Recognition of Diarrhea-Predominant Irritable Bowel Syndrome: Advancing Accurate Diagnosis and Appropriate Treatment

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Faculty Disclosures

- No real or apparent conflicts of interest to disclose
Learning Objectives

- Recognize the significant and pervasive impact of irritable bowel syndrome (IBS) on patients, families, and caregivers
- Utilize evidence-based guidelines and available diagnostic tools to facilitate timely and accurate diagnosis of IBS in patients with diarrhea
- Evaluate the efficacy and safety of newer treatments for irritable bowel syndrome with diarrhea (IBS-D)
Disease Overview
Overview of IBS

- IBS is the most frequently diagnosed functional gastrointestinal disorder (GI) in primary and secondary care
- Affects ~15% - 20% of the US population
- Characterized by abdominal discomfort accompanied by altered bowel function presenting as symptoms of constipation (IBS-C), diarrhea (IBS-D), or both (IBS-M) in the absence of structural or biochemical abnormalities
- Associated with high medical costs, frequent doctor visits, and missed workdays, and an overall detrimental impact on health-related quality of life (HRQOL)
QOL Is Significantly Worse for Patients with IBS vs the General US Population

QOL, quality of life; SF-36, 36-Item Short Form Health Survey; PF, physical functioning; RL-P, role limitations-physical; BP, bodily pain; GH, general health; EW-B, emotional well-being; RL-E, role limitations-emotional; E/F, energy/fatigue; SF, social functioning

The Impact of IBS on QOL Relative to Other Chronic Conditions

GERD, gastroesophageal reflux disease; DM, diabetes mellitus

Patient-identified Factors that Contribute to Disease Burden

<table>
<thead>
<tr>
<th>Factor</th>
<th>Respondents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social limitations</td>
<td>61.5</td>
</tr>
<tr>
<td>Cannot leave home</td>
<td>53.5</td>
</tr>
<tr>
<td>Work/school limitations</td>
<td>50.2</td>
</tr>
<tr>
<td>Limitations in thinking</td>
<td>49.6</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>45.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>42.2</td>
</tr>
<tr>
<td>Limitations in home activities</td>
<td>39.2</td>
</tr>
<tr>
<td>Poor quality of life</td>
<td>39</td>
</tr>
<tr>
<td>Incontinence</td>
<td>27.3</td>
</tr>
<tr>
<td>Other troubles</td>
<td>10.8</td>
</tr>
</tbody>
</table>

IBS Patients: Their illness experience and unmet needs, International Foundation for Functional Gastrointestinal Disorders (IFFGD); 2009.
Further evaluation revealed that 30% of patients with severe IBS symptoms reported being jobless vs only 5% of those with mild symptoms.

IBS Patients: Their illness experience and unmet needs, International Foundation for Functional Gastrointestinal Disorders (IFFGD); 2009.
Reduction in Productivity Attributed to GI Symptoms of IBS

IBS was associated with a 21% reduction in work productivity, equivalent to working less than 4 days in a 5-day work week.

# Economic Costs Associated with IBS in the US

<table>
<thead>
<tr>
<th>Annual Cost Category</th>
<th>Previous Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>$1.6 to $10.5 billion</td>
</tr>
<tr>
<td>Indirect</td>
<td>As high as $20 billion*</td>
</tr>
<tr>
<td>Total</td>
<td>$30 billion</td>
</tr>
</tbody>
</table>

*Based on costs associated with patients seeking medical attention.

Pathogenesis of IBS

EXTRINSIC FACTORS

Psychological stress, abuse (sexual, physical), smoking, diet

Infection, dysbiosis

Pathogenesis of IBS

EXTRINSIC FACTORS

Psychological stress, abuse (sexual, physical), smoking, diet

Infection, dysbiosis

INTRINSIC FACTORS

Genes

- SNPs, CNVs, indels
- Methylation, acetylation, miRNAs

Gut microbiota

Pathogenesis of IBS

EXTRINSIC FACTORS

Psychological stress, abuse (sexual, physical), smoking, diet

Infection, dysbiosis

INTRINSIC FACTORS

Genes

Gut microbiota

CENTRAL NEUROBIOLOGICAL/BEHAVIORAL INTERMEDIATE PHENOTYPE

Emotional regulation

Visceral sensation/pain modulation

Spinal afferents

GI transit secretion

PERIPHERAL INTERMEDIATE PHENOTYPE

HPA, hypothalamo-pituitary-adrenocortical [system].

