Pharmacotherapy for IBS

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Disclosures

• I have served as a consultant and/or speaker for the following: Allergan, Salix, Ironwood, IMHealth Sciences, Prometheus, Sebela

• I have received research support from: Prometheus
Objectives

1. Review the mechanisms of action for pharmacotherapies for IBS
2. Understand the clinical trial evidence for various pharmacotherapies for IBS and societal recommendations
3. Discuss new and emerging pharmacotherapies for IBS
IBS: Rome IV Criteria*

Recurrent abdominal pain at least 1 day per week associated with two or more of the following:
• Related to 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

Fermín Mearin et al. *Gastroenterology*. May 2016
IBS Treatment Depends on Severity

- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure

Diet, lifestyle advice
- Manage stress
- Drug therapy
- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure

Psychological treatments
- Goal: improved function
- Continuing care
  - Follow-up visit

Severe (25%)

Moderate (35%)

Mild (40%)
IBS = Symptom complex with Multiple Contributing Factors

- Post infectious
- Psychological Abuse History
- Inflammation
- Environmental Factors
- Brain - gut dysfunction
- Genetic Predisposition
- Food Sensitivity
- Abnormal Central Processing
- GI dysmotility
Primary Objective: To assess the efficacy of available pharmacological therapies in treating IBS compared with placebo

Multiple systematic reviews
- Included only parallel-group randomized controlled trials (RCTs) comparing pharmacological therapies with placebo in adults
- Cross-over trials were eligible for inclusion if extractable data were provided at the end of the first treatment period, prior to cross-over

Subjects had to be followed for at least 1 week and trials needed to include one or more of the following outcome measures:
1. Global assessment of IBS cure or improvement
2. Abdominal pain cure or improvement
3. Global IBS symptom or abdominal pain scores

IBS-C Pharmacotherapy

Prosecretory/Prokinetic Agents
Lubiprostone
Linaclotide
Plecanatide (submitted)
Tenapanor (in development)

5-HT₄ Agonists
Prucalopride
Velusetrag

Microbiome Agents
SYN-010 (in development)

Antidepressants
SSRIs
Fiber for IBS: Strong recommendation; moderate quality evidence

- 15 RCT, 946 patients; 1 trial at low risk for bias
- Soluble fiber (eg, ispaghula husk) but not bran improved IBS symptoms
  - RR of IBS not improving 0.83 (CI: 0.73-0.94); NNT=7
  - 36.6% reported adverse events with fiber vs 25.1% with placebo (RR: 1.06; 95% CI: 0.92-1.22)
  - Quality of studies generally low: short trials, general outcome endpoints
- Strong recommendation based on low cost and tolerability
Lubiprostone for IBS: Strong recommendation; moderate quality evidence

- Type 2 chloride channel activator; increases balanced ion and water secretion into gut; non-absorbed
- 3 RCT, 1366 patients; all at low risk for bias
- RR of IBS not improving 0.91 (CI: 0.87-0.95); NNT=12.5
  - IBS-C dose is 8 mcg BID and only approved in women
  - Adverse events more common than with placebo; diarrhea in IBS-C trials; NNH=10

Linaclotide for IBS: Strong recommendation; high quality evidence

- 14 amino acid peptide structurally similar to E coli heat stable toxin that binds to guanylate-cyclase C receptors = balanced ion and fluid secretion into gut and ENS modulation; non-absorbed
- 4 RCT, 2867 patients; all at low risk for bias
- RR of IBS not improving 0.81 (CI: 0.77-0.85); NNT=6
- IBS-C dose is 290 mcg daily; approved in men and women
- Adverse events more common than with placebo; diarrhea in IBS-C trials; NNH=7
Linaclotide: IBS-C Phase 3 Trials

**FDA Primary Endpoint: (≥6/12 Weeks)**

- Placebo (n=403): 13.9%
- Linaclotide 290 μg (n=401): 33.7%*

*P<0.0001 for all analyses of linaclotide vs placebo groups, using Cochran-Mantel-Haenszel test

