2nd Annual GI ReConnect

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GI Health Foundation

GI ReConnect

New Advances in IBS-C Management: Treatment and Diagnosis

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Disclosure Statement

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Faculty Disclosures

- Consultant: Alnylam Pharma
- Research Support: Bausch Pharmaceuticals, Takeda
- Speaker: Nestle, Salix
- Advisory Committee: Allergan, Bausch Pharmaceuticals, Progenity, Takeda
- Intellectual Property/ Patents: GI Pill

Educational Objectives

1. Recognize symptoms related to IBS-C and describe strategies for diagnosis
2. Which patient needs anorectal physiology testing?
3. What evidence is there for the efficacy and safety of current therapies available for IBS-C
4. How does patient-centered care get implemented?

Principles of IBS Management

- Exclude organic GI disease
- Make a *positive* diagnosis
- Establish a rapport with patient; educate and reassure
- Categorize IBS subtype based on prevalent stool form (BSFS)

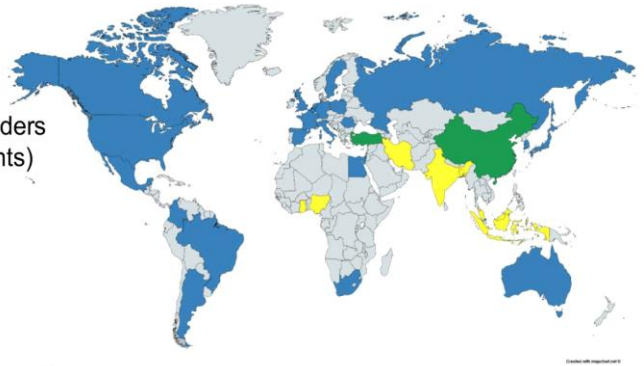
- **First line:** lifestyle and dietary modifications and OTC therapies targeting abnormal stool form/most bothersome symptoms
- Escalate to FDA approved/validated therapies
- Non-FDA/off-label/psychological therapies

BSFS, Bristol Stool Form Scale; FDA, Food and Drug Administration; OTC, over-the-counter.

Lacy B. et al. ACG Guidelines for IBS. AJG. 2021

IBS and CIC prevalence Globally

Disorders of Gut-Brain interaction- Largest Ever Global Epidemiology Study



A global epidemiological study of functional GI disorders

- 73,076 adults surveyed (33 countries, 6 continents)
- Data collection: By Internet (24 countries, blue), by household interview (7 countries, yellow), or both methods (China and Turkey, green).

Prevalence of meeting criteria for at least one of 22 functional GI disorders (%):

	All Participants	Females	Males
Internet surveys	40.3	46.5	34.2
Household surveys	20.7	23.1	18.3

Gastroenterology

Wake Forest School of Medicine

Atrium Health

Sperber A et al. Gastroenterology 2021

IBS and CIC prevalence

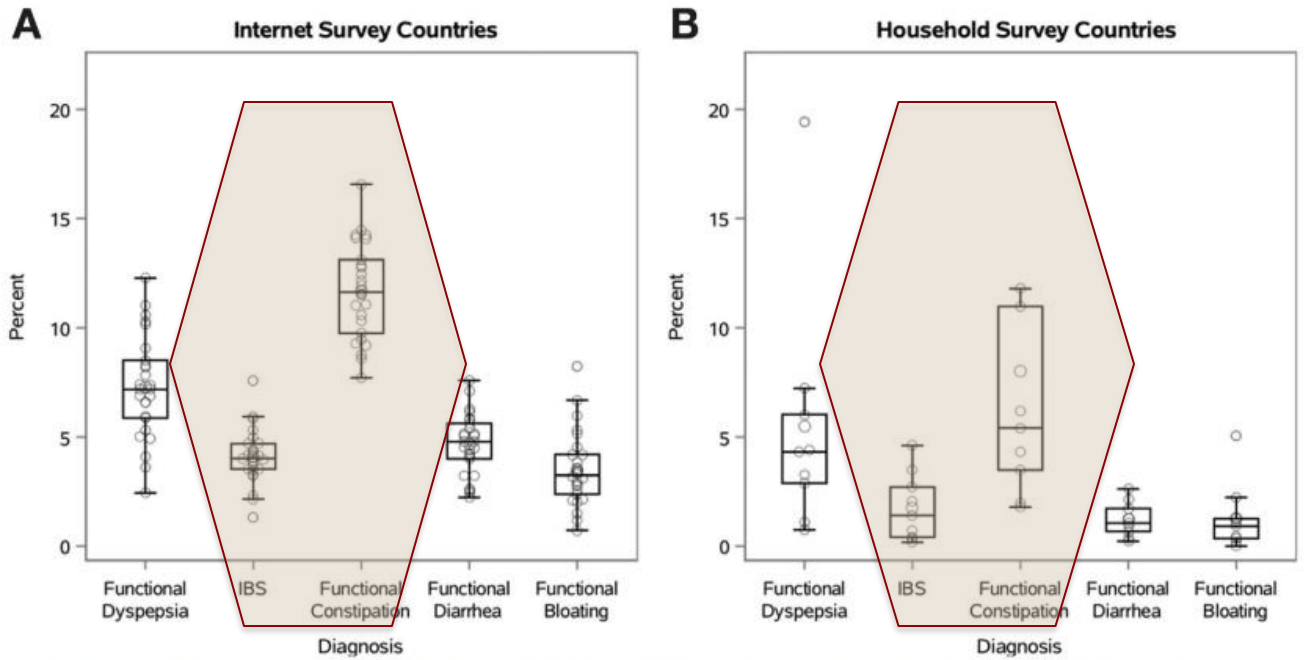


Figure 3. Distribution of country-specific (*circles*) and pooled (*boxes*) prevalence rates for 5 selected major FGIDs in the countries surveyed by Internet (N = 26) and household interviews (N = 9) with Rome IV criteria.

