



10TH ANNUAL
***DIGESTIVE DISEASES:
NEW ADVANCES***

September 29–30, 2023
Hyatt Regency Jersey City On The Hudson

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What's New Irritable Bowel Syndrome

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Cleveland OH



Disclosures

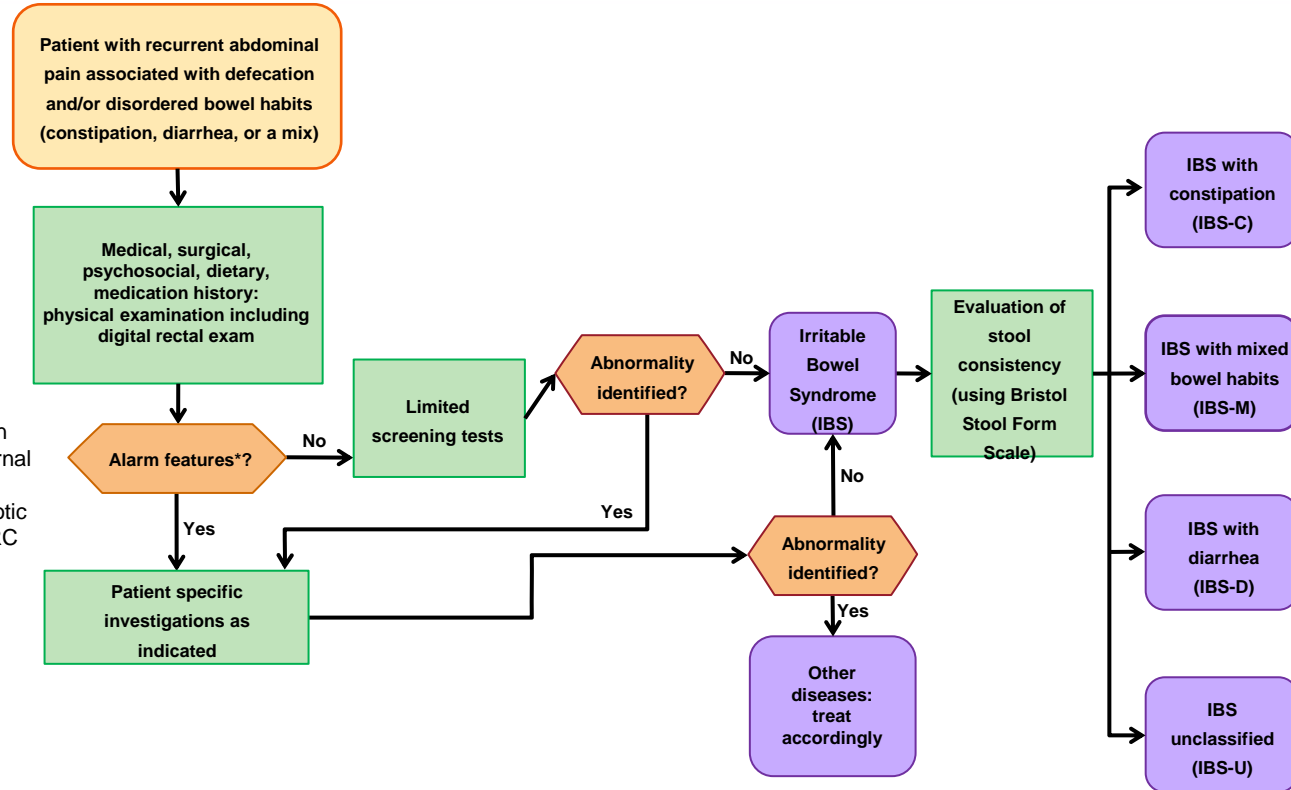
- Consultant: Ironwood, Vibrant, Ardelyx, Gimotti, Pfizer, BioAmerica
- Advisory Board: Atmo, Takeda, Aeon, Allakos, Arena, Gemelli, Evoke
- Data Monitoring Safety Board: Iqvia

IBS is Chronic Disorder of Gut-Brain Interaction (DGBI)

- 30's-40's; ♀ ≥ ♂; 4-11% adult population
- Intermittent abdominal pain/discomfort/bloating and altered bowel function
- Symptoms are frequently aggravated by food/stress
- Coexisting conditions are common including:
 - Chronic fatigue, fibromyalgia, migraine headaches,
 - interstitial cystitis, lower back pain, and anxiety/depression
- Willing to accept >2% risk of death in return for a 98% chance of cure
 - >50% willing to give up caffeine or alcohol, 40% would give up sex for 1 month in exchange of 1 month of relief

Diagnostic Algorithm for IBS

***Alarm features:** ≥ 50 years, blood in stools, iron deficiency anemia, nocturnal symptoms, unintentional weight loss, recent antibiotic use, and FH of IBD or CRC



Diagnostic Testing for Patients With Symptoms Suggestive of IBS

Test Recommended

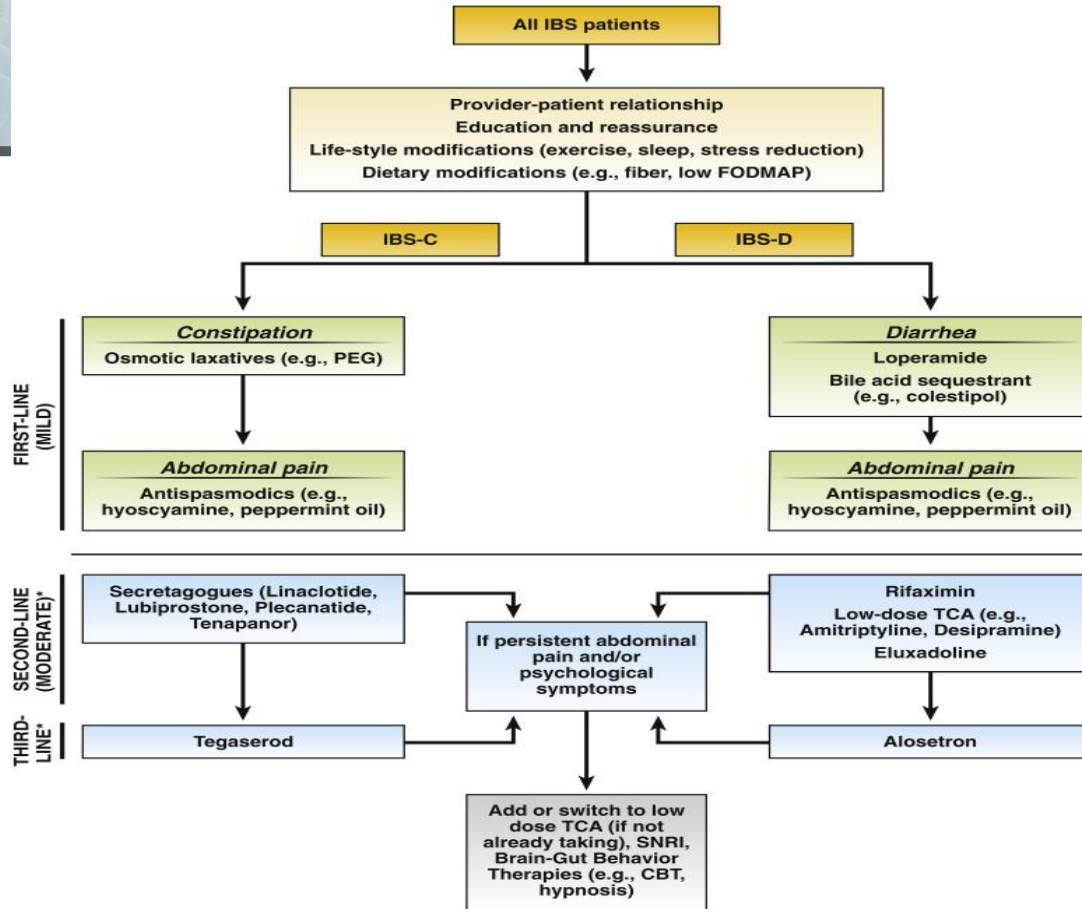
- CBC, TSH
- IBS-D
 - CRP or fecal calprotectin
 - IgA TtG ± quantitative IgA
 - When colonoscopy performed, obtain random biopsies
 - Fecal bile acids or serum 7 α C4 where available
 - Giardia Antigen
- IBS-C
 - Consider KUB r/o fecal loading (IBS-M)
 - Anorectal physiology testing if symptoms suggest pelvic floor dysfunction (IBS-C)

