Refractory IBS-D: An Evidence-Based Approach to Therapy

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Janice is a 30-year-old woman who presented to my irritable bowel syndrome (IBS) clinic for a second opinion regarding potential treatment options for her IBS-D (diarrhea). She was diagnosed with IBS-D by her previous gastroenterologist after a work-up that included negative serologies (normal CBC, comp, TSH, celiac testing) and a colonoscopy with biopsies.

Her symptoms have been present for the past 5 years and she denies having any specific precipitants. She is currently experiencing daily abdominal pain, which she describes as a pressure-fullness sensation radiating throughout her lower abdomen. It usually develops in the post-prandial setting and partially improves with defecation. Janice further describes recurrent bloating and distention, noting that she can look “9 months pregnant.” She is passing 3 to 4 Bristol 6-7 stools per day and although she identifies mucus in her stools, she does not see blood. There are no associated alarm signs or symptoms.

Janice has tried fiber (made her symptoms worse), loperamide (decreased her bowel movements to 2/day but no other improvements), dicyclomine and hyoscyamine (ineffective), and avoiding dairy and gluten (minimal response).

CBC = complete blood count; comp = comprehensive metabolic panel; TSH = thyroid-stimulating hormone.
What other treatment modalities can we recommend for Janice?
Based on Rome IV diagnostic criteria for IBS-D, which of the following would be considered the most effective treatment:

1. Antidiarrheal agents, which are effective at decreasing stool frequency and improving stool texture

2. Antispasmodic agents, which may improve abdominal discomfort

3. Agents that provide concurrent treatment of pain and alterations in stool form/texture
Recurrent abdominal pain on average at least 1 day per week in the last 3 months, associated with 2 or more of the following:

- Pain improved or worsened with defecation
- Associated with change in stool form
- Associated with change in stool frequency

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

Worldwide prevalence = 11.2% (women > men)

Treatment of IBS-D

**IBS-D**

Antidiarrheal?
- CBT/Hypnotherapy
- Diet modification
- Rifaximin*
- TCAs
- EnterraGam*
- Eluxadoline*
- Alosetron*/
- Ondansetron
- Probiotic
- IBgard
- Bile-acid binding agent

Antispasmodic?

*Denotes FDA approval

IBS-C = IBS with constipation; IBS-M = IBS with alternating constipation and diarrhea; CBT = cognitive behavioral therapy; TCAs = tricyclic antidepressants.
Searching for the Root Cause(s) of IBS-D: Potential Etiologies

- Bile acid malabsorption
- Altered secretion & motility
- Changes in brain-gut axis
- Food intolerance
- Alterations in serotonin

- Visceral hypersensitivity
- Post-infectious inflammation
- Alteration of the gut microbiome
- Small intestinal bacterial overgrowth (SIBO)
Breath Testing in IBS: Meta-Analysis

Forest plot of all age-sex matched studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Breath Test</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grover</td>
<td>Sucrose</td>
<td>2.29 (0.89, 5.87)</td>
<td>18.65</td>
</tr>
<tr>
<td>Lupascu</td>
<td>Glucose</td>
<td>10.89 (3.52, 33.71)</td>
<td>16.82</td>
</tr>
<tr>
<td>Pimentel</td>
<td>Lactulose</td>
<td>20.67 (5.29, 80.69)</td>
<td>14.68</td>
</tr>
<tr>
<td>Parodi</td>
<td>Glucose</td>
<td>4.30 (1.24, 14.98)</td>
<td>15.71</td>
</tr>
<tr>
<td>Scarpellini</td>
<td>Lactulose</td>
<td>24.27 (7.35, 80.15)</td>
<td>16.20</td>
</tr>
<tr>
<td>Collin</td>
<td>Lactulose</td>
<td>18.04 (6.55, 49.71)</td>
<td>17.94</td>
</tr>
<tr>
<td>Overall (I-squared = 67.9%, P=.008)</td>
<td></td>
<td>9.64 (4.26, 21.82)</td>
<td>100.00</td>
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</tbody>
</table>

Note: Weights are from random effects analysis.
TARGET 3: Rifaximin Retreatment and Safety Study

2,438 patients were treated and completed 2 weeks of rifaximin 550 mg in the open-label phase.

