



IBS WITH CONSTIPATION: Therapeutic Approaches

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Management of IBS: Patient-Centered Care

What do your patients really want from you?

- They want you to listen
- Education
- Reassurance
- A positive diagnosis
- Symptom improvement
 - Treatment options explained



Photo credit: Nensuria at Freepik.

IBS, irritable bowel syndrome.

Learning Objectives

- Implement individualized treatment plans for patients with irritable bowel syndrome with constipation (IBS-C) that incorporate data from randomized controlled trials and evidence-based recommendations
- Utilize patient-centric counseling strategies for patients with IBS-C to support prompt identification of inadequate or poorly tolerated therapy and support long-term therapeutic adherence

Patient Case

JL is a 32-year-old woman with a 9-month history of constipation associated with abdominal pain and bloating.

- The patient reports having a bowel movement “about every 3 days”; she says her stools are hard and that she needs to strain to pass them
- She reports occasional abdominal pain that is alleviated by having a bowel movement, but says she has a consistent feeling of incomplete evacuation and feels bloated “most of the time”
- She has used fiber supplements and OTC laxatives to relieve her constipation with inconsistent results; the patient also expresses concerns with becoming dependent on the use of stimulant laxatives

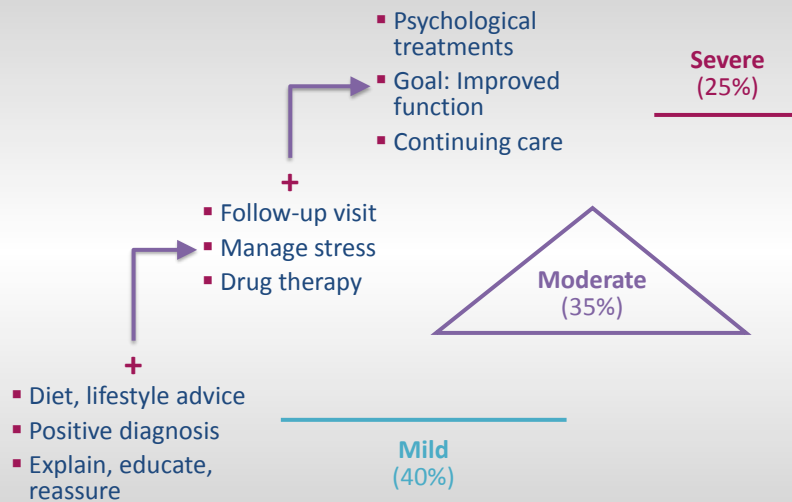
OTC, over-the-counter.

Medical Treatments for IBS-C

- Diet
- Fiber
- Probiotics
- Osmotic agents
- Chloride channel activators
- Guanylate cyclase-C activators
- CAM

CAM, complementary and alternative medicine.

Treatment Depends on Severity of IBS



Lacy BE, et al. *Gastroenterology*. 2016;150(6):1393-1407.

Dietary Therapy for IBS

- Elimination diet
- IgG elimination diet
- Low-carbohydrate diet
- Low-fructose/fructan diet
- Lactose-free diet
- Paleo diet
- **Low-gluten diet**
- **Low-FODMAP diet**

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; IgG, immunoglobulin G.

A Low-Gluten Diet for IBS

- 2 randomized controlled trials (RCTs)
 - 1 trial had low risk of bias; risk was unclear in the other
 - N=111
- Gluten-free diet was associated with reduced global IBS symptoms (RR=0.42; 95% CI: 0.11-1.55 [NS])
- Take-home message: little data to support a commonly employed treatment

NS, not significant; RR, risk ratio.
Dionne J, et al. *Am J Gastroenterol*. 2018;113(9):1290-1300.

