Patient-Centered Management of Irritable Bowel Syndrome

MICHIGAN MEDICINE
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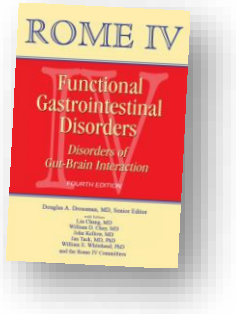
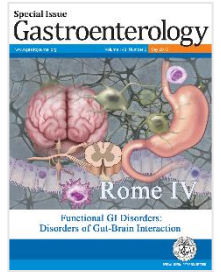


IBS: Rome IV Criteria*

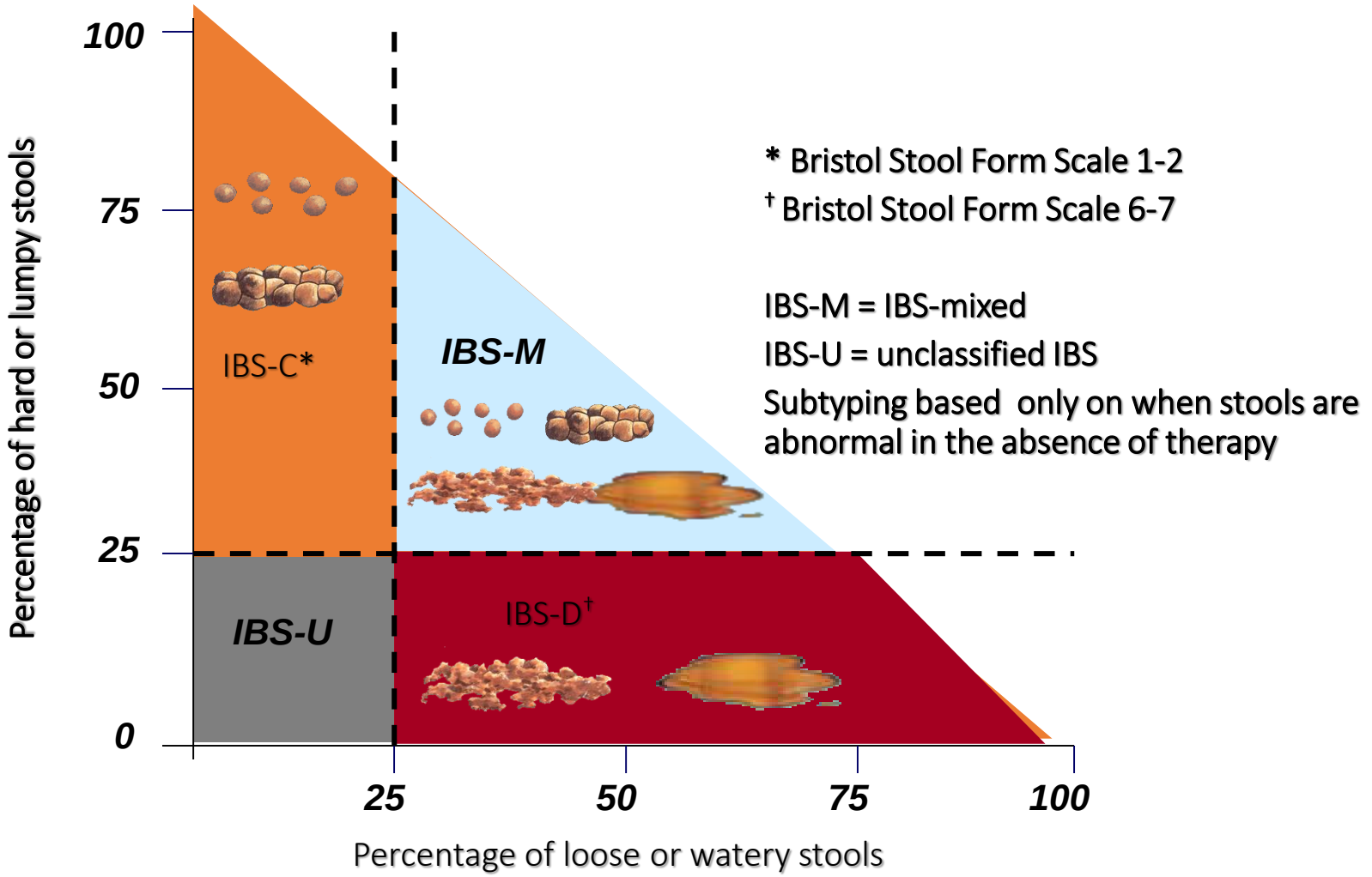


- **Recurrent abdominal pain 1 day per week associated with two or more of the following:**
- **Related to defecation**
- **Onset associated with a change in the frequency of stool**
- **Onset associated with a change in the form of stool**

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

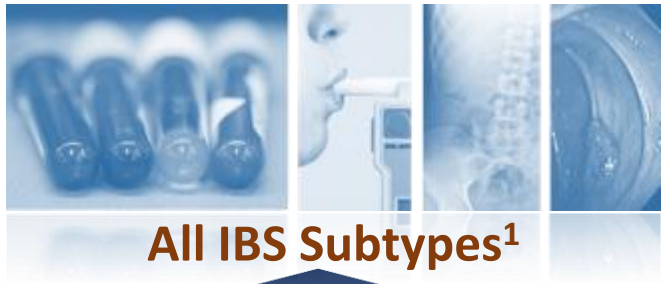
Mearin et al, Gastroenterol May 2016

IBS Subtypes Are Based on Stool Consistency



Mearin et al. Gastroenterology. May 2016

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



All IBS Subtypes[1]

CBC
Age-appropriate CRC screening

IBS-D[1,2]	IBS-M[1]	IBS-C[1]
• CRP or fecal calprotectin • IgA TtG ± quantitative IgA • When colonoscopy performed, obtain random biopsies • SeHCAT, fecal bile acids, or serum C_4 where available • Anti-CdtB/anti-vinculin antibodies[2]	• CRP or fecal calprotectin • IgA TtG ± quantitative IgA • Stool diary • Consider abdominal plain film to assess for fecal loading	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; SeHCAT, selenium homocholic acid taurine; Ttg, tissue transglutaninase.

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

Graded Integrative Treatment of IBS

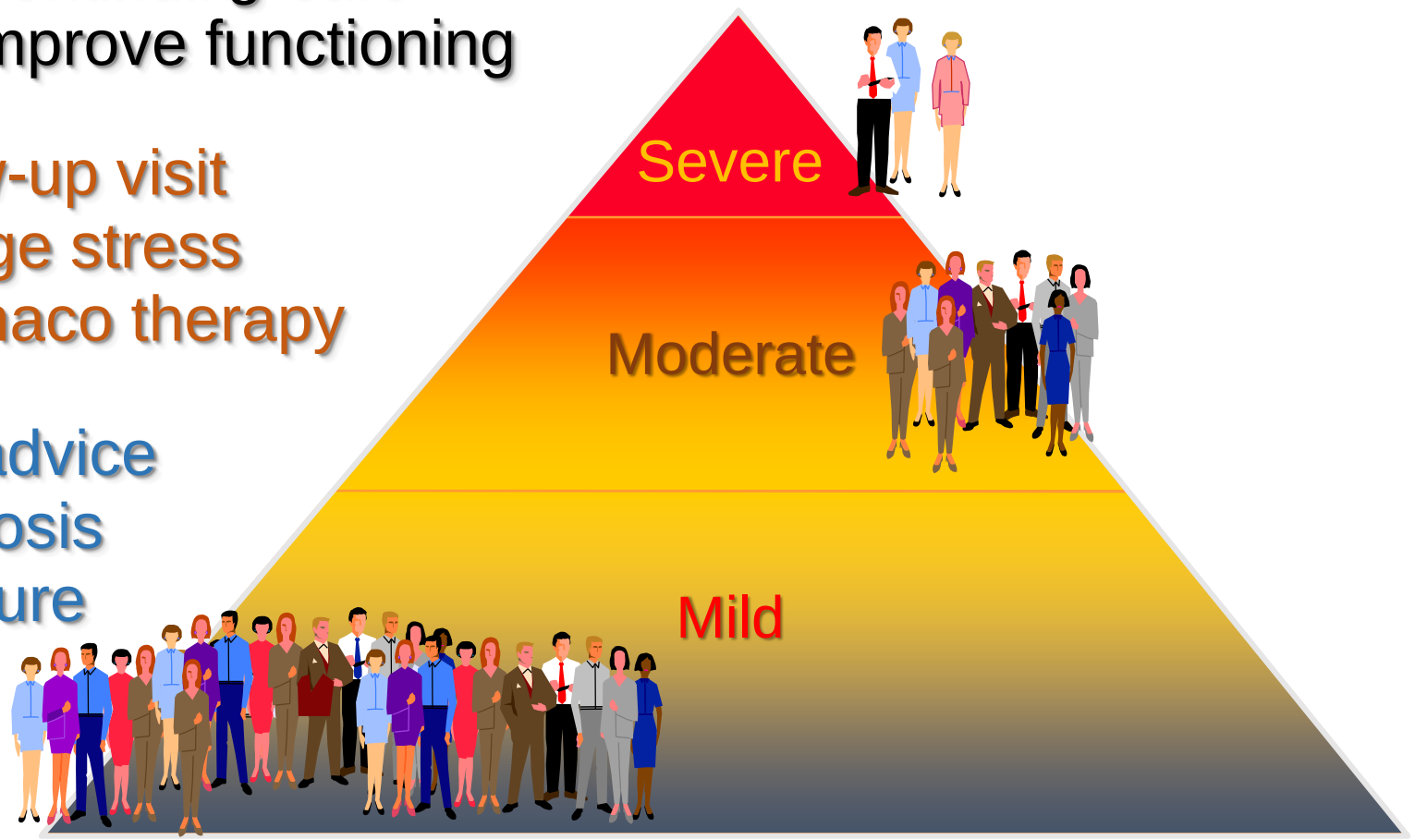
- Psychological treatments
- Continuing care
- Improve functioning

+

- Follow-up visit
- Manage stress
- Pharmaco therapy

+

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



Dietary Interventions for IBS: What is the Evidence?

What are FODMAPs?

- **Fermentable oligo-, di-, monosaccharides and polyols**
- **Fruits with fructose exceeding glucose**
  - Apples, pears, watermelon
- **Fructan containing vegetables**
  - Onions, leeks, asparagus, artichokes
- **Wheat based products**
  - Bread, pasta, cereal, cake, biscuits
- **Sorbitol and lactose containing foods**
- **Raffinose containing foods**
  - Legumes, lentils, cabbage, brussels sprouts

Eswaran & Chey, GI Cl North Am 2011;40:141
Shepherd, et al, Clin Gastro Hepatol 2008;6:765
Gibson & Shepherd. J Gastro Hepatol 2010;25:252

RCTs Evaluating the Low-FODMAP Diet for IBS

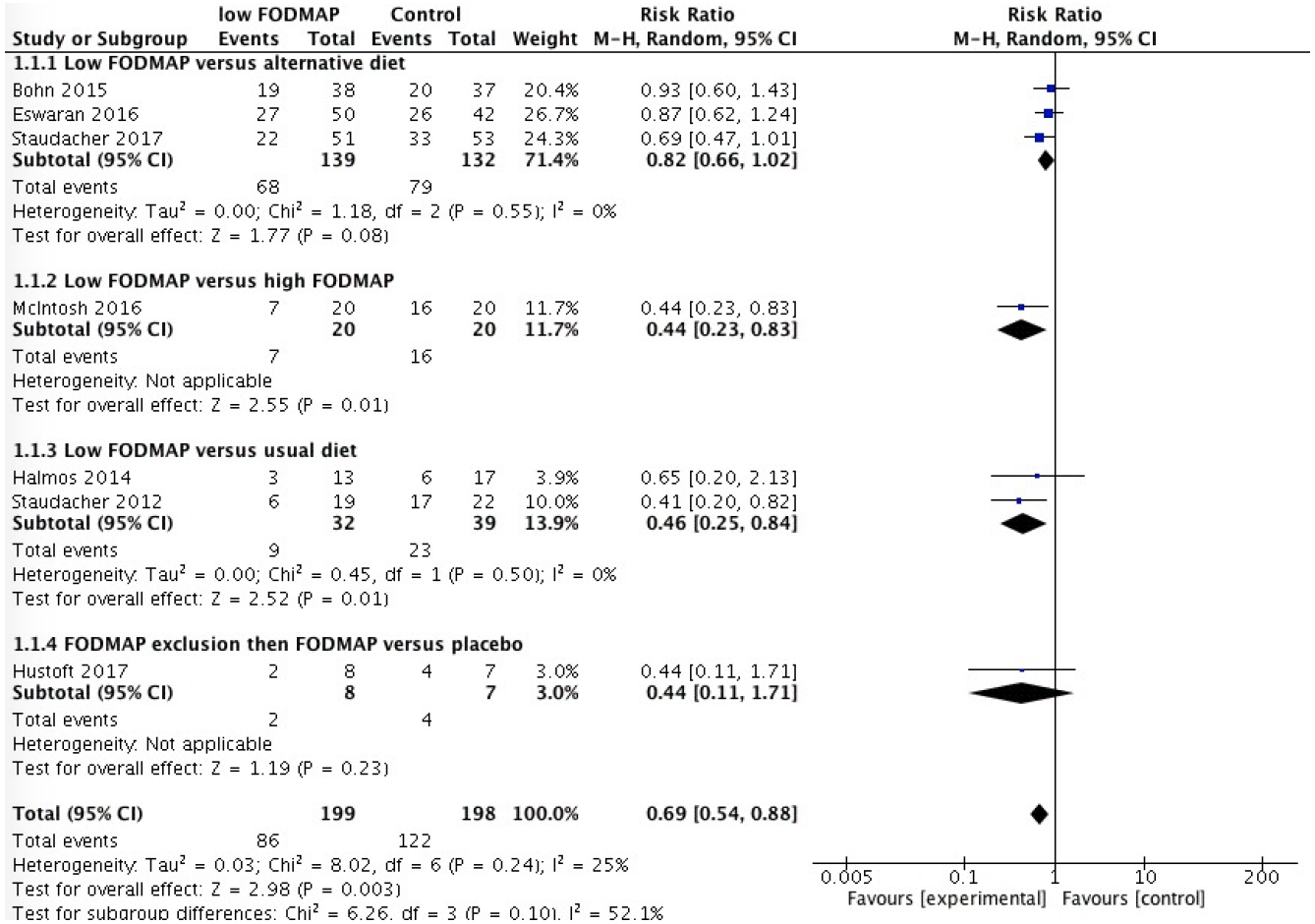
7 RCTs compared a low FODMAP diet with various controls in 397 participants

A low FODMAP diet was associated with reduced overall symptoms compared to controls (RR 0.69; 95% CI 0.54, 0.88, I2 25%)

The 3 RCTs that compared low FODMAP diet with rigorous control diets had the least heterogeneity between studies but also the least magnitude of effect

The overall quality of the data was “very low” according to GRADE criteria

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



Dionne JC et al. Presented at DDW 2018. Washington, DC: June 4, 2018; Abstract 1648.