Pathogenesis of IBS

EXTRINSIC FACTORS
- Psychological stress, abuse (sexual, physical), smoking, diet
- Infection, dysbiosis

INTRINSIC FACTORS
- Genes
- Gut microbiota

CENTRAL NEUROBIOLOGICAL/BEHAVIORAL INTERMEDIATE PHENOTYPE
- Emotional regulation
- Visceral sensation/pain modulation
- Spinal afferents
- GI transit secretion

PERIPHERAL INTERMEDIATE PHENOTYPE

CLINICAL PHENOTYPE
- Chronic fatigue, depression, anxiety
- Migraine, fibromyalgia
- Chronic abdominal pain or discomfort and altered bowel habits: IBS

Comorbidities Associated with IBS

- 91% of patients with IBS reported ≥1 comorbidity
- Average number reported was 5 (1 mental, 4 physical)
- Anxiety, depression, back pain, agoraphobia, tension headache, insomnia were associated with greater illness and symptom burden

Psychiatric Disorders
- Anxiety, major depression, somatization

Somatic Pain Syndromes
- Chronic fatigue syndrome, chronic pelvic pain, fibromyalgia

GI Disorders
- GERD, dyspepsia

Screening and Diagnosis
Clinical presentation:

- Recurrent abdominal pain and periods of loose stools (symptoms present since patient’s early 20’s)
- Increasing in frequency and severity of attacks over the past 6 months
- Stools are frequently watery (occasionally with mucus)
- Bowel movements 4 to 7 times per day
- Abdominal pain
  - Associated with bloating and gas
  - Exacerbated by eating
  - Relieved with defecation
- Weight loss of 9 lb over the past 3 to 4 months
Case Study #1: Physical Exam

- **Vital signs**
  - HR: 97 bpm
  - RR: 18 breaths/min
  - BP: 126/82 mm Hg

- **CV and pulmonary exam:**
  - Normal

- **Abdominal exam:**
  - Abdomen is flat
  - Bowel sounds are normal
  - Tympany in the upper-left quadrant
  - No organomegaly
  - Mild generalized tenderness

HR, heart rate; RR, respiratory rate; BP, blood pressure; CV, cardiovascular.
Case Study Discussion

- Individual symptoms have limited accuracy
- Alarm features are crucial for guidance
- Role of testing
- Recommended diagnostic tests
Typical Features of IBS

- Loose/frequent stools
- Constipation
- Bloating
- Abdominal cramping, discomfort, or pain

Symptoms:
- Brought on by food intake/specific food sensitivities
- Dynamic over time (change in pain location, change in stool pattern)

**Bloating vs Distention**

- Bloating describes the sensation of increased abdominal pressure and distention describes a change in abdominal girth.
- Pathophysiological mechanisms are likely different, but overlapping.
- Distention may be alleviated by relieving constipation, but the treatment of bloating may require approaches involving sensory modulation.

Available at: http://www.iffgd.org/site/manage-your-health/symptoms-causes/bloating-distension

# Diagnosis of IBS

## Rome III Criteria

1. Symptom onset ≥6 months prior to diagnosis

2. Recurrent abdominal pain or discomfort* ≥3 days/month in the last 3 months with ≥2 of the following:
   - Improvement with defecation
   - Onset associated with a change in stool frequency
   - Onset associated with a change in stool form (appearance)

*Discomfort defined as an uncomfortable sensation not described as pain.

