Evidence-Based Approach to Irritable Bowel Syndrome

Joel Heidelbaugh, MD, FAAFP, FACG

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The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated:

Faculty will briefly discuss the following commonly-used treatments for irritable bowel syndrome (IBS), which have not been approved by the U.S. FDA for treatment of various associated symptoms:

- Anti-spasmodics and anti-depressants (TCAs, and SSRIs) for the treatment of abdominal cramping and bloating
- Probiotics for the treatment of abdominal bloating
- Fiber, milk of magnesia (MOM) and polyethylene glycol (PEG) for the treatment of constipation
- Loperamide, diphenoxylate/atropine, and cholestyramine for the treatment of diarrhea

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Dr. Heidelbaugh is a family physician who has 17 years of teaching experience. His specialty topics include gastrointestinal disorders, men's health, and primary care urology. He is a member of the American Gastroenterological Association guideline panels for irritable bowel syndrome, inflammatory bowel disease, and Lynch syndrome. He is the co editor and co author of the textbook ROME IV: Functional Gastrointestinal Disorders for Primary Care and Non GI Clinicians, published through the Rome Foundation. In addition, he is the consulting editor of Primary Care: Clinics in Office Practice and the president elect of the American Society for Men's Health. Dr. Heidelbaugh believes that increasing awareness and education about gastrointestinal and men's health issues is an important trend in medical education, clinical practice, and research.

Learning Objectives

1. Apply evidence-based diagnostic criteria to evaluate patients presenting with recurrent or episodic abdominal pain for IBS.
2. Establish referral and follow-up protocol with a gastroenterologist for patients exhibiting red flags for other disease, for which endoscopic evaluation should be considered.
3. Develop treatment plans that involve positive patient-physician communication, shared decision making, and follow-up strategies that result in symptom relief and improved quality of life.

Audience Engagement System
Epidemiology, Burden of Illness and Misconceptions

High Prevalence and Incidence
- Common in Western Europe and North America, less common in Asia
- Estimated at 11% worldwide, 12% in US
- Patients often present between age 30 – 50 years of age
- Decrease in reporting in older patients
- (Are abnormal stools really abnormal?)
- 1.5 times more common in women than in men, commonly overlooked in men
- Average 14 hours lost work productivity per 40-hour week
- Gradual decrease in prevalence with increasing income
  - 8 - 16% in those making less than $20,000/year
  - 3 - 5% in those making more than $75,000/year
- 2nd only to GERD in burden of GI illness
  - $1.6 billion – direct costs
  - $19.2 billion – indirect costs


IBS Myths and Misconceptions
- Misconceptions
  - Purely a psychological-based diagnosis
  - Unknown mechanism(s)
  - Difficult to diagnose "diagnosis of exclusion"
- Reality
  - IBS is a REAL disorder and multifactorial
  - Majority of patients do not have psychological comorbidities!
  - Serotonin implicated in pathogenesis
  - Diagnosis can be made accurately in primary care!

AES Question #1
Which of the following are common patient perceptions regarding IBS?
1. IBS causes colon cancer
2. If you change your diet, you will cure IBS
3. IBS and IBD are related
4. IBS does not lead to malnutrition
5. IBS will stay the same regardless of age

Patient Perceptions of IBS

<table>
<thead>
<tr>
<th>Common Knowledge</th>
<th>Common Misconceptions</th>
<th>Most Desired Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of abdominal pain and constipation</td>
<td>Can develop into: Colitis, Surgical problem, Malnutrition, Cancer</td>
<td>• What foods to avoid? • What causes IBS? • Coping strategies to reduce symptoms?</td>
</tr>
<tr>
<td>• And/or diarrhea • And/or bloating</td>
<td>Triggers include stress at work, relationships, combinations of other (emotional) factors</td>
<td>Will worsen with age</td>
</tr>
</tbody>
</table>

