Under Pressure: The Need to Expedite IBS Diagnosis and Treatment in Primary Care

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Educational Partner:
CME Incite, LLC
Session 4: Under Pressure:  
The Need to Expedite IBS Diagnosis and Treatment in Primary Care

Learning Objectives
1. Diagnose IBS based on symptoms that may be shared with other functional gastrointestinal disorders or organic diseases.
2. Compare and contrast the efficacy and safety of available pharmacologic and nonpharmacologic treatment options for IBS.
3. Apply appropriate and comprehensive treatment strategies to enhance the care of patients with IBS.

Faculty
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Dr Lawrence Schiller was born in Philadelphia and attended Pennsylvania State University and Jefferson Medical College of Philadelphia. He completed his internal medicine training at Temple University Hospital, also in Philadelphia, and then served in the US Army Medical Corps for two years. Dr Schiller moved to Dallas in 1978 for gastroenterology training at the University of Texas (UT) Southwestern Medical Center, where he remained on the faculty at the medical school; he was also an attending physician at the Dallas VA Hospital for five years. In 1985, Dr Schiller moved to Baylor University Medical Center to continue research with Dr John Fordtran, and has been there ever since, most recently serving as program director for the gastroenterology fellowship.

Dr Schiller has been involved in patient care as a founding partner of Digestive Health Associates of Texas, one of the largest single-specialty gastroenterology practices in America, and has continued with research and education activities at Baylor and UT Southwestern. He is currently attending physician and chairman of the Institutional Review Board for the gastroenterology fellowship.

Dr Schiller has been elected to fellowships in the American College of Physicians and the American College of Gastroenterology (ACG) and has served as ACG governor of the North Texas region. Dr Schiller is currently ACG president-elect. He also has served as president of the Texas Society for Gastroenterology and Endoscopy. Dr Schiller has published more than 80 papers and 45 book chapters dealing with gastric physiology, intestinal transport, diarrheal diseases, and motility disorders.

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Deputy Commander of Medicine  
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Bethesda, Maryland

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Dr Cash earned his undergraduate degree in business administration (finance) with honors from the University of Texas in Austin. He earned his medical degree from the Uniformed Services University of Health Sciences and completed his internship, residency, and gastroenterology fellowship at the National Naval Medical Center in Bethesda, Maryland.

Dr Cash is a diplomate of the American Board of Gastroenterology. He is a fellow of the American College of Gastroenterology, the American Gastroenterological Association, and the American Society of Gastrointestinal Endoscopy, where he serves as chair of the Standards of Practice Committee. Dr Cash serves on the Rome Committee for Functional Gastrointestinal Disorders and has authored multiple articles and book chapters on a variety of gastrointestinal topics including irritable bowel syndrome and chronic constipation, colorectal cancer screening, CT colonography, acid peptic disorders, Barrett’s esophagus, and evidence-based medicine. He serves as associate editor for the American Journal of...
Dr. Cash is a consultant for Ironwood Pharmaceuticals, Inc.; Salix Pharmaceuticals, Inc.; Takeda Pharmaceutical Company; and Forest Laboratories, Inc. He serves as a speaker for Salix Pharmaceuticals, Inc. and Takeda Pharmaceutical Company.
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- Compare and contrast the efficacy and safety of available pharmacologic and nonpharmacologic treatment options for IBS
- Apply appropriate and comprehensive treatment strategies to enhance the management of patients with IBS

IBS, irritable bowel syndrome; GI, gastrointestinal.

Drug List

- A3309
- Alosetron
- Amitriptyline
- Atropine
- Cholestyramine
- Citaknopam
- Desipramine
- Diphenoxylate
- Doxepin
- Fluoxetine
- Hyoscyamine
- Imipramine
- Linadotide
- Loperamide
- Lubiprostone
- Paroxetine
- Prucalopride
- Psyllium
- Rifaximin

- No trade name
- Lottorex
- Elavit, Tryptizol, Laroxyl, etc
- Salbutamine
- Quextran
- Celexa
- Norpramin, Pertofane
- Lomotil, Lonox, Dimotil, etc
- Adapin, Silenor, Sinequan, etc
- Ceoxan, Sarafam, Fontex, etc
- A-Spas, Anapaz, Cytopaz, etc
- Amitizina
- Pavi, Anpax, Seroxat, Pexeva, etc
- Resolor
- Fiberall, Benefiber, Metamucil, etc
- Xifaxan

Pre-test Question 1

A 43-year-old patient presents with IBS symptoms for >3 months prior to initial visit without the presence of alarm features. What should be your next course of action?

