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

March 26, 2014
Anaheim, California

Educational Partner:

CME • INCITE
Session 1: 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, does not have anything to disclose.
Monique Pond, PhD, does not have anything to disclose.
Monique Johnson, MD, CCMEP, does not have anything to disclose.

Suggested Readings


SESSION 1
7:45–9am
Digesting the Facts in IBS: From Early Diagnosis to Effective Treatment Options

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

Drug List
- Lotronex
- Elavil, Tryptizol, Laroxyl, etc
- Celexa
- Norpramin, Pertofane
- Adapin, Silenor, Sinequan, etc
- Prozac, Sarafem, Fontex, etc
- Antideprim, Deprinmin, Deprinol, etc
- Linzess
- Amitiza
- Colofac
- Paxil, Aropax, Seroxat, Pexeva, etc
- Xifaxan
- Alosetron
- Amiptyline
- Citalopram
- Desipramine
- Doxepin
- Fluoxetine
- Imipramine
- Linazolidide
- Lubiprostone
- Mebeverine
- Paroxetine
- Rifaximin

Learning Objectives
- Evaluate the necessity of diagnostic testing in individual patients prior to the 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”

Presenter Disclosure Information
The following relationships exist related to this presentation:
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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.

FACT OR FICTION?
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


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-D who were ≥45 years (2.3%).


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>28</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>

Pretest Probability of Organic Disease1


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

<table>
<thead>
<tr>
<th>RCTs</th>
<th>N</th>
<th>Response*</th>
<th>RR of Unimproved Symptoms (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fiber</td>
<td>Placebo</td>
</tr>
<tr>
<td>Overall</td>
<td>12</td>
<td>591</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43%</td>
<td>0.87 (0.76-1.0)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>321</td>
<td>48%</td>
</tr>
<tr>
<td>Ispaghula</td>
<td>6</td>
<td>36%</td>
<td>0.78 (0.63-0.96)</td>
</tr>
<tr>
<td>Bran</td>
<td>6</td>
<td>221</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.02 (0.82-1.27)</td>
<td></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.

**Bifidobacterium animalis**

DN-173 010 for IBS-C

<table>
<thead>
<tr>
<th>Week</th>
<th>Probiotic (n=135)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 3</td>
<td>48 ± 76</td>
<td>57 ± 76</td>
</tr>
<tr>
<td>Week 6</td>
<td>65 ± 76</td>
<td>63 ± 76</td>
</tr>
</tbody>
</table>

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

*P=0.003

**What Are FODMAPs?**

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

- **Excess Fructose**
- **Lactose**
- **Fructans**
- **Sorbitol**
- **Raffinose**

Honey, apples, pears, peaches, mangoes, fruit juice, dried fruit

Milk, ice cream, cheese, whey, curd

Wheat (large amounts), rye (large amounts), onions, leeks, zucchini

Apricots, peaches, artificial sweeteners and gums

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

**IBS Symptoms Exacerbated by Fructose and Fructans**

- **FOcMAP + Fructose**
- **FOcMAP + Fructans**
- **FOcMAP + Mix FODMAP alone**

**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

**Global Relief of IBS Symptoms With TCAs/SSRIs**

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  - Imipramine, desipramine, amitriptyline, doxepin*; doses 10-150 mg
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- SSRIs: 5 studies (N=113 drug vs 117 control)
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  - Meta-analysis favors treatment

TCAs have more analgesic properties and SSRIs efficacy is most likely in patients with significant anxiety/depression.
Psychological Therapies for IBS

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>0.43-0.87</td>
<td>2-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relaxation training</td>
<td>5</td>
<td>234</td>
<td>0.82</td>
</tr>
<tr>
<td>0.63-1.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dynamic psychotherapy</td>
<td>2</td>
<td>273</td>
<td>0.60</td>
</tr>
<tr>
<td>0.39-0.90</td>
<td>2-25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>2</td>
<td>40</td>
<td>0.48</td>
</tr>
<tr>
<td>0.26-0.87</td>
<td>1.5-7</td>
<td></td>
<td></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>Lembo4</td>
<td>801</td>
<td>100</td>
<td>73</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td>Jonas5</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.

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

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

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
Effect of Lubiprostone on IBS-C: Patients With Follow-up Over 52 Weeks

Mean SBM Frequency per Month

<table>
<thead>
<tr>
<th>Month of Treatment</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/L Group (n=261)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>L/P/L Group (n=80)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P/L Group (n=179)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>


N=520 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.

SBM, spontaneous bowel movement.

Efficacy of Linaclotide in Patients With IBS-C

Mean Change From Baseline +/- SEM

<table>
<thead>
<tr>
<th>Weeks</th>
<th>BL</th>
<th>Linaclotide 290 µg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>-0.50</td>
<td>-0.50</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-0.75</td>
<td>-0.75</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>-1.00</td>
<td>-1.00</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>-1.25</td>
<td>-1.25</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>-1.50</td>
<td>-1.50</td>
</tr>
</tbody>
</table>


[⁎P<0.001 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.

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.


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

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.


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?

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