SEVEN different award types; INCREASED Junior Faculty FUNDING; NEW Mid-Career Bridge Funding; Med Resident and Student Awards

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Grant System Opens: September 8, 2020
Deadline: December 4, 2020

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Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

American College of Gastroenterology
How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.

MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 27: Making the Case for Screening 45-Year-Old Adults for CRC
Joseph C. Anderson, MD, MHDS, FACG
September 24, 2020 at Noon EDT

Week 28: Endoscopic Management of Obesity and Complications of Bariatric Surgery
Allison R. Schulman, MD, MPH
October 1, 2020 at Noon EDT

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Current and Emerging Concepts in Irritable Bowel Syndrome

Brooks D. Cash, MD, FACG
Dan and Lille Sterling Professor of Medicine
McGovern Medical School
Chief, Gastroenterology, Hepatology, and Nutrition
University of Texas Health Science Center
Houston, TX

Brian E. Lacy, MD, PhD, FACG
No conflicts of interest.
Objectives
1. Discuss the pathophysiology and diagnostic criteria for IBS
2. Explore the data for lifestyle and over-the-counter therapies for IBS symptoms
3. Review the mechanisms of action, efficacy, and safety profiles of FDA approved IBS therapies
4. Examine emerging therapies for IBS

Rome IV Criteria for IBS

- Recurrent abdominal pain at least 1 day/week (on average) in the last 3 months associated with ≥2 of the following:
  - Related to defecation
  - Associated with a change in stool frequency
  - Associated with a change in stool form
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Multifactorial Pathophysiology of IBS

- Genetic predisposition
- Psychosocial factors
- Visceral hypersensitivity
- Abnormal motility
- Inflammation, immune dysregulation
- Microbiome
- Malabsorption issues
- Diet

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Principles of IBS Management

- Exclude organic GI disease
- Make a positive diagnosis
- Establish a rapport; educate and reassure
- Categorize IBS subtype based on prevalent stool form (BSFS)
- First line: lifestyle and dietary modifications and OTC therapies targeting abnormal stool form/most bothersome symptoms
- Escalate to FDA approved/validated therapies
- Non-FDA/off-label/psychological therapies

Diagnostic Testing for Suspected IBS and No Alarm Features*

All IBS Subtypes

- CBF or fecal calprotectin
- IgA Tg x quantitative IgG
- Where colonoscopy performed, obtain random biopsies
- Serum 7-C4 or fecal bile acids where available

CE: Cholesterol ester; CBF, colorectal cancer screening; CRP, C-reactive protein; Ttg, tissue transglutaminase

Lifestyle Modifications (all have some evidence of benefit)

- Dietary
  - Low FODMAP
  - Gluten restriction
  - Keto/Mediterranean
  - Low fat
- Activity
  - Exercise
- Sleep hygiene
- Minimize/eliminate ETOH
  - Best evidence for IBS-D, likely due to decrease in metabolic byproducts
**Dietary Considerations in IBS**

- **FODMAPS** are an important trigger of meal-related symptoms in IBS.
- Low FODMAP diet found to improve overall symptom scores compared with typical diet in IBS patients.
- *Gluten-free* diet found to be beneficial in some patients with IBS.
- Wheat contains fructans and other proteins that may also cause symptoms in IBS patients.
- Most patients who associate their symptoms with wheat will have wheat sensitivity, not celiac disease.
- *Food antigens* found to cause changes in the intestinal mucosa of IBS patients that are associated with patient responses to exclusion diets.

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**Low FODMAP versus mNICE Diet for IBS-D: Adequate Relief & FDA Endpoint**

84 patients with IBS-D randomized to LFD or mNICE x 8 weeks and completed study.
- Median age was 45 years (range 18-86); 65 were women.
- >30% reduction in pain and decrease in BSFS >1 compared to baseline.