Primary Care Perceptions
- PCPs were less likely than gastroenterologists to believe that IBS was related to prior physical or sexual abuse, previous infection, or learned behavior, but were more likely to state that diet caused IBS, or due to a linkable genetic etiology
- A study found that PCPs in the Netherlands considered smoking, caffeine, diet, "hasty lifestyle," and lack of exercise as potential triggers for IBS symptoms, while PCPs in the UK considered food, infection, and travel as other possible triggers

**Health-Related Quality of Life**

- Patients with IBS have the same physical HRQOL scores as patients with diabetes, and lower physical HRQOL scores than patients with depression and GERD\(^1\)\(^2\).
- Psychological HRQOL scores are lower than patients with chronic renal failure, and can be so severe as to raise risk of suicidal behavior\(^3\).


**Pathophysiology of IBS**

**Impact on Quality of Life**

**AES Question #2**

Which of the following conditions is associated with IBS?

1. Coronary artery disease
2. Seasonal allergies
3. Interstitial cystitis
4. Rheumatoid arthritis
5. Hidradenitis suppurativa

**Other Associated Conditions**

- GI motility disorders
  - Dyspepsia, GERD, cyclic vomiting, gastroparesis, etc.
- Psychiatric disorders
  - Anxiety, depression, somatoform disorders, PTSD
- Chronic back pain
- Fibromyalgia, chronic fatigue syndrome
- Chronic headaches, "migraines"
- Chronic pelvic pain — men and women
- Functional urinary symptoms (e.g., interstitial cystitis)
- Dysmenorrhea
- Sexual dysfunction

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IBS and Symptom Overlap


Our Practices

- Most cases of IBS are diagnosed by gastroenterology
- Most research is done by gastroenterology
- Most patients with all forms of IBS are managed by primary care!
- Imperative that primary care has optimal understanding of perceptions and evidence behind diagnosis and treatment!

Diagnosis of Functional GI Disorders

Making the Diagnosis of IBS

- Take a careful history
- Look for warning signs
- Perform a thorough exam
- Use the Rome IV criteria
- Classify into the appropriate subtype
- Perform limited diagnostic tests

Key Points in the History

- Onset of symptoms (chronicity)
- Is abdominal pain present?
- Is constipation or diarrhea present?
- Other GI symptoms (think overlap)
- Presence of common non-GI symptoms
- Prior tests?
- Prior treatments?

Rome IV Criteria for IBS

Recurrence abdominal pain or discomfort at least 1 day/wk (on average) in the last 3 months associated with 2 or more of the following:

- Great associated with a change in frequency of stool
- Great 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

**Rome IV: Limited Diagnostic Tests**

- In the appropriate patient, consider
  - CBC, ESR or CRP, fecal calprotectin
  - Celiac serologies
- All patients do not require testing
- No role for colonoscopy in all patients


**IBS: The Value of the Physical Exam**

- Identify other causes of symptoms
- Confirmation that complaints are being taken seriously
- Reassurance of absence of concerning physical exam findings

**IBS Subtypes Are Based on Stool Consistency**

- IBS-C
- IBS-D
- IBS-U


**Stool Consistency but not Frequency Predicts Colon Transit Time**

- Bristol Stool Form Scale
- Type 1: Separate hard lumps
- Type 2: Sausage-like but lumpy
- Type 3: Sausage-like but with cracks in the surface
- Type 4: Smooth and soft
- Type 5: Soft lumps with clear-cut edges
- Type 6: Fluffy pieces with ragged edges, generally liquid
- Type 7: Watery, no solid pieces

**IBS-C vs. Chronic Idiopathic Constipation**

**AES Question #3**

Which of the following are considered “alarm features” for chronic constipation?

