2021 SCSG
GI SYMPOSIUM

Modern Management Strategies for IBS

Anthony Lembo, MD
Professor of Medicine, Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, MA Subtitle

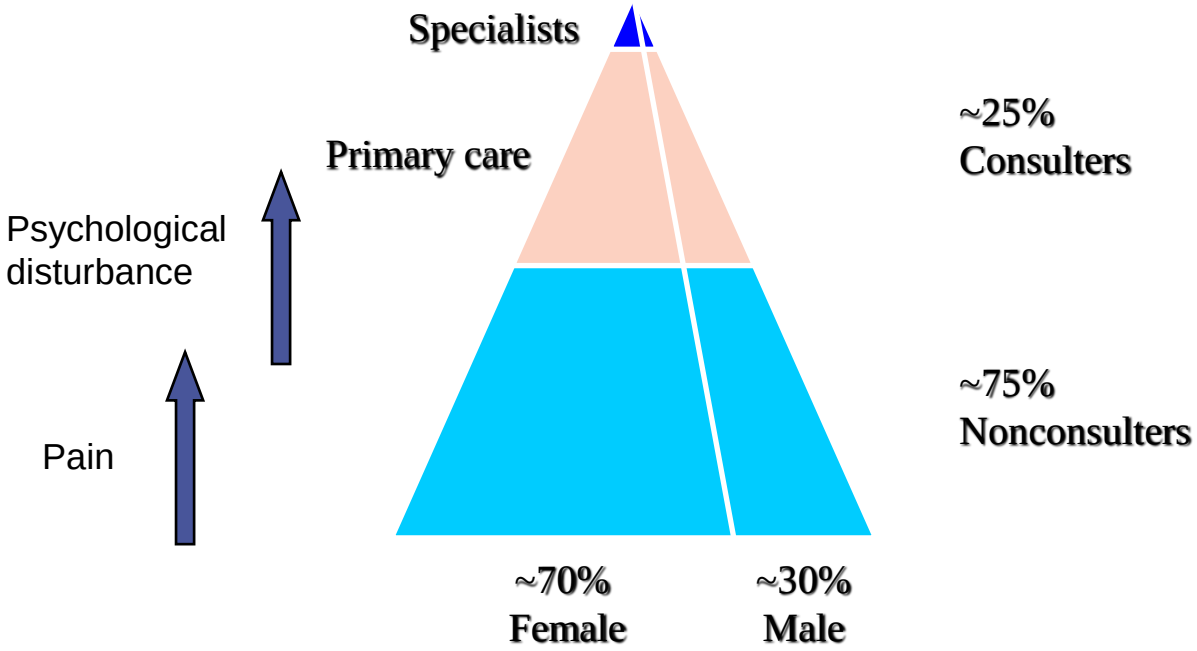
Disclosures

- Honorarium
  - Ironwood
  - Takeda
  - Mylan
  - Bayer
  - Shire
  - Arena
  - OrphoMed
  - Gemelli Biotech

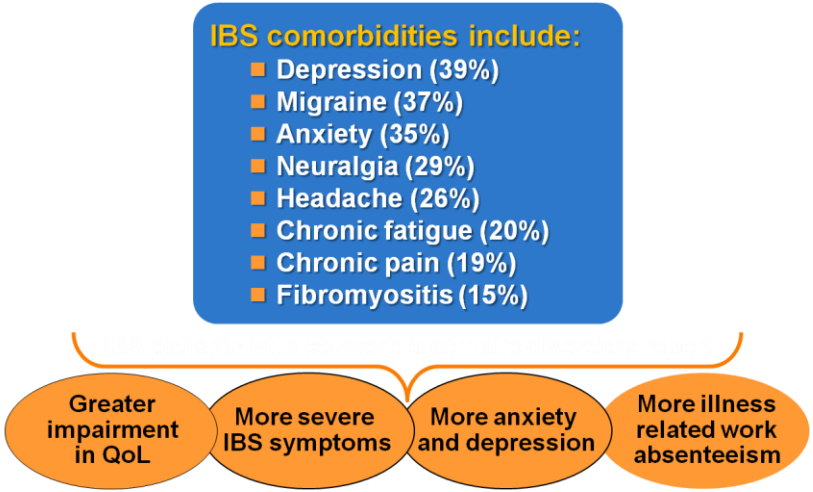
Objectives

- Doctor-Patient Relationship
- Lifestyle Management
- Diet
- Pharmacological Therapies
- Psychological Therapies

Who Seeks Medical Care for IBS?



IBS Frequently Co-exists with Other Pain Conditions and Psychological Factors



Consider ways to address when present:

Referral to appropriate specialties, central acting medications, psychological consultation

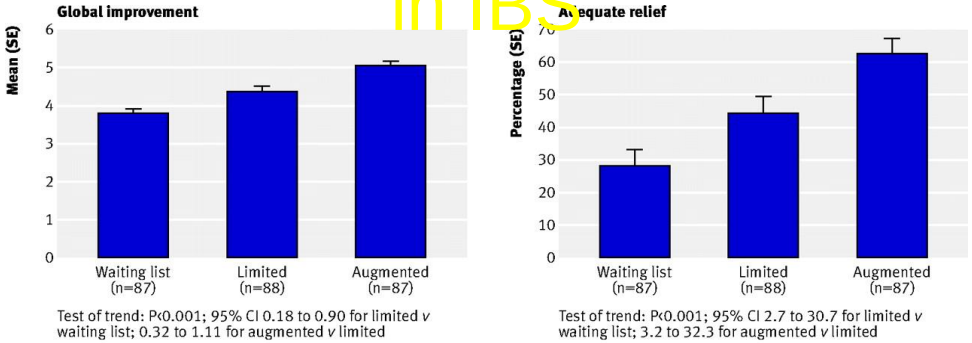
Ladabaum et al, Gastroenterology 2007; 132: W1172
Whitehead et al, Am J Gastroenterol 2007; 102: 2767–76
Vandvik et al, Aliment Pharmacol Ther 2004; 20: 1195–203