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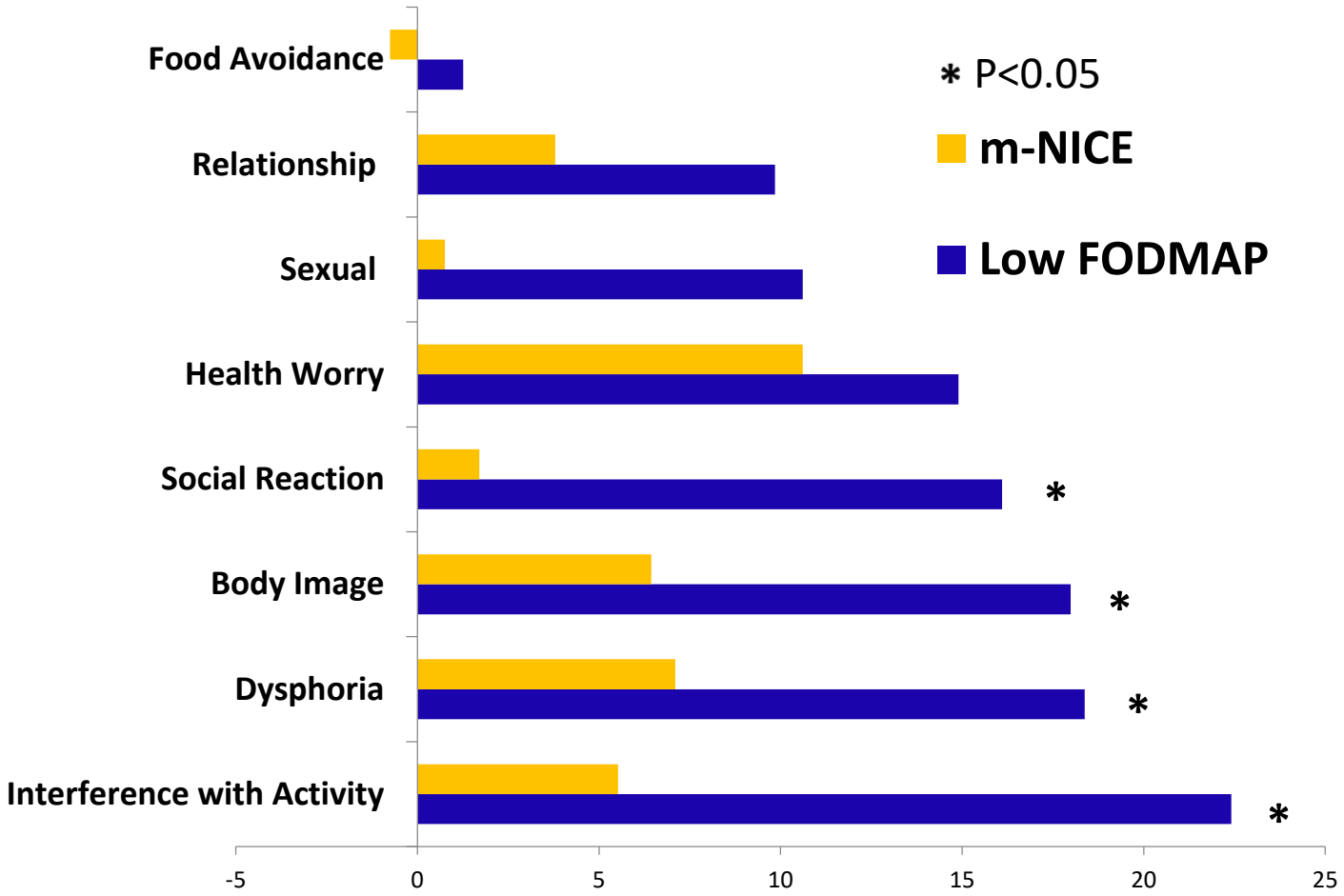
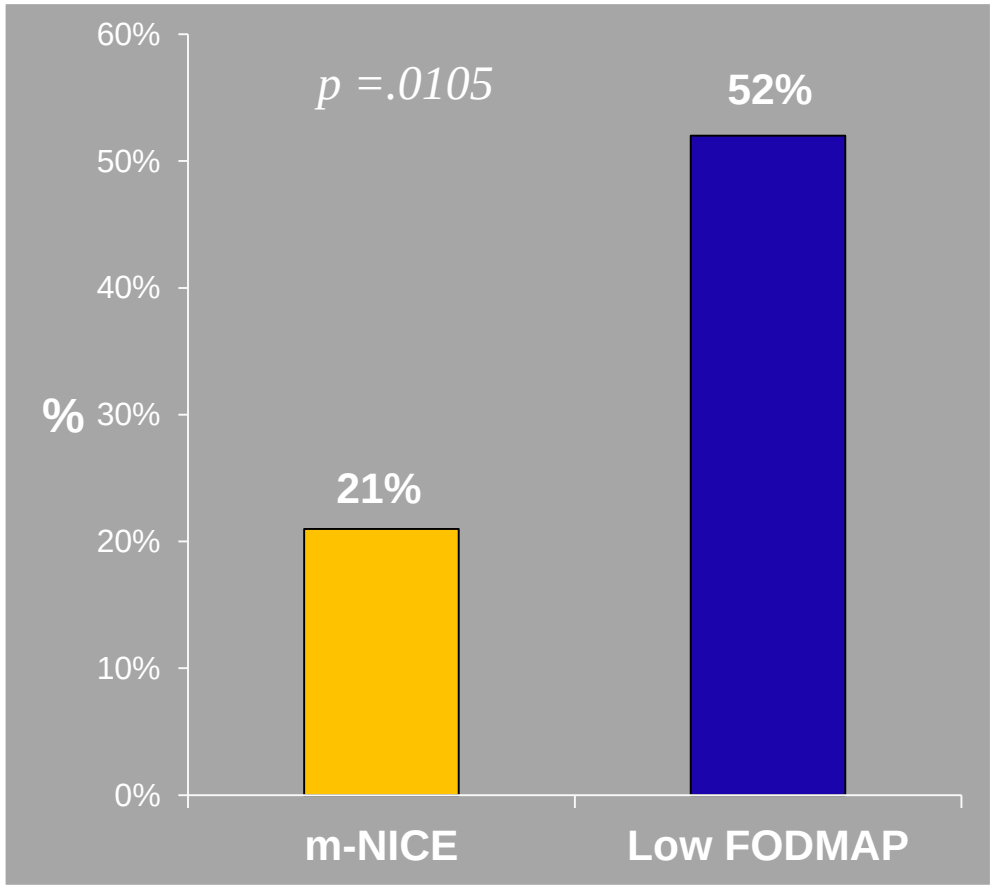
LFD vs. mNICE Diet: IBS-QOL Scores



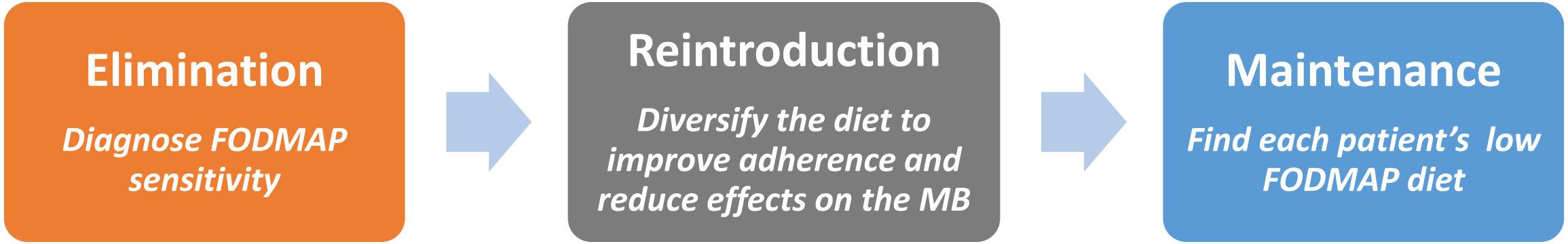
Improvement from Baseline ≥ 14



Meaningful Clinical Response

Eswaran, Chey, DDW 2016

3 Phases of the Low-FODMAP Diet: Elimination is the Beginning NOT the End!!



Additional Information:

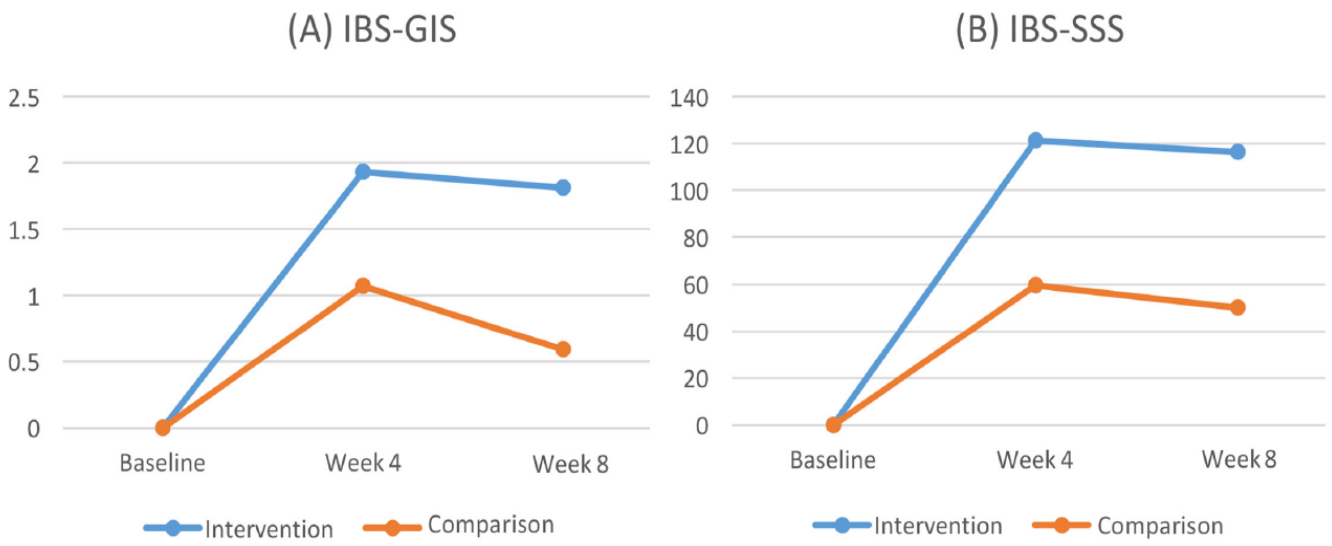
www.myginutrition.com

Monash University mobile app

Recent Books: Patsy Catsos, Danielle Capalino, Rachel Meltzer (teens), Kate Scarlata

Chey WD. Am J Gastroenterol 2016:111;366

Leukocyte Activation Test Elimination Diet

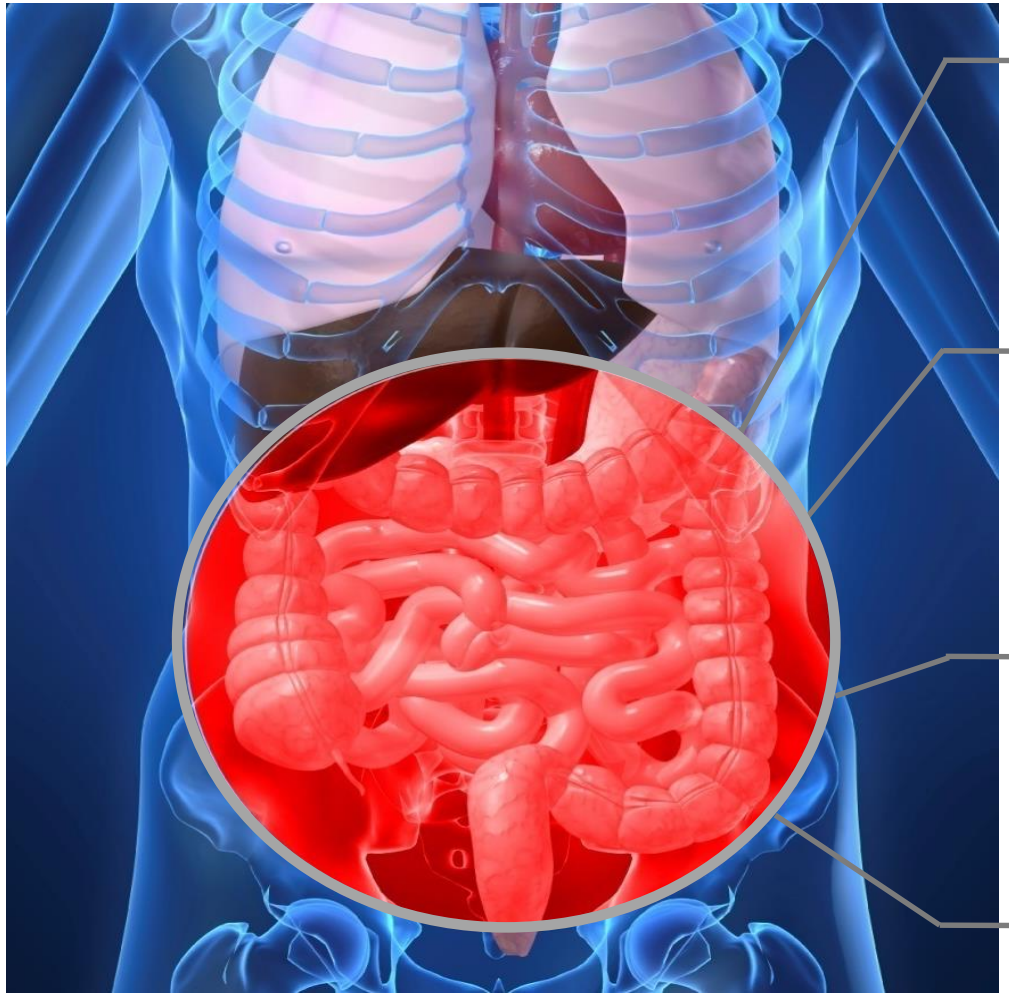


- Peripheral blood taken from 58 IBS pts
- LAT (n=29) vs. Sham (n=29) elimination diet x 4 weeks
- No significant benefits for adequate relief or IBS-QOL scores

Food	Frequency n (%)	High FODMAP
Strawberry	15 (26)	
Cinnamon	15 (26)	
Almond	12 (21)	X
Apple	12 (21)	X
Onion	12 (21)	X
Pear	11 (19)	X
Buckwheat	11 (19)	
Chickpea	11 (19)	
Ginger	11 (19)	
Raspberry	11 (19)	
Blueberry	10 (17)	
Hops	10 (17)	
Oats	10 (17)	
Olive	10 (17)	
Quinoa	10 (17)	
Sorghum	10 (17)	
Yellow squash	10 (17)	

Ali A et al. BMJ Open Gastroenterology. 2017;0:e000164.

