Diagnosing and Treating Irritable Bowel Syndrome and Chronic Idiopathic Constipation

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Chief, Division of Gastroenterology, Hepatology, and Nutrition

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- The seminar contains just this one lecture which was developed in September 2021
- You can participate at your own pace. Feel free to go back and re-watch the lectures at any time
- You may annotate the slides and your notes will be saved for you when you return
- You will have access to the course material for about six months after your initial registration
- You may send questions or comments to cme@scliver.com for a prompt reply.

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Your Faculty

Brooks D. Cash, MD

Brooks D. Cash, MD is Chief of the Division of Gastroenterology, Hepatology, and Nutrition at the University of Texas Health Science Center at Houston, where he is also the Dan and Lillie Sterling Professor of Clinical Gastroenterology and Endowed Director of the Chao-Ertan Directorship at the University of Texas McGovern Medical School.

Dr. Cash received 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 in Bethesda, MD, and completed his internship, residency, and gastroenterology fellowship at the National Naval Medical Center in Bethesda, MD. He served for 24 years in the United States Navy. Dr. Cash has chaired numerous professional society committees and served as course director for multiple national and regional scientific congresses. He has authored over 200 articles and book chapters on a wide variety of gastrointestinal topics and serves as a Senior Associate Editor for the American Journal of Gastroenterology. He is Fellow of the Rome Committee, serves on the Bowel Disorders section for the Rome V committee, and has been recognized as one of the best gastroenterologists in Houston by Houstonia magazine and a Top Doctor by Texas Monthly magazine.

Faculty Disclosure

Name	Organization	Affiliation	Unlabeled Products
Brooks D. Cash, MD	Takeda, Salix, AbbVie, QOL, RedHill	Consulting	None
Staff of University of Louisville CME and SCLRC	None		

We hope you both enjoy and benefit from the content of this program

Let’s Begin

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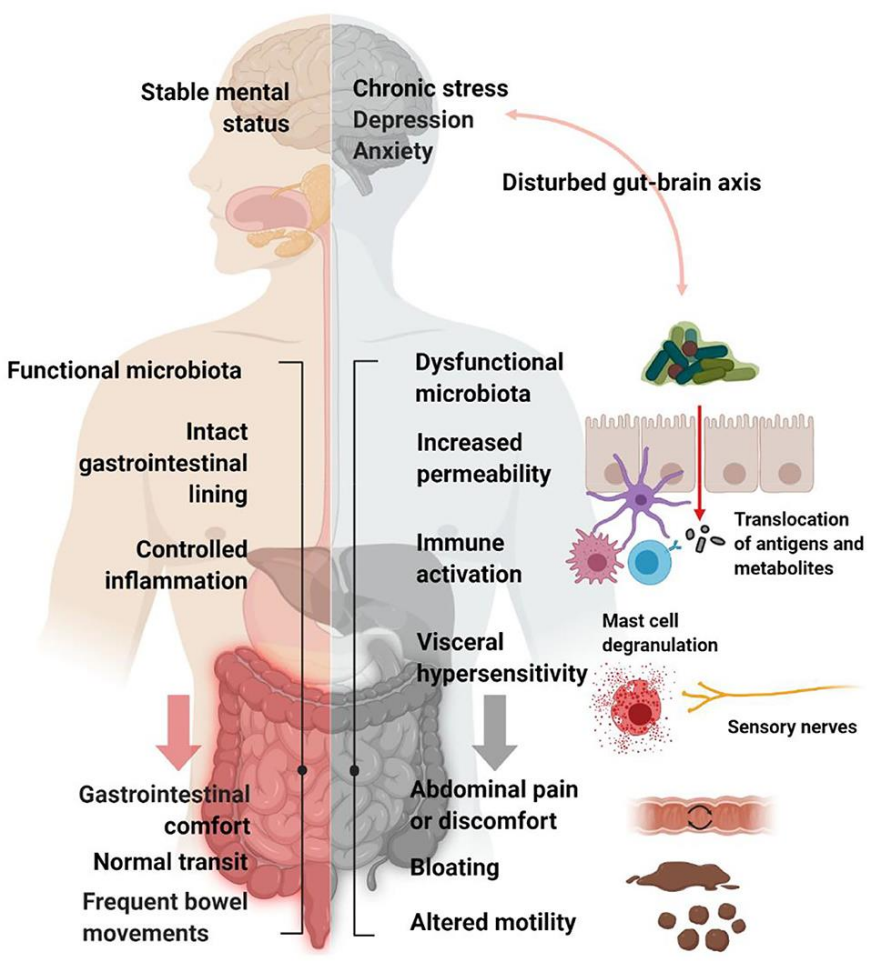
Epidemiology of IBS

- Estimated prevalence 5%-11%
- Women > Men
  - Younger (< age 50)
- Direct Medical Costs: $1.5-$10 Billion/year
  - Indirect Costs: 2-3X Direct Costs
- Significant negative impact on QOL
  - Drossman et al: Majority would trade 10-15 years of life for instant cure
  - Lacy et al: Would accept 1% chance of death for curative medication

Lacy BE, et al. Gastroenterology 2016;150:1393–407. Drossman DA, et al. J Clin Gastroenterol 2009;43(6):541–50. Lacy BE, et al. Am J Gastroenterol 2012;107:804–9

Complex IBS Pathophysiology



Carco C, et al. Front Cell Infect Microbiol; 09 September 2020 | https://doi.org/10.3389/fcimb.2020.00468

Defining and Characterizing IBS

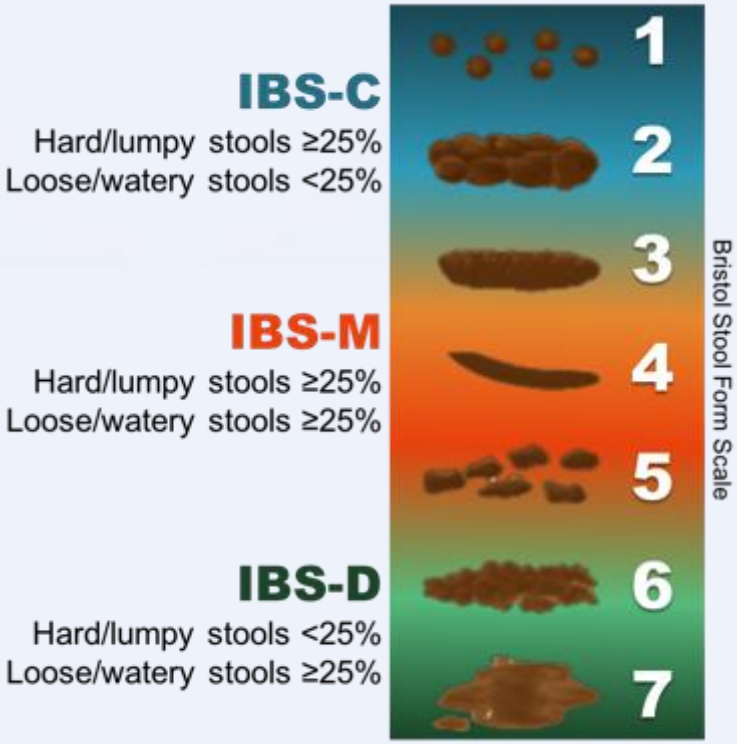
Rome IV Criteria for IBS[1]

Recurrent **abdominal pain,** on average, ≥1 day per week in the last 3 months, associated with ≥ 2 of the following:

- Related to defecation
- Change in frequency of stool
- Change in form (appearance) of stool

Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months before diagnosis

IBS Subtypes Based on Bristol Stool Forms[2,3]



IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrheal IBS-M, irritable bowel syndrome with mixed symptoms.

1. Lacy BE et al. Gastroenterology. 2016;150:1393-1407. **2.** Longstreth GF et al. *Gastroenterology*. 2006;130:1480-1491.
3. O'Donnell LJD, et al. *BMJ*. 1990;300:439-440.

Diagnostic Testing for Patients with Suspected IBS and No Concerning* Features

All IBS Subtypes[1]

CBC
Age-appropriate CRC screening

IBS-D[1,2]

- CRP or fecal calprotectin
- IgA TtG ± quantitative IgA
- When colonoscopy performed, obtain random biopsies
- Fecal bile acids or serum C_4 where available

IBS-M[1]

- CRP or fecal calprotectin
- IgA TtG ± quantitative IgA
- Stool diary
- Consider abdominal plain film to assess for fecal loading

IBS-C[1]

If severe or medically refractory, refer to specialist for physiologic testing

*__Alarm features__ include age ≥50 years old, blood in stools, nocturnal symptoms, unintentional weight loss, change in symptoms, recent antibiotic use, and family history of organic GI disease. C_4, 7α-hydroxy-4-cholesten-3-one; CBC, complete blood count; CRC, colorectal screening; CRP, C-reactive protein; Ttg, tissue transglutaminase.

1. Chey WD, et al. *JAMA*. 2015;313(9):949-958. 2. Pimentel M, et al. *PLoS ONE*. 2015;10(5):e0126438.

ACG Clinical Guideline: Management of Irritable Bowel Syndrome

Brian E. Lacy, PhD, MD, FACG[1], Mark Pimentel, MD, FACG[2], Darren M. Brenner, MD, FACG[3], William D. Chey, MD, FACG[4], Laurie A. Keefer, PhD[5], Millie D. Long, MDMPH, FACG[6] and Baha Moshiree, MD, MSc, FACG[7]

Irritable bowel syndrome (IBS) is a highly prevalent, chronic disorder that significantly reduces patients' quality of life. Advances in diagnostic testing and in therapeutic options for patients with IBS led to the development of this first-ever American College of Gastroenterology clinical guideline for the management of IBS using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Twenty-five clinically important questions were assessed after a comprehensive literature search; 9 questions focused on diagnostic testing; 16 questions focused on therapeutic options. Consensus was obtained using a modified Delphi approach, and based on GRADE methodology, we endorse the following: We suggest that a positive diagnostic strategy as compared to a diagnostic strategy of exclusion be used to improve time to initiating appropriate therapy. We suggest that serologic testing be performed to rule out celiac disease in patients with IBS and diarrhea symptoms. We suggest that fecal calprotectin be checked in patients with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. We recommend a limited trial of a low fermentable oligosaccharides, disacchardies, monosaccharides, polyols (FODMAP) diet in patients with IBS to improve global symptoms. We recommend the use of chloride channel activators and guanylate cyclase activators to treat global IBS with constipation symptoms. We recommend the use of rifaximin to treat global IBS with diarrhea symptoms. We suggest that gut-directed psychotherapy be used to treat global IBS symptoms. Additional statements and information regarding diagnostic strategies, specific drugs, doses, and duration of therapy can be found in the guideline.

Dietary Considerations in IBS

- **FODMAPS** are an important trigger of meal-related symptoms in IBS[1]
- Low FODMAP diet found to improve overall symptom scores compared with typical diet in IBS patients [2]
- **Gluten-free** diet found to be beneficial in some patients with IBS-D[3,4]
- Wheat contains fructans and other proteins that may also cause symptoms in IBS patients[5]
- Most patients who associate their symptoms with wheat will have **wheat sensitivity**, not celiac disease[6]
- **Food antigens** found to cause changes in the intestinal mucosa* of IBS patients that are associated with patient responses to exclusion diets[7]

*Breaks in intestinal mucosa, increased intervillous spaces, and increased intraepithelial lymphocytes demonstrated via confocal laser endomicroscopy in 22 of 36 patients with IBS.

1. Shepherd SJ et al. *Am J Gastroenterol*. 2013;108:707-717. **2.** Halmos EP et al. *Gastroenterology*. 2014;146:67-75.
3. Biesiekierski JR et al. Gastroenterology. 2011;106:508-514. **4**. Vazquez-Roque MI et al. Gastroenterology. 2013;144:903-911.e3.
5. Chey WD, et al. *JAMA*. 2015;313(9):949-958. **6.** Leonard MM et al. *JAMA*. 2017;318(7):647-656. **7.** Fritscher-Ravens A et al. *Gastroenterology*. 2014;147:1012-1020.

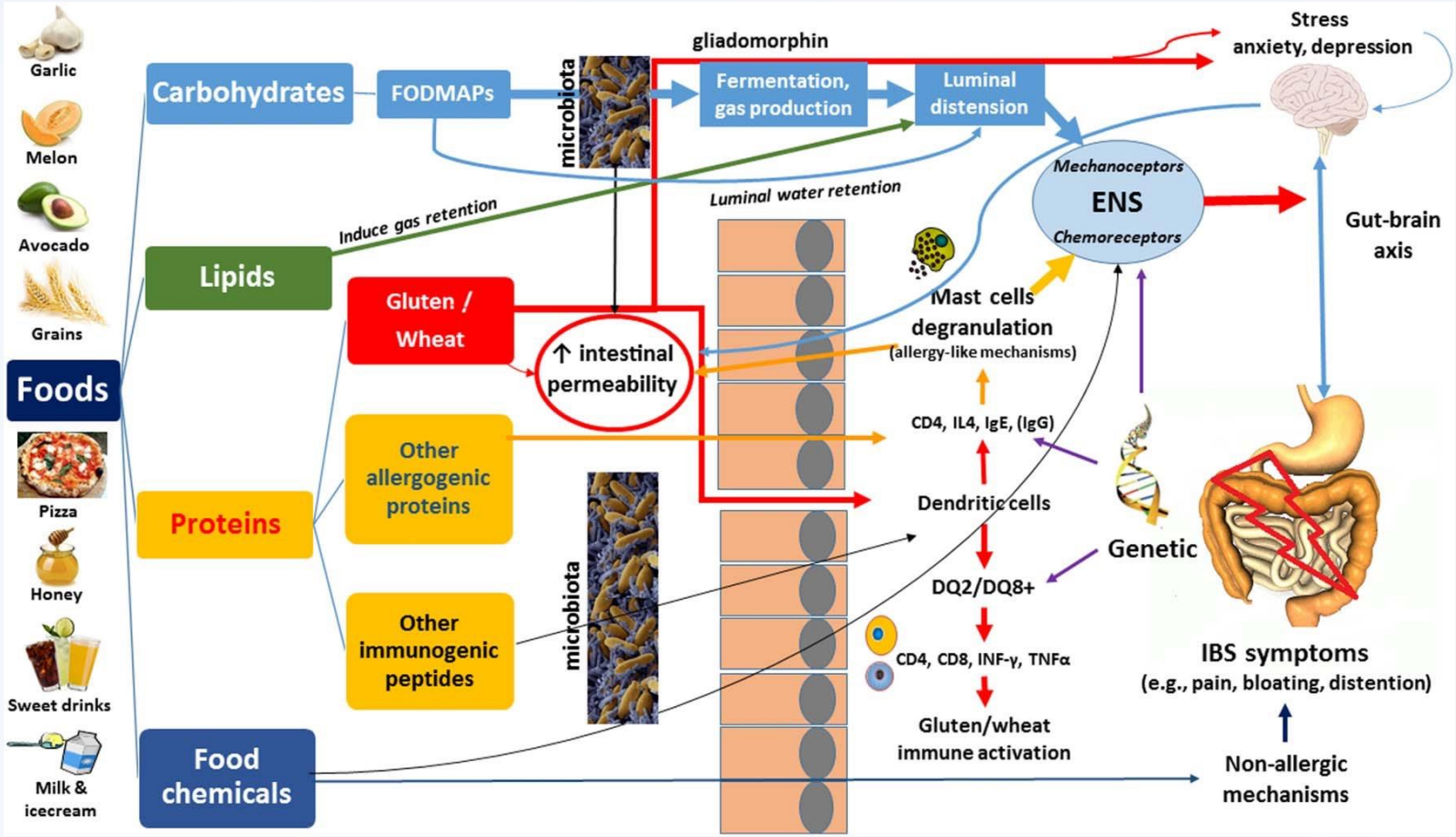
What are FODMAPs?

