Case Study Series

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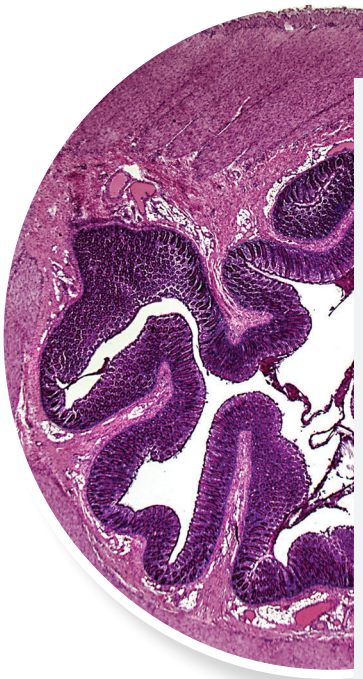
QOL-Guided Decision-Making to Switch Mechanism of Action in IBS-C: Applying JUST ASK Study Principles in Clinical Practice



Brennan Spiegel, MD, MSHS
Professor of Medicine, Public Health, and Biomedical Sciences
George and Dorothy Gourrich Chair in Digital Health Ethics
Director, Cedars-Sinai Center for Virtual Medicine and Health System Transformation
Director, Graduate Program in Health System Science
Director, Certificate Program in Applied Artificial Intelligence for Health Systems
Cedars-Sinai Site Director, Clinical and Translational Science Institute
Cedars-Sinai Medical Center
Los Angeles, California

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Cedars-Sinai Medical Center
Los Angeles, California

About the Patient

JS, a 38-year-old man, presented with long-standing complaints of persistent bloating, abdominal distension, constipation, incomplete evacuation, and reduced quality of life. He had unsuccessfully tried multiple over-the-counter therapies and interventions, including polyethylene glycol, stool softeners, and soluble fiber, over the past few years.

Prior lactulose breath testing demonstrated hydrogen-predominant small intestinal bacterial overgrowth, with hydrogen levels peaking at approximately 86 ppm within 90 minutes. He had previously experienced significant symptomatic improvement with rifaximin therapy; however, symptoms recurred approximately 2 months later.

Extensive evaluation ruled out alternative etiologies. A diagnosis of irritable bowel syndrome with constipation (IBS-C) was confirmed following a positive diagnostic approach recommended by the American College of Gastroenterology (ACG).

JS was started on the secretagogue linaclotide at 290 µg daily, but this resulted in intolerable diarrhea. Dose reduction to 145 µg daily improved tolerability modestly but did not adequately relieve bloating or constipation. Bowel frequency remained limited to approximately 2 to 3 bowel movements weekly, and these were associated with straining and a sense of incomplete evacuation.

At this point, clinical decision-making centered on whether to continue dose modification with the secretagogue linaclotide or to transition to a medication with a different mechanism of action (MOA).

This case was informed by emerging data presented at the 2026 Digestive Disease Week (DDW) from the IBS-C Joint Universal Single-Item Tool for Assessing Satisfaction and Key Metrics (JUST ASK) study. This study evaluated 11 questions and determined that the strongest predictor of therapeutic inadequacy was the answer to: "How satisfied are you with the improvement in your quality of life since starting the medicine for your IBS-C?" Unlike elaborate symptom-specific assessments focused on bowel frequency, stool consistency, and other abdominal and bowel symptoms, this holistic biopsychosocial question

On the Cover: Light micrograph of a cross section of a colon. Credit: Alvin Telser / Science Source

Making a Confident Symptom-Based IBS-C Diagnosis

1. Take a careful patient history

Note the chief complaints prompting consultation and the impact of what the patient has tried in the past.

- Presenting symptoms and timeline
- Potential triggers (eg, infection, stress)
- Diet
- Medications
- Comorbid conditions (fibromyalgia, interstitial cystitis, migraine headaches, chronic pain syndrome)

2. Perform a thorough physical examination, including a digital rectal examination *(always in the presence of a chaperone)*

- Patient appearance
- Vital signs
- Abdominal examination
- Signs of systemic and local diseases that might cause constipation
- Assess the anorectum and pelvic floor muscles
- Other relevant abnormalities

3. Rule out alarm features that are suggestive of an underlying organic gastrointestinal disorder

- New symptoms in patients over 50 years of age
- Unintended weight loss (>10% within 3 months)
- Hematochezia (unrelated to hemorrhoids or anal fissures)
- Symptoms that disrupt sleep or awaken the patient at night
- Fever, anemia, or rapidly progressing or acute symptoms
- A palpable mass, ascites, or lymphadenopathy
- A family history of colorectal cancer, polyposis syndrome, celiac disease, or IBD

4. Apply symptom-based Rome V criteria for clinical practice

- Abdominal pain/discomfort recurs on average at least 3 days per month and is associated with at least 2 of the following symptoms: related to defecation, associated with a change in the frequency of stool, or associated with a change in the form (appearance) of stool.
- Symptoms are bothersome, interfering with daily activities, requiring attention, or impacting QOL are present for at least 8 weeks.

5. Classify the appropriate IBS subtype using the BSFS

IBS subtype	Bowel movements	
	BSFS types 1 and 2	BSFS types 6 and 7
IBS-C	More than 25%	Less than 25%
IBS-D	Less than 25%	More than 25%
IBS-M	More than 25%	More than 25%
IBS-U	Cannot be determined	

Figure 1. Making a positive IBS diagnosis: 5 key features.

BSFS, Bristol Stool Form Scale; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed or alternating bowel habits; IBS-U, IBS without a significant pattern of abnormal stool or unclassified; QOL, quality of life.

better captured overall disease burden and informed if change in MOA was warranted.

JS's persistently diminished quality of life despite partial symptom response supported consideration of an alternative MOA. Therefore his IBS-C medication was switched to a retainagogue, tenapanor 50 mg twice daily.

