Current and Emerging Concepts in Irritable Bowel Syndrome

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Disclosures

- Consultant/Speakers’ Bureau: Salix, Allergan, Takeda, Ironwood, Alfasigma, Arena
- DSMB: Vibrant

Objectives

1. Discuss the pathophysiology and diagnostic criteria for IBS
2. Explore the data for lifestyle and over the counter therapies for IBS symptoms
3. Review the mechanisms of action, efficacy, and safety profiles of FDA approved IBS therapies
4. Examine emerging therapies for IBS
**Rome IV Criteria for IBS**

![Diagram showing the Rome IV Criteria for IBS](image)


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**Multifactorial Pathophysiology of IBS**

![Diagram showing multifactorial pathophysiology of IBS](image)

Principles of IBS Management

- Exclude organic GI disease
  - Make a positive diagnosis
  - Establish a rapport; educate and reassure
- Categorize IBS subtype based on prevalent stool form (BSFS)
- First line: lifestyle and dietary modifications and OTC therapies targeting abnormal stool form/most bothersome symptoms
- Escalate to FDA approved/validated therapies
- Non-FDA/off-label/psychological therapies

Diagnostic Testing for Suspected IBS and No Alarm Features*

- All IBS Subtypes1
  - CRP or fecal calprotectin
  - IgA TtG ± quantitative IgA
  - When colonoscopy performed, obtain random biopsies
  - Serum 7-C4 or fecal bile acids where available
- IBS-D1,2
  - CRP or fecal calprotectin
  - IgA TtG ± quantitative IgA
  - When colonoscopy performed, obtain random biopsies
  - Serum 7-C4 or fecal bile acids where available
- IBS-M1
  - CRP or fecal calprotectin
  - IgA TtG ± quantitative IgA
  - Stool diary/App
  - Consider abdominal plain film to assess for fecal loading
- IBS-C1
  - If severe or medically refractory, refer to specialist for physiologic testing

*Alarm Features include age ≥50 years old, blood in stools, nocturnal symptoms, unintentional weight loss, change in symptoms, recent antibiotic use, and family history of organic GI disease

Lifestyle Modifications (all have some evidence of benefit)

- **Dietary**
  - Low FODMAP
  - Gluten restriction
  - Keto/Mediterranean
  - Low fat
- **Activity**
  - Exercise
- **Sleep hygiene**
- **Minimize/eliminate ETOH**
  - Best evidence for IBS-D, likely due to decrease in metabolic byproducts

Dietary Considerations in IBS

- **FODMAPS** are an important trigger of meal-related symptoms in IBS\(^1\)
  - Low FODMAP diet found to improve overall symptom scores compared with typical diet in IBS patients\(^2\)
- **Gluten-free** diet found to be beneficial in some patients with IBS-D\(^3,4\)
  - Wheat contains fructans and other proteins that may also cause symptoms in IBS patients\(^5\)
  - Most patients who associate their symptoms with wheat will have *wheat sensitivity*, not celiac disease\(^6\)
- **Food antigens** found to cause changes in the intestinal mucosa of IBS patients that are associated with patient responses to exclusion diets\(^7\)

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Low FODMAP versus mNICE Diet for IBS-D: Adequate Relief & FDA Endpoint

84 patients with IBS-D randomized to LFD or mNICE x 4 weeks and completed study - median age was 43 years (range 19-68); 65 were women

Adequate Relief

FDA Composite Responder

>30% reduction in pain and decrease in BSFS >1 compared to baseline


IBS Pharmacologic Options by Symptom

Abdominal pain/discomfort

- Antispasmodics*
- Antidepressants*
- Lubiprostone
- Linacotide
- Plecanatide
- Alosetron
- Eluxadoline
- Tegaserod

Constipation

- Fiber*
- MOM/PEG solution*
- Lubiprostone
- Linacotide
- Plecanatide
- Tegaserod
- Tenapanor
- Prucalopride*

Diarrhea

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

Bloating

- Rifaximin
- Lubiprostone
- Linacotide
- Plecanatide
- Probiotics*

*Not currently FDA-approved for IBS


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OTC Options

- Antidiarrheals: Imodium, clays/binders
- Anti-spasmodics
- Peppermint oil
- Probiotics

