Modern Strategies to Treat IBS

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DDC 2/2024

No Disclosures

Objectives

- IBS definition- ROME IV
- Update on **treatments** available for IBS
  - IBS-C
  - IBS-D
  - Personalize treatment for IBS

IBS Definition

IBS 4.1% (3.9-4.2)

BS-C 1.3%
IBS-D 1.2%
IBS-M 1.3%
IBS-U 0.3%

FD 4.1%
FC 11.7%

Rome IV Criteria for IBS

Recurrent Abdominal PAIN
at least 1 day/ week in the last 3 months
associated with 2 or more of the following:

- **Related to defecation**
- **Associated with a change in frequency of stool**
- **Associated with a change in form (appearance) of stool**

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

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Lacy B et al. Gastroenterology. 2016;150:1393-1407
Sperber AD, et al. Gastroenterology 2021. 2021 Jan;160(1):99-114
. Sperber AD, et al. Gastroenterology 2021. 2021 Jan;160(1):99-114

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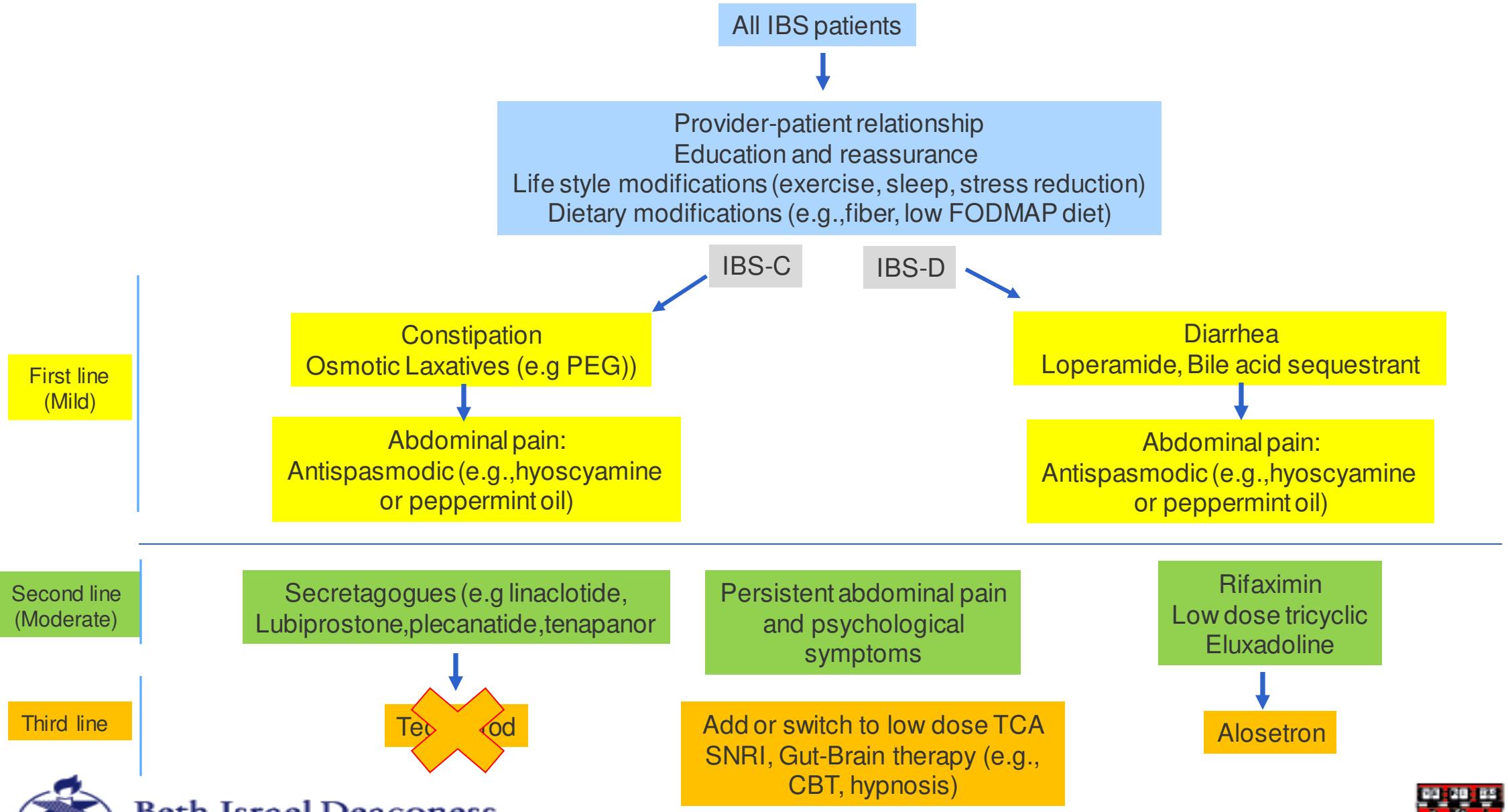
AGA Guidelines Target Approach to IBS



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Lembo, A et al. Gastroenterology 2022;163:137–151

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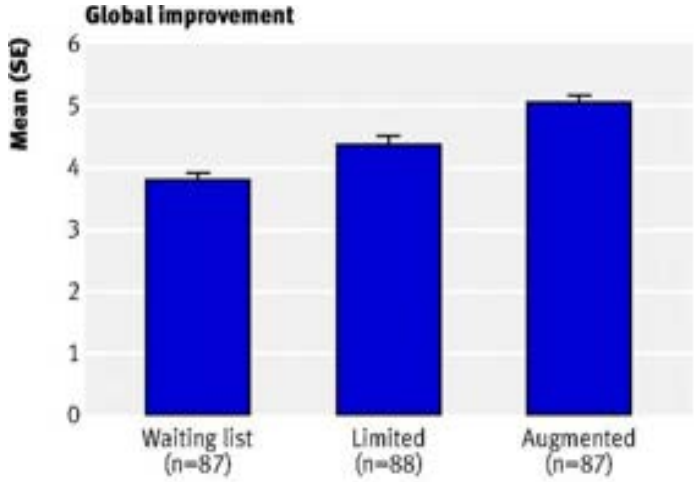
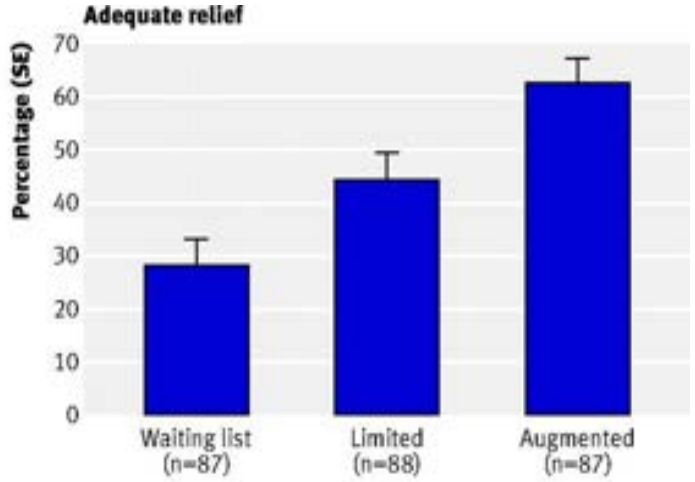
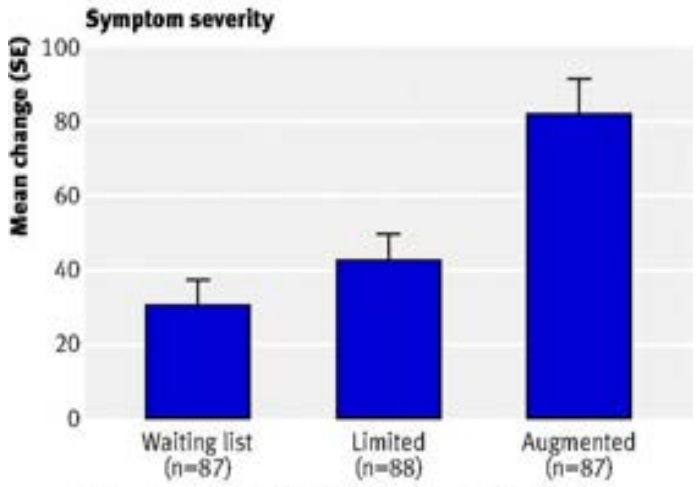
Augmented Practitioner Physician Relationship Can Improve Outcomes in IBS

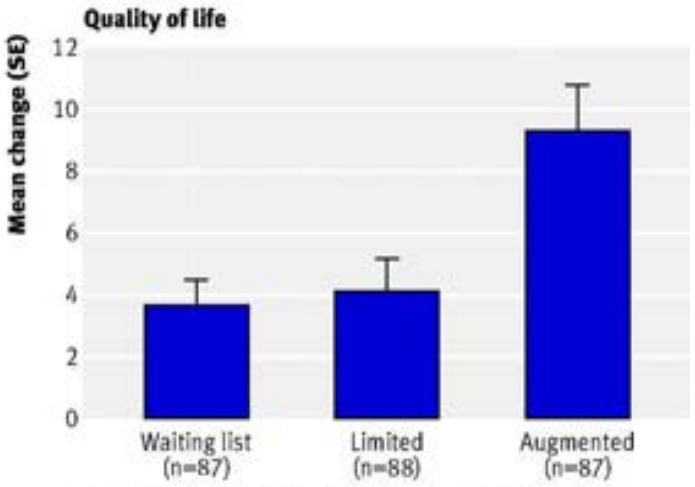
- Augmented (enhanced) Practitioner-Patient Relationship received:

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









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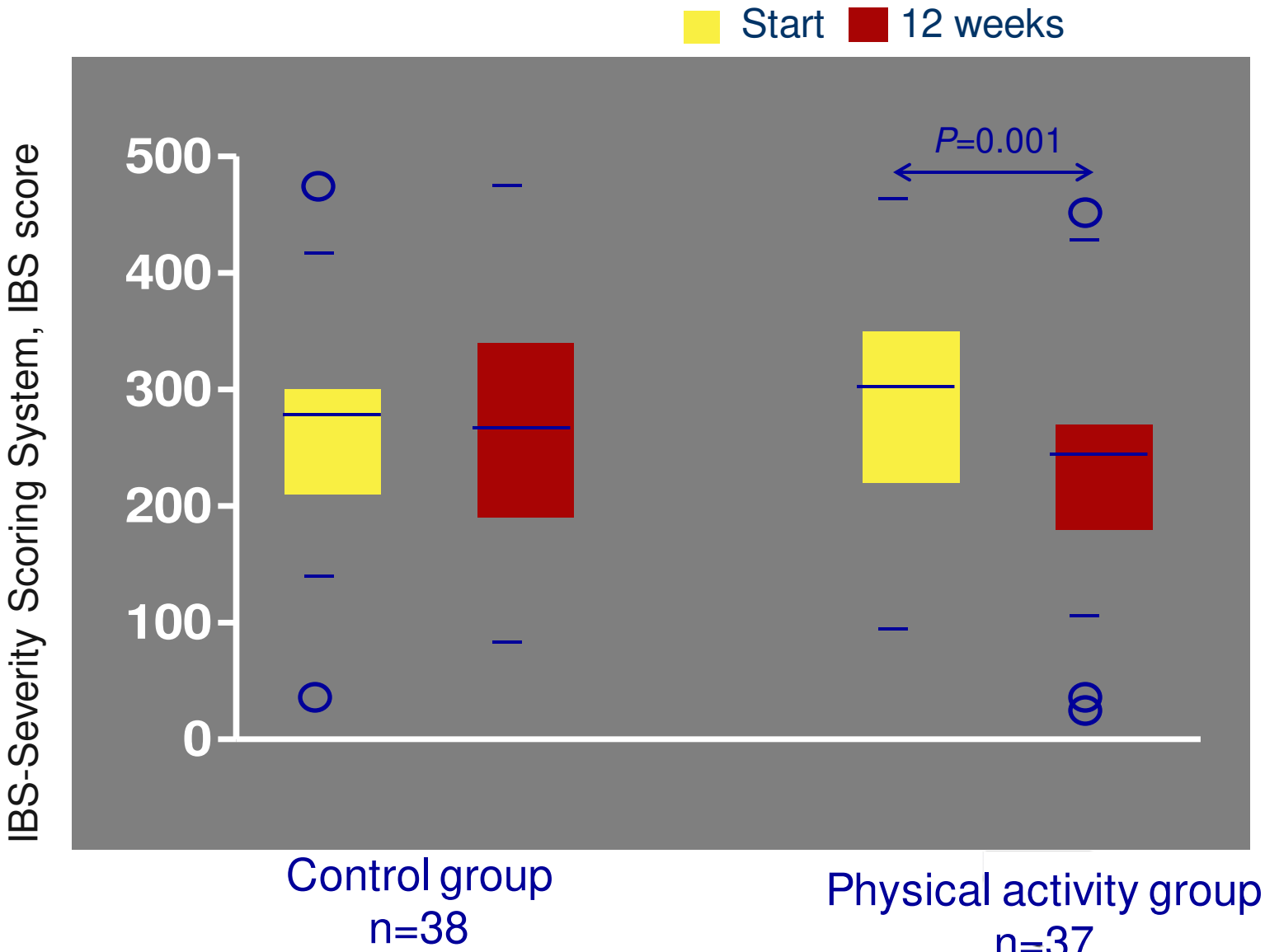
Kaptchuk et al., BMJ 2008