Pharmacologic Therapy Is Directed Toward the Dominant Symptoms



Diarrhea
- Loperamide*
- Alosetron/ondansetron
- Antibiotics*
- Eluxadoline
- TCAs

Constipation
- Fiber*
- Osmotic & stimulants*
- Lubiprostone
- Linactotide/Plecanatide
- Prucalopride

Abdominal pain/ discomfort
- Antibiotics
- Antispasmodics
- Antidepressants*
- Alosetron
- Lubiprostone
- Linaclotide/Plecanatide

Bloating
- Antibiotics*
- Probiotics*
- Lubiprostone
- Linaclotide/Plecanatide

*Not FDA-approved for IBS.

Chey WD, et al. JAMA. 2015;313:949-958
ACG Task Force on IBS. Am J Gastroenterol. 2018, in press.

Utility of Probiotics for IBS:

A Systematic Review & Meta-analysis

- **Fifty-three RCTs, 5545 patients**

- **RR of IBS symptoms persisting with probiotics vs. placebo was 0.81 (95%CI 0.74-0.88)**
  - **Probiotics had beneficial effects on global IBS, abdominal pain, bloating, & flatulence scores**
  - **Effects of individual species or combinations marginal to non-existant**
  - **NNT = 7 (95 % CI 5 – 12)**
  - **NNH = 35**

Ford et al. Am J Gastroenterol Suppl 2018

Probiotics in IBS:
ACG Task Force Recommendations

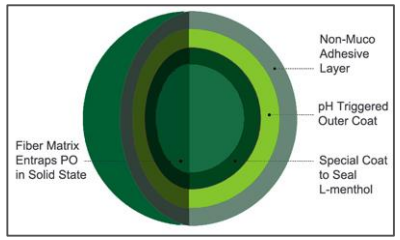
- **"We suggest probiotics, taken as a group, to improve global symptoms, as well as bloating and flatulence in IBS patients"**

- **Recommendations regarding individual species, preparations, or strains cannot be made at this time because of insufficient and conflicting data**

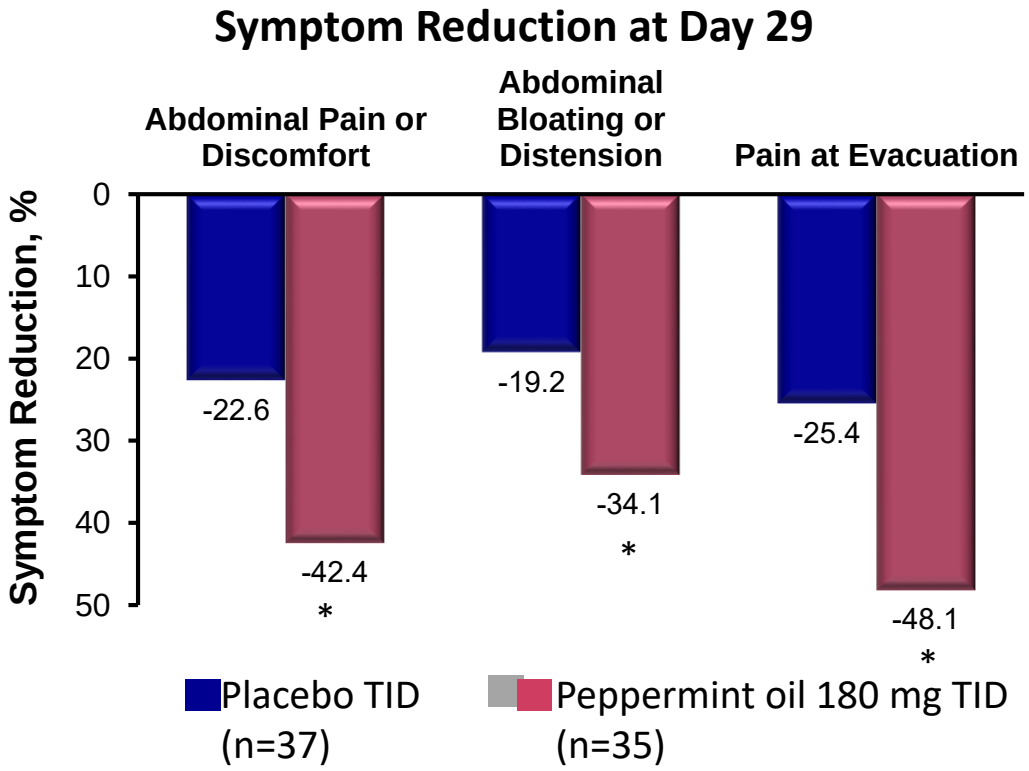
- **Recommendation: weak, Quality of evidence: low**

Ford et al. Am J Gastroenterol Suppl 2018

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 Total IBS Symptom Score**
- **Peppermint oil improved Total IBS Symptom Score (*P*<0.02) and frequency and intensity of individual IBS symptoms over 4 weeks**



****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

Overview of IBS-D Therapies

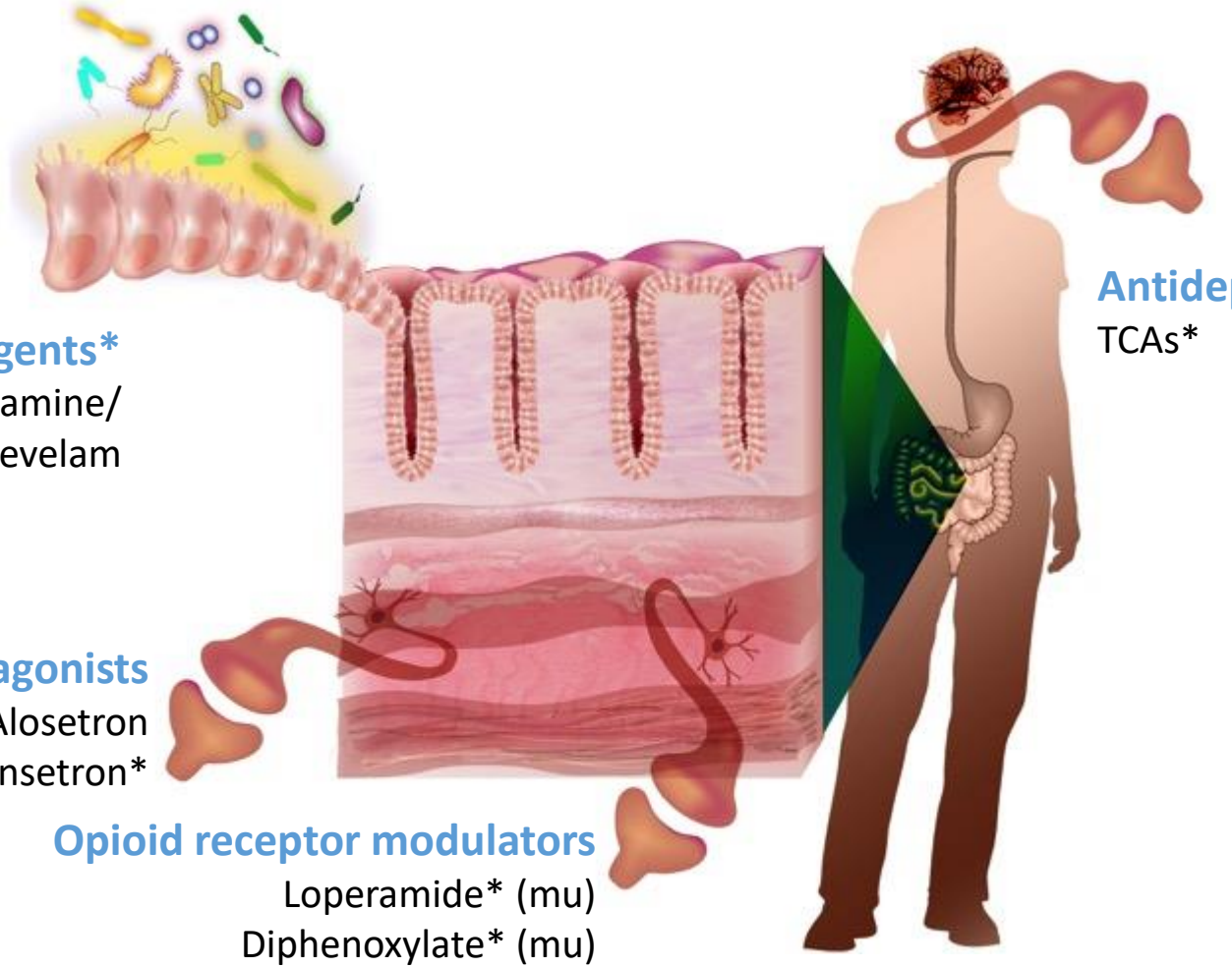
Modulation of gut flora
Diet
Rifaximin
Prebiotics, Probiotics*
FMT*

Bile acid binding agents*
Cholestyramine/
Colestid/Colesevelam

Antispasmodics*
Peppermint oil

5-HT_3 antagonists
Alosetron
Ondansetron*

Opioid receptor modulators
Loperamide* (mu)
Diphenoxylate* (mu)
Eluxadoline (mixed)

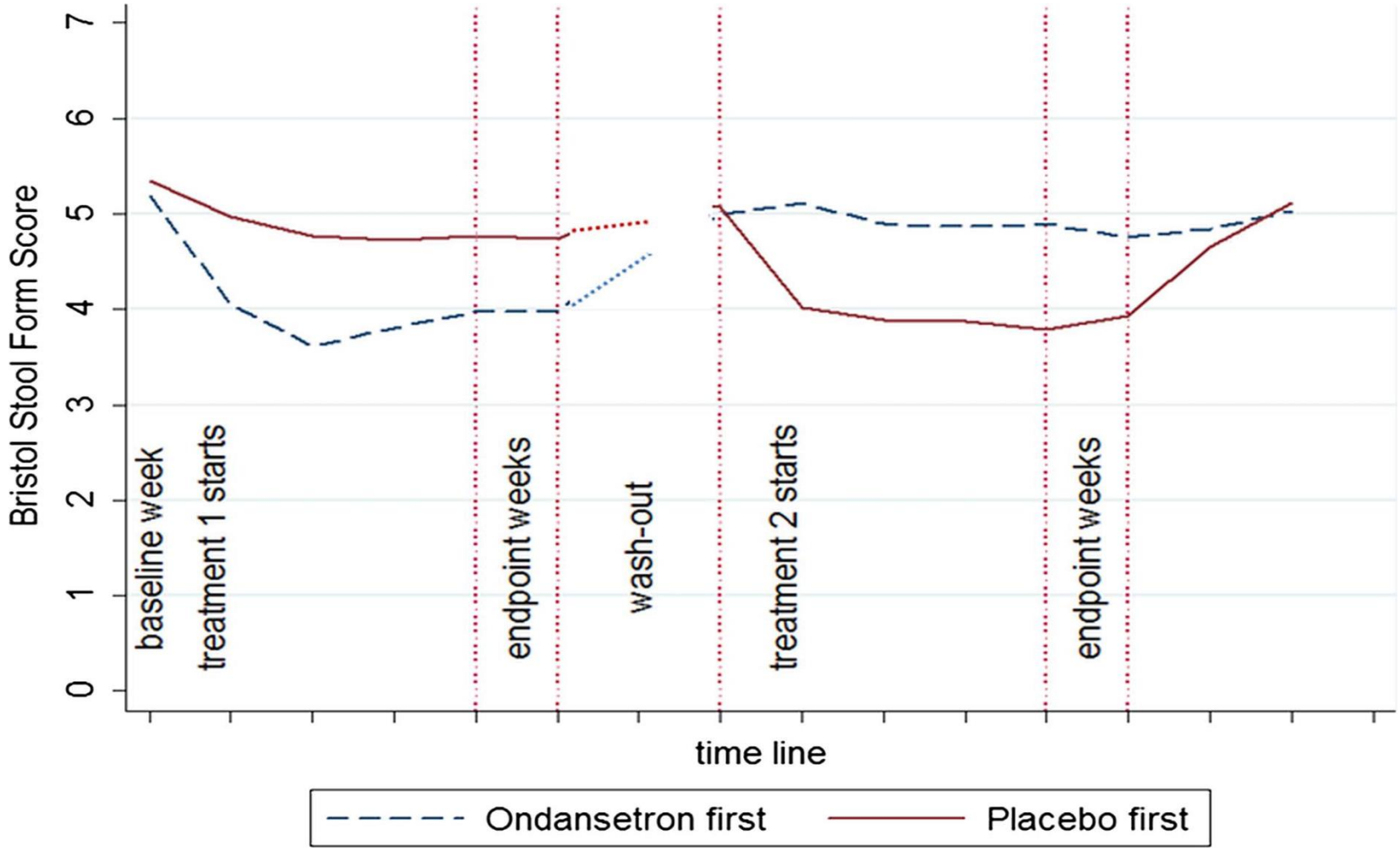


Antidepressants
TCAs*

*Not FDA-approved for management of IBS-D.