Sperber A et al. Gastroenterology 2021

IBS symptoms are stable over time regardless of treatments

- Among individuals meeting the Rome IV criteria at baseline, almost 30% fluctuated to another functional bowel disorder at 12 months, the majority of whom met the criteria for functional diarrhea.(Not FC)
- IBS of any subtype is unstable and treatments are not responsible for the instability between subtypes
- IBS-C was the most stable of subtypes
- IBS-M was the most unstable with respect to ROME IV but then also the most stable with respect to ROME III

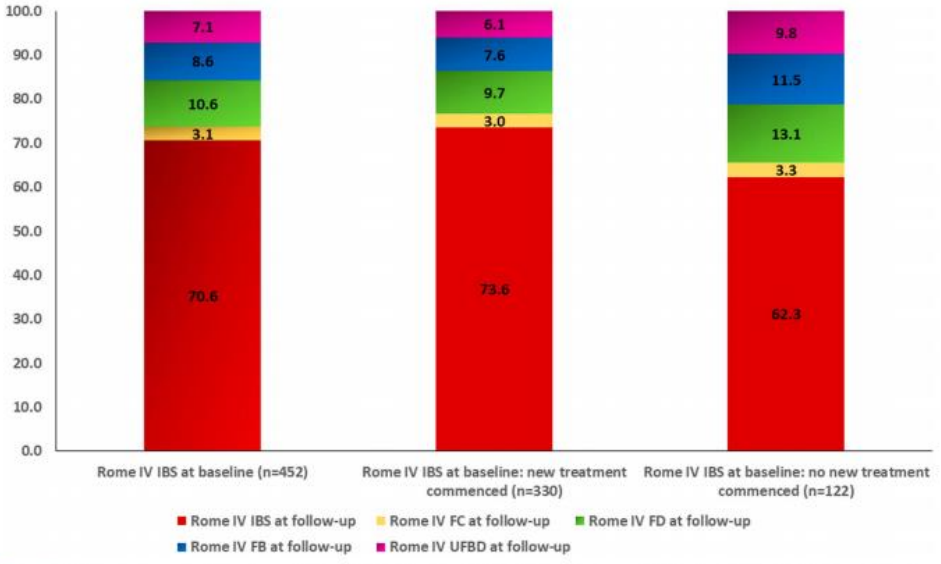


Figure 1. Stability of a diagnosis of IBS in those with Rome IV IBS at baseline. IBS, irritable bowel syndrome. FB, functional abdominal bloating or distension; FC: functional constipation; FD: functional diarrhea; UFBD: unspecified functional bowel disorder.

Barberio B et al. Am J Gastroenterol 2021;116:362–371

ACG Clinical Guidelines: 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]

All IBS Subtypes[1]

CBC
Age-appropriate CRC screening

IBS-D[1, 2]

- Fecal calprotectin &/or CRP, +/- Lactoferrin
- IgA TtG ± quantitative IgA
- Rule out Giardiasis if high risk factors exist
- When colonoscopy performed, obtain random biopsies
- Age 45 and up indicated

IBS-M[1, 2]

- Stool diary/ abdominal plain film to assess for fecal loading

IBS-C[1, 2]

Anorectal physiology testing

We suggest that anorectal physiology testing be performed in patients with IBS and symptoms suggestive of a pelvic floor disorder and/or refractory constipation not responsive to standard medical therapy. Consensus recommendation; unable to assess using GRADE methodology.

*__Alarm features__ include age ≥50 years old, blood in stools, nocturnal symptoms, unintentional w eight loss, change in symptoms, recent antibiotic use, and family history of organic GI disease.

CBC, complete blood count; CRC, colorectal screening; CRP, C-reactive protein; SeHCAT, selenium homocholic acid taurine; Ttg, tissue transglutaminase.

Lacy BE, Pimentel M, Brenner DM, Chey, BD, Keefer LA, Long MD, & Moshiree B et al. ACG Clinical Guideline: Management of IBS. *AJG*. 2021; Moshiree B. Satish SS. *Journal of Family Practice*. 2021

Prevalence of PFDs

- Urinary, fecal incontinence and pelvic organ prolapse are most common PFDs.
  - 24% of women have at least one PFD, 2.9% pelvic organ prolapse.
  - One in every 9 women will undergo surgery for a pelvic floor disorder
  - One in three women will suffer sphincter muscle damage during vaginal childbirth
  - 30% of women with urinary incontinence will have fecal incontinence as well.
  - 60% of nursing home residents have loss of bowel control and/or urinary incontinence
  - Data Based on survey of N=1961 subjects (Nygaard I et al. *JAMA*. 2008; 300:1311-6)

Age	No. of Women	Urinary Incontinence (n=331)	Fecal Incontinence (n = 176)	Pelvic Organ Prolapse (n= 58)	≥ 1 Pelvic Floor Disorder (n= 470)
20-39	641	6.9%	2.9%	1.6%	9.7%
40-59	668	17.2%	9.9%	3.8%	26.5%
60-79	488	23.3%	14.4%	3%	36.8%
≥ 80	150	31.7%	21.6%	4.1%	49.7%
Overall	1961	15.7 %	9%	2.9%	23.7%
P- value		< .001	< .001	.14	< .001