Low-FODMAP Diet

Minimizes intake of foods high in
Fermentable **O**ligo-, **D**i-, **M**onosaccharides **A**nd **P**olyols



Excess Fructose

Honey, apples, pears, peaches, mangos, fruit juice, dried fruit



Fructans

Wheat (large amounts), rye (large amounts), onions, leeks, zucchini



Sorbitol

Apricots, peaches, artificial sweeteners, artificially sweetened gums

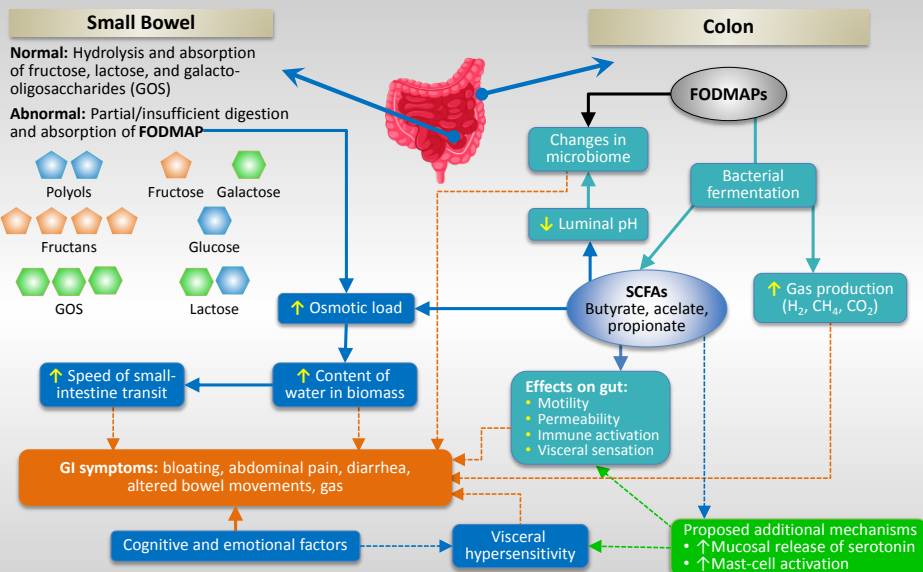


Raffinose

Lentils, cabbage, Brussels sprouts, asparagus, green beans, legumes

Shepherd SJ, et al. *J Am Diet Assoc.* 2006;106(10):1631-1639; Shepherd SJ, et al. *Clin Gastroenterol Hepatol.* 2008;6(7):765-771; Gibson PR, et al. *J Gastroenterol Hepatol.* 2010;25(2):252-258.

FODMAPs and the GI Tract



GI, gastrointestinal; SCFAs, short-chain fatty acids.

Werlang ME, et al. *Gastroenterol Hepatol.* 2019;15(1):16-26.
<http://www.gastroenterologyandhepatology.net/files/2019/01/gh0119Werlang-1.pdf>

RCTs Evaluating the Low-FODMAP Diet for IBS

- 7 RCTs compared a low-FODMAP diet with various controls (N=397)

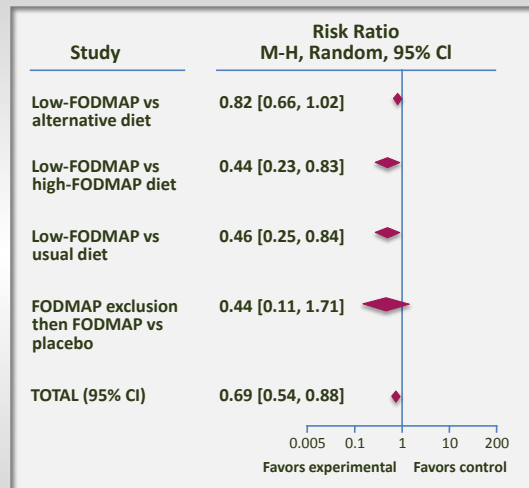
- Low-FODMAP diet was associated with reduced overall symptoms compared to controls (RR=0.69; 95% CI: 0.54-0.88; I²=25%)

- 3 RCTs compared low-FODMAP diets with rigorous control diets

- Showed the least heterogeneity between studies but also the least magnitude of effect

- Overall quality of the data was "very low" (GRADE criteria)

- Most studies had high risk of bias
- Heterogeneity between study designs
- Imprecision in the estimate of effect



GRADE, Grades of Recommendation Assessment, Development and Evaluation; I², percentage of variation across studies due to heterogeneity; MH, Mantel-Haenszel
Dionne J, et al. *Am J Gastroenterol.* 2018;113(9):1290-1300.