1. Alternating diarrhea and constipation
2. Celiac disease
3. Worsening GERD
4. New onset constipation in the elderly
5. Macrocytic anemia
Alarm Features for Chronic Constipation

- Age > 50 years; > 45 years if African-American
- New onset constipation in elderly
- Severe symptoms not investigated
- Rectal bleeding
- Weight loss
- Family history of organic GI disease
- Palpable abdominal/rectal mass

Investigate and treat appropriately; colonoscopy may be indicated


Pretest Probability of Organic Disease

<table>
<thead>
<tr>
<th>Organic Disease</th>
<th>IBS Patients (%)</th>
<th>Control/Population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis/IBD</td>
<td>0.51-0.98</td>
<td>0.3-1.2</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0-0.51</td>
<td>0-6 (varies with age)</td>
</tr>
<tr>
<td>Lactose malabsorption</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>4.2</td>
<td>5-9</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>3.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Celiac disease: antibodies</td>
<td>7.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Celiac disease: confirmed</td>
<td>0.41</td>
<td>0.44</td>
</tr>
</tbody>
</table>


When to Refer to a Specialist?

- Warning Signs or Alarm Features
- New onset of symptoms over age 50
- Rectal bleeding/bloody stools
- Unexplained weight loss
- Family history of colon cancer or inflammatory bowel disease
- Abnormal physical examination
- Severe or progressive symptoms
- Failure to improve with fiber or laxative therapies

Other Tests for Chronic Constipation

For patients with severe symptoms or poor response to laxatives consider:

- Balloon expulsion: Suspected outlet problems/dyssynergia
- Anorectal manometry: Suspected dyssynergia; Hirschsprung disease
- Defecography: Suspected outlet problems/pelvic floor dysfunction
- Colonic transit testing: Sitz markers or wireless pH-motility capsule

Other Tests for Chronic Constipation

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
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</table>


Treatment of Constipation-and Diarrhea-Related Functional GI Disorders
Improving Patient-Physician Interactions

• Listen (it’s hard - don’t interrupt!!!)
• Understand fears
• Review goals
• Set expectations
  – Short-term
  – Long-term
• Develop a logical treatment plan together
• Arrange for routine follow-up

Managing IBS: What Do Your Patients Want?

• They want you to listen
  – Understand their history (symptoms, work, home)
• Education about their condition
  – Address questions or concerns
  – Address uncertainty of IBS
• Reassurance
• A positive diagnosis
  – Review diagnostic criteria and results with patients
• Symptom improvement

Managing IBS: What Do Your Patients Want?

• They want you to listen
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  – Address questions or concerns
  – Address uncertainty of IBS
• Reassurance
• A positive diagnosis
  – Review diagnostic criteria and results with patients
• Symptom improvement

IBS & Low FODMAP Diet

Fermentable Oligo-, Di-, Monosaccharides And Polyols

Excess Fructose

Fructans

Sorbitol

Raffinose

Honey, apples, pears, peaches, mango, fruit juice, dried fruit
Wheat (large amounts), rye (large amounts), onions, leeks, zucchini
Apricots, peaches, artificial sweeteners, artificially sweetened gums
Lentils, cabbage, Brussels sprouts, asparagus, green beans, legumes

Graded Treatment of Chronic Constipation

Address psychosocial factors
• Manage stress
• Goals: Improve functioning
• Continuing care
• Realistic & shared goals
• Pharmacotherapy

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

IBS & Low-Gluten Diet

Quality of evidence: very low.

Impact of Physical Activity

IBS Severity Scoring System

- 102 IBS pts by Rome II
- 12 wk intervention
- 20-60" moderate to vigorous activity 3-5 times/week


IBS Pharmacologic Therapies

Abdominal pain/discomfort
- Antidepressants
- Antispasmodics
- Probiotics
- Flaxseeds
- Pectin

Constipation
- Fiber
- Lactulose
- Stimulant laxatives
- Loperamide

Fibersupplementation
- Mild constipation symptoms
- May or may not help with pain
- Soluble probably better than insoluble
  - "Start low and titrate slow"
- Gas and bloating are the main side effects

Anti-spasmodics
- For postprandial abdominal pain
- Not effective for chronic abdominal pain
- Avoid in the elderly

Fiber and stool softeners (docusate) are most useful in patients with mild, infrequent constipation
- Best evidence for psyllium up to 25 grams/day
- Their role in patients with significantly delayed colon transit or dysynergia is limited
- Fiber may worsen symptoms in patients with significantly delayed colon transit or dysynergic defecation

AES Question #4

Which of the following novel mechanisms has shown promise in the pharmacologic treatment of IBS?

