ACG International Webinar Series:

ACG 2021 Clinical Guideline: Management of Irritable Bowel Syndrome

Hosted by Central America GI Associations

Speaker: Brian E. Lacy, PhD, MD, FACP
Professor of Medicine
Mayo Clinic
Jacksonville, FL

Moderator: Joaquin E. Ligoria, MD, FACP, FACP
Hospital Centro Medico
President Guatemalan Association of Gastroenterology, Hepatology and Gastrointestinal Endoscopy

ACG MEMBERSHIP BENEFITS

ACG is a community of over 15,000 GI professionals from around the world who are committed to providing quality care.

- Free Subscription to The American Journal of Gastroenterology
- Complimentary registration to the ACG Annual Scientific Meeting and dedicated International Reception
- Discount registration on ACG’s Annual Postgraduate Course and other ACG courses
- Complimentary access to the online ACG Education Universe
- Member only access to ACG’s Online Communities the Circles. Topics include: GI, Hepatitis, ACG & CCFA 180, Functional GI Health and Nutrition, and Women in GI

BENEFITS SPECIFICALLY DESIGNED FOR INTERNATIONAL MEMBERS

- International Relations Committee
- ACG Governors in Brazil, Central America, India, Italy, Japan, Mexico, Pakistan, Portugal, the United Kingdom, and the West Indies
- International GI Training Grant
- International Leadership Award
- ACG-sponsored faculty at international GI meetings

Become a Member: GI.ORG/JOIN-ACG

American College of Gastroenterology
ACG International Webinar Series
Join us for an upcoming webinar!

June
Hepatocellular Carcinoma – Hosted by Pakistan Society for the Study of Liver Diseases
Speaker: Patricia D. Jones, MD, MSPH
Moderator: Dr. Zaigham Abbas
Date: Saturday, June 5th at 12:00 pm EST

August
Clinical Pearls for the Management of Pregnancy in IBD
Speaker: Sunanda V. Kane, MD, MSPH, FACP
Moderator: Dr. Gillian Watermeyer, MD
Date: Tuesday, August 31st at 12:00 pm EST

Visit https://gi.org/education/international-virtual-grand-rounds/ to Register

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.
ACG 2021 Clinical Guideline: Management of Irritable Bowel Syndrome

May 20, 2021

Brian E. Lacy, PhD, MD, FACG
Professor of Medicine
Mayo Clinic
Jacksonville, FL

Why an ACG Guideline on IBS?

- IBS is prevalent and is a common source of referrals
- IBS causes a significant impact to the health care system
- Monographs, position statements and narrative reviews provide valuable information but are not subject to rigorous GRADE methodology
- Significant new information on IBS is available
What we did and did not do

• Focused on key diagnostic and therapeutic questions
• Goal was to address key issues that could be used in clinic today
• Not meant to be a comprehensive review of all IBS subject areas
• Key suggestions about what NOT to do; these may be even more important than what to do

How did we prepare this guideline?

• Careful review of the literature to identify key issues
• Panel of experts assembled
• 25 key questions developed using PICO format (population, intervention, comparator, outcome)
  – 9 diagnostic; 16 therapeutic
• Evaluation and management issues primarily focused on options available in North America

PICO Statements and Methods

Table 3. Population, intervention, comparator, and outcome statements evaluated in the IBS guideline

<table>
<thead>
<tr>
<th>Internal question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should patients with IBS and diarrhea symptoms be checked for celiac disease?</td>
<td>Adult patients with IBS and diarrhea</td>
<td>Serologic tests for celiac disease</td>
<td>Adult patients without celiac disease</td>
<td>Prevalence of patients with IBS and celiac disease</td>
<td>1. Cohort studies</td>
</tr>
<tr>
<td>Can fecal calprotectin, fecal lactulose, and/or CRP be used to rule out IBD in patients with IBS and diarrhea symptoms?</td>
<td>Adults patients with IBS and diarrhea</td>
<td>Evaluation of CRP, fecal calprotectin, and fecal lactulose</td>
<td>Patients with IBD, healthy controls</td>
<td>Clinical utility of testing to detect IBD in IBS patients (sensitivity, specificity, and positive and negative predictive value)</td>
<td>1. Cohort studies</td>
</tr>
<tr>
<td>Should IBS patients be routinely checked for stool pathogens?</td>
<td>Adult patients with IBS and diarrhea</td>
<td>Tests for stool pathogens</td>
<td>Healthy controls; patients with known Giardia infection</td>
<td>Prevalence of enteric pathogens in patients with IBS</td>
<td>1. Population studies</td>
</tr>
<tr>
<td>Should patients younger than 45 years routinely undergo colonoscopy for IBS symptoms?</td>
<td>Adult patients with IBS</td>
<td>Colonoscopy</td>
<td>Adults undergoing screening colonoscopy</td>
<td>Prevalence of abnormal colonoscopic findings in patients with IBS</td>
<td>1. Prospective trials</td>
</tr>
</tbody>
</table>

How did we prepare this guideline?