Ondansetron for IBS-D: Stool Form

R, DB, dose titration (4-8 mg tid) x 5 wks

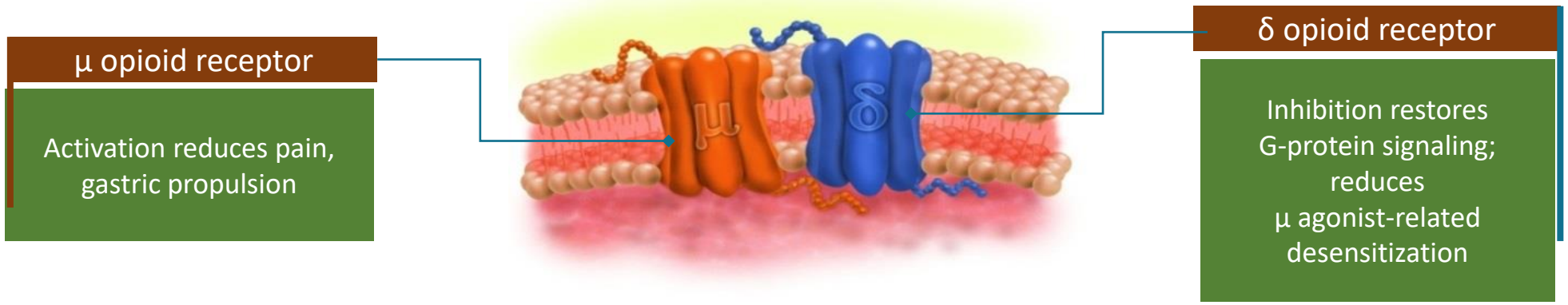


120 pts with IBS-D (Rome III)
Primary endpoint: Avg stool consistency in last 2 weeks of treatment
Improvements in urgency, frequency, bloating but NOT pain

Garsed et al. Gut 2014;63:1617–25

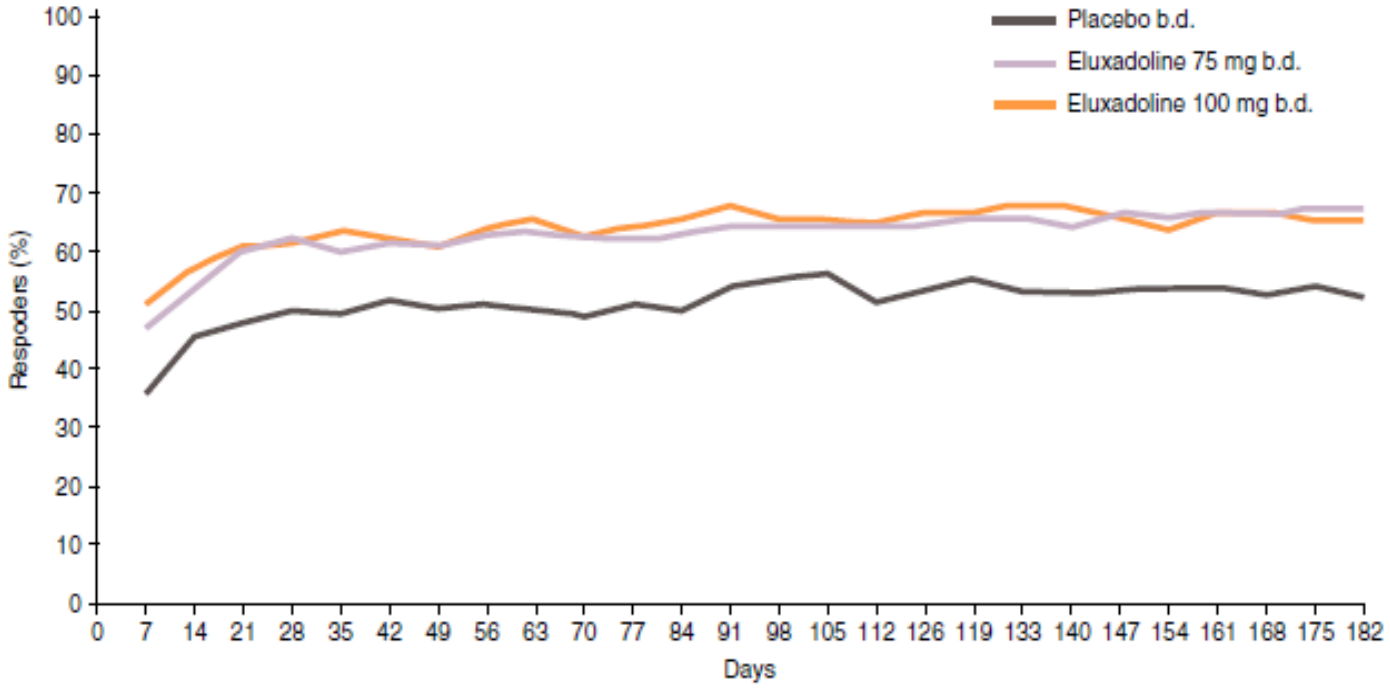
Eluxadoline in IBS-D

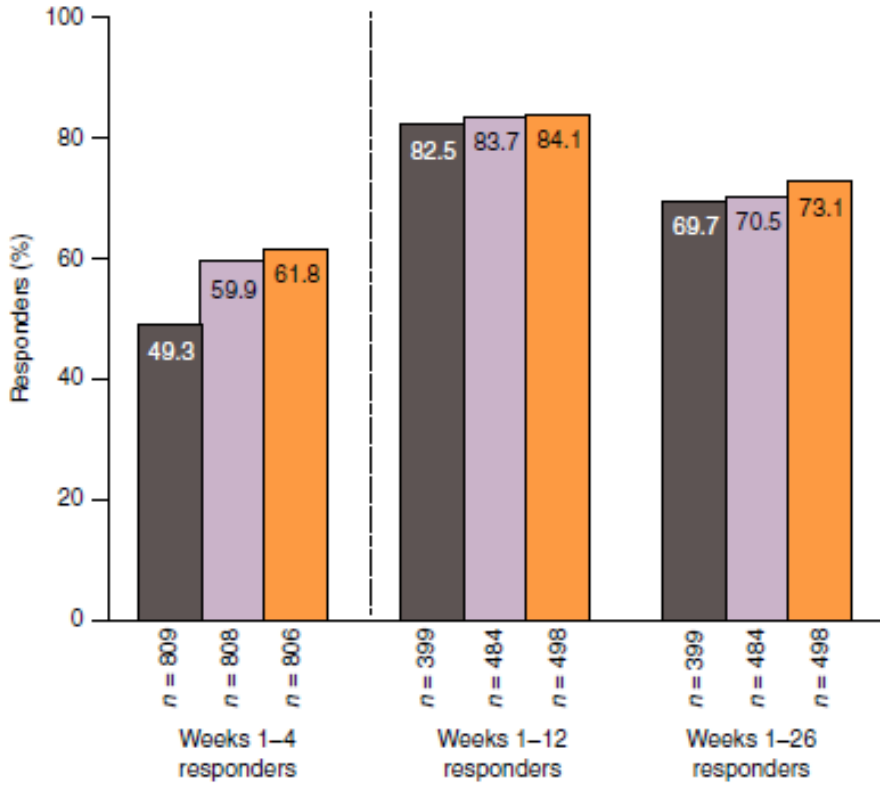
- Mixed opioid receptor agonist/antagonist
  - Mu receptor agonist
  - Delta receptor antagonist & Kappa receptor agonist
- Low systemic exposure after oral administration
- Animal studies suggest eluxadoline can improve diarrhea and pain in IBS-D patients with limited constipation



Fujita W, et al. Biochemical Pharmacology. 2014. http://dx.doi.org/10.1016/j.bcp.2014.09.015;
Wade PR, et al. British Journal of Pharmacology. 2012;167:1111-1125;

Early response predicts a sustained response with Eluxadoline in IBS-D patients: Adequate Relief Endpoint





Post-hoc analysis from 2 Phase III clinical trials

>70% of those week 1-4 responders were sustained responders over 26 weeks

Chey WD, et al. Aliment Pharmacol Ther 2017

Eluxadoline in the Clinic

Dosing

- 100 mg BID taken with food
  - 75 mg BID in patients unable to tolerate 100 mg BID, receiving concomitant OATP1B1 inhibitors, who have mild or moderate hepatic impairment

Discontinuation due to constipation

0.2%, 1.1%, and 1.7% with placebo, eluxadoline 75 mg, and 100 mg, respectively

- **Sphincter of Oddi spasm**
  0.5% (8/1666) patients receiving eluxadoline;
  7/8 with 100 mg dose; ALL without gallbladder

- **Pancreatitis**
  0.3% (5/1666); 3 associated with heavy alcohol use, 1 biliary sludge, 1 sphincter of Oddi spasm

- **Contraindications**
  - Bile duct obstruction
  - Sphincter of Oddi dysfunction
  - History of pancreatitis
  - Severe liver impairment
  - Severe constipation
  - Consumption of >3 alcoholic drinks/day

VIBERZI (eluxadoline) [prescribing information]. Actavis Pharma, Inc.; Parsippany, NJ: 2016.

Rifaximin for Global Improvement in IBS: A meta-analysis

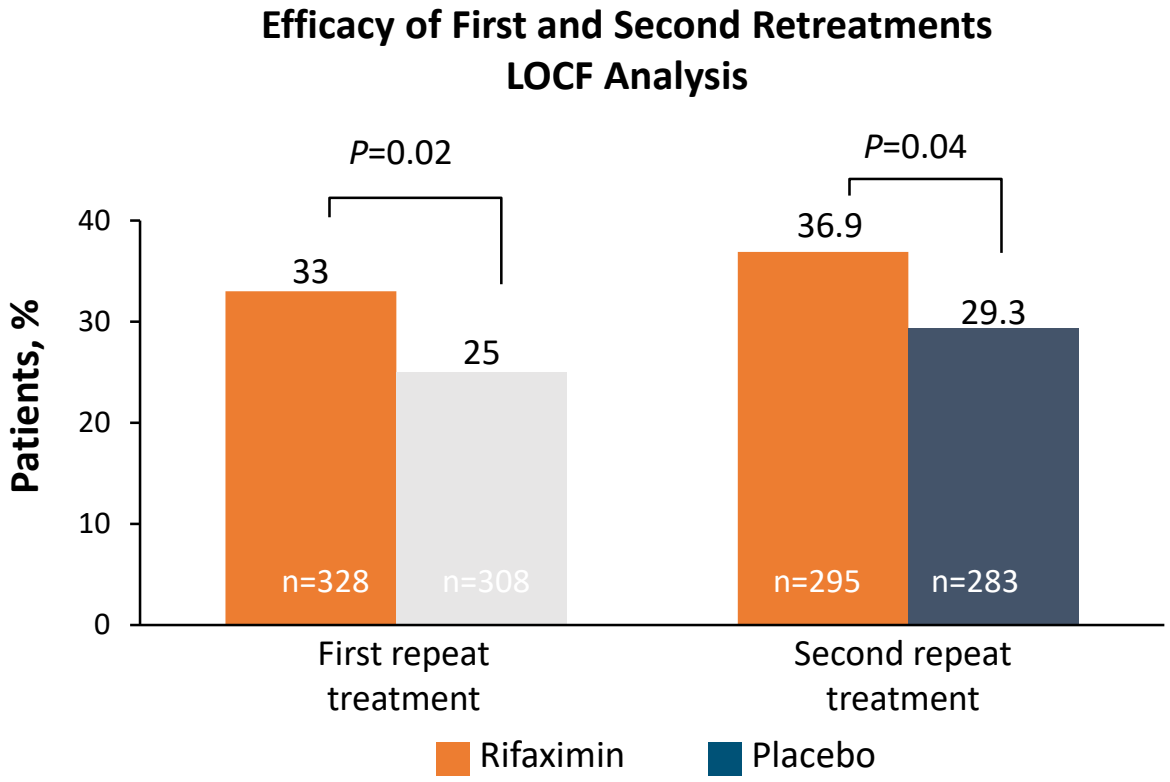
Measure Outcomes	Response rates (%)		Weight	ARR	NNT
	Rifaximin	Placebo			
Sharara	27.0	9	1.4%	18%	5.6
Pimental	32.5	9	1.6%	23.5%	4.3
Lembo	52.3	44.2	25.2%	8.1%	12.3
Target 1	40.8	31.2	34.9%	9.6	10.4
Target 2	40.6	32.2	36.8%	8.4	11.9
Overall	**43.3**	**34.2**	**100%**	**9.1**	**11.0**

Heterogeneity: $\chi^2=5.26$, $df=4$ $I^2=24\%$ $p=0.26$

Menees et al. Am J Gastroenterol 2012;107:28-35

TARGET 3:

Efficacy of First and Second Retreatments



- **Urgency and bloating improved significantly with both repeat treatments**
- **Abdominal pain and stool consistency improved significantly with first retreatment**
- **At time of recurrence, IBS-D symptoms were less severe compared to symptoms at onset of study**

LOCF, last observation carried forward.
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. Gastroenterol 2016;151(6):1113-1121

Rifaximin in the Clinic

Dosage

550 mg TID for 2 weeks

Recurrence of symptoms can be retreated up to 2 times with the same regimen[1]

Contraindications

History of hypersensitivity to rifaximin, rifamycin, or any component of rifaximin

Most Common Reported Adverse Events (≥2%)*[2]

Adverse Events	Rifaximin 550 mg (n=1,008)	Placebo (n=829)
	n (%)	
Headache	55 (5.5)	51 (6.2)
URT infection	45 (4.5)	47 (5.7)
Nausea	41 (4.1)	31 (3.7)
Abdominal pain	40 (4.0)	39 (4.7)
Diarrhea	35 (3.5)	26 (3.1)
Urinary tract infection	32 (3.2)	18 (2.2)

Pooled safety analysis demonstrated no difference between rifaximin and placebo for any adverse event[2]

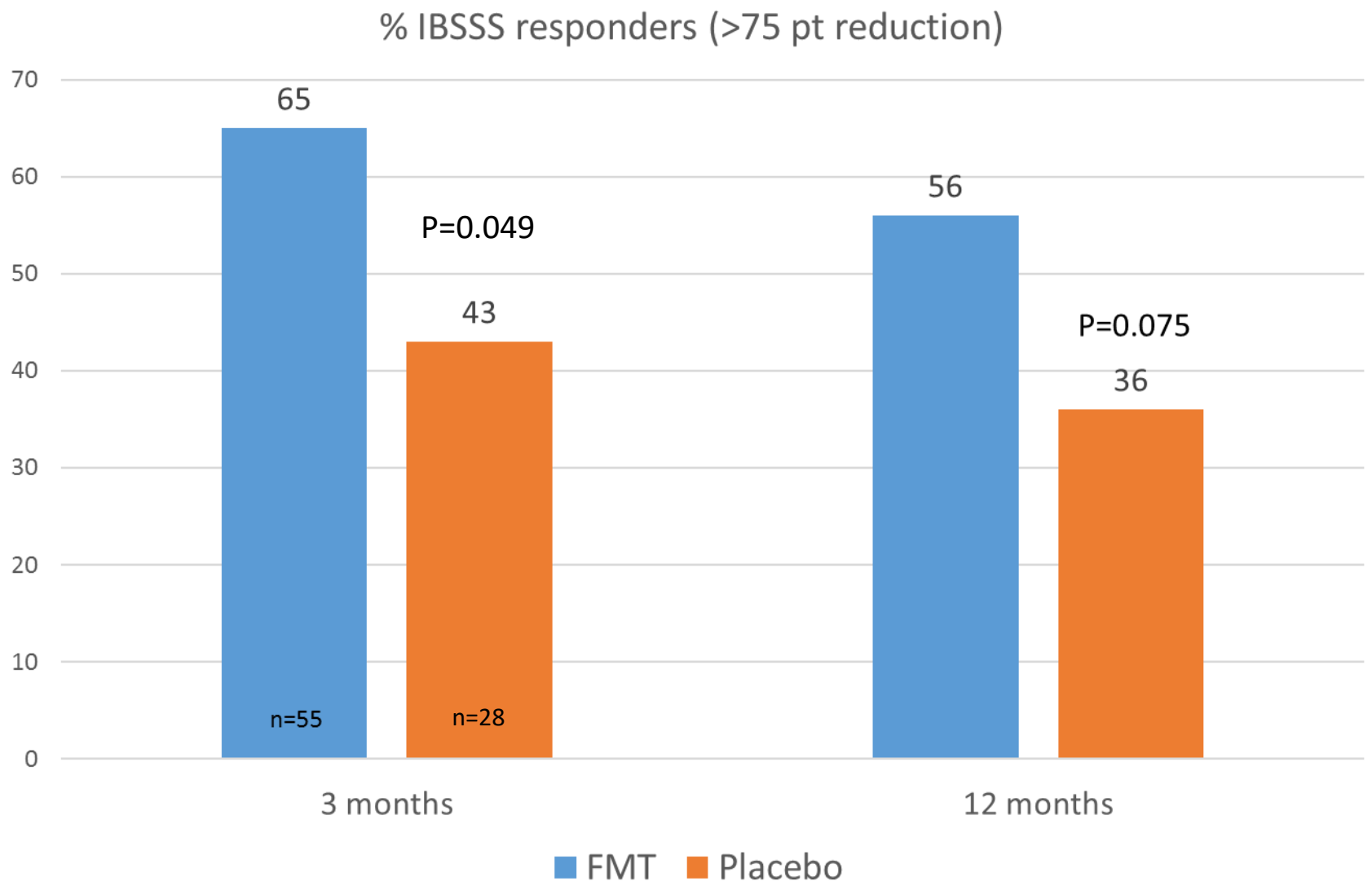
*Pooled analysis of Phase 2b and 3 trials of rifaximin in non-IBS C

TID, three times daily; URT, upper respiratory tract.

