Evidence-Based Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation: Stepping Up Therapy to Improve Outcomes

SPEAKER
Philip Schoenfeld, MD, MSEd, MSc

12:30 – 1:30 PM

Disclosures
This session is supported by independent educational grants from Allergan and Ironwood Pharmaceuticals, Inc. and Salix Pharmaceuticals, Inc.

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Educational Objectives
- Recognize typical symptoms of IBS and CIC and differentiate them from other common GI disorders
- Identify patients with suspected IBS/CIC with alarm symptoms who require further diagnostic investigation
- Identify lack of utility of most diagnostic testing in patients with suspected IBS/CIC, appropriateness of making a proactive diagnosis based on symptoms, practical strategies for educating patients about their disorder, and importance of initiating treatment at initial visit
- Utilize OTC therapies and FDA-approved prescription therapies based on RCT data and evidence-based guidelines

Syllabi/slides for this program are a supplement to the live CME session and are not intended for other purposes.
### Patient Case: Elizabeth

**Does she have post-infectious IBS?**

**Does she have any symptoms that would trigger a colonoscopy?**

(i.e., does she have any danger or alarm signs)

- Weight loss: Negative
- Hematochezia: Negative
- Nocturnal Diarrhea: Negative
- No family history of colon cancer, celiac disease, or Crohn’s disease
- Vegan diet. Does drink alcohol.

#### Symptom Description

- **21 years old**
- Complains of intermittent diarrhea and cramping for 1 year.
- Bloating after most meals.
- Symptoms started shortly after getting “stomach flu” after visiting Cancun on Spring Break.

**Does she have post-infectious IBS?** **PROBABLY**

**Does she have any symptoms that would trigger a colonoscopy?** (i.e., does she have any danger or alarm signs) **NO**

**What diagnostic tests are indicated?**

- Work-Up for Infectious Diarrhea, CBC, and C-reactive protein

**What if Elizabeth had these symptoms for many years? How would that alter use of diagnostic tests or treatment?**

Only needs CBC and C-reactive protein.

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Defining Irritable Bowel Syndrome (IBS) and Chronic Constipation

- **IBS:** Abdominal pain or discomfort in association with altered bowel habits for at least 3 months.¹
- **Chronic Constipation:** Unsatisfactory defecation characterized by infrequent stools, difficult stool passage or both²
  - Straining, hard/lumpy stools, prolonged time to stool, incomplete evacuation, or need for manual maneuvers


IBS is a disorder of colonic motility

It is NOT a diagnosis of exclusion

Your initial approach: education and diet changes and over-the-counter (OTC) medicines!

Educating the Patient: IBS is Due to Colonic Dysmotility

Altered bowel function is due to colonic dysmotility

Abdominal discomfort is due to "spasm" of colonic smooth muscle.

Complicated by visceral hypersensitivity. Minimal distention/"squeezing" may cause cramping/bloating.

**Educating the Patient: IBS Is Due to Colonic Dysmotility**

Altered bowel function is due to colonic dysmotility

Abdominal discomfort is due to “spasm” of colonic smooth muscle.

Complicated by visceral hypersensitivity. Minimal distention/"squeezing" may cause cramping/bloating.

**What causes colonic dysmotility?**

- Altered colonic bacteria
- Altered colonic neuro-receptors
- Altered brain-gut communication
- ???

**Altered bowel function is due to colonic dysmotility**

Abdominal discomfort is due to "spasm" of colonic smooth muscle.

Complicated by visceral hypersensitivity. Minimal distention/"squeezing" may cause cramping/bloating.

This provides multiple “targets” for treatment of IBS and Chronic Constipation (CC)

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**Start with Invasive Diagnostic Investigation (e.g., colonoscopy, CT scan, etc.) if Alarm Symptoms Are Present**

- Onset of new symptoms after age 50
  - This is a very concerning alarm symptom: do colonoscopy and consider CT scan or abdominal ultrasound
- Hematochezia
- Nocturnal diarrhea
- Unexplained Weight loss ≥10 pounds
- Family history of colorectal cancer, Crohn’s disease, celiac disease

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- Hematochezia
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- Unexplained Weight loss > 10 pounds
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Get CBC to rule out anemia—possible sign of occult GI bleeding.
Get C-reactive protein (CRP). Elevated CRP suggests inflammatory bowel disease.