Micronutrient Deficiencies With Low-FODMAP Diet

Variable	Low FODMAP (n=41)			mNICE (n=37)		
	Baseline	Week 4	P value within group	Baseline	Week 4	P value within group
Energy (kcal)	2043 ± 653	1691 ± 600.7	0.01*	2005 ± 511	1835 ± 714	0.04*
Number of daily meals	5.43 ± 1.7	4.92 ± 1.5	0.01*	5.52 ± 1.7	4.8 ± 1.4	0.004*
Polyunsaturated fatty acids (g)	18.6 ± 7.2	17.6 ± 9.8	0.62	20.1 ± 7.9	16.1 ± 8.6	0.04*
Retinol (mcg)	493.9 ± 379.2	350.2 ± 179.0	0.03*	427.9 ± 207.5	350.6 ± 218.7	0.12
Thiamin (vitamin B1) (mg)	1.6 ± 0.6	1.3 ± 0.6	0.009*	1.8 ± 0.6	1.6 ± 0.8	0.32
Riboflavin (vitamin B2) (mg)	2.0 ± 0.8	1.7 ± 0.6	0.045*	1.9 ± 0.6	1.8 ± 0.8	0.40
Vitamin B6 (mg)	1.7 ± 0.6	2.1 ± 0.8	0.045*	1.8 ± 0.8	2.0 ± 1.1	0.40
Calcium (mg)	969.5 ± 422.9	752.3 ± 300.3	0.009*	961.4 ± 375.8	855.1 ± 408.3	0.25

*No significant differences from baseline were seen for daily intake of cholesterol, saturated fatty acids, monounsaturated fatty acids, caffeine, beta carotene, total alpha-tocopherol equivalents, vitamin D, vitamin E, vitamin K, vitamin C, niacin, pantothenic acid, folate, and vitamin B12.

mNICE, modified National Institute for Health and Care Excellence guideline-based diet.

Faria JP, et al. Presented at: American College of Gastroenterology Annual Scientific Meeting; October 16-18, 2017; Orlando, FL.

Bulking Agents for IBS-C: Systematic Review and Meta-Analysis

	RCTs	N	Response*		RR of Unimproved Symptoms (95% CI)	NNT (95% CI)
			Fiber	Placebo		
Overall	12	591	48%	43%	0.87 (0.76-1.0)	11 (5-100)
Ispaghula	6	321	48%	36%	0.78 (0.63-0.96)	6 (3-50)
Bran	5	221	46%	46%	1.02 (0.82-1.27)	

*Improved or resolved symptoms.

- Insoluble fiber was **not** more effective than insoluble fiber—and sometimes worsened symptoms
- Soluble fiber improved global symptoms
- 4 out of 5 bran studies were of poor quality

NNT, number needed to treat; RCTs, randomized controlled trials; RR, relative risk.
Ford AC, et al. *Am J Gastroenterol.* 2014;109(10):1547-1561.

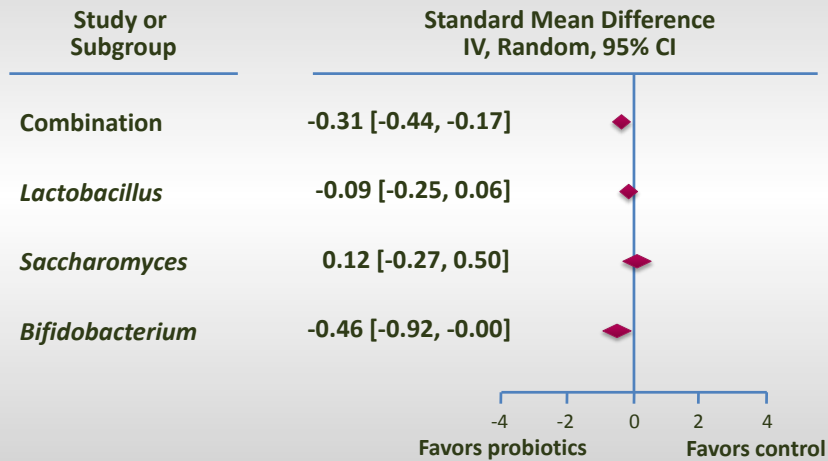
Probiotics: Putative Mechanisms of Action

- Competitive inhibition
- Barrier protection
- Immune effects
- Anti-inflammatory effects
- Production of various substances (enzymes, SCFAs, bacteriocidal agents)
- Ability to alter local pH and physiology
- Ability to provide nutrition to colonocytes

SCFAs, short-chain fatty acids.
Camilleri M. *J Clin Gastroenterol.* 2006;40(3):264-269.