- Dyssynergic defecation: in IBS (40% on average, range 20-80%) and seen in all subtypes of IBS and all genders
- Prevalence of DD in IBD is 45-97% without Ileal pouch anal anastomosis (IPAA) and 25-75% with IPAA (Rezaie et al)

Rezaie A et al. *Inflamm Bowel Dis.* Volume 24, Number 5, May 2018; Nygaard et al. *JAMA.* Sept 17, 2008 (National Health and Nutrition Examination Survey); Suttor VP et al. *Dis Colon Rectum*. 2010; 53(2): 156-160; Prott G. Et al. *Neurogastroenterol Motil*. 2010 Jul; 22(7): 764-9; Mulak A, Paradowski L. *Int. J Colorectal Dis*. 2010 Aug; 25(8): 1011-6.

ACG Guidelines 2021: Consensus opinion

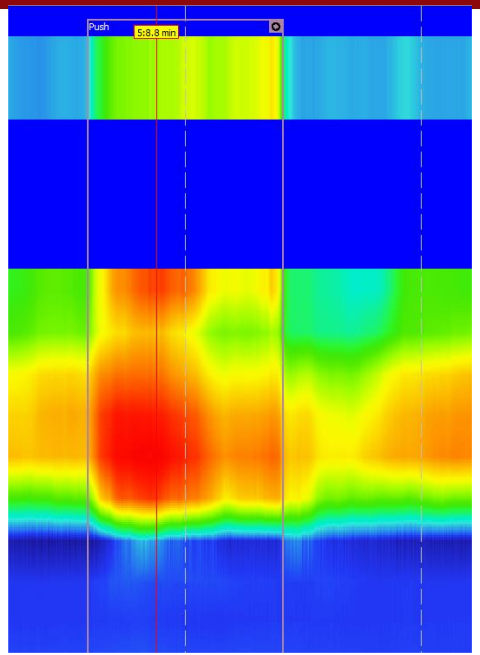
Push Maneuver During ARM

- Anorectal physiology testing : Can be performed in patients with IBS and symptoms suggestive of a PFD and/or refractory constipation not responsive to standard medical therapy.

- Both IBS-D and IBS-C patients had abnormal anorectal function based on either ARM or BET (Prevalence is as high as 40%)

- Rectal hypersensitivity is common in all subtypes based on ARM
- Recommendation made based on response to biofeedback therapy which improves bloating and pain

- Symptoms seen most in IBS-C that may suggest obstructive defecation:
  - Digital disimpaction, anal pain and longer symptom duration

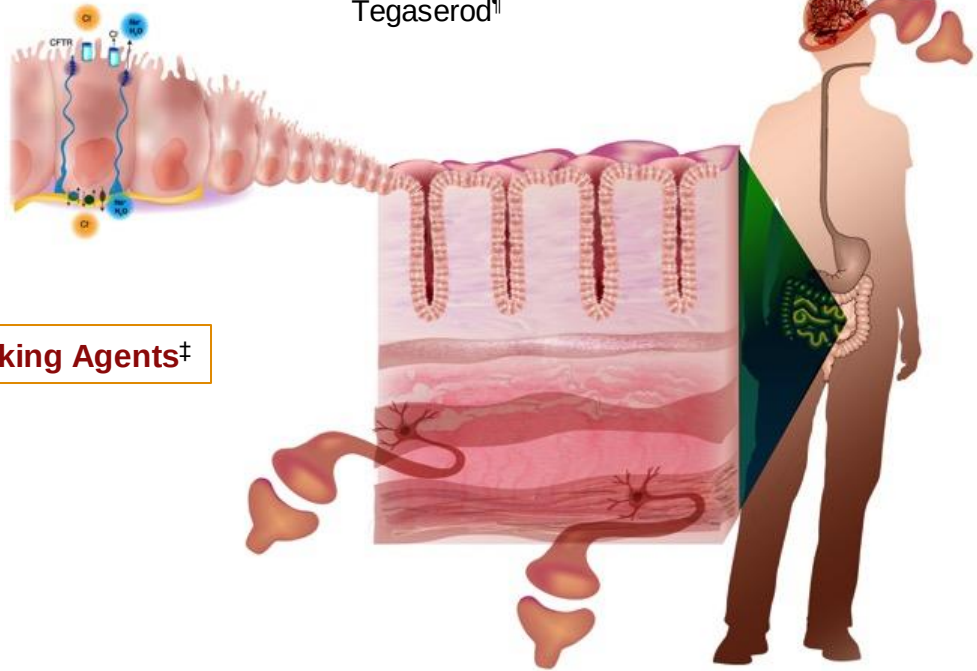


Lacy BE, et al. ACG Clinical Guideline: Management of IBS. AJG 2021
Suttor VP et al. Dis Colon Rectum 2010; 53 (2): 156-160.
Patcharatrakul T. J Clin Gastroenterol. 2011 Aug; 45 (7): 593-8.
Baker J et al. Clinical and Translational Gastro 2015:6, 2e105.

Overview of IBS-C Therapies: Mechanisms of Action

Prokinetic Agents
Tegaserod¶

Prosecretory Agents
Lubiprostone†
Linaclotide†
Plecanatide†
Tenapanor*



Fiber/Bulking Agents‡

†FDA-approved for CIC and IBS-C
¶FDA-approved for IBS-C.