Recommendations to Foster Physician Presence and Connection With Patients

- **Prepare with intention**
  - take a moment to prepare and focus before greeting a patient
- **Listen intently and completely**
  - sit down, lean forward, avoid interruptions
- **Agree on what matters most**
  - find out what the patient cares about and incorporate these priorities into the visit agenda
- **Connect with the patient's story**
  - consider life circumstances that influence the patient's health; acknowledge positive efforts; celebrate successes
- **Explore emotional cues**
  - notice, name, and validate the patient's emotions

Zulman et al. *JAMA.* 2020;323(1):70-81

A “Patient-Centered” Therapeutic Encounter Can Improve Clinical Outcomes in IBS



Features of an Augmented Patient-Clinician Relationship Used in this study:

- Warm, empathetic, and confident
- Active listening
- 20sec of thoughtful silence
- Physical contact
- increased time (30 min over 3 weeks)

Kaptchuk et al., BMJ 2008

Life Style Management

- General Lifestyle Recommendations
  - Exercise
  - Sleep
  - Eat well
  - Reduce stress
- Helpful for Everyone!!!

Food is a Key Trigger of IBS

- > 70% of individuals report food triggers symptoms
- Mechanisms:
    - Allergy (rare)
    - Intolerance / Sensitivity (common)
        - Malabsorption (e.g., FODMAPs)
        - Pharmacological factors (e.g., caffeine)
        - “Reactions”
            - Gluten (non-celiac gluten sensitivity)

General Dietary Recommendations

- Maintain a brief diary of dietary intake and symptoms
- Common triggers include:
  - Fatty/greasy food
  - Alcohol, Caffeine
  - Poorly absorbed carbohydrates (FODMAPs)
    - Fructans
      - bread and pasta,onions, shallots, garlic, barley, cabbage, broccoli, pistachio, artichoke, and asparagus
    - Polyols
      - Stone fruits (cherries, peaches, and plums), apples, apricots, pears, bell peppers, sweet potatos, dried fruit, juices, low-sugar foods often contain sorbitol/mannitol

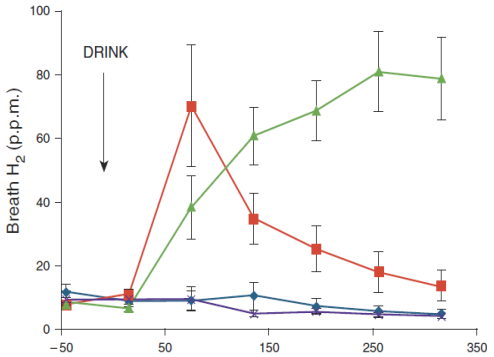
FODMAPs

Fermentable
Oligosaccharides — Fructans, Galactans
Disaccharides — Lactose
Monosaccharides — Fructose
And
Polyols — Sugar Alcohols