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### Stool Pattern Guides Initial Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Constipation</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Separate hard lumps, like nuts</td>
</tr>
<tr>
<td>2</td>
<td>Sausage-like but lumpy</td>
</tr>
<tr>
<td>3</td>
<td>Like a sausage but with cracks in the surface</td>
</tr>
<tr>
<td>4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>5</td>
<td>Soft blobs with clear-cut edges</td>
</tr>
<tr>
<td>6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>7</td>
<td>Watery, no solid pieces</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Diarrhea</strong></th>
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<tr>
<td>1</td>
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<td>2</td>
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<td>6</td>
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### Patient Case-Elizabeth-Possible Post-infectious IBS

- Stool studies, CBC, C-reactive protein-normal.
- Altered her diet. Eating more whole grains.
- Taking loperamide and peppermint oil daily.
- Diarrhea is better. Peppermint oil helps a little with cramping. Next steps?

Managing IBS and Chronic Constipation
Start with OTC treatments and diet changes
“Step-Up” Therapy if patient only gets limited relief with diet changes and OTC therapies!

**What causes colonic dysmotility in IBS**

What causes colonic dysmotility?
- Altered colonic bacteria
- Altered colonic neuro-receptors
- Altered brain-gut communication
- ???

This provides multiple “targets” for treatment of IBS and Chronic Constipation (CC)


**Patient Case-Elizabeth: Stepping Up Therapy**

Rifaximin (Xifaxan®) - poorly absorbed antibiotic. Alters colonic bacteria

Eluxadoline (Viberzi®)-mixed opioid receptor agonist-Stimulates colonic receptor

Tricyclic antidepressant (e.g., Pamelor®)-moderates brain-gut communication

Tri-cyclic antidepressants are not FDA-approved for IBS-D

**Many patients use probiotics, a “natural” treatment to alter gut microbiota and improve “digestion”**

Are Probiotics Effective?
Limitations of Probiotics for Treating IBS

- **ACG Recommendation**
  Insufficient and conflicting data prevent making recommendations about any individual species, preparation, or strain

- **Most generic probiotics do not contain viable bacterial species as listed on the label based on multiple microbiology studies**

My Approach: For patients who want to use probiotics, I start by encouraging them to eat yogurt.

Rifaximin (Xifaxan®)

- FDA-approved for IBS-diarrhea. Demonstrated efficacy for abdominal pain and diarrhea.
- Safety and tolerability: "well-tolerated" and no increase in adverse events vs placebo in RCTs
  - <0.4% is absorbed
- Dosing
  - 550 mg po tid x 14 days
  - May repeat up to 2x if/when symptoms recur

Rifaximin vs Placebo for IBS-D in RCTs

- **Global IBS Responder** for Rifaximin vs Placebo: OR = 1.48
  - *English Translation: Rifaximin-treated patients are approximately 48% more likely to respond compared to placebo-treated patients*
- **Adequate Relief-Bloating Responder** for Rifaximin vs placebo: OR = 1.55
  - *English Translation: Rifaximin-treated patients are approximately 55% more likely to respond compared to placebo-treated patients*
- **Rifaximin superior to placebo for abdominal pain, stool consistency, and fecal urgency**

What is an effective, well-tolerated, and safe “microbiome” treatment?

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Antidepressants Are Superior To Placebo For Improving IBS Symptoms

- Tricyclic antidepressants (TCAs) for IBS-D¹-⁴
  - Improve abdominal pain
  - Side effect is constipation >> treats diarrhea
  - Side effect is drowsiness >> use qhs

  **Our preferred agent is nortriptyline (Pamelor®) 10-25 mg qhs**

Antidepressants Are Superior To Placebo For Improving IBS Symptoms

- If the patient can’t tolerate TCAs, then use SSRI/SNRIs¹-⁴
  - Improve abdominal pain. Minimal impact on stool.
  - Use for IBS-C, too

  **Our preferred agent is duloxetine***(Cymbalta®) 30-60 mg qd

Antidepressant action

**Visceral analgesia**

Changes in motility

Smooth muscle relaxation

FDA-approved for neuropathic pain**

Cognitive Behavioral Therapy is another option if you can find an appropriate therapist.