**FDA Primary Endpoint:**
≥30% reduction worst abdominal pain and increase ≥1 CSBM, both for ≥6/12 weeks

Plecanatide for IBS: Weak recommendation; low quality evidence

• 16 amino acid peptide structurally similar to uroguanylin that binds to guanylate-cyclase C receptors = balanced ion and fluid secretion into gut and ENS modulation; non-absorbed

• 3 RCT, 2612 patients; all at low risk for bias

• RR of IBS not improving 0.88 (CI: 0.84-0.92); NNT=10

• Dose in IBS-C is 3 mg daily; recently approved in men and women with IBS-C
  • Adverse events more common than with placebo; diarrhea in IBS-C trials; NNH=33
**Plecanatide: IBS-C Phase 3 Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (n=354)</th>
<th>Plecanatide 3 mg (n=351)</th>
<th>Plecanatide 6 mg (n=349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>04</td>
<td>17.8</td>
<td>30.2</td>
<td>29.5</td>
</tr>
</tbody>
</table>

**Overall Responder Rates (%)**

*P<0.001 vs placebo.

ITT population; values are percentages; bars represent 95% CIs.

Tenapanor (In development)

- **NHE3 Inhibitor**
  - selectively inhibits sodium uptake in the intestines, trapping water and phosphate in GI lumen; pain modulation via TRPV-1
- In development for hyperphosphatemia, and IBS-C
- 2 Phase 3 trials complete in IBS-C
  - Primary and secondary endpoints met
  - Well tolerated; diarrhea most common AE
Tenapanor: IBS-C Phase 3 Trial

Responder Analysis ≥ 6 of 12 Weeks

Cochran–Mantel–Haenszel test, stratified by pooled investigator site; intention-to-treat analysis

Chey et al. ACG/WCOG 2017
## Tenapanor: IBS-C Phase 3 Trial

<table>
<thead>
<tr>
<th></th>
<th>Tenapanor 50 mg BID (n=293)</th>
<th>Placebo (n=300)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined responder</strong> (abdominal pain and CSBM responder)</td>
<td>36.5%</td>
<td>23.7%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>CSBM responder</strong> (increase ≥ 1 CSBM from baseline)</td>
<td>47.4%</td>
<td>33.3%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Ab pain responder</strong> (≥ 30% pain reduction from baseline)</td>
<td>49.8%</td>
<td>38.3%</td>
<td>p=0.004</td>
</tr>
</tbody>
</table>

Data on file, Ardelyx; press release Oct 11, 2017
IBS-D Pharmacotherapy

**Modulation of gut flora**
- Rifaximin

**Probiotics, Prebiotics, Synbiotics***

**Bile Acid Binders***
- Cholestyramine/
  - Colesevelam

**5-HT₃ antagonists**
- Alosetron
- Ondansetron***

**Opioid receptor modulators**
- Loperamide* (mu)
- Diphenoxylate* (mu)
- Eluxadoline (mixed)

**Antidepressants***
- TCAs
- SSRIs
- SNRIs

**Medical Foods/Supplements***
- Peppermint Oil
- Serum derived bovine immunoglobulin

*Not FDA approved for IBS-D*
Probiotics for IBS: Weak recommendation; low quality evidence

• 53 RCT, 5545 patients; 26 trials at low risk for bias

• Probiotics superior to placebo
  • RR of IBS not improving 0.81 (CI: 0.74-0.88); NNT=7
    • Combination probiotics: RR=0.79 (0.68-0.91)
  • Symptoms most likely to improve: pain, bloating, flatulence
  • Significant heterogeneity and evidence of publication bias
  • Low rate of adverse events vs placebo
Antibiotics for IBS: Weak recommendation; high quality evidence

- 9 RCT, 2845 patients; 7 studied rifaximin (2654 patients) 550 mg TID x 2 weeks
- Rifaximin superior to placebo: RR of IBS not improving 0.82 (CI: 0.72-0.95); NNT=8
  - Adverse events equal to placebo; 2/3 responders need repeat treatment

Efficacy of First and Second Retreatments

LOCF Analysis

Urgency and bloating improved significantly with both repeat treatments.