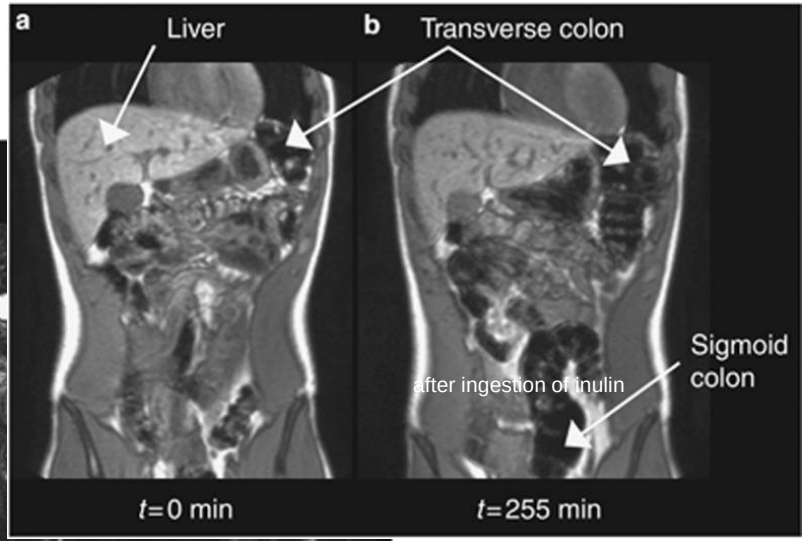
Examples of FODMAPs

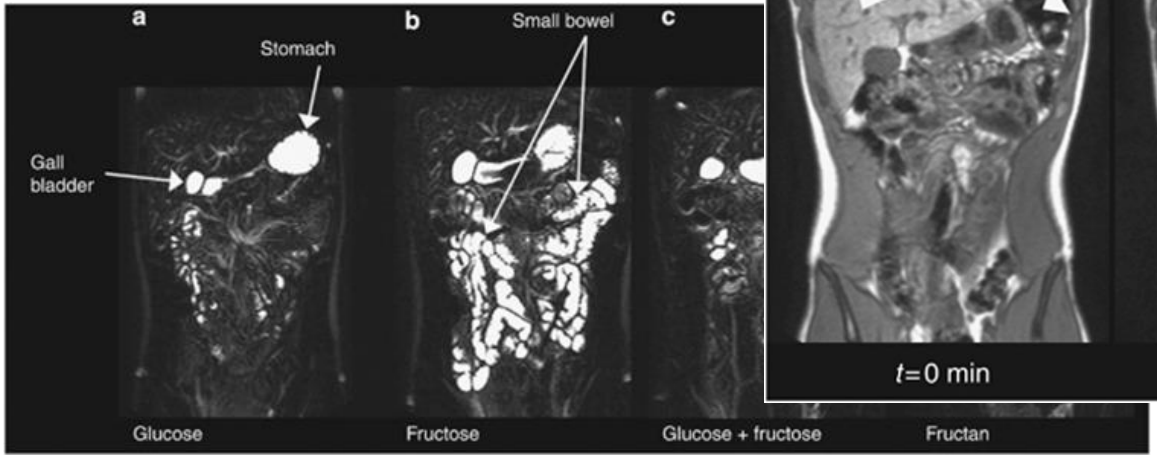
Excess Fructose	Lactose	Fructans	Galactans	Polyols
fruit apple, mango, pear, cherries, watermelon **sweeteners** sugar, high-fructose corn syrup **other** honey, asparagu	**milk** milk from cows, goats, or sheep; custard, ice cream, yogurt **cheeses** soft unripened cheeses (eg, cottage cheese, ricotta)	**vegetables** onion, leek, garlic, shallots, artichokes, asparagus, peas, beetroot, chicory **cereals** wheat, barley, rye	**legumes** baked beans, chickpeas, kidney beans, lentils	**fruit** apple, pear, apricot, cherries, peaches, nectarines, plums, watermelon **vegetables** cauliflower, mushrooms **sweeteners** sorbitol, mannitol c

FODMAPs Are Not All Equal



- Fructans undergo greatest fermentation
  Fructose but not inulin distends the small bowel with water
- Adding glucose to fructose reduces the effect
- Inulin distends the colon with gas more than fructose



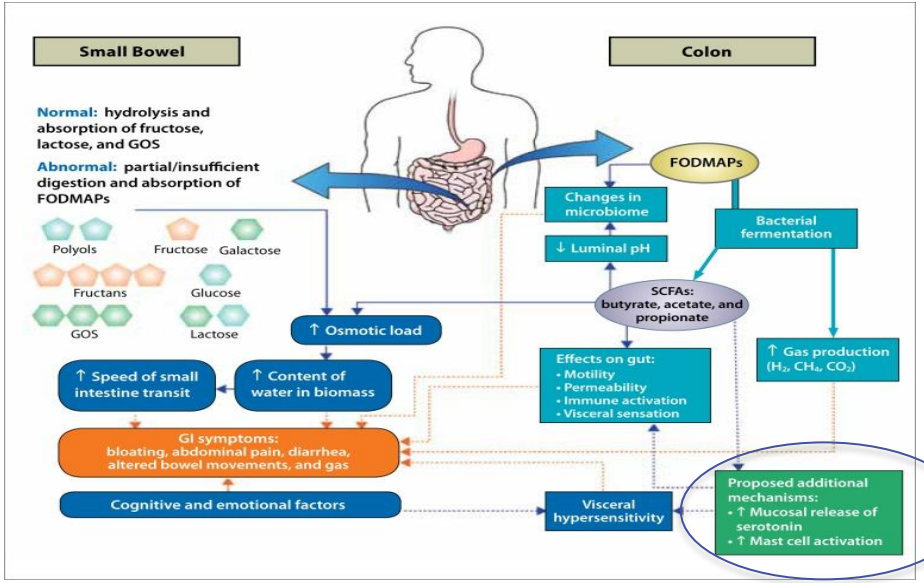


Low-FODMAP Diet in IBS

ACG

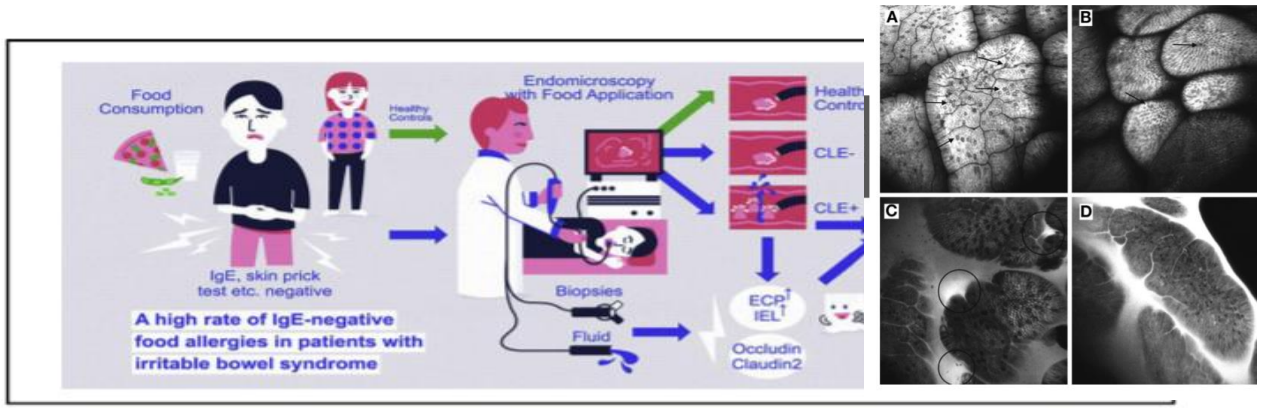
- ACG Guideline recommends: limited trial of a low FODMAP diet to improve global symptoms.
  - Conditional recommendation; very low quality of evidence.
  - 7 RCTs (all high risk of bias)
    - Low-FODMAP vs:
      - usual diet (n=2)
      - placebo controlled FODMAP rechallenge (n=1)
      - high FODMAP (n=1)
      - other diets (eg. NICE) n=3 [non-significant trend]
  - Only the initial diet phase evaluated other phases (gradual reintroduction and personalization of the diet) have not been adequately studied
  - Pitfills: Complex, Costly, Most effective GI dietician, possible negative impact on QOL
  - Unanswered questions: effects on the gut microbiota. development of ARFID, cibophobia, nutritional deficiencies

How Do FODMAPs Cause IBS Symptoms?