---

**IBS Pharmacologic Options by Symptom**

- **Constipation**
  - Laxant
  - MEGYPS/Glucagon
  - Lubiprostone
  - Plecanatide
  - Topiramate
  - Tegaserod
  - Tegaserod
  - Topiramate
  - Topiramate

- **Diarrhea**
  - Loperamide
  - Diphenoxylate
  - Diphenoxylate
  - Cholestyramine
  - Ascorbate
  - Aluminate
  - Eluxadoline

---
OTC Options

• Antidiarrheals: Imodium, clays/binders
• Anti-spasmodics
• Peppermint oil
• Probiotics

Conventional Nonspecific Agents for IBS-D

Recommendations from an American College of Gastroenterology monograph

There is insufficient evidence to recommend loperamide for use in IBS

2 Clinical trials
42 Patients treated

Recommendation
Strong
Quality of evidence
Very Low

There is insufficient evidence to recommend antispasmodics available in US

23 Clinical trials
2,154 Patients treated

Recommendation
Weak
Quality of evidence
Low

*Recommendation revised to reflect evidence for products available in US

Peppermint Oil

• Active ingredients: L-menthol, rosmarinic acid, limonene
  • Primary effect: Ca²⁺ channel smooth muscle relaxation
  • Possible mediation via TRPM8, k-opoid agonist, antibacterial, anti-inflammatory, carminative
• Dose unclear; typically 90-180 mg up to TID
• 7 RCT, 634 patients
• NNT = 4
• AEs similar to placebo: GERD, dyspepsia reported
Probiotics

- 53 RCT, 5545 patients; 50% trials at low risk for bias
  - Significant heterogeneity
  - Evidence of publication bias
- Probiotics superior to placebo
  - NNT=7
    - Combination probiotics: RR = 0.79 (0.68-0.91)
  - IBS dose/brand: unknown
  - Symptoms most likely to improve pain, bloating, flatulence
  - Low rate of AEs

FDA Approved Therapies for IBS-D

- Rifaximin
- Eluxadoline
- Alosetron

Rifaximin for IBS-D

TARGET 1 & TARGET 2 Trials

- Poorly absorbed antibiotic; inhibits protein synthesis
- Dosing 550 mg TID x 2 weeks
- 7 RCT; 2654 patients
- NNT=8
- AEs similar to placebo
- 2/3 responders need repeat treatment
  - No value in re-treating non-responders


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Rifaximin for IBS-D
TARGET 3 Trial

- Retreatment Efficacy
- First Repeat Treatment: P = 0.04
- Second Repeat Treatment: P = 0.09

Responder defined as:
- Responding to IBS-related abdominal pain and stool consistency for 12 weeks
- Recurrence defined as:
- Loss of response for 3 of 4 weeks

Urgency and bloating improved significantly with both repeat treatments
Abdominal pain and stool consistency improved significantly with first retreatment

Eluxadoline for IBS-D
IBS-3001 & IBS-3002 Trials
- Mixed opioid receptor modulator
  - μ,δ opioid receptor agonist; K opioid antagonist
- Dosing: 100 mg BID
- 3 RCT, 3235 patients
- NNT= 13
- AEs: Constipation, abdominal pain, SO spasm, pancreatitis
  - Constipation defined as no GI or h/f loperamide, heavy ET users
- Contraindicated: TMT, GB, heavy ETOH users

Eluxadoline in Patients Who Failed Loperamide
RELIEF Trial
- Phase IV multicenter DBRCT
- Subjects: Patients
  - Subjectively reporting loperamide use in prior 12 months failing to provide adequate control of IBS-D symptoms
  - AEs: Rates comparable in both groups; no SAES

Primary Composite = Patient meets composite response criteria an ≥50% of days, defined as 40% improvement in WAP & WAP.
Secondary WAP: defined as ≥50% improvement in WAP compared to baseline at 12 weeks.
Secondary WAP: defined as ≥50% improvement in WAP compared to baseline at 12 weeks.
**Alosetron for IBS-D**