Test Not Recommended Routinely

- Stool testing including O&P (other than giardia)
 - With no travel to high-risk areas
- Colonoscopy < 45 years of age
- Food allergy or sensitivity testing
- Lactulose or glucose breath testing
- Imaging: X-ray, Ultrasound, CT, MRI

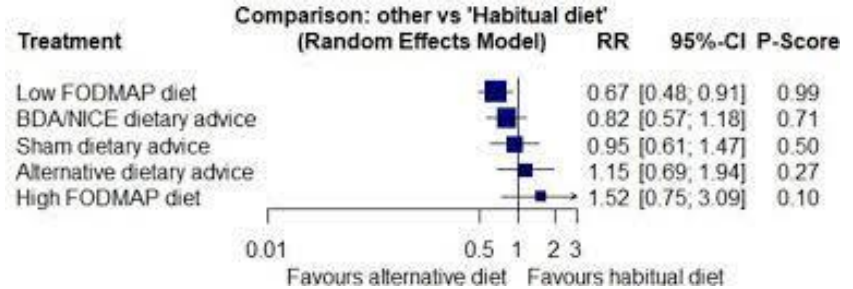
7 α C4 = 7 α -hydroxy-4-cholesten-3-one; CBC, complete blood count; CRC, colorectal screening; CRP, C-reactive protein; Ttg, tissue transglutaminase. Chey WD et al. *JAMA*. 2015;313(9):949-958; Smalley W et al. *Gastroenterology*. 2019; 157: 851–854; Lacy BE et al. *Am J Gastroenterology*. 2021;116:17–44; Moayyedi P et al. *J Can Assoc Gastroenterol*. 2019;2:6–29; Vasant DH et al. *Gut*. 2021; 70: 1214–1240.

Clinical Decision Support Tool: IBS Treatment



Low FODMAP Diet Systematic Review and Network Meta-Analysis

13 Studies
Global IBS symptoms
Low FODMAP diet was superior
to other interventions



Antispasmodics

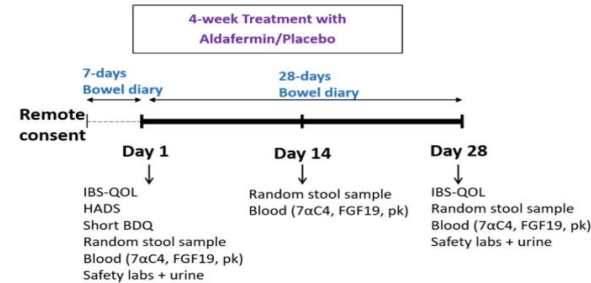
- Peppermint Oil
 - Enteric coated, delayed release
 - Meta-analyses¹ support efficacy in IBS
 - NNT = 4 global improvement; NNT = 7 abdominal pain
- Anticholinergics
 - Hyoscyamine, dicyclamine
 - Small, single-center, older studies with inconsistent results
 - Extensive experience in improving intermittent pain, frequently used prn

Bile Acids in IBS-D

- Bile acid malabsorption: prevalence estimates 25-50% in IBS-D
- Open-label trial with BA sequestrant in IBS showed promise in relieving symptoms
- FGF-19 regulates BA synthesis
 - FGF19 is released from the ileal enterocytes in response to bile acids and suppresses bile acids synthesis in hepatocytes

Effects of FGF19 Analogue Aldafermin in Patients With Bile Acid Diarrhea: A Randomized, Placebo-Control Trial

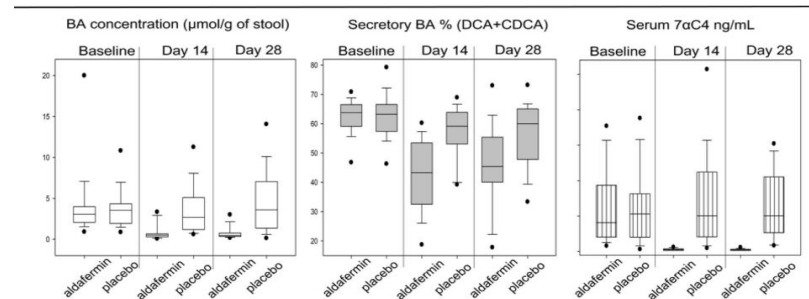
BouSaba et al in press



30 women

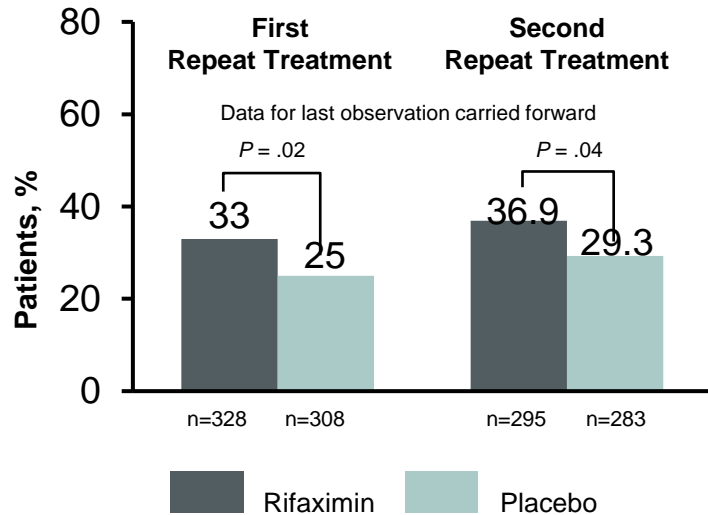
No change in pain or stool frequency (days 1-28)

Numerical improvement in consistency days 15-28



Rifaximin for IBS-D

Retreatment Efficacy FDA Responder

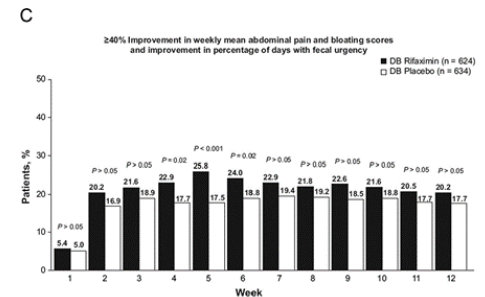
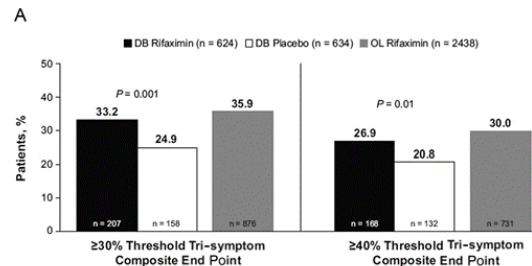


