Case Study Series

Gastroenterology & Hepatology

September 2025

Individualizing Treatment in IBS-C Management: The Key to Improving and Maintaining Successful Outcomes

Bryan Curtin, MD, MHSc
Director of Neurogastroenterology and Motility
The Institute for Digestive Health and Liver Disease
Mercy Medical Center
Baltimore, Maryland

ON THE WEB:
gastroenterologyandhepatology.net

Indexed through the National Library of Medicine
(PubMed/Medline), PubMed Central (PMC), and EMBASE

Individualizing Treatment in IBS-C Management: The Key to Improving and Maintaining Successful Outcomes

Bryan Curtin, MD, MHSc
Director of Neurogastroenterology and Motility
The Institute for Digestive Health and Liver Disease
Mercy Medical Center
Baltimore, Maryland

About the Patient

JG, a 42-year-old woman with a history of hypertension, presents at the gastrointestinal (GI) motility clinic with a 5-year history of persistent abdominal bloating, abdominal discomfort, and constipation. Her symptoms began following an episode of viral gastroenteritis, which affected multiple family members. Although others recovered fully, JG continued to experience these abdominal and bowel symptoms. Notably, she developed bloating accompanied by straining during defecation and a sensation of incomplete evacuation. Her stool consistency became harder, corresponding to Bristol Stool Form Scale (BSFS) type 1. Previously her bowels "worked like clockwork" but now they are unpredictable.

She reports daily persistence of symptoms, with abdominal pain occurring at least 5 days per week, typically associated with the absence of bowel movements. Over the course of her illness, she has intermittently struggled with hemorrhoids. She previously underwent evaluation by a gastroenterologist, including endoscopy and colonoscopy; both procedures were unremarkable apart from the presence of mild hemorrhoids.

She has tried multiple over-the-counter agents, including polyethylene glycol (MiraLAX) and senna, as well as several holistic remedies and probiotics, with minimal symptomatic improvement. A previous prescription of linaclotide led to intolerable diarrhea, prompting her to discontinue the medication.

She identifies bloating and abdominal distension as the most disruptive symptoms affecting her quality of life (QOL), noting progressive worsening throughout the day in tandem with abdominal pain. She expresses significant apprehension around attending social events or dining out, because of concern that her symptoms will escalate. Symptom severity has led her to miss work.

Her physical examination is largely unremarkable. There is mild abdominal tenderness on palpation without guarding or rebound. Cardiovascular and pulmonary examinations are within normal limits. Surgical history is notable only for a cholecystectomy performed 10 years ago. Family history is negative for colorectal cancer, polyposis syndromes, celiac disease, or inflammatory bowel disease (IBD).

I discussed with JG that her clinical history and symptom profile are consistent with a diagnosis of irritable bowel syndrome with constipation (IBS-C). Upon inquiry regarding diagnostic testing, I explained that IBS is a symptom-based diagnosis, and although no definitive test exists to confirm it, her presenting symptoms fulfill the criteria for a confident diagnosis.

I reassured JG that although IBS-C is not curable, there are US Food and Drug Administration (FDA)–approved therapeutic options available that can lead to substantial improvement in both her abdominal and bowel symptoms, as well as overall QOL. I emphasized that the central goal of IBS-C management is significantly improved QOL through symptom control.

Following a review of the complex multifactorial

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

pathophysiology underlying the disorder, I discussed the efficacy, safety profiles, and mechanism of action (MOA) of FDA-approved treatments for IBS-C. I emphasized that the complex pathophysiology of IBS-C necessitates a trial-and-error approach to therapy. Given her prior intolerance to the secretagogue linaclotide, we elected to initiate tenapanor, a first-in-class sodium/hydrogen exchanger isoform 3 (NHE3) inhibitor (retainagogue), at 50 mg twice daily. A follow-up visit was scheduled at 10 weeks to evaluate therapeutic response.

At her 10-week follow-up, JG reported marked improvement across all symptom domains. Stool consistency improved, with BSFS type 3 noted approximately 70% of the time, and straining during defecation was significantly reduced. Abdominal pain and bloating had subsided to the extent that she no longer missed work and had resumed normal social activities, including dining out, without apprehension.

In the Clinic . . .

Patients do not necessarily seek consultation from the GI motility unit initially for the symptoms JG has. They normally go to their primary care physician or a gastroenterologist first. If initial testing and evaluation is not fruitful, they will commonly be referred to a GI motility specialist.

I see patients struggle for at least 2 years with constipation and abdominal symptoms before seeking a GI motility consultation because most patients assume that "it is a phase and things will improve." I have also seen patients who have come back 30 years after first presenting to the clinic to see if there are novel therapeutic options. There are many more options for the treatment of IBS-C now than there were even 10 years ago.

It is clear that patients who present with concurrent constipation and abdominal symptoms have suffered for a long time. This combination often significantly impacts their QOL, either socially or at work, and is a significant consideration before they undertake activities considered normal.

They present at the GI motility clinic generally after trying over-the-counter medications and lifestyle modifications including diet and exercise, and sometimes "failing" an FDA-approved IBS-C medication (as in case of JG). The first specialist visit is a critical point in the patient's care, not only to make a proper diagnosis but also to establish a foundation for a solid physician–patient relationship moving forward.