- Partially selective 5-HT3 antagonist
- 8 RCT, 4341 patients (predominantly women)
- NNT=7.5
- AEs: constipation, colon ischemia: 1/1000 patient-yrs
- 0.5 mg BID starting dose; may increase to 1 mg BID if well tolerated
- Current indication: Female patients with severe IBS-D not responding adequately to conventional therapy

**Antidepressants**

- 18 RCT, 1127 patients
- Antidepressants in general: NNT= 4; pain mostly
  - TCAs: 12 RCT, 787 patients; NNT= 4; Strong rec, high evidence
  - SSRIs: 7 RCT, 356 patients; NNT= 5; Weak rec, low evidence
  - SNRIs not yet studied in large RCTs
- AEs more common with antidepressants; NNH= 8.5

**General Approach to Prescribing Antidepressants in IBS**

- Consider specific symptoms
  - TCAs in IBS-D, SSRIs in IBS-C
  - Consider side effect profiles
  - Start with low dose and titrate slowly by response; allow 4-8 weeks for maximal response
  - Continue at minimum effective dose for 6-12 months
  - Gradual taper to prevent withdrawal symptoms

---

**Bulking Agents for IBS-C: Systematic Review and Meta-analysis: Strong rec, weak evidence**

<table>
<thead>
<tr>
<th>RCTs</th>
<th>N</th>
<th>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>30%</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>

*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

**FDA Approved Therapies for IBS-C**

- Linaclotide
- Plecanatide
- Lubiprostone
- Tegaserod
- Tenapanor

**Linaclotide for IBS-C**

- 14 aa peptide structurally similar to guanylin/uroguanylin; binds to guanylate-cyclase C receptors to promote ion and fluid secretion into gut and ENS modulation.
- 4 RCT, 2867 patients.
- IBS-C dose: 290 mcg daily.
- NNT=6.
- AEs: diarrhea.

*P<0.001 for all analyses of linaclotide vs placebo groups, using Cochran-Mantel-Haenszel test.

Linaclotide for IBS-C

Weeks
CSBM Mean Change from Baseline, g/24 h

Treatment Period
Placebo
Linaclotide 290 µg

Placebo
Linaclotide 290 µg

Linaclotide 290 µg/Placebo
Linaclotide 290 µg/Patient

N=800

*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

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Linaclotide: Abdominal Pain Over 26 Weeks

ITT population, observed cases, LS mean presented. P-values adjusted for ANCOVA at each week. Bars represent 95% CI.

P<0.001 for week 1
P<0.0001 for weeks 2-26

Plecanatide for IBS-C

• 16 aa peptide structurally similar to uroguanylin
  • Ik greater binding affinity at GC-C receptors at pH 7
• 3 RCT; all at low risk for bias, n=2612
• IBS-C dose: 3mg daily
• NNT=10
• AEs: diarrhea

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Lubiprostone: Strong rec, mod evidence

- Type 2 chloride channel activator; increases balanced ion and water secretion into gut
- 3 RCT, 1366 patients
- IBS-C dose: 8 mcg BID only approved in women
- NNT=12.5
- AEs: diarrhea and nausea


Tegaserod for IBS-C

- Mixed 5-HT (serotonin) agonist (prokinetic)
- Approved for women ≤ 65 yo with ≤ 1 CV risk factor
- Dose: 6 mg PO BID
- AEs: Diarrhea, abdominal pain, headache, nausea

Mixed 5-HT agonist (prokinetic)

No demonstrable risk of MACE events with tegaserod

Risk of CV and stroke events with ZELENOB vs comparators

<table>
<thead>
<tr>
<th>CV Events</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-adjusted</td>
<td>0.93</td>
<td>0.72–1.21</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.96</td>
<td>0.78–1.20</td>
</tr>
<tr>
<td>Stroke Events</td>
<td>Hazard Ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Non-adjusted</td>
<td>0.99</td>
<td>0.93–1.06</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.99</td>
<td>0.94–1.06</td>
</tr>
</tbody>
</table>

N=2201

*Defined as patients who do not have a history of ischemic cardiovascular disease and who have no more than one cardiovascular disease risk factor.