Original Research

Rifaximin Treatment for Individual and Multiple Symptoms of Irritable Bowel Syndrome With Diarrhea: An Analysis Using New End Points

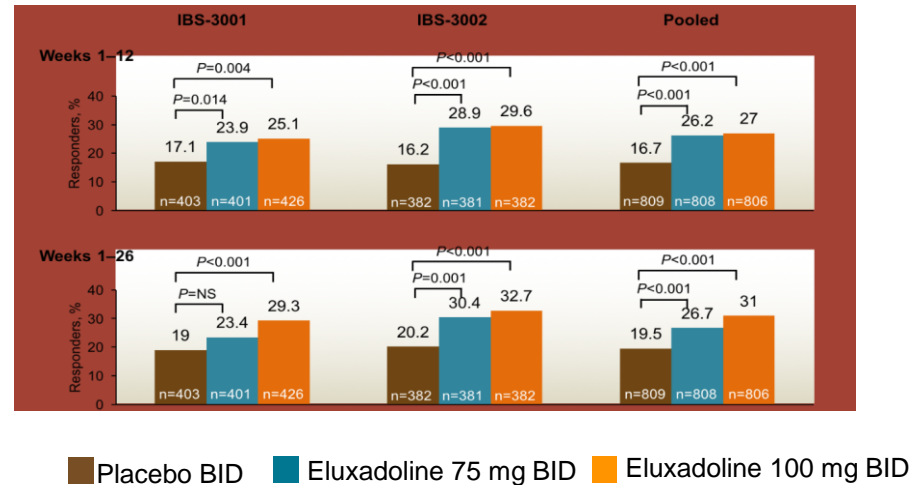
Brian E. Lacy, MD, PhD¹; Lin Chang, MD²; Satish S.C. Rao, MD, PhD³; Zeev Heimanson, PharmD⁴; and Gregory S. Sayuk, MD, MPH⁵

A novel tri-symptom composite end point (abdominal pain, bloating, fecal urgency),



Eluxadoline a Mu-opioid Agonist for IBS-D

- μ - and κ -opioid receptor agonist and δ -opioid receptor antagonist
- 3 RCT, 3235 patients
- Dosing: 100 mg BID
- AEs: Constipation, abdominal pain, SO spasm, pancreatitis
 - Contraindicated if no GB or h/o pancreatitis, heavy ETOH users



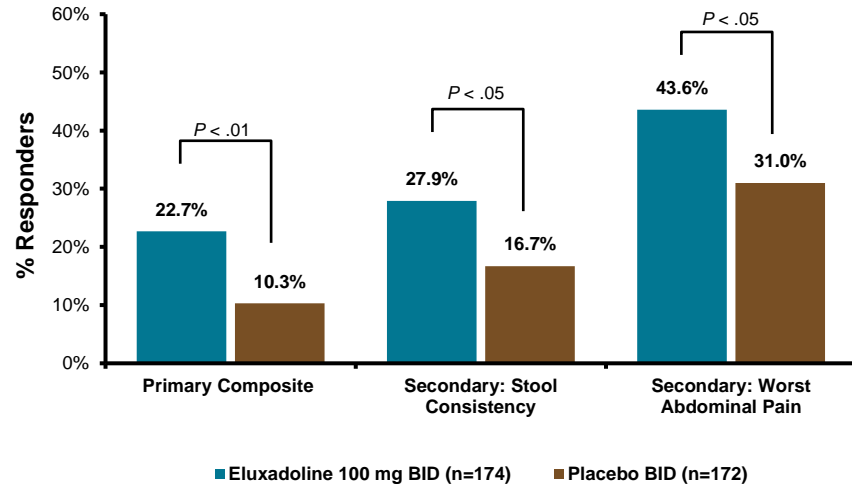
Composite responder defined as: $\geq 30\%$ reduction in worst abdominal pain AND improvement in stool consistency of < 5 on the BSFS for $\geq 50\%$ of days in the trial.

Fujita W et al. *Biochemical Pharmacology*. 2014;92(3):448-4565; Wade PR et al. *British Journal of Pharmacology*. 2012;167(5):1111-1125;

Lembo AJ et al. *N Engl J Med*. 2016;374(3):242-253.

Eluxadoline for IBS-D: Phase IV Trial Loperamide Failures

- Self-report failure to respond to loperamide failures in the prior 12 months to adequately control IBS-D symptoms
- AE rates comparable in both groups; no SAEs



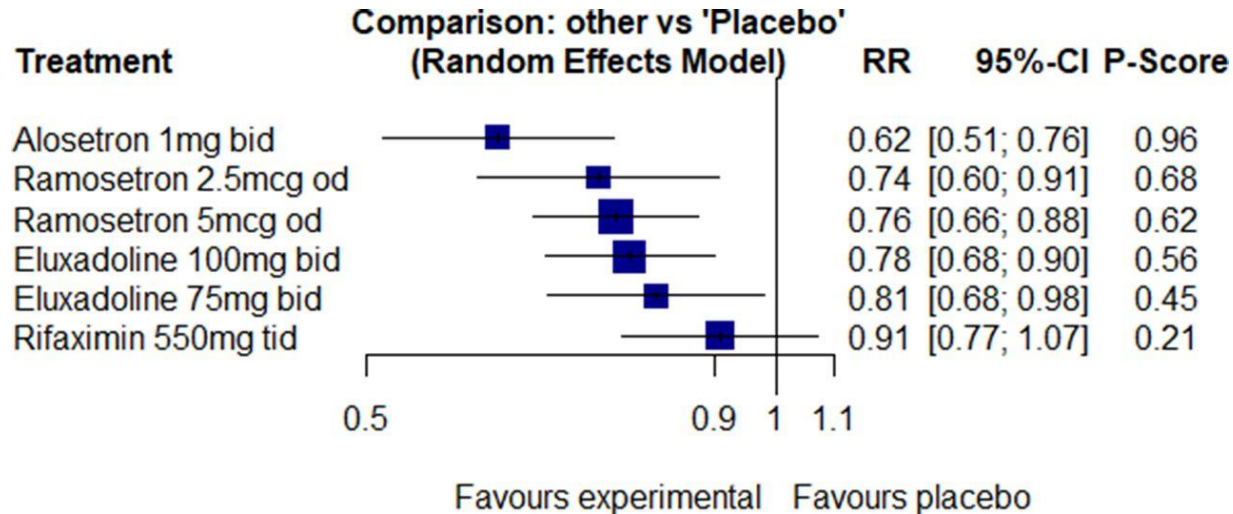
Primary Composite = Patient met composite response criteria on $\geq 50\%$ of days, defined as $\geq 40\%$ improvement in WAP c/w BL and BSS < 5 OR absence of a BM if accompanied by $\geq 40\%$ improvement in WAP.

Secondary Stool Consistency defined as BSS < 5 on $\geq 50\%$ of days.

Secondary WAP defined as $\geq 40\%$ improvement in WAP compared to BL, on $\geq 50\%$ of days.

Brenner DM et al. *Am J Gastroenterol*. 2019;114(9):1502-1511.