Werlang, Palmer, Lacy. Gastroenterol Hepatol (N Y).

Many Patients With Irritable Bowel Syndrome Have Atypical Food Allergies Not Associated With Immunoglobulin E

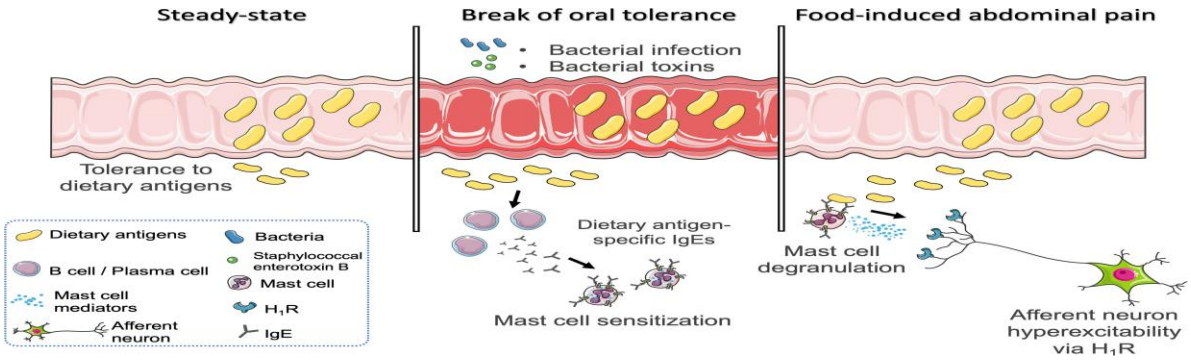


Conflocal Light Endoscopy positivity: wheat (60%), yeast(20%), milk(9%), soy(6%), egg(4%)

Frischer-Ravens et al. Gastroenterology 2019;157:109–118

Article

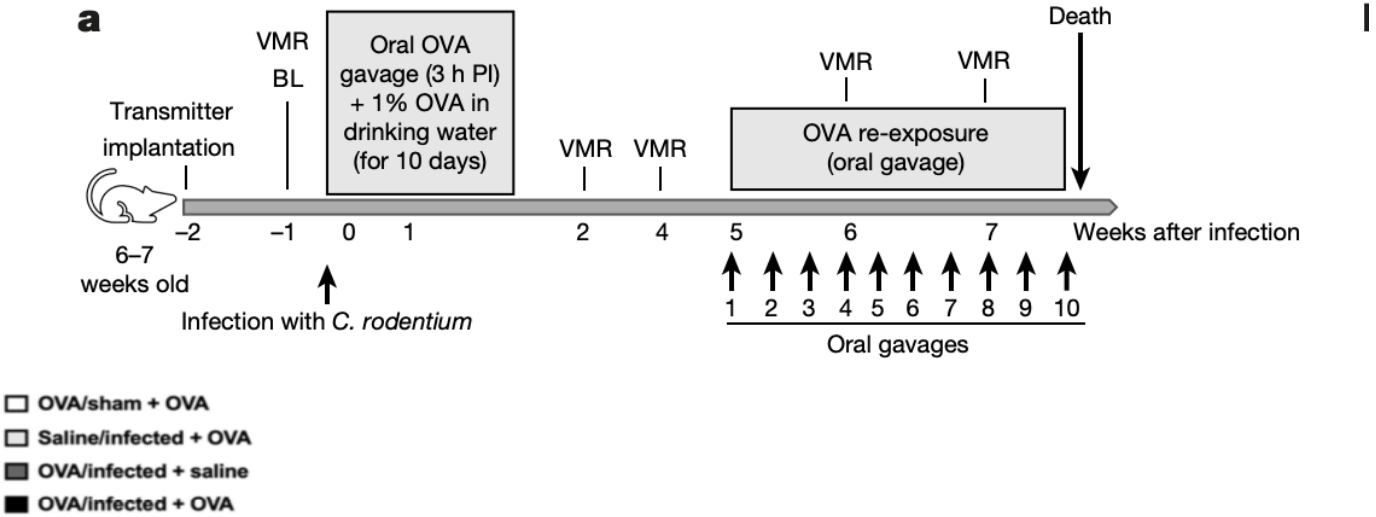
Local immune response to food antigens drives meal-induced abdominal pain



IgE food antibodies detected only in colonic tissue, indicating a local rather than systemic immune response against dietary antigens!

Javier Aguilera-Lizarraga et a; Nature | Vol 590 | 4 February 2021

Study Design



Javier Aguilera-Lizarraga et a; Nature | Vol 590 | 4 February 2021

Similar Findings in IBS patients…..