## Subtyping IBS by Predominant Stool Pattern

<table>
<thead>
<tr>
<th>IBS Subtype</th>
<th>Hard or Lumpy Stool Frequency</th>
<th>Loose or Watery Stool Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-C</td>
<td>≥25%</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>IBS-D</td>
<td>&lt;25%</td>
<td>≥25%</td>
</tr>
<tr>
<td>IBS-M</td>
<td>≥25%</td>
<td>≥25%</td>
</tr>
</tbody>
</table>


### ACG Guideline Recommendations for Diagnostic Testing

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine diagnostic testing*</td>
<td>NOT recommended for patients with typical symptoms and no alarm features</td>
</tr>
<tr>
<td>Serologic screening for celiac sprue</td>
<td>Recommended for patients with IBS-D and IBS-M</td>
</tr>
<tr>
<td>Lactose breath testing</td>
<td>Recommended if lactose maldigestion persists despite dietary modification</td>
</tr>
<tr>
<td>Breath testing for SIBO</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Routine colonic imaging</td>
<td>NOT recommended for patients &lt; 50 years of age with typical IBS symptoms and no alarm features</td>
</tr>
<tr>
<td>Colonoscopic imaging</td>
<td>Recommended for IBS patients with alarm features and those &gt; 50 years of age</td>
</tr>
<tr>
<td>Random biopsies</td>
<td>Consider to rule out microscopic colitis if colonoscopy is performed</td>
</tr>
</tbody>
</table>

*CBC, serum chemistries, thyroid function studies, stool for ova and parasites, abdominal imaging.
ACG, American College of Gastroenterology; CBC, complete blood cell count; SIBO, small intestine bacterial growth.
Potential Biomarkers for IBS-D: anti-CdtB and anti-vinculin

Accuracy of Patient-reported GI Symptom Measures

Percentage of patients whose recall deviated ≥2 units from electronic diary data*

Number of stools
Days with fluffy stools
Days abdominal pain
Days with sausage stools
Days with urgency
Worst urgency
Worst abdominal pain
Average abdominal pain
Days with hard, lumpy stools
Average urgency
Days with watery stools

*Diary data was collected close to the time of patients’ experiences and was minimally vulnerable to distortion from forgetting and recall bias.

Case Study #1: Diagnosis

- Diagnostic testing: Results are negative for celiac disease
- Diagnosis: Based upon the patient’s symptoms and the absence of any alarm features, the patient is diagnosed with IBS-D
Red Flags for Organic Conditions Other than IBS

- Fever
- Unexplained weight loss
- Rectal bleeding or melena
- Nocturnal diarrhea
- Unexplained iron-deficiency anemia
- Symptom onset after 50 years of age
- Severe or progressively worsening symptoms
- Family history of organic gastroenterological diseases (eg, colon cancer, celiac disease, or IBD)

IBD, inflammatory bowel disease.
Management of IBS-D
Goals of Treatment

- Improve individual symptoms
- Ameliorate global symptoms
- Prevent complications
- Reduce impact on the individual and society

Case Study #2: 32-year-old man

- **Medical history**
  - Diagnosed with traveler’s diarrhea 2 years ago by PCP
  - Since that time, persistent GI symptoms, including bloating, cramping, and loose and watery stools (3-5 times per day)
  - Bowel function was normal prior to the trip

PCP, primary care provider.
Case Study #2 (cont’d)

- **Treatment history**
  - Increased fiber intake exacerbates symptoms
  - Antidiarrheal medications, useful for fecal urgency and diarrhea, fail to relieve pain and bloating
  - Unresponsive to anticholinergics

- **Additional comments**
  - Patient is frustrated with the lack of effective symptom management
Lack of symptom control/response to conventional therapies is common

- IBS-D in men vs women
- Precipitation of disease by infection
- Newer pharmacologic management strategies
Overview of Treatment Approaches

- Pharmacologic treatment
- Nonpharmacologic approaches
  - Dietary modification
  - Psychological interventions
  - Biofeedback training
Pharmacologic Treatment Options
# Conventional Pharmacotherapies for the Treatment of IBS-D