Efficacy of IBS-D Treatment: Network Meta-Analysis



"We found all drugs to be superior to placebo, but alosetron and ramosetron appeared to be the most effective."

ACG and AGA Guidelines: Recommendations for IBS-D Therapies

	ACG Recommendation ¹			AGA Recommendation ²		
	For or Against	Type	Quality of evidence	For or Against	Type	Quality of evidence
Loperamide				+	Conditional	Very low
Rifaximin Retreatment ^b	+	Strong	Moderate	+	Conditional	Moderate
				+	Conditional	Moderate
Alosetron ^a	+ ^a	Conditional	Low	+	Conditional	Moderate
Eluxadoline	+	Conditional	Moderate	+	Conditional	Moderate
Bile acid sequestrants	–	Conditional	Very low			

Treatment comparisons should not be made. For all recommendations, the treatment is recommended or suggested over no drug treatment.

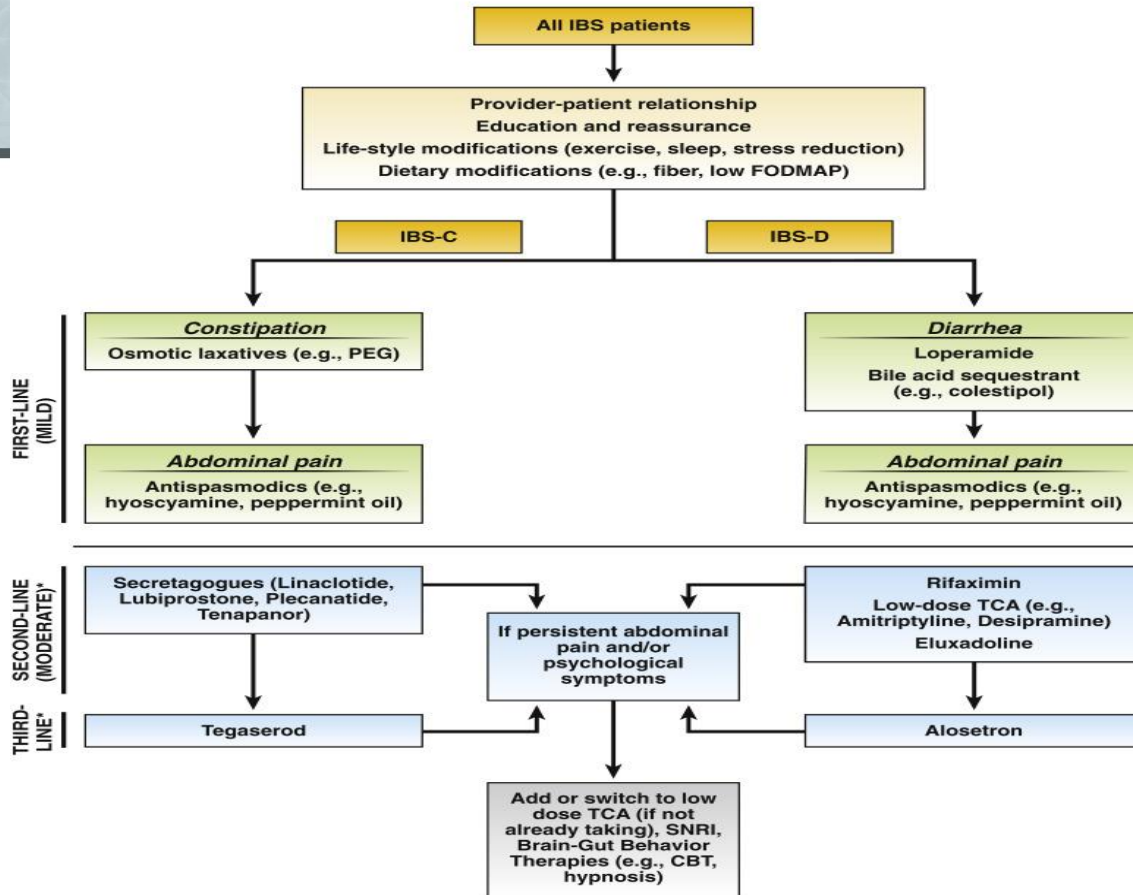
+, Recommends or suggests use; –, Recommends or suggests against use.

^aLimited to women with severe symptoms who have failed conventional therapy.

^bIn patients with initial response to rifaximin who develop recurrent symptoms.

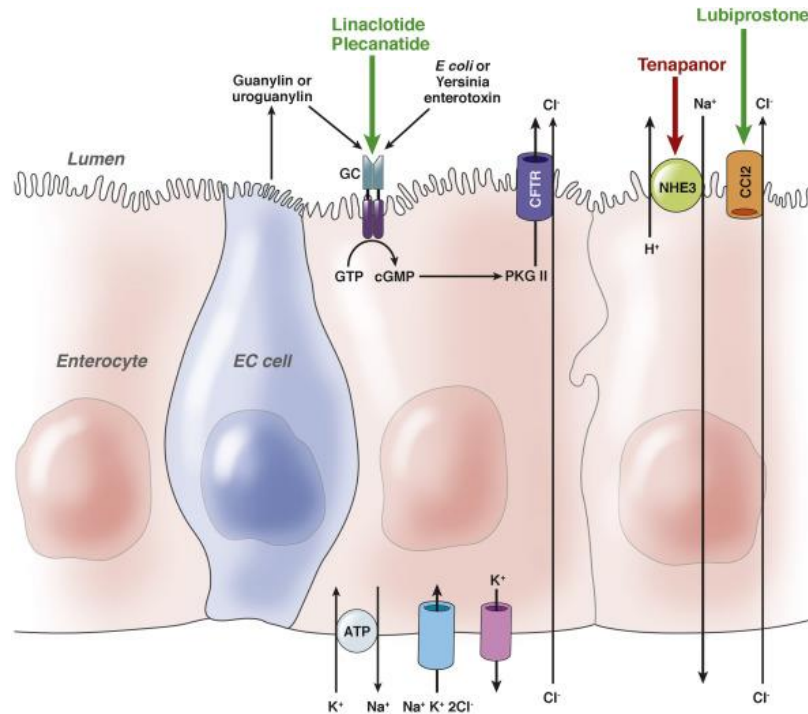
1. Lacy BE et al. *Am J Gastroenterology*. 2021;116:17–44; 2. Lembo A et al. *Gastroenterology*. 2022;163(1):137-151.