ACG IBS/CIC Combined Guideline Recommendations 2021

TABLE 8 ACG Task Force on IBS/CIC* Systematic Reviews on Pharmacologic Treatment of IBS-C and chronic constipation[a]

	IBS-C[28]				Chronic constipation[3]			
Agent	Number of RCTs	N	RR of remaining symptomatic vs placebo (95% CI)	Strength of evidence	Number of RCTs	N	RR of remaining symptomatic vs placebo (95% CI)	Strength of evidence
Fiber								
Insoluble fiber (eg, bran)	6	441	0.90 (0.79-1.03)	Moderate	3[b]	293	0.25 (0.16-0.37)	Low
Soluble fiber (eg, psyllium)	7	499	0.83 (0.73-0.94)	Moderate				
Laxatives								
Stimulants					2	735	3 (2-3.5)	Moderate
PEG	2	181	—[c]	Low	4	573	0.52 (0.41-0.65)	High
Antidepressants								
SSRIs	7	356	0.68 (0.51-0.91)	Low				
Prosecretory agents								
Lubiprostone	3	1366	0.91 (0.87-0.95)	Moderate	4	651	0.67 (0.58-0.77)	High
Linaclotide	4	2867	0.81 (0.77-0.85)	High	3	1582	0.84 (0.80-0.87)	High
Plecanatide	3	2612	0.88 (0.84-0.92)	Moderate				
Prokinetic agents								
Prucalopride					8	3140	0.81 (0.75-0.86)	Moderate

*Chronic idiopathic constipation (CIC) is another term for chronic constipation.

[a]Tenapanor and tegaserod were not included in the ACG systematic reviews on IBS-C and chronic idiopathic constipation. Plecanatide was not included in the ACG systematic review on chronic constipation.

[b]2 trials used psyllium and 1 trial used inulin/maltodextrose combination.

[c]No dichotomous data reported.

Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; PEG, polyethylene glycol; RCT, randomized controlled trial; RR, relative risk; SSRI, selective serotonin reuptake inhibitor.

NNT

12.5 (p <0.01

8 (p<.0001)

9.5 (P<0.001)

Moshiree B. Rao SS. JFP 2021

Lacy BE, Pimentel M, Brenner DM, Chey, BD, Keefer LA, Long MD, & Moshiree B et al. ACG Clinical Guideline: Management of IBS. AJG 2021

Management Strategies IBS-C

Constipation	Bloating	Pain
• Water soluble fiber • *OTC Laxatives • Lubiprostone • Linaclotide • Plecanatide • Tenapanor • **Tegaserod (restricted use)	• Lubiprostone • Linaclotide • Plecanatide • *Low FODMAP • ~~Probiotics~~ →	• ~~Antispasmodics~~ → • Lubiprostone • Linaclotide • Plecanatide • **SSRIs • **Psychological Therapy

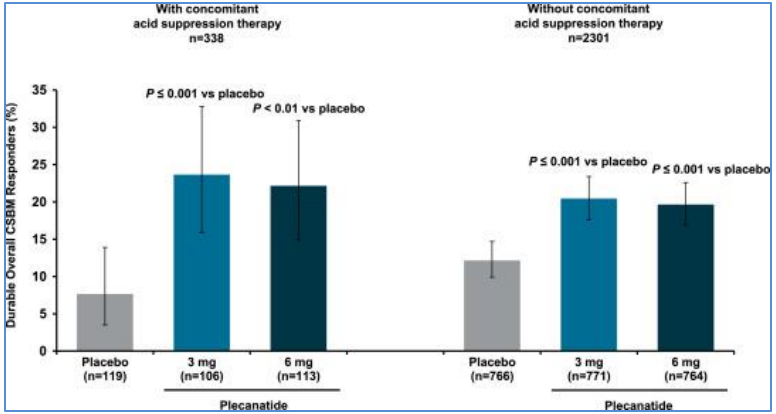
Target management at predominant symptom

P.Oil, Peppermint Oil; *CIC only; ** IBS-C only.

Adapted from Moayyedi et al. *United European Gastroenterology Journal*. 2017; 5(6): 773-788.