Fermentable oligo-, di-, monosaccharides and polyols

	**Excess Fructose**	Honey, apples, pears, peaches, mangos, fruit juice, dried fruit
	**Fructans**	Wheat (large amounts), rye (large amounts), onions, leeks, zucchini
	**Lactose**	Milk (cow, goat, or sheep), custard, ice cream, yogurt, soft unripened cheeses (e.g., cottage cheese, ricotta)
	**Sorbitol**	Apricots, peaches, artificial sweeteners, artificially sweetened gums
	**Raffinose**	Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes

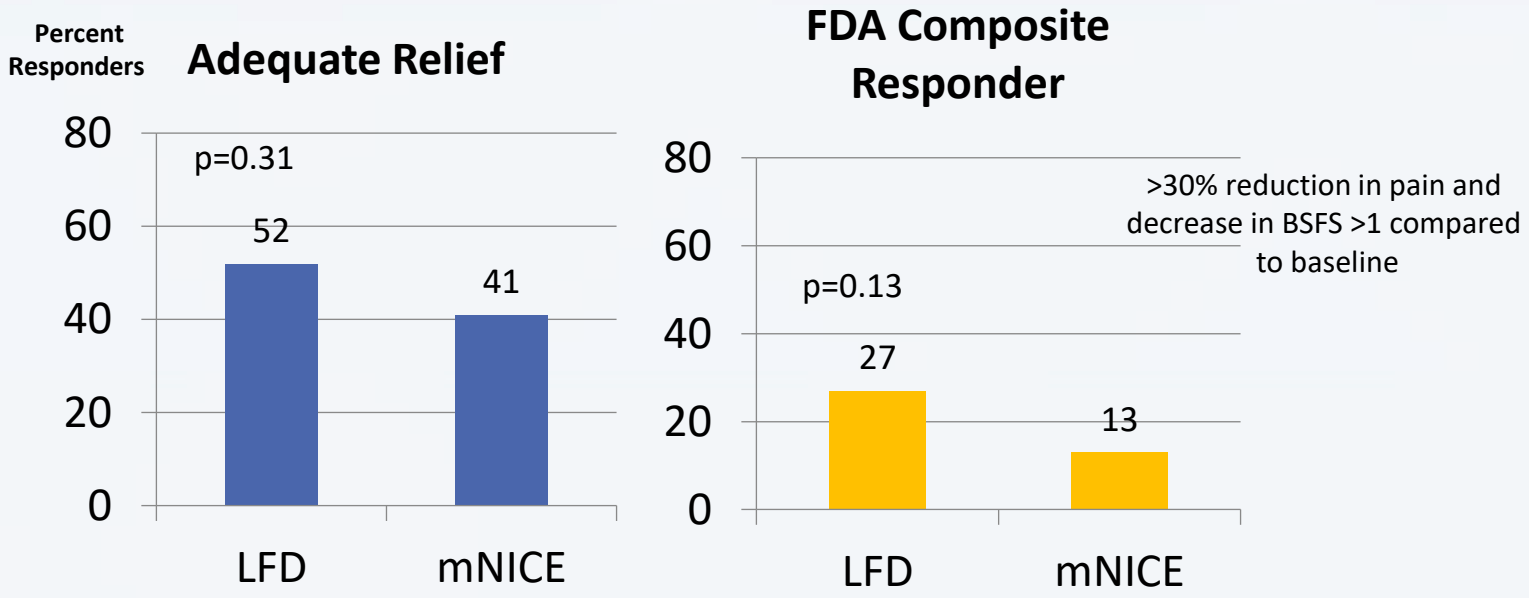
1. Shepherd SJ, et al. *Clin Gastroenterol Hepatol*. 2008;6:765-771; 2. Shepherd SJ, Gibson PR. *J Am Diet Assoc*. 2006;106:1631-1639; 3. Barrett JS, Gibson PR. *Ther Adv Gastroenterol*. 2012;5:261-268.

FODMAP Pathophysiology



De Giorgio R, et al. Gut 2016;65:169-78.

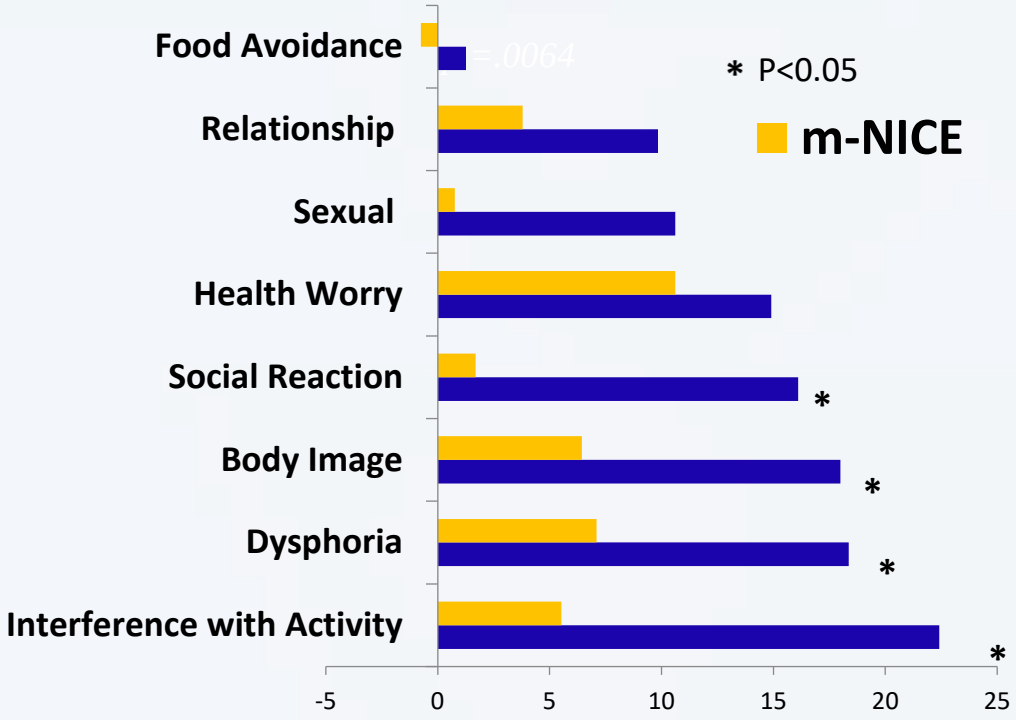
Low FODMAP vs. mNICE Diet for IBS-D: Adequate Relief & FDA Endpoint



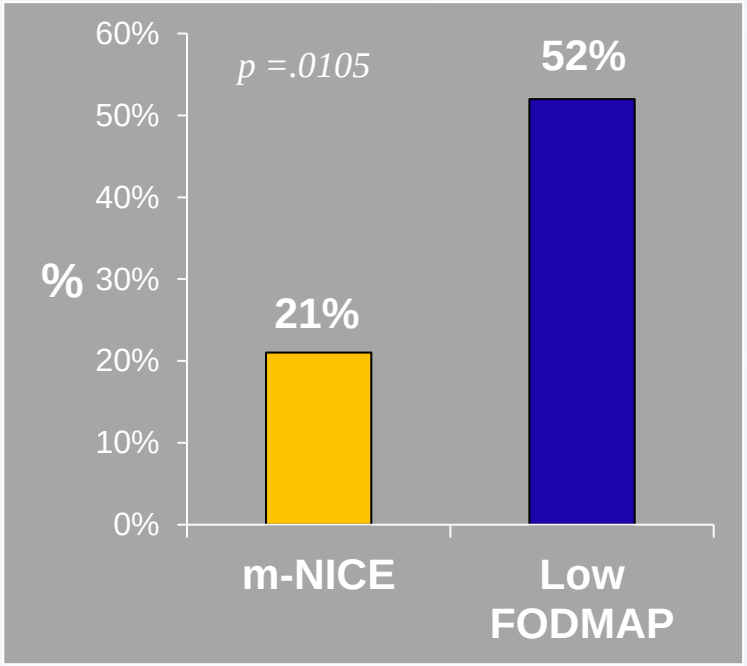
84 patients with IBS-D (45 LFD; median age, 65 women, 43 years [range, 19-68]) randomized to LFD or mNICE x 4 weeks

Eswaran, et al, Am J Gastroenterol 2016;111:1824

LFD vs. mNICE Diet: IBS-QOL Scores



Improvement from Baseline ≥ 14

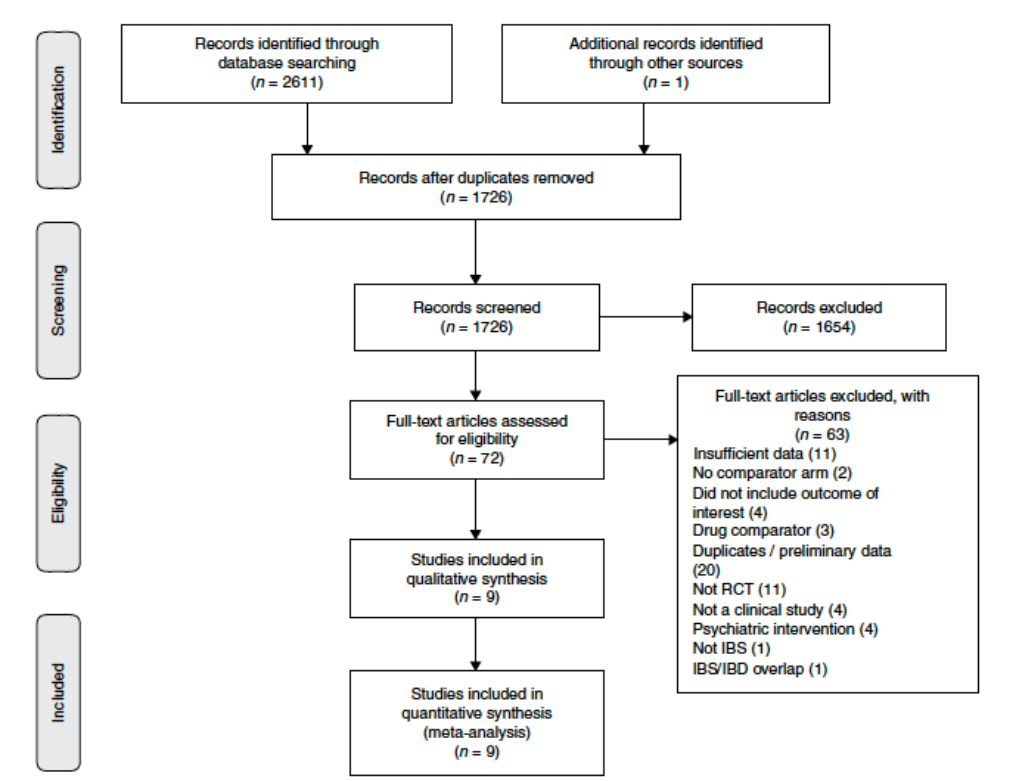


Meaningful Clinical Response

Eswaran, et al. Clin Gastroenterol Hepatol 2017

Low FODMAP Diet

Conditional Recommendation; Very Low Quality of Evidence



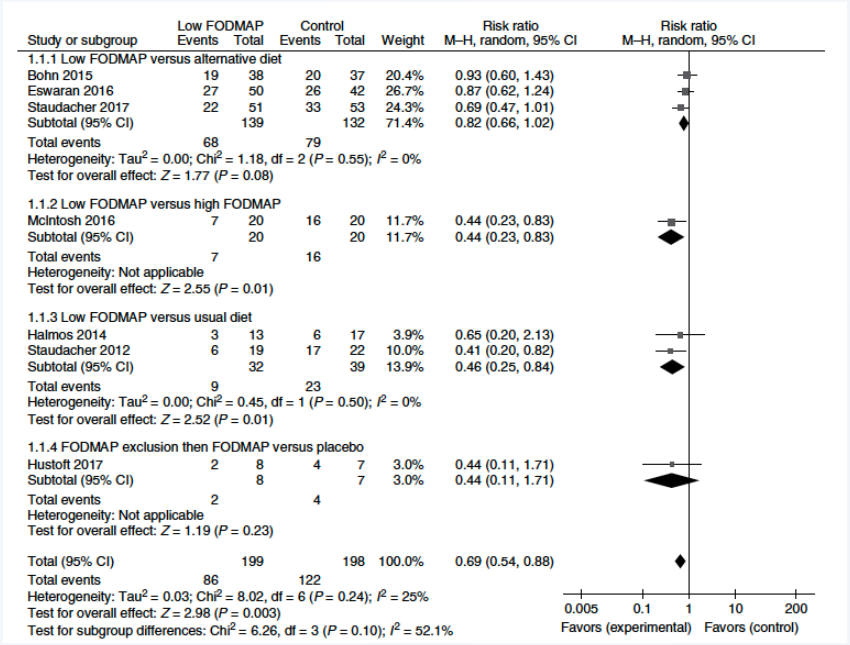
- Primary outcome: global improvement in IBS symptoms
  - If global improvement was not reported, abdominal pain was outcome of interest
  - If different definitions of improvement were used, used most stringent outcome reported minimizing placebo response rate
- Secondary outcomes included general quality of life and any occurrence of adverse events

Dionne J, et al. Am J Gastroenterol 2018;113:1290-1300.