Clinical Decision Support Tool: IBS Treatment



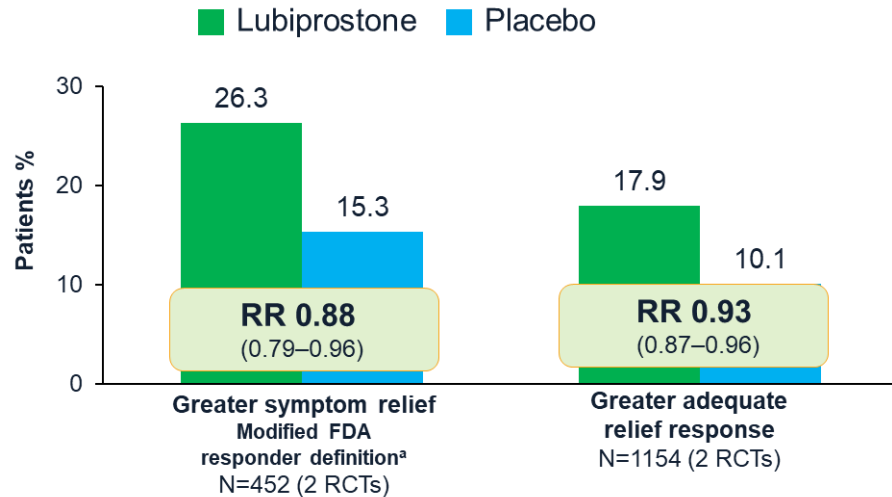
Secretagogues for IBS-C

Mechanism of Action

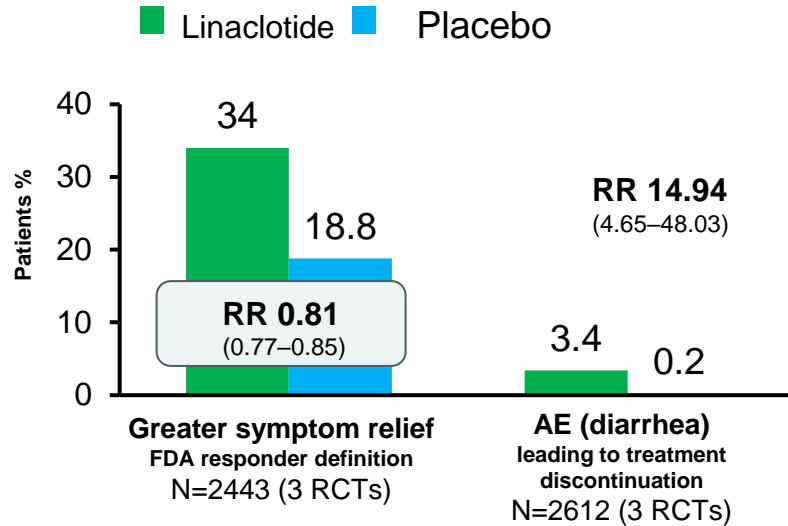


Lubiprostone (CLC2 Activator) for IBS-C

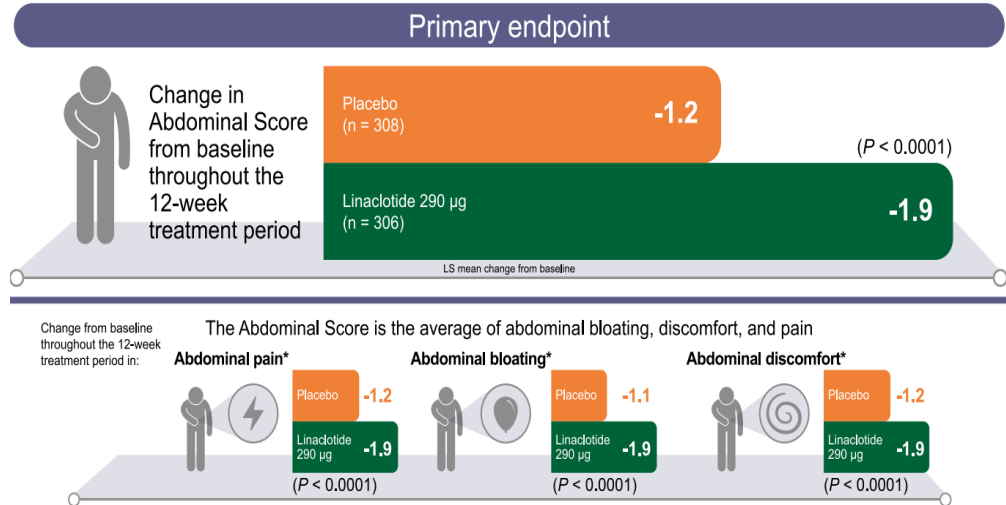
IBS-C dose: 8 mcg BID only approved in women



Linaclootide (GC-C Agonist) for IBS-C

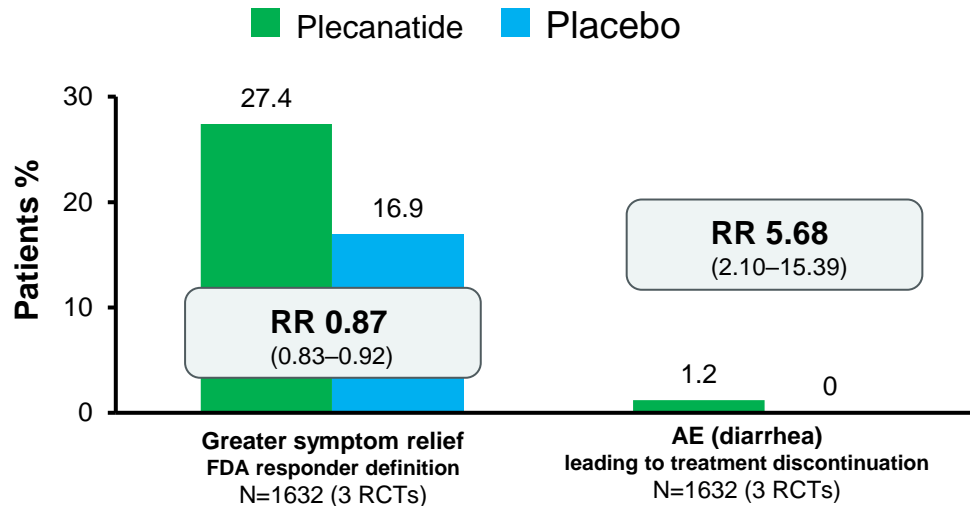


Phase 3b trial uses novel Abdominal Score to demonstrate linaclootide reduces severity of abdominal symptoms in patients with IBS-C



Plecanatide (GC-C Agonist) for IBS-C

- pH sensitive
- 3 RCT, n=2612
- IBS-C: 3mg daily



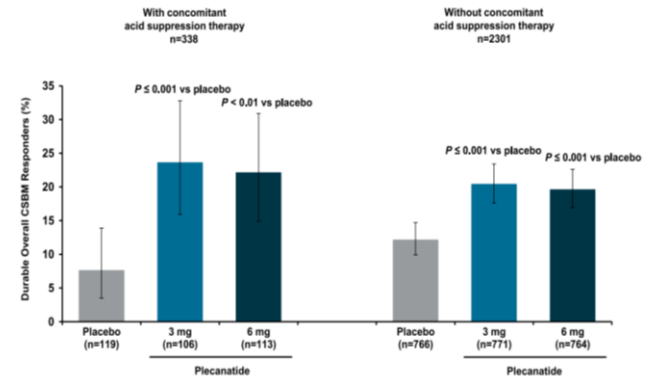
Clinical Therapeutics/Volume 44, Number 1, 2022