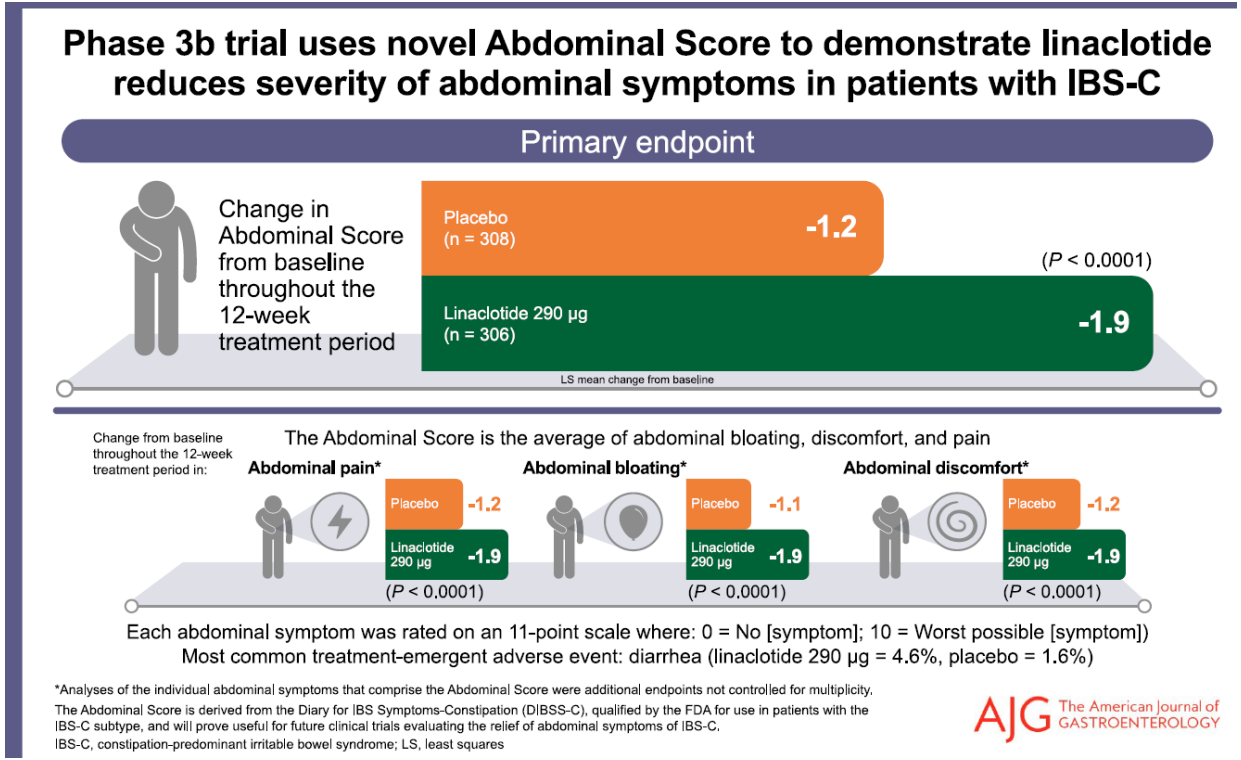
Does My PPI Affect the Efficacy of plecanatide?

- The Effect of Acid Suppression Therapy on the Safety and Efficacy of Plecanatide: Analysis of Randomized Phase III Trials
- Plecanatide is an analogue of uroguanylin that replicates its pH-sensitive activity and binds to guanylate cyclase-C receptors
- Pooled Data from two RCTS in CIC with plecanatide 3 mg and 6 mg, N= 338 (of 2639 total)
- Efficacy response rates on acid suppressors were 23.6% with plecanatide 3 mg (P = 0.001 vs placebo) and 7.6% with placebo.
- Responses were similar in patients not using acid suppressors: 20.4% (plecanatide 3 mg, P < 0.001), 19.6% (plecanatide 6 mg, P < 0.001), and 12.1% (placebo)
- PPI therapy does not change efficacy of Plecanatide



Moshiree B, Schoenfeld P, Franklin H, Rezaie A et al. *Clin Ther*. 2022. Jan 24:S0149-2918(21)00462-8.

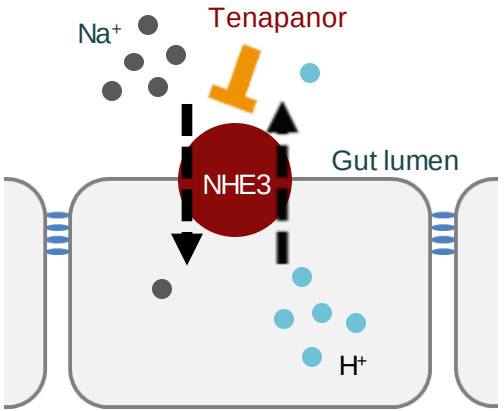
Linaclotide For Global IBS-C Symptoms Including Bloating – Towards Patient-Centered Care



Chang L, Lacy B, Moshiree B et al. *AJG*. 2021.

Tenapanor: Minimally Systemic, Small-Molecule Inhibitor of Gastrointestinal NHE3

- Na+/H+ exchanger isoform 3 (NHE3) is the major absorptive Na+/H+ exchanger in the gut[1]
- Specific inhibitor of NHE3 which reduces absorption of dietary sodium and phosphate in preclinical and clinical studies[2–3]
- Also used to treat hyperphosphatemia in patients with end-stage renal disease on dialysis[4–5]