Low FODMAP Diet

Conditional Recommendation; Very Low Quality of Evidence

Low FODMAP Diet



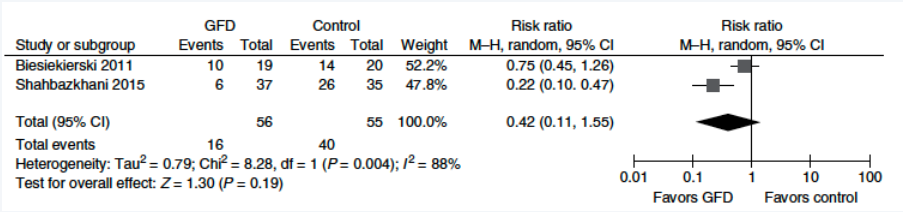
Study or subgroup	Low FODMAP Events	Total	Control Events	Total	Weight	Risk ratio M–H, random, 95% CI
1.1.1 Low FODMAP versus alternative diet						
Bohn 2015	19	38	20	37	20.4%	0.93 (0.60, 1.43)
Eswaran 2016	27	50	26	42	26.7%	0.87 (0.62, 1.24)
Staudacher 2017	22	51	33	53	24.3%	0.69 (0.47, 1.01)
Subtotal (95% CI)		139		132	71.4%	0.82 (0.66, 1.02)
Total events	68		79			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.18$, df = 2 ($P = 0.55$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.77$ ($P = 0.08$)						
1.1.2 Low FODMAP versus high FODMAP						
McIntosh 2016	7	20	16	20	11.7%	0.44 (0.23, 0.83)
Subtotal (95% CI)		20		20	11.7%	0.44 (0.23, 0.83)
Total events	7		16			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 2.55$ ($P = 0.01$)						
1.1.3 Low FODMAP versus usual diet						
Halmos 2014	3	13	6	17	3.9%	0.65 (0.20, 2.13)
Staudacher 2012	6	19	17	22	10.0%	0.41 (0.20, 0.82)
Subtotal (95% CI)		32		39	13.9%	0.46 (0.25, 0.84)
Total events	9		23			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.45$, df = 1 ($P = 0.50$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.52$ ($P = 0.01$)						
1.1.4 FODMAP exclusion then FODMAP versus placebo						
Hustoft 2017	2	8	4	7	3.0%	0.44 (0.11, 1.71)
Subtotal (95% CI)		8		7	3.0%	0.44 (0.11, 1.71)
Total events	2		4			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 1.19$ ($P = 0.23$)						
Total (95% CI)		199		198	100.0%	0.69 (0.54, 0.88)
Total events	86		122			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.02$, df = 6 ($P = 0.24$); $I^2 = 25\%$						
Test for overall effect: $Z = 2.98$ ($P = 0.003$)						
Test for subgroup differences: $Chi^2 = 6.26$, df = 3 ($P = 0.10$); $I^2 = 52.1\%$						

Risk ratio M–H, random, 95% CI

0.005 0.1 1 10 200

Favors (experimental) Favors (control)

Gluten Free Diet



Study or subgroup	GFD Events	Total	Control Events	Total	Weight	Risk ratio M–H, random, 95% CI
Biesiekierski 2011	10	19	14	20	52.2%	0.75 (0.45, 1.26)
Shahbazkhani 2015	6	37	26	35	47.8%	0.22 (0.10. 0.47)
Total (95% CI)		56		55	100.0%	0.42 (0.11, 1.55)
Total events	16		40			
Heterogeneity: $Tau^2 = 0.79$; $Chi^2 = 8.28$, df = 1 ($P = 0.004$); $I^2 = 88\%$						
Test for overall effect: $Z = 1.30$ ($P = 0.19$)						

Risk ratio M–H, random, 95% CI

0.01 0.1 1 10 100

Favors GFD Favors control

Conclusions

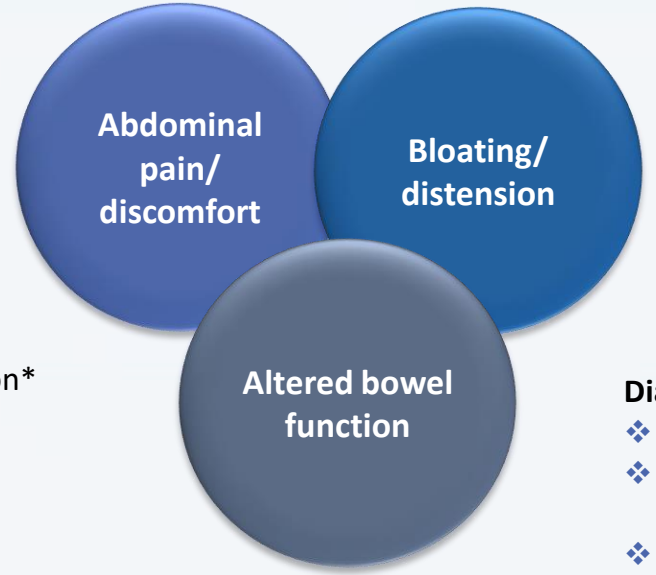
1) There is very low-quality evidence that a low FODMAP diet is effective in reducing symptoms in IBS patients
2) There is insufficient evidence to recommend a GFD to reduce IBS symptoms

Dionne J, et al. Am J Gastroenterol 2018;113:1290-1300.

IBS Pharmacologic Options by Symptom

Abdominal Pain/discomfort

- Antispasmodics*
- Antidepressants*
- Lubiprostone
- Linaclotide
- Plecanatide
- Alosetron
- Rifaximin
- Eluxadoline
- Tegaserod



Bloating

- Rifaximin
- Lubiprostone
- Linaclotide
- Plecanatide
- Probiotics*

Constipation

- Fiber*
- MOM/PEG solution*
- Lubiprostone
- Linaclotide
- Plecanatide
- Tegaserod
- Tenapanor
- Prucalopride*

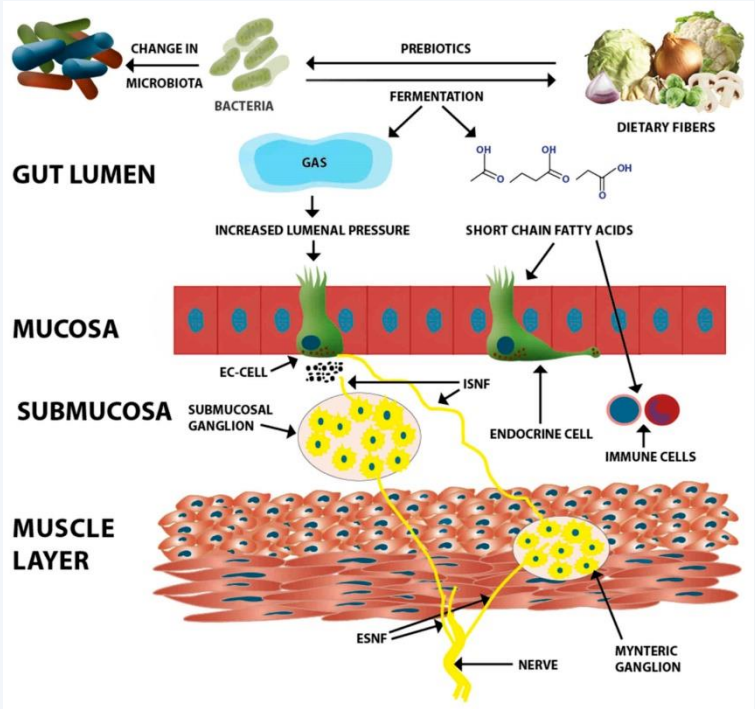
Diarrhea

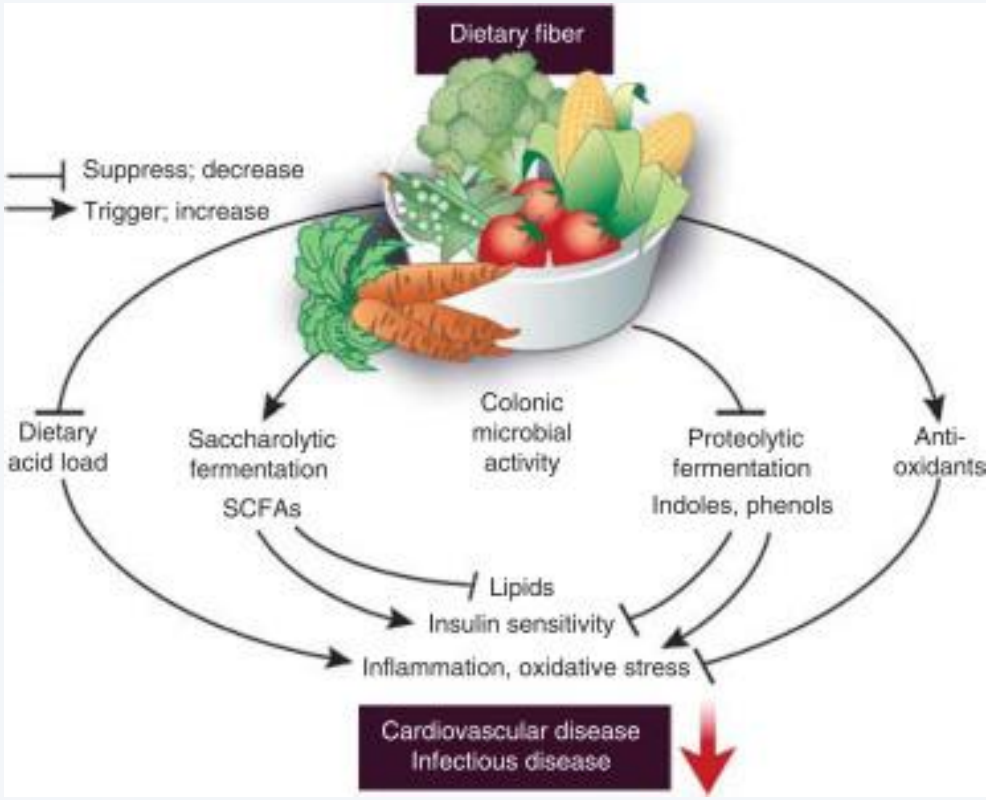
- Loperamide*
- Diphenoxylate-atropine*
- Cholestyramine*
- Alosetron
- Rifaximin
- Eluxadoline

*These agents are not currently FDA-approved for IBS. TCAs, tricyclic antidepressants.

Brandt LJ, et al. *Am J Gastroenterol*. 2002;97(11 suppl):S7-S26. Drossman DA, et al. *Gastroenterology*. 2002;123:2108-2131.

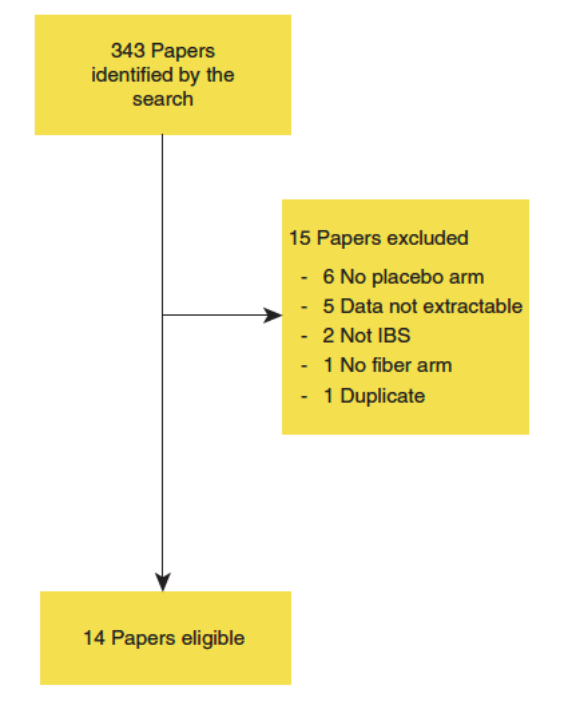
Fiber Mechanism of Action





Soluble Fiber

Strong Recommendation; Moderate Quality of Evidence

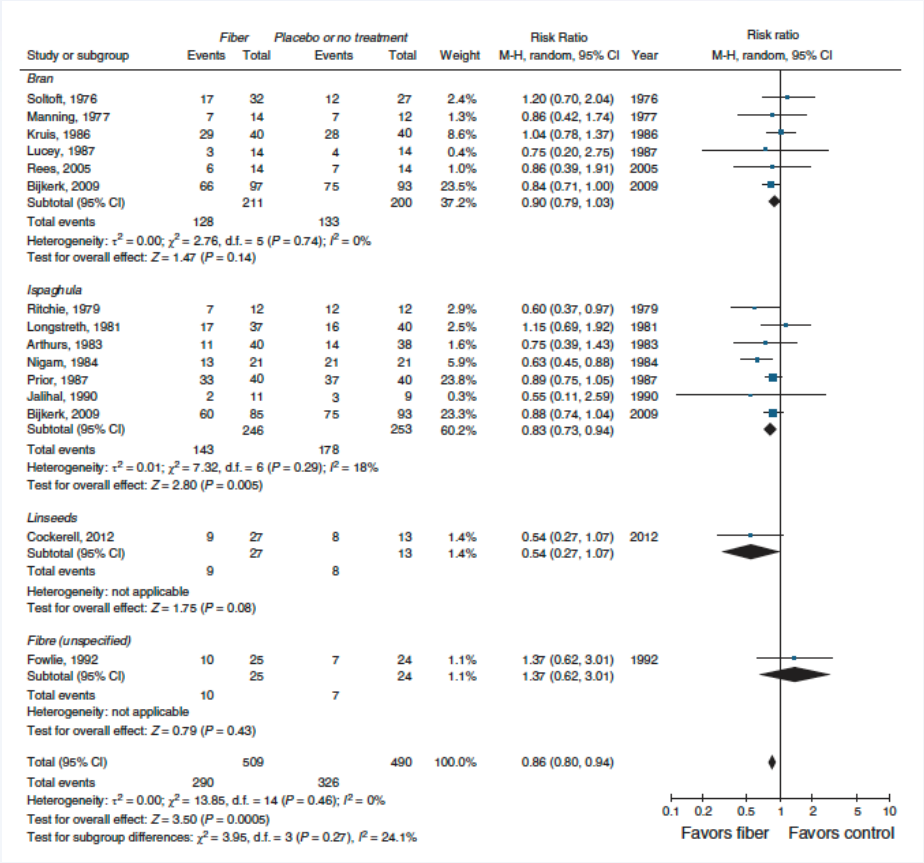


- Outcome of interest: improvement in global IBS symptoms preferable
  - If not reported then improvement in abdominal pain
- Reporting of outcomes: patient-reported preferable; if not available then investigator-reported
- Time of assessment: upon completion of therapy.
- Denominator used: true intention-to-treat analysis; if not available then all evaluable patients

Moayyedi P, et al. Am J Gastroenterol 2014;109:1367-74.