1. Watch and wait for emergence of alarm features
2. Perform routine lab tests (CBC, CMP, TSH, stool O+P, abdominal imaging)
3. Refer for colonoscopy
4. Begin treatment for IBS immediately
5. Unsure

CBC, complete blood count; CMP, comprehensive metabolic panel; TSH, thyroid-stimulating hormone; O+P, ova and parasites.

Pre-test Question 2

How would you distinguish IBS from other functional GI disorders, such as functional constipation (FC) or functional diarrhea (FD)?

1. Pain is more prominent than bowel disturbance in functional constipation or functional diarrhea
2. Pain is more prominent than bowel disturbance in IBS
3. Frequency of bowel habits differs between FC/FD and IBS
4. Changes in diet have more impact on patients with IBS than on patients with FC or FD
5. Unsure

Pre-test Question 3

Which of the following therapies is an evidence based treatment option for patients with IBS-C?

1. Hyoscyamine
2. Lubiprostone
3. Loperamide
4. Alosetron
5. Unsure

IBS-C, IBS Constipation.
Pre-test Question 4

What medication would you recommend for a 57-year-old woman with severe IBS-D who has previously tried anticholinergics, loperamide, SSRIs and dietary changes, but still has abdominal pain and urgency?

1. Diphenoxylate with atropine
2. Lubiprostone
3. Polyethylene glycol
4. Alosetron
5. Any of the above
6. Unsure

IBS-D, IBS Diarrhea; SSRIs, selective serotonin reuptake inhibitors; PEG, polyethylene glycol.

Case Study 1

AC, a 45-year-old woman, presents with a 6-year history of abdominal pain and variable bowel habits

- Crampy pain is located in left lower quadrant
- Pain peaks just before bowel movement
- Pain is relieved by defecation
- Bowel movements vary in consistency from loose to hard
- Frequency of bowel movements varies from once weekly to 4 times per day

Case History (cont’d)

- Other symptoms include indigestion, early satiety, bloating, excessive flatulence, and belching
- Patient has experienced no weight loss or rectal bleeding
- Previous evaluation included colonoscopy with biopsies (negative), endoscopy with biopsies (negative), and abdominal sonogram (negative)
- Patient has tried lactose-free diet, increased dietary fiber, dicyclomine, and hyoscyamine, all without benefit
- Physical examination is unremarkable

ARS Question: What Additional History Would You Obtain?

1. Past surgical history
2. History of migraine headaches
3. Discussion of life stressors and relation to symptoms
4. Discussion of physical and sexual abuse
5. Family history of digestive symptoms

ARS Question: What Would You Do Next?

1. Laboratory tests: CBC, CMP, TSH
2. Pelvic examination
3. Diet and symptom diary for 2 weeks
4. CT scan of abdomen/pelvis
5. Repeat colonoscopy and endoscopy
RECOGNIZING AND EXPEDITING THE DIAGNOSIS OF IBS

Lawrence R. Schiller, MD, FACG

Prevalence and Impact of IBS

- Worldwide prevalence: 7% to 10%
- 1.5 times more prevalent in women
- More commonly diagnosed in patients <50 years of age
- More common in lower socioeconomic groups
- Patients with IBS have more physician visits, more hospitalizations, more missed workdays, more prescriptions, and more diagnostic tests than those without the disorder

Diagnostic Paradigm for IBS

- IBS is a syndrome—a collection of symptoms
- Diagnosis is possible by taking a thorough history of symptoms
- Since symptoms may be due to other disorders, the provider must consider alternative organic diagnoses
- Serious organic illnesses typically produce alarm symptoms

IBS: Signs and Symptoms

- Abdominal pain
  - Anywhere in abdomen
  - Characteristically relieved by defecation
- Altered stool frequency
  - Excess frequency: >2 bowel movements/day
  - Infrequency: <3 bowel movements/week
- Altered stool form
  - Loose to lumpy

IBS Subtypes

- IBS-C: Constipation-predominant IBS
- IBS-D: Diarrhea-predominant IBS
- IBS-M: Mixed IBS (hard and loose stools over periods of weeks and months)
- IBS-U: Unsubtyped IBS

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

Additional IBS "testing," including routine laboratory tests and colonoscopy, unnecessary unless alarm features present
Alarm Features in IBS