Given JS's prior favorable response to rifaximin and to address the ongoing concern for microbiome-mediated symptom recurrence, a structured microbiome-targeted dietary intervention under guidance of a gastrointestinal (GI) dietitian was also suggested.

Given JS's penchant for technology and how it is transforming patient management, we discussed a recent National Institutes of Health (NIH)–funded study presented at the 2026 DDW on gut-directed cognitive behavioral therapy (CBT) delivered through virtual reality (VR). The study found that patients using an 8-week home-based VR CBT program experienced a significant reduction in severity of abdominal pain and interference of symptoms in daily life. JS expressed interest in trying this approach as an adjunct to the other strategies discussed.

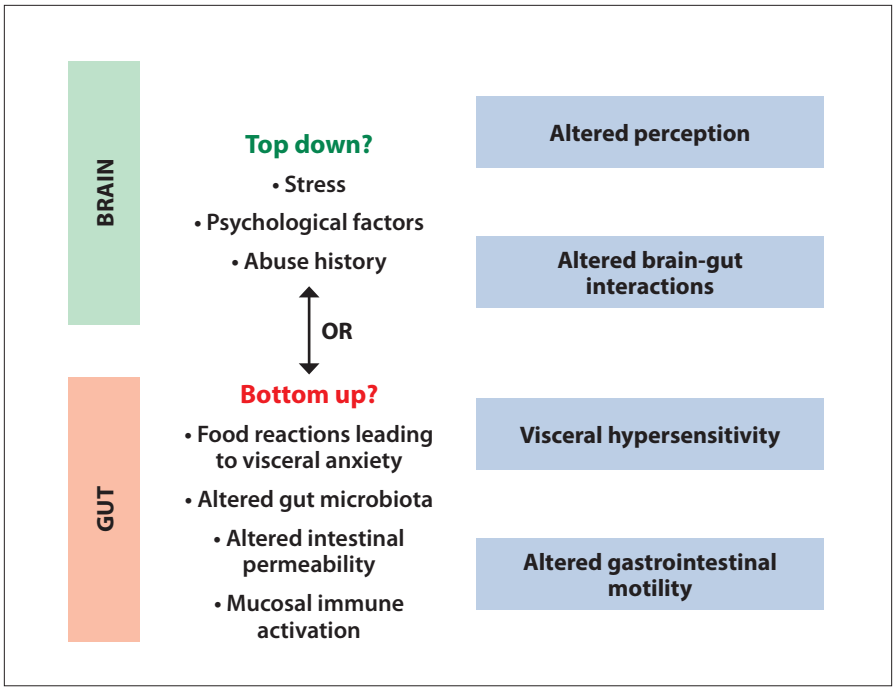

Figure 2. IBS: gut-brain or brain-gut?

IBS, irritable bowel syndrome. Courtesy of Kimberly Orleck, PA-C.

Follow-up was planned at 3 months to evaluate therapeutic response, tolerability, and the relative contribution of each intervention.

How to Confidently Diagnose IBS-C

There are currently no validated biomarkers or objective diagnostic tests for IBS-C. Consistent with ACG recommendations, diagnosis should be made using a positive, symptom-based approach. This includes a detailed patient history, thorough physical examination, ruling out alarm features suggestive of an underlying organic GI disorder, applying symptom-based Rome V criteria, and subtype classification using the Bristol Stool Form Scale (Figure 1).[1-7]

Note that the symptom-based Rome V criteria, a June 2026 update to Rome IV, are designed for clinical practice, not research. They emphasize a patient-centered, biopsychosocial approach to diagnosis and management, and include discomfort alongside pain as a diagnostic symptom and lower the threshold frequency to at least 3 days/month (from at least 1 day/week in Rome IV).

Selective testing may be appropriate in specific clinical contexts, such as serologic evaluation for celiac disease in patients with diarrhea-predominant IBS symptoms, fecal calprotectin or lactoferrin and C-reactive protein to rule out inflammatory bowel disease, and colonoscopy in patients old enough for colorectal cancer screening.

In JS's case, a comprehensive evaluation ruled out alternative etiologies. His long-standing symptoms of bloating, abdominal distension, constipation, incomplete evacuation, and reduced quality of life were therefore sufficient to establish a definitive diagnosis of IBS-C.

What to Tell Your Patients About IBS

IBS is a disorder of gut-brain interaction characterized by recurrent abdominal pain associated with alterations in bowel habits. It affects many adults (9.2% reported pooled prevalence from 53 studies using Rome III criteria from 38 countries comprising 395,385 participants) and is associated with substantial reductions in health-related quality of life often comparable to those observed in diabetes, end-stage renal disease, and gastroesophageal reflux disease.[8,9]

IBS-C is a common subtype with hallmark symptoms of abdominal pain and hard stools or infrequent bowel movements. Patients frequently report additional GI symptoms, including bloating, abdominal discomfort, straining, and a persistent sensation of incomplete evacuation.

The pathophysiology of IBS is complex and multifactorial.[10-17] Altered GI motility, visceral hypersensitivity, immune activation, microbiome alterations, and altered central nervous system processing have been implicated in IBS (Figure 2).[6] The specific cause of symptoms cannot be precisely identified, and symptom exacerbations, or flares, may be triggered by different factors at different time points. Dietary components can provoke symptoms in some instances, whereas psychological stress, GI infections, or antibiotic exposure may be responsible in others.