RCTs of Probiotics vs Placebo in IBS

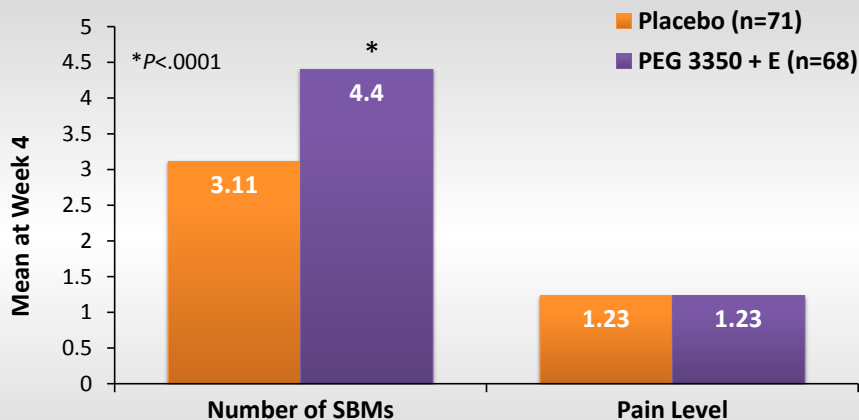
Effect on global symptom or abdominal pain scores



IV, independent variable; RCTs, randomized controlled trials.

Ford AC, et al. *Aliment Pharmacol Ther.* 2018;48(10):1044-1060.

PEG 3350 + E Improves SBMs But Not Pain in IBS-C

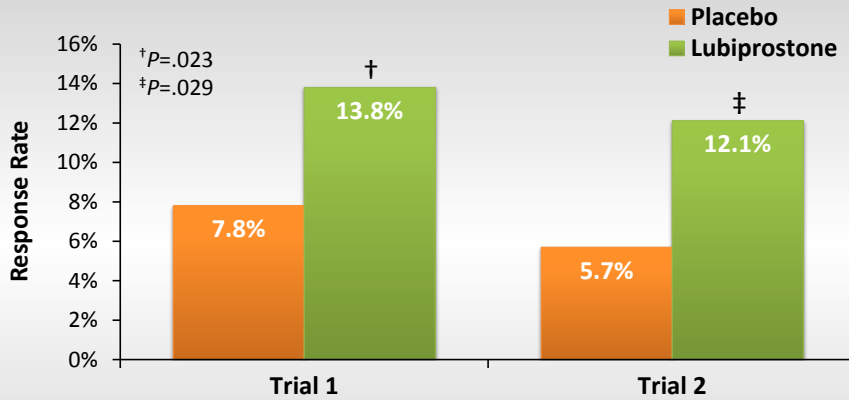


Note: PEG 3350 + E is not approved for this indication in the United States.

E, electrolytes; PEG, polyethylene glycol; SBMs, spontaneous bowel movements.

Chapman RW, et al. *Am J Gastroenterol.* 2013;108(9):1508-1515.

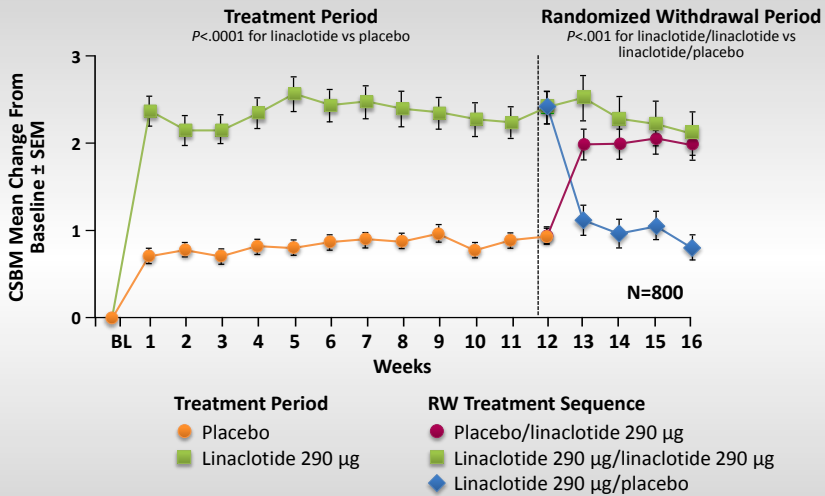
Overall Responder Rates* to Lubiprostone in IBS-C Patients



Overall responders defined as subjects who were monthly responders for ≥2 out of any 3 months.