12 IBS patients/ 12 HV

Food antigens injected into the rectosigmoid

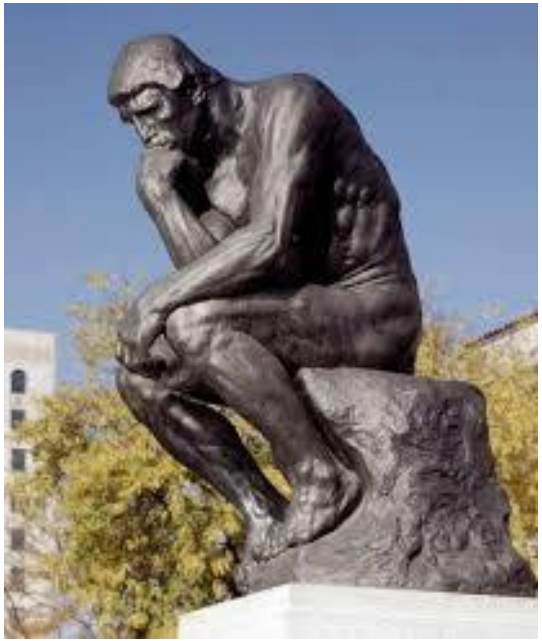
Gluten, wheat, soy, and cow milk

All participants had negative skin-prick test, total IgE, tryptase, antigen-specific IgE in serum

The injection resulted in all of the IBS groups generating localized immune reactions similar to that seen in the mice, to at least one of the food antigens. Only 2 reaction in control (gluten+soy)

Javier Aguilera-Lizarraga et a; Nature | Vol 590 | 4 February 2021

Treatments for IBS



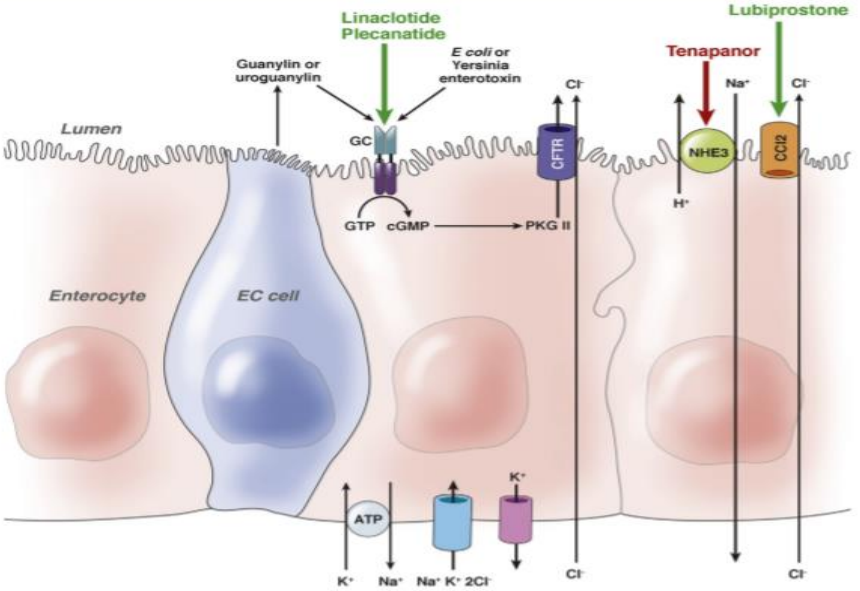
Pharmacologic Treatment of IBS-C

First line (after psyllium)

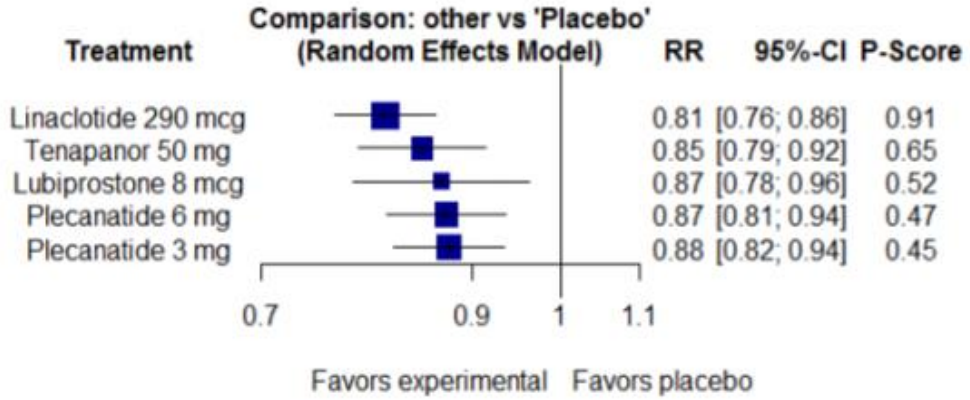
- Psyllium
- Osmotic laxatives (PEG)

Second line

- Secretotogues
  - Lubiprostone* (8 mcg BID in women with IBS
  - Linaclotide* (290 mcg QD)
  - Plecanitide* (3 mg QD)
  - Tenapanor* 50 mg BID (not yet available)



Efficacy of Secretotogues is Similar for Most End Points



Black CJ et al. Gastroenterology2018 Dec;155(6):1753-1763.

Tegaserod, a 5-HT4 Partial Agonist

- Recently FDA reapproved, 6 mg BID for women < 65 years
- Contraindicated in patients with h/o MI, stroke TIAs, or angina, or ischemic colitis, ESRD, hepatic impairment (Child-Pugh B or C)

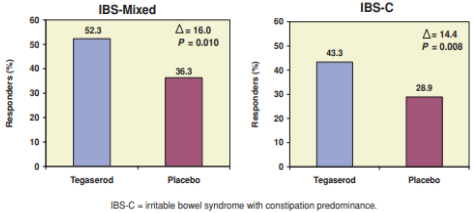


Figure 2. Responder rates for patients' overall satisfactory relief (75% rule). IBS-C = irritable bowel syndrome with constipation predominance.