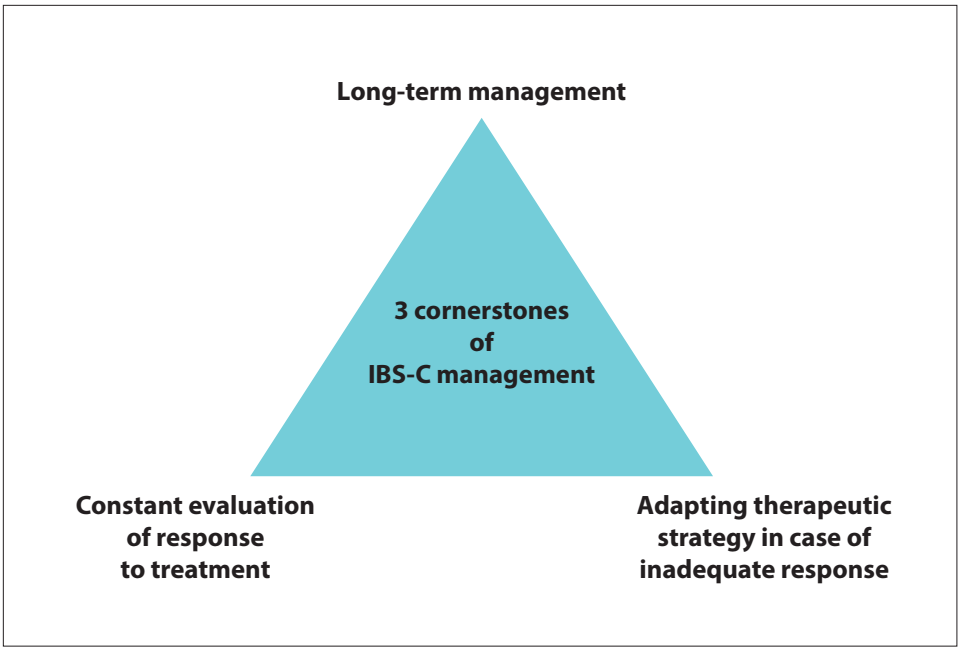

Figure 3. Cornerstones of IBS-C management.

IBS-C, irritable bowel syndrome with constipation.

Regardless of the underlying cause of these symptoms and flares, the basic principles of managing IBS-C are consistent (Figure 3). Effective IBS-C management requires a long-term, individualized strategy with ongoing assessment of treatment response and timely adjustment of therapeutic approaches when symptoms are inadequately controlled.

Over-the-Counter Options vs FDA-Approved Treatment Options for IBS-C

Many patients suffer from prolonged symptoms before receiving a formal diagnosis of IBS-C, and even after diagnosis, initiation of US Food and Drug Administration (FDA)–approved therapy is often delayed. By such time, most patients have already tried a variety of over-the-counter products including stool softeners, soluble fiber supplements, and laxatives.[18,19] Although these agents may provide partial relief, they do not address the full spectrum of IBS-C symptoms and none are approved by the FDA for this indication (Table 1).

To date, the FDA has approved 5 medications for IBS-C: tegaserod (2002), lubiprostone (2006), linaclotide (2012), plecanatide (2017), and tenapanor (2019; United States launch in 2022). These agents have been evaluated in large, randomized, placebo-controlled trials and follow-up analyses and have demonstrated efficacy across multiple abdominal and bowel endpoints (Table 2; Figure 4).[20-31]

Tegaserod, a serotonergic agent, was withdrawn from the market owing to concerns about potential cardiovascular risk. Then tegaserod was reintroduced and subse-

Table 1. Over-the-Counter Options Fail to Treat Cardinal Symptoms of IBS-C

Over-the-counter options	Improve bowel symptoms	Improve abdominal symptoms	Approved by the FDA
Stool softeners	??	x	x
Soluble fiber	√	??	x
Laxatives			
Osmotic	√	x	x
Stimulant	√	x	x
Saline	√	x	x

FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation.

Table 2. Available FDA-Approved Medications for IBS-C Have Been Evaluated Across a Range of Abdominal and Bowel Symptoms

FDA-approved medication	Primary endpoint studied	Other endpoints studied
Lubiprostone	Overall responder status[a]	• Abdominal discomfort or pain • Bloating • Constipation severity • Stool consistency • Straining
Linaclotide	FDA combined endpoint[b]	• Abdominal pain response • Reduction in abdominal pain of 30% or greater • CSBM response • Increase of at least 1 CSBM from baseline
Plecanatide	FDA combined endpoint[b]	• Abdominal pain • Stool frequency/consistency • Change in BSFS score • Change in CSBM • Change in straining score • Novel trisymptom composite endpoint[c]
Tenapanor	FDA combined endpoint[b]	• Abdominal pain response • Abdominal discomfort response • Rate of abdominal bloating response • Abdominal cramping response • Abdominal fullness response • Abdominal score[d] • CSBM

[a]Calculated from the weekly assessments of symptom relief. A patient was considered an overall responder if they were a monthly responder for at least 2 of the 3 months of the study. Monthly responders were defined as patients who rated their IBS symptoms as being at least moderately relieved for all 4 weeks of the month or significantly relieved for at least 2 weeks of the month, with no ratings of moderately or severely worse.

[b]Defined as an improvement of at least 30% from baseline in average daily worst abdominal pain score and an increase of at least 1 CSBM from baseline, both in the same week for 6 or more out of 12 weeks.

[c]Consisting of abdominal pain, abdominal bloating, and CSBMs.

[d]Average of weekly scores for abdominal pain, discomfort, and bloating symptoms.

BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation.

quently withdrawn again in 2022 for business reasons. It will therefore not be discussed further.[32]

The 4 currently available FDA-approved therapies have favorable safety profiles. Lubiprostone is most commonly associated with nausea, diarrhea, and abdominal distension, whereas linaclotide, plecanatide, and tenapanor primarily cause diarrhea.[24-29] In a 55-week open-label safety study (T3MPO-3), tenapanor was well tolerated, with no new safety signals and a 1.6% discontinuation rate owing to diarrhea.[30]

Although these medications have been available for several years, no head-to-head trials have been conducted; therefore, comparative efficacy remains unknown. However, 2 network meta-analyses provide indirect comparisons, demonstrating that all FDA-approved IBS-C therapies are superior to placebo for global symptom improvement and show broadly similar efficacy across most endpoints, including abdominal bloating.[33,34]

When Does MOA of FDA-approved IBS-C Medications Become an Important Consideration?