<table>
<thead>
<tr>
<th>Class (Agents)</th>
<th>Evidence</th>
<th>Efficacy</th>
<th>Most Common AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidiarrheals</strong> (Diphenoxylate hydrochloride/</td>
<td>Very low</td>
<td>Beneficial for diarrhea, but not global symptoms or pain</td>
<td>Constipation</td>
</tr>
<tr>
<td>atropine sulfate, loperamide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antispasmodics</strong> (Dicyclomine hydrochloride,</td>
<td>Low</td>
<td>Some agents offer benefits for global symptoms and pain</td>
<td>Dry eyes/mouth, sedation, constipation</td>
</tr>
<tr>
<td>hyoscyamine sulfate)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse effects

Eluxadoline treatment resulted in more patients reporting a ≥30% reduction in abdominal pain score and a stool-consistency score <5 on ≥50% of the days‡.

‡Represents composite primary efficacy end point.
*P<.05; †P<.001.

Adverse Effects of Treatment with Eluxadoline

- Most commonly observed:

<table>
<thead>
<tr>
<th>AE</th>
<th>Placebo (%)</th>
<th>75 mg Eluxadoline (%)</th>
<th>100 mg Eluxadoline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>2.5</td>
<td>7.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.4</td>
<td>8.1</td>
<td>7.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4.1</td>
<td>5.8</td>
<td>7.2</td>
</tr>
</tbody>
</table>

- Pancreatitis developed in 5 (2 in the 75 mg group and 3 in the 100 mg group) of the 1666 patients in the safety population (0.3%)

Rifaximin Treatment Is Associated in Sustained Reduction of IBS Symptoms Over 12 Weeks

Two weeks of treatment with rifaximin resulted in a greater percentage of patients achieving adequate relief of global IBS symptoms.

**TARGET 3 Trial**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>1st Repeat Treatment</th>
<th>2nd Repeat Treatment</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifaximin (n=328)</td>
<td>Placebo (n=308)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgency</td>
<td>48.5%</td>
<td>39.6%</td>
<td>.0251</td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td>50.3%</td>
<td>42.2%</td>
<td>.0345</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>53.0%</td>
<td>43.8%</td>
<td>.0212</td>
<td></td>
</tr>
<tr>
<td>Stool consistency</td>
<td>45.1%</td>
<td>37.0%</td>
<td>.0241</td>
<td></td>
</tr>
</tbody>
</table>
Safety and Tolerability of Rifaximin

UTI, urinary tract infection; URTI, upper respiratory tract infection

Impact of Alosetron Treatment in Women with Severe IBS-D

Alosetron treatment resulted in improved HRQOL, ability to engage in daily activities, and treatment satisfaction over PBO in women with severe IBS-D.

PBO, placebo; QD, once daily; BID, twice daily.

*P < 0.05; **P < 0.01; ***P < 0.001

## Adverse Effects of Alosetron

<table>
<thead>
<tr>
<th>Most common AEs (%)</th>
<th>Placebo (N=176)</th>
<th>Alosetron 0.5 mg qd (N=175)</th>
<th>1 mg qd (N=172)</th>
<th>1 mg bid (N=176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>5</td>
<td>9</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Headaches</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

### AEs for symptoms of potential ischemic colitis* (%)

<table>
<thead>
<tr>
<th>AEs for symptoms of potential ischemic colitis* (%)</th>
<th>Placebo (N=176)</th>
<th>Alosetron 0.5 mg qd (N=175)</th>
<th>1 mg qd (N=172)</th>
<th>1 mg bid (N=176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Bloody diarrhea or rectal bleeding</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Worsening of abdominal pain</td>
<td>&lt;1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Bloody diarrhea or rectal bleeding and worsening of abdominal pain</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*In 43/44 patients, these events were associated with other medical conditions.

Alosetron: Black Box Warnings

- Infrequent, but serious GI adverse reactions (eg, ischemic colitis, serious complications of constipation) have been reported; some have resulted in hospitalization and, rarely, blood transfusion, surgery, or death.