Conventional Nonspecific Agents for IBS-D

Recommendations from an American College of Gastroenterology monograph

There is insufficient evidence to recommend loperamide for use in IBS
- 2 Clinical trials
- 42 Patients treated
- Recommendation Strong
- Quality of evidence Very Low

There is insufficient evidence to recommend antispasmodics available in US*
- 23 Clinical trials
- 2,154 Patients treated
- Recommendation Weak
- Quality of evidence Low

*Recommendation revised to reflect evidence for products available in US

Peppermint Oil

- Active ingredients: L-menthol, rosmarinic acid, limonene\(^1\)
  - Primary effect: Ca\(^{2+}\) channel smooth muscle relaxation
  - Possible mediation via TRPM8, k-opioid agonist, antibacterial, anti-inflammatory, carminative\(^2\)
- Dose unclear; typically 90-180 mg up to TID
- 7 RCT, 634 patients
- NNT = 4
- AEs similar to placebo: GERD, dyspepsia reported


Probiotics

- 53 RCT, 5545 patients; 50% trials at low risk for bias
  - Significant heterogeneity
  - Evidence of publication bias
- Probiotics superior to placebo
  - NNT=7
    - Combination probiotics: RR = 0.79 (0.68-0.91)
  - IBS dose/brand: unknown
  - Symptoms most likely to improve pain, bloating, flatulence
  - Low rate of AEs

FDA Approved Therapies for IBS-D

- Rifaximin
- Eluxadoline
- Alosetron

Rifaximin for IBS-D
TARGET 1 & TARGET 2 Trials

- Poorly absorbed antibiotic; inhibits protein synthesis
- Dosing 550 mg TID x 2 weeks
- 7 RCT; 2654 patients
- NNT= 8
- AEs similar to placebo
- 2/3 responders need repeat treatment
  - No value in re-treating non-responders

**Rifaximin for IBS-D**

**TARGET 3 Trial**

**Retreatment Efficacy**

Responder defined as
- Responding to IBS-related abdominal pain and stool consistency for ≥2 of 4 weeks
- Loss of response for ≥3 of 4 weeks

**Urgency and bloating improved significantly with both repeat treatments**

**Abdominal pain and stool consistency improved significantly with first retreatment**

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>First Repeat Treatment</th>
<th>Second Repeat Treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rifaximin</td>
<td>Placebo</td>
</tr>
<tr>
<td>n=328</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>n=308</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=295</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=283</td>
<td></td>
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</tbody>
</table>

*Data for last observation carried forward*


**Eluxadoline for IBS-D**

**IBS-3001 & IBS-3002 Trials**

- Mixed opioid receptor modulator
  - μ/κ-opioid receptor agonist; δ-opioid antagonist $^{1,2}$
- Dosing: 100 mg BID
- 3 RCT, 3235 patients
- NNT= 13
- AEs: Constipation, abdominal pain, SO spasm, pancreatitis
  - Contraindicated if no GB or h/o pancreatitis, heavy ETOH users

**Composite Responder Rates**

**Composite responder defined as**
- 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


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Eluxadoline in Patients Who Failed Loperamide RELIEF Trial

- Phase IV multicenter DBRCT
- Subjects: Patients subjectively reporting loperamide use in prior 12 months failing to provide adequate control of IBS-D symptoms
- AEs: Rates comparable in both groups; no SAEs

Primary Composite = Patient met composite response criteria on ≥50% of days, defined as ≥40% improvement in WAP c/w BL and BSS <5 OR absence of a BM if accompanied by ≥40% improvement in WAP.
Secondary Stool Consistency defined as BSS <5 on ≥50% of days.
Secondary WAP defined as ≥40% improvement in WAP compared to BL, on ≥50% of days.