Lubiprostone, linaclotide, and plecanatide are secretagogues, and tenapanor is the only first-in-class retainagogue.

Secretagogues increase chloride and bicarbonate ion secretion into the intestinal lumen, resulting in water secretion and thus accelerating colonic transit and improving stool consistency and frequency. Lubiprostone activates type-2 chloride channels, whereas linaclotide and plecanatide are agonists of the guanylate cyclase-C (GC-C) receptor. Linaclotide exhibits pH-independent activity and binds GC-C receptors throughout the small intestine and colon, whereas plecanatide demonstrates greater activity in the more acidic environment of the small intestine.

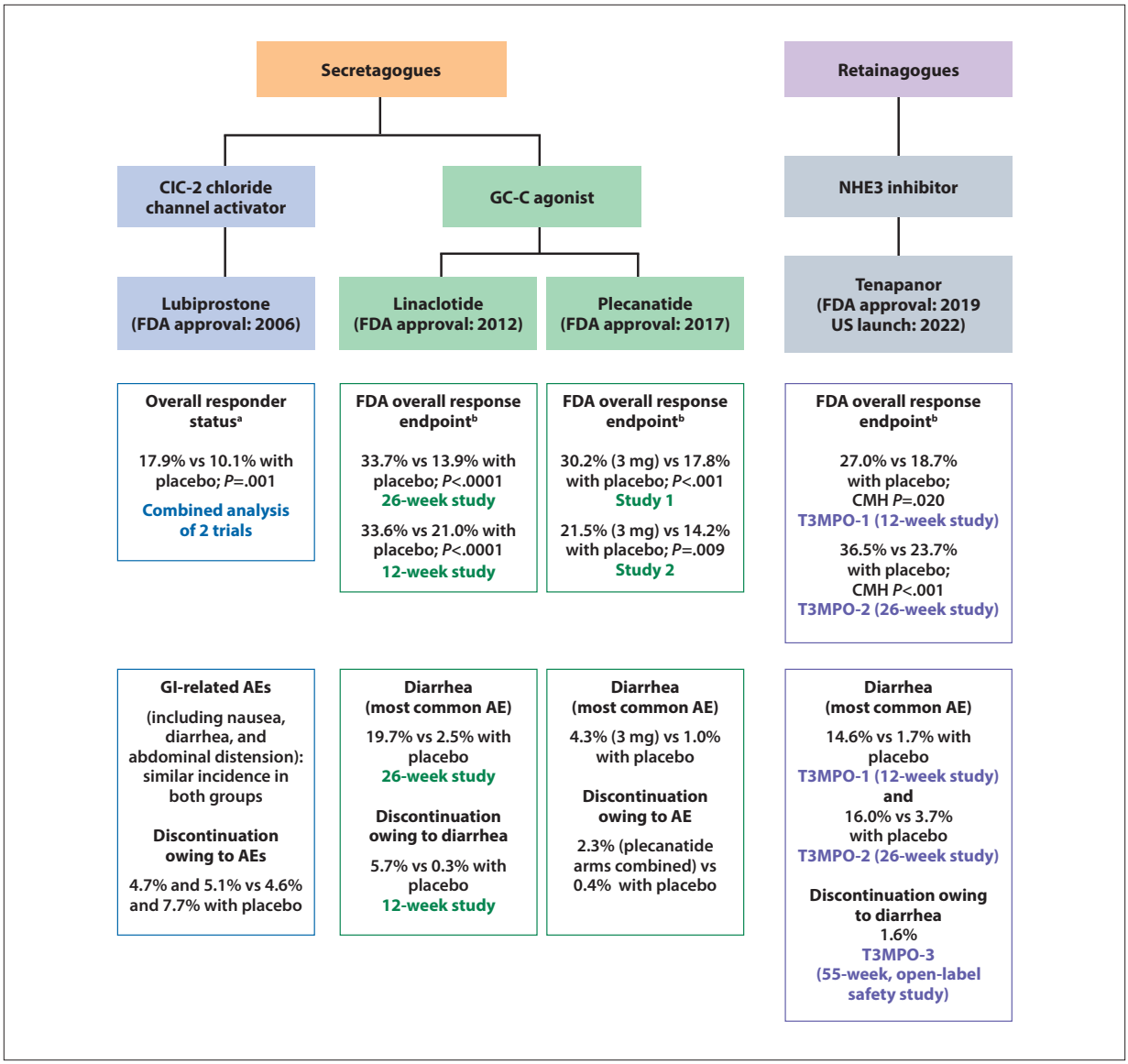

Figure 4. Currently available FDA-approved treatment options for IBS-C and their efficacy and safety data.

[a]Overall responder status was calculated from the weekly assessments of symptom relief. Monthly responders were defined as patients who rated their IBS symptoms as being at least moderately relieved for all 4 weeks of the month or significantly relieved for at least 2 weeks of the month, with no ratings of moderately or severely worse. A patient was considered an overall responder if they were monthly responders for at least 2 of the 3 months of the study.

[b]Defined as an improvement of at least 30% from baseline in average daily worst abdominal pain score and an increase of at least 1 CSBM from baseline, both in the same week for 6 or more out of 12 weeks.

AE, adverse event; CMH, Cochran-Mantel-Haenszel; CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; GC-C, guanylate cyclase-C; GI, gastrointestinal; IBS-C, irritable bowel syndrome with constipation; NHE3, sodium/hydrogen exchanger isoform 3.