1. XIFAXAN® (rifaximin) [prescribing information]. Salix Pharmaceuticals; Raleigh, NC: May 2015;

2. Schoenfeld P, et al. *Aliment Pharmacol Ther*. 2014;39:1161-1168.

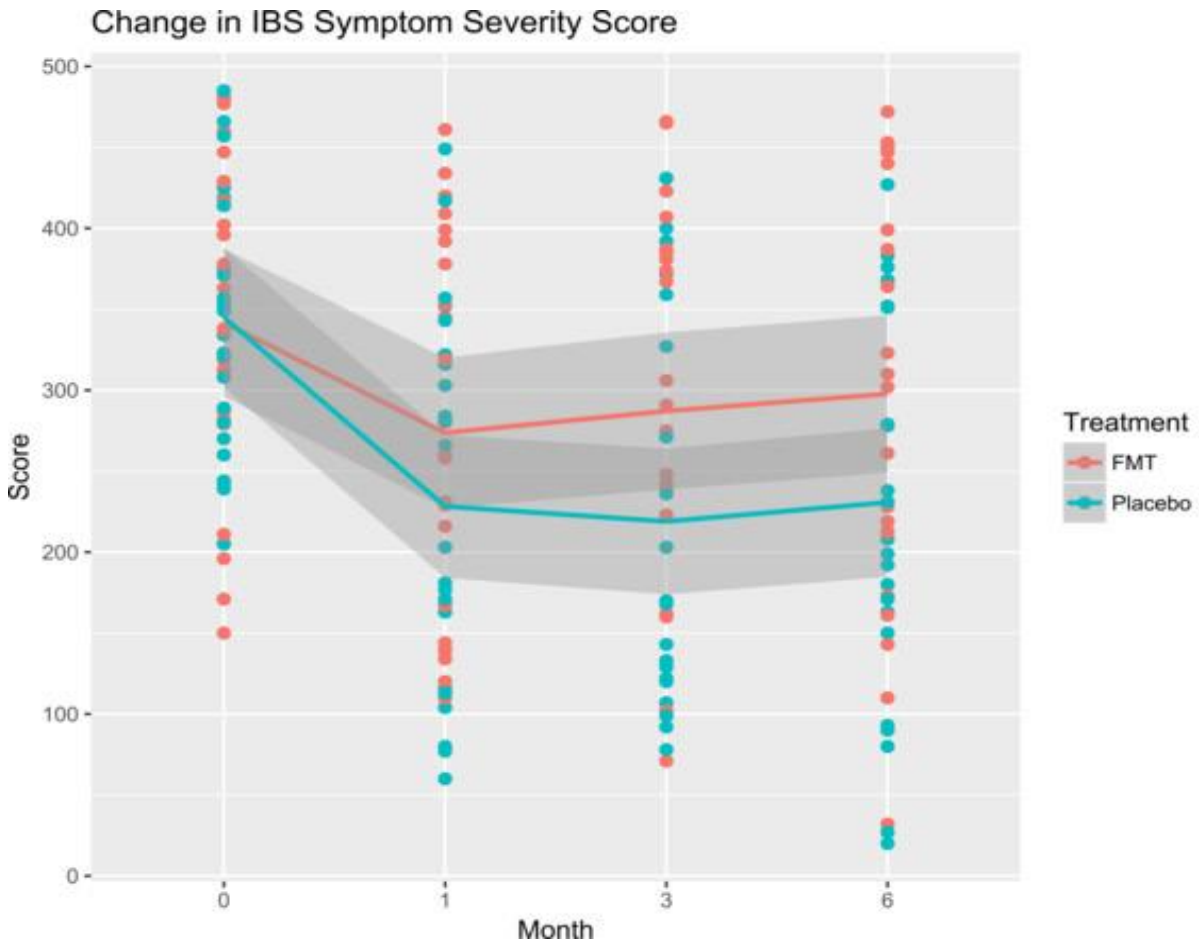
FMT for NC-IBS: First RCT data

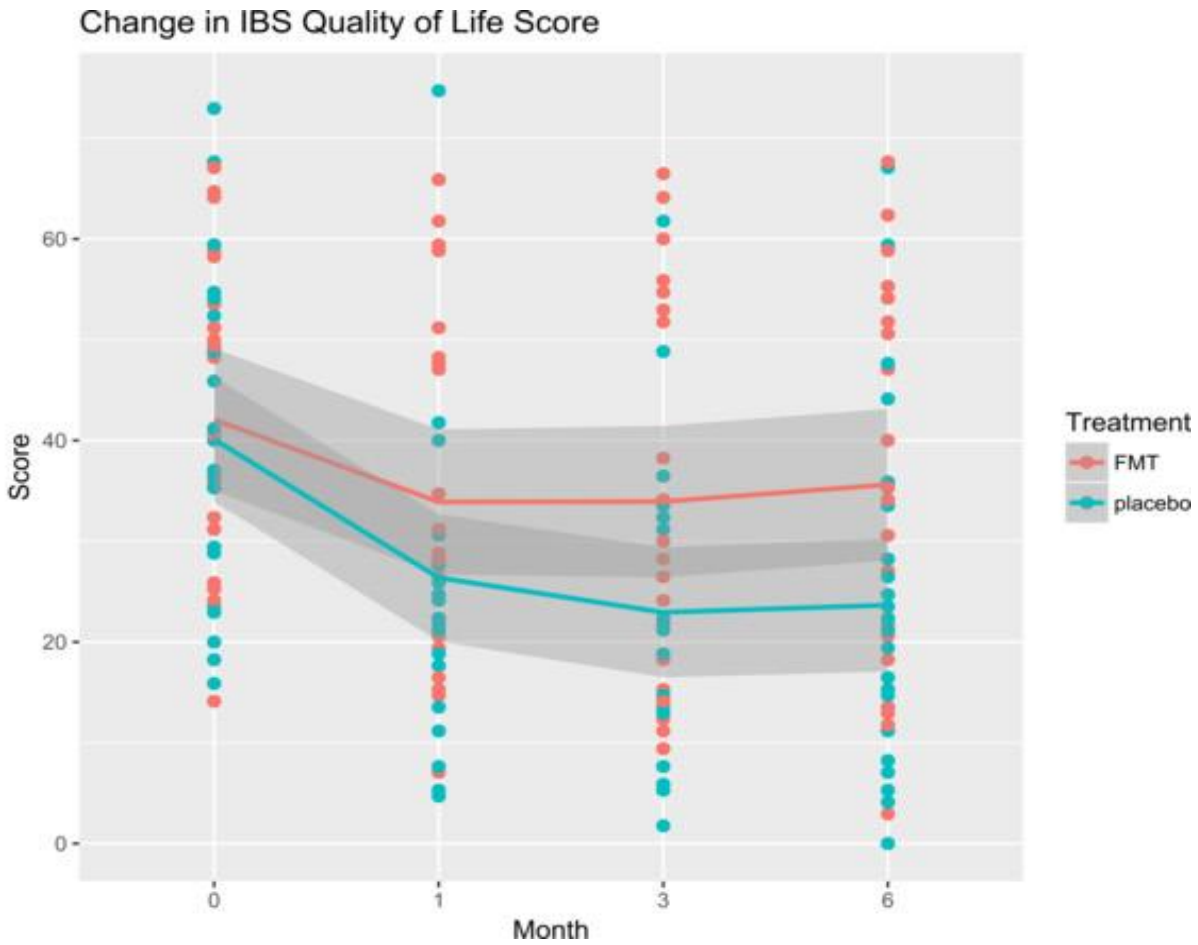


- 90 Norwegian moderate to severe NC-IBS pts randomized to FMT (fresh or frozen donor stool) or placebo (pts own stool)
  - Loperamide given at time of transplant
  - Delivered via colonoscopy

Holger et al. Lancet Gastroenterol Hepatol 2018

FMT for IBS: RCT from Denmark





52 mod to severe IBS got FMT or placebo capsules
Followed for 6 months

Significant stool microbiome changes noted

Halkjaer et al. Gut 2018;67:2107–2115

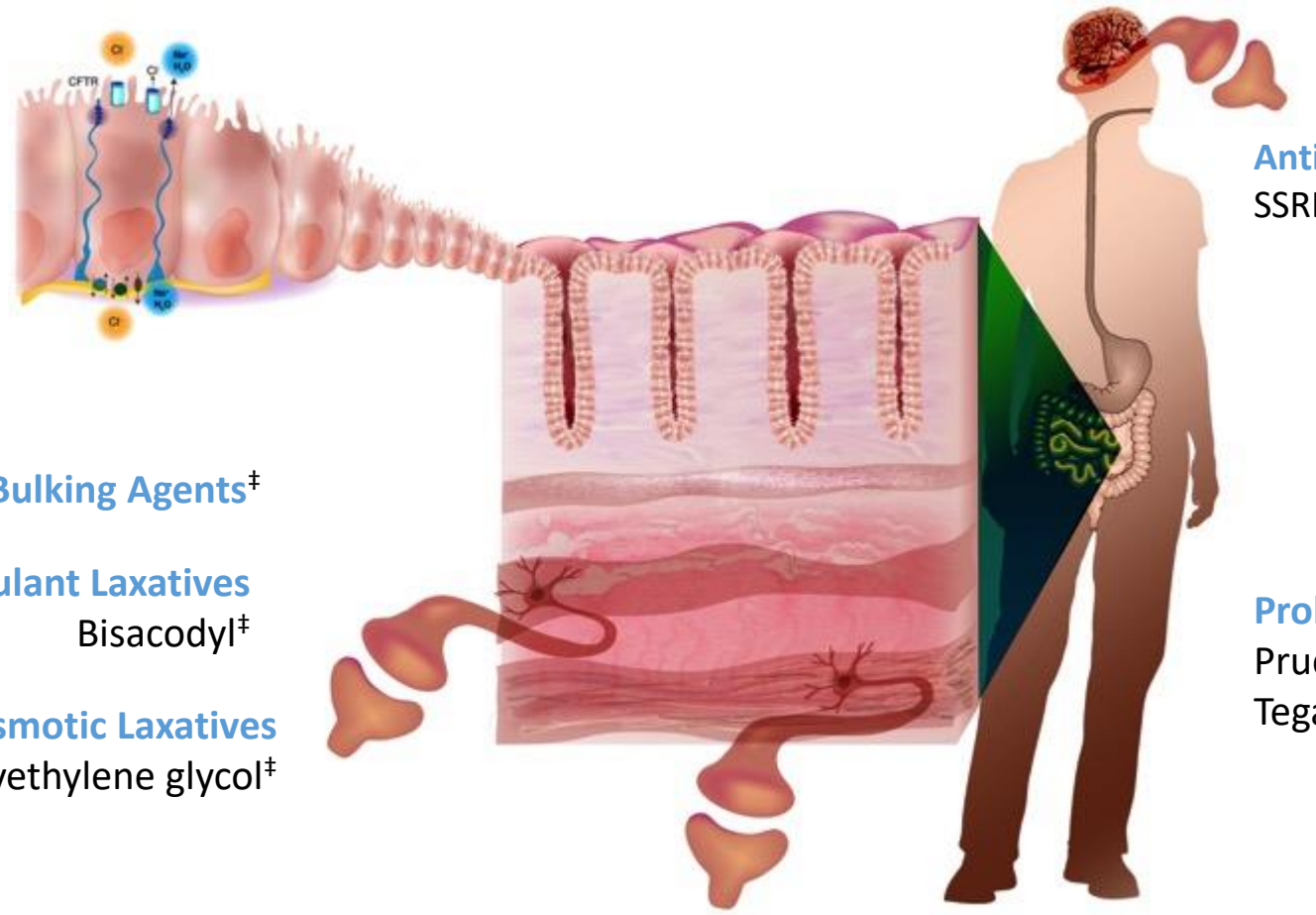
FMT for IBS: Systematic Review & Meta-analysis

- 4 studies involving 254 participants met eligibility
- No significant difference in global improvement of IBS symptoms was observed at 12 weeks in FMT vs placebo
  - RR = 0.93; 95% CI 0.48–1.79
  - Significant heterogeneity (I^2 = 79%)
  - Study quality deemed 'very low'
  - Colonic or NJ delivery may be more effective than oral capsules
  - Placebo response over 60% with oral capsules
- **Bottom Line: Current evidence from RCTs does not suggest a benefit of FMT for global IBS symptoms**