1. Chloride channel activation
2. Sodium channel activation
3. Potassium channel activation
4. Magnesium channel activation

Chloride Channels in Intestinal Transport

Chloride in the small intestine is secreted via a basolateral chloride channel (CLC). This chloride is then transported into the gut lumen, which is necessary for water and solute transport. Chloride channels play a critical role in maintaining the osmolarity of the gut lumen and are targets for drug development in IBS.
**Lubiprostone for IBS-C:**

Data From 2 Phase III Trials


**Effects of Guanylate Cyclase-C Receptor Activation**


Animal studies suggest that main effects occur in the proximal small intestine.

**Linaclotide Phase 3 IBS-C Trial**

Abdominal Pain Over 26 Weeks

P = 0.007 for Week 1

P < 0.0001 for Weeks 2-26

### Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Lin 266 µg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>*ITT Population, Observed Cases, LS-Means presented, <em>P</em>-values based on ANCOVA at each week. Bars represent 95% confidence intervals.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TEAEs Occurring in ≥ 3% in Lin 266 µg Group and Lin 266 µg > Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lin 266 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEAE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE</td>
<td>187 (46%)</td>
<td>212 (53%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (2%)</td>
<td>71 (18%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (4%)</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>URI</td>
<td>13 (3%)</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 (3%)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>7 (2%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>4 (1%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (2%)</td>
<td>13 (3%)</td>
</tr>
</tbody>
</table>

### Loperamide* for IBS-D

- Low doses (2 mg once or twice daily) may be effective to decrease stool frequency and 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/bloating, constipation, dry mouth, fatigue.

*FDA-approved for diarrhea, but not for IBS-D.

**Linaclotide Phase 3 IBS-C Trial**

<table>
<thead>
<tr>
<th></th>
<th>Weeks 1–12</th>
<th>Weeks 1–26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any TEAE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo N=403</td>
<td>187 (46%)</td>
<td>228 (57%)</td>
</tr>
<tr>
<td>Lin 266 µg N=402</td>
<td>212 (53%)</td>
<td>263 (65%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo N=403</td>
<td>7 (2%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Lin 266 µg N=402</td>
<td>71 (18%)</td>
<td>78 (20%)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo N=403</td>
<td>17 (4%)</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>Lin 266 µg N=402</td>
<td>17 (4%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td><strong>URI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo N=403</td>
<td>13 (3%)</td>
<td>22 (5%)</td>
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<td>Lin 266 µg N=402</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Placebo N=403</td>
<td>14 (3%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Lin 266 µg N=402</td>
<td>15 (4%)</td>
<td>18 (4%)</td>
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<tr>
<td><strong>Flatulence</strong></td>
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<tr>
<td><strong>Headache</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo N=403</td>
<td>8 (2%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Lin 266 µg N=402</td>
<td>13 (3%)</td>
<td>13 (3%)</td>
</tr>
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</table>

**Diphenoxylate-Atropine**

- A synthetic opiate agonist with a structure similar to meperidine.
- Atropine is added to discourage deliberate abuse or overdose of diphenoxylate.
- Schedule V controlled substance.
- First approved by FDA in 1960.
- No prospective studies.

*Diphenoxylate-atropine for IBS-D.
Antispasmodics for IBS-D

- 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)


Bile Acid Sequestrants* for IBS-D

- 20%-30% of patients with IBS-D or functional diarrhea have bile acid malabsorption (BAM)
- Up to 10% of IBS-D patients have evidence of severe BAM
- Bile acids accelerate colonic transit, increase stool frequency, and reduce consistency
- Best test: 75SeHCAT
- Cholestyramine, colesevelam hydrochloride may improve sx

*Off-label use, not FDA approved for IBS-D.