Favors Tegaserod Favors Comparator

Hazard Ratio 95% Confidence Interval

Non-adjusted† Non-adjusted† Adjusted‡ Adjusted‡

CV Events Stroke Events CV and stroke events with ZELNORM vs comparators

†Unadjusted by Cox proportional hazards regression.
‡Adjusted for age, sex, region, calendar year, and baseline history of hypertension, treated hypertension, hyperlipidemia, diabetes, treated diabetes, obesity, smoking, acute coronary syndrome, history of MI, and acute MI by Cox proportional regression.
Tenapanor

- NHE3 Inhibitor: traps water and phosphate in GI lumen; pain modulation via TRPV-1
- 50 mg BID resulted in significantly higher CSBM responder rate than placebo
- Primary endpoint: Increase ≥1 CSBM/week from baseline for ≥6/12 treatment weeks
- FDA approved for IBS-C 9/2019
- Most frequent AEs: diarrhea, headache, nausea, abdominal pain

Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=308)</th>
<th>Tenapanor 50 mg BID</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 CSBM increase</td>
<td>48.3</td>
<td>50.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥30% abdominal pain reduction</td>
<td>60.7</td>
<td>64.1</td>
<td></td>
</tr>
<tr>
<td>≥30% abdominal pain reduction and ≥1 CSBM increase in the same week</td>
<td>50.0</td>
<td>52.8</td>
<td></td>
</tr>
</tbody>
</table>

Secondary Endpoints

- Chey WD et al. Am J Gastroenterol 2017;112:763–774
- Lackner JM et al. 2018 Digestive Disease Week Annual Scientific Meeting. Abstract 455.

Bile Acid Sequestrants

- BAM: prevalence estimates 1%; 25-50% in IBS-D
- Excess bile acids in colon
  - Increase visceral sensation and fluid secretion via intracellular cAMP, mucosal permeability and/or Cl secretion
- Uncontrolled trials of bile acid sequestrants suggest benefit in IBS; 4-16 gm/day
  - Availability of 7C4 serum test may identify likely responders; needs more study
Ramosetron

- High 5-HT3 binding affinity: potent and prolonged receptor blockade and antiemetic effects compared with older 5-HT3 antagonists
- Approved in Asia
- Meta-analysis of 4 IBS RCTs; 1623 patients (ramosetron vs placebo)
  - Overall IBS relief OR 1.70 (95% CI: 1.48 to 1.95)
  - Relief of abdominal pain/discomfort OR 1.41 (95% CI: 1.24 to 1.59)
  - Improvement in diarrhea OR 1.71 (95% CI: 1.40 to 2.08)
  - Higher rates of constipation; no colon ischemia

Mast cell stabilizers

- Ketotifen
  - Up to 6 mg BID increased discomfort threshold with visceral hypersensitivity, improved abdominal pain bloating, flatulence, diarrhea, incomplete evacuation, HRQOL (n=15)1
  - No effect on release of tryptase and histamine from rectal biopsies demonstrated, mechanisms other than mast cell stabilization H1 receptor antagonism may be involved1
- Cromolyn (disodium cromoglycate)
  - Significantly decreased abdominal pain behaviors induced by colorectal distension in animal model independent of mast cell mediator release2


TRPV Agents

- Up-regulation/sensitization of receptors on peripheral nerve terminals of nociceptors is an important mechanism of visceral hypersensitivity
- Transient reporter potential channel V1 (TRPV1), is involved in this process
  - Responsive to capsaicin, heat, acidosis, and endovanilloids
- Ebastine: H1RA
  - Small placebo-controlled study (n=55) showed 20 mg/d reduced visceral hypersensitivity and abdominal pain in patients with IBS