- Comprehensive literature review performed
- Emphasis on R, DB, PC trials
  - ≥ 10 subjects; ≥ 4 weeks
- Modified Delphi approach used to obtain consensus
- Monthly meetings by teleconference
- One in-person meeting
- GRADE analysis by experts
GRADE Methodology

- Grading of Recommendations, Assessment, Development and Evaluation
- Quality of evidence determined
- Strength of recommendation provided

GRADE Recommendations and Quality of Evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong - The strength of recommendation is given as strong if most patients should receive the recommended course of action</td>
<td>High – the estimate of effect is unlikely to change with new data</td>
</tr>
<tr>
<td>Conditional - The strength of recommendation is given as conditional if many patients should have this recommended course of action, but different choices may be appropriate for some patients</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Very low - estimate of effect is very uncertain</td>
</tr>
</tbody>
</table>
STATEMENT 1. WE RECOMMEND THAT SEROLOGIC TESTING BE PERFORMED TO RULE OUT CELIAC DISEASE IN PATIENTS WITH IBS AND DIARRHEA SYMPTOMS.

- **Strong recommendation; moderate quality of evidence.**
- Seroprevalence of celiac disease was 1.4% in a study of 18K NA subjects
- Biopsy proven CD in NA estimated at 0.5%
- Meta-analysis of 36 studies (n = 15,256; 9,275 had IBS)
  - presence of antibodies -2.6% (CI 1.6-3.8%)
  - biopsy proven - 3.3% (CI 2.3 -4.5%)
- Increased CD rates in IBS subgroups:
  - IBS-D – 5.7% (CI 3.0 -9.1%)
  - IBS-M – 3.4% (CI 1.4 -6.2%)
  - IBS-C – 2.1% (CI 0.9 -3.8%)
- **Bottom line:** check celiac serologies in patients with IBS-D, IBS-M symptoms


STATEMENT 2. WE SUGGEST THAT EITHER FECAL CALPROTECTIN\(^1\) OR FECAL LACTOFERRIN \(^2\) AND C-REACTIVE PROTEIN\(^1\) BE CHECKED IN PATIENTS WITHOUT ALARM FEATURES AND WITH SUSPECTED IBS AND DIARRHEA SYMPTOMS TO RULE OUT INFLAMMATORY BOWEL DISEASE.

- \(^1\)**Strong recommendation; moderate quality of evidence (CRP, fecal calprotectin)**
- \(^2\)**Strong recommendation; very low quality of evidence (fecal lactoferrin)**
- The pretest probability of IBD in IBS patients is low (<0.5 – 1.2%)
- However, the absence of a biomarker for IBS raises concerns over missed IBD
- ESR cannot discriminate between IBS and IBD – do not use this
- CRP < 0.5 mg/dl - < 1% chance of having IBD
- fCalprotectin compared to endoscopy: sensitivity of 93%; specificity of 96%
- fLactoferrin has a lower sensitivity (67-86%) but higher specificity (96-100%)

13


14
STATEMENT 3. WE RECOMMEND AGAINST ROUTINE STOOL TESTING FOR ENTERIC PATHOGENS IN ALL IBS PATIENTS.

- Conditional recommendation; low quality of evidence.
- Post-infection IBS accounts for at least 11% of cases (W > M; prior antibiotics)
- Viruses, bacteria and parasites are all potential culprits
- For most patients, these infections resolve spontaneously, and IBS does not develop
- However, RR of developing IBS after Giardiasis is 3.4 (CI 2.9-3.9); testing is indicated

<table>
<thead>
<tr>
<th>Table 5. Centers for Disease Control and Prevention listing of risk factors for development of Giardia infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors for Giardiasis</td>
</tr>
<tr>
<td>Children in childcare settings, in particular, diaper-aged children</td>
</tr>
<tr>
<td>Close contacts of people with Giardiasis (for example, people living in the same household) or people who care for those sick with Giardiasis</td>
</tr>
<tr>
<td>People who drink water or use ice made from places where Giardia may live (for example, untreated or improperly treated water from lakes, streams, or wells)</td>
</tr>
<tr>
<td>Backpackers, hikers, and campers who drink unsanitary water or who do not practice good hygiene (for example, proper handwashing)</td>
</tr>
<tr>
<td>People who swallow water while swimming and playing in recreational water</td>
</tr>
<tr>
<td>People exposed to human feces through sexual contact</td>
</tr>
<tr>
<td>International travelers where Giarda may live, especially in lakes, rivers, springs, ponds, and streams</td>
</tr>
<tr>
<td>Modified from Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWEDI). 2015 (Public Domain).</td>
</tr>
</tbody>
</table>

STATEMENT 4. WE RECOMMEND AGAINST ROUTINE COLONOSCOPY IN PATIENTS WITH IBS SYMPTOMS UNDER AGE 45 WITHOUT WARNING SIGNS.