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

Further investigation warranted
Consider colonoscopy

ACG Recommendations: Evaluation of IBS With No Alarm Features

- Routine laboratory tests (CBC, CMP) and TSH, stool O&P, abdominal imaging → not recommended
- Serologic testing for celiac disease (IBS-D/M) → recommended
- Lactose breath testing → selected cases
- Colonoscopy → recommended if >50 years of age, with biopsies in refractory IBS-D (to exclude microscopic colitis)

Proposed Pathophysiology of IBS: 2012

- Dysmotility
- Hypersensitivity
- Disordered brain processing
- Enteric nervous system dysfunction
- SERT activity
- Postinfectious IBS
- Somatization syndrome
- Small intestinal bacterial overgrowth
- Mast cell dysfunction
- Dysbiosis
- Food intolerances
- Food allergy
- Genetics

Practice Pearl

- Dysmotility
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- Food intolerances
- Food allergy
- Genetics

Differential Diagnosis of IBS

- Other functional GI disorders
  - Functional constipation, functional diarrhea
  - Pain less prominent than bowel disturbance
  - Functional abdominal pain
  - Bowel disturbance less prominent
Differential Diagnosis of IBS With Diarrhea

- Dietary factors
  - Lactose
  - Gluten
  - Other FODMAPS
- Drugs
- Infection
  - Giardiasis
  - Amebiasis
- Malabsorption
- Celiac disease

- Inflammatory bowel disease
- Crohn’s disease
- Ulcerative colitis
- Microscopic colitis
- Psychological
  - Panic disorder
  - Somatization
  - Depression

Post-test Question 1

A 43-year-old patient presents with IBS symptoms for >3 months prior to initial visit without the presence of alarm features. What should be your next course of action?

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4. Begin treatment for IBS immediately
5. None of the above
6. Unsure

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5. Unsure

Current and Emerging Treatment Options for Patients with IBS

Brooks D. Cash, MD, AGAF, FASGE, FACG

Treatment Depends on Severity of IBS

- Psychological treatments
- Goal: improved function
- Continuing care
- Follow-up visit
- Manage stress
- Drug therapy
- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure

- Severe (25%)
- Moderate (35%)
- Mild (40%)
Diet and IBS

- Lifestyle
  - Survey of 1242 patients: following interventions improved symptoms
  - Small meals (69%), avoiding fat (64%), increasing fiber (58%), avoiding milk products (54%)
  - Food allergy—limited evidence
  - Lactose—higher % of lactose maldigestion
  - Gluten—studies indicate possible link
  - Fructose intolerance—studies indicate possible link


Psychological Treatments Show Greater Efficacy Than Usual Care

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IBS Pharmacologic Therapies by Symptom

Abdominal pain/discomfort
- Antispasmodics*
- Antidepressants*
- TCAa/SSRIs
- Alosetron (5HT-3 antagonist)

Bloating
- Rifaximin*
- ? Probiotics

Constipation
- Fiber
- MOM/PEG solution*
- Lubiprostone (chloride channel activator)

Diarrhea
- Loperamide*
- Cholestyramine*
- Alosetron
- Rifaximin*

Evidence-Based Summary of Medical Therapies for IBS-C

PEG for IBS-C

No adult studies of laxatives in IBS-C
- 27 adolescents: PEG improved number of bowel movements (P<0.05) but not pain in IBS-C patients

Psyllium Can Improve IBS Symptoms

- Randomized, placebo-controlled trial (N=275 patients with IBS)
- Primary endpoint: adequate symptom relief 22 weeks in previous month, analyzed after 1, 2, and 3 months

RESULT
- Higher % responders in psyllium vs placebo group during first month (57% vs 35%)
- Higher % responders through 2 months of treatment (59% vs 41%)

Lubiprostone: Overall Responder Rate in IBS-C Trials

- 2 Phase III 12-week randomized controlled trials
- Results: patients receiving lubiprostone (8 μg BID) twice as likely to achieve overall response
- 7.8% difference (P=0.001) vs placebo

Ensure absence of mechanical obstruction before beginning therapy.