Soluble Fiber

Strong Recommendation; Moderate Quality of Evidence



Study or subgroup	Fiber Events	Fiber Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, random, 95% CI	Year
Bran							
Soltoft, 1976	17	32	12	27	2.4%	1.20 (0.70, 2.04)	1976
Manning, 1977	7	14	7	12	1.3%	0.86 (0.42, 1.74)	1977
Kruis, 1986	29	40	28	40	8.6%	1.04 (0.78, 1.37)	1986
Lucey, 1987	3	14	4	14	0.4%	0.75 (0.20, 2.75)	1987
Rees, 2005	6	14	7	14	1.0%	0.86 (0.39, 1.91)	2005
Bijkerk, 2009	66	97	75	93	23.5%	0.84 (0.71, 1.00)	2009
Subtotal (95% CI)		211		200	37.2%	0.90 (0.79, 1.03)	
Total events	128		133				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.76$, d.f. = 5 ($P = 0.74$); $I^2 = 0\%$							
Test for overall effect: $Z = 1.47$ ($P = 0.14$)							
Ispaghula							
Ritchie, 1979	7	12	12	12	2.9%	0.60 (0.37, 0.97)	1979
Longstreth, 1981	17	37	16	40	2.5%	1.15 (0.69, 1.92)	1981
Arthurs, 1983	11	40	14	38	1.6%	0.75 (0.39, 1.43)	1983
Nigam, 1984	13	21	21	21	5.9%	0.63 (0.45, 0.88)	1984
Prior, 1987	33	40	37	40	23.8%	0.89 (0.75, 1.05)	1987
Jalihal, 1990	2	11	3	9	0.3%	0.55 (0.11, 2.59)	1990
Bijkerk, 2009	60	85	75	93	23.3%	0.88 (0.74, 1.04)	2009
Subtotal (95% CI)		246		253	60.2%	0.83 (0.73, 0.94)	
Total events	143		178				
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 7.32$, d.f. = 6 ($P = 0.29$); $I^2 = 18\%$							
Test for overall effect: $Z = 2.80$ ($P = 0.005$)							
Linseeds							
Cockerell, 2012	9	27	8	13	1.4%	0.54 (0.27, 1.07)	2012
Subtotal (95% CI)		27		13	1.4%	0.54 (0.27, 1.07)	
Total events	9		8				
Heterogeneity: not applicable							
Test for overall effect: $Z = 1.75$ ($P = 0.08$)							
Fibre (unspecified)							
Fowlie, 1992	10	25	7	24	1.1%	1.37 (0.62, 3.01)	1992
Subtotal (95% CI)		25		24	1.1%	1.37 (0.62, 3.01)	
Total events	10		7				
Heterogeneity: not applicable							
Test for overall effect: $Z = 0.79$ ($P = 0.43$)							
Total (95% CI)		509		490	100.0%	0.86 (0.80, 0.94)	
Total events	290		326				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 13.85$, d.f. = 14 ($P = 0.46$); $I^2 = 0\%$							
Test for overall effect: $Z = 3.50$ ($P = 0.0005$)							
Test for subgroup differences: $\chi^2 = 3.95$, d.f. = 3 ($P = 0.27$), $I^2 = 24.1\%$							

Conclusion: Soluble fiber is effective in treating IBS. Bran did not appear to be of benefit, although there was no evidence of harm from this intervention

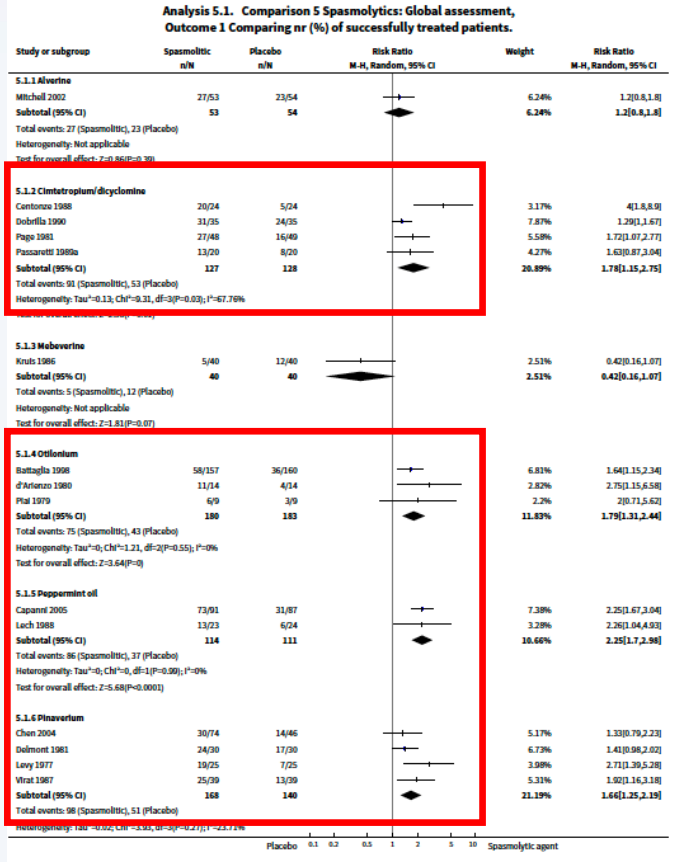
Moayyedi P, et al. Am J Gastroenterol 2014;109:1367-74.

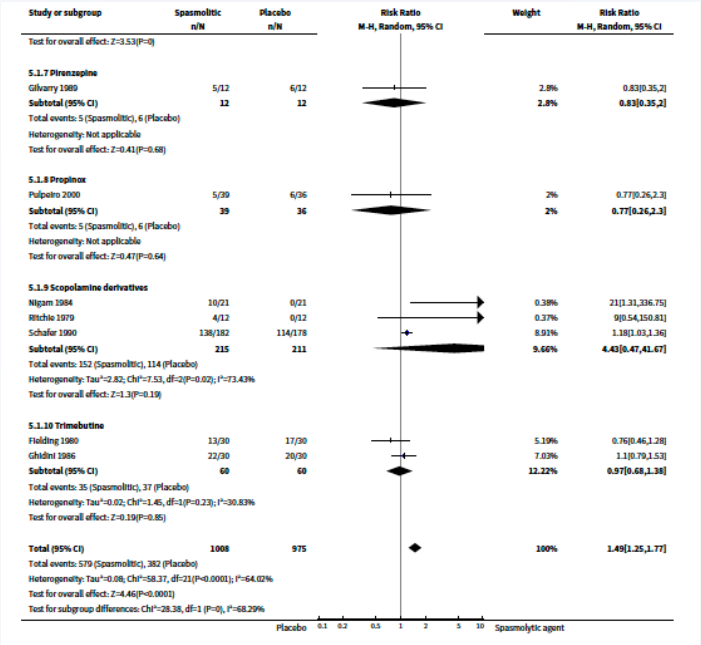
Do Not Use Antispasmodics Available in US

Conditional Recommendation; Very Low Quality of Evidence

- Used for decades for IBS
  - Goals of therapy: decrease motility, increase colonic transit time, improve abdominal pain
- Diverse group of therapies
  - Direct smooth muscle relaxants: papaverine, mebeverine, PO
  - Anticholinergic agents: butylscopolamine, hyoscine, cimetropium bromide, pirenzepine
  - Ca^{+2} channel blockers: alverine citrate, otilonium bromide, pinaverium bromide
- ACG Guidelines only considered US-available agents
  - Dicyclomine: 2 studies (n=193); some symptom improvement, AEs 30% greater than placebo
  - Hyoscyamine: 1 study (n=25), comparable to placebo, high AE
  - Hyoscine (scopolamine): 3 studies (n=978), inconsistent results

Global Antispasmodic Data: Cochrane Review





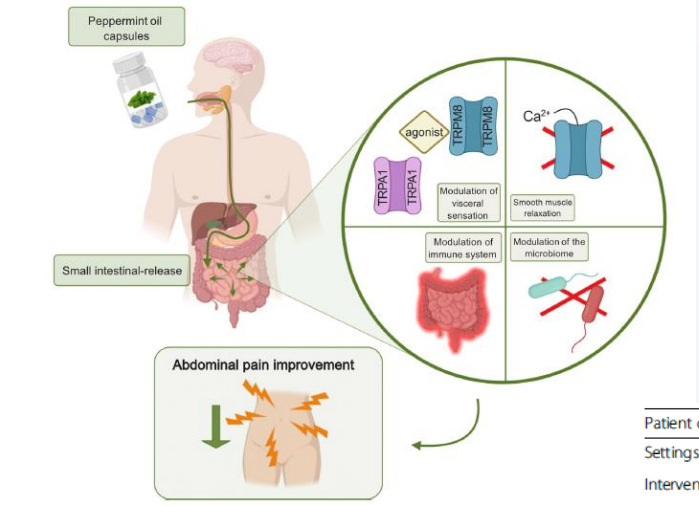
Global improvement supports

- Cimetropium/dicyclomine
- Otilonium
- PO
- Pinaverium

Ruepert L, et al. Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD003460.

Peppermint Oil

Conditional Recommendation; Low Quality of Evidence



- 2019 Meta-analysis: 12 RCT, 835 patients; all scheduled PO (not PRN)
  - Overall RR for PO vs placebo 2.39 (95% CI 1.93–2.97)
  - Abdominal pain RR for PO 1.78 (95% CI 1.43–2.20)
  - NNT with PO was 3 for overall IBS symptoms and 4 for abdominal pain

Patient or Population: Patients with Active IBS

Settings: Outpatients

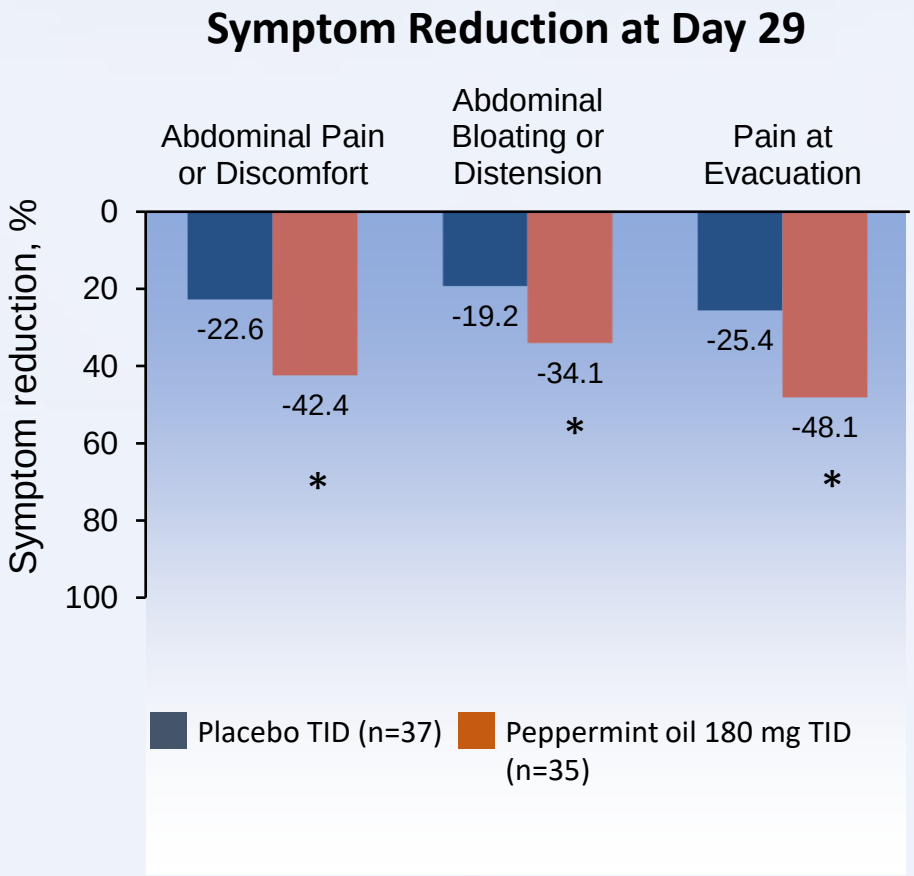
Intervention: Enteric-coated Peppermint Oil Capsules vs. Placebo

Outcomes	Illustrative Comparative Risk*					
	Assumed risk	Corresponding risk				
	Control (per 1000)	Peppermint Oil vs. Placebo (per 1000)	Relative Risk (95% CI)	No. Participants (Studies)	Quality of Evidence (GRADE)	NNT (95% CI)
Global improvement in IBS symptoms	250†	598 (483 to 743)	2.39 (1.93–2.97)	507 (7)	⊕⊕⊕⊕‡ High	3 (2–4)
Improvement in abdominal pain	303†	539 (433 to 666)	1.78 (1.43–2.20)	556 (6)	⊕⊕⊕○§ Moderate	4 (3–6)
Adverse events	21†	29 (18 to 47)	1.40 (0.87–2.26)	671 (8)	⊕⊕○○‖ Low	125 (29-∞)

Colomer E, et al. Front Pharmacol 2021; Feb 18;11:629026. doi: 10.3389/fphar.2020.629026

Triple-Coated Peppermint Oil for IBS

- RCT of triple-coated peppermint oil microspheres in IBS-M or IBS-D (N=72)
  - Randomized to peppermint oil 180 mg TID or placebo for 4 weeks
  - Primary analysis based on TISS
- Peppermint oil improved TISS (*P*<0.02) and frequency and intensity of individual IBS symptoms over 4 weeks
- Most frequent AE with peppermint oil and placebo was dyspepsia (2.9% vs 0%)



*P<0.05.

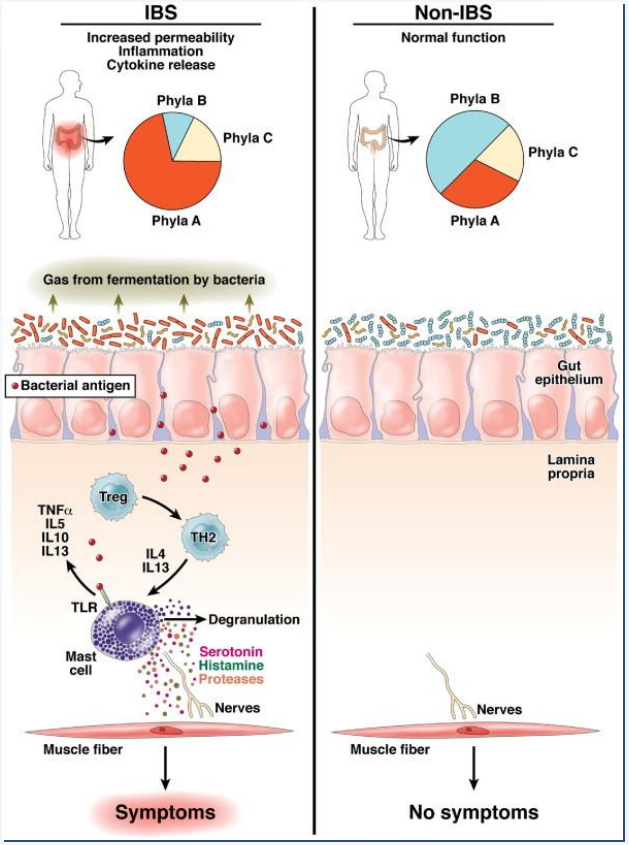
AEs, adverse events; TISS, Total IBS Symptom Score; URT, upper respiratory tract.

Cash BD, et al. *Dig Dis Sci.* 2016;61:560-571.