Original Research

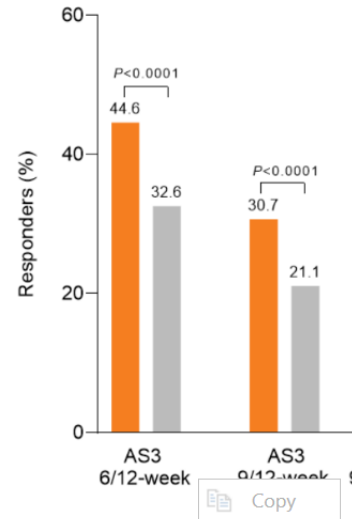
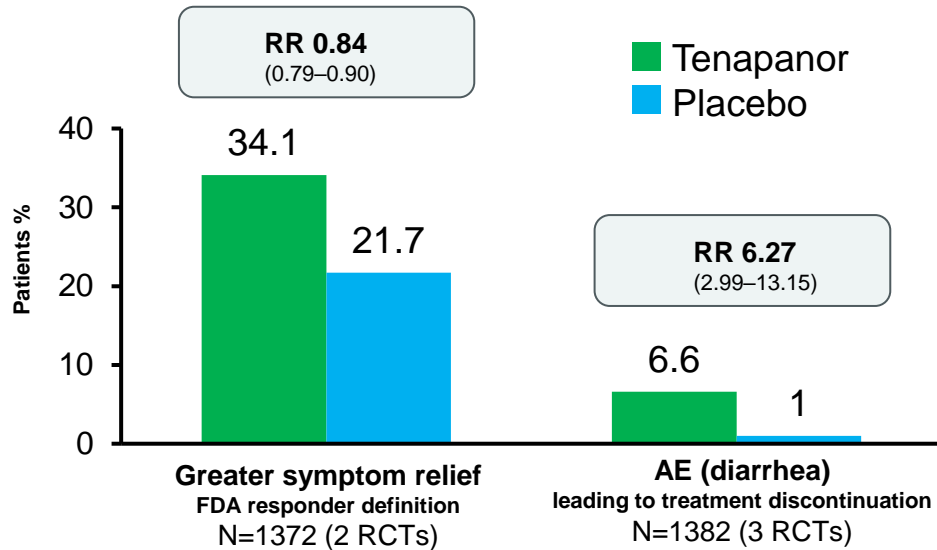
The Effect of Acid Suppression Therapy on the Safety and Efficacy of Plecanatide: Analysis of Randomized Phase III Trials

Baharak Moshiree, MD, MSc¹; Philip Schoenfeld, MD, MEd, MSc²; Howard Franklin, MD³; and Ali Rezaie, MD, MSc⁴

Two 12-week Phase III trials in CIC

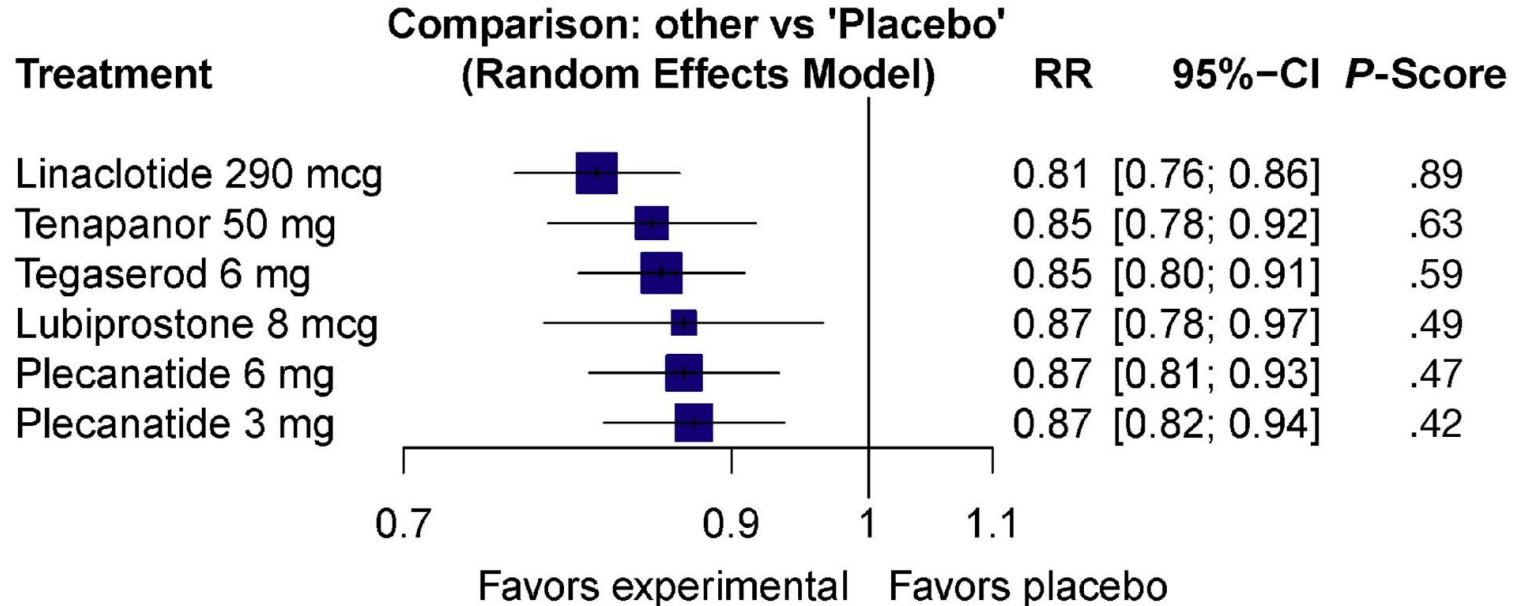


Tenapanor for IBS-C



Abdominal Symptom (AS3) Composite score:
abdominal pain, discomfort, bloating

Efficacy of IBS-C Treatments Network Meta-Analysis



“Efficacy similar among individual drugs and dosages for most end points”

ACG and AGA Guidelines: Recommendations for IBS-C Therapies

	ACG Recommendation ¹			AGA Recommendation ²		
	For or Against	Type	Quality of evidence	For or Against	Type	Quality of evidence
PEG	-	Conditional	Low	+	Conditional	Low
Lubiprostone	+	Strong	Moderate	+	Conditional	Moderate
GC-C agonists	+	Strong	High			
Linaclotide				+	Strong	High
Plecanatide				+	Conditional	Moderate
Tegaserod ^a	+	Conditional	Low	+	Conditional	Moderate
Tenapanor				+	Conditional	Moderate