Alosetron for IBS-D

- Partially selective 5-HT₃ antagonist
- 8 RCT, 4341 patients (predominantly women)
- NNT=7.5
- AEs: constipation, colon ischemia: 1/1000 patient-yrs
- 0.5 mg BID starting dose; may increase to 1 mg BID if well tolerated
- Current indication: Female patients with severe IBS-D not responding adequately to conventional therapy¹


¹ American College of Gastroenterology
Antidepressants
Variable Recs and Strength of Evidence

• 18 RCT, 1127 patients
• Antidepressants in general: NNT= 4; pain mostly
  • TCAs: 12 RCT, 787 patients; NNT= 4; Strong rec, high evidence
  • SSRIs: 7 RCT, 356 patients; NNT= 5; Weak rec, low evidence
  • SNRIs not yet studied in large RCTs
• AEs more common with antidepressants; NNH= 8.5


General Approach to Prescribing Antidepressants in IBS

• Consider specific symptoms1,2
  – TCAs in IBS-D, SSRIs in IBS-C
  – SSRI/SNRI for anxiety
• Consider side effect profiles1,2
  – SSRIs may be better tolerated than TCAs
• Start with low dose and titrate slowly by response; allow 4-8 weeks for maximal response1,3
• Continue at minimum effective dose for 6-12 months1,2
  – Long-term therapy may be warranted for some patients
  – Gradual taper to prevent withdrawal symptoms

Bulking Agents for IBS-C: Systematic Review and Meta-analysis: Strong rec, weak evidence

<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

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FDA Approved Therapies for IBS-C

- Linaclotide
- Plecanatide
- Lubiprostone
- Tegaserod
- Tenapanor
Linaclotide for IBS-C

- 14 aa peptide structurally similar to quanylin/uroguanylin; binds to guanylate-cyclase C receptors to promote ion and fluid secretion into gut and ENS modulation
- 4 RCT, 2867 patients
- IBS-C dose: 290 mcg daily
- NNT=6
- AEs: diarrhea

**FDA Primary Endpoint:**
≥30% reduction worst abdominal pain and increase ≥1 CSBM, both for 26/12 weeks

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


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Linaclotide: Abdominal Pain Over 26 Weeks

ITT population, observed cases, LS-mean presented: *P*-values based on ANCOVA at each week. Bars represent 95% CI.

ITT, intention to treat; LS, least squares.


Plecanatide for IBS-C

- 16 aa peptide structurally similar to uroguanylin
  - 8x greater binding affinity at GC-C receptors at pH <7
- 3 RCT, all at low risk for bias, n=2612
- IBS-C dose: 3mg daily
- NNT=10
- AEs: diarrhea

*P<0.001 vs placebo...
Lubiprostone for IBS-C

- Type 2 chloride channel activator; increases balanced ion and water secretion into gut
- 3 RCT, 1366 patients
- IBS-C dose: 8 mcg BID only approved in women
- NNT=12.5
  - AEs: diarrhea and nausea

![Graph showing overall responders with Lubiprostone vs Placebo]


Tegaserod for IBS-C

- Mixed 5-HT (serotonin) agonist (prokinetic)
- Approved for women < 65 yo with ≤ 1 CV risk factor
- Dose: 6 mg PO BID
- AEs: Diarrhea, abdominal pain, headache, nausea

![Graph showing pooled post hoc analysis of patients with low CV risk]

Pooled, post hoc analysis patients with low CV risk
- Study B301 (n=325)
- Study B358 (n=1181)
- Study B307 (n=336)
- Study B351 (n=359)

(N=2201)

Considerable or complete relief at least 50% of last 4 weeks in 12-week study or at least somewhat relieved 100% of the last 4 weeks.

*Defined as patients who do not have a history of ischemic cardiovascular disease and who have no more than one cardiovascular disease risk factor.
No demonstrable risk of MACE events with tegaserod

Risk of CV and stroke events with tegaserod vs comparators

<table>
<thead>
<tr>
<th>CV Events*</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-adjusted†</td>
<td>0.93</td>
<td>0.72–1.21</td>
</tr>
<tr>
<td>Adjusted‡</td>
<td>0.95</td>
<td>0.73–1.23</td>
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</table>

<table>
<thead>
<tr>
<th>Stroke Events</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-adjusted†</td>
<td>0.89</td>
<td>0.45–1.75</td>
</tr>
<tr>
<td>Adjusted‡</td>
<td>0.90</td>
<td>0.46–1.77</td>
</tr>
</tbody>
</table>

*CV events include acute coronary syndrome, MI, coronary revascularization.
†Unadjusted by Cox proportional hazards regression.
‡Adjusted for age, sex, region, calendar year, and baseline history of hypertension, treated hypertension, hyperlipidemia, statins, diabetes, treated diabetes, obesity, smoking, stroke, fibrates, angina, acute coronary syndrome, history of MI, and acute MI by Cox proportional regression.