Abdominal pain and stool consistency improved significantly with first retreatment.

LOCF, last observation carried forward.

Responder defined as subjects responding to IBS-related Abdominal Pain and Stool Consistency for ≥2 of 4 weeks.

Recurrence defined as a loss of response for ≥3 of 4 weeks.

Eluxadoline for IBS: Weak recommendation, high quality evidence

- Mixed opioid receptor modulator approved for IBS-D
  - Mu (μ) opioid receptor agonist and kappa (κ) opioid receptor agonist; delta (δ) opioid receptor antagonist\(^1,2\)
- 3 RCT, 3235 patients; all 3 studies at low risk of bias
- RR of IBS not improving 0.90 (CI: 0.86-0.95); NNT= 13
  - Greatest effect on stool consistency vice pain
- Well tolerated; adverse events similar to placebo
  - Contra-indicated if no gallbladder due to pancreaticobiliary AEs
  - Avoid in heavy ETOH users
  - Controlled substance due to OR binding: Schedule V

Eluxadoline: IBS-D Phase III Trials

Eluxadoline: IBS-D Phase III Trials

Composite responder:

• ≥30% reduction in worst abdominal pain score AND improvement in stool consistency of <5 on the Bristol Stool Scale†

• Daily improvement in BOTH symptoms on at least 50% of days in the trial

**Figure:**

<table>
<thead>
<tr>
<th>Weeks 1-12</th>
<th>IBS-3001</th>
<th>IBS-3002</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder, %</td>
<td>Placebo BID</td>
<td>Eluxadoline 75 mg BID</td>
<td>Eluxadoline 100 mg BID</td>
</tr>
<tr>
<td>n=403</td>
<td>17.1</td>
<td>23.9</td>
<td>25.1</td>
</tr>
<tr>
<td>n=401</td>
<td>16.2</td>
<td>28.9</td>
<td>29.6</td>
</tr>
<tr>
<td>n=426</td>
<td>16.7</td>
<td>26.2</td>
<td>27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks 1-26</th>
<th>IBS-3001</th>
<th>IBS-3002</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder, %</td>
<td>Placebo BID</td>
<td>Eluxadoline 75 mg BID</td>
<td>Eluxadoline 100 mg BID</td>
</tr>
<tr>
<td>n=403</td>
<td>19</td>
<td>23.4</td>
<td>29.3</td>
</tr>
<tr>
<td>n=401</td>
<td>20.2</td>
<td>30.4</td>
<td>32.7</td>
</tr>
<tr>
<td>n=426</td>
<td>19.5</td>
<td>26.7</td>
<td>31</td>
</tr>
</tbody>
</table>

**Legend:**

- Placebo BID
- Eluxadoline 75 mg BID
- Eluxadoline 100 mg BID

### Eluxadoline Safety

#### Most Common Adverse Events in Phase 3 Trials

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n=808)</th>
<th>Eluxadoline 75 mg (n=859)</th>
<th>Eluxadoline 100 mg (n=807)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation*</td>
<td>20 (2.5)</td>
<td>60 (7.4)</td>
<td>74 (8.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (5.1)</td>
<td>65 (8.1)</td>
<td>64 (7.5)</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>33 (4.0)</td>
<td>47 (5.9)</td>
<td>62 (7.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (1.4)</td>
<td>32 (4.0)</td>
<td>36 (4.2)</td>
</tr>
<tr>
<td>Gastroenteritis‡</td>
<td>27 (3.4)</td>
<td>36 (4.4)</td>
<td>19 (2.2)</td>
</tr>
<tr>
<td>URI</td>
<td>32 (4.0)</td>
<td>27 (3.3)</td>
<td>47 (5.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>27 (3.3)</td>
<td>33 (4.1)</td>
<td>23 (2.7)</td>
</tr>
</tbody>
</table>

