IBS

- Psychological treatments
- Goal: improved function
- Continuing care
- Follow-up visit
- Manage stress
- Drug therapy
- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure


IBS Pharmacologic Therapies by Symptom

**Abdominal pain/discomfort**
- Antispasmodics*
- Antidepressants*
  - TCAs/SSRIs
- Alosetron
- Lubiprostone
- Linaclotide

**Bloating/ distension**
- Rifaximin
- Lubiprostone
- Linaclotide
- Probiotics*

**Constipation**
- Fiber*
- MOM/PEG solution*
- Lubiprostone
- Linaclotide
- ?Plecanatide

**Diarrhea**
- Loperamide*
- Diphenoxylate-atropine*
- Cholestyramine*
- Alosetron
- Rifaximin
- Eluxadoline

*These agents are not currently FDA-approved for IBS. TCAs, tricyclic antidepressants.
IBS-C Treatment Options

- Probiotics
- Fiber
- Osmotic agents
- Chloride channel activators
- Guanylate cyclase C activators

Bulking Agents for IBS-C: Systematic Review and Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>RCTs</th>
<th>N</th>
<th>Response*</th>
<th>RR of Unimproved Symptoms (95% CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12</td>
<td>591</td>
<td>48%</td>
<td>43%</td>
<td>0.87 (0.76-1.0)</td>
</tr>
<tr>
<td>Ispaghula</td>
<td>6</td>
<td>321</td>
<td>48%</td>
<td>36%</td>
<td>0.78 (0.63-0.96)</td>
</tr>
<tr>
<td>Bran</td>
<td>5</td>
<td>221</td>
<td>46%</td>
<td>46%</td>
<td>1.02 (0.82-1.27)</td>
</tr>
</tbody>
</table>

*Improved or resolved symptoms.

- Insoluble fiber was not more effective and sometimes worsened symptoms
- Soluble fiber improved global symptoms
- 4 out of 5 bran studies of poor quality

CI = confidence interval; NNT = number needed to treat; RCTs = randomized, controlled trials; RR = relative risk

Ford, Quigley, Lacy et al, Am J Gastroenterol 2014
PEG 3350+E Improves SBMs in IBS-C

SBMs = spontaneous bowel movements; PEG = polyethylene glycol
PEG 3350+E is not approved for use in the US


Overall Responder Rates† to Lubiprostone in IBS-C Patients

*Therapeutic gain = treatment response rate minus placebo response rate
Trial 1 = 6.0%; Trial 2 = 8.4%
Lubiprostone is approved to treat IBS-C in women


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Efficacy of Linaclotide in Patients With IBS-C

### CSBM Mean Change from Baseline +/- SEM

<table>
<thead>
<tr>
<th>Treatment Period*</th>
<th>Weeks</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>BL</td>
</tr>
<tr>
<td>Linaclotide 290 µg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
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<td>6</td>
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<td>7</td>
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<td></td>
<td>8</td>
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<tr>
<td></td>
<td>9</td>
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<td></td>
<td>10</td>
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<td>11</td>
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<td>12</td>
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<td>13</td>
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<td></td>
<td>14</td>
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<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>16</td>
</tr>
</tbody>
</table>

### RW Period†

<table>
<thead>
<tr>
<th>RW Treatment Sequence</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/linaclotide 290 µg</td>
<td>BL</td>
</tr>
<tr>
<td>Linaclotide 290 µg/linaclotide 290 µg</td>
<td>1</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>2</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>3</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>4</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>5</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>6</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>7</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>8</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>9</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>10</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>11</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>12</td>
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<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>13</td>
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<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>14</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>15</td>
</tr>
<tr>
<td>Linaclotide 290 µg/placebo</td>
<td>16</td>
</tr>
</tbody>
</table>

*P < 0.0001 for linaclotide patients vs placebo patients (ANCOVA).
†P < 0.001 for linaclotide/linaclotide patients vs linaclotide/placebo patients (ANCOVA).


Linaclotide Phase 3 IBS-C Trial: Abdominal Pain Over 26 Weeks

### Change in Worst Abdominal Pain, %

<table>
<thead>
<tr>
<th>Trial Week</th>
<th>BL</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linaclotide 290 µg</td>
<td>0</td>
<td>-10</td>
<td>-20</td>
<td>-30</td>
<td>-40</td>
<td>-50</td>
<td>-60</td>
<td>-70</td>
<td>-80</td>
<td>-90</td>
<td>-100</td>
<td>-110</td>
<td>-120</td>
<td>-130</td>
</tr>
</tbody>
</table>

P=0.0007 for week 1
P=0.0001 for weeks 2-26

N=804

ITT, intention to treat; LS, least squares.