Tenapanor

- NHE3 Inhibitor: traps water and phosphate in GI lumen; pain modulation via TRPV-1
- 50 mg BID resulted in significantly higher CSBM responder rate than placebo
  - Primary endpoint: Increase ≥1 CSBM/week from baseline for ≥6/12 treatment weeks
- FDA approved for IBS-C 9/2019
- Most frequent AEs: diarrhea, headache, nausea, abdominal pain

Chey WD et al. Am J Gastroenterol 2017; 112:763–774

American College of Gastroenterology
Emerging and Alternative IBS Therapies

• Bile acid sequestrants - small, uncontrolled trials suggest benefit in IBS-D
• Ramosetron – selective 5HT₃ antagonist (IBS-D)
• Tachykinin antagonists
• Peripheral cannabinoids – orinab
• Mast cell stabilizers
• Glutamine
• TRPV agents
• Human milk oligosaccharides
• FMT

Holvoet T et al. 2018 Digestive Disease Week Annual Scientific Meeting. Abstract 617.
Lackner JM et al. 2018 Digestive Disease Week Annual Scientific Meeting. Abstract 455.

Bile Acid Sequestrants

• BAM: prevalence estimates 1%; 25-50% in IBS-D
• Excess bile acids in colon
  • increase visceral sensation and fluid secretion via intracellular cAMP, mucosal permeability and/or Cl⁻ secretion
• Uncontrolled trials of bile acid sequestrants suggest benefit in IBS; 4-16 gm/day
  • Availability of 7C4 serum test may identify likely responders; needs more study

Ramosetron

- High 5-HT\textsubscript{3} binding affinity: potent and prolonged receptor blockade and antiemetic effects compared with older 5-HT\textsubscript{3} antagonists
  - Approved in Asia
- Meta-analysis of 4 IBS RCTs; 1623 patients (ramosetron vs placebo)
  - Overall IBS relief OR 1.70 (95% CI: 1.48 to 1.95)
  - Relief of abdominal pain/discomfort OR 1.41 (95% CI: 1.24 to 1.59)
  - Improvement in diarrhea OR 1.71 (95% CI: 1.40 to 2.08)
  - Higher rates of constipation; no colon ischemia


Mast cell stabilizers

- Ketotifen
  - Up to 6 mg BID increased discomfort threshold with visceral hypersensitivity, improved abdominal pain bloating, flatulence, diarrhea, incomplete evacuation, HRQOL (n=15)\textsuperscript{1}
  - No effect on release of tryptase and histamine from rectal biopsies demonstrated, mechanisms other than mast cell stabilization H1 receptor antagonism may be involved\textsuperscript{1}
- Cromolyn(disodium cromoglycate)
  - Significantly decreased abdominal pain behaviors induced by colorectal distension in animal model independent of mast cell mediator release\textsuperscript{2}

TRPV Agents

- Up-regulation/sensitization of receptors on peripheral nerve terminals of nociceptors is an important mechanism of visceral hypersensitivity
  - Transient reporter potential channel V1 (TRPV1), is involved in this process
  - Responsive to capsaicin, heat, acidosis, and endovanilloids

- Ebastine: H1RA
  - Small placebo-controlled study (n=55) showed 20 mg/d reduced visceral hypersensitivity and abdominal pain in patients with IBS


Human Milk Oligosaccharides (HMOs)

HMOs in infant health¹
- Primary determinant of gut microbiota
- Involved in maturation of gut barrier and gut immune function; bind pathogens

HMOs in IBS²³
- Specifically increase bifidobacteria abundance
- Increase concentration of metabolites essential for gut barrier functioning and immune modulation