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Eluxadoline (Viberzi®) in IBS-D

- Mixed opioid receptor activity localized to intestine
- Minimally absorbed
- Animal studies
  - Improves diarrhea and pain symptoms of IBS-D


Eluxadoline

- FDA-approved for IBS-diarrhea. Decreases abdominal pain and diarrhea based on RCTs.
- Dosing: 100 mg po bid taken with food. May decrease to 75 mg po bid if patient can’t tolerate this dose
- Constipation is most common side effect: 7-8%
- Rare severe adverse event: pancreatitis
  - Contraindications: cholecystectomy

1. Viberzi (eluxadoline) [prescribing information]. Allergan USA, Inc. Irvine, CA; 2017

Eluxadoline vs Placebo for IBS-D in RCTs

- Responder* for Eluxadoline vs Placebo: OR = 1.84 (95% CI: 1.44-2.34)
  - English Translation: Eluxadoline-treated patients are approximately 84% more likely to respond compared to placebo-treated patients
- Eluxadoline significantly better than placebo
  - ≥50%/day with no fecal urgency
  - ≥50% of days with significantly* decreased abdominal pain

*FDA-Responder Endpoint: reduction of abdominal pain by ≥30% from baseline and stool consistency score < 5 on the same day. If had this outcome on > 50% of days, then qualified as study responder. Lembo A et al. N Engl J Med 2016; 374: 242-252.

Cost of Prescription

IBS-D Treatments:
Use websites of branded drugs to get co-pay cards* and coupon websites for generic drugs

*Co-pay cards for commercially-insured patients; Medicare patients cannot use co-pay cards

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Patient Case: Matt

• 52 year old man with constipation, bloating and cramping for last 4-5 years
• Symptoms worsened over past year after he tore his ACL in right knee while playing basketball.
• Less active and gaining weight.
• Has 3 stools per week: rabbit pellets or huge, hard stools with straining

• He minimizes symptoms, but his brother made him go see his family practice physician.
• Never had a colonoscopy
• No weight loss but does have intermittent hematochezia

Patient Case: Matt
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FDA-Approved Treatment Recommendations for IBS-C and Chronic Constipation

- Linaclotide (Linzess®) and Plecanatide® are superior to placebo for treatment of IBS-C and chronic constipation¹
- Lubiprostone (Amitiza®) is superior to placebo for treatment of IBS-C and chronic constipation¹
- Both are strong recommendations based on high quality evidence


Linaclotide (Linzess®) Is FDA-approved For IBS-C and Chronic Constipation

- Take on empty stomach in morning
  - IBS-C: 290 mcg qd
  - Chronic Constipation: 145 mcg qd or 72 mcg qd
- Minimally absorbed
  - Only "side effect" is diarrhea
- Efficacy demonstrated in large RCTs


Plecanatide (Trulance®) Is FDA-approved For IBS-C and Chronic Constipation

- Take any time (doesn’t require empty stomach)
  - IBS-C and Chronic Constipation: 3mg qd (only one dose)
- Minimally absorbed
  - Only “side effect” is diarrhea or bothersome stools: occurs in ~ 5%
- Efficacy demonstrated in large RCTs


Linaclotide (Linzess®) and Plecanatide (Trulance®) bind and activate the Guanylate Cyclase-C Receptor

Different mechanisms of action to treat constipation and abdominal discomfort

Linaclotide Phase 3 IBS-C Trial: Complete Spontaneous Bowel Movements (CSBMs) and Abdominal Pain

![Graph showing CSBMs and Abdominal Pain over trial weeks]

- CSBMs: Placebo vs Linaclotide 290 µg
- Abdominal Pain: Significant improvement with linaclotide

![Graph showing placebo vs linaclotide 290 µg for CSBMs and Abdominal Pain]

- P<0.0001 for each of the 26 weeks in the treatment period for both SBMs and CSBMs.

Plecanatide (Trulance®)-Phase 3 Chronic Idiopathic Constipation Study: Improvements in Spontaneous Bowel Movements

- Study 1
- Placebo vs Trulance 3 mg:
  - Mean Weekly SBMs (Number/Week)
  - Similar results were observed in Study 2.

Plecanatide (Trulance®)-Phase 3 IBS-C Study-Improvement in Abdominal Pain

- Mean Change From Baseline in Abdominal Pain
- Placebo vs Trulance 3 mg (q.o.s.):
  - Treatment Time (Weeks)

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Lubiprostone (Amitiza®)

- Lubiprostone (Amitiza®) activates the chloride channel type 2 (CIC-2) receptor on the surface of the intestinal epithelium
- For Chronic Constipation: 24 mcg bid
- Nausea is the most common side effect
  - Minimized by taking lubiprostone (Amitiza®) with food and by lowering dose

ACG Recommendations: Treatment of Chronic Constipation

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulking agents</td>
<td>Fiber</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Osmotic laxatives</td>
<td>PEG (e.g., MiraLax®)</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Stimulant laxatives</td>
<td>Bisacodyl</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>Linaclotide</td>
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<tr>
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*Strength of recommendations and quality of evidence determined using GRADE (Grading of Recommendations Assessment Development and Evaluation).


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