Loperamide for IBS-D

- Low doses 2 mg once or twice daily may be effective to decrease stool frequency, improve stool consistency
- No impact on symptoms of abdominal discomfort, bloating, or global IBS
- 2 randomized controlled trials in IBS (N=42) show efficacy for diarrhea
- Adverse effects: dizziness, abdominal pain/bloat, constipation, dry mouth, fatigue


Alosetron: Therapeutic Gain for IBS-D

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*Comparison metranol vs 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
- Ischemic colitis usually occurs within the first month of therapy if it occurs
- Prescribing program mandated by FDA
- Requires patient to sign attestation form


Bifidobacteria Infantis 35624 for IBS Global Assessment of Relief

- SGA (Subjects’ Global Assessment): a yes/no response to the following question:

“Please consider how you felt in the past week in regard to your IBS, in particular your general well being, and symptoms of abdominal discomfort or pain, bloating or distension, and altered bowel habit. Compared with the way you felt before beginning the medication, have you had adequate relief of your IBS symptoms?”


**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 – Meta-analyses**

- 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.


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**Practice Pearl**

**Evidence for Emerging Therapies in IBS-C and IBS-D**

**Linaclotide* (Guanylate Cyclase-C Agonist) for IBS-C**

- Phase III randomized controlled trial in IBS-C of 290 μg of once-daily linaclotide followed by a 4-week randomized withdrawal period
- N=800 (n=405 receiving linaclotide, n=395 placebo)

**RESULT**

- Linaclotide-treated patients experienced significant improvement in all 4 endpoints (P<0.05) compared to placebo treated patients
- No evidence of rebound worsening with randomized withdrawal of linaclotide
- Diarrhea most common adverse event (19.5% vs 3.5%, P<0.05)


* Linaclotide not currently FDA-approved for IBS.

**Changes From Baseline in CSBM with Linaclotide* Treatment**

Changes From Baseline in CSBM with Linaclotide* Treatment

- Treatment Period
  - Placebo
  - Linaclotide 290 μg

* Linaclotide not currently FDA-approved for IBS. CBSM, complete spontaneous bowel movements. RW, randomized withdrawal.

Post-test Question 3  
Which of the following therapies is an evidence based treatment option for patients with IBS-C?

1. Hyoscymine
2. Lubiprostone
3. Loperamide
4. Alosetron
5. Unsure

Rifaximin* Trials: Global Relief of IBS Without Constipation

- 2 Phase III randomized controlled trials; N=1260 patients
- Rifaximin 550 mg tid x 2 weeks; patients followed additional 10 weeks
- 40.7% vs 31.7% with adequate relief of global symptoms ($P<0.001$)

T-I: TARGET I trial; T-II: TARGET II trial; Comb: Combination of both trials.
*Rifaximin is not currently FDA-approved for IBS.

Summary of IBS Therapy

- Treatment depends on severity of IBS symptoms
- Management of diet, exercise, and sleep build foundation for success of other therapies
- Limited evidence but useful starting points
- Pharmacologic therapies directed at predominant symptoms
- Evidence-based treatments include
  - IBS-C: lubiprostone, SSRIs
  - IBS-D: alosetron, TCAs
  - Antibiotics and probiotics may help with bloating
  - Centrally acting therapies (eg, antidepressants) in select patients may help with improving general well being
- Novel agents in development
  - Linaclotide and rifaximin are promising therapies for IBS

Post-test Question 4  
What medication would you recommend for a 57-year-old woman with severe IBS-D who has previously tried anticholinergics, loperamide, SSRIs and dietary changes, but still has abdominal pain and urgency?

1. Diphenoxylate with atropine
2. Lubiprostone
3. Polyethylene glycol
4. Alosetron
5. Any of the above
6. Unsure
Case Study 2

JM, a 38-year-old woman with a 16-year history of abdominal pain, bloating, and constipation
- Married, 3 children, teacher, occasional ethanol, no tobacco use
- Pain eased by defecation
- Feels like she does not completely evacuate her bowels; experiences severe straining, 2 bowel movements/week
- Misses time from work due to symptoms

Case History

- History of anxiety; currently on SSRI
- No family history of organic GI disease; mother suffers from “constipation”
- She has increased fiber intake, but this led to more bloating
  - Tried exercise and dietary changes without success
- Laxatives soften stool, but have no effect on abdominal pain, straining, or sense of complete evacuation

ARS Question: What Additional History Would You Obtain?

1. Past surgical history
2. History of migraine headaches
3. Discussion of life stresses and relation to symptoms
4. Discussion of physical and sexual abuse
5. Family history of digestive symptoms

ARS Question: What Would You Do Next?

Knowing she is currently taking an SSRI without success, what would be your next step?

1. Lab tests: CBC, CMP, TSH
2. Pelvic examination
3. Trial of FODMAP diet
4. Suggest switching from SSRI to TCA
5. Colonoscopy with biopsy
6. Psychiatry consultation to treat anxiety