Increase Physical Activity Improves GI Symptoms in IBS

- 12 weeks of moderate-vigorous activity
- 3-5 times/week vs. usual care



Johannesson E, et al. Am J Gastroenterol, 2011;106(5):915-22

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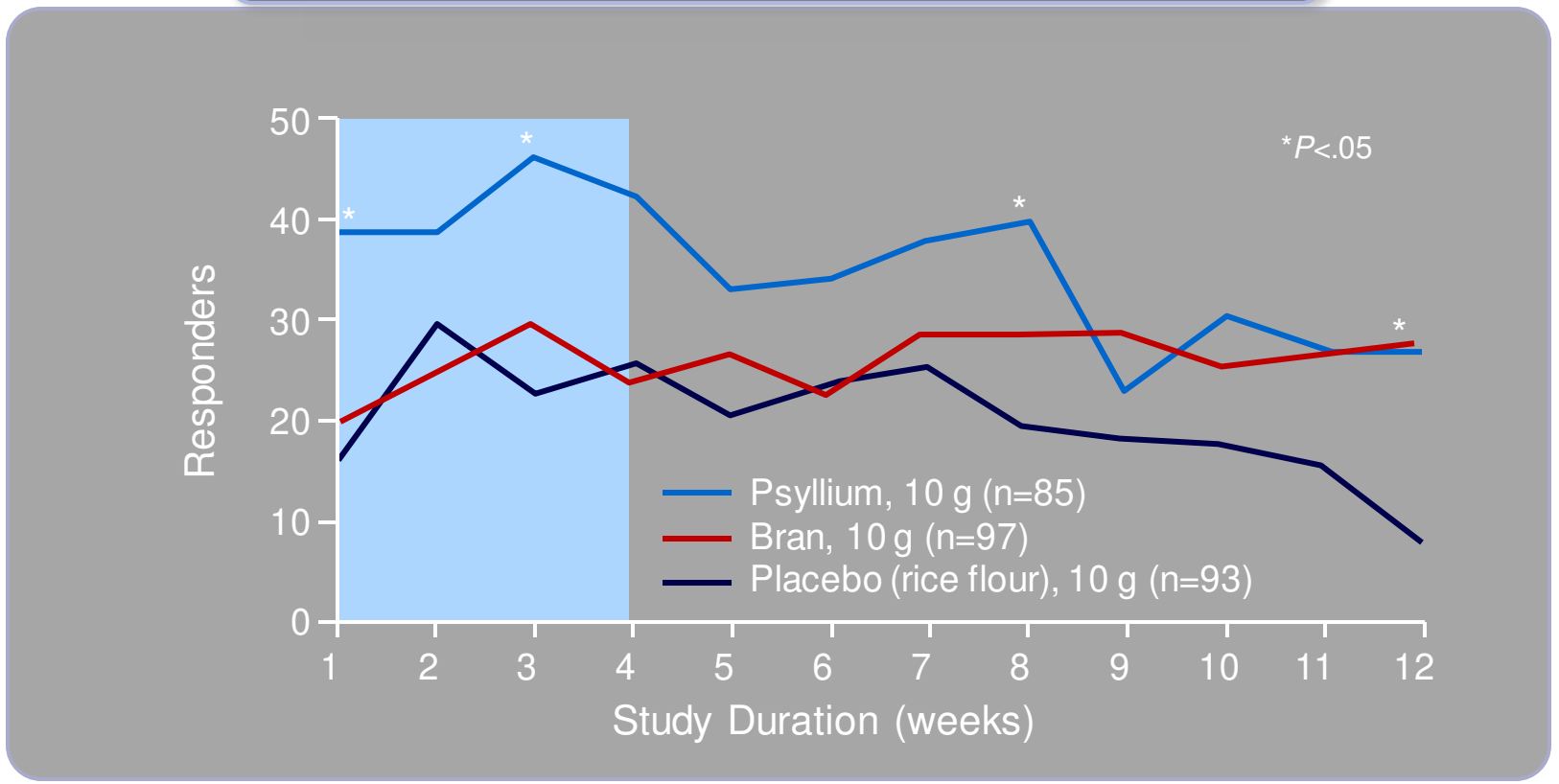
Soluble Fiber (Psyllium) May be Effective in Some IBS Patients

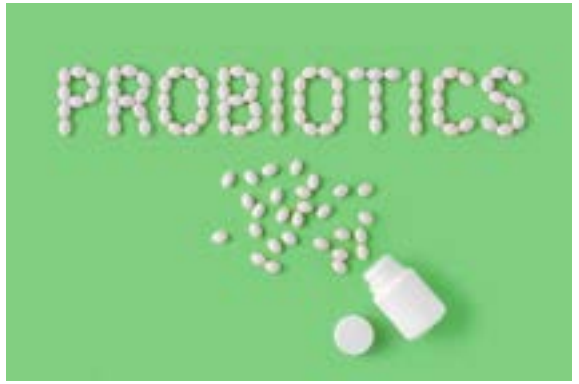
Proportion of patients with adequate relief of symptoms each week[1]



- Fiber can exacerbate bloating, flatulence, distention, and discomfort.
- Dose should be titrated gradually

Bijkerk CJ, et al. BMJ. 2009:339:B3154-B3160.
ACG Task Force on IBS. Am J Gastroenterol. 2009;104(suppl 1):S1-S35.
Eswaran S, et al. Am J Gastroenterol. 2013;108:718-727.

Probiotics: Recommendations Regarding Individual Combination, Species, or Strains cannot be made



- Meta-analysis NNT of 7 (95 % CI 4 – 12.5)
  - Might improve, abdominal pain, bloating, and flatulence scores
  - **Bifidobacteria** are more likely to improve gastrointestinal symptoms than lactobacilli.
  - Sub-analysis showed only combination probiotics, ***Lactobacillus plantarum DSM 9843*** and ***E. coli DSM17252***, to be effective

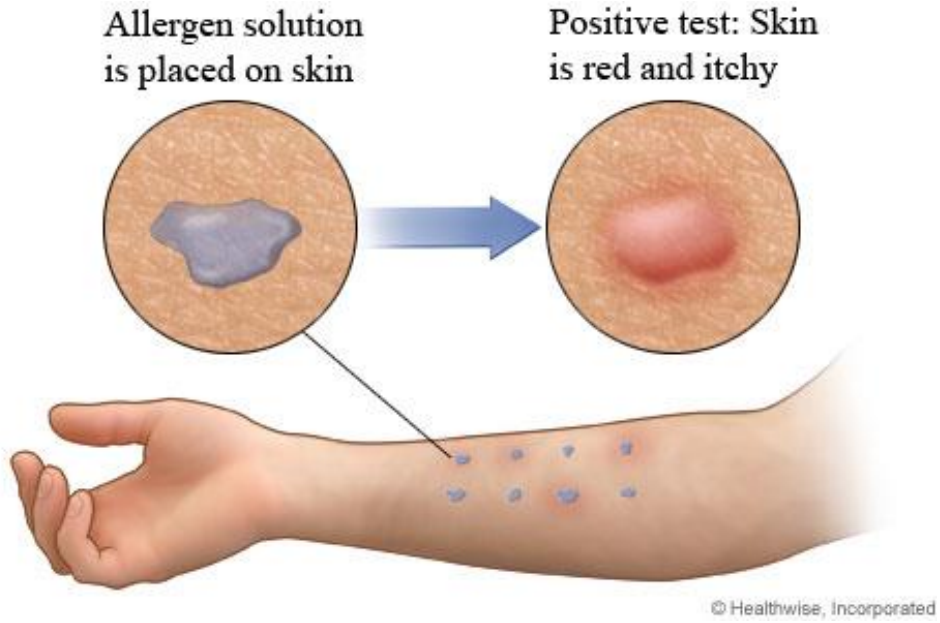
- RCT : Probiotic **Bifidobacterium longum NCC3001** reduced depression but not anxiety scores

- Lab4 probiotic (**Lactobacillus** and **Bifidobacterium**)
  - IBSS score, anxiety and depression, “normalize stools”

Ford AC, et al. Am J Gastroenterol. 2014;109:1547-1561.
Pinto-Sanchez MI et al. Gastroenterology.2017; 2017 Aug;153(2):448-459.
BH Mullish, et al. Neurogastroenterolo Motili.2024.Jan 29:e14751.Online ahead of print .

Food as a Trigger GI Symptoms

- Perceptions of food intolerance in IBS
  - 2X vs. general population
  - Symptoms with eating a meal
  - 28% within 15 min
  - 93% within 3 hrs



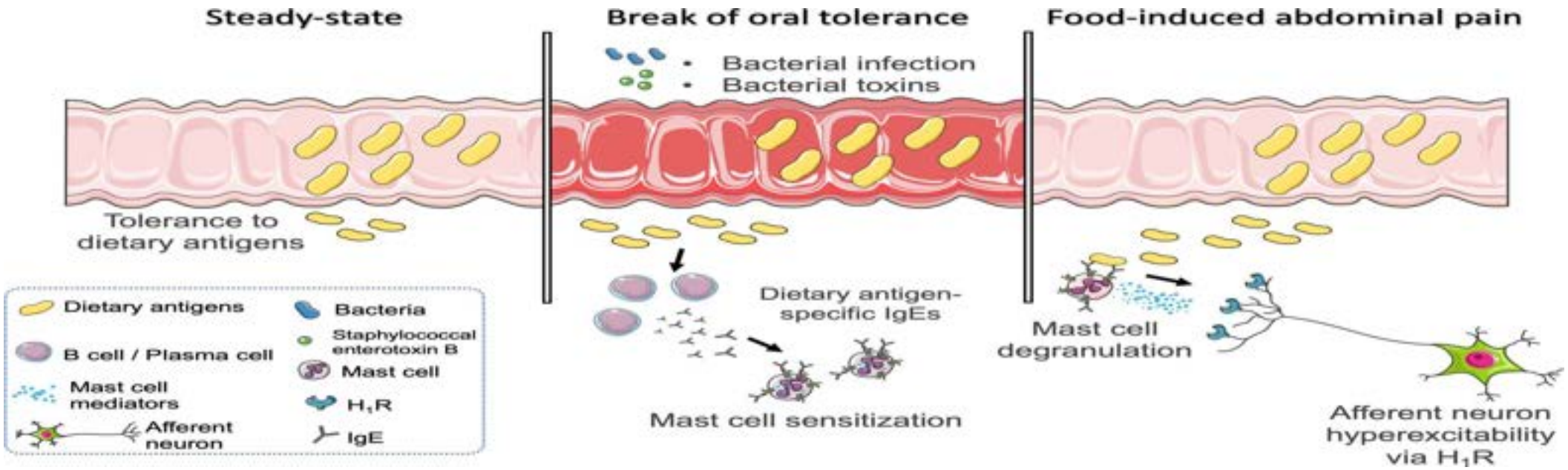
- Multiple testing for dietary allergies
  - Skin prick tests: No correlation results and symptoms
  - Food-specific immunoglobulins: IgE
  - Non-validated tests: delay hypersensitivity IgG

- Dietary therapies
  - Gluten-free diet found to be beneficial in some patients with IBS-D particularly those who are HLA DQ2/8 +
  - Lactose intolerance, Fat/Bile malabsorption, other breath tests

Mullin GE *et al.* Nutr Clin Pract 2010 ; 25 : 192 – 8 .
Gibson PR, Shepherd SJ. Am J Gastoenterol. 2012 ay;107(5):657-66.
Vazquez-Roque MI et al. Gastroenterology. 2013;144:903-911.

Hypothesis

- A breakdown of oral tolerance to food antigens caused by a bacterial infection underlies food-induced visceral hypersensitivity

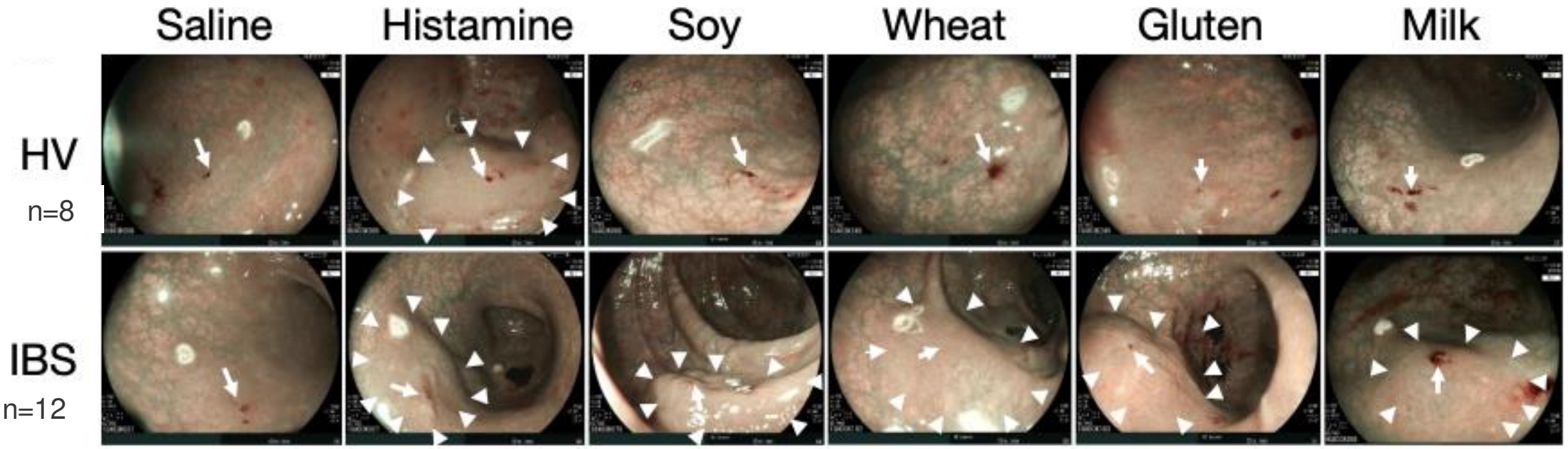


Aguilera-Lizarraga J et al; Nature | Vol 590 | 4 February 2021

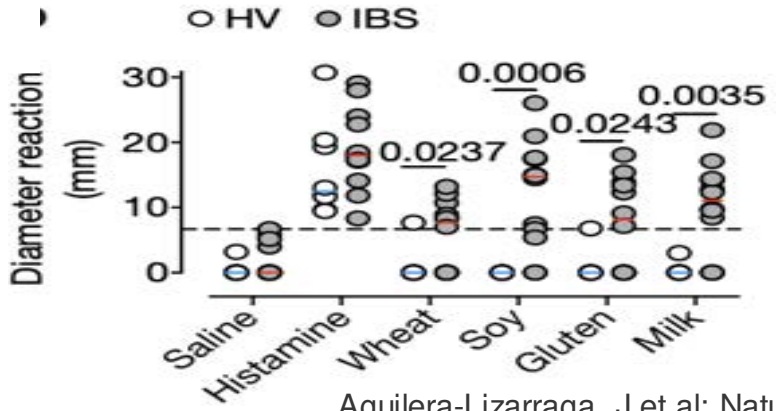
Role of Local Reactions to Foods

Rectal Submucosal Injections

Only 2 reactions in the control group (gluten and soy)