*All constipation events were non-serious – 1.4% of patients receiving eluxadoline and 0.2% receiving placebo discontinued due to non-serious constipation;  
†Abdominal pain = abdominal pain, abdominal pain upper, abdominal pain lower;  
‡Gastroenteritis = gastroenteritis and viral gastroenteritis

#### Sphincter of Oddi spasm (SOS)

All events resolved upon treatment discontinuation, typically improving by the following day; 80% of cases occurred within 1 week of treatment, and the rest within 1 month.

- 2 (0.2%) Eluxadoline 75 mg (n=807)
- 8 (0.8%) Eluxadoline 100 mg (n=1,032)

- 1 patient had abdominal pain and elevated hepatic enzymes
- 1 patient had abdominal pain and lipase elevation <3x ULN
- 1 patient had pancreatitis, occurring within minutes of taking treatment

#### Pancreatitis

All pancreatic events resolved with lipase normalization upon treatment discontinuation; 80% resolved within 1 week.

- 2 (0.2%) Eluxadoline 75 mg (n=807)
- 3 (0.3%) Eluxadoline 100 mg (n=1,032)

- 3 patients had excessive alcohol intake
- 1 patient had biliary sludge
- 1 patient discontinued treatment prior to symptom onset

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Alosetron for IBS: Weak recommendation; moderate quality evidence

- Partial selective 5-HT₃ antagonist
- 8 RCT, 4341 patients (predominantly women; 1 trial at low risk for bias)
- RR of IBS not improving 0.79 (CI: 0.69-0.90); NNT=7.5
  - More adverse events with alosetron than placebo; NNH=10; constipation; colon ischemia: 1/1000 patient-years
  - 0.5 mg BID starting dose; female patients with chronic, severe IBS-D who have not responded adequately to conventional therapy
  - REMS program eased in 2016; remains a 3rd line pharmacotherapy
  - May increase to 1 mg BID if well tolerated

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (Random) 95% CI</th>
<th>RR (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camilleri (1999)</td>
<td>179/290</td>
<td>54/80</td>
<td>0.91 (0.77, 1.09)</td>
<td>0.99 (0.80, 1.23)</td>
</tr>
<tr>
<td>Bardhan (2000)</td>
<td>166/345</td>
<td>57/117</td>
<td>0.83 (0.74, 0.93)</td>
<td>0.79 (0.71, 0.89)</td>
</tr>
<tr>
<td>Camilleri (2000)</td>
<td>191/324</td>
<td>229/323</td>
<td>0.47 (0.39, 0.55)</td>
<td>0.88 (0.76, 1.01)</td>
</tr>
<tr>
<td>Lembo (2001)</td>
<td>144/532</td>
<td>156/269</td>
<td>0.68 (0.57, 0.85)</td>
<td>0.91 (0.78, 1.10)</td>
</tr>
<tr>
<td>Chey (2004)</td>
<td>167/351</td>
<td>197/363</td>
<td>0.83 (0.71, 0.98)</td>
<td>0.76 (0.67, 0.86)</td>
</tr>
<tr>
<td>Chang (2005)</td>
<td>268/534</td>
<td>77/128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krause (2007)</td>
<td>279/529</td>
<td>122/176</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>3,214</strong></td>
<td><strong>1,773</strong></td>
<td><strong>0.79 (0.69, 0.90)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Bile Acid Sequestrants

- Bile acid malabsorption: prevalence estimates 1%; 25-50% in IBS-D
  - 3 established types of BAM (maybe 4)
- Excess bile acids in colon
  - Stimulate enteroendocrine cells and accelerate colonic transit
  - Activate visceral sensation and fluid secretion: increase intracellular cAMP, mucosal permeability and/or chloride ion secretion
- Small, uncontrolled trials of bile acid sequestrants suggest benefit in IBS
Ondansetron