Do Not Use Probiotics for Global IBS Sxs

Conditional Recommendation; Very Low Quality of Evidence

- Ford et al. 2018 meta-analysis
  - 37 RCTs, 4403 patients
    - Significant heterogeneity
    - Publication bias
  - Probiotics superior to placebo: modest impact on abdominal pain
    - None on bloating
    - Combination probiotics: RR = 0.79 (0.68-0.91)
  - Unknown best dose/brand/combination
  - Low rate of AEs



Ford AC et al. *Aliment Pharmacol Ther*. 2018;48:1044-60.

Conventional Nonspecific Agents for IBS-D

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**

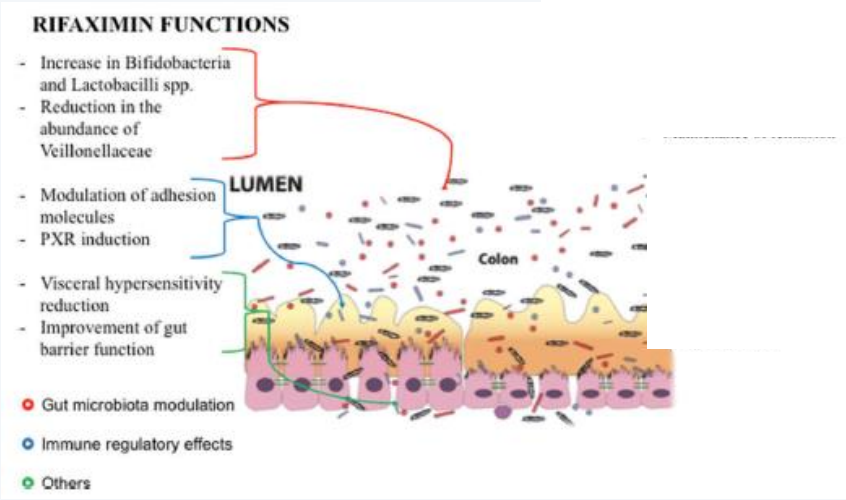
*Recommendation revised to reflect evidence for products available in US. RR, relative risk.

ACG Task Force on IBS. Ford AC, et al. *Am J Gastroenterol*. 2014;109(Suppl 1):S2-S26.

Rifaximin Mechanism of Action

Poorly absorbed antibiotic; inhibits protein synthesis

- Increased solubility in small bowel
- Modulation of gut microbiota
  - SIBO/Dysbiosis treatment
- Anti-inflammatory effects
  - Decreased production of cytokines and chemokines
- Decreases visceral sensitivity
- ? Improvement of intestinal permeability

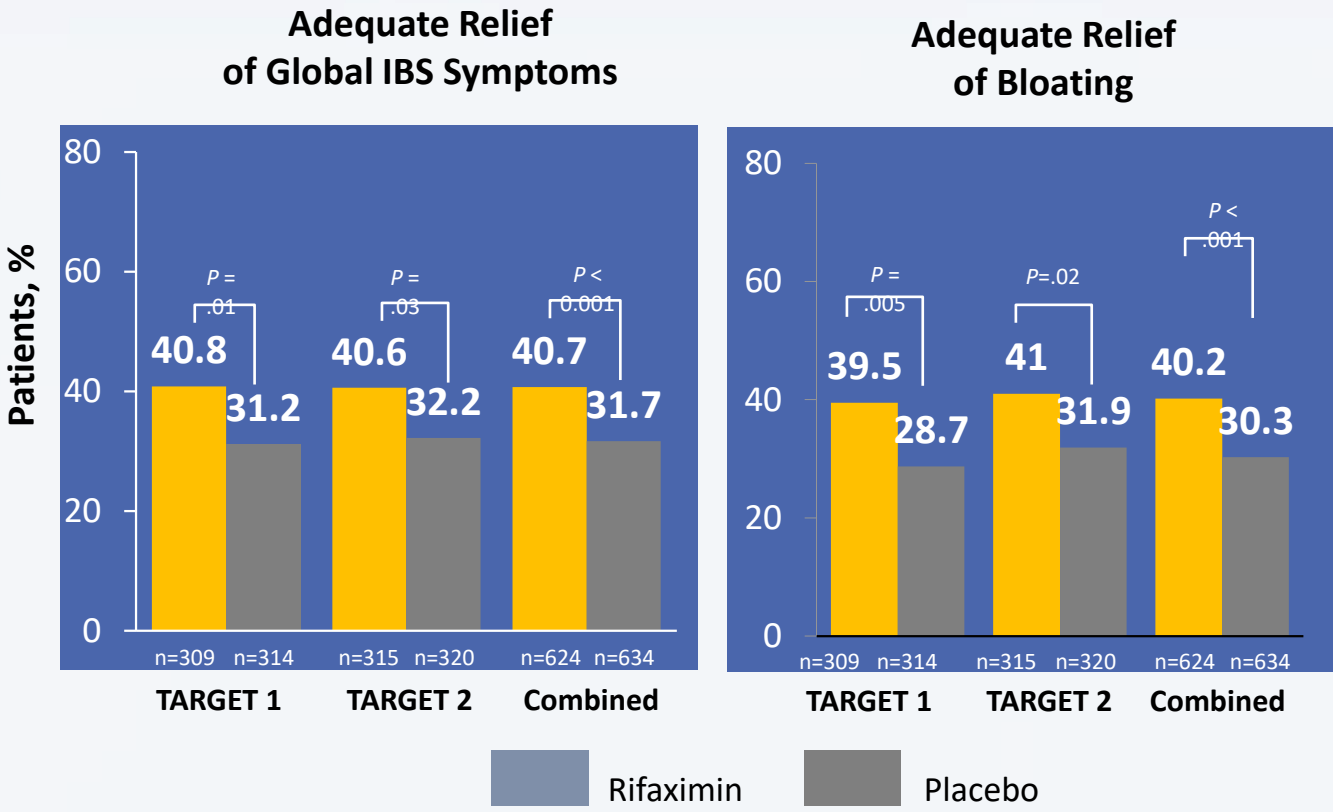


Lopetuso LR, et al. Expert Opin Invest Drugs;2018:27:543-51. Chey WD, et al. Ther Adv Gastroenterol 2020;13:1-16.

Rifaximin for IBS-D

Strong Recommendation; Moderate Quality of Evidence

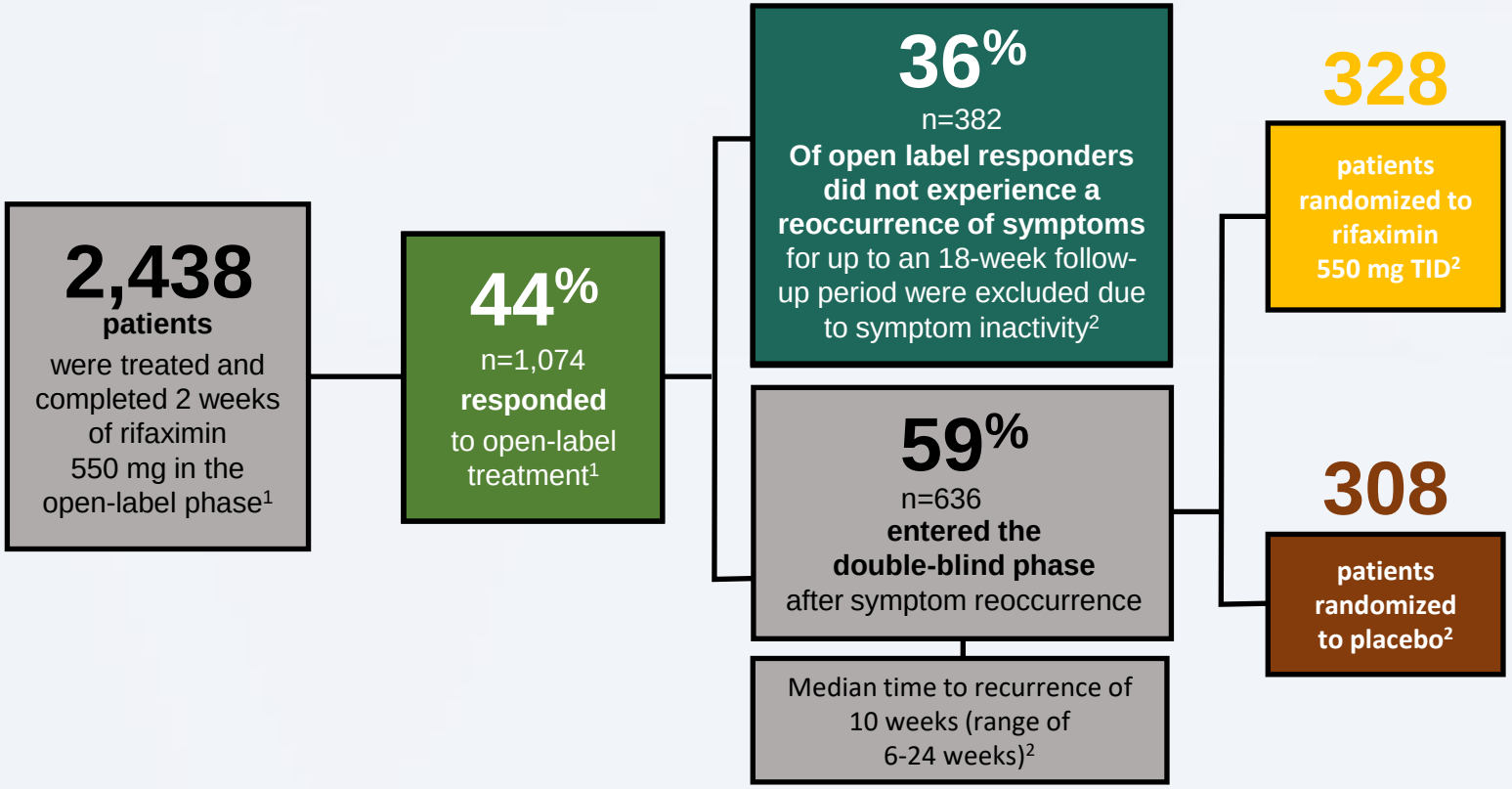
- Dosing 550 mg TID x 2 weeks
- 7 RCT; 2654 patients
- AEs similar to placebo
- 2/3 responders need re-treatment
  - No value in re-treating non-responders



Pimentel M et al. *N Engl J Med.* 2011;364(1):22-32.

Rifaximin: TARGET 3 Trial

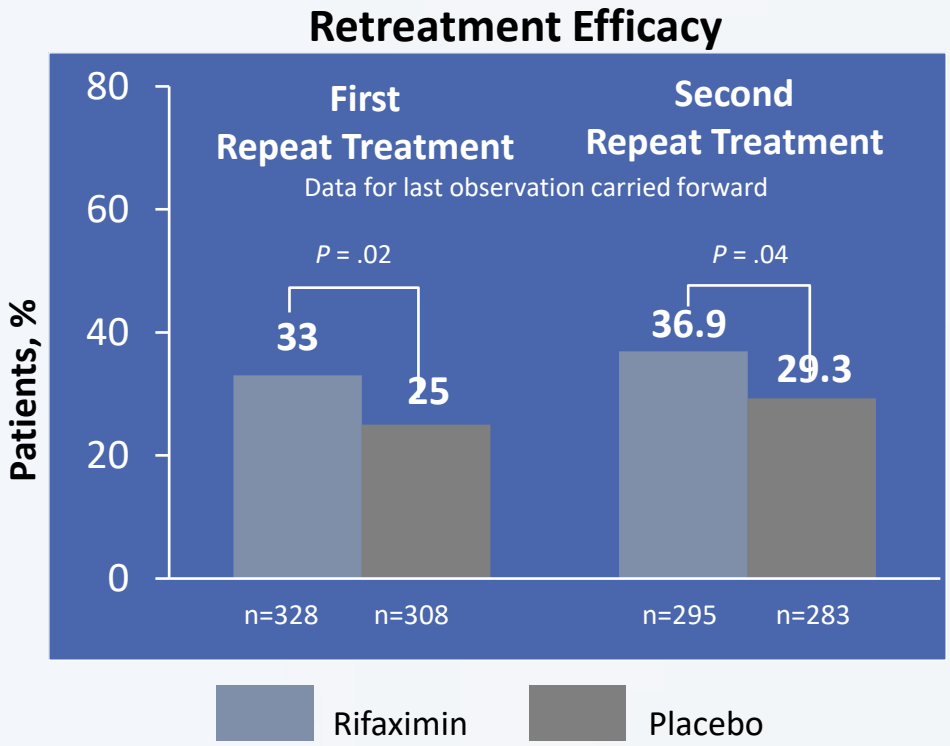
Study Design and Patient Disposition



Lembo A et al. *Gastroenterology*. 2016;151(6):1113-1121.

Rifaximin for IBS-D

Strong Recommendation; Moderate Quality of Evidence



Recurrence Definition:

- Loss of response for ≥3 of 4 weeks

Responder Definition:

- ≥ 30% improvement in IBS-related abdominal pain and stool consistency for ≥ 2 of 4 weeks post-treatment

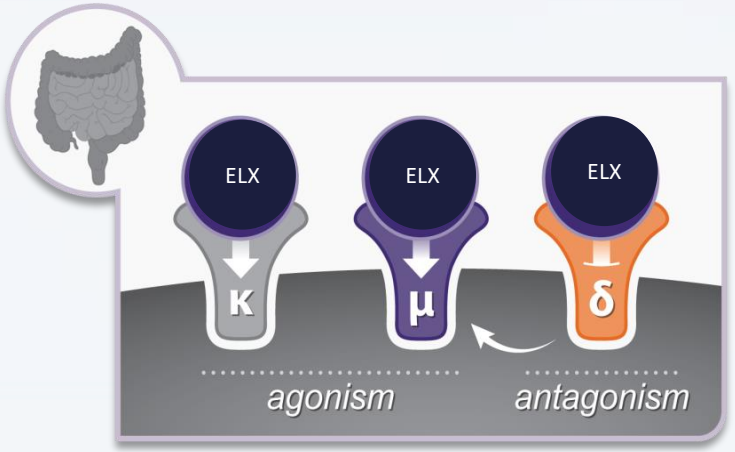
Urgency and bloating improved significantly with both repeat treatments

Abdominal pain and stool consistency improved significantly with first retreatment

Lembo A et al. *Gastroenterology*. 2016;151(6):1113-1121.