- Conditional recommendation; low quality of evidence.
- Large US study did not identify polyps or cancer more frequently in IBS patients
  - 7.7% IBS patients with polyps vs. 26.1% for non-IBS patients
- Discomfort during colonoscopy is not a marker for the presence of IBS
- CRC is unlikely in a young patient without a family history and no warning signs
- Microscopic colitis is unlikely in patients under age 60
- A normal colonoscopy does not reassure IBS patients
- Bottom line: perform age-appropriate screening
- If symptoms persist despite reasonable therapeutic intervention(s), then colonoscopy is reasonable, but don’t be surprised if normal
STATEMENT 5. WE SUGGEST A POSITIVE DIAGNOSTIC STRATEGY AS COMPARED TO A DIAGNOSTIC STRATEGY OF EXCLUSION FOR PATIENTS WITH SYMPTOMS OF IBS TO IMPROVE TIME TO INITIATE APPROPRIATE THERAPY.

- Consensus recommendation; unable to assess using GRADE methodology.
- Although no serologic biomarker available, a thoughtful history, careful PE, limited diagnostic testing and use of Rome IV is quite accurate
- Extensive testing is unlikely to unearth uncovered diagnoses
- Extensive testing does not reassure patients
- At one year, patients randomized to a positive diagnostic strategy did just as well as those randomized to a diagnosis of exclusion; no cases of celiac, IBD, cancer found
- Earlier diagnosis leads to earlier treatment
- **Bottom line:** be confident; make the diagnosis; initiate treatment at the first visit

STATEMENT 6. WE RECOMMEND A POSITIVE DIAGNOSTIC STRATEGY AS COMPARED TO A DIAGNOSTIC STRATEGY OF EXCLUSION FOR PATIENTS WITH SYMPTOMS OF IBS TO IMPROVE COST EFFECTIVENESS.

- Strong recommendation; high quality of evidence.
- Clear, positive diagnostic language makes a difference
  - “you have IBS” NOT “it’s possible that you might have”
  - “your diagnosis is IBS” NOT “there are a lot of things you might have, and one is IBS”
- Interestingly, patients with an organic disease are more likely to be given a diagnosis using positive language, compared to those with IBS.
- A large, health-care based study in both IBS-D and IBS-C patients showed that 80% of costs were associated with a diagnosis of exclusion approach
- A prospective study of 300 patients in a primary care setting demonstrated that health care costs were 40% lower with a positive diagnostic strategy
- **Bottom line:** Use a positive diagnostic strategy to minimize testing and costs
STATEMENT 7. WE SUGGEST THAT CATEGORIZING PATIENT'S BASED ON AN ACCURATE IBS SUBTYPE IMPROVES PATIENT THERAPY.

- Consensus recommendation; unable to assess using GRADE methodology.
- Although abdominal pain is a defining characteristic, bowel habits are critical to diagnosis.
- Bristol Stool Form Scale can be used to help patients assess bowel symptoms.
- Stool consistency should be determined based on the days with abnormal bowel movements, OFF therapy, ideally for 2 weeks.
- FDA approved treatments were developed with an emphasis on IBS subtype.
- Still no approved medications for IBS-M.

---

Type 1
Type 2
Type 3
Type 4
Type 5
Type 6
Type 7

FC: Functional constipation
FDr: Functional diarrhea
IBS-C: Irritable bowel syndrome with predominant constipation
IBS-D: Irritable bowel syndrome with predominant diarrhea
IBS-M: Irritable bowel syndrome with mixed bowel habits (D and C)

Lacy BE, Mearin FC, et al. Gastroenterology 2016; 150: 1393-1407
STATEMENT 8. WE DO NOT RECOMMEND TESTING FOR FOOD ALLERGIES AND FOOD SENSITIVITIES IN ALL IBS PATIENTS UNLESS THERE ARE REPRODUCIBLE SYMPTOMS CONCERNING FOR A FOOD ALLERGY.