Table 5. IBS Symptoms Over the Entire Treatment Period (ITT Patients)

	IBS-Mixed			IBS-C		
Assessment	Tegaserod 6 mg b.i.d.	Placebo	*P* Value	Tegaserod 6 mg b.i.d.	Placebo	*P* Value
Abdominal discomfort/pain	2.66	2.83	0.310	2.84	2.95	0.588
Bloating	2.83	2.99	0.303	3.08	3.16	0.335
No. of bowel movements*	9.78	8.34	<0.001	6.88	6.06	<0.001
No. of days with no bowel movements*	1.39	1.68	0.001	2.31	2.48	0.020
Stool consistency	3.95	3.49	<0.001	3.53	2.89	<0.001
No. of days with normal stool consistency*†	3.90	3.91	0.731	3.69	3.39	0.120
No. of days with straining*	2.42	2.87	0.023	3.08	3.55	0.018
No. of days with urgency*	2.01	1.88	0.030	1.37	1.16	0.057

Mean values are presented, unless noted.
*Normalized to 7 days.
†Normal stool consistency is defined as stool consistency score 3–5 inclusive.

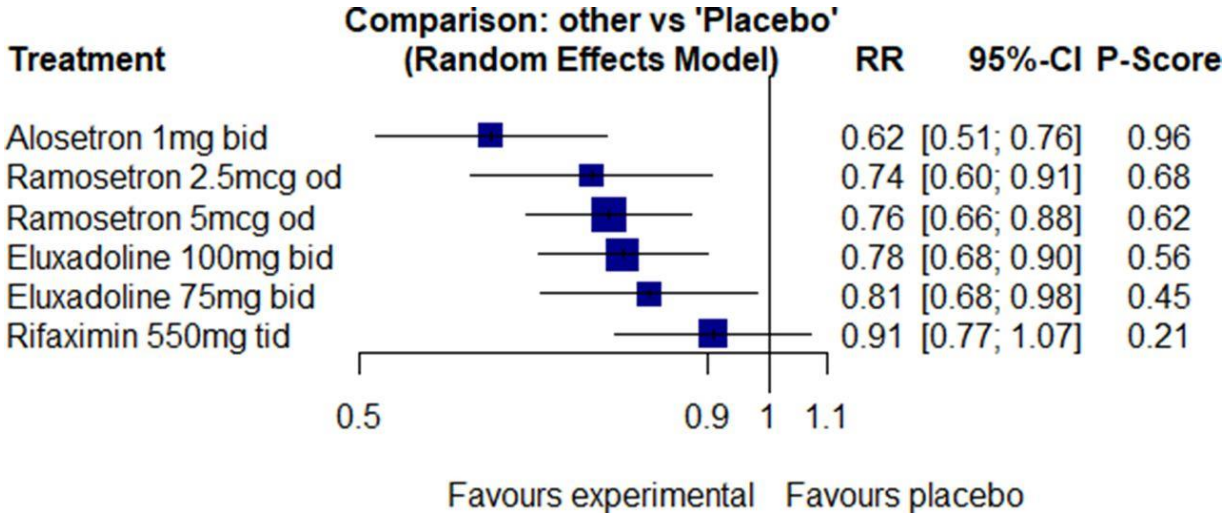
Pharmacologic Treatment of IBS-D

- First line
  - Anti-diarrheal agents (loperamide)
  - Bile acid sequestrants (cholestryramine)

- Second line
  - Rifaximin* (550 mg TID x 14 days); FDA approved for retreatment x 2
  - Eluxadoline* (100 mg BID)
    - SOD and Pancreatitis (avoid in patients >3 drinks a day or s/p CCY)

- Third line
  - Alosetron* (0.5 QD – 1 BID; females)
    - Restricted due to ischemic colitis (1:1000) and severe constipation

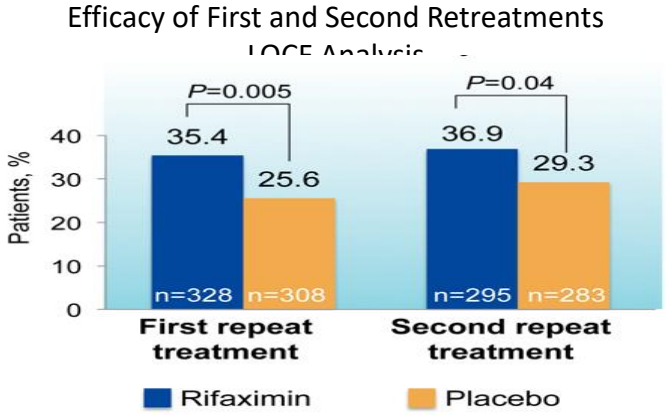
Efficacy of IBS-D Treatment



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

Black CJ et al. Gut 2019 Apr 17.

TARGET 3: Efficacy of Retreatment



LOCF, last observation carried forward.

Urgency and bloating improved significantly with both repeat treatments

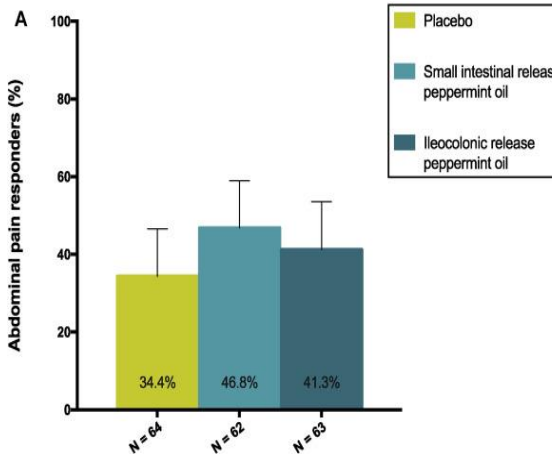
Abdominal pain and stool consistency improved significantly with first retreatment

Responder defined as subjects responding to IBS-related Abdominal Pain and Stool Consistency for ≥ 2 of 4 weeks.
Recurrence defined as a loss of response for ≥3 of 4 weeks.