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



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Aguilera-Lizarraga J et al; Nature | Vol 590 | 4 February 2021

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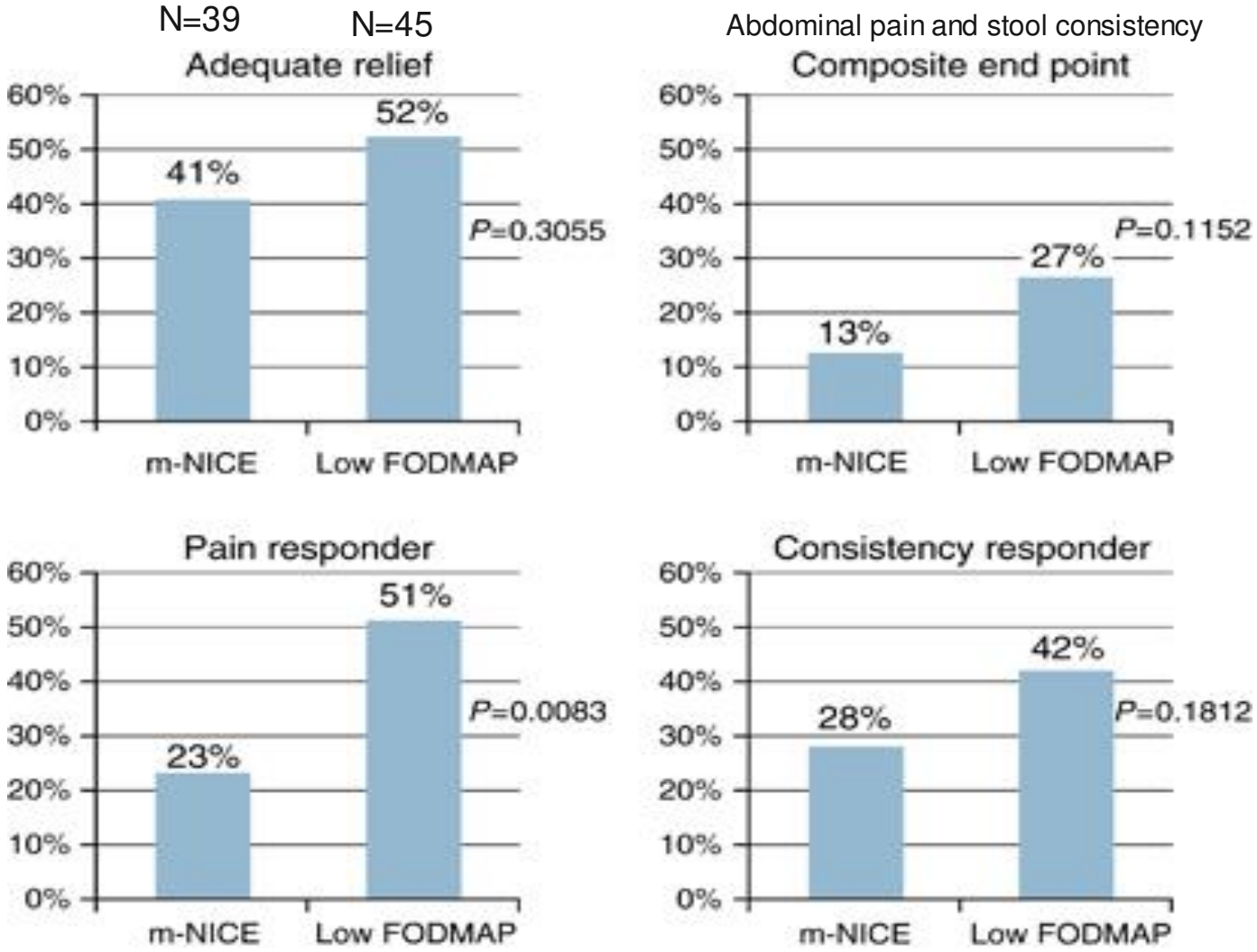
A 4 Wks RCT Comparing the Low FODMAP Diet vs. Modified NICE* Guidelines in US Adults with IBS-D

Example from the NICE guideline for IBS:

Reduce resistant starches
- whole grains, sweetcorn, and muesli that contains bran
- undercooked or reheated potato or maize/corn
- oven chips, crisps, potato waffles, fried rice
- part-baked and reheated breads, such as garlic bread, pizza base
- processed food such as potato or pasta salad, or manufactured biscuits and cakes
- ready meals containing pasta or potato, such as lasagne, shepherd's pie, macaroni cheese
- dried pasta



Eswaran et al. Am J Gastroenterol 2016; 111:1824–1832

*Diet based on National Institute for Health and Care Excellence (NICE)

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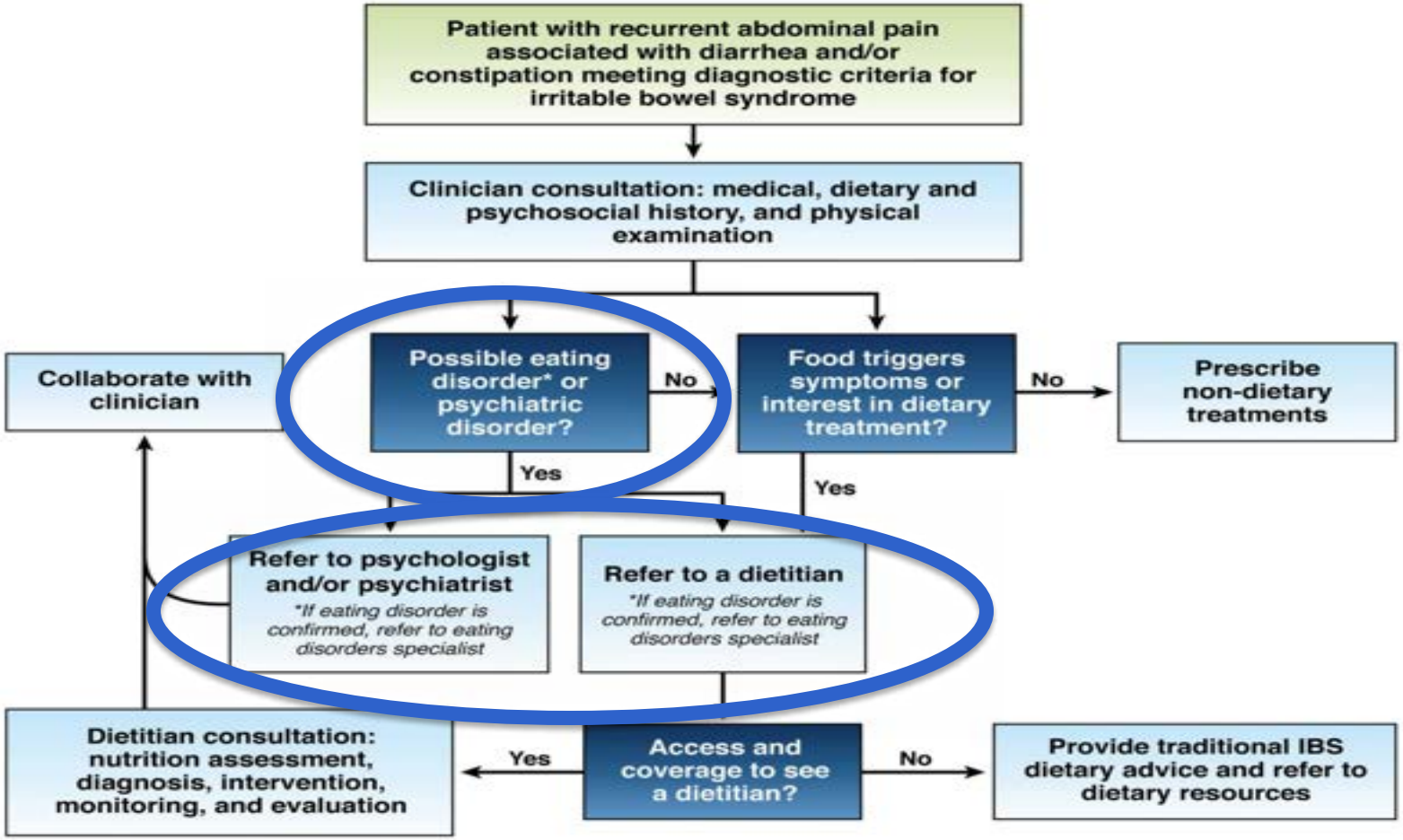
Current Diets Have Shown Modest Effects in IBS

Low-FODMAP

- ACG and AGA recommends: limited trial of a low FODMAP diet to improve global symptoms
  - Conditional recommendation; very low quality of evidence
- Only the initial diet phase evaluated other phases
  - gradual reintroduction and personalization of the diet have not been adequately studied
- Pitfalls
  - Complex, Costly, Most effective GI dietician, possible negative impact on QOL
- Unanswered questions
  - Effects on the gut microbiota, development of ARFID, cibophobia, nutritional deficiencies

Investigate Eating Disorders before Recommending Dietary Interventions



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Chey W.D. et al. Gastroenterology 2022;162:1737–1745

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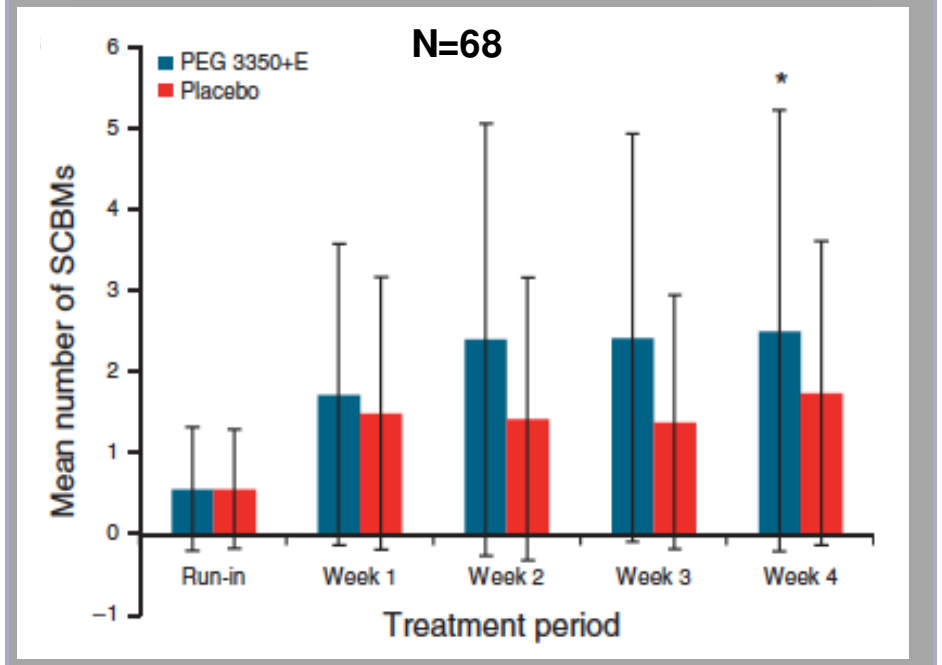
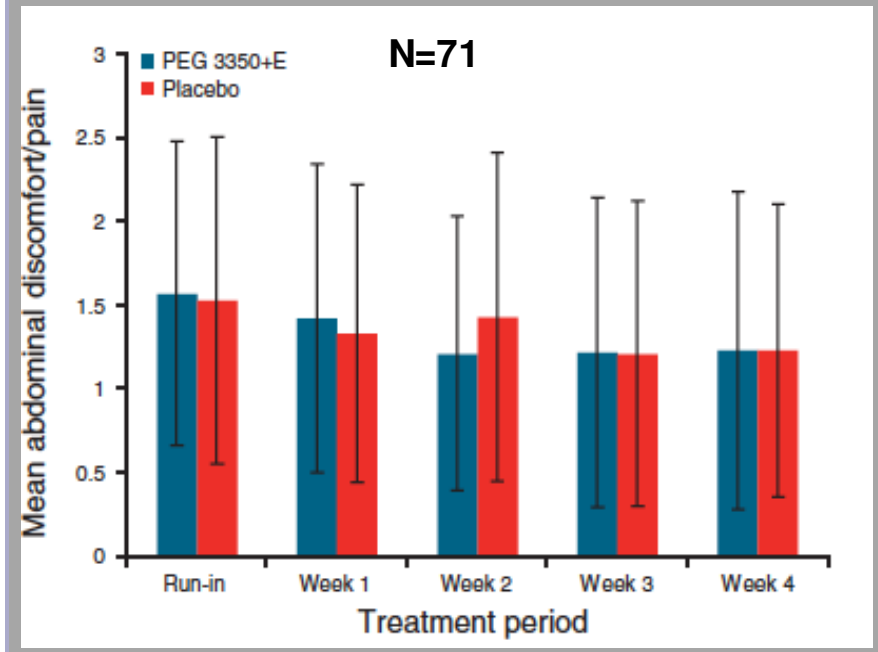
First Line IBS-C :Polyethylene Glycol (PEG) Improves Bowel Movements but Does not Improve Abdominal Discomfort/Pain in IBS-C

Spontaneous Complete Bowel Movements (SCBMs)



*P<.0001.

