Digesting the Facts in IBS: From Early Diagnosis to Effective Treatment Options

March 20, 2014
Houston, Texas

Educational Partner:

CME INCITE
Session 4: Digesting the Facts in IBS: From Early Diagnosis to Effective Treatment Options

**Learning Objectives**

1. Evaluate the necessity of diagnostic testing in individual patients prior to diagnosis of irritable bowel syndrome (IBS).
2. Choose appropriate nonpharmacologic or pharmacologic therapies to aid patients with IBS.
3. Manage the symptoms of IBS over the long term through effective treatment strategies.

**Faculty**

**Brian E. Lacy, MD, PhD**  
Professor of Medicine  
Geisel School of Medicine at Dartmouth  
Hanover, New Hampshire  
Chief, Section of Gastroenterology and Hepatology  
Dartmouth-Hitchcock Medical Center  
Lebanon, New Hampshire

Dr Brian Lacy is the current professor of medicine at the Geisel School of Medicine at Dartmouth and section chief of the division of gastroenterology and hepatology at the Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

Dr Lacy’s clinical and basic science research interests focus on disorders of gastrointestinal motility, with an emphasis on irritable bowel syndrome, dyspepsia, gastroparesis, acid reflux disease, constipation, intestinal pseudoobstruction, achalasia, and visceral pain. He is the author or coauthor of more than 85 peer reviewed articles and the author or coauthor of numerous textbook chapters on gastrointestinal motility disorders and functional bowel disorders. Dr Lacy is a reviewer for a number of scientific journals and is a member of the American College of Gastroenterology, the American Gastroenterology Association, the American Motility Society, and the Rome committee. Dr Lacy is the coauthor of *Healing Heartburn*: a book for the general public on acid reflux disease, the author of *Making Sense of IBS*: a book for the general public on irritable bowel syndrome, and the editor and author of *Curbside Consultations in IBS: 49 Clinical Questions*.

Dr Lacy earned his doctorate in cell biology from Georgetown University, Washington, DC, and his medical degree from the University of Maryland, Baltimore. Dr Lacy was a resident in internal medicine at the Dartmouth-Hitchcock Medical Center, where he continued his training as chief resident and then as a fellow in gastroenterology. He is board certified in gastroenterology.

**Spencer Dorn, MD, MPH, MHA**  
Assistant Professor of Medicine  
Vice Chief of Gastroenterology  
Division of Gastroenterology and Hepatology  
University of North Carolina at Chapel Hill  
Chapel Hill, North Carolina

Dr Spencer Dorn is assistant professor of medicine at the University of North Carolina and vice chief of the UNC Division of Gastroenterology and Hepatology. Administratively, he works to improve quality of care, operational efficiency, and patient experiences. Academically, he conducts clinical trials for functional gastrointestinal (GI) disorders, performs health services research, and examines the impact of health policy and regulations on gastroenterology. His clinical practice focuses on functional GI and motility disorders.
Dr Dorn graduated with highest distinction from the University of Michigan and summa cum laude from SUNY at Brooklyn College of Medicine. He earned a master of public health (epidemiology) and later a master of healthcare administration (health care management and policy) from UNC.

Dr Dorn completed his internal medicine training at Brigham and Women’s Hospital, where he was a clinical fellow at Harvard Medical School. He subsequently trained at UNC as a National Institutes of Health post doctoral research fellow in digestive diseases epidemiology and functional GI disorders, and later as a clinical fellow in gastroenterology and hepatology.

**Faculty Financial Disclosure Statements**

The presenting faculty have reported the following:

Brian E. Lacy, MD, PhD, is on the scientific advisory board of Ironwood Pharmaceuticals, Forest Laboratories, and Takeda.

Spencer Dorn, MD, MPH, MHA, receives research support from Forest Labs, Lexicon Pharmaceuticals, Salix Pharmaceuticals, and Synergy Pharmaceuticals.

**Education Partner Financial Disclosure Statement**

The content collaborators at CME Incite have reported the following:

Rose O’Connor, PhD, has no financial relationships to disclose.

Monique Pond, PhD, has no financial relationships to disclose.

Monique Johnson, MD, CCMEP, has no financial relationships to disclose.

**Suggested Reading List**


SESSION 4
12:30–1:45pm
Digesting the Facts in IBS: From Early Diagnosis to Effective Treatment Options

SPEAKERS
Spencer Dorn, MD, MPH, MHA
Brian E. Lacy, MD, PhD, FACG

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Spencer Dorn, MD, MPH, MHA, has done research support for Forest Laboratories, Lexicon Pharmaceuticals, Salix Pharmaceuticals, and Synergy Pharmaceuticals.
► Brian E. Lacy, MD, PhD, FACG, serves on the scientific advisory board for Ironwood Pharmaceuticals, Forest Laboratories, and Takeda.