Lembo A, et al. Gastroenterology

Additional Treatments for Pain Predominant

- Antispasmodics:
  - Hyoscyamine* (0.125 mg - .25 mg 3-4 times a day)
  - Dicyclomine* (10-20 mg QID)
    - » ACG recommends *against* the use of antispasmodics currently available in the United States to treat global IBS symptoms.
      Conditional recommendation; low quality of evidence
    - » Limited data – old studies of poor quality.
    - » Side effects are common, particularly in the elderly
  - Peppermint Oil (180 mg – 200 mg QID; enteric coated)
    - » ACG suggest use of peppermint to provide relief of IBS
      Conditional recommendation; low quality of evidence

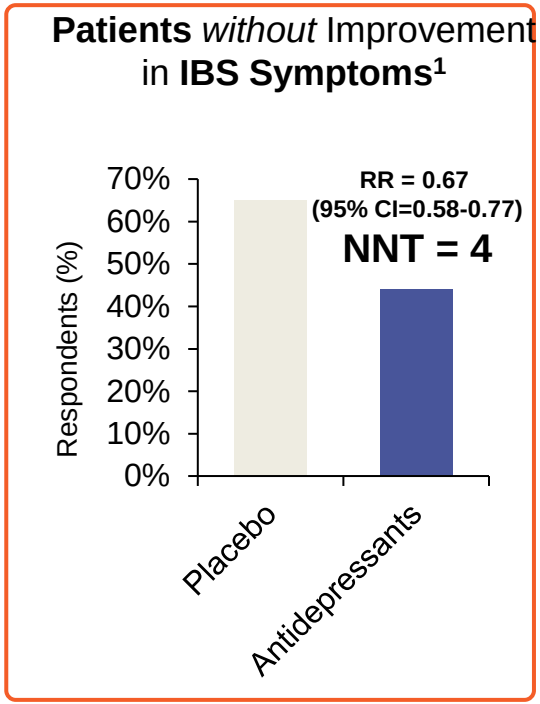


Weerts et al. Gastroenterology 2020; 158:123-126

*FDA approved for IBS

Additional Treatments for Pain Predominant Symptoms

- Antidepressants
- Effective at reducing IBS symptoms and abdominal pain[1]
- Adverse effect profiles may guide use in IBS subtypes[2]



1. Ford AC, et al. *Am J Gastroenterol*. 2014;1350-1365.
2. Chey WD, et al. *JAMA*. 2015;313:949-958.

Additional Treatments for Pain Predominant Symptoms

1st Line

TCAs
(amitriptyline, nortriptyline, imipramine, desipramine)

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

Consider when anxiety, depression, and phobic features are prominent with FGIDs

Tetracyclic antidepressant
(mirtazapine, mianserin, trazodone)

Treatment of early satiety, N/V, weight loss and disturbed sleep

SNRIs
(duloxetine,venlafaxine, desvenlafaxin, milnacipran)

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

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

Antidepressants – Tips for improving Effectiveness

- Inform patients of expected AE (e.g. sedation, agitation, anticholinergic)
- Start low (10-25 mg/d) and advance slowly, especially in the elderly and those with somatization disorder
- Try to reach a daily dose of 50 mg
- Switch to an alternative TCA or SSRI if intolerance or SE occur
- Use adverse-effect profiles to help select

Psychological Therapy for IBS

Therapy	Trials	N	RR (95% CI)	NNT (95% CI)
Cognitive behavioral therapy (CBT)	**9**	**610**	**0.60 (0.44-0.83)**	**3 (2-6)**
Relaxation training or therapy	6	255	0.77 (0.57-1.04)	–
Hypnotherapy	**5**	**278**	**0.74 (0.63-0.87)**	**4 (3-8)**
Multi-component psychological therapy	**5**	**335**	**0.72 (0.62-0.83)**	**4 (3-7)**
Self-administered, minimal-contact CBT	3	144	0.53 (0.17-1.66)	–
CBT via Internet	2	140	0.75 (0.48-1.17)	–
Dynamic psychotherapy	2	273	0.60 (0.39-0.93)	3.5 (2-25)
Stress management	2	98	0.63 (0.19-2.08)	–
Multi-component therapy via telephone	1	126	0.78 (0.64-0.93)	–
Mindfulness meditation training	1	75	0.57 (0.32-1.01)	–
Total	**36**	**2334**	**0.68 (0.61-0.76)**	

Ford AC, et al. *Am J Gastroenterol.* 2014 Sep;109:1350-1365.

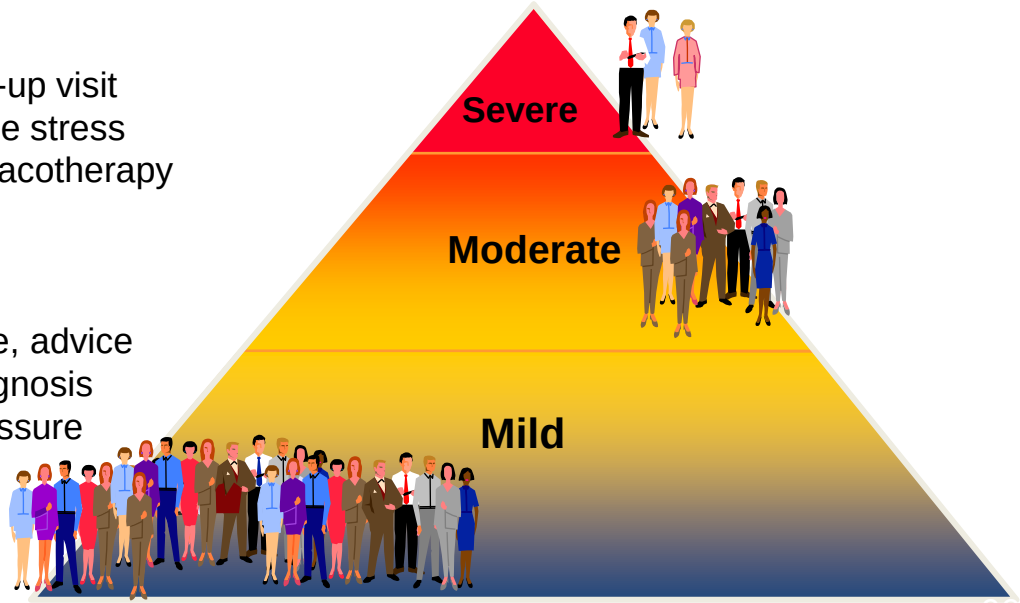
CI=confidence interval; NNT=number needed to treat; RR=risk ratio; – = not provided.