- Consensus recommendation; unable to assess using GRADE methodology.
- Up to 20% of the general population reports adverse reactions to food
- When rechallenged, only 2-3% report recurrent symptoms
- Up to 50% of IBS patients report adverse reactions to food
- True food allergies are uncommon – 1% of adults
- More likely to occur in atopic individuals
- Typically IgE mediated, less commonly non-IgE or a mixed response
- Diagnosis is based on typical symptoms
- Skin prick test is positive in only 50% of patients with true food allergies
- **Bottom line:** Most adverse reactions are intolerances not allergies. Reassure your patient
Classic Symptoms of Food Allergies

- Itching of palate and lips
- Mouth, tongue, lip swelling (angioedema)
- Rhinorrhea/periorbital edema
- Bronchospasm and laryngospasm
- Nausea, vomiting
- Abdominal pain/diarrhea
- Urticaria
- Dysphagia
- Hypotension
- Anaphylaxis

Common Food Allergies

- **Children**
  - Cow’s milk - 2.5%
  - Egg – 1.5%
  - Wheat – 1.0 - 3%
  - Peanut – 1.0%
  - Soy – 0.4%
  - Tree nut – 0.5%
  - Shellfish – 0.1%
  - Finned fish – 0.1%
  - Sesame – 0.1%

- **Adults**
  - Shellfish – 2%
  - Peanut – 0.6%
  - Tree nut – 0.6%
  - Fish – 0.4%
  - Cow’s milk – 0.3%
  - Egg – 0.2%
  - Wheat – 0.4%
  - Sesame – 0.1%

Sicherer, Sampson, J Clin All Immunol 125; 2009
STATEMENT 9. WE SUGGEST THAT ANORECTAL PHYSIOLOGY TESTING BE PERFORMED IN PATIENTS WITH IBS AND SYMPTOMS SUGGESTIVE OF A PELVIC FLOOR DISORDER AND/OR REFRACTORY CONSTIPATION NOT RESPONSIVE TO STANDARD MEDICAL THERAPY.

- Consensus recommendation; unable to assess using GRADE methodology.
- Prevalence of anorectal dysfunction approaches 40% in tertiary care practice
- Not limited to IBS-C; seen in IBS-D and IBS-M as well
- Symptoms are not predictive of DD
- Accurate diagnosis of DD requires testing with 2 of 3 tests being abnormal:
  - Anorectal manometry (ARM)
  - Balloon expulsion test (BET)
  - MR defecography

DD – dyssynergic defecation

Position 1
Check anal tone at rest
Ask patient to squeeze

Position 3
Expulsion

Table 6. Clinical symptoms, rectal examination findings, and anorectal physiologic testing suggestive of a pelvic floor disorder

<table>
<thead>
<tr>
<th>Testing</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal examination findings on inspection</td>
<td>Dermatitis/dermal erythema</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>Rectal ulcer</td>
</tr>
<tr>
<td>Gaping anus</td>
<td>Hemorrhoids</td>
</tr>
<tr>
<td>Fistula or fissure</td>
<td>Rectal scar</td>
</tr>
<tr>
<td>Anorectal abscess</td>
<td></td>
</tr>
<tr>
<td>Digital rectal examination findings suggesting dyssynergic defecation</td>
<td>Abnormal sensory perception of stool (perineal sensation testing)</td>
</tr>
<tr>
<td>Rectal distension and stool impaction</td>
<td>Contraction of the distal rectum and stool:</td>
</tr>
<tr>
<td>Abnormal relaxation of external anal sphincter and puborectalis muscles (or no relaxation with Valsalva maneuver)</td>
<td></td>
</tr>
</tbody>
</table>

Anorectal physiology findings suggesting pelvic floor disorders

| Uncordinated abdominal, rectoanal, and pelvic floor muscles           |
| Rectal hypotonicity                                                   |
| Paradoxical increase in anal sphincter pressure/puborectalis muscle pressure during relaxation or simulated evacuation |
| Prolonged balloon expulsion time                                    |
| Inadequate anal relaxation during push maneuvers                      |
| Inadequate abdominal/rectal propulsive forces                        |

*Many of these symptoms and examination findings are seen in all subtypes of irritable bowel syndrome and are not specific to pelvic floor dysfunctions.*
STATEMENT 10. WE RECOMMEND A LIMITED TRIAL OF A LOW FODMAP DIET IN PATIENTS WITH IBS TO IMPROVE GLOBAL SYMPTOMS.

- Conditional recommendation; very low quality of evidence.
- Multiple diets for IBS; most have not been tested
- Best studied - low FODMAP
- Remember: short term use
- 3 stages – substitute, reintroduce, personalize
- Long term use: risk for vitamin and micronutrient deficiencies

Proposed Mechanisms of low FODMAP diet

Werlang, Palmer, Lacy. Gastroenterol Hepatol 2019
STATEMENT 11. WE SUGGEST THAT SOLUBLE, BUT NOT INSOLUBLE, FIBER BE USED TO TREAT GLOBAL IBS SYMPTOMS.