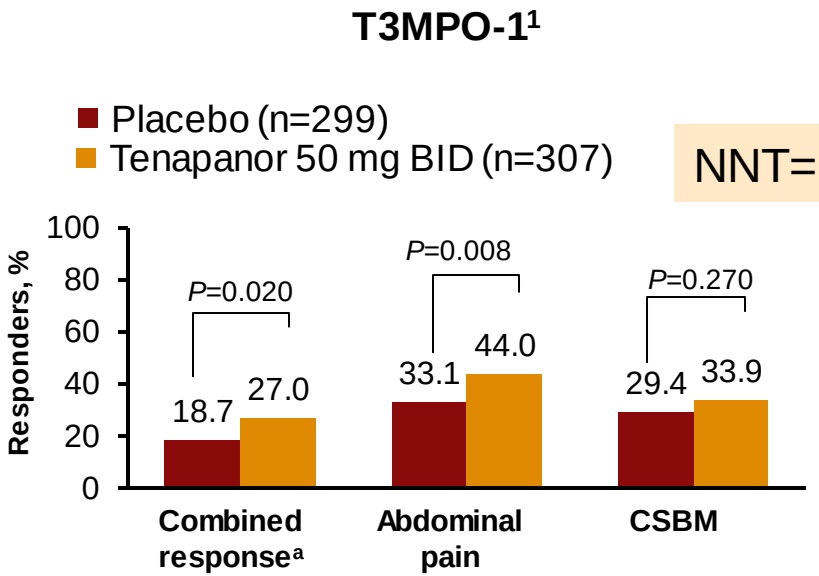


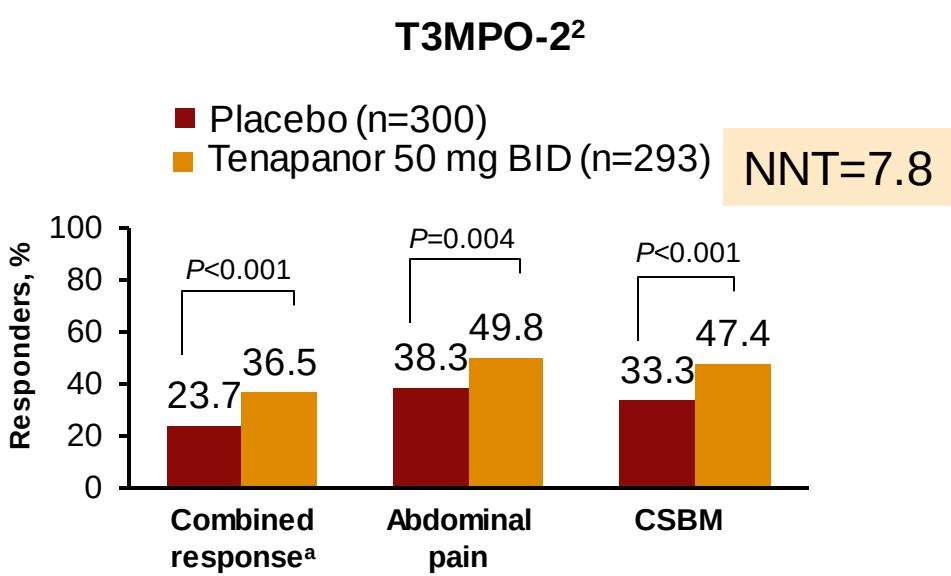
IBS-C, constipation-predominant irritable bowel syndrome; NHE3, sodium/hydrogen (Na+/H+) exchanger isoform 3

1. Girardi ACC et al. *Am J Physiol Cell Physiol*. 2012;302:C1569–87; 2. Spencer AG et al. *Sci Transl Med*. 2014;6:227ra36;
3. Labonté ED et al. *J Am Soc Nephrol*. 2015;26:1138–49; 4. Chey WD et al. *Am J Gastroenterol*. 2017;112:763–774;
5. Block GA et al. *J Am Soc Nephrol*. 2017;28:1933–1942.

Tenapanor in IBS-C: Efficacy in Pivotal Controlled Studies

Responder rates analyses for 6 of 12 weeks treatment



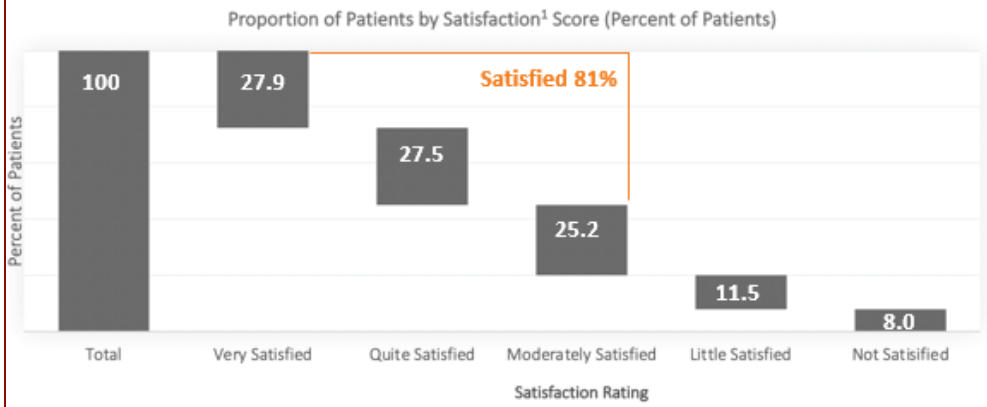


[a]Primary endpoint, defined as a reduction of ≥30.0% in average weekly worst abdominal pain and an increase of ≥1 weekly CSBM from baseline, both in the same week, for ≥6 of the first 12 treatment weeks.

1. Chey WD et al. *Am J Gastroenterol.* 2020;115:281-293. 2. Chey WD et al. *Am J Gastroenterol.* 2021;116:1294-1303.

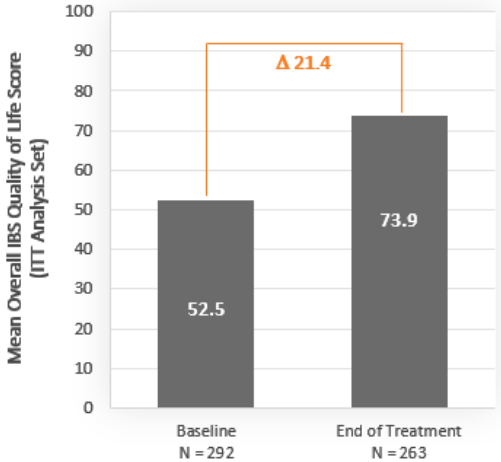
T3MPO-2: The Effect of Tenapanor on Treatment Satisfaction and Overall Quality of Life Score

Proportion of Patients by Satisfaction[1] Score in T3MPO-2
(Percent of Patients)



81% of subjects were moderately satisfied or better on Tenapanor!