Eluxadoline Mechanism of Action

- Mixed opioid receptor modulator
  - μ/κ-opioid receptor agonist; δ-opioid antagonist [1,2]
  - Decreases visceral pain, colonic transit, GI secretions



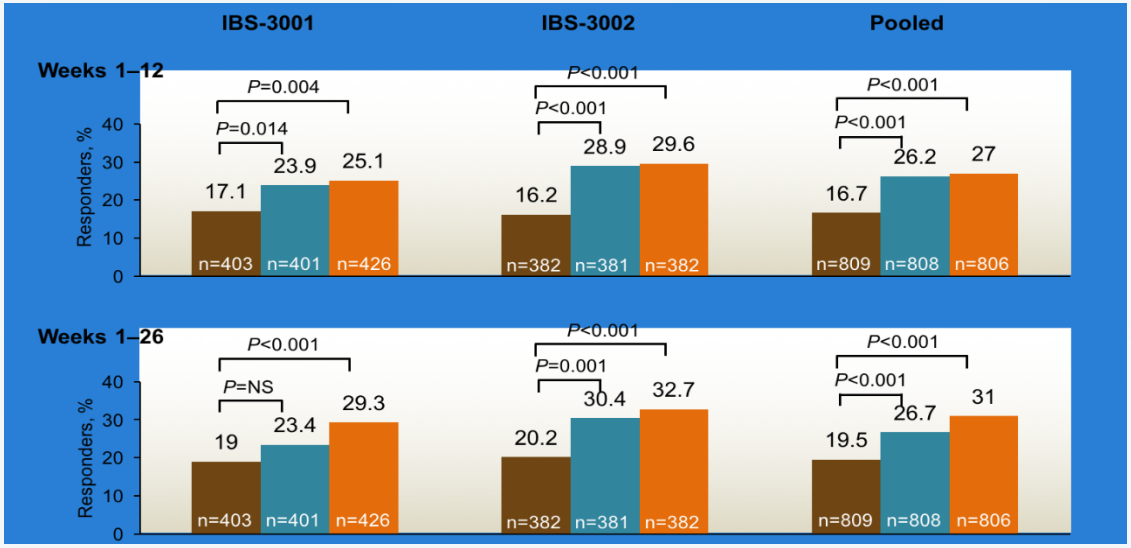
μ/κ-opioid stimulation: decreases motility, Cl secretion, and visceral pain
δ-opioid blockade: restores G-protein signaling, modulating anti-motility effect and enhancing peripheral analgesia

Barbara G, et al. Gastroenterology 2016;150:1305-18.

Eluxadoline for IBS-D

Conditional Recommendation; Moderate Quality of Evidence

- 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

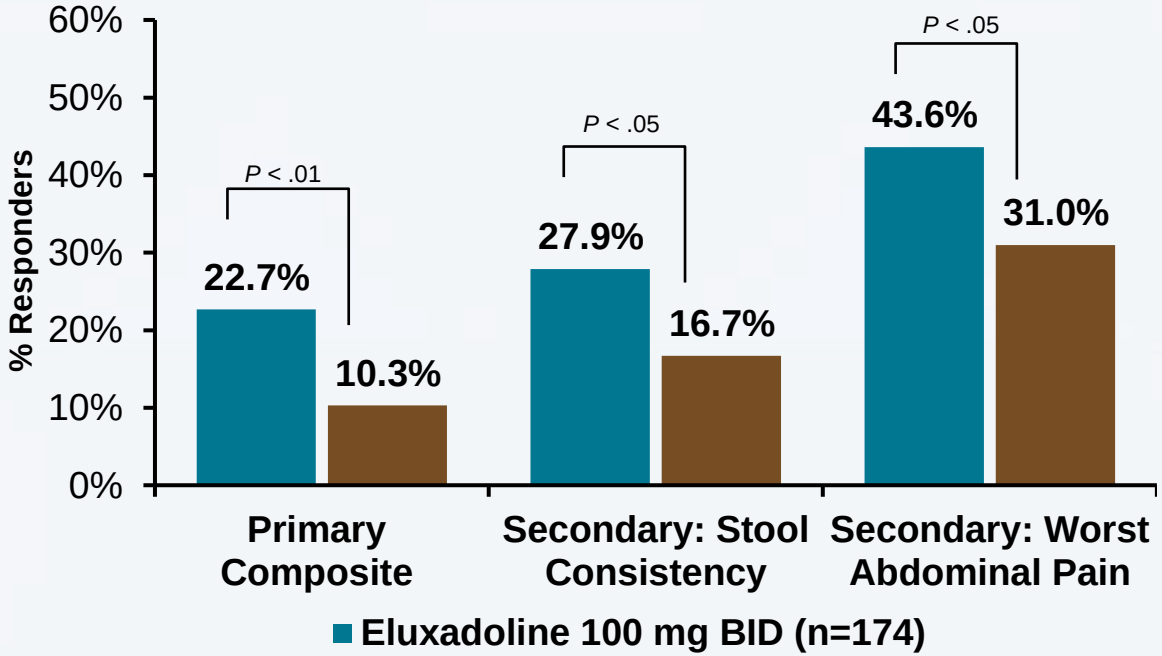
- 30% reduction in worst abdominal pain score AND improvement in stool consistency of <5 on the Bristol Stool Scale
- Daily improvement in BOTH symptoms on at least 50% of days in the trial

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

Conditional Recommendation; Moderate Quality of Evidence

- Phase 4 RCT
- Subjects: Subjective loperamide failures (prior 12 months) for adequate control of IBS-D symptoms
- AE rates comparable in both groups; no SAEs

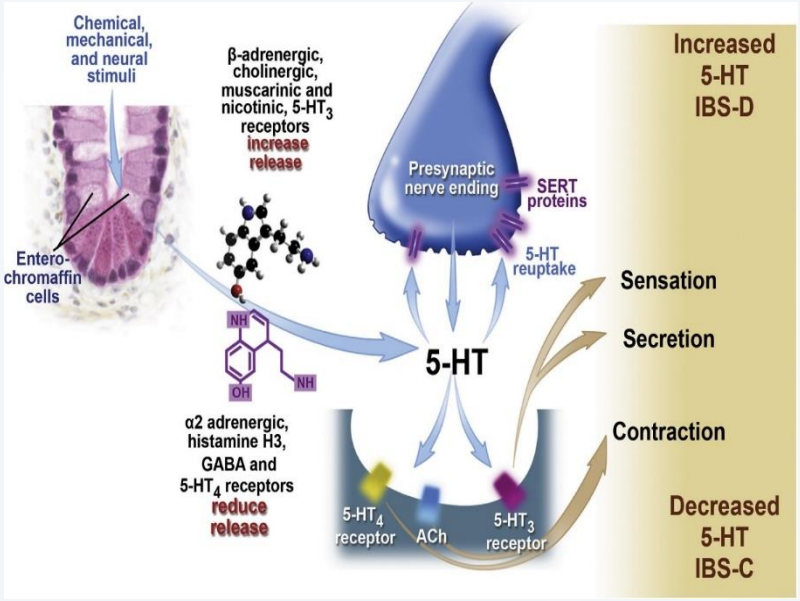


Primary Composite = Patient met composite response criteria on ≥50% of days, defined as ≥40% improvement in WAP c/w BL and BSS <5 OR absence of a BM if accompanied by ≥40% improvement in WAP.
Secondary Stool Consistency defined as BSS <5 on ≥50% of days.
Secondary WAP defined as ≥40% improvement in WAP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

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

Alosetron Mechanism of Action

- Selective serotonin type-3 (5-HT_3) receptor antagonist
- Inhibits activation of nonselective cation channels, modulating the enteric nervous system
  - Decreases visceral pain, colonic transit, GI secretions

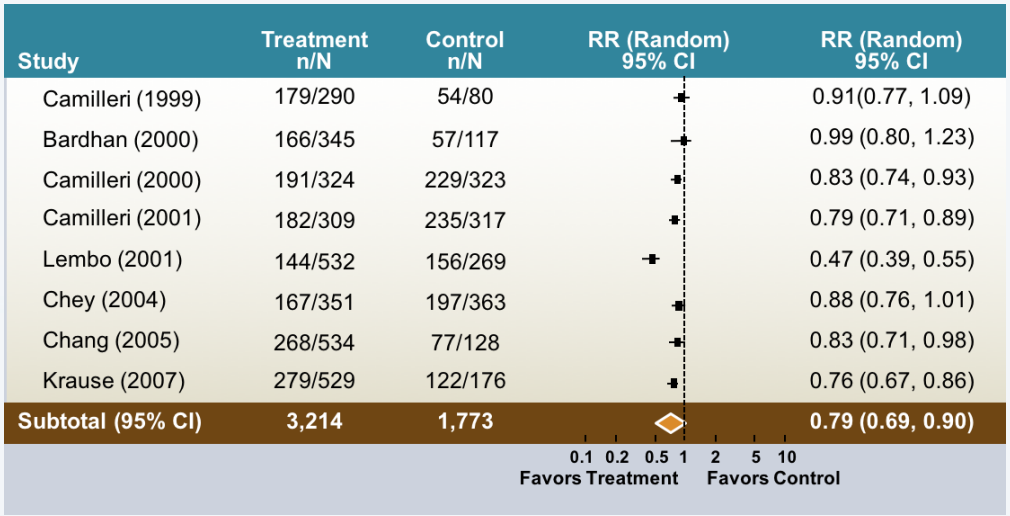


Barbara G, et al. Gastroenterology 2016;150:1305-18.

Alosetron

Conditional Recommendation; Low Quality of Evidence

- 8 RCT, 4341 patients
- 0.5 mg BID starting dose; can increase to 1 mg BID if well tolerated
- Current indication: Female patients with severe IBS-D not responding adequately to conventional therapy[1]
- AEs: constipation, colon ischemia: 1/1000 patient-years

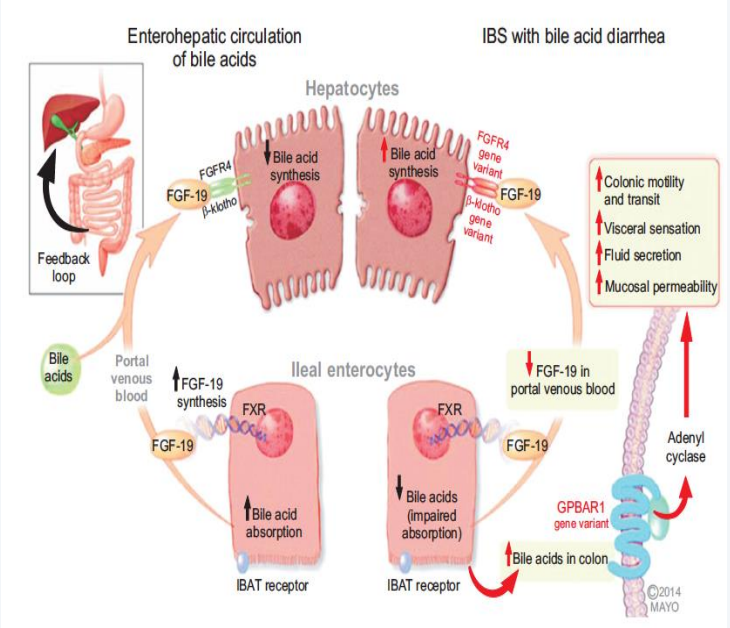


US National Library of Medicine Daily Med. Alosetron hydrochloride tablet. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7a6c2fbb-a76a-497e-8cf2-a6dca8945a9d. Accessed May 26, 2020. Ford AC et al. *Am J Gastroenterol*. 2014;109(Suppl 1):S2-S26.

Do Not Use Bile Acid Sequestrants

Conditional Recommendation; Very Low Quality of Evidence

- Bile acid malabsorption: prevalence estimates 25-50% in IBS-D
  - increase visceral sensation and fluid secretion via intracellular cAMP, mucosal permeability and/or Cl^- secretion
- Limited data in IBS
  - 8 week open-label trial of colestipol in 27 patients
    - 23 noted improvement in IBS symptoms; 55% were responders (adequate relief ≥50% weeks 5–8)
  - Open-label trial of colesevelam in 12 patients
    - Increased bile acid retrieval from stool with modest reduction in BSFS



Camilleri M. Gut Liver. 2015;9:332-339. Bajor A, et al. Gut 2015;64:84-92. Camilleri M, et al. Aliment Pharmacol Ther 2015;41:438-48.

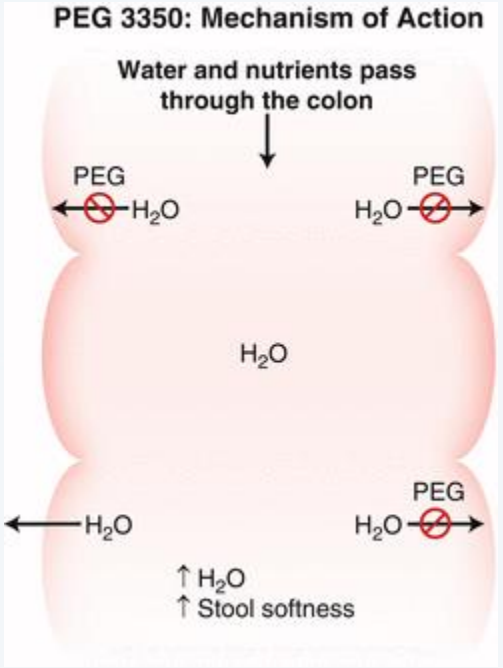
Do Not Use PEG Alone for IBS-C

Conditional Recommendation; Low Quality of Evidence

- Abundant evidence supporting PEG for constipation
- PEG not proven to improve IBS-related abdominal pain

  - 3 small studies (n=42, 139, 48) with variable patient populations/endpoints; pain effect negative in all
- If PEG does not alleviate abdominal pain, it cannot alleviate global symptoms of IBS-C

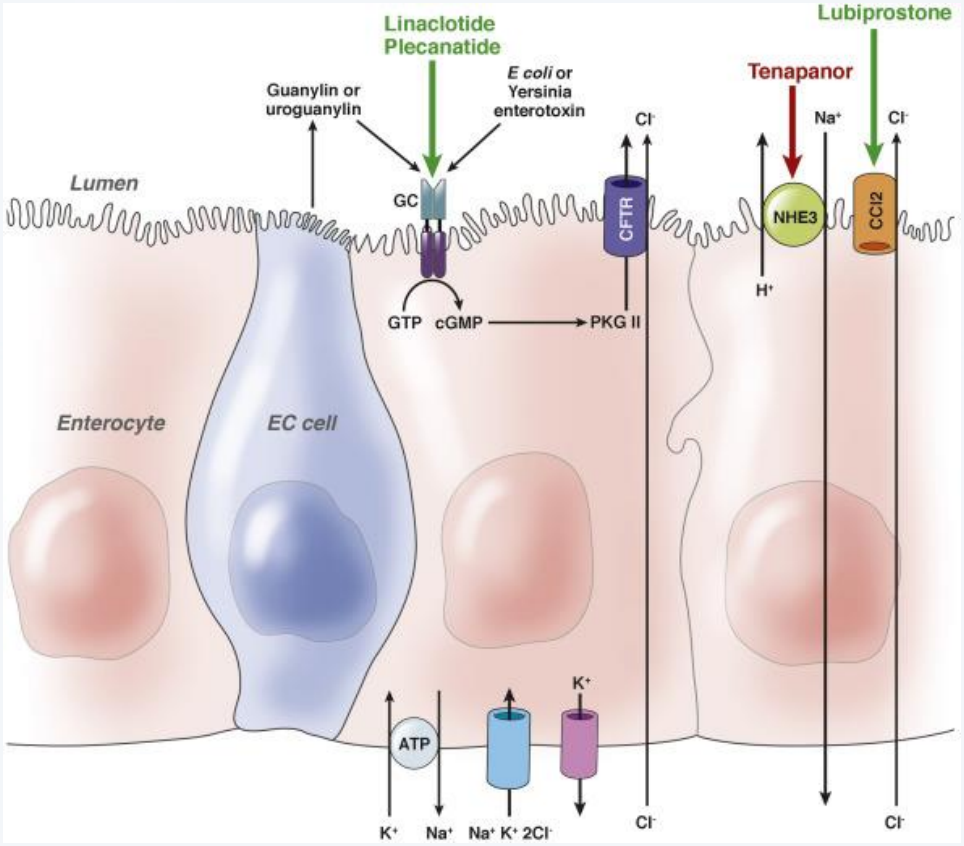
  - Guideline recommends against use of PEG alone for global IBS-C symptoms, but recognizes that PEG is first-line treatment of constipation in IBS, due low cost and availability



1. Awad RA, et al. Colorectal Dis 2010;12:1131–8. 2. Chapman RW, et al. Am J Gastroenterol 2013;108:1508–15. 3. Khoshoo V, et al. Aliment Pharmacol Ther 2006;23:191–6.