Abdominal Discomfort/Pain



- Between 1 - 3 sachets of PEG 3350 + E (13.8 g per day) or matching placebo were administered
- Patients adjusted the dose based on stool consistency

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

E=electrolytes.

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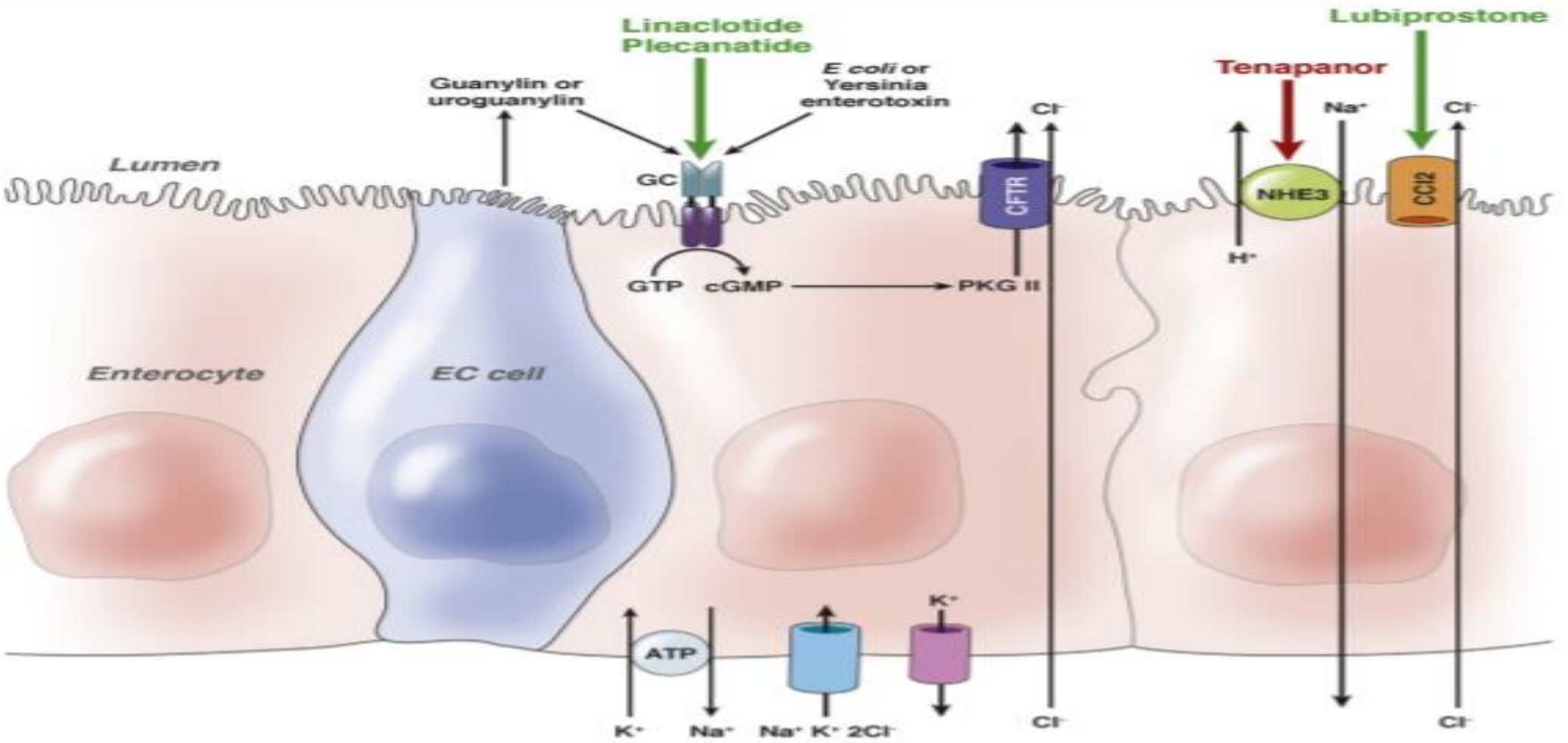
Second line Secretagogues
FDA approved for IBS-C



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Tack J, Gastroenterology 2018;155:1677–1691

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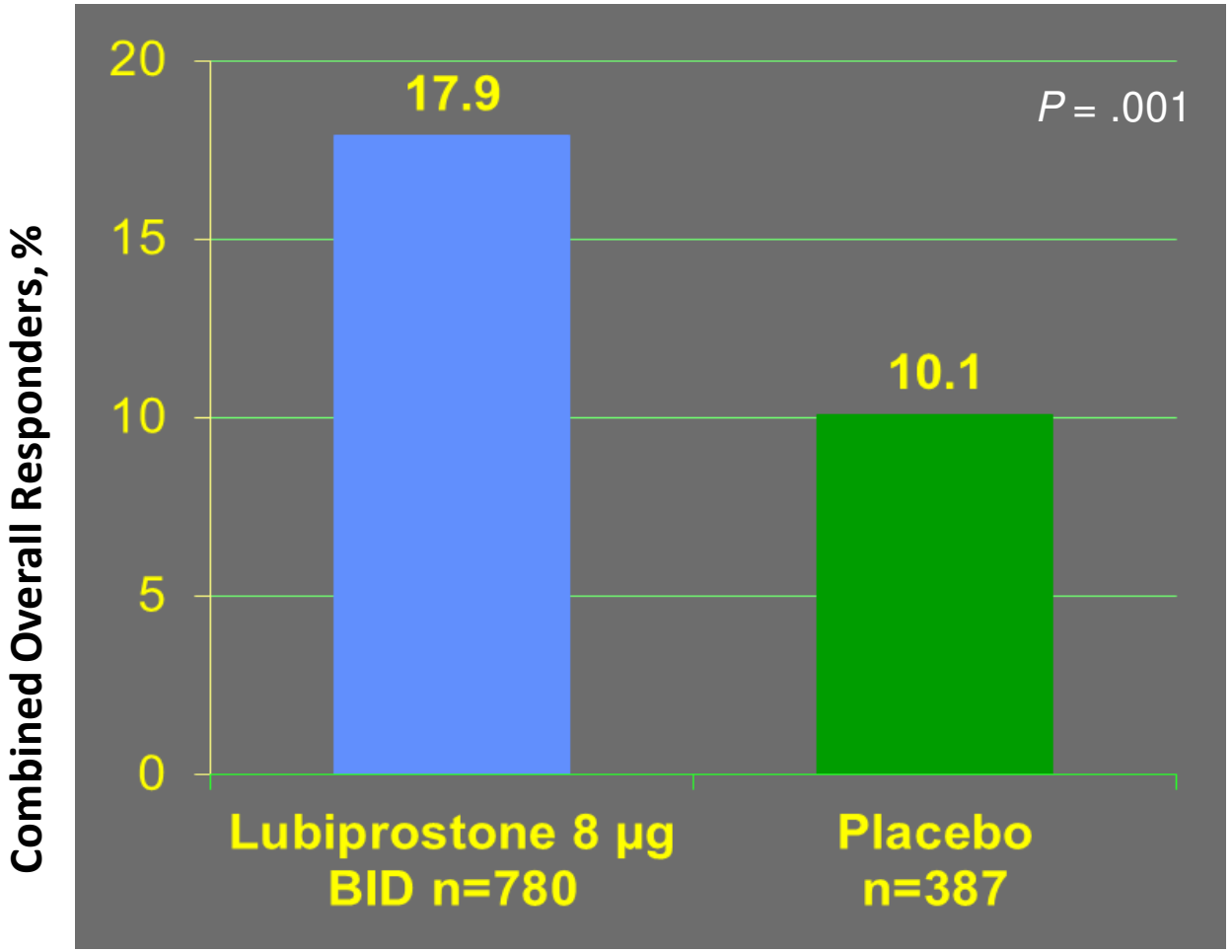
Lubiprostone (Cl Channel Activator/Amitiza) 8ug BID improves Symptoms of IBS-C



- Two 12-wk Phase III Trials
- Overall responder
  - monthly responder ≥ 2 out of the 3 months
- Monthly responder
  - At least moderate relief 2/4 wk *or* significant relief >2/4 wk
- Abdominal discomfort / pain, bloating, straining and severity of constipation, increased BM frequency and stool consistency.
- Most common AEs: Nausea (4% vs 8%)
  Diarrhea (4% vs 7%)

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

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Linaclotide (Guanylate Cyclase C Agonist/Linzess)

290 µg QD Improved Abdominal and Bowel Symptoms

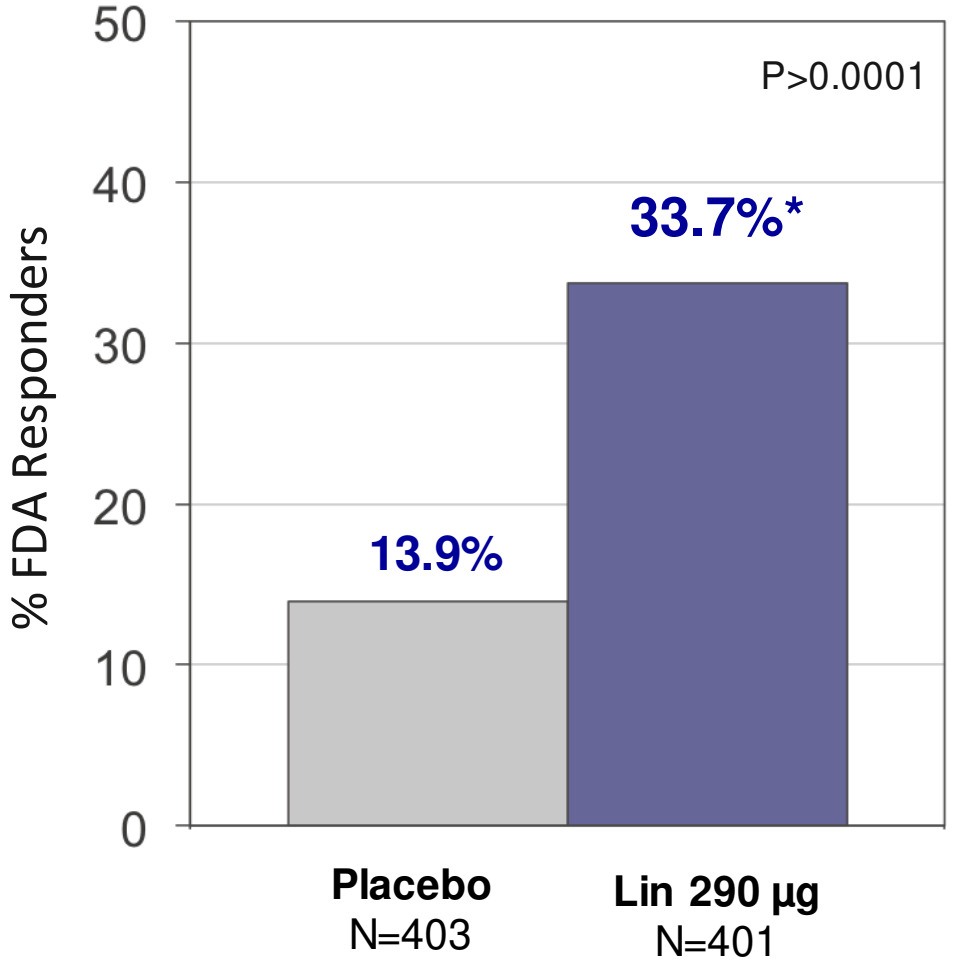
Associated with IBS-C over 26 weeks of Treatment

FDA Responder

Abdominal Pain Responder

CSBM +1 Responder

≥30% abdominal pain reduction + increase ≥1 CSBM from baseline; **in the same week for 50% of weeks (i.e, 6 out of 12 weeks)**



RTC 290 ug QD
26 weeks
IBS-C

Abdominal pain, bloating ,SBM & CSBM

Most common AEs:
- Diarrhea: 3% vs 20%
- Abdominal pain: 5% vs. 7%

Linaclotide 290 ug FDA approved for IBS-C woman & men

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Chey WD, Lembo AJ et al. AM J Gastroenterol 2012 Nov;107(11):1702-12