Increase in Overall Quality of Life Score[2] at End of Treatment Compared With Baseline in T3MPO-2



41% improvement from baseline to end of treatment and significantly higher compared with placebo

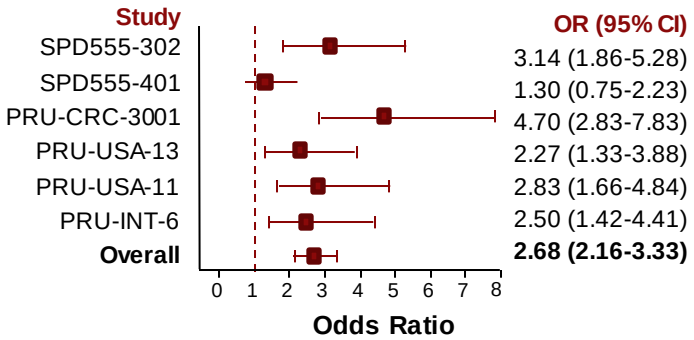
[1]Treatment satisfaction was assessed on a numerical scale from 1 to 5 (1 = not at all satisfied, 2 = a little satisfied, 3 = moderately satisfied, 4 = quite satisfied, 5 = very satisfied). Treatment satisfaction was recorded at the end of each month during the treatment period through week 20 and then again at week 26.

2Quality of life was assessed using the IBS-QOL, a 34-question instrument that measures 8 subscales relevant to patients with IBS: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual relationships, and overall quality of life. [1]$P = 0.011$

Chey WD et al. *Am J Gastroenterol.* 2021;116:1294-1303.

Prucalopride Improved SCBMs in Adults With CIC Across 6 RCTs

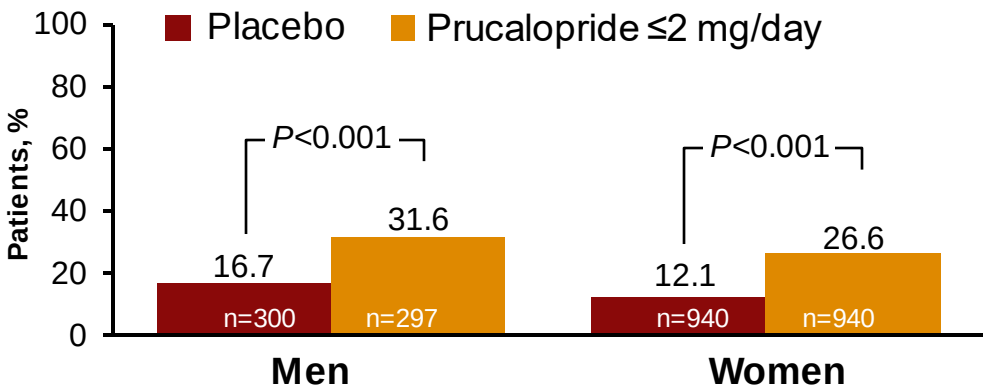
Average frequency ≥ 3 SCBMs over 12 weeks



Most common AEs

GI (nausea, diarrhea, abdominal pain)

Proportion of patients in pooled population with mean frequency >3 SCBMs/week over 12-week treatment period



NNT= 6-7 (men and women)

CI, confidence interval; OR, odds ratio; SCBM, spontaneous complete bowel movement.

Camilleri M et al. *Dig Dis Sci*. 2016;61:2357-2372.

Potential Benefit With Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis

	Articles	RCTs	Intervention	CAM	Placebo	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality	Effect estimate (95% CI)	
Abdominal pain	55	67		n = 3175	n = 2438						Very low	SMD	
	7	8	Body-based	168	140	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	−0.04 (−0.36 to 0.28)	
	15	15	Dietary supplements	497	442	Ser.	Ser.	Ser.	Ser.	No Ser.	Low	0.13 (−0.26 to 0.51)	
	6	6	Energy healing	232	232	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	0.21 (−0.20 to 0.61)	
	17	17	Herbal	1206	1078	Ser	Ser.	Ser.	No Ser.	Ser.	Low	0.47 (0.20–0.75)	
	14	14	Mind-body based	1072	546	V. Ser.	Ser.	Ser.	Ser.	Ser.	Very low	0.29 (−0.01 to 0.59)	
Overall response	44	56		3033	2340						Low	RR	NNT
	5	6	Body-based	145	125	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	1.32 (0.89–1.95	8 (3–23)
	7	7	Dietary supplements	225	207	Ser.	No Ser.	No Ser.	No Ser.	No Ser.	Moderate	1.95 (1.02–3.73)	4 (2–189)
	3	4	Energy healing	151	148	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	1.32 (0.99–1.76)	10 (4–303)
	20	20	Herbal	1506	1327	Ser.	No Ser.	No Ser.	No Ser.	Ser.	Moderate	1.57 (1.31–1.88)	5 (4–9)
	12	12	Mind-body based	1006	533	V. Ser.	No Ser.	No Ser.	No Ser.	Ser.	Low	1.67 (1.13-2.49)	5 (3-25)

NOTE. Totals of articles and RCTs do not amount to the sum of the included studies because several articles include multiple RCTs from different CAM categories. Body-based = relaxation, etc. Dietary supplements = aloe vera, etc. Energy healing = acupuncture, etc. Herbal = Curcuma, Tong-Xie, etc. Mind-body based = cognitive behavioral therapy, hypnotherapy, etc.
Ser., Serious; V., Very.