Adapted from Brenner DM. *Gastroenterol Hepatol* (N Y). 2023;19(12)(suppl 6):749-756.[31]

Tenapanor is a locally acting inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3).[35-38] Inhibition of NHE3 reduces sodium absorption, leading to increased luminal water retention and accelerated intestinal transit. In animal models, NHE3 inhibition has also been associated with reduced visceral hypersensitivity and improved abdominal symptoms, potentially through reconstitution of tight junctions between intestinal epithelial cells (decreasing intestinal permeability) and antagonism of transient receptor potential vanilloid 1 channels.

This difference in MOA is clinically relevant when a patient does not achieve adequate symptom improvement

Table 3. Indication, Dosage, and Administration of Currently Available FDA-Approved Medications for IBS-C

FDA-approved agent	FDA-approved indication for	Dosage	Administration
Lubiprostone	Women >18 years of age	8 μg orally twice daily	With food and water
Linaclotide	Adults	290 μg orally once daily	On empty stomach at least 30 minutes prior to a meal at approximately the same time each day
Plecanatide	Adults	3 mg orally once daily	With or without food
Tenapanor	Adults	50 mg orally twice daily	Immediately prior to breakfast or the first meal of the day and immediately prior to dinner

FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation.

with one class of therapy. Because the underlying cause of IBS-C symptoms may vary across individuals, even among patients with similar clinical presentations, management often requires a trial-and-error approach. After an IBS-C diagnosis is established, initiating treatment with one of the 4 available FDA-approved therapies at recommended dosing is appropriate (Table 3). Ongoing assessment of treatment response is essential, and inadequate improvement should prompt consideration of switching to an agent with a different MOA.

In the Clinic . . .

The distinct MOAs of FDA-approved medications give the physicians an opportunity to switch to another class of medications in case of inadequate response to one class of medications.

What Is an Adequate Trial?

Setting clear expectations at the initiation of IBS-C therapy is critical for optimizing treatment outcomes. Constipation-related symptoms often improve within the first 2 weeks of therapy, whereas abdominal pain, discomfort, and bloating may improve more gradually over several additional weeks.[39,40] Recent post hoc analyses of phase 3 tenapanor trials support this pattern, demonstrating median times to response of approximately 2 weeks for complete spontaneous bowel movements and 4 to 5 weeks for abdominal symptoms (Figure 5).[39] Premature discontinuation may therefore result in missed clinical benefit.

An adequate therapeutic trial generally requires at least 8 weeks of continuous treatment before response is formally assessed at a scheduled follow-up visit. In JS's case, a follow-up evaluation was planned 3 months after switching therapy, allowing sufficient time to determine clinical response.

How to Conduct a Meaningful Follow-up: Insights From the JUST ASK Study

After an adequate trial with an FDA-approved therapy for IBS-C, treatment response must be evaluated during follow-up. A key challenge in routine practice is determining how to conduct a focused, efficient, and clinically meaningful assessment.

Detailed questioning about individual symptoms and their degree of improvement is fraught with challenges. Patients may struggle to accurately compare their current condition with baseline symptom severity. Moreover, time constraints during follow-up visits can also limit the feasibility of comprehensive symptom-by-symptom assessments. This highlights the need for a more succinct and reliable method of evaluating response.

Treatment satisfaction is an important component of successful long-term IBS-C management, as unrecognized dissatisfaction may contribute to persistent symptoms, delayed treatment optimization, and reduced quality of life. Yet lengthy patient-reported outcome instruments are impractical in routine clinical settings to quickly assess treatment satisfaction.

To address this gap, the IBS-C JUST ASK study evaluated whether a brief, single-item question could reliably assess treatment satisfaction.[41] This national survey enrolled adults meeting Rome IV criteria for IBS-C who were currently taking medication for symptom management.

Responses to 11 candidate single-item questions were compared with validated instruments, including the Treatment Satisfaction Questionnaire for Medication II, IBS Symptom Severity Scale (IBS-SSS), IBS Quality of Life (IBS-QOL) questionnaire, and Patient-Reported Outcomes Measurement Information System (PROMIS) Gastrointestinal Belly Pain Scale. Convergent validity was