44% n=1,074* responded to open-label treatment.

59% n=636 entered the double-blind phase after symptom recurrence.

36% n=382 of open-label responders didn’t experience a recurrence of symptoms for up to an 18-week follow-up period, were excluded due to symptom inactivity.

328 patients randomized to rifaximin 550 mg TID.

308 patients randomized to placebo.

*Responder: ≥30% reduction in mean weekly abdominal pain score + ≥50% reduction in # days per week with Bristol 6-7 stools for ≥2 of 4 weeks

TARGET 3 = Targeted, Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for Non-C IBS.

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.

Increased Bile Acid Synthesis in IBS-D

Overall univariate association $P = .02$

* $P = .01$ vs controls

** $P = .01$ vs IBS-C/FC

FC = functional constipation.

Bile Acid Sequestrants* in IBS-D

• Abnormal C4 level in 19% of IBS-D patients
• 75SeHCAT test correlates with hepatic bile acid synthesis, bowel habits, and colonic transit time in IBS patients
• Symptom response to open-label colestipol in patients with abnormal 75SeHCAT retention supports a role for bile acids in the pathophysiology of IBS-D

*Colestipol.

SeHCAT = 75Se-labelled homocholic acid-taurine;
IBS-SSS = IBS Severity Scoring System.

**P < .01 vs baseline.
# What Are FODMAPs?

Fermentable oligo-, di-, monosaccharides and polyols (FODMAPs)

<table>
<thead>
<tr>
<th>Excess Fructose</th>
<th>Honey, apples, pears, peaches, mangos, fruit juice, dried fruit</th>
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</thead>
<tbody>
<tr>
<td>Fructans</td>
<td>Wheat (large amounts), rye (large amounts), onions, leeks, zucchini</td>
</tr>
<tr>
<td>Lactose</td>
<td>Milk (cow, goat, or sheep), custard, ice cream, yogurt, soft unripened cheeses (eg, cottage cheese, ricotta)</td>
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<tr>
<td>Sorbitol</td>
<td>Apricots, peaches, artificial sweeteners, artificially sweetened gums</td>
</tr>
<tr>
<td>Raffinose</td>
<td>Lentils, cabbage, Brussels sprouts, asparagus, green beans, legumes</td>
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Potential Role of FODMAPs in IBS Symptoms

SCFA = short-chain fatty acid.

For ≥50% of weeks 3 and 4

Adequate Relief of GI Symptoms

- mNICE Diet: N=45, Adequate Relief 41%
- Low FODMAP Diet: N=38, Adequate Relief 52%

mNICE = modified National Institute for Health and Care Excellence. Patients were instructed to eat small frequent meals, avoid trigger foods, and avoid excess alcohol and caffeine. FODMAP-containing foods were not excluded from the mNICE diet.

**US Randomized Controlled Trial: Low FODMAP vs mNICE Diets for IBS-D**

**Abdominal Pain Scores**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
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</thead>
<tbody>
<tr>
<td><strong>mNICE Diet</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low FODMAP Diet</strong></td>
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</table>

**Bloating Scores**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
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<tr>
<td><strong>mNICE Diet</strong></td>
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*P values refer to the change WITHIN group comparing to baseline score.*

*P*≤.05; *oP*≤.001; *§P*≤.0001.

Which of the following treatments would you recommend for Janice?

1. Bile acid sequestrants
2. FODMAPs
3. Rifamixin
Global IBS Symptoms: Other Pharmacologic and Alternative Strategies
Eluxadoline in IBS-D

• Involves mixed opioid receptor activity\(^1,^2\)
  - Mu (\(\mu\)) opioid receptor agonist and kappa (\(\kappa\)) opioid receptor agonist
  - Delta (\(\delta\)) opioid receptor antagonist

• Has low systemic exposure after oral administration\(^2\)

• Results of animal studies suggest eluxadoline can improve the diarrheal and hyperalgesia symptoms of IBS-D with limited constipation\(^1,^2\)

Phase 4, multicenter DBRCT evaluating efficacy, safety, and tolerability of eluxadoline in patients subjectively reporting loperamide use in prior 12 mos failing to provide adequate control of IBS-D symptoms.