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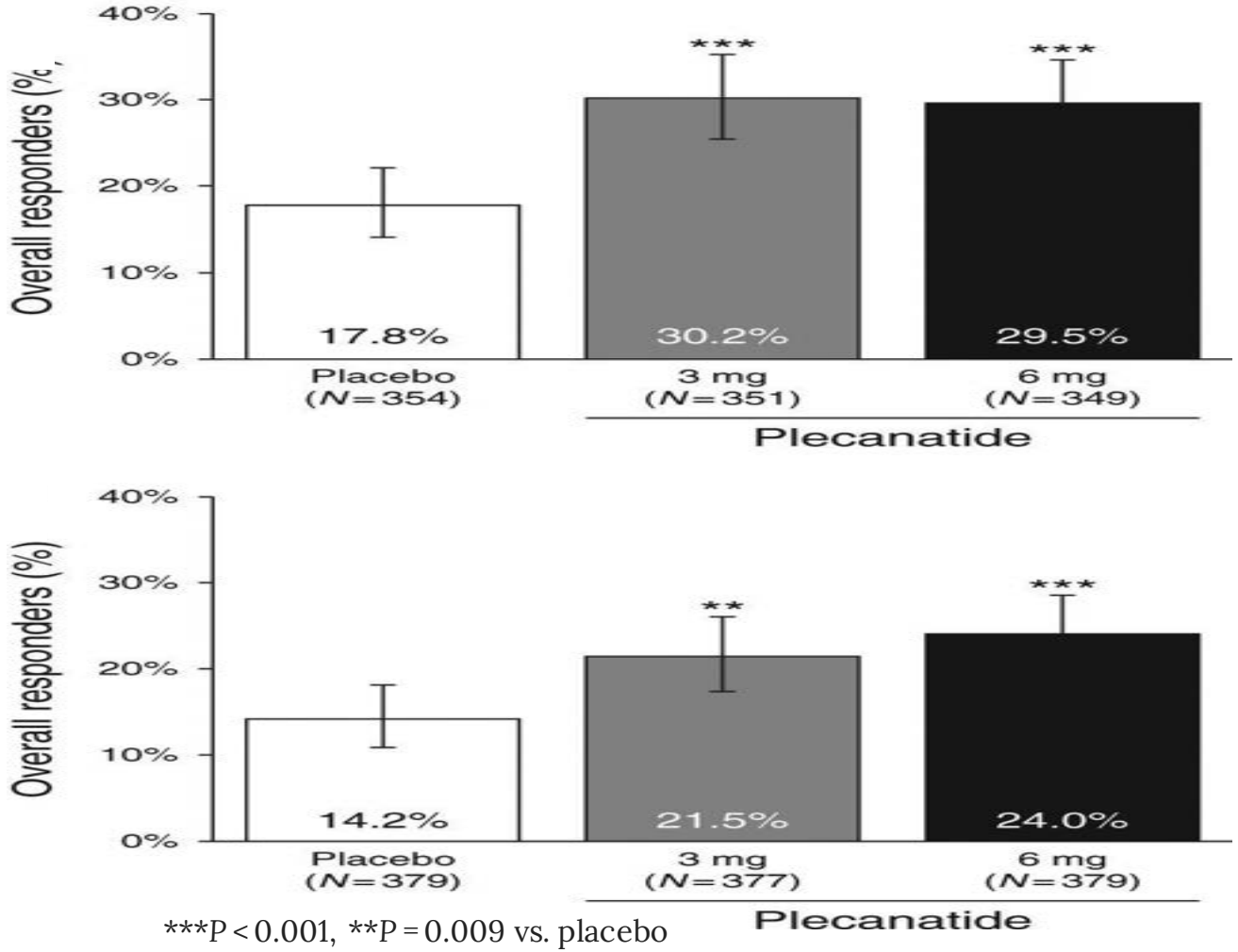
Plecanatide (Guanylate Cyclase C Agonist/Trulance) 3mg QD Improved Symptoms of IBS –C for 12 wks

- 2 RTC's
- Primary end point:
  - Overall responders (≥30% reduction from baseline in worst abdominal pain plus an increase of ≥1 CSBM from baseline the same week for ≥6 of 12 treatment weeks)
- Secondary end points:
  - stool frequency/consistency, straining, abdominal symptoms
- Side effects: Diarrhea
  - 3.2% of the 3-mg group
  - 3.7% of the 6-mg group



***P < 0.001, **P = 0.009 vs. placebo

Brenner et al. AM J Gastroenterol 2018;113:735-745

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Efficacy of Tenapanor in IBS-C in Two Phase III RTC's

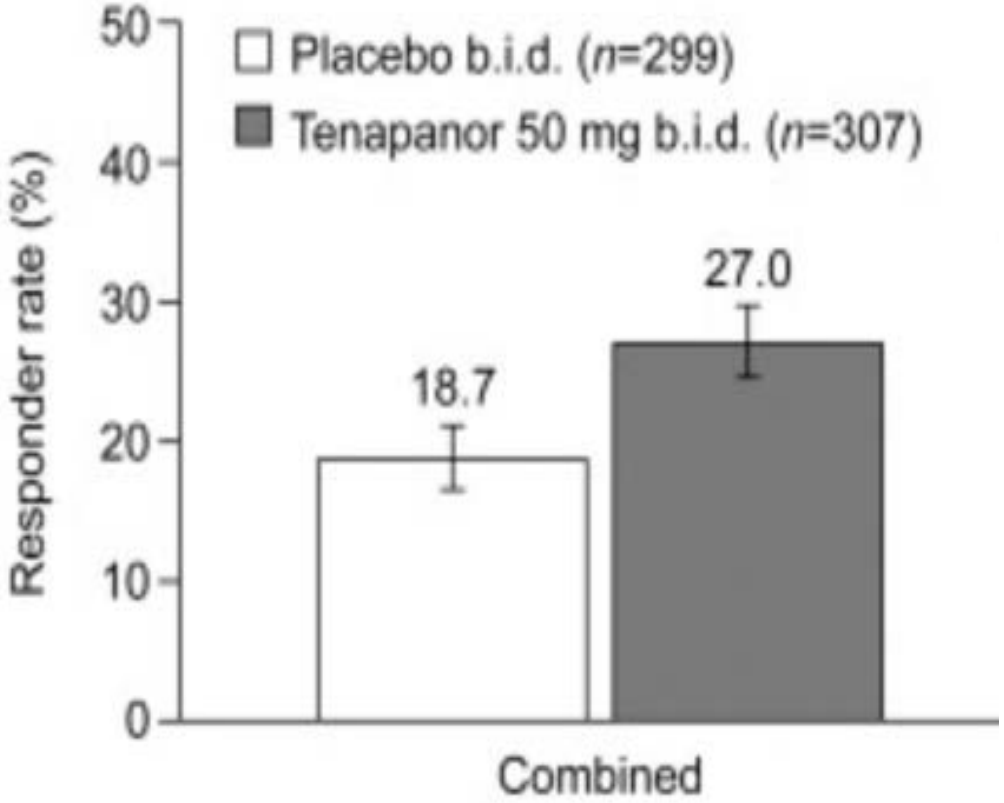
Na/H exchange inhibitor

*≥30% abdominal pain reduction + increase ≥1 CSBM from baseline

AE diarrhea in 14-16%

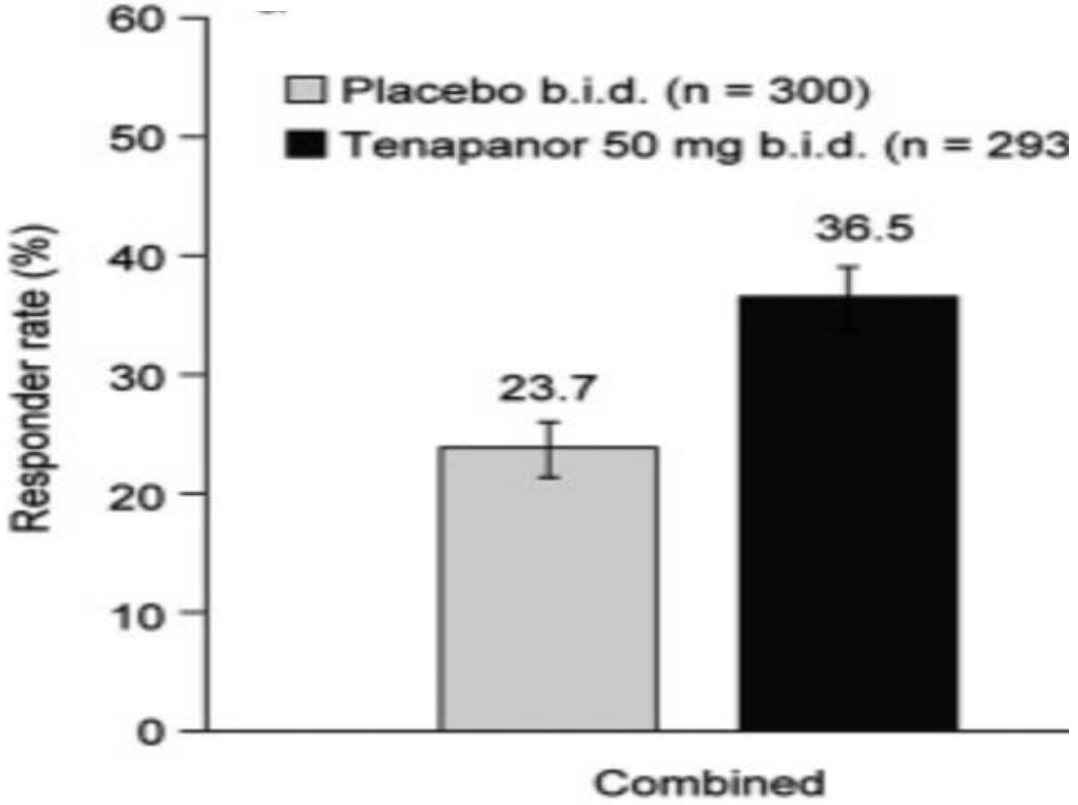
T3MPO-1

629 patients, 12 weeks f/u



T3MPO-2

620 patients, 26 weeks f/u



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Chey WD, Lembo A et al.Am J Gastroenterol. 2020Feb;115(2):281-293.
Chey WD, Lembo Aet al. Am J Gastroenterol 2021 Jun 1;116(6):1294-1303.

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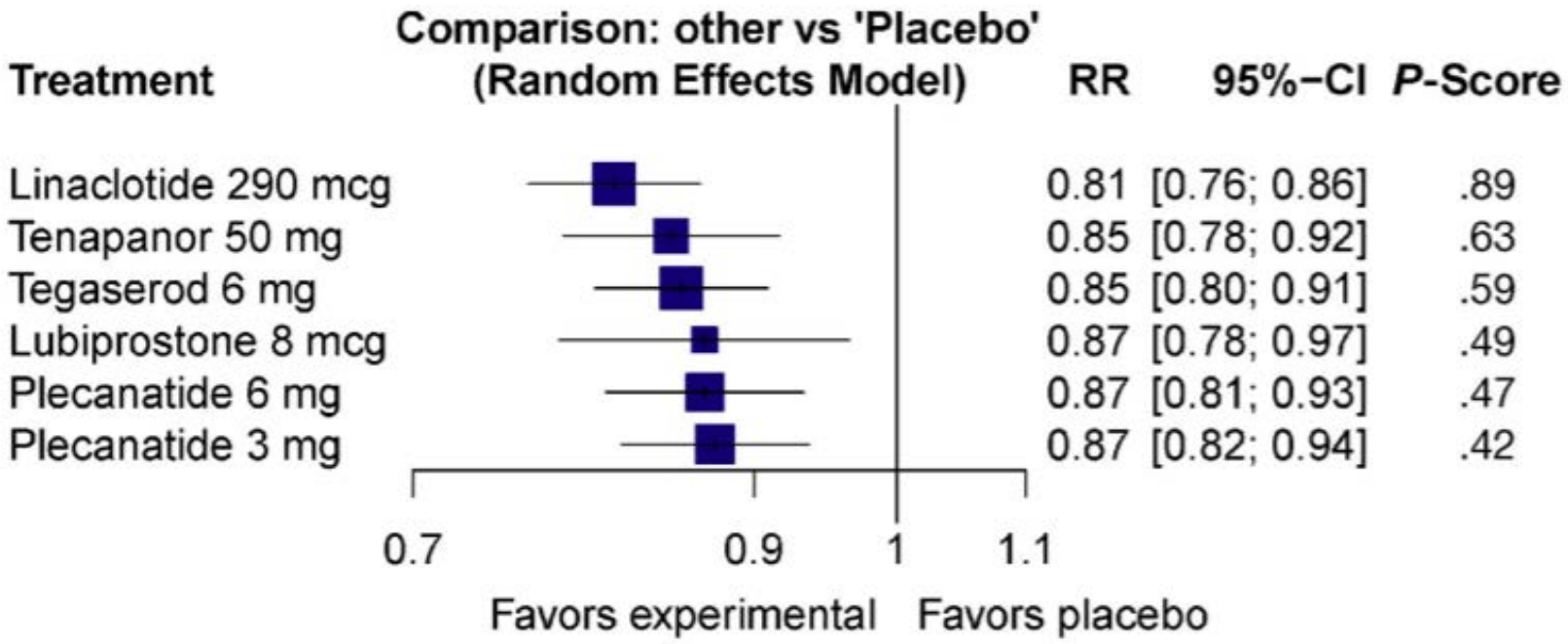
Efficacy of FDA Approved IBS-C treatments
Systematic Review and Network Meta-analysis

FDA Endpoint Responder rates
≥30% improvement in abdominal pain + ≥1CSBM /wk

Prucalopride?



"Efficacy was similar among individual drugs and dosages for most end points."

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Black CJ et al. CGH 2020 May ;18:1238–1239.