- Prescribing physicians must be enrolled in Prescribing Program for Lotronex.

- Indicated only for women with severe IBS-D that have not responded adequately to conventional therapy.

- Discontinue immediately in patients who develop constipation or symptoms of ischemic colitis; do not resume in those who develop ischemic colitis.
Case Study #2: Diagnosis and Management

- **Diagnosis:** Patient is diagnosed with post-infectious IBS-D based upon symptoms and clinical history
- **Management:** Because the patient has not responded well to over-the-counter therapies, he is prescribed a 2-week course of rifaximin
- **Follow-up:** 3 months following the end of the treatment course
Nonpharmacological Management of IBS-D
Effects of Fiber Supplementation on Symptoms of IBS

- Soluble fiber supplementation is effective for improving global IBS symptoms\(^1\)
- Recommended fiber intake among patients with IBS is difficult to achieve and sustain\(^2\)

### Table: Risk Ratio

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soltoft, 1976</td>
<td>1.20 (0.70, 2.04)</td>
<td></td>
</tr>
<tr>
<td>Manning, 1977</td>
<td>0.86 (0.42, 1.74)</td>
<td></td>
</tr>
<tr>
<td>Kruis, 1986</td>
<td>1.04 (0.78, 1.37)</td>
<td></td>
</tr>
<tr>
<td>Lucey, 1987</td>
<td>0.75 (0.20, 2.75)</td>
<td></td>
</tr>
<tr>
<td>Rees, 2005</td>
<td>0.86 (0.39, 1.91)</td>
<td></td>
</tr>
<tr>
<td>Bijkerk, 2009</td>
<td>0.84 (0.71, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0.90 (0.79, 1.03)</td>
<td></td>
</tr>
<tr>
<td>Ritchie, 1979</td>
<td>0.60 (0.37, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Longstreth, 1981</td>
<td>1.15 (0.69, 1.92)</td>
<td></td>
</tr>
<tr>
<td>Arthurs, 1983</td>
<td>0.75 (0.39, 1.43)</td>
<td></td>
</tr>
<tr>
<td>Nigam, 1984</td>
<td>0.63 (0.45, 0.88)</td>
<td></td>
</tr>
<tr>
<td>Prior, 1987</td>
<td>0.89 (0.75, 1.05)</td>
<td></td>
</tr>
<tr>
<td>Jalihal, 1990</td>
<td>0.55 (0.11, 2.59)</td>
<td></td>
</tr>
<tr>
<td>Bijkerk, 2009</td>
<td>0.88 (0.74, 1.04)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0.83 (0.73, 0.94)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Additional details regarding study weight calculations available in the original publication.

CI, confidence interval.

Implementation of a Low-FODMAP Diet for IBS

**Teach Patients**
- Assistance from a trained dietician is ideal
- Alternatively, vetted books, web-based resources, and mobile apps may be employed

**Gauge Response**
- 2 to 4 week period
- Bloating and abdominal pain are most likely to respond
- Diarrhea is more likely to improve than constipation

**Reintroduce Foods**
- Foods with individual FODMAPs should be reintroduced in a stepwise manner for responders

- The full low-FODMAP diet is not intended to last a lifetime
- The low-FODMAP diet is not intended for people without GI symptoms

FODMAP, fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols.
Low FODMAP diet vs *Lactobacillus rhamnosus* GG in IBS

A significant reduction in the IBS-SSS was observed in the low FODMAP and *L. rhamnosus* GG groups compared to the normal Danish/Western diet group at Week 6 (*P* < .01)

IBS-SSS, IBS severity score system.

Gluten-Free Diet in Patients with IBS-D

BM, bowel movement; BSFS, Bristol Stool Form Scale; GCD, gluten-containing diet; GFD, gluten-free diet.