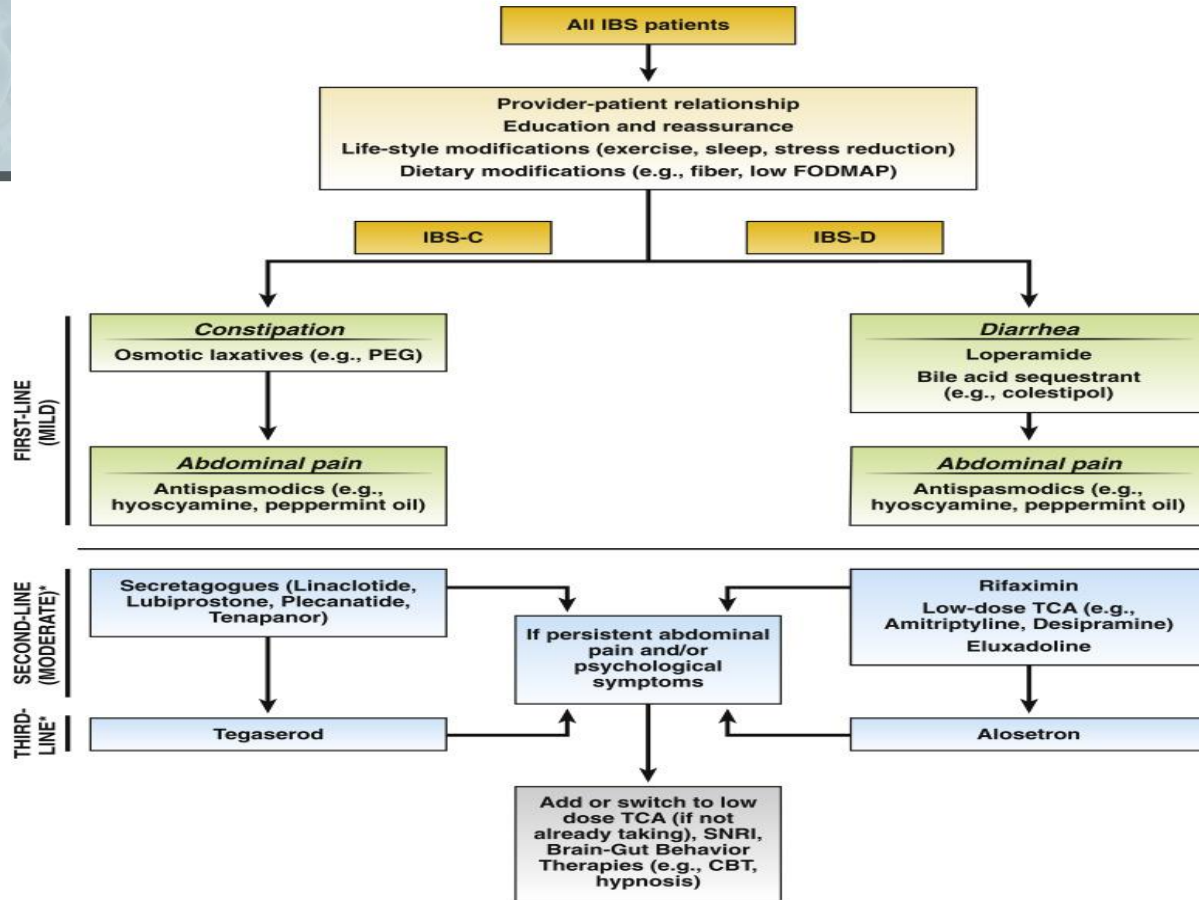
Treatment comparisons should not be made. For all recommendations, the treatment is recommended or suggested over no drug treatment.

+, Recommends or suggests use; -, Recommends or suggests against use.

^aLimited for use of tegaserod in women <65 years of age with ≤1 cardiovascular risk factors who have not adequately responded to secretagogues.

1. Lacy BE et al. *Am J Gastroenterology*. 2021;116:17–44; 2. Chang L et al. *Gastroenterology*. 2022;163(1):118-136.

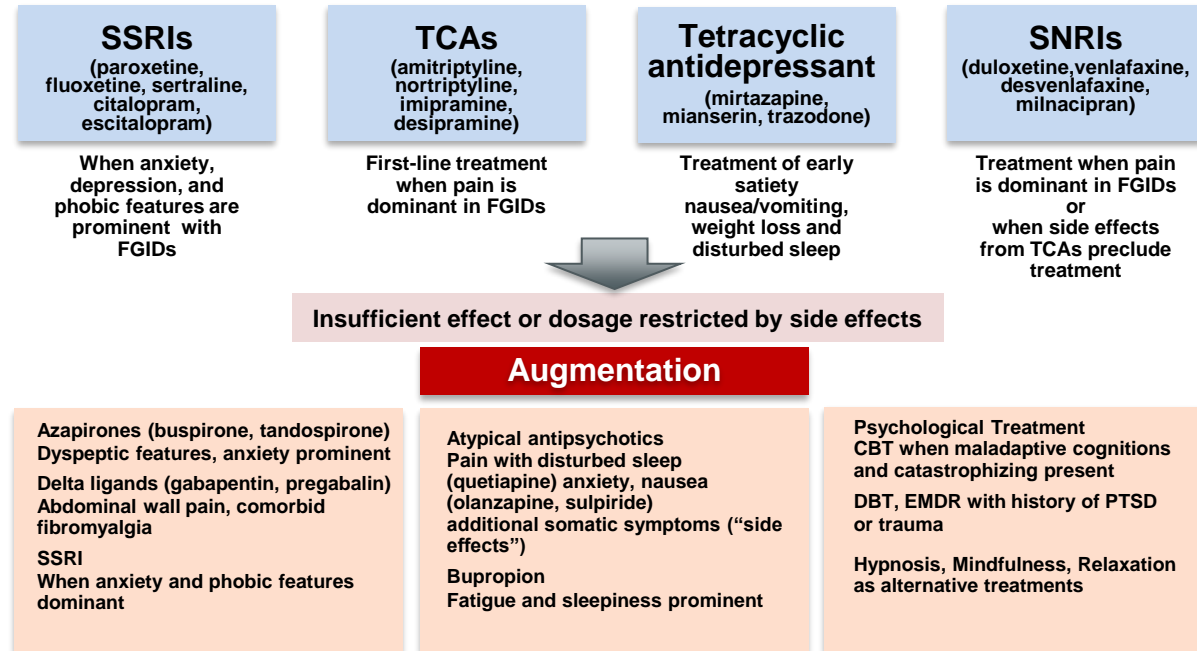
Clinical Decision Support Tool: IBS Treatment



*Selection of the medication should be based on the clinical features and needs of the patient.

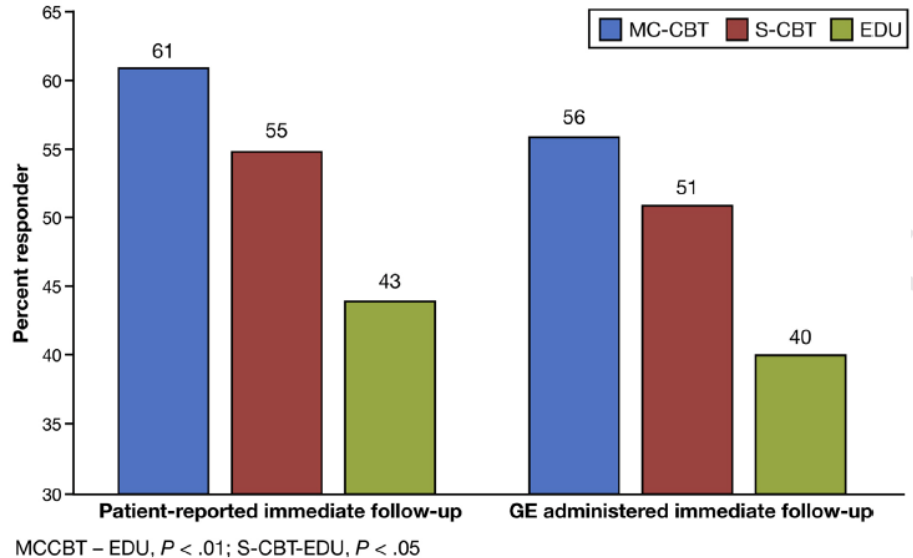
TCA, tricyclic antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; PEG, polyethylene glycol; CBT, cognitive behavioral therapy

Neuromodulation for DGBI



Cognitive Behavioral Therapy (CBT)

- Prospective randomized active comparator study; Rome III > moderate severity
- N=436 SUNY Buffalo/ Northwestern University
- MC-CBT ((N=146) 4 sessions); S-CBT ((N=146) 10 sessions); EDU ((N=145) 4 sessions)
- 1^o Endpoint: CGI-I (1-7 scale w/6-7 moderate/substantial improvement considered a responder)