Xu, et al. Am J Gastroenterol in press

Overview of IBS-C/CIC Therapies

Prosecretory Agents
Lubiprostone*
Linaclotide†
Plecanatide†



Fiber/Bulking Agents‡

Stimulant Laxatives
Bisacodyl‡

Osmotic Laxatives
Polyethylene glycol‡

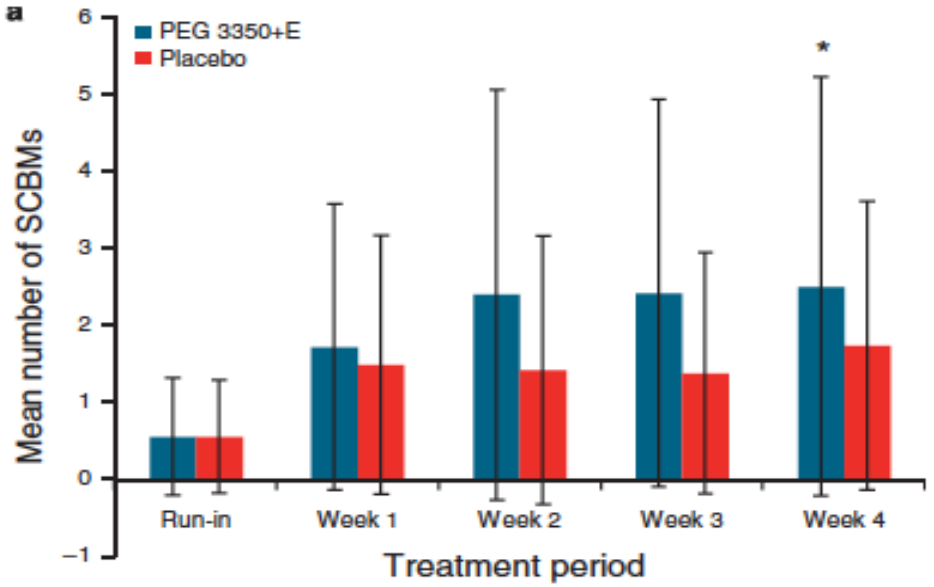
Antidepressants
SSRIs¶

Prokinetics
Prucalopride*
Tegaserod*

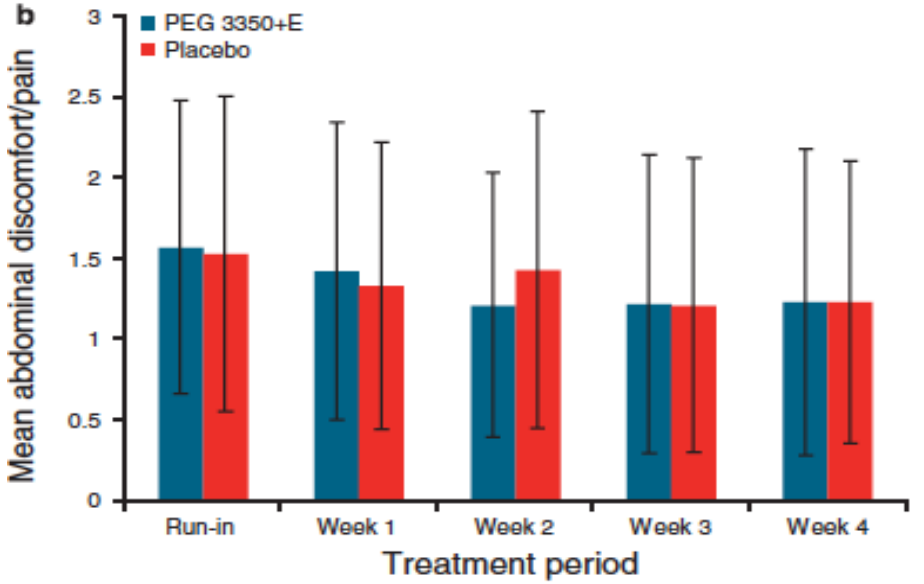
*FDA-approved for CIC in adults and IBS-C in women ≥18 years of age; †FDA-approved for CIC and/or IBS-C; ‡Approved for occasional constipation; ¶Not FDA-approved for CIC or IBS-C.

Polyethylene Glycol for IBS-C: Results from an RCT

Spontaneous Complete Bowel Movements



Abdominal Discomfort/Pain



N=143 *P<0.0001

<u>ACG Task Force Recommendation:</u>

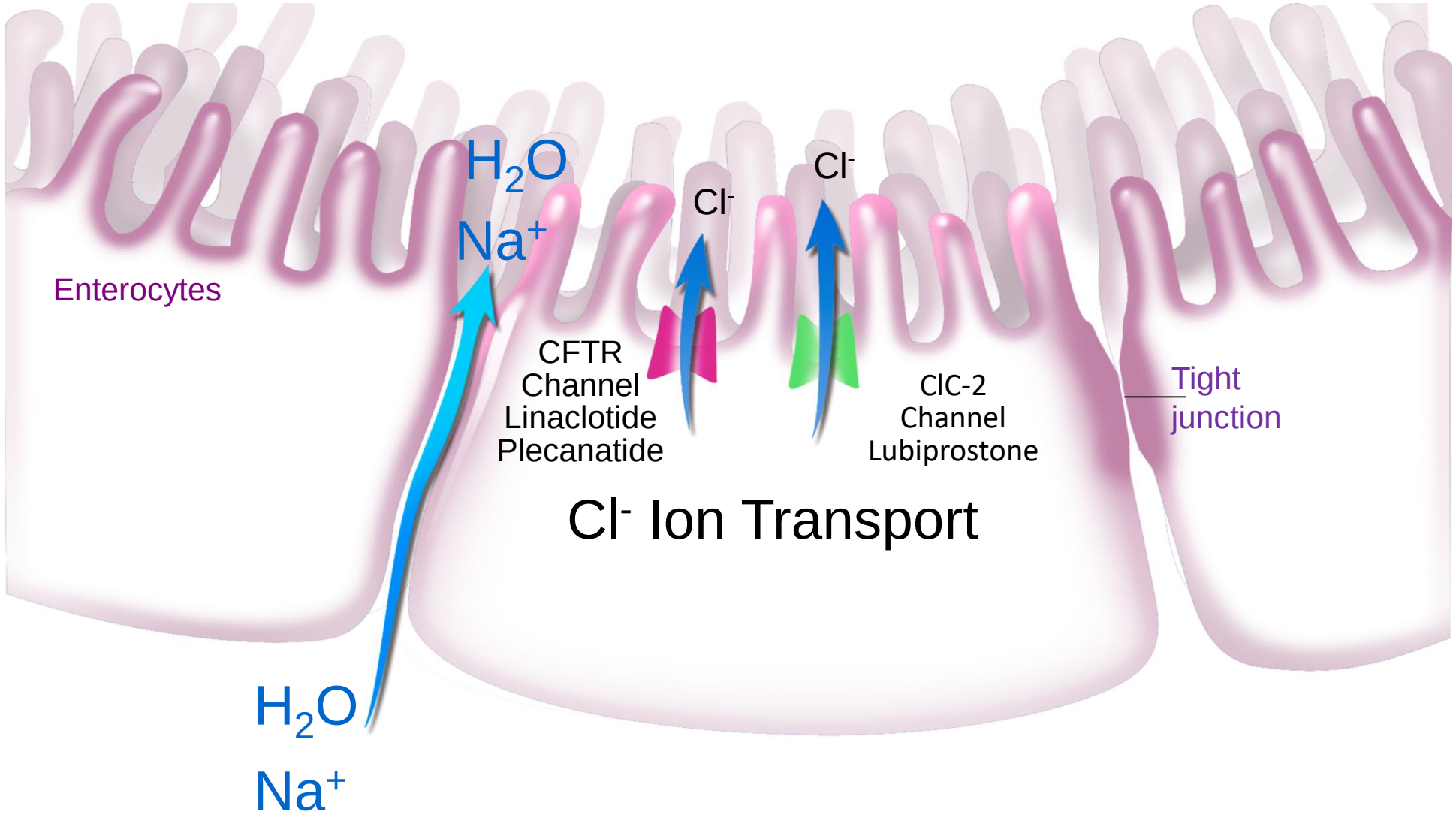
There is no evidence that PEG improves overall symptoms and pain in patients with IBS

Recommendation: weak

Quality of evidence: very low

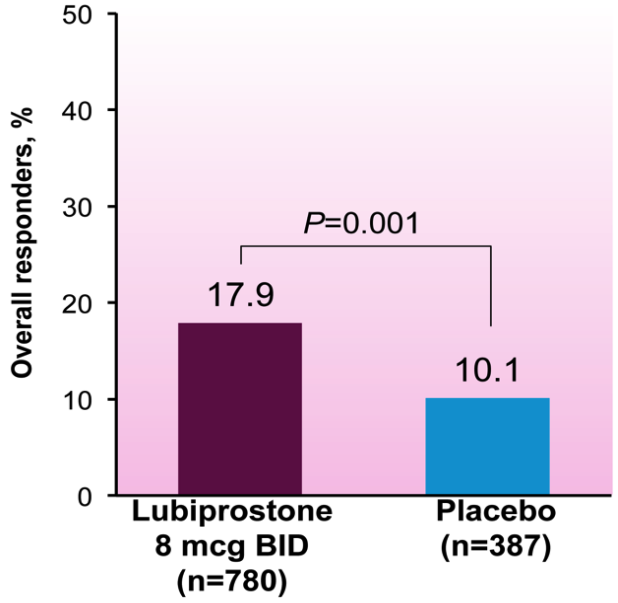
Chapman RW, et al. Am J Gastroenterol. 2013, Ford et al. Am J Gastroenterol 2014; 109:S2–S26

Intestinal Chloride Channels

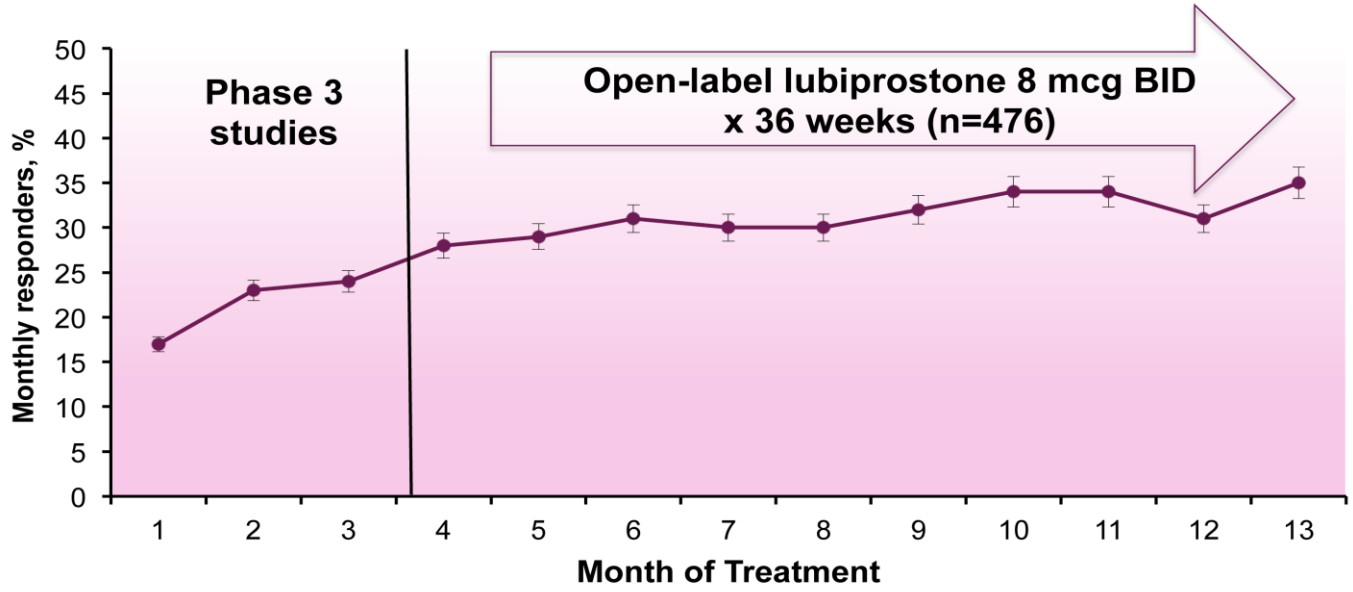


Lubiprostone for IBS-C

Overall Responders
at 12 Weeks
in Phase 3 Trials[1]*



Monthly Responder Rates
in Randomized Withdrawal/Extension Studies[2]



*Defined as monthly responder for ≥2 of 3 months. Monthly responder defined as having at least moderate relief for 4 of 4 weeks or significant relief for 2 of 4 weeks.

1. Drossman DA, et al. Aliment Pharmacol Ther. 2009;29:329-341.
2. Chey WD, et al. Aliment Pharmacol Ther 2012;35:587.

Lubiprostone in the Clinic

Dosage for IBS-C
8 µg BID

Dosage for CIC
24 µg BID

Take with food and water to minimize nausea

Most Common Adverse Events in IBS-C and CIC Trials*

Adverse Events	IBS-C		CIC	
	PBO n=435	LUB 8 µg BID n=1,011	PBO n=316	LUB 24 µg BID n=1,113
	%			
Nausea	4	8	3	29
Diarrhea	4	7	1	12
Abdominal pain	5	5	3	8
Abdominal distension	2	3	2	6

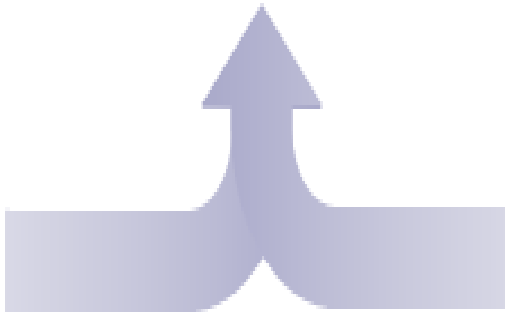
*Includes only those events associated with treatment (possibly or probably related, as assessed by investigator)

Amitiza (lubiprostone) [prescribing information]. Sucampo Pharma Americas, LLC; Bethesda, MD: April 2013.