Billings W et al. Potential Benefit With Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2021 Aug;19(8):1538-1553.e14.

FDA approved CBT Smartphone Apps help with mental health specialist shortages

- Not enough Laurie Keefer, Megan Riehl, Tiffany Taft, Elyse Thakur or Miranda van Tilburgs to go around!
- Mahana has the first prescription-only, FDA-cleared mobile app that delivers cognitive behavioral therapy for IBS.
- Pilot feasibility study of internet-based unguided CBT therapy
- N=25 participants were randomized to receive an unguided web-based, CBT program for IBS.
- Primary outcome was changes in IBS symptom severity (IBS Symptom Severity Scale [IBS-SSS}
- IBS symptom severity significantly improved at 2-month ($p < 0.001$) and 3-month follow-up ($p < 0.0001$)
  - Within-group effect size between baseline and 3-month follow-up IBS-SSS scores was large ($d = 1.14$) and 63.6% experienced a clinically meaningful improvement (ie, ≥50-point IBS-SSS score reduction)

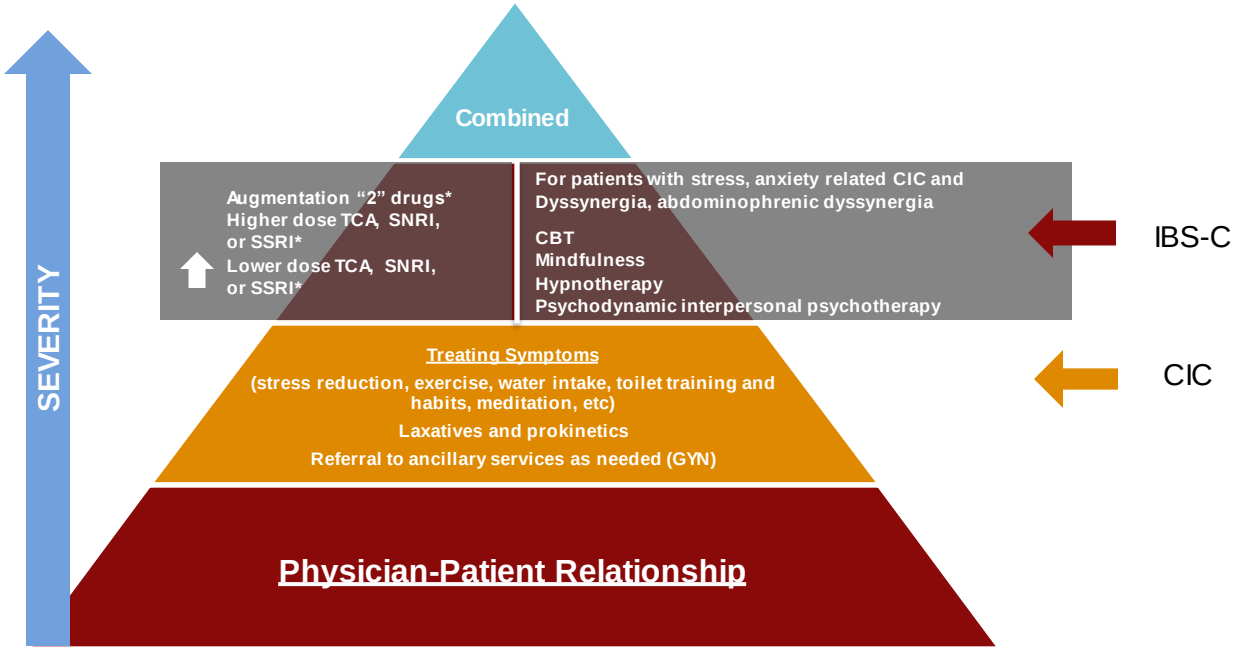
Owusu JT et al. NGM 2021

Summary of Non-Pharmacologic Therapies Recommended for IBS

Recommendation/Suggestion	GRADE of Recommendation
We suggest that anorectal physiology testing be performed in pts with IBS and symptoms suggestive of a pelvic floor disorder and/or refractory constipation not responsive to standard medical therapy. Due to favorable response to biofeedback therapy	Unable to assess using GRADE Methodology
We recommend a limited trial of a low FODMAP diet in patients with IBS to improve global IBS symptoms.	Conditional recommendation, very low quality of evidence
We suggest that soluble, not insoluble, fiber be used to treat global IBS symptoms.	Strong recommendation; moderate quality of evidence.
We suggest against the use of probiotics for the treatment of global IBS symptoms.	Conditional recommendation; very low quality of evidence.
We suggest that gut-directed psychotherapies be used to treat global IBS symptoms.	Conditional recommendation; very low quality of evidence.
Using currently available evidence, we recommend against the use of fecal transplantation for the treatment of global IBS symptoms.	Strong recommendation; very low quality of evidence.

Lacy BE, Pimentel M, Brenner DM, Chey, BD, Keefer LA, Long MD, & Moshiree B et al.
ACG Clinical Guideline: Management of IBS. AJG 2021

Treatment for Any DBGI: Pharmacotherapy and Behavioral Therapy



CBT=cognitive behavioral therapy; SNRI=selective norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
*Closely monitor side effects.
Adapted from Keefer L et al. Gastroenterology. 2016;150:1408-1419.