- Strong recommendation; moderate quality of evidence.
- Fiber remains misunderstood
- Soluble – psyllium, oat bran, barley
- Insoluble – wheat bran, whole grains
- SR & MA – 15 RCTs, 946 patients
- Fiber was consistently better than pl.
- Bran did not help
- **Bottom line:** soluble fiber, especially for IBS-C patients, is reasonable


STATEMENT 12. WE RECOMMEND AGAINST THE USE OF ANTI-SPASMODICS CURRENTLY AVAILABLE IN THE UNITED STATES TO TREAT GLOBAL IBS SYMPTOMS.

- Conditional Recommendation: Low quality of evidence
- Widely used; > 3 million Rx/yr. – but little evidence to support their use
- 23 studies in IBS
- 2 for dicyclomine; 3 for hyoscine (scopolamine); 1 for hyoscyamine
- The other agents are not available in the US
- No agent available in US studied using Rome criteria
- Only 1 study performed in the US – dicyclomine
  - n = 71; 34 randomized to dicyclomine
  - 2-week trial; 40 mg bid – qid
  - pain improved compared to placebo
  - 69% reported AEs

Brenner DM, Lacy BE. Am J Gastroenterol 2021; in press
STATEMENT 13. WE SUGGEST THE USE OF PEPPERMINT TO PROVIDE RELIEF OF GLOBAL IBS SYMPTOMS.

- Conditional recommendation; low quality of evidence.
- Meta-analysis – 12 RCTs
- N = 835 patients
- RR for improving abdominal pain: 1.78 (CI 1.43-2.20)

STATEMENT 14. WE SUGGEST AGAINST PROBIOTICS FOR THE TREATMENT OF GLOBAL IBS SYMPTOMS.

- Conditional recommendation; very low level of evidence.
- Probiotics are popular; 6-7 billion dollars/yr. in US
- Theoretically appealing; data is less convincing
- Precise mechanism unknown; likely varies from patient to patient
- Meta-analysis – 37 trials in IBS; n = 4403
- Single agents generally not better than placebo
- Combination agents slightly better than placebo (RR = 0.79; CI 0.68-0.91)
- But, significant heterogeneity (I²=72%) and publication bias
- Bottom line: we still have a lot to learn

STATEMENT 15. WE SUGGEST AGAINST THE USE OF PEG PRODUCTS TO RELIEVE GLOBAL IBS SYMPTOMS IN THOSE WITH IBS-C.

- **Conditional recommendation; low quality of evidence.**
- Inexpensive, widely available; improves constipation symptoms
- 2 RCTs total in IBS patients
- Largest trial = 139 Pts
- Constipation improved, but not abdominal pain
- **Bottom line:** PEG helps constipation but not global symptoms


**Intestinal Chloride Channels**

- **Cl⁻ Ion Transport**

- **H₂O**
- **Na⁺**
- **Cl⁻**

- **Enterocytes**
- **CFTR Channel**
- **Linaclotide**
- **Plecanatide**
- **CIC-2 Channel**
- **Lubiprostone**
- **Tight junction**
STATEMENT 16. WE RECOMMEND THE USE OF CHLORIDE CHANNEL ACTIVATORS TO TREAT GLOBAL IBS-C SYMPTOMS.

- Strong recommendation; moderate quality of evidence.
- Lubiprostone is a prostaglandin E1 analog that binds to type 2 chloride channels
- Approved for the treatment of women with IBS-C – 8 mcg bid
- 3 RCTs; 1 high quality systematic review
- Compared to placebo, global IBS-C symptoms were more likely to improve
- NNT – 12.5
- Benefits persisted in an open-label extension study (n = 515)
- Nausea develops in 11%; improves by taking with food; usually resolves

Lubiprostone for IBS-C: Data from 2 Phase III Trials

- 12-week treatment period
- Overall responder = monthly responder for at least 2 of 3 months
- Monthly responder = at least moderate relief for 4/4 weeks or significant relief for 2/4 weeks

Drossman DA et al. Gastroenterology 2007; 132:639f
STATEMENT 17. WE RECOMMEND THE USE OF GUANYLATE CYCLASE ACTIVATORS TO TREAT GLOBAL IBS-C SYMPTOMS.