Alosetron for IBS-D

- A 5-HT3 antagonist
- Reduces stool frequency and abdominal pain; improves urgency
- Treatment population: women with chronic, severe IBS-D who have failed other treatments
  - Dose: 0.5-1.0 mg QD to BID
- 8 large, R, DB, PC trials have shown benefits for global and individual symptoms of IBS (NNT = 8)
- Patient education regarding possible serious adverse effects
  - 0.05 cases of ischemic colitis/1000 patient-years
  - 0.36 cases of severe constipation/1000 patient-years
- If ischemic colitis occurs, it is usually within the first month
- Prescribing program mandated by FDA


Eluxadoline for IBS-D

- Mu (μ) opioid receptor agonist
- Delta (δ) opioid receptor antagonist
- Low systemic absorption and bioavailability
  - Low potential for drug-drug interactions
- Common adverse events include nausea and constipation
- No signs of dependence or withdrawal during clinical trials

Complementary and Alternative Treatments for Functional GI Disorders

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

SCFA: short chain fatty acids

Bifidobacteria Infantis 35624 for IBS Global Assessment of Relief


Randomized Trial of Dried Plums for Chronic Constipation

- Dried plums contain large amounts of fiber and sorbitol
- 8-week RCT single-blinded cross-over study examined treatment with dried plums (prunes, 50 g/day or 6 prunes) compared with psyllium (11 g/day fiber) taken BID
  - 40 patients with chronic constipation
  - Dried plums resulted in a greater improvement in constipation symptoms compared with psyllium
    - More CSBMs (3.5 ± 0.2 vs 2.8 ± 0.2, *P* = 0.006)
    - Softer stools (3.2 vs 2.8 on the BSFS, *P* = 0.02)
    - Overall constipation symptoms (both groups improved, NS)

Current Therapeutic Guidelines: American Gastroenterological Association

AGA Guideline for Pharmacologic Treatment of IBS

- Multidisciplinary guideline development
  - Gastroenterologists
  - Epidemiologists
  - Primary Care
  - Patient Representative
  - Rigorous COI exclusions *(NB: No one is paid!)*
- Clinical Practice and Quality Measures Committee
  - Guideline
  - Technical Review
AGA Guideline for Pharmacologic Treatment of IBS

• **GRADE Methodology**
  - Grading of Recommendations Assessment, Development, and Evaluation System
  - High/Moderate/Low Quality Evidence
  - Strong/Conditional (Weak) Strength of Evidence

• **PICO**
  - Patient Problem or Population
  - Intervention
  - Comparison
  - Outcome(s)

1. Use linaclotide (over no drug tx) in IBS-C
   - Strong recommendation; high quality evidence

2. Use lubiprostone (over no drug tx) in IBS-C
   - Conditional recommendation; moderate quality evidence

3. Use laxatives [PEG] (over no drug tx) in IBS-C
   - Conditional recommendation; low quality evidence

4. Use rifaximin (over no drug tx) in IBS-D
   - Conditional recommendation; moderate quality evidence

5. Use alosetron (over no drug tx) in IBS-D
   - Conditional recommendation; moderate evidence

6. Use loperamide (over no drug tx) in IBS-D
   - Conditional recommendation; very low quality evidence

7. Use TCAs (over no drug tx) in IBS
   - Conditional recommendation; low quality evidence

8. Do not use SSRIs for IBS patients
   - Conditional recommendation; low quality evidence

9. Use antispasmodics (over no drug tx) in IBS
   - Conditional recommendation; low quality evidence

Practice Recommendations

• Constipation is a multi-symptom condition that must be appropriately defined
• The main causes of constipation are slow colon transit and/or disordered defecation - more often functional than organic in etiology
• Diet and lifestyle changes help with most mild, moderate, or intermittent constipation symptoms, and should always be tried first
• Laxatives including osmotics, stimulants, and prosecretory agents improve symptoms in many patients
• Biofeedback and physical therapy are the preferred treatments for dyssynergic defecation and have modest results
• When patients fail to respond to laxatives, diagnostic testing can help to determine the etiology of constipation symptoms
• Gain skill in using newer agents, know when to refer to gastroenterology
• A multi-disciplinary approach is optimal for severely affected patients