Off-Label/Investigational Discussion
► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Drug List
► Lotronex
► Elavil, Tryptizol, Laroxyl, etc
► Celoxa
► Nortomar, Pertofane
► Adipin, Silenor, Sinequan, etc
► Prozac, Sarafem, Fontex, etc
► Antideprin, Deprimin, Deprinol, etc
► Lispress
► Amitiza
► Colofac
► Paxil, Aropax, Seroxat, Pexeva, etc
► Xifaxan
► Alosetron
► Amtriptyline
► Citalopram
► Desipramine
► Doxepin
► Fluoxetine
► Imipramine
► Liacidozide
► Lubiprostone
► Mebeverine
► Paroxetine
► Rifaximin

Learning Objectives
► Evaluate the necessity of diagnostic testing in individual patients prior to diagnosis of irritable bowel syndrome (IBS)
► Choose appropriate nonpharmacologic or pharmacologic therapies to aid patients with IBS
► Manage the symptoms of IBS over the long term through effective treatment strategies

Today’s Agenda
► Fact or Fiction?
  Select 1 for Fact
  Select 2 for Fiction
► Discussion of Case Study 1: “Diane”
► Discussion of Case Study 2: “Mary”

Audience participation will enhance this program.

Rome III Criteria for IBS
Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with ≥2 of the following:
► Improvement with defecation
► Onset associated with a change in frequency of stool
► Onset 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

Consider IBS a Diagnosis of Exclusion, %

IBS Experts (n=27)

Community Clinicians (n=281)

Clinicians who believed IBS was a diagnosis of exclusion ordered 1.6 times more tests and spent $364 more on diagnostic tests per patient (P<0.0001).

Positive IBS Diagnosis May Reduce Diagnostic Testing and Resource Utilization

Alarm Features for IBS

- Refractory or worsening abdominal symptoms
- Older patient (≥50 years; ≥45 years if African-American)
- Blood in stools
- Anemia
- Weight loss (unintentional)
- Anorexia
- Family history of organic gastrointestinal disease

If present, investigate and treat appropriately; colonoscopy may be indicated.

Yield of Colonoscopy in IBS

<table>
<thead>
<tr>
<th>Lesion</th>
<th>IBS Patients n=466 (%)</th>
<th>Controls n=451 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomas</td>
<td>36 (7.7)</td>
<td>118 (26.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperplastic polyps</td>
<td>39 (8.4)</td>
<td>52 (11.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>IBD</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>7 (1.5)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Microscopic colitis was more common in a subset of patients with IBS who were ≥45 years (2.3%).

Histologic Findings in IBS Patients and Controls; Populations Not Matched for Age or Gender

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</tr>
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</table>

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>0.51-0.96</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>8.7</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>

Bulking Agents for IBS-C: Systematic Review and Meta-analysis

<table>
<thead>
<tr>
<th>RCTs</th>
<th>N</th>
<th>Response* Fiber</th>
<th>Placebo</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>

*Response was defined as improvement in Abdominal Discomfort (FDDQL), %

Heterogeneity with ispaghula
No evidence of publication bias
4 out of 5 bran studies of poor quality

CI, confidence interval; NNT, number needed to treat; RCT, randomized, controlled trial; RR, relative risk.

Bifidobacterium animalis DN-173 010 for IBS-C

<table>
<thead>
<tr>
<th>Week 3</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>48*</td>
<td>57</td>
</tr>
</tbody>
</table>

Stool frequency increased in patients with <3 bowel movements/week

*P<0.003

Probic: fermented milk product (Activia™) containing B. animalis 1.25 x 10^10 CFU per serving, Streptococcus thermophilus, and Lactobacillus bulgaricus

CFU, colony forming unit; FDDQL, Functional Digestive Disorders QoL Questionnaire.
What Are FODMAPs?

**Fermentable Oligo-, Di-, Monosaccharides And Polyols**

- Excess Fructose: Honey, apples, pears, peaches, mangos, fruit juice, dried fruit
- Lactose: Milk, ice cream, cheese, whey, curd
- Fructans: Wheat (large amounts), rye (large amounts), onions, leeks, zucchini
- Sorbitol: Apricots, peaches, artificial sweeteners and gums
- Raffinose: Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes


Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes

Sorbitol

Raffinose

Antispasmodics for IBS

- 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)


Global Relief of IBS Symptoms With TCAs/SSRIs

- TCAs: 9 studies (N=319 drug vs 256 control)
  - Imipramine, desipramine, amitriptyline, doxepin*: doses 10-150 mg
  - Meta-analysis favors treatment
- SSRIs: 5 studies (N=113 drug vs 117 control)
  - Fluoxetine, paroxetine, citalopram*: dose 10-40 mg
  - Meta-analysis favors treatment


*These agents are not currently FDA approved for IBS.

SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Psychological Therapies for IBS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trials</th>
<th>N</th>
<th>RR 95% CI</th>
<th>NNT 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive behavior therapy</td>
<td>7</td>
<td>491</td>
<td>0.60</td>
<td>3</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>5</td>
<td>234</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Dynamic psychotherapy</td>
<td>2</td>
<td>273</td>
<td>0.60</td>
<td>3.5</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>2</td>
<td>40</td>
<td>0.48</td>
<td>2</td>
</tr>
</tbody>
</table>


Alosetron: Therapeutic Gain for IBS-D

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Female, %</th>
<th>Response: Alosetron, %</th>
<th>Response: Placebo, %</th>
<th>Therapeutic Gain, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camilleri1</td>
<td>370</td>
<td>53</td>
<td>60</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Camilleri2</td>
<td>647</td>
<td>100</td>
<td>41</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Camilleri3</td>
<td>626</td>
<td>100</td>
<td>43</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Lembo</td>
<td>801</td>
<td>100</td>
<td>73</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td>Jones</td>
<td>623</td>
<td>100</td>
<td>58</td>
<td>48</td>
<td>10</td>
</tr>
</tbody>
</table>

*Comparison mebeverine† instead of placebo.
†Mebeverine not available in the US.


Improvements in IBS Symptom Scores: Low FODMAP vs Control Diet

*P≤0.001
†P<0.05
Alosetron for IBS-D

- Female patients with chronic, severe IBS-D who failed other treatments
  - Dose: 0.5-1.0 mg QD to BID
  - Patient education regarding possible serious adverse effects of severe constipation or ischemic colitis
    - 0.95 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 of therapy
  - Prescribing program mandated by FDA
    - Requires patient to sign attestation form

BID, twice a day; QD, once a day.

Rifaximin*: Most Extensively Studied Antibiotic for IBS

- Not systemically absorbed
- Doses studied for IBS: 400 mg BID to 550 mg TID
- Primary adverse effects include headache, abdominal pain, and upper respiratory tract infection

*This agent is not currently FDA approved for IBS.

PEG for IBS-C

- 139 adults with IBS-C were randomized to placebo or PEG 3350 plus electrolytes (PEG 3350+E)
- During Week 4 of treatment, PEG improved number of SBMs (P<0.0001) but not pain in IBS-C patients

SBM, spontaneous bowel movement; PEG, polyethylene glycol.

Efficacy of Linaclotide in Patients With IBS-C

- N=800 IBS-C patients who completed 12 or 16 weeks of a placebo-controlled Phase 3 trial; patients enrolled in the extension study all received lubiprostone 8 µg BID
- *P<0.0001 for linaclotide patients vs placebo patients (ANCOVA).
- †P<0.001 for linaclotide/linaclotide patients vs linaclotide/placebo patients (ANCOVA).

ANCOVA, analysis of covariance; RW, randomized withdrawal.
**Linaclotide Phase 3 IBS-C Trial: Abdominal Pain Over 26 Weeks**

**Importance of Patient-Provider Relationship**

- IBS patients who received placebo, augmented with empathetic HCP care reported significantly better outcomes than patients receiving placebo with limited HCP interactions
  - Improvements in
    - Global
    - Adequate relief
    - Symptom severity
    - QoL

59% of IBS patients receiving only placebo and warm, empathetic care reported a decrease in symptom severity score at 6 weeks.


QoL, quality of life.

**Partnering With Patients to Improve Treatment Adherence and Overall Outcomes**

- Identify patients likely to have poor adherence
- Provide clear instruction to simplify medication regimen
- Listen and partner with patient to customize regimen
- Reinforce desirable behaviors at follow-up visits

A good patient-physician relationship can improve adherence to treatment and patient satisfaction.

INTRODUCING DIANE

**What should be our first course of action?**

**Which treatment would you recommend for Diane?**
How should we manage Diane’s case over the long term?

INTRODUCING MARY

Was it necessary to perform these tests before diagnosing Mary with IBS?

Since Mary’s diagnosis is IBS-D, which treatment would you offer her first?

How should we manage Mary’s case over the long term?

Key Takeaways
- Diagnose IBS in the absence of diagnostic test results in patients without alarm features
- Low-FODMAP diet, probiotics, psychological therapy all have clinical efficacy data in IBS
  - Linaclotide and lubiprostone are FDA approved for IBS-C
  - Alosetron is FDA approved for women with IBS-D
- Strategies to successfully manage symptoms of IBS over the long term include
  - Regular assessment of IBS symptom response
  - Adjustment of treatment strategy, if necessary
  - Development of patient-physician partnership
  - Aim to improve treatment adherence and patient satisfaction