Effect of Ondansetron 4-8 mg TID for 5 Weeks in Patients with Rome III IBS-D (N=120)*

- Improvement also noted in stool frequency and urgency
- No effect on abdominal pain or bloating

*Randomized, double-blind, dose-titration study. Primary endpoint was average stool consistency in last 2 weeks of treatment. Improvements in urgency, frequency, bloating but NOT pain.
Antispasmodics for IBS: Weak recommendation; very low quality evidence

- 26 RCT, 2811 patients; 2 trials at low risk for bias
  - 13 different antispasmodics; high degree of heterogeneity between studies
- RR of IBS not improving 0.65 (CI: 0.56-0.76); NNT=5
  - Only 1 study of dicyclomine (97 pts) RR=0.65 (CI: 0.45-0.95); remainder of antispasmodics not available/marketed in US
  - Adverse events 60% > with probiotics vs placebo: dry eyes/mouth, CNS symptoms; NNH 22
- Evidence for benefit is modest; do appear to exact short-term benefit
Peppermint Oil for IBS: Weak recommendation; low quality evidence

• Primary effect: smooth muscle relaxation akin to dihydropyridine Ca\(^{+2}\) channel antagonists
  • Active ingredients: L-menthol, rosmarinic acid, limonene
  • Possible mediation via TRPM8, kappa opioid agonist, antibacterial, anti-inflammatory, carminative

• 7 RCT, 634 patients; 2 trials at low risk of bias

• RR of IBS not improving 0.54 (CI: 0.39-0.76); NNT=4
  • Adverse events similar to placebo: GERD, dyspepsia reported

Peppermint Oil SST

- Triple-coated, sustained release microspheres of peppermint oil
- IBSREST Trial: PO-SST 180mg TID for 4 weeks improved Total IBS Symptom Score (TISS)
  - Abdominal pain, bloating, pain at evacuation, and urgency
- Post-hoc analysis shows benefit in IBS-M

Antidepressants for IBS: Strong recommendation; high quality evidence

• 18 RCT, 1127 patients; 4 studies at low risk of bias
• Antidepressants in general: RR of IBS not improving 0.66 (CI: 0.57-0.76); NNT= 4; pain mostly
  • TCAs: 12 RCT, 787 patients; RR 0.65 (CI: 0.55-0.77); NNT= 4
  • SSRIs: 7 RCT, 356 patients; RR 0.68 (CI: 0.51-0.91); NNT= 5
• SNRIs not yet studied in large RCTs²
• Adverse events more common with antidepressants; NNH= 8.5

ACG Monograph Recommendations Against Use

- Loperamide: 2 RCT (1 IBS-D/1 IBS-M), 42 patients
  - RR of IBS not improving 0.42 (CI: 0.14-1.42)
- PEG: 2 RCT, 181 patients
  - Conflicting results with spontaneous BM; no improvement in pain
- 5-ASA: 3 RCT, 464 patients
  - RR of IBS not improving 0.85 (CI: 0.75-0.97); NNT= 9
  - May actually work; need more studies to opine
Pharmacologic Approach to IBS: Take Home Points

• Diet, lifestyle modifications, OTC therapies remain first line, despite lack of level 1 evidence
• Guideline process and recommendations do not always reflect contemporary practice
• Best evidence (despite ratings)
  • IBS-D: Rifaximin, Eluxadoline, Alosetron
  • IBS-C: Linaclotide, Plecanatide, Lubiprostone
  • Adjunctive therapies (use at any point)
    • Peppermint oil (for all subtypes); TCAs (for IBS-D/M with pain)-allow 4 weeks minimum; antispasmodics
• Pipeline: Tenapanor, SYN-010, Prucalopride
Thank You