Linaclotide Phase 3 IBS-C Trial

Composite Responder (FDA Interim Endpoint)

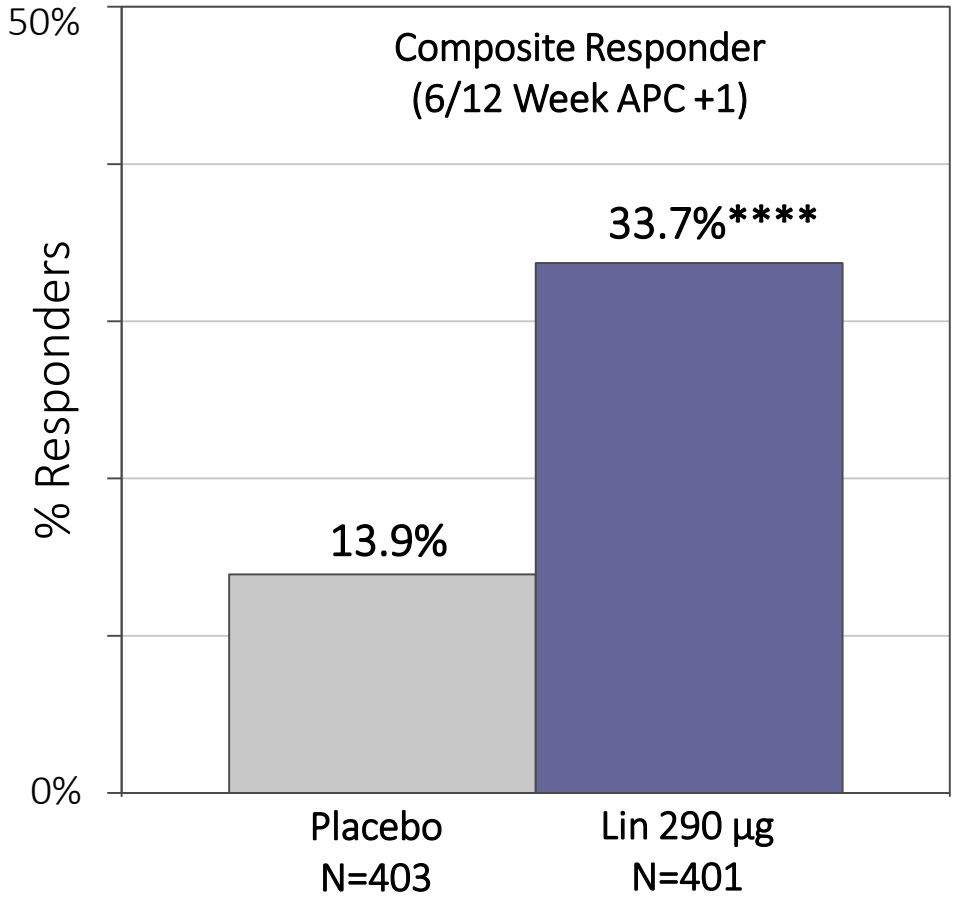
≥30% abdominal pain reduction + increase ≥1 CSBM from baseline; in the same week



Abdominal Pain Responder

CSBM +1 Responder

Most common side effect Diarrhea 18% wks 1-12



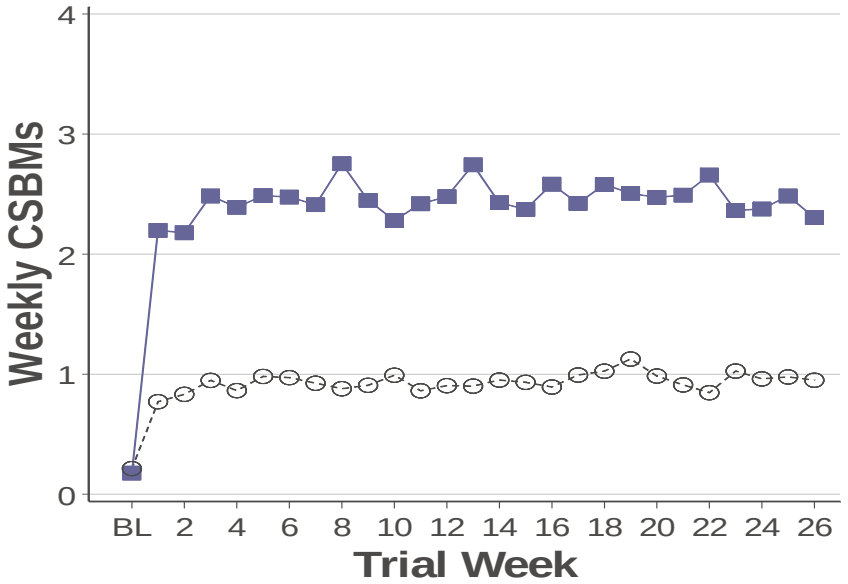
****p< 0.0001, ITT Population (290 µg vs. placebo, CMH test)

Chey et al. Am J Gastroenterol 2012;107(11):1702-12

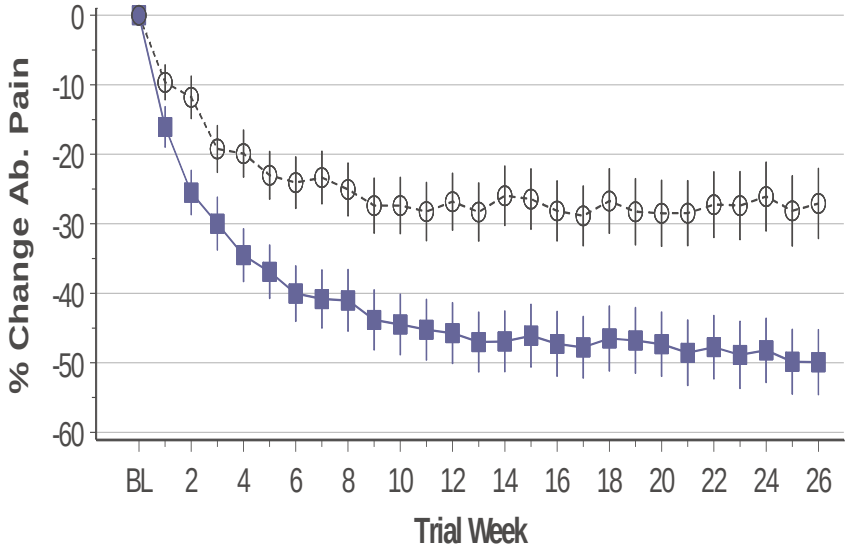
Linaclotide Phase 3 IBS-C Trial

CSBM and Abdominal Pain over 26 weeks

CSBMs



Abd Pain



$p < 0.0001$ for each of the 26 Weeks in the Treatment Period for both SBMs and CSBMs

Treatment Groups
■ 290 µg ○ Placebo

ITT Population, mean weekly rates presented, p-values based on ANCOVA at each week (observed cases)

Chey et al. Am J Gastroenterol 2012;107(11):1702-12

Linaclotide in the Clinic

Dosage

CIC: 145 µg once daily

IBS-C: 290 µg once daily

- Take on empty stomach ≥30 minutes before first meal of the day
- Can mix with water or applesauce for dose reduction or patients with difficulty swallowing
- Not approved for patients <18 years of age

Common GI Adverse Events in IBS-C and CIC Trials*

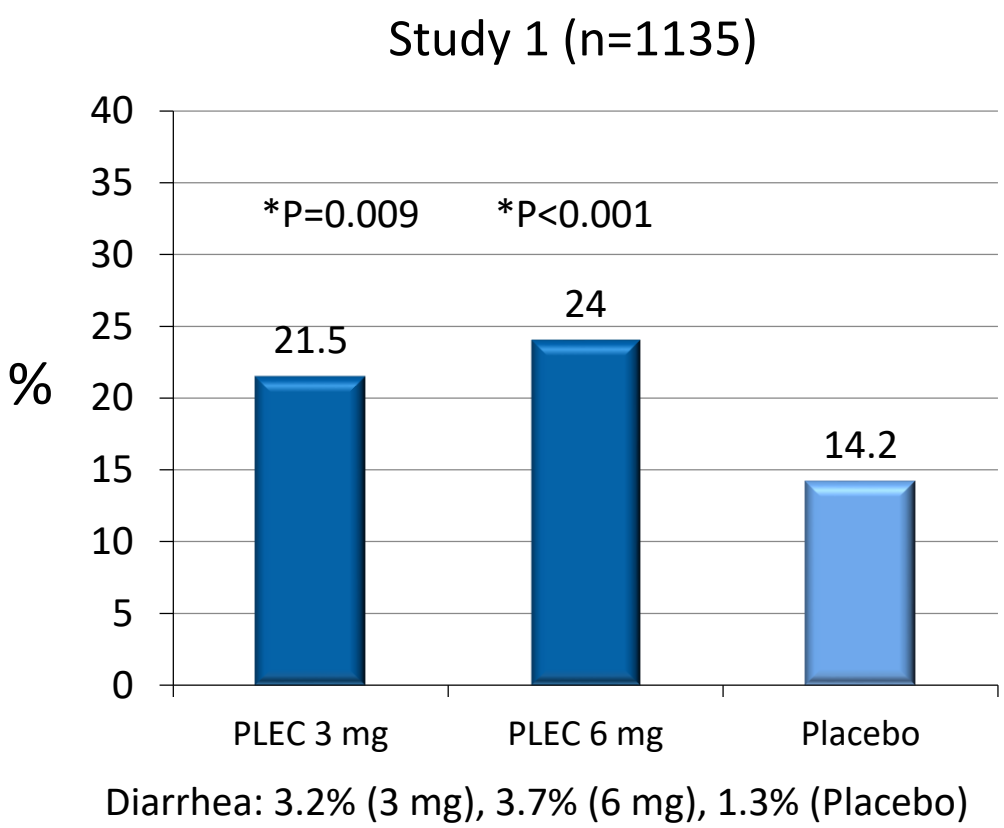
	IBS-C		CIC	
	PBO n=798	LIN 290 µg n=807	PBO n=423	LIN 145 µg n=430
Adverse Event	%			
Diarrhea	3	20	5	16
Abdominal pain†	5	7	6	7
Flatulence	2	4	5	6
Abdominal distension	1	2	2	3

*Occurring in ≥2% of linaclotide-treated patients and at an incidence greater than placebo.

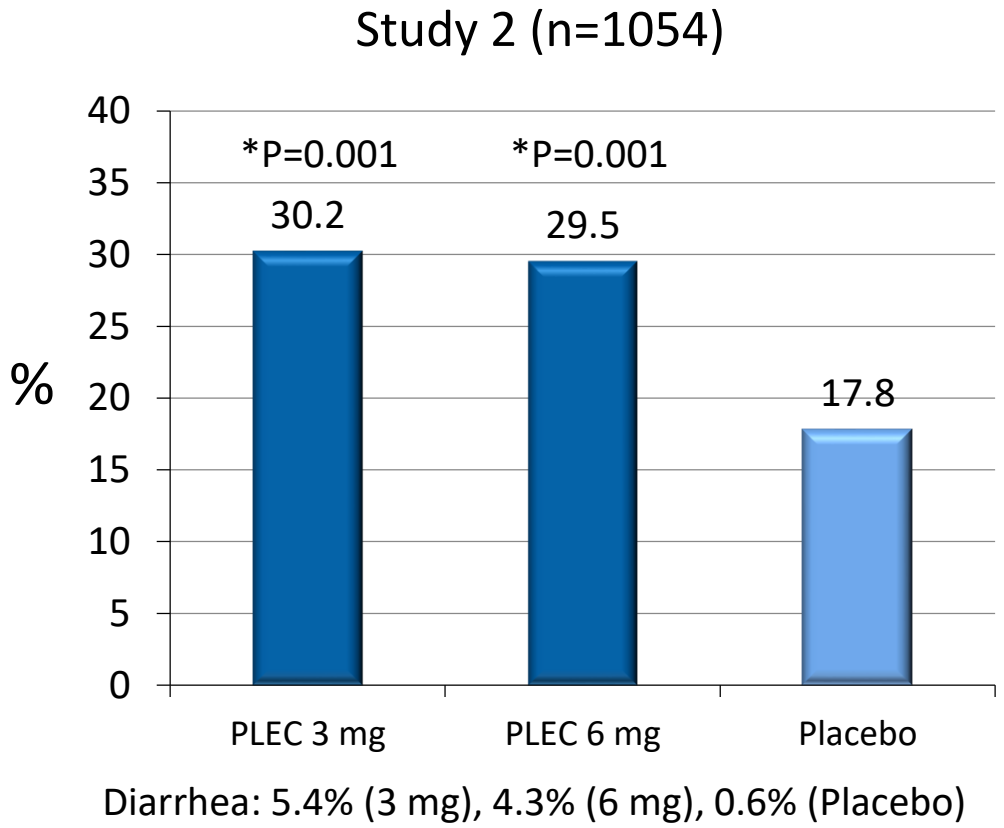
†Includes abdominal pain, upper abdominal pain, and lower abdominal pain.

LINZESS (linaclotide) [prescribing information]. Forest Pharmaceuticals, Inc. St. Louis, MO: July 2014.

Plecanatide Improved Overall Responder Rate vs Placebo in IBS-C Phase 3 RCTs



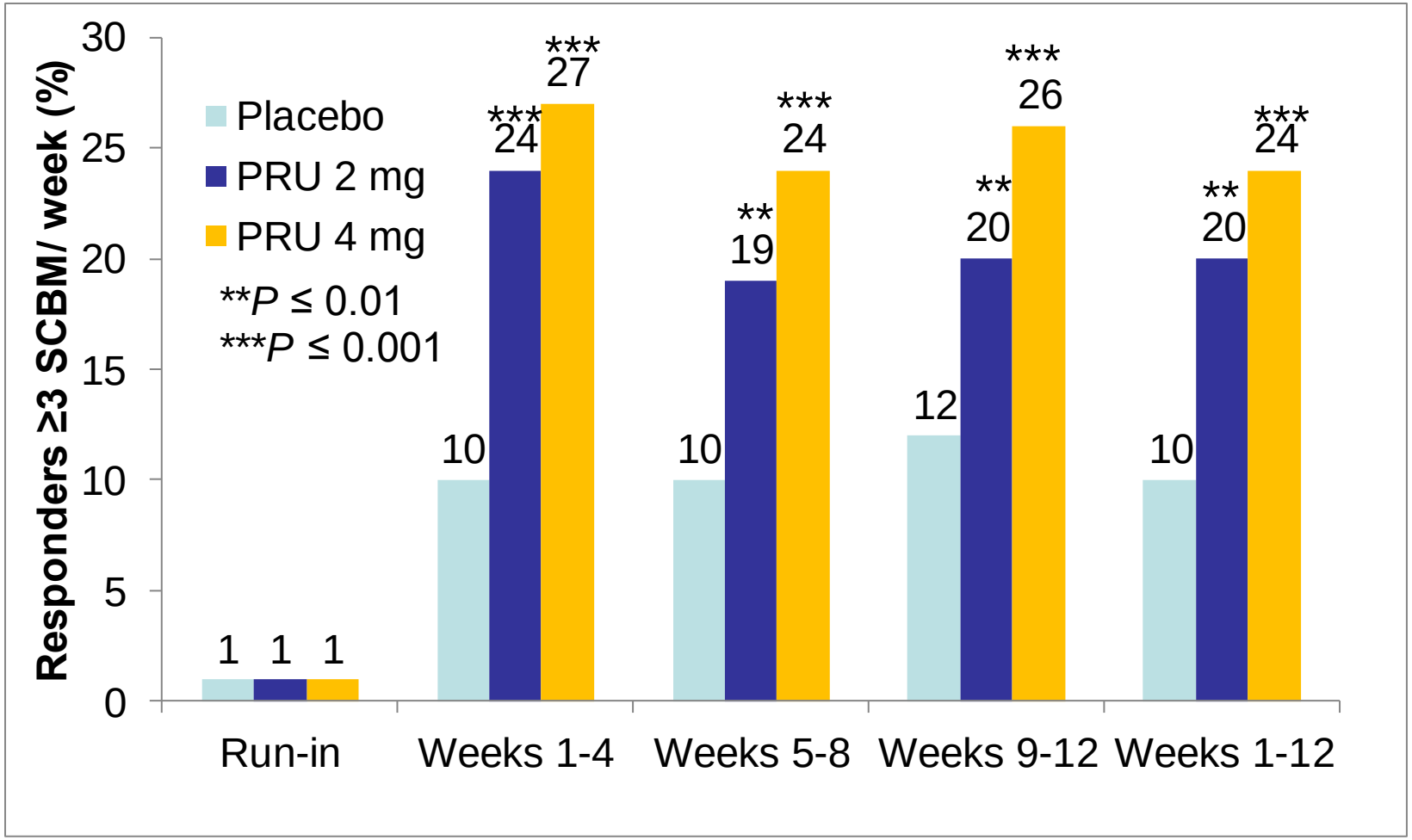
Diarrhea: 3.2% (3 mg), 3.7% (6 mg), 1.3% (Placebo)



Diarrhea: 5.4% (3 mg), 4.3% (6 mg), 0.6% (Placebo)

Miner PB et al. Am J Gastroenterol 2017;112:613-621

Prucalopride for Chronic Constipation
Results from a Phase III RCT



ITT Population = 713 pts

Laxative use and QoL improved with prucalopride

Tack J, et al. *Gut*. 2009;58:357-365.