- Strong recommendation; high quality of evidence.
- GC-C agonists bind to receptors on intestinal epithelial cells to stimulate intestinal fluid secretion and peristalsis.
- Two FDA approved medications
  - linaclotide – 290 mcg – 14 a.a.; guanylin analog; approved in 2012
  - plecanatide – 3 mg – 16 a.a.; uroguanylin analog; approved in 2018
- Linaclotide – 3 large North American phase IIb/III trials
  - OR of responding 2.43 (compared to placebo); NNT = 6
- Plecanatide 3 large phase IIb/III trials
  - OR of responding 1.87 (compared to placebo); NNT = 9

Efficacy of Linaclotide in Patients With IBS-C

![Chart showing CSBM Mean Change from Baseline +/− SEM over weeks for Treatment Period and RW Period.]

ANCOVA = analysis of covariance; RW = randomized withdrawal


*P < 0.0001 for linaclotide patients vs placebo patients (ANCOVA).
†P < 0.001 for linaclotide/linacolotide patients vs linaclotide/placebo patients (ANCOVA).
Efficacy of Plecanatide in Patients with IBS-C

- Responder defined as a patient who was both an Abdominal Pain responder (≥ 30% reduction in worst abdominal pain) and Stool Frequency Responder (an increase of ≥ 1 CSBM from baseline), in the same week, for ≥ 6 weeks of the 12 treatment weeks.

Brenner et al, Am J Gastroenterol 2018; 113:735-745

STATEMENT 18. WE SUGGEST THAT THE 5-HT₄ AGONIST TEGASEROD BE USED TO TREAT IBS-C SYMPTOMS IN WOMEN < AGE 65 WITH ≤ 1 CARDIOVASCULAR RISK FACTORS WHO HAVE NOT ADEQUATELY RESPONDED TO SECRETAGOGUES.

- Conditional recommendation; low quality of evidence.
- Serotonin plays a vital role in GI motor and sensory function
- 11 RCTs have evaluated the efficacy of tegaserod in patients with IBS-C
- 3 pivotal studies (published) led to FDA approval
- A systematic review and MA of 11 studies: n = 9,242 IBS patients
  - Patients treated with tegaserod were less likely to have persistent IBS-C symptoms
  - (RR = .85; CI 0.80 – 0.90)
- Most common AE – diarrhea
- Storied history
  – approved 2002; voluntary withdrawal 2007; reapproved 2019

American College of Gastroenterology
Tegaserod for IBS-C in women: Pooled Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Tegaserod n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>OR (95%) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>46/212 (21.7)</td>
<td>24/214 (11.2)</td>
<td>2.21 (1.28–3.81), .004</td>
</tr>
<tr>
<td>307</td>
<td>43/203 (21.2)</td>
<td>28/204 (13.7)</td>
<td>1.70 (1.01–2.88), .047</td>
</tr>
<tr>
<td>351</td>
<td>54/208 (26.0)</td>
<td>36/209 (17.2)</td>
<td>1.68 (1.05–2.69), .030</td>
</tr>
<tr>
<td>358</td>
<td>347/737 (47.1)</td>
<td>237/713 (33.2)</td>
<td>1.77 (1.43–2.19), &lt;.001</td>
</tr>
<tr>
<td>Pooled</td>
<td>490/1360 (36.0)</td>
<td>325/1340 (24.3)</td>
<td>1.79 (1.51–2.13), &lt;.001</td>
</tr>
</tbody>
</table>

Pooled data from 4 randomized clinical trials in the on-label population (tegaserod 6 mg b.i.d.: n=1360; placebo: n=1340)

Primary Efficacy Responder Rate: ≥30% reduction in weekly abdominal pain intensity and ≥50% increase in stool frequency (≥1/week) for at least 6 of 12 weeks

Adverse events were similar between groups. No significant cardiovascular or suicide events related to tegaserod were observed


Bile Acids and IBS-D

- Bile acid diarrhea prevalence
  - 10-30% in IBS-D
- Excess bile acids in colon
  - Stimulate enteroendocrine cells and accelerates colonic transit
  - Activate visceral sensation and fluid secretion (through increased intracellular cAMP, increased mucosal permeability or chloride ion secretion)
- Diagnostic tests
  - $^{75}$SeHCAT (23-seleno-25-homotaurocholic acid)
  - C4 testing (7-alpha-hydroxy-4-cholesten-3-one)
- Treatment
  - cholestyramine, colesevelam, colestipol

American College of Gastroenterology
STATEMENT 19. WE DO NOT SUGGEST THE USE OF BILE ACID SEQUESTRANTS TO TREAT GLOBAL IBS-D SYMPTOMS.