*Therapeutic gain = treatment response rate minus placebo response rate.
 Note: Lubiprostone is approved to treat IBS-C in women.
 Amitiza [package insert]. Bethesda, MD: Takeda Pharmaceutical Company, Ltd; 2013.

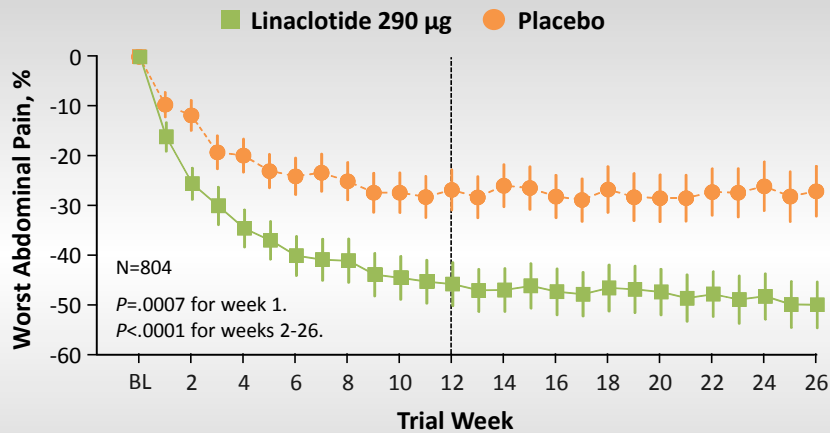
Efficacy of Linaclotide in Patients With IBS-C



BL, baseline; CSBM, complete spontaneous bowel movement; RW, randomized withdrawal; SEM, standard error of the mean.

Rao S, et al. *Am J Gastroenterol.* 2012;107(11):1714-1724.

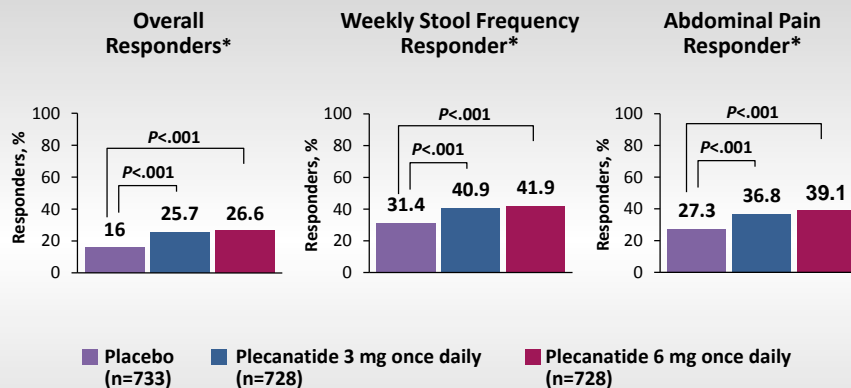
Linacotide Phase 3 IBS-C Trial: Abdominal Pain Over 26 Weeks



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

ANCOVA, analysis of covariance; BL, baseline; ITT, intention to treat; LS, least squares.
Chey WD, et al. *Am J Gastroenterol.* 2012;107(11):1702-1712.

Plecanatide for IBS-C



*Study population was patients meeting Rome III criteria for IBS-C. Overall responder defined as a patient who had both a $\geq 30\%$ reduction in worst abdominal pain and an increase of ≥ 1 CSBM from baseline in the same week for ≥ 6 weeks of the 12 treatment weeks.

CSBM, complete spontaneous bowel movement.
Brenner DM, et al. *Am J Gastroenterol.* 2018;113(5):735-745.

Summary

- Multiple treatment options are now available for IBS-C
- Assess symptom severity in order to recommend the best therapy
- Don't forget to focus on the basics—listen, educate, reassure
- Ensure that therapeutic trials are long enough to properly assess efficacy
- New treatment options will be available within the next few years