Secretagogues for IBS-C

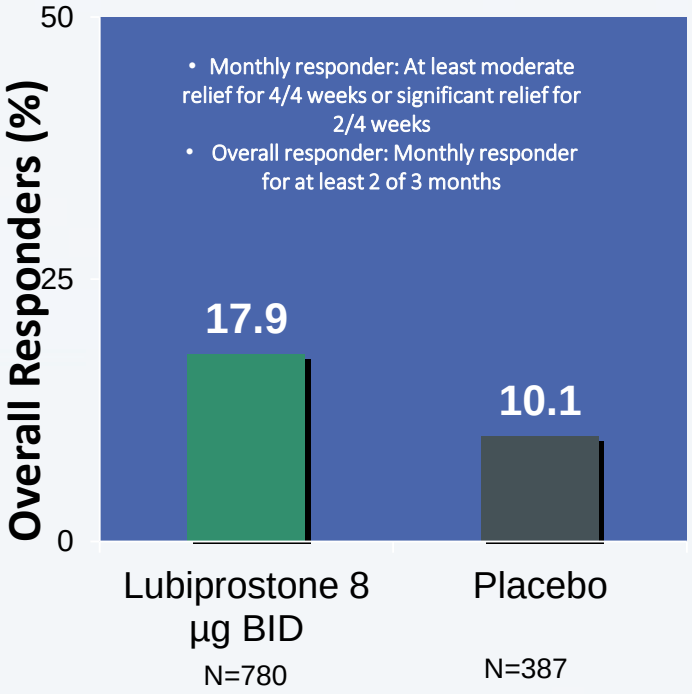
Mechanism of Action



Lubiprostone (CLC2 activator) for IBS-C/CIC

Strong Recommendation; Moderate Quality of Evidence

- Type 2 chloride channel activator; increases ion and water secretion into gut
- 3 RCT, n=1366
- IBS-C dose: 8 mcg BID only approved in women; CIC dose: 24 mcg BID all adults
- AEs: diarrhea and nausea



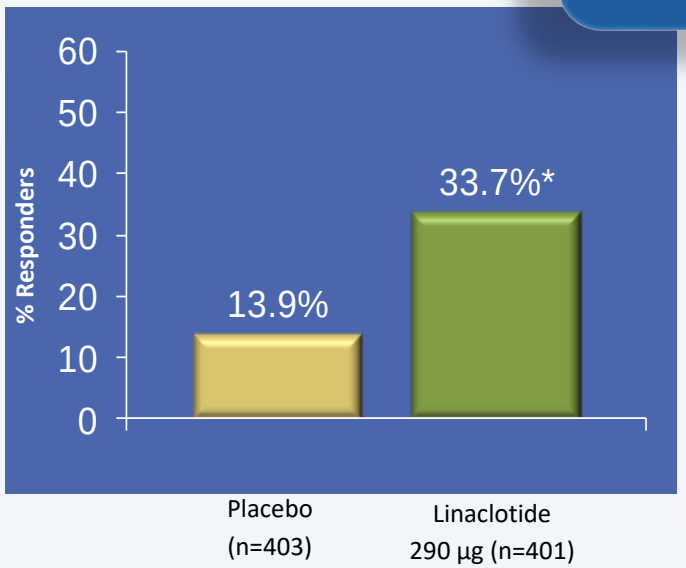
Drossman DA et al. *Aliment Pharmacol Ther*. 2009;29:329-341.

Linaclotide (GC-C Agonist) for IBS-C

Strong Recommendation; High Quality of Evidence

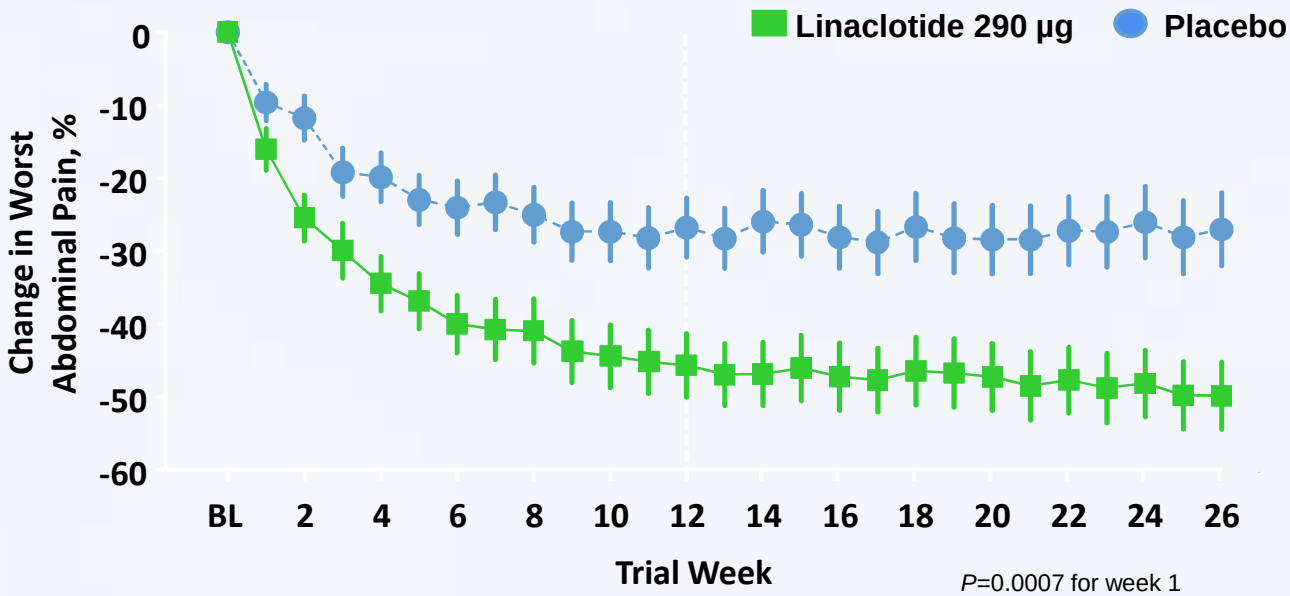
- 14 aa peptide structurally similar to guanylin/ uroguanylin
- 4 RCT, n=2867
- IBS-C dose: 290 mcg daily; CIC dose: 72 mcg or 145 mcg daily
- AEs: diarrhea

FDA Primary Endpoint: ≥30% reduction worst abdominal pain and increase ≥1 CSBM, both for ≥6/12 weeks



*P<0.0001 for all analyses of linaclotide vs placebo groups, using Cochran-Mantel-Haenszel test

Linaclotide: Abdominal Pain Over 26 Weeks



ITT population, observed cases, LS-mean presented: *P*-values based on ANCOVA at each week. Bars represent 95% CI.

N=804

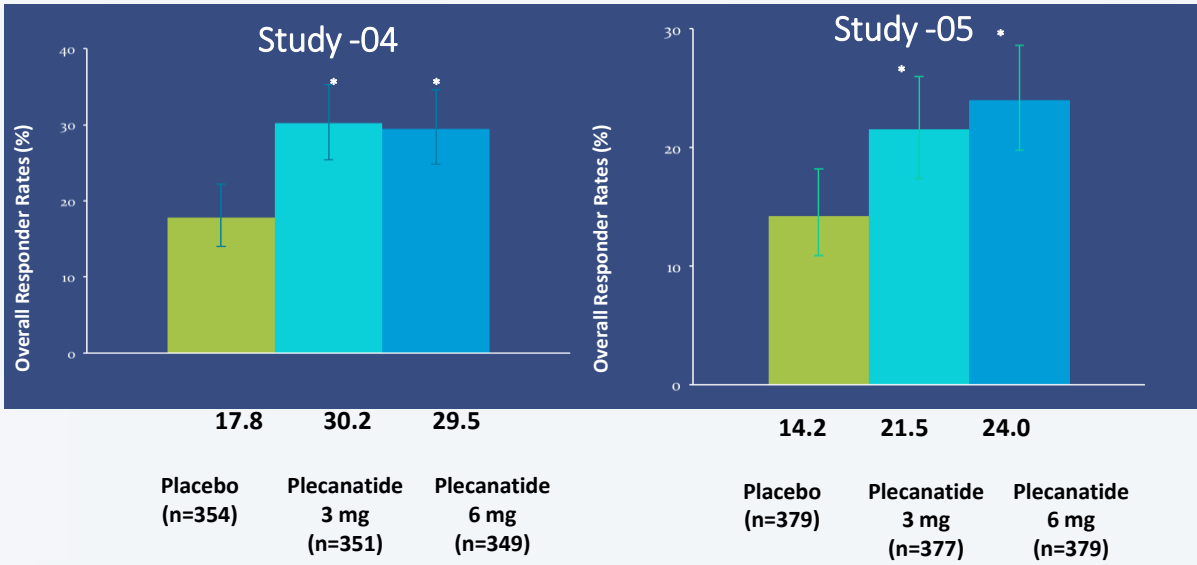
ITT, intention to treat; LS, least squares.

Chey WD, et al. *Am J Gastroenterol*. 2012;107:1702-1712.

Plecanatide (GC-C Agonist) for IBS-C

Strong Recommendation; High Quality of Evidence

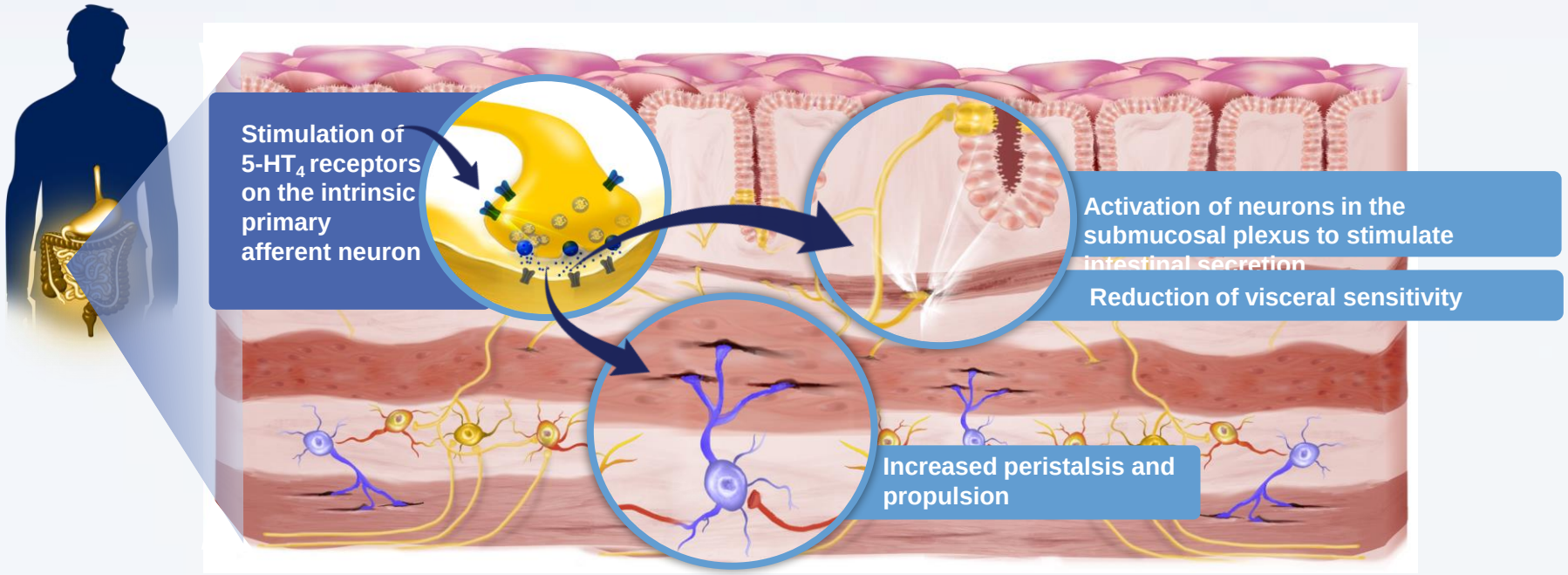
- 16 aa peptide structurally similar to uroguanylin
  - 8x greater binding affinity at pH <7
- 3 RCT, n=2612
- IBS-C and CIC dose: 3mg daily
- AEs: diarrhea



*P<0.001 vs placebo..

Brenner D, et al. Am J Gastroenterol 2018; In press.