- Conditional recommendation; very low level of evidence.
- Theory is intriguing
  - Bile salts cause diarrhea; cholecystectomy is more common in IBS patients (OR = 2.09)
- But limited data – only 2 small studies in IBS-D patients (n = 27; n = 12)
- Bile acid sequestrants may help diarrhea but are unlikely to help other cardinal global symptoms
- Testing is challenging
  - SeHCAT is the best test but not available in the US
  - Stool studies can be useful
  - Serum C4 (high) and FGF19 (low) is supportive of BAM
- **Bottom line:** we need better data

STATEMENT 20. WE RECOMMEND THE USE OF RIFAXIMIN TO TREAT GLOBAL IBS-D SYMPTOMS.

- Strong recommendation; moderate level of evidence.
- 2 large RCTs (Target 1, Target 2)
- Target 3 = retreatment trial
  - interestingly, 36% of patients did not relapse within 18 weeks
  - rifaximin superior to placebo at improving global IBS-D symptoms
- Meta-analysis of 5 studies; NNT = 5
- NNH = 8971
  + breath test prior to therapy associated with higher response rates
Rifaximin Trials: Global Relief of IBS Without Constipation

- 2 Phase 3 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 1 trial; T-II, TARGET 2 trial; Comb, Combination of both trials.
*Rifaximin is FDA-approved for non-constipation IBS.

STATEMENT 21. WE RECOMMEND THAT ALOSETRON BE USED TO RELIEVE GLOBAL IBS-D SYMPTOMS IN WOMEN WITH SEVERE SYMPTOMS WHO HAVE FAILED CONVENTIONAL THERAPY.

- Conditional recommendation; low quality of evidence.
- Alosetron - a 5-HT₃ antagonist
- Storied history
  – approved in February 2002; withdrawn November 2000; reintroduced June 2002
- Approved for women with severe IBS-D Sx who have failed “traditional therapy”
- 2 separate meta-analyses have been performed (8 RCTs and 3 RCTs)
- RR of symptom persistence 0.79 (CI 0.69 – 0.90); NNT = 7.5
- Overall symptom improvement (RR = 1.58; CI 1.42-1.75)
- Most common AE: constipation
- Uncommon AE: ischemic colitis (1: 1,000 patient-years of exposure)
- Burdensome prescribing rules have faded away
STATEMENT 22. WE SUGGEST THAT MIXED OPIOID AGONISTS/ANTAGONISTS BE USED TO TREAT GLOBAL IBS-D SYMPTOMS.

- Conditional recommendation; moderate quality of evidence.
- Eluxadoline – mixed mu/kappa opioid receptor agonist; delta antagonist
- Approved for men and women with IBS-D
- 2 large RCTs led to FDA approval in May 2015 (n = 2,423)
- 26-week trial and 52-week trial
- Primary endpoint: combined abdominal pain and stool consistency responder
- 29% response rate (eluxadoline) vs. 19.5% response rate (placebo) – weeks 1-26
- NNT = 10 & 9 for the 100 mg bid dose (weeks 1-12 and 1-26)
- Recent prospective studies have demonstrated improvement in patients with prior loperamide failure

Eluxadoline and IBS-D:
Primary endpoint of composite responders – pooled data

Safety of Eluxadoline in Patients with IBS with Diarrhea

• 2,814 IBS-D patients (Rome III criteria)
• Placebo vs. eluxadoline (75 or 100 mg b.i.d.)
• 1 Phase 2 study (12 weeks) and 2 Phase 3 studies (26 and 52 weeks)
• Most frequent AEs:
  – Constipation (2.5% vs. 7.4% vs. 8.1%)
  – Nausea (5.0 vs. 8.1 vs. 7.1%)
• 10 Patients had Sphincter of Oddi Spasm (0.5%); all occurred in patients with prior CCY
• Who not to use? alcohol abuse, prior CCY, prior pancreatitis


STATEMENT 23. WE RECOMMEND THAT TRICYCLIC ANTIDEPRESSANTS BE USED TO TREAT GLOBAL SYMPTOMS OF IBS.

• Strong recommendation; moderate quality of evidence.
• Strong body of evidence supporting use in chronic somatic neuropathic conditions
• Improve visceral and central (CNS) pain by acting on NE and DA receptors
• May improve abdominal pain via anticholinergic effects
• May improve mild depression
• 12 RCTs analyzed (n = 787)
• 6 different TCAs analyzed
• 1 study – IBS-D only; the other studies were mixed
• RR of symptoms not improving on a TCA 0.65 (CI 0.55 – 0.77)
• NNT = 4.5
### Table 7. Tricyclic antidepressants