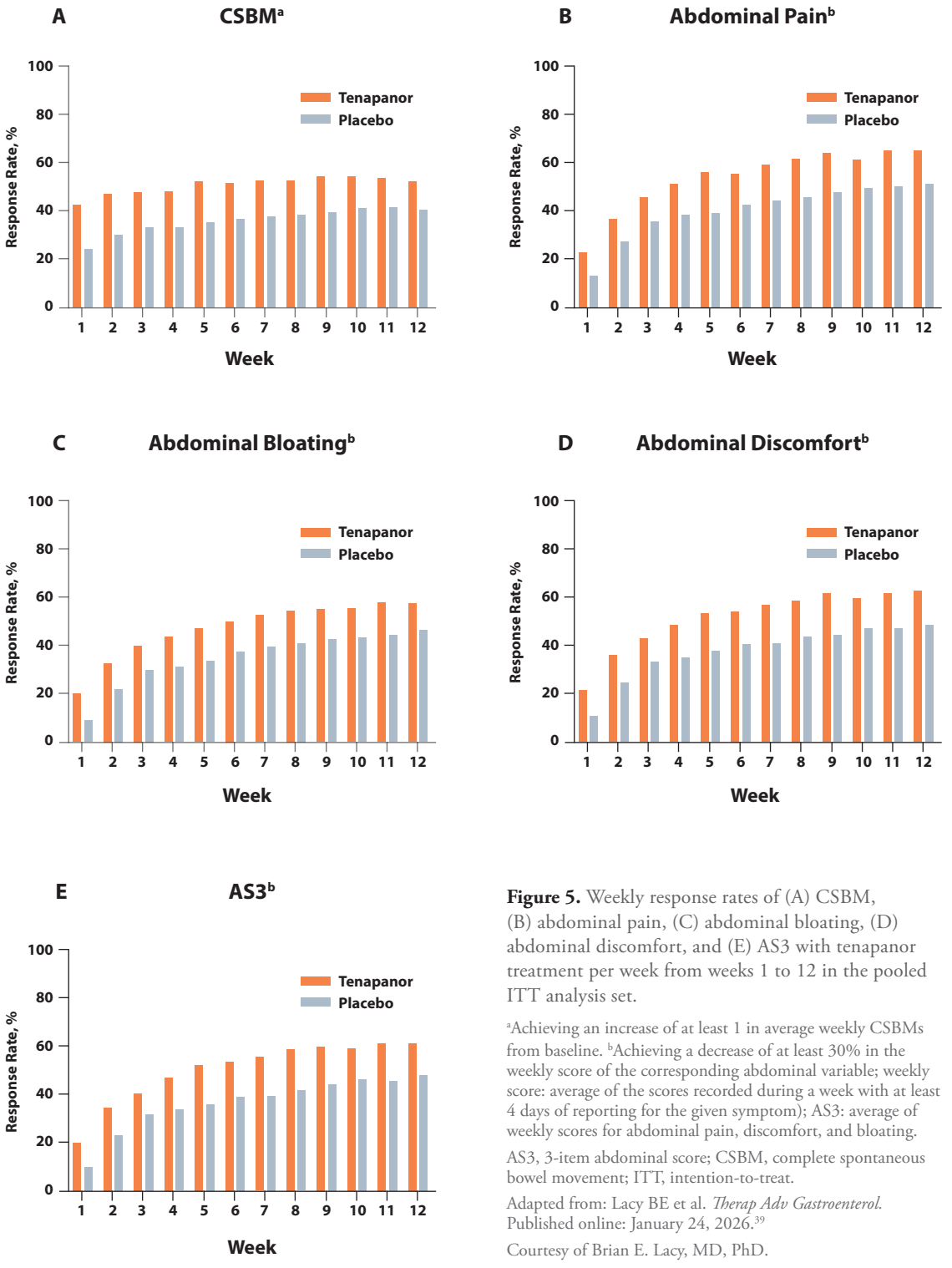

Figure 5. Weekly response rates of (A) CSBM, (B) abdominal pain, (C) abdominal bloating, (D) abdominal discomfort, and (E) AS3 with tenapanor treatment per week from weeks 1 to 12 in the pooled ITT analysis set.

[a]Achieving an increase of at least 1 in average weekly CSBMs from baseline. [b]Achieving a decrease of at least 30% in the weekly score of the corresponding abdominal variable; weekly score: average of the scores recorded during a week with at least 4 days of reporting for the given symptom); AS3: average of weekly scores for abdominal pain, discomfort, and bloating.

AS3, 3-item abdominal score; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat.

Adapted from: Lacy BE et al. *Therap Adv Gastroenterol.* Published online: January 24, 2026.[39]

Courtesy of Brian E. Lacy, MD, PhD.