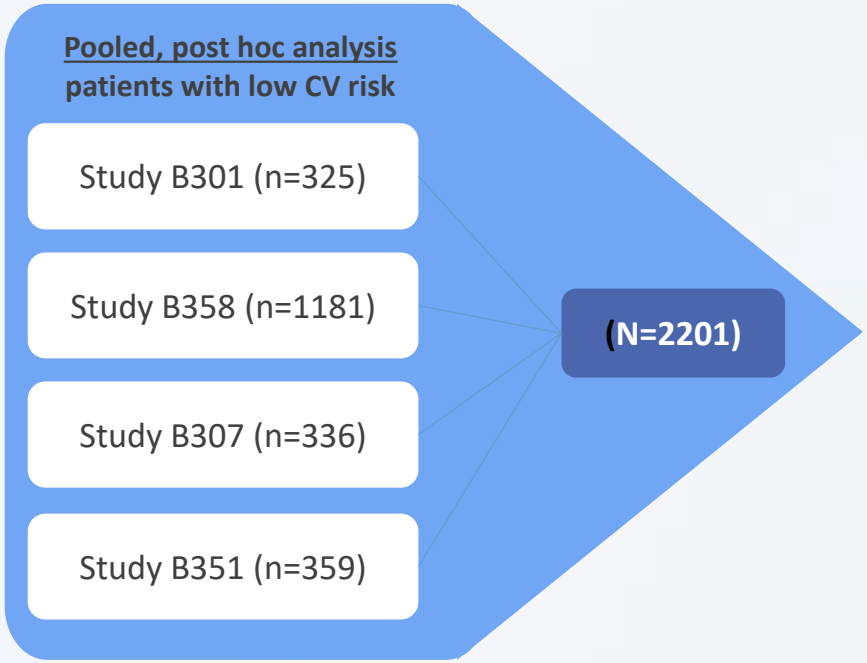
Tegaserod Mechanism of Action



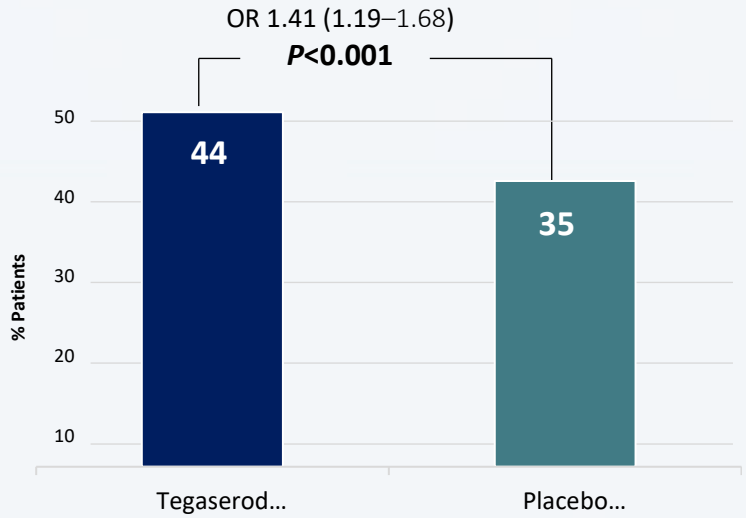
Gershon MD. *Rev Gastroenterol Disord*. 2003;3(suppl 2):S25-S34. 2.

Tegaserod for IBS-C

Conditional Recommendation; Low Quality of Evidence



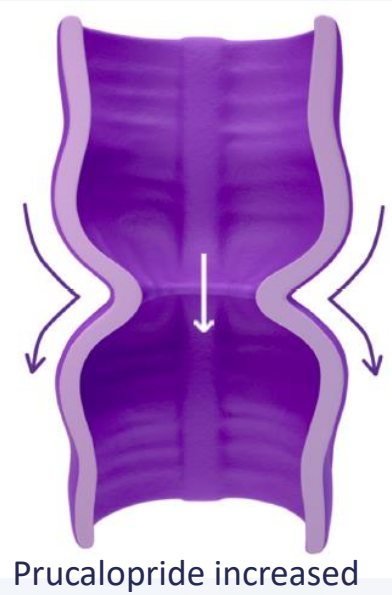
- **Mixed serotonin (5-HT) agonist (prokinetic)**
- **Approved for women < 65 years with ≤ 1 CV risk factor**
- **Dose: 6 mg PO BID**
- **AEs: Diarrhea, abdominal pain, headache, nausea**



Considerable or complete relief at least 50% of last 4 weeks in 12-week study, or at least somewhat relieved 100% of the last 4 weeks.

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

Prucalopride Mechanism of Action



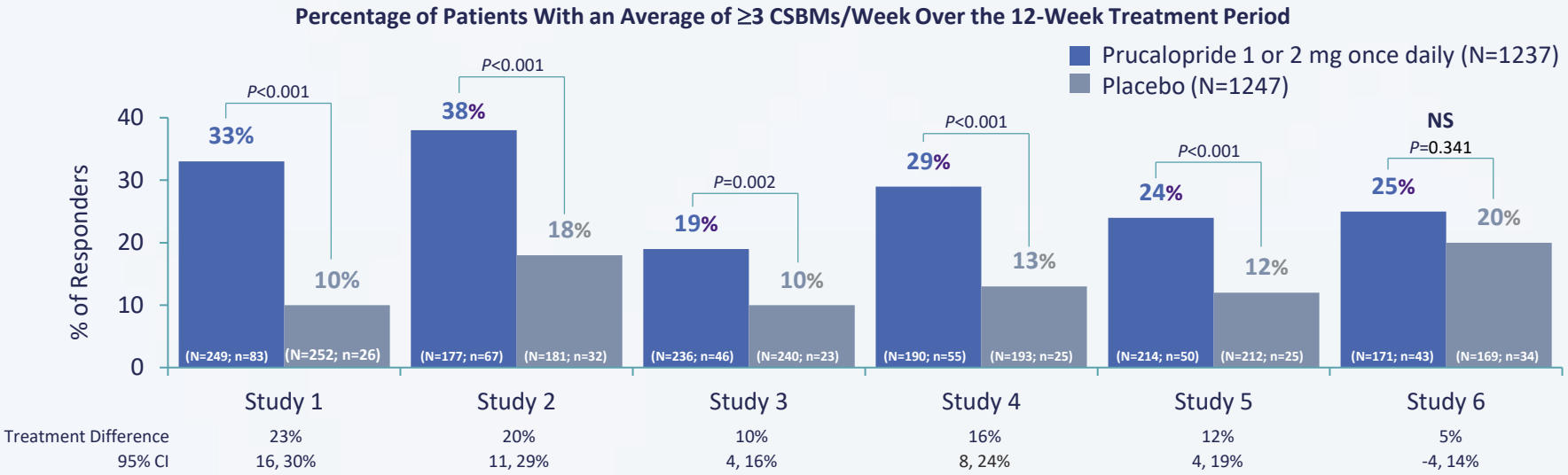
Prucalopride increased **number and amplitude** of HAPCs

Selective 5-HT_4 receptor agonist stimulates colonic peristalsis (HAPCs), increasing bowel motility

- Following a single 2 mg dose in patients with CIC, prucalopride **increased the number of HAPCs** during the first 12 hours compared with an osmotic laxative treatment
- Prucalopride 4 mg once daily **increased the amplitude of HAPCs** in healthy subjects without affecting colonic phasic activity compared with placebo
- Prucalopride was devoid of effects mediated via 5-HT_{2A}, 5-HT_{2B}, 5-HT_3, motilin, or CCK-A receptors *in vitro* at concentrations exceeding 5-HT_4 receptor affinity by 150-fold or greater

Prucalopride for CIC
6 RCTs

PRIMARY EFFICACY ENDPOINT:



In all studies, improvement in the frequency of CSBMs/week was seen as early as week 1 and was maintained through week 12.

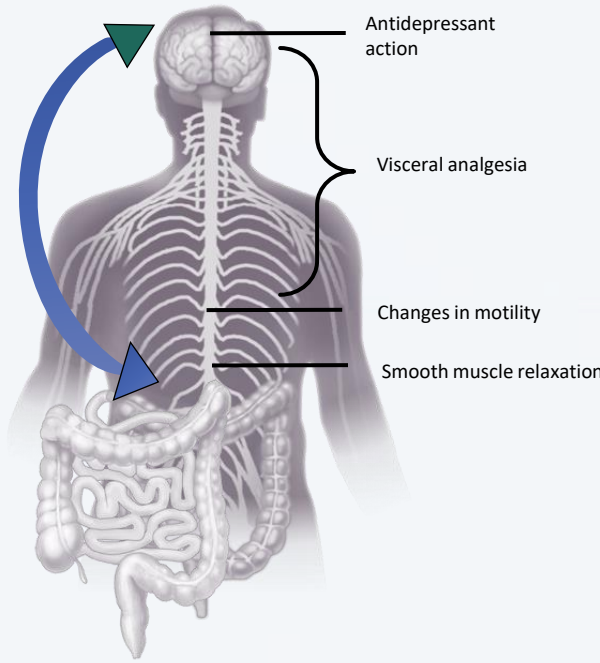
P-values based on a Cochran-Mantel-Haenszel test. N=number of patients per treatment group. n=number of responders. CI=confidence interval. NS=not significant.

Prucalopride - Prescribing Information. Lexington, MA: Shire LLC.

Antidepressants/Neuromodulators

Strong Recommendation; Moderate Quality of Evidence

- 18 RCT, 1127 patients
- Antidepressants in general: NNT= 4; pain mostly
  - TCAs: 12 RCT, 787 patients; Strong rec; high quality evidence
  - SSRIs: 7 RCT, 356 patients; Weak rec; low quality evidence
  - SNRIs not yet studied in large RCTs[2]
- AEs more common with antidepressants; NNH= 8.5



1. Ford AC et al. *Am J Gastroenterol*. 2014;109:1350-1365; 2. Grover M, Drossman DA. *Gastroenterol Clin N Am*. 2011;40:183-206. 3. Chey WD et al. *Gut Liver*. 2011;5:253-266. 4.Gorard DA, et al. *Aliment Pharmacol Ther.* 1994;8:159-166.

General Approach to Prescribing Antidepressants in IBS

- Consider specific symptoms[1,2]
  - TCAs in IBS-D, SSRIs in IBS-C
  - SSRI/SNRI for anxiety
- Consider side effect profiles[1,2]
  - SSRIs may be better tolerated than TCAs
- Start with low dose and titrate slowly by response; allow 4-8 weeks for maximal response[1-3]
- Continue at minimum effective dose for 6-12 months[1,2]
  - Long-term therapy may be warranted for some patients
  - Gradual taper to prevent withdrawal symptoms

RCTs, randomized, controlled trials; SNRIS, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

1. Sobin WH et al. *Am J Gastroenterol*. 2017;112 (5):693-702. **2.** Grover M, Drossman DA. *Gastroenterol Clin N Am*. 2011;40:183-206. **3.** Dekel R et al. *Expert Opin Invest Drugs*. 2013;22 :329-339.

Neuromodulation for DGBI

SSRIs
(paroxetine, fluoxetine, sertraline, citalopram, escitalopram)

When anxiety, depression, and phobic features are prominent with FGIDs

TCAs
(amitriptyline, nortriptyline, imipramine, desipramine)

First-line treatment when pain is dominant in FGIDs

Tetracyclic antidepressant
(mirtazapine, mianserin, trazodone)

Treatment of early satiety nausea/vomiting, weight loss and disturbed sleep

SNRIs
(duloxetine,venlafaxine, desvenlafaxine, milnacipran)

Treatment when pain is dominant in FGIDs or when side effects from TCAs preclude treatment

Insufficient effect or dosage restricted by side effects

Augmentation

Azapirones (buspirone, tandospirone)
Dyspeptic features, anxiety prominent

Delta ligands (gabapentin, pregabalin)
Abdominal wall pain, comorbid fibromyalgia

SSRI
When anxiety and phobic features dominant

Atypical antipsychotics
Pain with disturbed sleep (quetiapine)
anxiety, nausea (olanzapine, sulpiride)
additional somatic symptoms ("side effects")

Bupropion
Fatigue and sleepiness prominent

Psychological Treatment
CBT when maladaptive cognitions and catastrophizing present

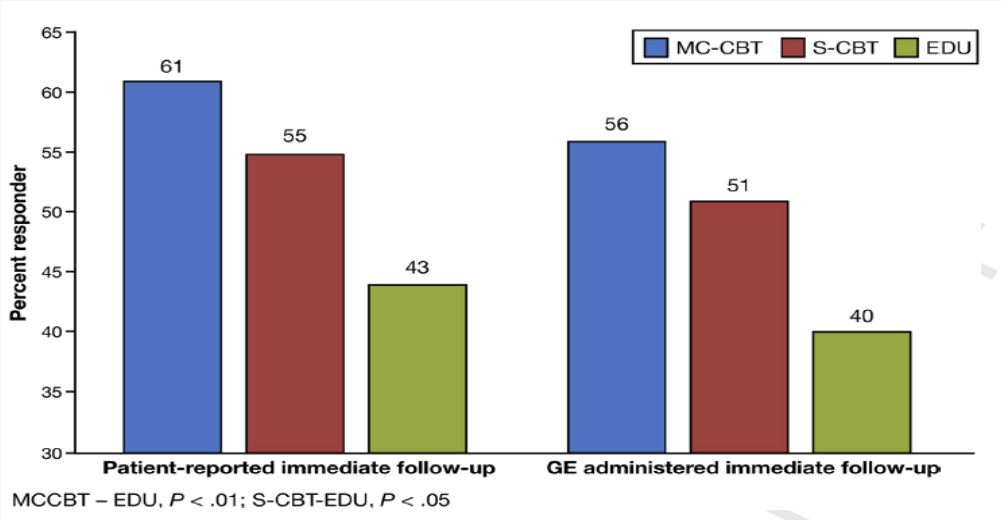
DBT, EMDR with history of PTSD or trauma

Hypnosis, Mindfulness, Relaxation as alternative treatments

Drossman DA et al. Gastroenterology 2018;154:1140–1171

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)
- 1^0 Endpoint: CGI-I (1-7 scale w/6-7 moderate/substantial improvement considered a responder



MCCBT-Minimal Contact CBT; S-CBT-Standard CBT; EDU-Education; CGI-I (Clinical Global Impressions-Improvement-Scale; GE (Gastroenterologist)

Lackner J, Jaccard J, Keefer LK, Brenner DM, et al. Gastroenterology 2018 *(epub ahead of print)*

Do Not Use FMT for IBS

Strong Recommendation; Very Low Quality of Evidence

Xu et al.: Systematic review of 4 studies (Rome III) (n=254; 152 FMT)

- ITT analysis: 49.3% response to FMT vs 51% with placebo FMT
- No difference in global IBS symptoms in patients who received FMT compared with placebo (RR 0.93; 95% CI 0.48–1.79, P 5 0.83)
- NJ and colonoscopy more likely to report global symptom improvement

Ianiro et al.: SR with meta-analysis of 5 RCTs (n = 267)

- Included 2 published articles and 3 study abstracts
- Stool delivered during colonoscopy was superior to autologous stool in 2 RCTs; placebo capsules superior in 2 RCTs
- One study showed a trend toward improvement in IBS symptoms using donor stool through a NJ tube

Xu D, et al. Am J Gastroenterol 2019;114:1043-50. Ianiro G, et al. Aliment Pharmacol Ther 2019;50:240-8.

Management of IBS and CIC: Take Home Points

- Make a positive diagnosis (exclude alarm features)
- Abdominal pain required for IBS and differentiates IBS-C from CIC
  - Recognize significant overlap; Treatment is largely the same
- Diet, lifestyle modifications, OTC (loperamide, PEG, fiber) therapies first line
- Best clinical trial evidence
  - **IBS-D**: Rifaximin, Eluxadoline, Alosetron
  - **IBS-C**: Linaclotide, Plecanatide, Lubiprostone, Tegaserod
  - **CIC:** Linaclotide, Plecanatide, Lubiprostone, Prucalopride
  - 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

Thank You for Your Participation

please forward any questions to:
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