<table>
<thead>
<tr>
<th>Name</th>
<th>Subtype</th>
<th>Recommended daily doses (mg)</th>
<th>Most common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amtriptyline available in 10-25, 50-75, and 100-mg tablets</td>
<td>Tertiary amine</td>
<td>50-100</td>
<td>Dry mouth, urinary retention, sedation, cardiac arrhythmias, sexual dysfunction, constipation, weight gain, and blurry vision</td>
</tr>
<tr>
<td>Imipramine available in 50-100-mg tablets</td>
<td>Tertiary amine</td>
<td>50-100</td>
<td>Dry mouth, urinary retention, sedation, cardiac arrhythmias, sexual dysfunction, constipation, weight gain, and blurry vision</td>
</tr>
<tr>
<td>Desipramine available in 25-100, and 100-mg tablets</td>
<td>Secondary amine</td>
<td>25-100</td>
<td>Dry mouth, urinary retention, cardiac arrhythmias, weight gain, dizziness, nausea, and headache</td>
</tr>
<tr>
<td>Norplantipine available in 10-25, and 75-mg tablets</td>
<td>Secondary amine</td>
<td>25-75</td>
<td>Dry mouth, urinary retention, cardiac arrhythmias, weight gain, dizziness, nausea, and headache</td>
</tr>
</tbody>
</table>

Tricyclic antidepressants should not be used in patients with known bundle branch block or Q prolongation. Mechanism of action of tricyclic antidepressants primarily involves inhibition of serotonin and noradrenergic receptors. Blockade of muscarinic and adrenergic receptors also occurs, but to a lesser degree. Secondary amines generally have less anticholinergic and antihistaminic effects and are thus less likely to cause sedation or constipation. Tertiary amines (amtriptyline and imipramine) are more likely to have anticholinergic and antihistaminic side effects.
STATEMENT 24. WE SUGGEST THAT GUT DIRECTED PSYCHOTHERAPIES BE USED TO TREAT GLOBAL IBS SYMPTOMS.

- Conditional recommendations; very low quality of evidence.
- IBS is a disorder of gut-brain interaction (DGBI)
- Powerful bidirectional highway
- Multiple Gut Directed Psychotherapies
  - Cognitive Behavioral Therapy (CBT)
  - Hypnotherapy
- These therapies target cognitive and affective factors that drive symptom experience
- Large RCTs for CBT show benefit: NNT of 4
- Bottom line: Don’t save for last ditch effort

Gut directed hypnotherapy is similar to low FODMAP diet for IBS

- RCT; 3 arms; n = 74
- Hypnotherapy vs. low FODMAP vs. combination
- 6 week trial
- Median age ~ 38 yrs
- Results: improvement occurred in all 3 groups
  - No difference between the 3 groups

Peters et al, APT 2016; 44: 447-459
STATEMENT 25. WE RECOMMEND AGAINST THE USE OF FECAL TRANSPLANT FOR THE TREATMENT OF GLOBAL IBS SYMPTOMS.

- **Strong recommendation; very low quality of evidence.**
- The gut microbiome plays a role in symptom generation in some IBS patients
- Altering the gut microbiome improves IBS symptoms in some patients
- FMT – fecal microbiota transplantation – effectively treats *C. difficile* colitis
- Could FMT help IBS patients?
- Meta-analysis of 4 studies; n = 254 (152 received FMT)
- Different methods used; different donors
- At 12 weeks, FMT response = 49.3%; placebo response = 51%
- Separate meta-analysis of 5 articles (n = 267). Donor stool better than autologous; NJ infusion may be better
- **Bottom line:** too early for clinical use; needs to be studied much more thoroughly

---

Efficacy of Fecal Microbiota Transplantation in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis

742 citations identified
7 studies were potentially relevant
4 studies with 254 patients met criteria
Summary

• First ever ACG Guidelines on IBS

• Things to avoid
  – Routine stool testing
  – Routine colonoscopy in young patients without warning signs
  – Routine testing for food allergies
  – Routine, long-term use of anti-spasmodic agents
  – Routine use of probiotics in all IBS patients
  – PEG products for IBS-C
  – FMT (except in a research setting)

Summary

• Practices to incorporate
  – Serologic testing for celiac disease in patients with IBS-D and IBS-M
  – Fecal calprotectin + CRP to help distinguish IBS from IBD
  – Adopt a positive diagnostic strategy and use definitive words
  – Consider anorectal testing in those with persistent symptoms
  – Secretagogues for IBS-C (chloride channel and GC-C agonists)
  – Tegaserod for women < 65 with persistent IBS-C symptoms
  – Rifaximin, alosetron and opioid agonists/antagonists for IBS-D
  – TCAs for visceral pain
  – Gut directed hypnotherapy
Thank you.

Questions?