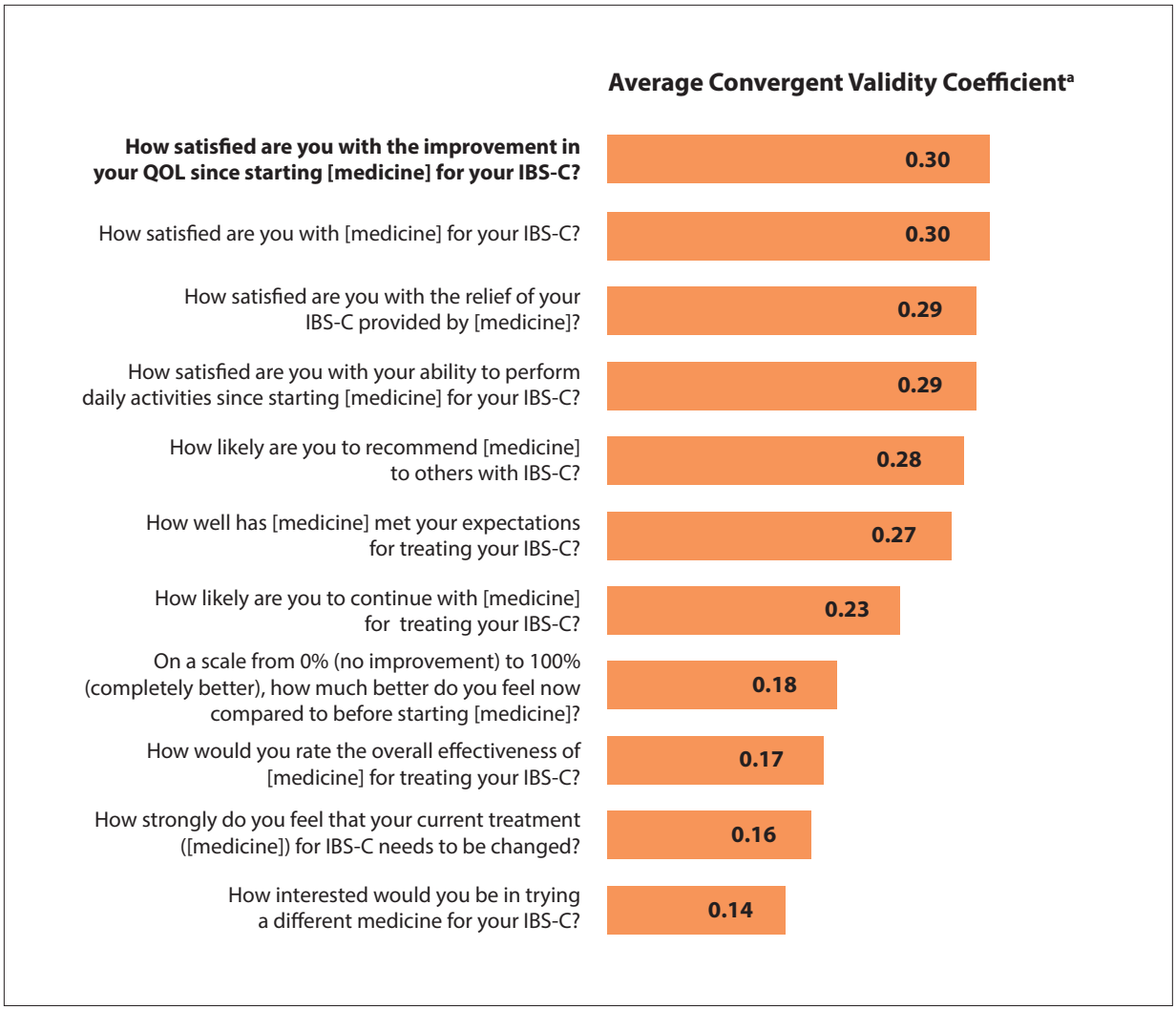

Figure 6. JUST ASK study: Pearson correlations of candidate single-item questions with validated medication satisfaction and IBS symptom/QOL scales (N=554).[41]

[a]Average convergent validity coefficient calculated by averaging the absolute values of correlations to all legacy surveys: TSQM2 R^2, TSQM2, IBS Quality of Life, IBS Symptom Severity Scale, PROMIS Gastrointestinal Belly Pain Scale.

IBS-C, irritable bowel syndrome with constipation; QOL, quality of life; PROMIS, Patient-Reported Outcomes Measurement Information System; TSQM2, Treatment Satisfaction Questionnaire for Medication II.

assessed using Pearson correlation coefficients, and the strongest-performing items were those with the highest average correlations (Figure 6).

Results presented at DDW 2026 showed that among 554 adults who completed the survey, of whom most (81.8%) were taking an FDA-approved IBS-C medication, the answer to a single, clinically intuitive question demonstrated strong convergent validity: "How satisfied are you with the improvement in your quality of life since starting [medicine] for your IBS-C?"

This concise, single-item assessment offers a practical, patient-centered approach for rapidly evaluating treatment satisfaction in routine care, enabling earlier identification of inadequate response and hence more timely therapeutic adjustment.

In JS's case, clinical decision-making regarding whether to continue dose modification with linaclotide or transition to a therapy with a different MOA was also guided by a similar holistic question: "How effective is your current medication in improving your overall quality of life?" This approach captured JS's persistent diminished quality of life despite partial symptom improvement, supporting the decision to switch to an agent with a different MOA.

In the Clinic . . .

In case of inadequate response, clinicians often struggle with the best course of action.

The JUST ASK study addressed this need by identifying a simple, single, predictive, evidence-based question that could help clinicians decide if a new MOA is necessary: "How satisfied are you with the improvement in your quality of life since starting [medicine] for your IBS-C?"

Persistent diminished quality of life may be the most clinically meaningful indicator that a change in therapeutic MOA is needed in IBS-C.

Multimodal Treatment Framework

Refractory IBS-C often benefits from incorporating pharmacologic, dietary, microbiome-directed, and behavioral approaches in management.

CBT incorporating VR is emerging as a novel approach in IBS management. In an NIH-funded randomized controlled pilot trial presented at DDW 2026, 73 people with IBS (24.7% with IBS-C and 63% with severe IBS [IBS-SSS >300]) were randomized to VR CBT (n=36) and sham VR (n=37) for 8 weeks.[42] After using the assigned program for a median of 210 mins, VR CBT was associated with better numerical scores for abdominal pain (PROMIS Gastrointestinal Belly Pain Scale) and quality of life (IBS-QOL), higher proportion of patients achieving clinically meaningful improvement in symptoms (≥50-point reduction in IBS-SSS from baseline), and significantly lower mean IBS-SSS scores. These improvements were attributed to reductions in abdominal pain severity and frequency, abdominal distension, and interference with daily activities.

In JS's case, the JUST ASK study question prompted switching IBS-C therapy to a different MOA, tenapanor 50 mg twice daily. Given the ongoing concern for microbiome-mediated symptom recurrence and his prior favorable response to rifaximin, a structured microbiome-targeted dietary intervention was implemented under the guidance of a GI dietitian. JS was also receptive to incorporating VR-delivered CBT as an adjunctive modality. This multimodal approach was adopted to enhance the durability of therapeutic response by addressing biological and behavioral drivers of his symptoms.

Conclusion

The complex, multifactorial pathophysiology of IBS-C necessitates a trial-and-error approach when initiating FDA-approved therapies, as the underlying cause of symptoms varies across individuals. When a patient exhibits inadequate improvement with one class of medication, transitioning to an agent with a different MOA is often warranted.

A central clinical challenge is determining whether a response is truly inadequate or whether dose adjustment or continued therapy may yield desired benefit. Time constraints during routine follow-up visits frequently limit comprehensive assessment across all abdominal and bowel symptom domains, and in the absence of objective biomarkers, clinicians must rely heavily on patient recall of symptom changes.

This case illustrates how a single, quality-of-life–focused question derived from the JUST ASK study can serve as a practical and reliable tool for evaluating overall treatment benefit and guide decisions regarding MOA switching.

Long-term successful IBS-C management requires periodic reassessment and adapting therapeutic strategy in case of inadequate response. This makes the single quality-of-life–focused question from the JUST ASK study invaluable to both the physicians and the patients by enabling efficient, patient-centered evaluation of treatment effectiveness.

Disclosures

Dr Spiegel serves on the advisory boards of Ardelyx, Exact Sciences, and Guardant Health. His institution has received research funding from Ardelyx, Ironwood Pharmaceuticals, Freenome, and Guardant Health.