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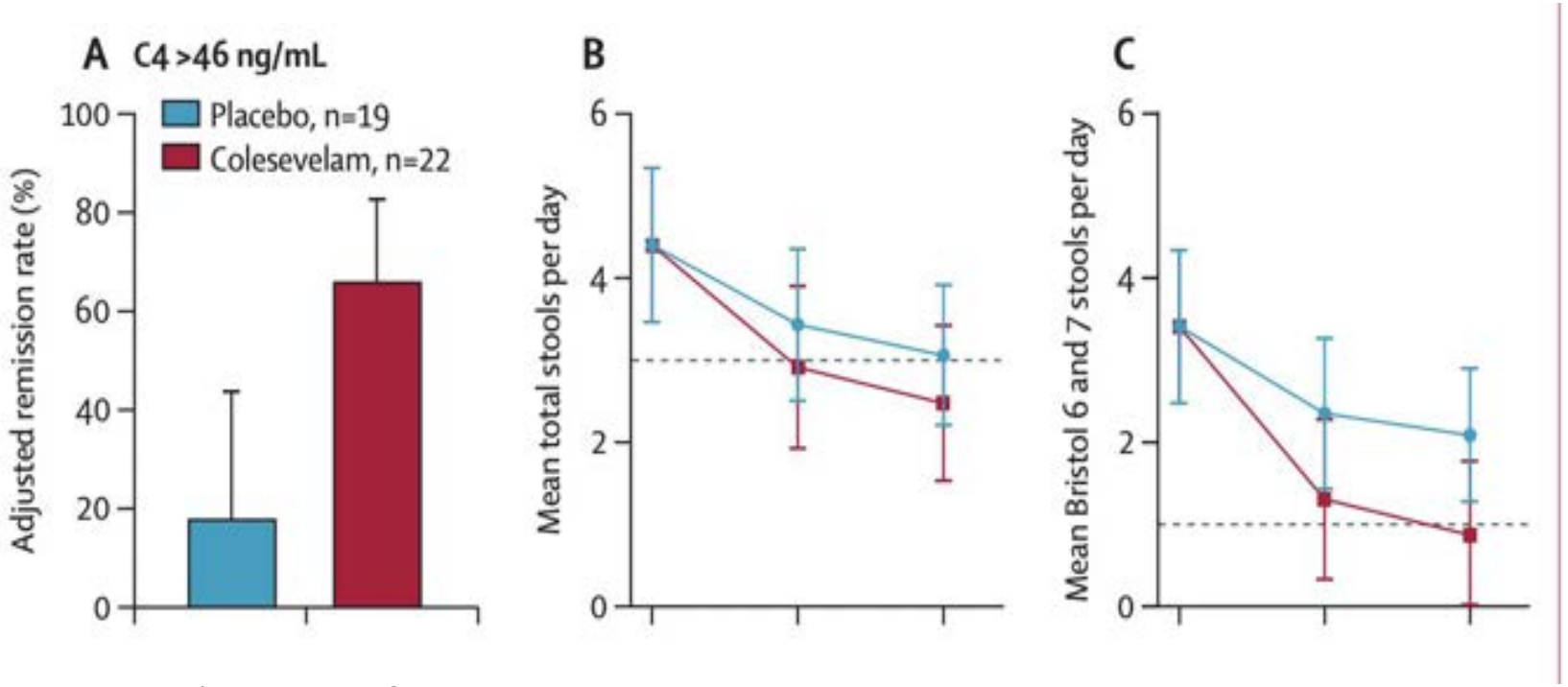
First Line IBS-D :Loperamide for IBS-Diarrhea

- Only antidiarrheal studied in IBS
- Three RCTs of low-intermediate quality
- ↓ Stool frequency and improved stool consistency but not abdominal pain or global IBS symptoms

Brandt LJ et al. Am J Gastroenterol 2002; 97 suppl:S7

Second Line IBS-D Role of Colesevelam in Bile Acid Diarrhea

- RCT phase 4
- IBS M, D and FD
- 7AC4>46
- N=22
- N=19 placebo
- 625mg 2 pills BID
- AE nausea, bloating and abdominal pain



Borup C et.al;Lancet Gastroenterol Hepatol. 2023 Apr;8(4):321-331

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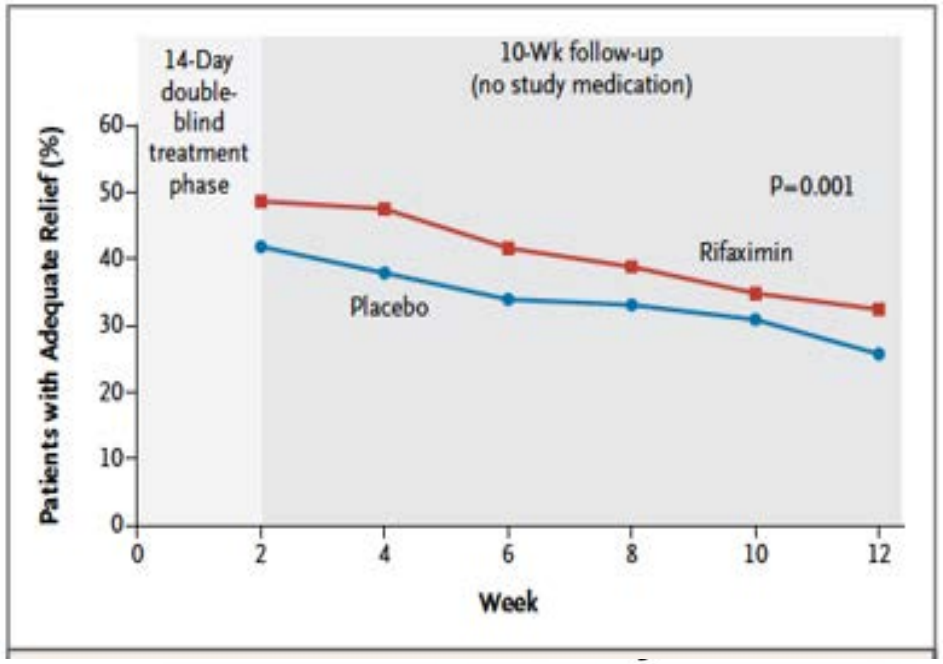
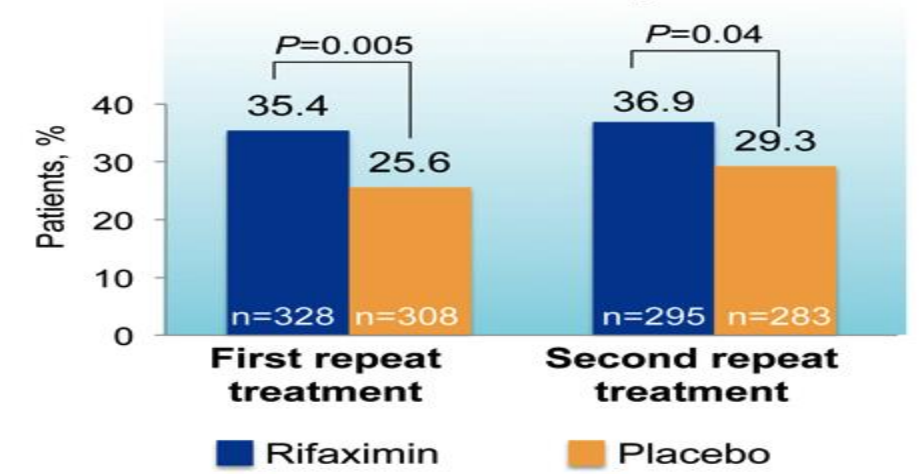
RTC Phase III Trials (Target 1, 2 and 3) Rifaximin for IBS-D

- Limited systemic absorption (<0.4%)
- *In vitro* activity against G+ and G- aerobic and anaerobic bacteria
  - Though intestinal flora not significantly altered; MOA not clear
- 2 Phase III trials showed efficacy (i.e., adequate relief) in global IBS-D sx and IBS-bloating
  - ~10% Δ over placebo
- Rifaximin 550 mg TID x 2 weeks vs placebo
- Target 3 retreatment : Urgency and bloating improved significantly with both repeat treatments





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Pimintel M, Lembo A et al; TARGET Study Group. N Engl J Med. 2011;364:22-32.

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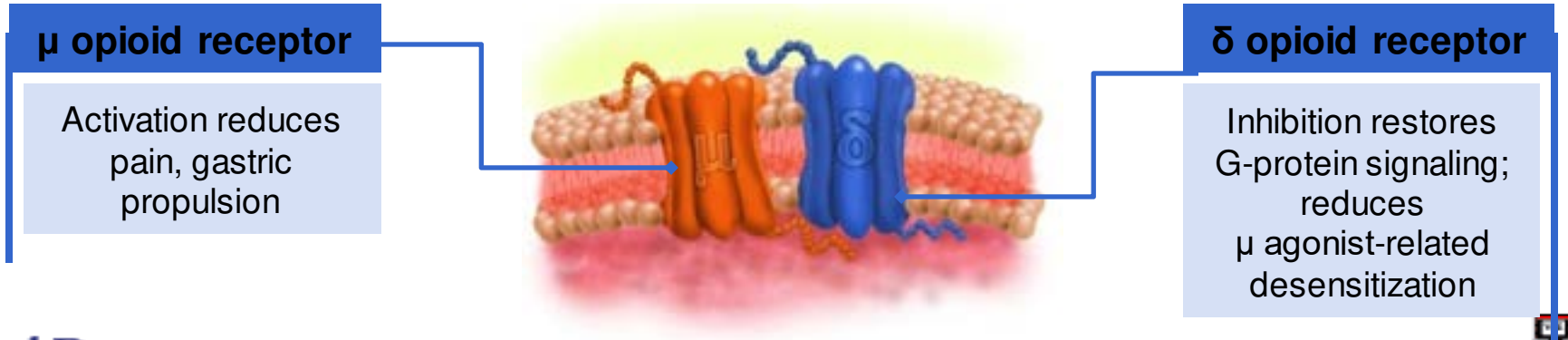
Eluxadoline for IBS-D

- Mixed mu (μ) opioid receptor agonist / delta (δ) opioid receptor antagonist
- Low systemic absorption
- 25% response vs. 16% placebo response (phase 3)
- FDA approved 75 and 100 mg BID for IBS-D
- Sphincter of Oddi Dysfunction in 10/1666 (0.6%)
- Pancreatitis 5/1666 (0.3%)
  - Death (2 pts- both had a hx of cholecystectomy)
  - Contraindicated if alcohol intake is > 3 drinks per day



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Lembo A et al. NEJM 2016

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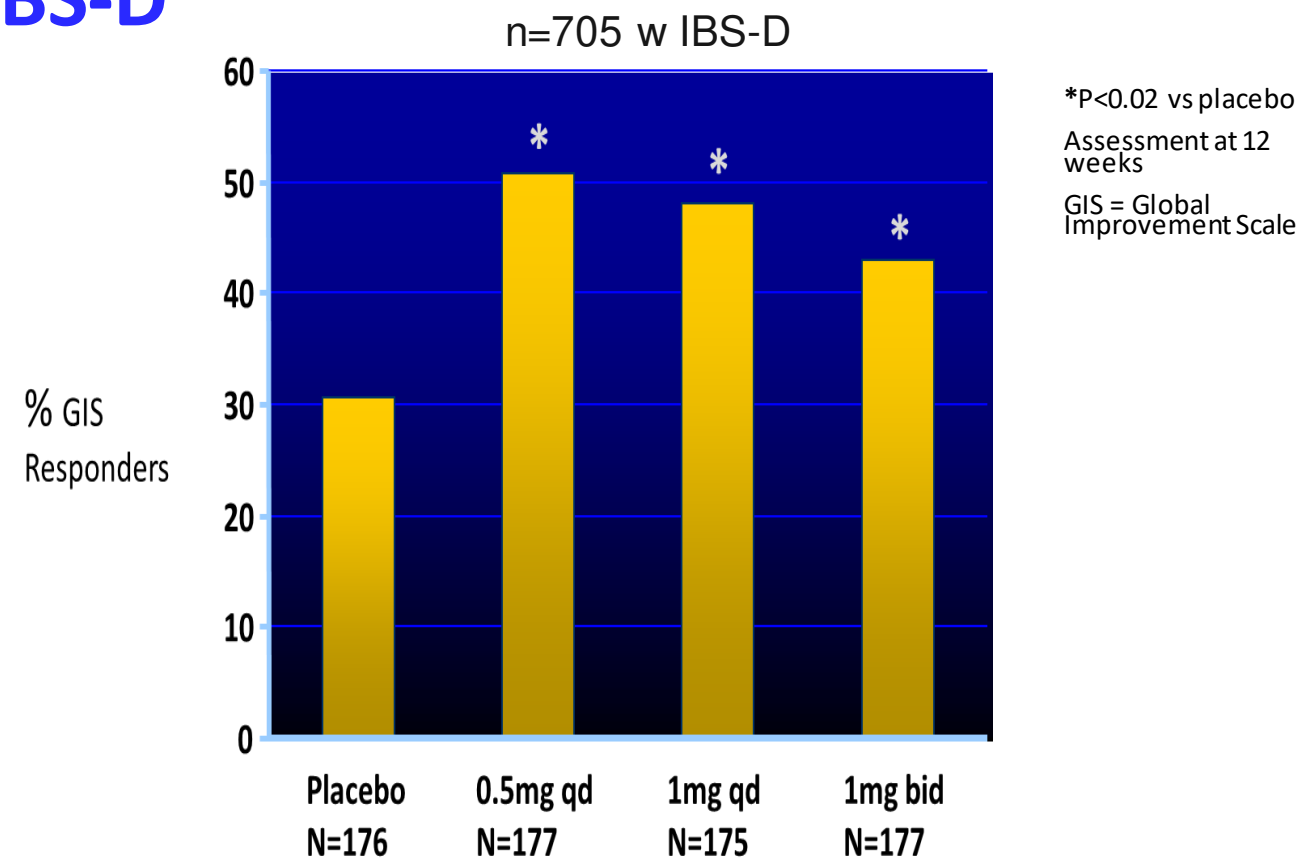
Third Line IBS-D: Alosetron, a 5-HT3 antagonist, Improves Global Symptoms in Women with Severe IBS-D