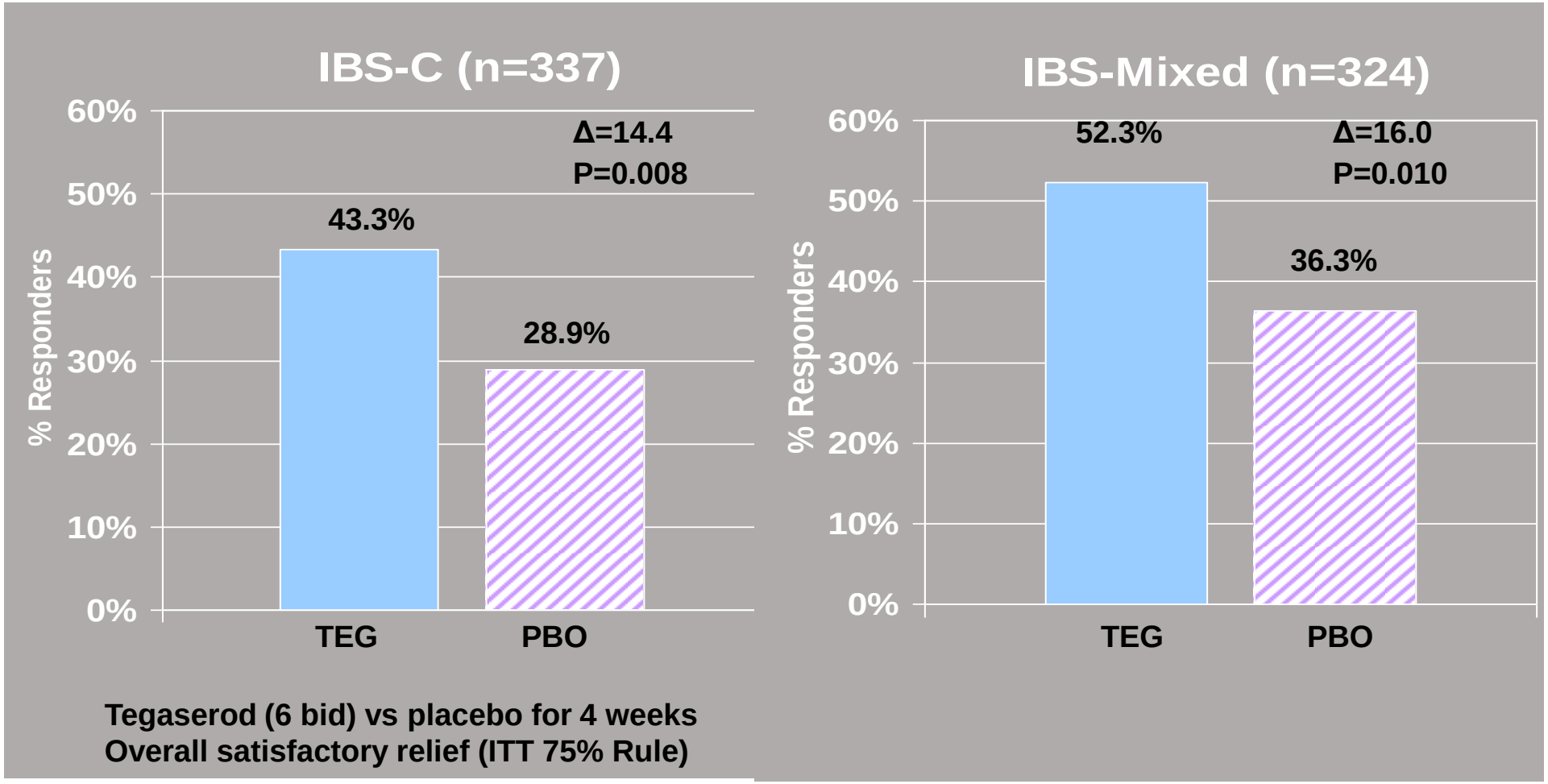
Phase III Studies of Prucalopride for Chronic Constipation: Adverse Events

AE	% Reported	
	Prucalopride	Placebo
Headache	25-30%	12-17%
Nausea	12-24%	8-14%
Diarrhea	12-19%	3-5%
SAE	2.7%	2%
Discontinuation	4-15%	2-7%

Prucalopride 2 or 4 mg QD
No effect on vital signs or ECG parameters.

Tack J, et al. *Aliment Pharmacol Ther*. 2012;35:745-767.

Tegaserod for IBS-C and IBS-M: Results from a multi-center RCT

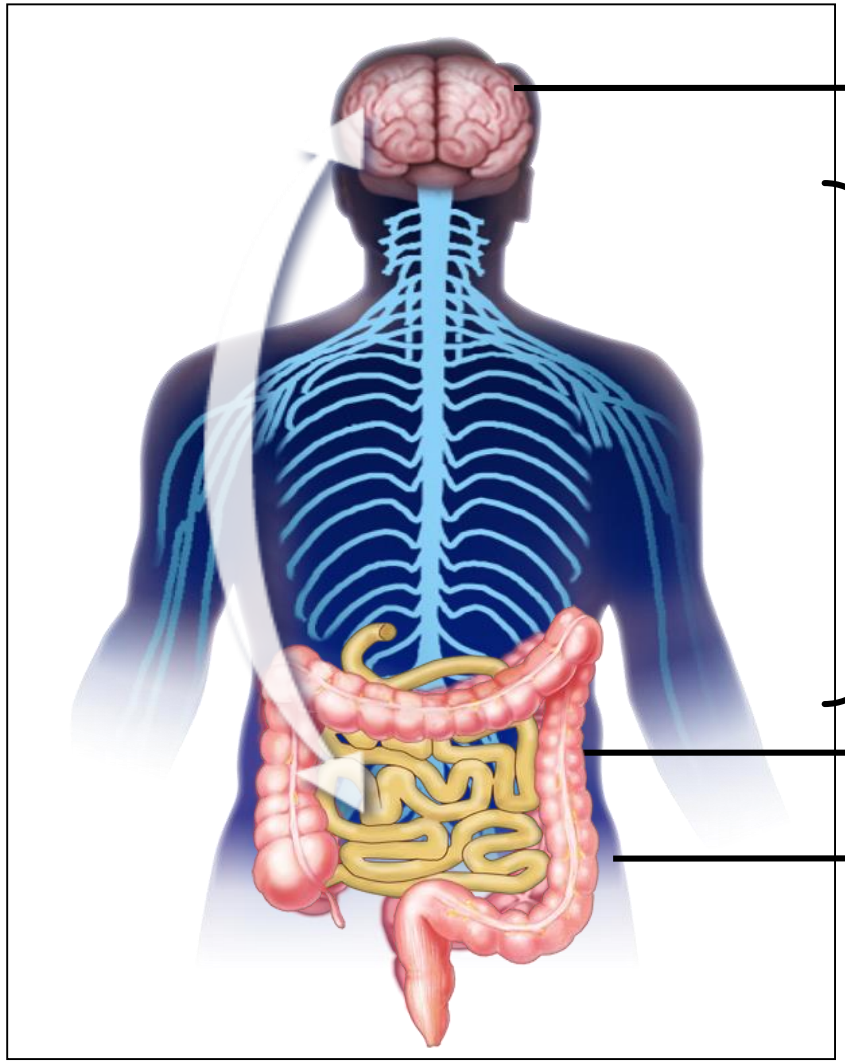


Tegaserod (6 bid) vs placebo for 4 weeks
Overall satisfactory relief (ITT 75% Rule)

Chey, et al. Am J Gastroenerol 2008

Centrally Acting Therapies for IBS

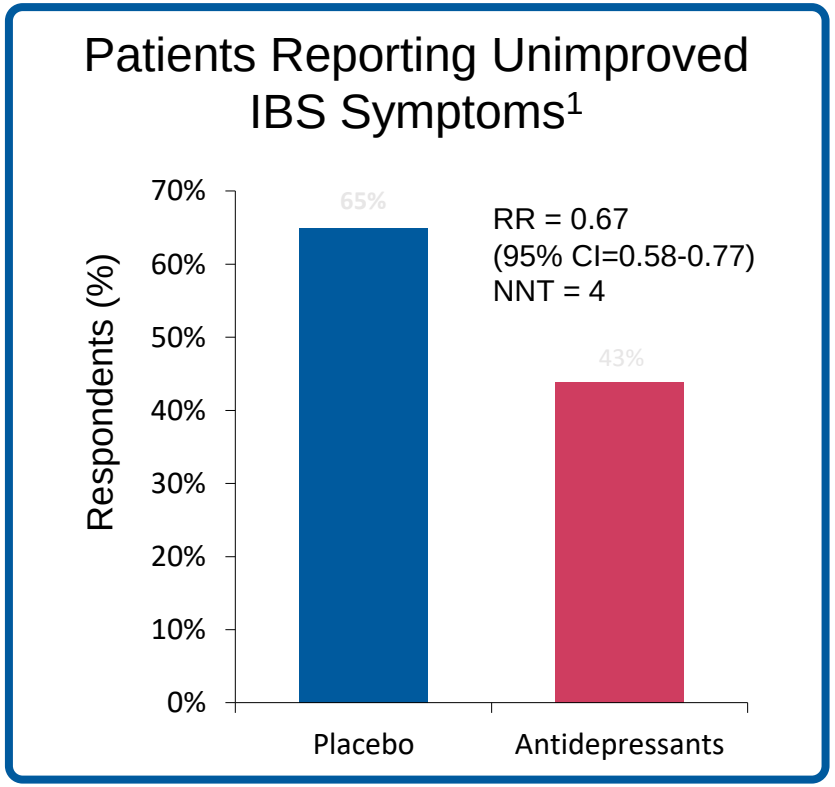
Antidepressant Action in IBS



Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

Antidepressants for IBS

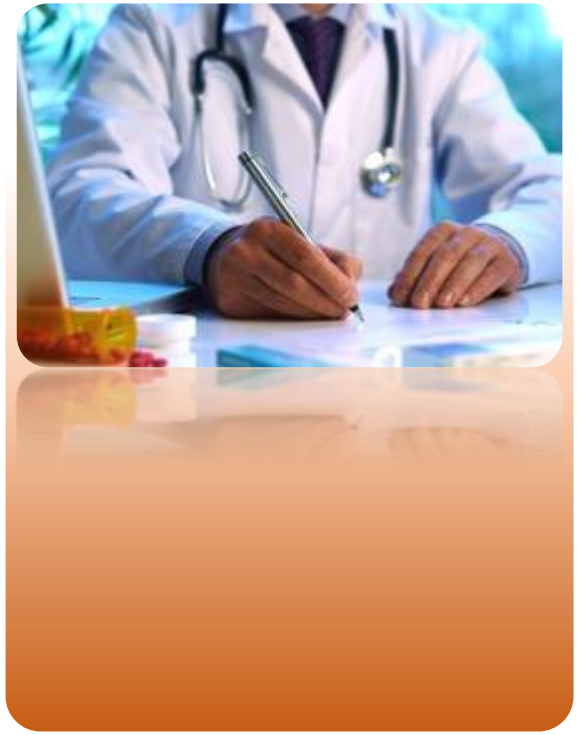
- Effective at reducing IBS symptoms and abdominal pain[1]
- Adverse effect profiles may guide use in IBS subtypes[2]
  - TCAs may cause constipation and may best suited for patients with IBS-D
  - SSRIs may cause diarrhea and may be best suited for patients with IBS-C



RR=relative risk; SSRI=selective serotonin-reuptake inhibitor; TCA=tricyclic antidepressant.

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

General Approach to Prescribing Antidepressants in IBS



- Consider specific symptoms[1,2]
  - TCAs in IBS-D, SSRIs in IBS-C
  - TCAs?SNRI for pain
  - 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.

Psychological Therapies for IBS
Subgroup analysis according to type of therapy

	Trials	N	RR 95% CI	NNT 95% CI
Cognitive behavior therapy	7	491	0.60 0.42 – 0.87	3 2 – 7
Relaxation training	5	234	0.82 0.63 – 1.08	
Dynamic psychotherapy	2	273	0.60 0.39 – 0.93	3.5 2 – 25
Hypnotherapy	2	40	0.48 0.26 – 0.87	2 1.5 – 7

Ford AC et al. Gut 2009;58:367

Summary

- An integrative care model which incorporates diet, behavior, and medications maximizes clinical outcomes
- At present, treatment is chosen based upon an IBS patient's most bothersome symptoms
- The heterogeneous pathogenesis of IBS explains the marginal therapeutic gains of drugs targeting specific mechanistic pathways

- In the future, biomarkers will allow subgrouping of IBS patients based upon symptoms AND aberrant pathophysiology which will allow migration from a treatment strategy based upon empiric therapy to a precision medicine model

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