References

1. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116(1):17-44.
2. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *J Clin Med*. 2017;6(11):99.
3. Drossman DA, Tack J. Rome Foundation clinical diagnostic criteria for disorders of gut-brain interaction. *Gastroenterology*. 2022;162(3):675-679.
4. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920-924.
5. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. *Am J Gastroenterol*. 2002;97(11):2812-2819.
6. Orleck K. Making patient quality of life the focus of IBS-C management. *Gastroenterol Hepatol (N Y)*. 2025;21(11)(suppl 7):1-14.
7. The Rome Foundation. Rome V: A Global Framework for Disorders of Gut–Brain Interaction. Accessed: June 14, 2026. https://theromefoundation.org/rome-v-a-global-framework-for-disorders-of-gut-brain-interaction/
8. Oka P, Parr H, Barberio B et al. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*. 2020;5:908-917.
9. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology*. 2000;119(3):654-660.
10. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *Lancet*. 2020;396(10263):1675-1688.
11. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol*. 2014;20(22):6759-6773.
12. Camilleri M. Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med*. 2012;367(17):1626-1635.
13. Camilleri M. Management of the irritable bowel syndrome. *Gastroenterology*. 2001;120(3):652-668.
14. Barbara G, Barbaro MR, Fuschi D, et al. Inflammatory and microbiota-related regulation of the intestinal epithelial barrier. *Front Nutr*. 2021;8:718356.

15. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol*. 2012;303(7):G775-G785.
16. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome—a meta-analysis. *Am J Gastroenterol*. 2006;101(8):1894-1899.
17. Lacy BE. Managing IBS-C: focus on symptom control. *Gastroenterol Hepatol (NY)*. 2024;20(4):216-226.
18. Jin J. JAMA patient page. Over-the-counter laxatives. *JAMA*. 2014;312(11):1167.
19. Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol*. 2013;108(9):1508-1515.
20. Amitiza (lubiprostone) [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; August 2023.
21. Linzess (linaclotide) [package insert]. North Chicago, IL: AbbVie, Inc.; June 2023.
22. Trulance (plecanatide) [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; April 2021.
23. Ibsrela (tenapanor) [package insert]. Waltham, MA: Ardelyx, Inc.; April 2022.
24. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*. 2009;29(3):329-341.
25. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107(11):1702-1712.
26. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol*. 2012;107(11):1714-1724.
27. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. *Am J Gastroenterol*. 2018;113(5):735-745.
28. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo controlled phase 3 trial (T3MPO-1). *Am J Gastroenterol*. 2020;115(2):281-293.
29. Chey WD, Lembo AJ, Yang Y, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 26-week, placebo controlled phase 3 trial (T3MPO-2). *Am J Gastroenterol*. 2021;116(6):1294-1303.
30. Lembo AJ, Chey WD, Rosenbaum DP. An open-label, long-term safety trial of tenapanor in patients with irritable bowel syndrome with constipation (IBS-C): T3MPO-3. Poster P0338. *Am J Gastroenterol*. 2018;113(suppl):S252.
31. Brenner DM. Mechanism of action considerations in the management of IBS-C. *Gastroenterol Hepatol (N Y)*. 2023;19(12)(suppl 6):749-756.
32. Alfasigma USA, Inc. Press release: ZELNORM® (tegaserod): Notice of Withdrawal from Market. https://www.prnewswire.com/news-releases/zelnorm-tegaserod-notice-of-withdrawal-from-market-301578099.html. Accessed May 20, 2026.
33. Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. *Gastroenterology*. 2018;155(6):1753-1763.
34. Nelson AD, Black CJ, Houghton LA, Lugo-Fagundo NS, Lacy BE, Ford AC. Systematic review and network meta-analysis: efficacy of licensed drugs for abdominal bloating in irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2021;54(2):98-108.
35. Eutamene H, Charmot D, Navre M, et al. Visceral antinociceptive effects of RDX5791, a first-in-class minimally systemic NHE3 inhibitor on stress-induced colorectal hypersensitivity to distension in rats. *Gastroenterology*. 2011;140:S57-S58.
36. Spencer AG, Labonte ED, Rosenbaum DP, et al. Intestinal inhibition of the Na+/H+ exchanger 3 prevents cardiorenal damage in rats and inhibits Na+ uptake in humans. *Sci Transl Med*. 2014;6(227):227ra36.
37. Sinagra E, Rossi F, Raimondo D, et al. Tenapanor for the treatment of irritable bowel syndrome with constipation. *Expert Rev Clin Pharmacol*. 2020;13(5):473-479.
38. Li Q, King A, Liu L, et al. Tenapanor reduces IBS pain through inhibition of TRPV1-dependent neuronal hyperexcitability in vivo. Presented at: American College of Gastroenterology Annual Scientific Meeting; October 13-18, 2017; Orlando, FL, US. *Am J Gastroenterol*. 2017;112(suppl):S255.
39. Lacy BE, Shin AS, Cangemi DJ, Yang Y, Zhao S, Rosenbaum DP. Tenapanor is associated with earlier and sustained symptom relief in IBS-C: a post hoc analysis. *Therap Adv Gastroenterol*. Published online: January 24, 2026.
40. Brenner DM, Lacy BE, Ford AC, et al. Linaclotide reduced response time for irritable bowel syndrome with constipation symptoms: analysis of 4 randomized controlled trials. *Am J Gastroenterol*. 2023;118(5):872-879.
41. Clark A, Li R, Spiegel BMR, Almario CV. A single question about quality-of-life improvement identifies treatment satisfaction in IBS-C: results from the "JUST ASK" study. Presented at: Digestive Disease Week; May 2-5, 2026; Chicago, Illinois.
42. Krut ZG, Eberlein S, Tetrault E, et al. Virtual reality-delivered cognitive behavioral therapy improves IBS symptoms: results from an NIH-funded multicenter pilot randomized controlled trial. Presented at: Digestive Disease Week; May 2-5, 2026; Chicago, Illinois.


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