IBS-D Treatment Options

- Diet
- **Probiotics**
- Anti-diarrheal agents
- Smooth muscle anti-spasmodics
- Bile acid sequestrants
- 5-HT\textsubscript{3} antagonists
- Antidepressants
- **Antibiotics**
- Mu-opioid agonists/delta-opioid antagonists
- Psychological interventions
- CAM

CAM, complementary and alternative medicine
Probiotics: Putative Mechanisms of Action

• Competitive inhibition
• Barrier protection
• Immune effects
• Anti-inflammatory effects
• Production of various substances (enzymes, SCFA, bacteriocidal agents)
• Ability to alter local pH and physiology
• Provides nutrition to colonocytes


Bifidobacteria infantis 35624 for IBS Global Assessment of Relief

SGA: (Subjects’ Global Assessment) a yes/no response to the following question:
"Please consider how you felt in the past week in regard to your IBS, in particular your general well being, and symptoms of abdominal discomfort or pain, bloating or distension, and altered bowel habit. Compared with the way you felt before beginning the medication, have you had adequate relief of your IBS symptoms?"

**Loperamide for IBS-D**

- Low doses 2 mg once or twice daily may be effective to decrease stool frequency, improve stool consistency
- 2 randomized controlled trials in IBS (N=42) show efficacy for diarrhea
- No impact on symptoms of abdominal discomfort, bloating, or global IBS
- Adverse effects: dizziness, abdominal pain/bloat, constipation, dry mouth, fatigue


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**Antispasmodics for IBS**

- 22 randomized controlled trials comparing 12 different antispasmodics vs placebo (N=1778 patients)
- Significant heterogeneity among studies
- Many agents not available in US
- Appear most useful for abdominal pain
- In meta-analysis, symptoms persist in 39% of patients receiving antispasmodics vs 56% of placebo-treated patients (RR: 0.68; 95% CI: 0.57-0.81)

Alosetron: Therapeutic Gain for IBS-D

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Female, %</th>
<th>Response: Alosetron, %</th>
<th>Response: Placebo, %</th>
<th>Therapeutic Gain, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camilleri¹</td>
<td>370</td>
<td>53</td>
<td>60</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Camilleri²</td>
<td>647</td>
<td>100</td>
<td>41</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Camilleri³</td>
<td>626</td>
<td>100</td>
<td>43</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Lembo⁴</td>
<td>801</td>
<td>100</td>
<td>73</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td>Jones⁵*</td>
<td>623</td>
<td>100</td>
<td>58</td>
<td>48</td>
<td>10</td>
</tr>
</tbody>
</table>

¹Comparison mebeverine* instead of placebo.
²Mebeverine not available in the US.


Global Relief of IBS Symptoms With TCAs/SSRIs

- TCAs: 9 studies (N=319 drug vs 256 control)
  - Imipramine, desipramine, amitriptyline, doxepin*; doses 10-150 mg
  - Meta-analysis favors treatment (NNT = 4)
- SSRIs: 5 studies (N=113 drug vs 117 control)
  - Fluoxetine, paroxetine, citalopram*; dose 10-40 mg
  - Meta-analysis favors treatment (NNT = 4)
- TCAs have more analgesic properties, and SSRI efficacy is most likely in patients with significant anxiety/depression.

*These agents are not currently FDA approved for IBS.
SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants
Rifaximin Trials: Global Relief of IBS Without Constipation

• 2 Phase 3 randomized controlled trials; N=1260 patients
• Rifaximin 550 mg TID x 2 weeks; patients followed additional 10 weeks
• 40.7% vs. 31.7% with adequate relief of global symptoms ($P < 0.001$)


Retreatment with Rifaximin Study Design - Target 3

Screening/Treatment 1 Phase
Study Day 1
7-13 d PBO
2w RFX
4w f/u
Non-Responders Withdrawn

Treatment 2 Phase
Up to 18w

Non-Responders with recurrent symptoms

Maintenance Phase 1

Follow up

Primary Evaluation Period

Obtain Daily/Weekly Symptom Diary

Stool sample collection
Target 3: Patient Flow

n = 2579

Responder at End of Treatment 2 Phase
n = 1074 (41.6%)

Non-Responder
n = 1257

Discontinued
Early
n = 248

Experienced Relapse (eligible for rand)
n = 692

No Relapse
n = 382 (35.6%)