Treatment with *Bifidobacterium infantis* Capsule Reduces Symptoms of IBS

- Abdominal pain/discomfort: -0.29
- Bloating: -0.33
- Distension: -0.29
- Urgency: -0.45
- Incomplete evacuation: -0.39
- Straining: -0.36

Overall: * -0.36

Impact of Psychological Intervention on IBS Symptoms

- Red shading indicates P<0.05

- Interventions examined included a range of therapies:
  - Cognitive
  - Cognitive behavioral
  - Relaxation
  - Psychodynamic
  - Mindfulness
  - Gut-directed hypnosis

### Study Hedges’s g and 95% CI

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges’s g (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchard 1992a</td>
<td>0.606 (-0.25,1.47)</td>
</tr>
<tr>
<td>Blanchard 1992b</td>
<td>0.427 (-0.07,0.92)</td>
</tr>
<tr>
<td>Blanchard 1993</td>
<td>1.029 (0.04,2.02)</td>
</tr>
<tr>
<td>Blanchard 2007a</td>
<td>0.138 (-0.23,0.50)</td>
</tr>
<tr>
<td>Craske 2011</td>
<td>0.201 (-0.46,0.86)</td>
</tr>
<tr>
<td>Drossman 2003</td>
<td>0.424 (0.13,0.72)</td>
</tr>
<tr>
<td>Galovski 1998</td>
<td>1.565 (0.30,2.83)</td>
</tr>
<tr>
<td>Greene 1994</td>
<td>1.490 (0.53,2.45)</td>
</tr>
<tr>
<td>Heymann-Monnikes 2000</td>
<td>1.128 (0.29,1.96)</td>
</tr>
<tr>
<td>Hunt 2009</td>
<td>0.412 (0.12,0.94)</td>
</tr>
<tr>
<td>Jarrett 2009</td>
<td>0.947 (0.53,1.37)</td>
</tr>
<tr>
<td>Kapchuck 2008</td>
<td>0.671 (0.37,0.98)</td>
</tr>
<tr>
<td>Keefer 2001</td>
<td>0.102 (-0.91,1.12)</td>
</tr>
<tr>
<td>Kennedy 2006</td>
<td>0.649 (0.30,1.00)</td>
</tr>
<tr>
<td>Lackner 2008</td>
<td>1.533 (0.92,2.14)</td>
</tr>
<tr>
<td>Lähmann 2010</td>
<td>1.164 (0.69,1.63)</td>
</tr>
<tr>
<td>Lindfors 2012a</td>
<td>0.488 (0.07,0.90)</td>
</tr>
<tr>
<td>Lindfors 2012b</td>
<td>0.426 (-0.14,0.99)</td>
</tr>
<tr>
<td>Ljotsson 2010</td>
<td>1.175 (0.72,1.63)</td>
</tr>
<tr>
<td>Ljotsson 2011a</td>
<td>0.397 (0.11,0.69)</td>
</tr>
<tr>
<td>Ljotsson 2011b</td>
<td>0.760 (0.20,1.32)</td>
</tr>
<tr>
<td>Mahvi-Shirazi 2012</td>
<td>1.997 (1.33,2.67)</td>
</tr>
<tr>
<td>Moss-Morris 2010</td>
<td>0.927 (0.03,1.02)</td>
</tr>
<tr>
<td>Neff 1987</td>
<td>1.014 (0.10,1.93)</td>
</tr>
<tr>
<td>Payne 1995</td>
<td>1.541 (0.27,2.81)</td>
</tr>
<tr>
<td>Ringstrom 2010</td>
<td>0.273 (-0.05,0.60)</td>
</tr>
<tr>
<td>Roberts 2006</td>
<td>0.605 (0.16,1.05)</td>
</tr>
<tr>
<td>Robinson 2006</td>
<td>1.121 (0.13,0.37)</td>
</tr>
<tr>
<td>Sanders 2007</td>
<td>1.347 (0.30,2.39)</td>
</tr>
<tr>
<td>Shinonuki 2010</td>
<td>-0.843 (-1.81,-0.07)</td>
</tr>
<tr>
<td>Tchakchak 2003</td>
<td>0.339 (-0.19,0.86)</td>
</tr>
<tr>
<td>Van Der Veek 2007</td>
<td>0.405 (0.01,0.80)</td>
</tr>
<tr>
<td>Van Dulmen 1996</td>
<td>0.363 (0.21,0.94)</td>
</tr>
<tr>
<td>Vollmer 1998</td>
<td>1.267 (0.36,2.17)</td>
</tr>
<tr>
<td>Zernicke 2012</td>
<td>0.490 (0.07,0.91)</td>
</tr>
</tbody>
</table>