**Primary Composite** = patients meet daily 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 = BSS <5 on ≥50% of days.

**Secondary**: Worst Abdominal Pain (WAP) = ≥40% improvement in WAP compared to BL, on ≥50% of days.

DBRCT = double blind randomized controlled trial.

Brenner DM, et al. RELIEF trial. Presented at the Annual Scientific Meeting of the ACG; October 5-10, 2018; Philadelphia, PA. [Abstract 344].

*P<.01; †P<.05; ‡P<.05.
Peppermint Oil (PO)

- **Peppermint oil: 1° active component L-menthol**
  - Antispasmodic, anti-inflammatory, 5-HT₃, bactericidal properties
  - Approved as first-line therapy for IBS by European Medicines Agency (EMA)
  - Meta-analysis:
    - Reduces global IBS symptoms and abdominal pain
    - More effective than antispasmodics, TCAs, fiber
    - Number needed to treat: 2-4
    - Associated with increased adverse events (heartburn, abdominal pain, anal burning)

- **Potential benefit if side effects can be minimized/mitigated**

TCAs = tricyclic antidepressants.

Components of TISS include abdominal pain/discomfort, bloating/distention, constipation/diarrhea, pain at evacuation, passage gas/mucus, sense incomplete evacuation (IE), urgency.

Total adverse events: PO=2 (5.7%), Placebo =4 (10.8%)

TISS = Total IBS Symptom Score; PO = peppermint oil.

Cognitive Behavioral Therapy (CBT)

- Irritable Bowel Syndrome Outcome Study (IBSOS)
- Prospective randomized, active comparator study; Rome III > moderate severity
- N=436 SUNY Buffalo/Northwestern University
- MC-CBT ([N=146] 4 sessions); S-CBT ([N=146] 10 sessions); EDU ([N=145] 4 sessions)
- 10 Endpoint: CGI-I (1-7 scale w/6-7 moderate/substantial improvement considered a responder)

Week 12: Global Improvement of IBS Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Patient-reported immediate follow-up</th>
<th>GE-administered immediate follow-up</th>
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<tbody>
<tr>
<td>MC-CBT</td>
<td>61%</td>
<td>56%</td>
</tr>
<tr>
<td>S-CBT</td>
<td>55%</td>
<td>51%</td>
</tr>
<tr>
<td>EDU</td>
<td>43%</td>
<td>40%</td>
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MCCBT - EDU, P < .01; S-CBT-EDU, P < .05.

MCCBT = Minimal Contact CBT; S-CBT=Standard CBT; EDU = Education; CGI-I (Clinical Global Impressions-Improvement-Scale; GE (Gastroenterologist).

Physician-Patient Communication

• Clinician-patient communication can be enhanced by asking open-ended questions, actively listening to the patient, displaying empathy,\(^1\) understanding the patient’s perspective, sharing information,\(^2\) and setting realistic goals and expectations regarding medications

• A strong patient-physician relationship can improve diagnosis, adherence to medications, and self-management\(^2\)

• Effective clinician-patient communication is associated with better outcomes, increased patient satisfaction, and decreased utilization of care\(^1\)

Summary

• IBS is a common disorder affecting 10% to 15% of the international population\(^1\)

• Pathogenesis is heterogeneous
  ▪ Identification and development of diagnostic studies for underlying mechanisms of action (MOAs) will likely improve treatment outcomes

• Treatments are based on subtype but with no specific algorithms
  ▪ Prognostic data are lacking or poor
  ▪ Decision based on personal preferences can lead to Pharmaceutical vs. “Natural/CAM”
  ▪ Communicating openly with patients and allowing them to participate in the process lead to improved outcomes\(^2\)

CAM = complimentary or alternative medicine.