HMOs: Change in Total % of Stool Consistency (BSFS)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>50.3%</td>
<td>32.9%</td>
<td>30.9%</td>
<td>30.7%</td>
</tr>
<tr>
<td>Normal</td>
<td>9.3%</td>
<td>39.6%</td>
<td>42.8%</td>
<td>42.8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40.4%</td>
<td>27.5%</td>
<td>26.3%</td>
<td>26.5%</td>
</tr>
</tbody>
</table>

N=317

Significantly reduced total % of abnormal stools (diarrhea + constipation) compared to baseline at P < .001


Fecal Microbiota Transplant for IBS

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study population</th>
<th>Setting</th>
<th>Study Site</th>
<th>Sample Size</th>
<th>IBS Criteria</th>
<th>IBS Subtypes</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2017¹</td>
<td>Single center</td>
<td>Primary care</td>
<td>Norway</td>
<td>90</td>
<td>Rome III</td>
<td>IBS-D 53% IBS-C 47%</td>
<td>Decrease in IBS-SSS &gt; 75 points at 3 months</td>
</tr>
<tr>
<td>Holvoet 2018²</td>
<td>Single center</td>
<td>Tertiary care</td>
<td>Belgium</td>
<td>64</td>
<td>Rome III</td>
<td>Predominant bloating and non-C</td>
<td>Yes to question of improvement in overall symptoms and abdominal bloating at 12 weeks</td>
</tr>
<tr>
<td>Aroniadis, 2018³</td>
<td>Multi-center</td>
<td>Primary, secondary, and tertiary care</td>
<td>USA</td>
<td>48</td>
<td>Rome III</td>
<td>IBS-D</td>
<td>Decrease in IBS-SSS ≥ 50 points at 12 weeks</td>
</tr>
<tr>
<td>Halkjaer, 2018⁴</td>
<td>Two centers</td>
<td>Tertiary care</td>
<td>Denmark</td>
<td>52</td>
<td>Rome III</td>
<td>All subtypes</td>
<td>Decrease in IBS-SSS ≥ 50 points at 3 months</td>
</tr>
</tbody>
</table>

FMT, fecal microbiota transplantation; IBS-QOL, Irritable Bowel Syndrome-Quality of Life Measure; HADS; IBS-Hospital Anxiety and Depression Scale

Vibrating Capsule

Orally administrated vibrating capsule stimulates bowel motility by mechanically inducing vibrations in the large intestine

**ACTIVATING BASE UNIT**

The base unit activates the capsule prior to use. After placing a vibrating capsule into the designated groove, an activation signal is transmitted by the base unit to the capsule

**PATIENT REPORTING APP**

Patients report bowel activity:
- Allowing the physician to adjust the treatment
- Longitudinal, personalized data collection for further development of treatment plans

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Vibrating Capsule Proof of Concept Trial

- 24 patients with CIC (Rome III) randomized to vibrating vs sham capsule (2/week x 8 weeks)
- Endpoints:
  - Primary: Vibrating capsule vs sham colonic geometric center at 48 hours and t1/2 of ascending colon emptying
  - Secondary: colonic geometric center at 8 and 24 hours and slope of progression of colonic geometric center over the 48 hours of the transit study
- Phase III trials ongoing for CIC with modified stimulation regimen

Management of IBS: Take Home Points

• Make a positive diagnosis with judicious diagnostic testing
• Diet, lifestyle modifications, OTC (loperamide, fiber) therapies first line
• Best clinical trial evidence
  • IBS-D: Rifaximin, Eluxadoline, Alosetron
  • IBS-C: Linaclotide, Plectanatide, Lubiprostone, Tegaserod, Tenapanor
• Adjunctive therapies (use at any point)
  • Peppermint oil (for all subtypes); TCAs, SNRIs (for IBS-D/M with pain)-allow 4 weeks minimum; antispasmodics; CBT; Diet; Probiotics; Bile acid sequestrants
• Rich pipeline targeting specific etiologies/symptoms
  • Serotonergics, HMOs, tachykinin antagonists, mast cell stabilizers, FMT, glutamine, TRP agonists, cannabnoids

Thank You!

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Questions?

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