Safety Profile of Alosetron

- Black-box warning
- Ischemic colitis
  - 2 per 1000 pts over 3 months
  - 3 per 1000 pts over 6 months
- Constipation dose dependant
  - Alosetron (1 mg bid) = 29%
  - Placebo = 6%



Prescribing Program: 0.5 mg BID, increase 1 mg BID if tolerated

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Alosetron [package insert]. GlaxoSmithKline; 2006
Krause R et al. Am J Gastroenterol 2007; 102:1709

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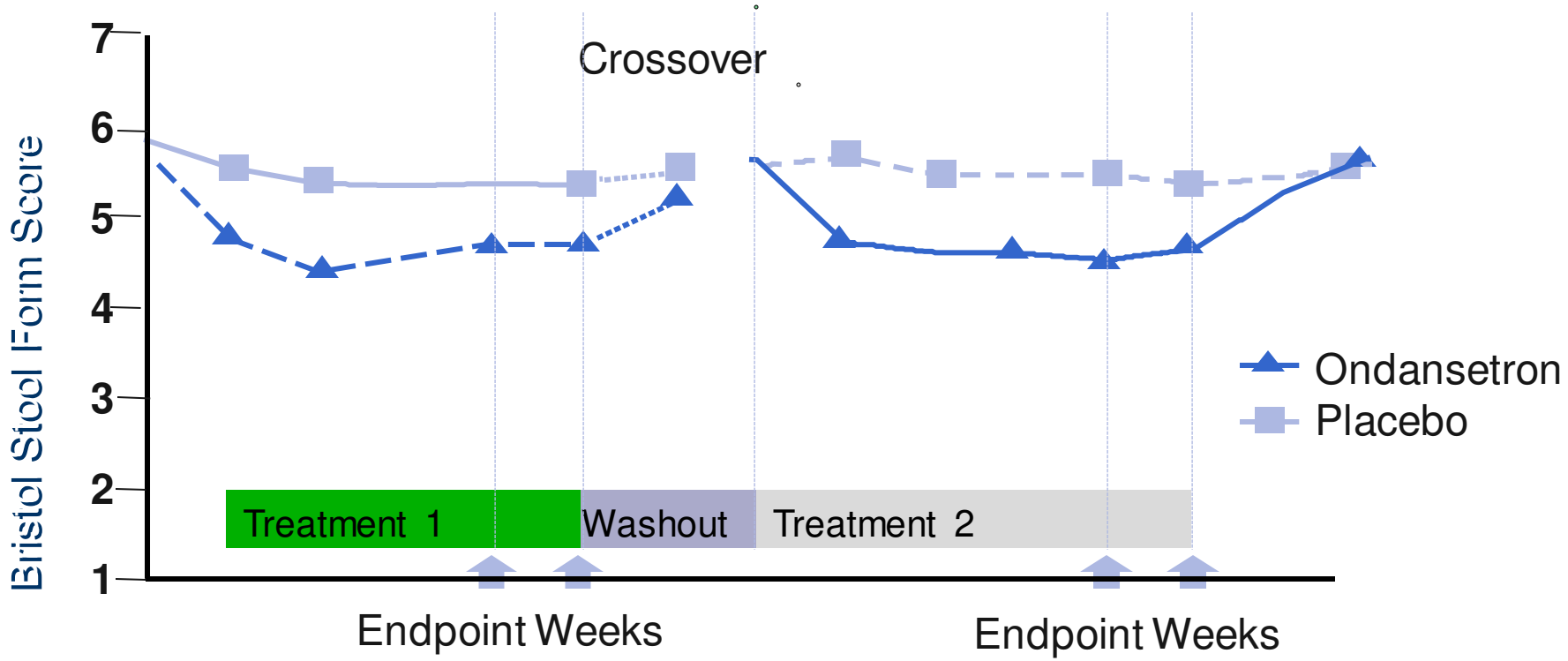
Ondansetron (5HT 3 antagonist)for IBS-D: Data From a Single Center Study

Effect of Ondansetron 4 to 8 mg TID for 5 Weeks in Patients With Rome III IBS-D (N = 120)**

No improvement in pain

RTC Dose-titration study. Primary endpoint: average stool consistency in last 2 weeks of treatment. Improvements in urgency, frequency, bloating but NOT pain. *Off-label



People w less severe diarrhea benefit the most

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Garsed K, et al Gut. 2014;63:1617-25.

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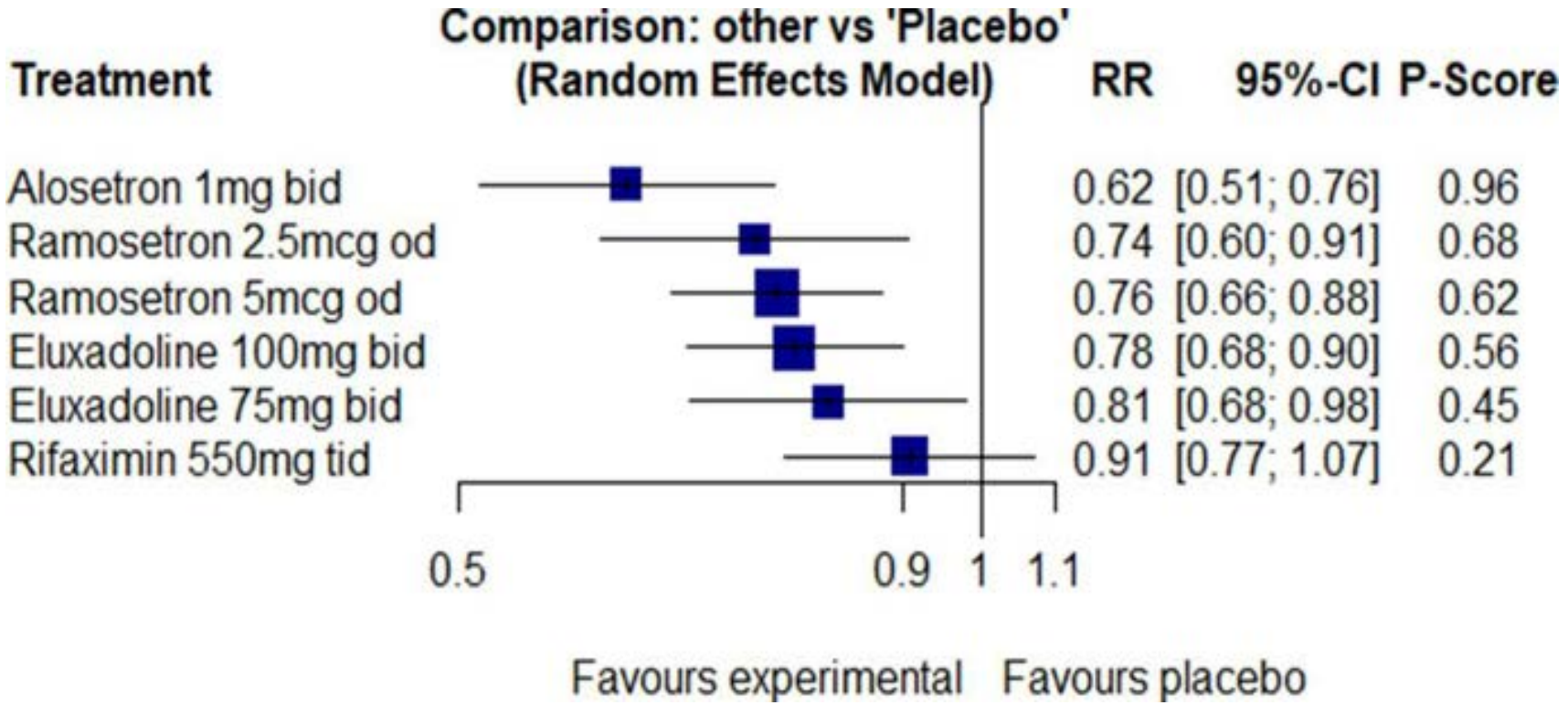
Efficacy of FDA Approved IBS-D treatments
Systematic Review and Network Meta-analysis



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

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Black CJ et al. Gut 2019 Apr 17. pii: gutjnl-2018-318160

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First line Pain Antispasmodics in IBS : Limited Evidence

- Most are anticholinergics – reduce bowel contraction
  - Side effects: dry mouth, constipation, urinary retention, blurred vision
  - Examples include: Dicyclomine, Hyoscyamine, Peppermint oil

- Limited evidence: low quality studies, single center, small n's

- Enteric coated peppermint oil (200 mg) appears to be more effective than placebo
  - Delayed release peppermint oil available in the US

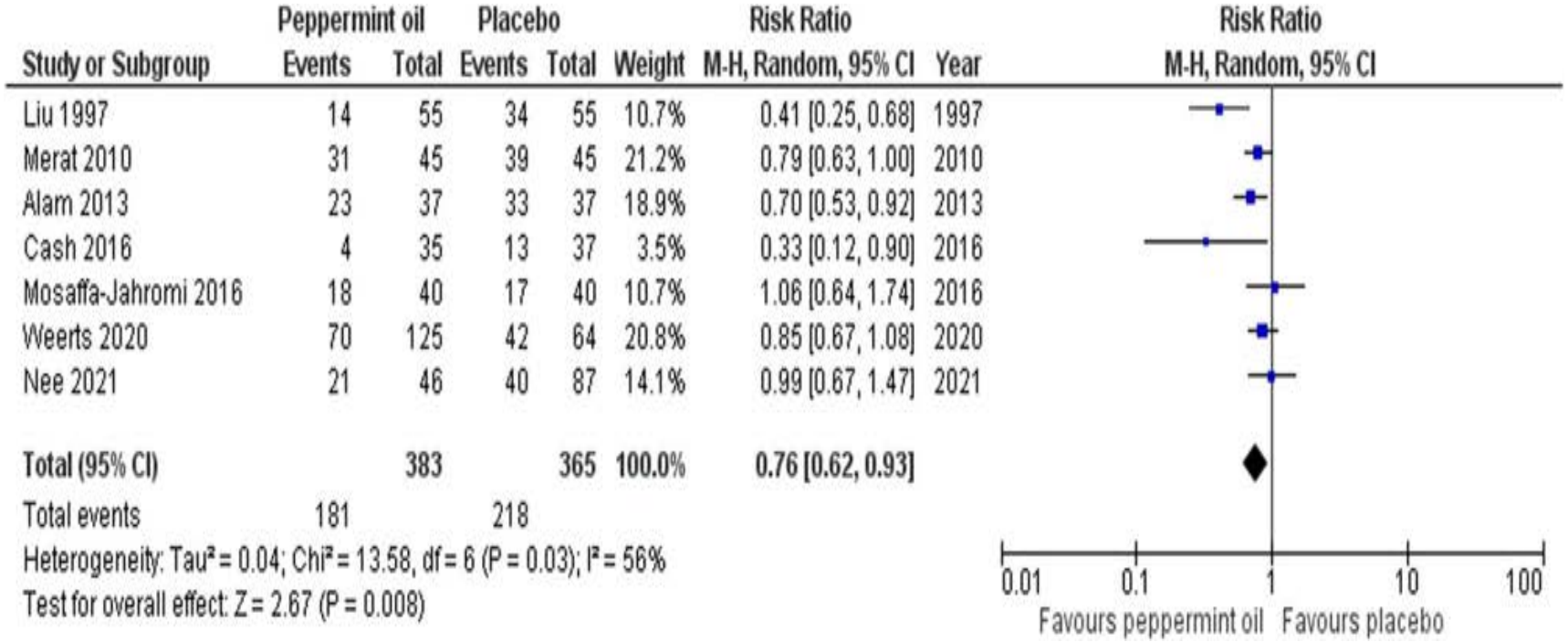
Efficacy of Peppermint Oil Drugs IBS
Systematic Review and Network Meta-analysis

- 10 RTCs (1030 patients)
- Improved
  - Global symptoms

  RR=0.65 (0.43-0.98) NNT=4
  - Abdominal pain

  RR=0.76 (0.62-0.93) NNT=7

- Higher risk for AE
  - RR = 1.57; 95% CI 1.04-2.37
  - GERD, dyspepsia, flatulence



Study or Subgroup	Peppermint oil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Liu 1997	14	55	34	55	10.7%	0.41 [0.25, 0.68]	1997
Merat 2010	31	45	39	45	21.2%	0.79 [0.63, 1.00]	2010
Alam 2013	23	37	33	37	18.9%	0.70 [0.53, 0.92]	2013
Cash 2016	4	35	13	37	3.5%	0.33 [0.12, 0.90]	2016
Mosaffa-Jahromi 2016	18	40	17	40	10.7%	1.06 [0.64, 1.74]	2016
Weerts 2020	70	125	42	64	20.8%	0.85 [0.67, 1.08]	2020
Nee 2021	21	46	40	87	14.1%	0.99 [0.67, 1.47]	2021
Total (95% CI)		**383**		**365**	**100.0%**	**0.76 [0.62, 0.93]**	
Total events	181		218				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 13.58$, $df = 6$ ($P = 0.03$); $I^2 = 56\%$

Test for overall effect: $Z = 2.67$ ($P = 0.008$)

Low quality of evidence

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Ingrosso M, et al;Aliment Pharmacol Ther. 2022 Sep;56(6):932-941.