Discontinued Early
n = 37

Rfx 550mg TID
n = 328

Placebo
n = 308

Discontinued Early
n = 44

Open label

Double-blind

Randomized Patients
Age: 46.8
Sex: 69% female

Retreatment with Rifaximin in IBS-D

IBS-related Abdominal Pain and Stool Consistency (Worst Case Analysis)

First and Second Repeat Treatment Phases

p = 0.0232

p = 0.0263

p = 0.0023

Responder: Patient responding to IBS-related Abdominal Pain (≥30% improvement) and Stool consistency (≥50% decrease in # BMs with type 6 or 7) from baseline for ≥2 of the 4 weeks

Eluxadoline for IBS-D: Rationale

- Mixed mu (μ) opioid receptor agonist / delta (δ) opioid receptor antagonist
- Low systemic absorption and bioavailability
  - Low potential for drug–drug interactions
- Animal studies suggest eluxadoline should improve the diarrheal symptoms of IBS-D with limited constipation and durable analgesia

<table>
<thead>
<tr>
<th>μ opioid receptor</th>
<th>Δ opioid receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation reduces pain, gastric propulsion</td>
<td>Inhibition restores G-protein signaling; reduces μ agonist-related desensitization</td>
</tr>
</tbody>
</table>


Phase 3 study design

<table>
<thead>
<tr>
<th>IBS-3001</th>
<th>IBS-3002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescreen (≤1 wk)</td>
<td>Prescreen (≤1 wk)</td>
</tr>
<tr>
<td>Screening (2–3 wks)</td>
<td>Screening (2–3 wks)</td>
</tr>
<tr>
<td>Double-blind treatment (26 wks)</td>
<td>Double-blind treatment (26 wks)</td>
</tr>
<tr>
<td>Double-blind safety continuation (26 wks)</td>
<td>Blinded PBO withdrawal (4 wks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Randomization (Day 1)</th>
<th>Efficacy 12 wks (FDA)</th>
<th>Efficacy 26 wks (EMA)</th>
<th>End of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-3001</td>
<td>Tx, therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS-3002</td>
<td>Tx, therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Definition of primary endpoint: composite responder**

**FDA guidance / EMA draft guidance**

**Responder must meet both criteria on same day:**

- Daily pain responder:
  - WAP scores improved by ≥30% compared to average baseline pain
- Daily stool consistency responder:
  - BSS score <5 (or in absence of BM, if accompanied by ≥30% improvement in WAP compared to average baseline pain)

- Above met on at least 50% of days in Weeks 1–12 (FDA), Weeks 1–26 (EMA)
- Minimum 60 days (FDA) / 110 days (EMA) diary compliance
- Bonferroni adjustment: to preserve the family-wise error rate for each active group vs placebo (p<0.025)

**Phase 3 baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>3001</th>
<th>3002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened, n</td>
<td>2832</td>
<td>2521</td>
</tr>
<tr>
<td>Randomized, n</td>
<td>1281</td>
<td>1146</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>44.9 (13.7)</td>
<td>45.9 (13.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>838 (65.4)</td>
<td>768 (67.0)</td>
</tr>
<tr>
<td>&gt;65 years, n (%)</td>
<td>115 (9.0)</td>
<td>126 (11.0)</td>
</tr>
<tr>
<td>Cholecystectomy, n (%)</td>
<td>272 (21.2)</td>
<td>224 (19.5)</td>
</tr>
<tr>
<td>Loperamide use, n (%)</td>
<td>466 (36.3)</td>
<td>408 (35.6)</td>
</tr>
<tr>
<td>BSS, mean (SD)</td>
<td>6.3 (0.4)</td>
<td>6.2 (0.4)</td>
</tr>
<tr>
<td>WAP, mean (SD)</td>
<td>6.2 (1.5)</td>
<td>6.0 (1.5)</td>
</tr>
<tr>
<td>No. BMs/day, mean (SD)</td>
<td>4.9 (2.8)</td>
<td>4.8 (3.0)</td>
</tr>
<tr>
<td>GSS, mean (SD)</td>
<td>2.9 (0.5)</td>
<td>2.8 (0.5)</td>
</tr>
</tbody>
</table>

*aIn previous year
SD, standard deviation
Primary endpoint: composite responders – pooled data

![Graph showing responders over time and treatment groups.

Summary

- IBS is a constantly evolving field
- Rome IV 2016 – new definition
- Our understanding of IBS physiology continues to expand
- Expect new treatment options within the next few years
- Expect a greater emphasis on patient requirements and patient-centered outcomes