Human Milk Oligosaccharides (HMOs)

HMOs in infant health:
- Primary determinant of gut microbiota
- Involved in maturation of gut barrier and gut immune function; bind pathogens
- Specifically increase bifidobacteria abundance
- Increase concentration of metabolites essential for gut barrier functioning and immune modulation

HMOs in IBS:
- Decrease in total % of stool consistency (BSFS)
  - Significantly reduced total % of abnormal stools (diarrhea + constipation) compared to baseline at \( P < .001 \)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study population</th>
<th>Setting</th>
<th>Study Site</th>
<th>Sample Size</th>
<th>IBS Criteria</th>
<th>IBS Subtypes</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2017</td>
<td>Single center</td>
<td>Primary care</td>
<td>Norway</td>
<td>90</td>
<td>Rome III</td>
<td>IBS-D, IBS-C</td>
<td>Decrease in IBS-SOS &gt; 75 points at 3 months</td>
</tr>
<tr>
<td>Holvoet, 2018</td>
<td>Single center</td>
<td>Tertiary care</td>
<td>Belgium</td>
<td>64</td>
<td>Rome III</td>
<td>Predominant bloating and non-C</td>
<td>Yes to question of improvement in overall symptoms and abdominal bloating at 12 weeks</td>
</tr>
<tr>
<td>Aroniadis, 2018</td>
<td>Multi-center</td>
<td>Primary, secondary, and tertiary care</td>
<td>USA</td>
<td>68</td>
<td>Rome III</td>
<td>IBS-D</td>
<td>Decrease in IBS-SOS ≥ 50 points at 12 weeks</td>
</tr>
<tr>
<td>Halkjaer, 2018</td>
<td>Two centers</td>
<td>Tertiary care</td>
<td>Denmark</td>
<td>52</td>
<td>Rome III</td>
<td>All subtypes</td>
<td>Decrease in IBS-SOS ≥ 50 points at 5 months</td>
</tr>
</tbody>
</table>

FMT, fecal microbiota transplantation; IBS-QOL, Irritable Bowel Syndrome Quality of Life Measure; HADS, Hospital Anxiety and Depression Scale
Vibrating Capsule

Orally administrated vibrating capsule stimulates bowel motility by mechanically inducing vibrations in the large intestine.

VIBRATING CAPSULE

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PATIENT REPORTING APP

ACTIVATING BASE UNIT

The base unit activates the capsule prior to use. After placing a vibrating capsule into the designated groove, an activation signal is transmitted by the base unit to the capsule.

Vibrating Capsule Proof of Concept Trial

- 24 patients with CIC (Rome III) randomized to vibrating vs sham capsule (2/week x 8 weeks)
  - Endpoints:
    - Primary: Vibrating capsule vs sham colonic geometric center at 48 hours and t1/2 of ascending colon emptying
    - Secondary: colonic geometric center at 8 and 24 hours and slope of progression of colonic geometric center over the 48 hours of the transit study
  - Phase III trials ongoing for CIC with modified stimulation regimen

Management of IBS: Take Home Points

- Make a positive diagnosis with judicious diagnostic testing
- Diet, lifestyle modifications, OTC (loperamide, fiber) therapies first line
- Best clinical trial evidence
  - IBS-D: Rifaximin, Eluxadoline, Alosetron
  - IBS-C: Linacotide, Plecanatide, Lubiprostone, Tegaserod, Tenapanor
- Adjunctive therapies (use at any point)
  - Peppermint oil (for all subtypes); TCAs, SNRIs (for IBS-D/M with pain)-allow 4 weeks minimum; antispasmodics; CBT; Diet; Probiotics; Bile acid sequestrants
- Rich pipeline targeting specific etiologies/symptoms
  - Serotonergics, HMOs, tachykinin antagonists, mast cell stabilizers, FMT, glutamine, TRP agonists, cannabinoids

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Thank You!
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Questions?
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