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Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment [ATLANTIS]

	3 months				6 months			
	Low-dose amitriptyline (n=232)	Placebo (n=231)	Effect*, 95% CI	p value	Low-dose amitriptyline (n=232)	Placebo (n=231)	Effect*, 95% CI	p value
Primary outcome								
IBS-SSS†								
Mean total IBS-SSS‡, SD	173·0 (106·6), n=219	194·6 (107·5), n=213	-23·3 (-42·0 to -4·6)	0·014	170·4 (107·7), n=204	200·1 (114·5), n=197	-27·0 (-46·9 to -7·1)	0·0079
Change in IBS-SSS from baseline, SD	-99·8 (107·7)	-76·1 (107·1)	"	"	-99·2 (112·9)	-68·9 (109·3)	"	"

RCT
55 PCP practices
18 ≥, Rome IV IBS
n=463, 68%F, 32%M

IBS-SSS score ≥75 points

1:1 low-dose oral amitriptyline 10 mg QD up to 30 mg dose (titration over 3 weeks) vs placebo for 6 months

D/C AE- 13 % drug and 9 % placebo before 6 months

Pregabalin for IBS
Duloxetine

Ford et al. Lancet . 2023 Oct 16:S0140-6736(23)01523-4..

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Third Line : Systematic Review and Meta-analysis 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.

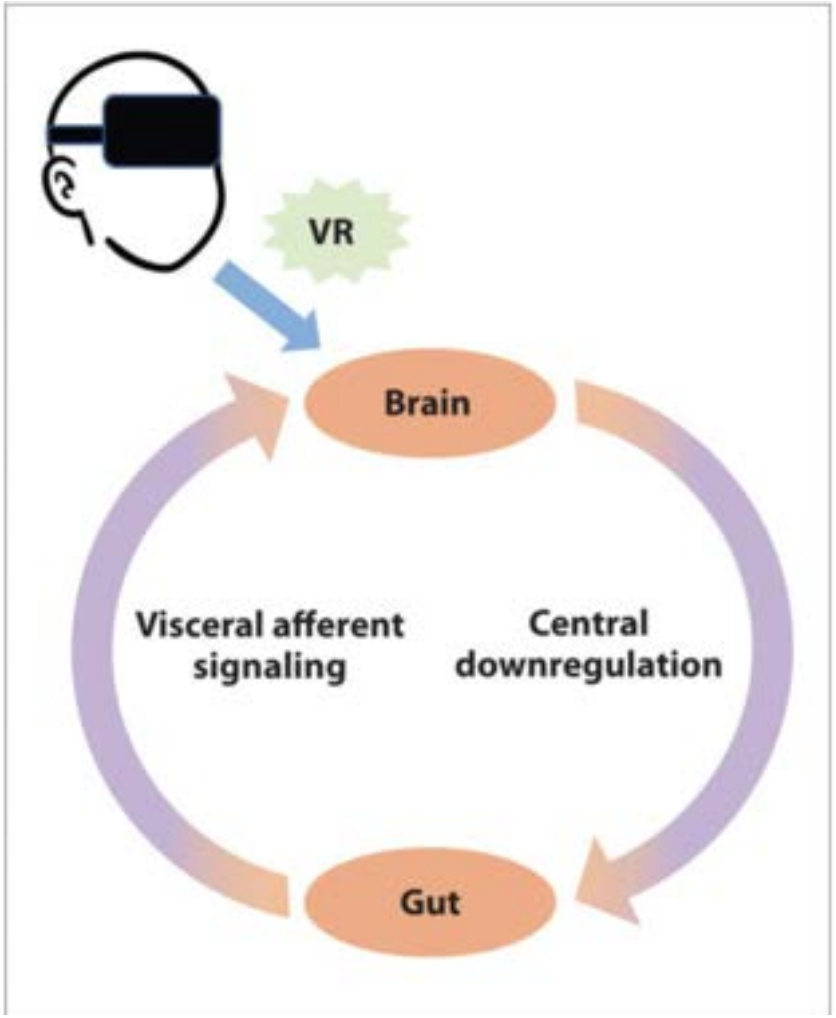
CI=confidence interval; NNT=number needed to treat; RR=risk ratio; – = not provided.

Comparison of Different Therapies for IBS

	Cognitive Behavioral therapy	Gut Directed Hypnotherapy	TCAs	Rifaximin	Linaclotide
Number Needed to Treat (NNT)	4	5	4.5	10	5-8

Ford et al; AJG 2019
Meenas et al;2012
Thomas et al; 2013

Available GI Psychotherapy Apps



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Spiegel BMR, Liran O, Gale R et al. *Am J Gastroenterol.* 2022;117(3):495–500.

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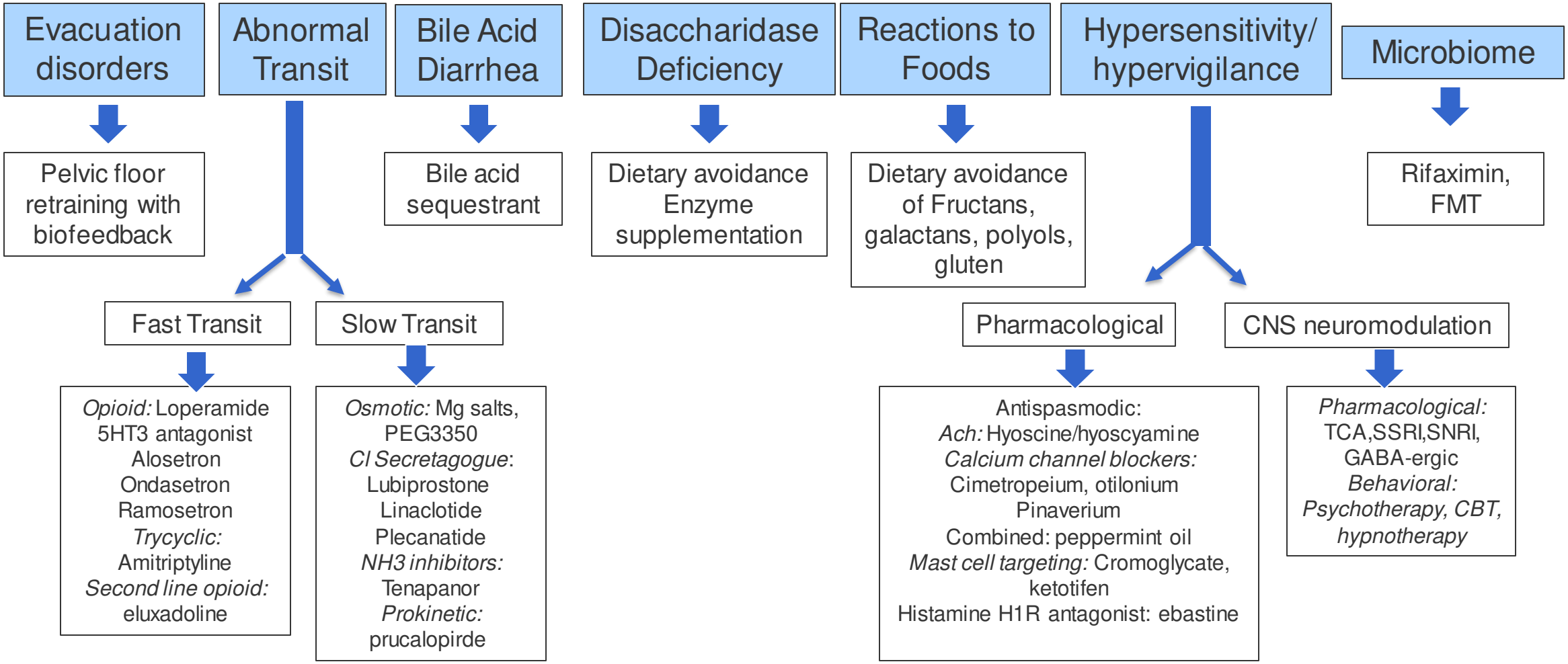
Therapeutic Choices Guided by History , Pathophysiology and Biomarkers



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Adapted from Camilleri M, Boeckxstaens G. Gut 2022;0:1-10.

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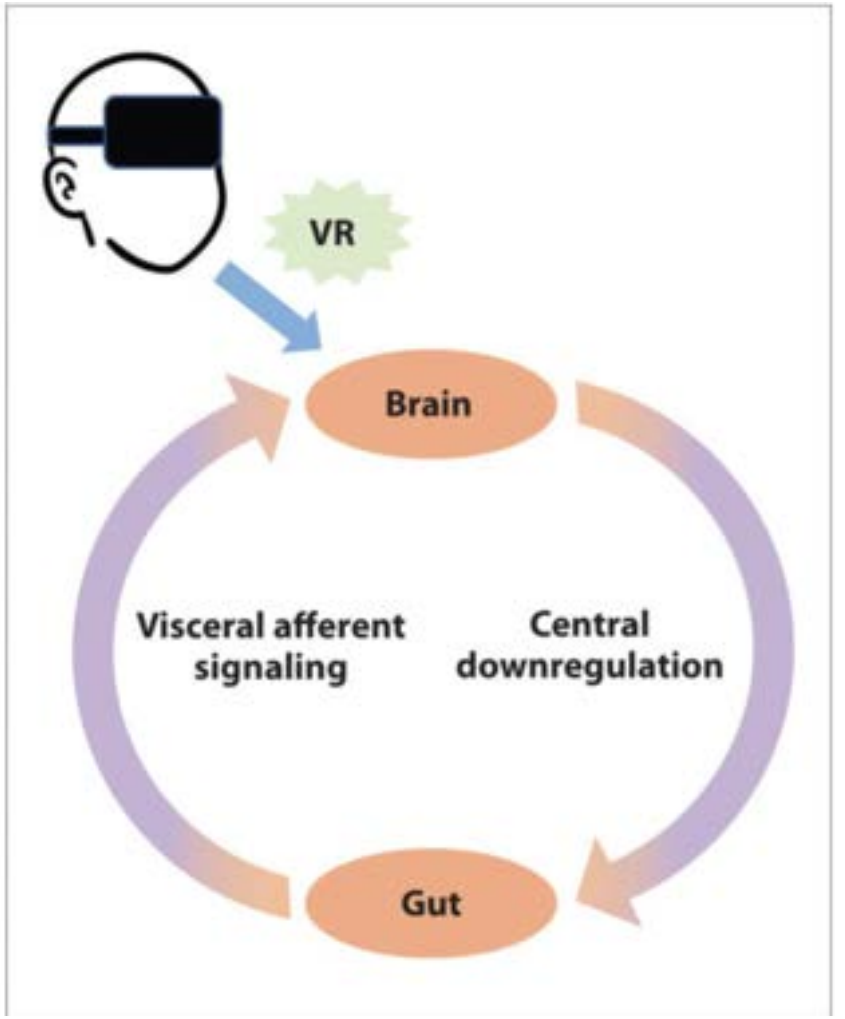
Take Home Points

- Importance to give the appropriate diagnosis IBS vs FC vs FD
- Importance of patient physician relation and lifestyle modifications
- Use biomarkers when available (7AC4, ARM, Transit studies, BT etc.)
- If diet interventions needed screen for Eating Disorders, ARFID
- Use first, second and third line and of treatment for IBS-C and IBS-D
- Use biomarkers when available (7AC4, ARM, Transit studies, BT etc.)
- Address IBS severity and refer to GI psychology, Apps
- Use antispasmodics, TCA, SNRI when necessary

We still have unmet needs…

Qualitative Validation of a Novel VR Program for IBS: a VR1 study

Treatment Room Description	Representative Images
Room Name: Exam Room **Description:** Patients virtually embody the role of a doctor to examine a patient and discover anatomical and physiological aspects of IBS, including motility, visceral hypersensitivity, bacterial overgrowth, and the brain-gut axis. **Panel A:** Patient becomes the doctor and applies a stethoscope to the abdomen, hearing bowel sounds. **Panel B:** Hologram of the digestive tract highlights the role of carbohydrates and bacterial fermentation and introduces bacterial overgrowth. **Panel C:** Description of the brain-gut axis and its role in IBS.	
Room Name: Chill Room **Description:** Relaxing scenes feature gut-directed hypnotherapy, mindful meditation, and breathing techniques to help patients learn to positively influence their brain-gut axis. **Panel A:** Gaze-based selection menu offers a range of guided experiences with male or female voice option. **Panel B:** As the patient inhales, an expanding mandala emits blue steam to fill and cleanse the lungs. **Panel C:** As the patient breathes out, metaphorical red vapors are exhaled in exchange for the cleansing air.	
Room Name: Theater of the Mind **Description:** Patients enter a "movie theater" representing their mind. Scenes on the screen depict thoughts as patients learn CBT techniques to replace negative thoughts about IBS with more supportive cognitions. **Panel A:** User is in a public restroom stall, hears sounds of people outside, and is told people are waiting (other trigger scenes not shown). **Panel B:** The patient selects among a list of emotions that the bathroom scene triggers, followed by a series of CBT exercises to restructure maladaptive cognitions.	
Room Name: Zoom Out Room **Description:** Through a series of "zoom out" maneuvers, patients gain perspective about the global community of people with IBS and, in the process, gain new perspectives about themselves as a person with IBS. **Panel A:** Standing atop a building, patients see others with IBS in their community, each marked by a green light. **Panel B:** Patients next "zoom" into space, where they can see the worldwide community of IBS patients. **Panel C:** Patients learn from themselves in an avatar-based "self-chat" dialog.	



Uncomplicated GI specific anxiety?

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Spiegel BMR, Liran O, Gale R et al. *Am J Gastroenterol.* 2022;117(3):495–500.

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