Modern Strategy to Treating IBS

- Psychological treatments
- Continuing care
- Improve functioning

- Follow-up visit
- Manage stress
- Pharmacotherapy

- Diet, lifestyle, advice
- Positive diagnosis
- Explain, reassure



Cognitive Behavioral Therapy for IBS

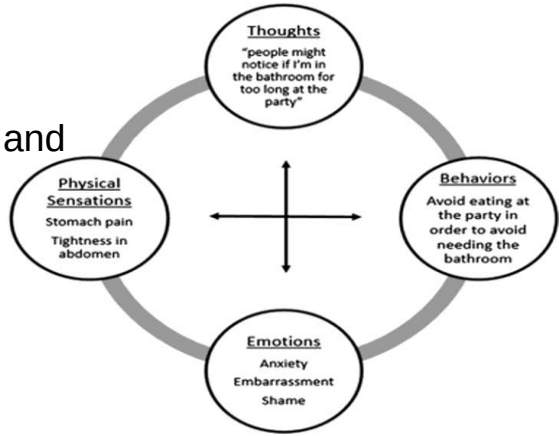
- Focuses primarily on:
  - psychoeducation about the stress response and its relationship to GI symptoms;
  - Building insight into cognitive/behavioral responses to IBS symptoms or fear of symptoms;
  - Modifying those responses to decrease distress related to IBS

- No standardized protocol (e.g. 4 sessions over 10 wks as effective as 10 sessions over 10 wks).

- Can be delivered in groups or internet-based protocols

- Meta-analyses: CBT is highly effective in improving bowel symptoms, QOL, and psychological distress independent on its effects on psychological distress.

- Improvements persist long-term



Ballou and Keefer Clin Transl Gastroenterol. 2017 Jan; 8(1): e214

Lackner et al. *Clin Gastroenterol Hepatol. 2010 May; 8(5):426-32*.

Hypnotherapy

- “Clinical hypnosis is an altered state of awareness, perception or consciousness that is used, by licensed and trained doctors, for treating a psychological or physical problem.” *American Society of Clinical Hypnosis*

- It is a highly relaxed state (not sleep) in which a patient is open and receptive to suggestions about changes in symptoms and illness experience

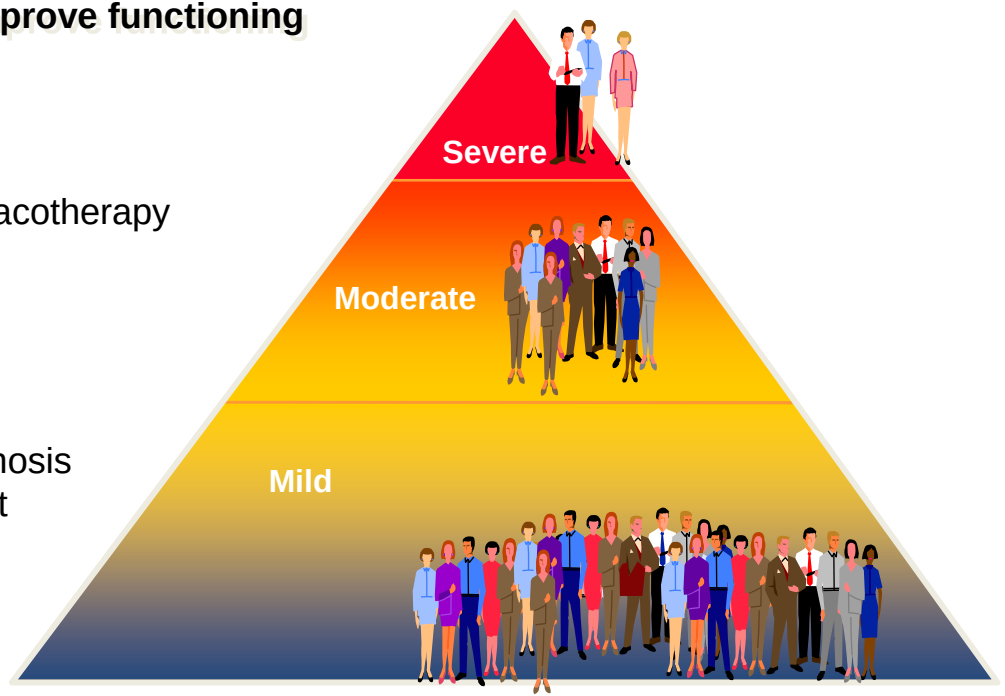
- The practice of medical hypnosis has been used for thousands of years, in many different cultures. Not the same as “stage hypnosis”

Probiotics in IBS

- Probiotics appear to improve global symptoms, bloating, and flatulence though the level of evidence is low
- Recommendations regarding individual species, preparations, or strains cannot be made

Summary: Graded Treatment Response for IBS

- **Multidisciplinary approach**
- **Psychological treatments**
- **Improve functioning**

Pharmacotherapy

Diet, lifestyle
Positive Diagnosis
Doctor-Patient
Reassurance