THE RED SECTION: DIGITAL DIALOGUE

Behavioral Health Digital Therapeutics for Patients With Irritable Bowel Syndrome: A Primer for Gastroenterologists


Saleh, Zachary M. MD¹; Chey, William D. FACP, AGAF, FACP, RFF²; Berry, Sameer K. MD, MBA²

[Author Information](#) ⓘ

The American Journal of Gastroenterology ():10.14309/ajg.0000000000002220, March 20, 2023. | DOI: 10.14309/ajg.0000000000002220

BUY

PAP

 Metrics

Gut-Directed Hypotherapy

Regulora (MetaMe Health) - FDA-cleared, UNC protocols

Nerva - Available to download. [Dr. Simone Peters](#) and Monash Univ. includes psychoeducation readings, and breathing techniques

Non-IBS options: [Hypnosis](#), [OpenCare 2.0](#), and [Sympto Health](#)

Cognitive Behavioral Therapy

Mahana IBS - FDA-cleared

Zemedy (Bold Health) - Available to download. Chat bot AI Coach named Elle

ACG and AGA Guidelines: General IBS Therapies

	ACG Recommendation ¹			AGA Recommendation ²		
	For or Against	Type	Quality of evidence	For or Against	Type	Quality of evidence
Low FODMAP diet	+	Conditional	Very low			
Antispasmodics	-	Conditional	Low	+	Conditional	Low
Peppermint oil	+	Conditional	Low			
Probiotics	-	Conditional	Very low			
TCAs	+	Strong	Moderate	+	Conditional	Low
SSRIs				-	Conditional	Low
Gut-directed psychotherapies	+	Conditional	Very low			

+, Recommends or suggests use; -, Recommends or suggests against use.

1. Lacy BE et al. *Am J Gastroenterology*. 2021;116:17-44; 2. Lembo A et al. *Gastroenterology*. 2022;163(1):137-151.

Probiotics in IBS

ACG IBS Guideline

Recommendation

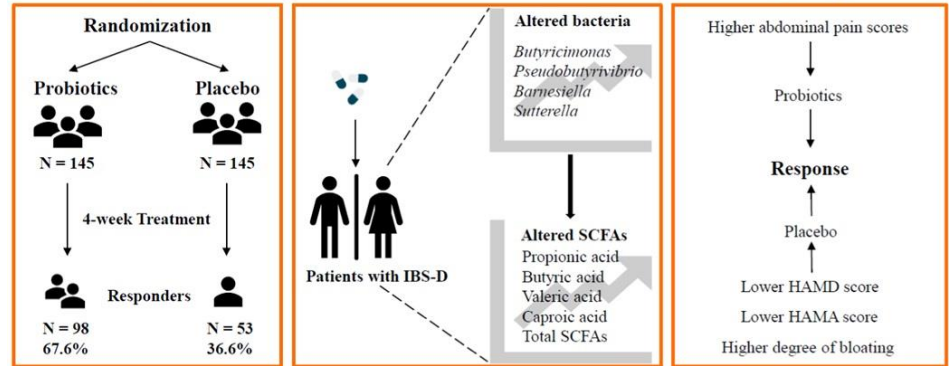
We suggest against probiotics for the treatment of global IBS symptoms.

Conditional recommendation; very low level of evidence.

Although a number of individual studies have shown efficacy, in general, most studies are of low quality (single center, lack of rigorous endpoints)

Lack of consistency (i.e., Single vs. multiorganism cocktails, dose of probiotic, combination treatments)

The Short-term Efficacy of Bifidobacterium Quadruple Viable Tablet in Patients with Diarrhea-Predominant Irritable Bowel Syndrome: Potentially Mediated by Metabolism rather than Diversity Regulation

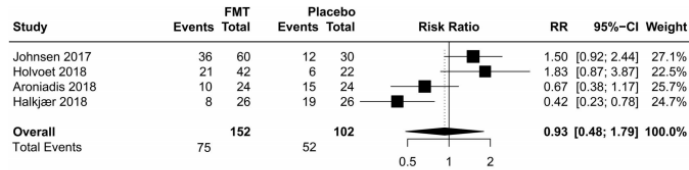


Bai et al. *Am J Gastroenterol.* [2023]. [doi: 10.14309/ajg.000000000002147]
Visual abstract by Zhiyue Xu, MD @Zhiyue Xu

AJG The American Journal of GASTROENTEROLOGY

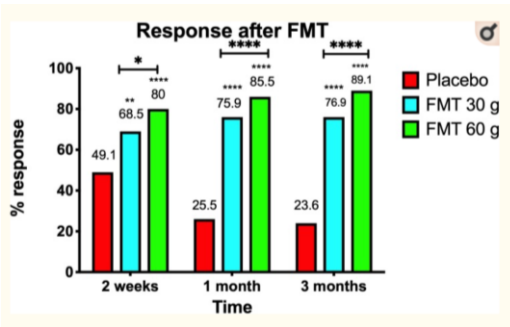
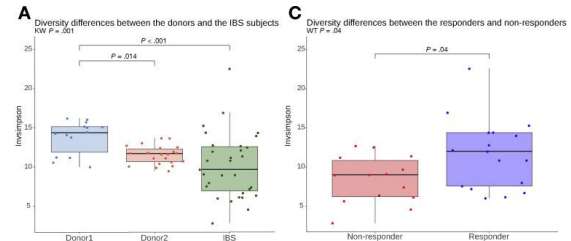
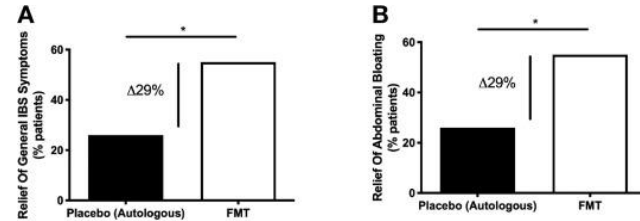
Fecal Microbiota Transplant for IBS

Meta-Analysis of FMT for IBS



Weights are from random effects analysis
 Heterogeneity: $I^2 = 79\%$, $\chi^2 = 14.47$ ($p < 0.01$)
 Clinical Response to FMT: $z = -0.22$ ($p = 0.83$)

Figure 2 Forest plot of all studies for efficacy of FMT vs placebo on global improvement of IBS symptoms. CI, confidence interval; FMT, fecal microbiota transplantation; IBS, irritable bowel syndrome; RR, risk ratio.



- Single 'super donor'
- Frozen FMT
- Distal duodenum via EGD
- 165 IBS patients (all subtype)
- Responder: decrease > 50 IBS-SSS

62 (2:1) IBS-D/M with severe bloating
 2 healthy donors
 Fresh FMT via NJT
 Adequate relief of IBS and bloating at week 12
 High diversity and bacterial composition at baseline – greater success

Take Home Points

- Make a positive diagnosis (exclude alarm features)
- Diet, lifestyle modifications, OTC (loperamide, PEG, fiber) therapies are first line
- Best clinical trial evidence
 - **IBS-D:** Rifaximin, Eluxadoline, Alosetron
 - **IBS-C:** Linaclotide, Plecanatide, Lubiprostone, Tegaserod
 - **Pain:** Peppermint oil (for all subtypes); TCAs, SNRIs (for IBS-D/M with pain)-allow 4 weeks minimum; antispasmodics
 - **Psychological:** CBT, hypnosis