Long-term Management
Patient Education and Support

- Providing education on IBS-D and options for treatment
- Ensuring treatment adherence
- Managing medication side effects
- Setting patient expectations
Patient Misconceptions Regarding the Natural History of IBS

Fear of Symptoms Impacts QOL in Patients with IBS: IBSOS Study

IBSOS, irritable bowel syndrome outcome study.
Additional IBS Resources

- International Foundation for Functional Gastrointestinal Disorders

- Institute for Functional Medicine
  - [https://www.functionalmedicine.org/](https://www.functionalmedicine.org/)

- Irritable Bowel Syndrome Association

- IBS Page
IBS-D is a highly prevalent functional bowel disorder that imposes a tremendous burden due to its pervasive negative impact on the physical, social, and economic well-being of affected individuals.

Diagnosis is based upon a thorough clinical history and physical examination, in conjunction with application of the Rome III criteria.

Treatment options include several pharmacologic and non-pharmacologic strategies, which have demonstrated efficacy at reducing symptoms of IBS-D and improving patient QOL.

Long-term management should be individualized and include education and support to foster patient understanding of the disease, ensure treatment adherence, and guide therapeutic expectations.
Q & A
Thank You!
Back up slides
# IBS-D Is Associated with Lower Disease-Specific QOL vs IBS-C

<table>
<thead>
<tr>
<th>IBS-QOL Subscale</th>
<th>IBS-C (n = 54)</th>
<th>IBS-D (n = 56)</th>
<th>IBS-M (n = 121)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interference with activity</td>
<td>82.3</td>
<td>59.6</td>
<td>61.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Social reaction</td>
<td>80</td>
<td>59.6</td>
<td>61.6</td>
<td>.0082</td>
</tr>
<tr>
<td>Food avoidance</td>
<td>61.1</td>
<td>45</td>
<td>47.2</td>
<td>.0203</td>
</tr>
<tr>
<td>Relationships</td>
<td>84.7</td>
<td>75.4</td>
<td>73.3</td>
<td>.0304</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>69.2</td>
<td>57.1</td>
<td>58</td>
<td>.06</td>
</tr>
<tr>
<td>Health worry</td>
<td>64.3</td>
<td>60.9</td>
<td>57.3</td>
<td>.28</td>
</tr>
<tr>
<td>Sexual</td>
<td>73.9</td>
<td>74.6</td>
<td>68.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Body image</td>
<td>69.2</td>
<td>66</td>
<td>64.9</td>
<td>.631</td>
</tr>
<tr>
<td>Total</td>
<td>74.5</td>
<td>61.6</td>
<td>63</td>
<td>.0105</td>
</tr>
</tbody>
</table>

Potential Pathophysiological Mechanisms Underlying Bloating and Distention

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Evidence to Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas excess</td>
<td>Occasional cause of bloating, unlikely to be responsible in the majority of patients</td>
</tr>
<tr>
<td>Gas handling</td>
<td>Patients demonstrate normal gas volumes, but abnormal intestinal gas handling</td>
</tr>
<tr>
<td>Sensory dysfunction</td>
<td>Visceral <em>hyposensitivity</em> is linked to distention, whereas <em>hypersensitivity</em> is linked to bloating but not necessarily distention</td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>Impact of motility patterns or transit time is uncertain; bloating is seen with IBS-D and IBS-C, which are associated with rapid and slow transit, respectively</td>
</tr>
<tr>
<td>Abnormal anterior wall muscular activity</td>
<td>Suggested muscle weakness, and impaired viscerosomatic reflexes and abdominal-wall dystony with bloating in IBS</td>
</tr>
<tr>
<td>Carbohydrate intolerance and altered gut flora</td>
<td>Small bowel bacterial overgrowth is not consistently observed in IBS, but may account for symptoms in some patients</td>
</tr>
</tbody>
</table>

Celiac disease (CD) is an autoimmune GI condition with symptoms similar to IBS

CD, diagnosed by positive serology and biopsy, is more prevalent among IBS vs non-IBS populations (although conflicting data exists)

The frequency of abnormal IgA-class AGAs in suspected IBS cases raises the possibility that gluten may cause symptoms in sensitive individuals, even in the absence of developed CD

<table>
<thead>
<tr>
<th>Diagnostic Parameter</th>
<th>Pooled OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive IgA-class AGAs</td>
<td>3.40 (1.62-7.13)</td>
</tr>
<tr>
<td>Positive EMAs or tTGA</td>
<td>2.94 (1.36-6.35)</td>
</tr>
<tr>
<td>Biopsy-proved celiac disease</td>
<td>4.34 (1.78-10.6)</td>
</tr>
</tbody>
</table>

AGA, anti-gliadin antibody; EMA, endomysial antibody; IgA, immunoglobulin A; OR, odds ratio; tTGA, tissue transglutaminase.
General Approach to Treatment with Probiotics

- Quality and consistency may be questionable
  - Shelf-life limitations
  - Lack of government-sanctioned quality-control standards

- Clinical trial data in IBS-D are limited, contradictory, strain-dependent and are derived from small patient samples
  - VSL#3® double-blind, placebo-controlled study; 8-week treatment (n=25)
    - Results: no improvement of small-bowel or colonic transit; no effect on bowel dysfunction, abdominal pain, flatulence, or urgency

- Potential benefits must be weighed against economic costs

# Emerging Food-based Approaches to IBS Management

<table>
<thead>
<tr>
<th>Functional Foods</th>
<th>Medical Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health benefits beyond basic nutrition</strong> (eg, disease prevention and/or treatment)</td>
<td><strong>FDA category for specific dietary management of a disease or condition</strong></td>
</tr>
<tr>
<td>Includes the following:</td>
<td><strong>Given under physician supervision, but do not require a prescription</strong></td>
</tr>
<tr>
<td>– Conventional foods with bioactive components</td>
<td><strong>Must comply with the following:</strong></td>
</tr>
<tr>
<td>– Foods enriched or fortified with bioactive food compounds</td>
<td>– FDA-labeling requirements</td>
</tr>
<tr>
<td>– Synthesized food ingredients that provide or are precursors to compounds with health benefits</td>
<td>– Ingredients are known and comply with FDA regulations</td>
</tr>
</tbody>
</table>

FDA, US Food and Drug Administration.

# Biofeedback in the Treatment of IBS

<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic stethoscope to provide auditory feedback to modify colonic motility</td>
<td>Symptom improvement in 5/5 patients; results not subsequently replicated</td>
</tr>
<tr>
<td>Rectosigmoid area balloon probe used to provide visual feedback on bowel motility</td>
<td>14/21 patients learned the technique; no clinical correlations were shown</td>
</tr>
<tr>
<td>Forehead EMG biofeedback and thermal biofeedback as nonspecific relaxation training techniques to counteract the effects of stress in patients with IBS</td>
<td>Symptoms improved in ~50% of 40 patients with refractory IBS in 3 months; no control group or long-term follow-up</td>
</tr>
<tr>
<td>Combined progressive muscle relaxation, thermal biofeedback, cognitive therapy, and education</td>
<td>No improvement over an attention-placebo condition</td>
</tr>
</tbody>
</table>


EMG, electromyography.
Psychological Interventions for the Treatment of IBS

- Types of psychological intervention
  - Cognitive therapy
  - Cognitive behavioral therapy
  - Relaxation
  - Psychodynamic
  - Mindfulness
  - Gut directed hypnosis

- Systematic review and meta-analysis suggests significant improvement of symptoms and psychological well-being