Making a confident IBS-C diagnosis and initiating treatment with an appropriate FDA-approved agent for IBS-C are among the many objectives of this first patient visit. The following sections explore practical strategies for effectively managing IBS-C, viewed through the framework of both the first patient visit and follow-up visit.

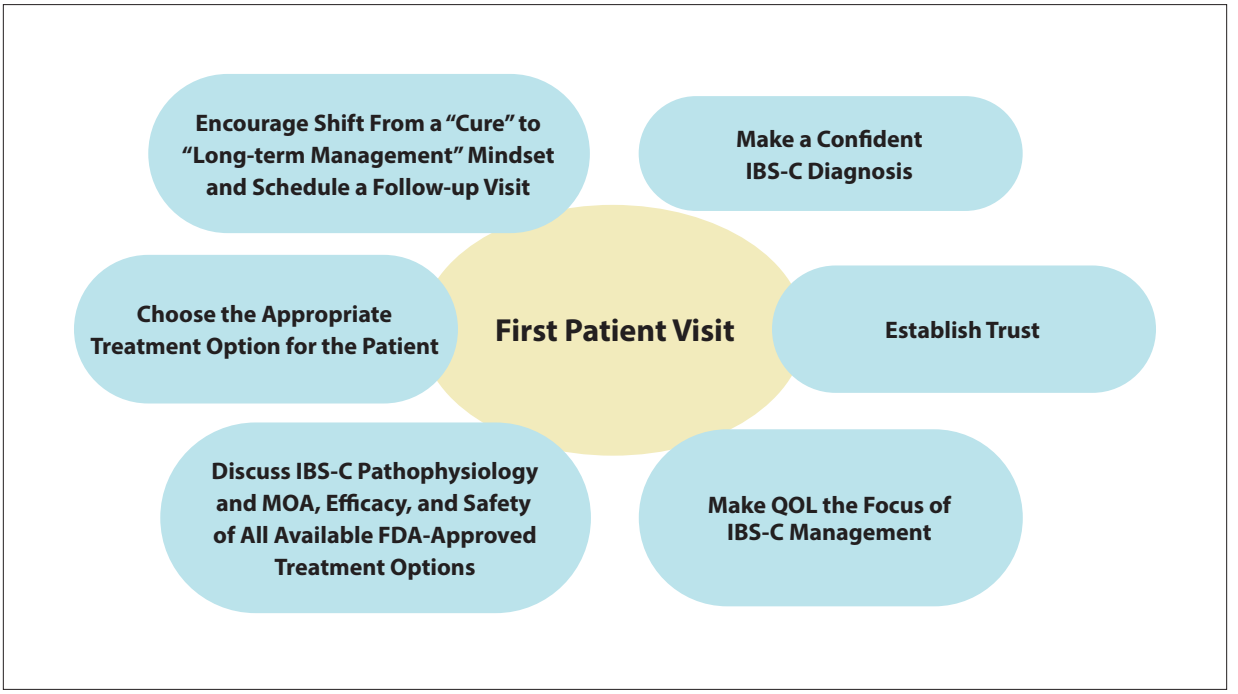

Figure 1. Objectives of the first patient visit.

FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation; MOA, mechanism of action; QOL, quality of life.

First Patient Visit

The initial consultation for patients with symptoms of IBS-C has multiple key objectives, foremost making a confident diagnosis through a positive diagnostic approach (Figure 1).

Equally critical is establishing trust, which serves as the foundation for successful long-term management. This requires patient education, empathic listening, and attention to all patient concerns. Clinicians should tailor discussions to the patient's level of understanding, emphasizing the chronic nature of IBS-C and reassuring patients that significant improvement in QOL is the central goal of therapy.

Explaining the multifactorial complex pathophysiology of IBS-C is also essential. This sets the stage for discussing the different MOAs, efficacy, and safety profiles of available FDA-approved therapies. Shared decision-making is vital in selecting an appropriate treatment based on individual presentation and prior response.

Finally, clinicians should reinforce the need to transition from a "cure" mindset to one focused on chronic long-term symptom management. The importance of follow-up visits must be emphasized, both to assess therapeutic efficacy and to adapt the treatment plan when necessary.

Make a Confident IBS-C Diagnosis

The hallmark complaints in IBS-C are a combination of constipation-related symptoms and abdominal symptoms, most commonly abdominal pain and bloating. In contrast to conditions such as IBD, IBS-C lacks validated diagnostic tests or biomarkers. As a result, a diagnosis of exclusion is not required; rather, a positive, symptom-based diagnostic approach is appropriate. The American College of Gastroenterology (ACG) also endorses a positive diagnostic strategy for IBS-C, which supports early diagnosis, avoiding unnecessary testing and ultimately allowing for more timely initiation of appropriate therapy.[1]

The diagnosis of IBS-C is guided by the Rome IV Diagnostic Criteria for Irritable Bowel Syndrome.[2-4] Specifically, the criteria require a history of recurrent abdominal pain and/or bloating associated with altered stool form or frequency, in the absence of alarm features such as unintentional weight loss, hematochezia (unrelated to hemorrhoids or anal fissures), or concerning family history (Figure 2).[5] A thorough clinical assessment is essential to rule out these red flag symptoms.

Diagnosis of IBS-C requires that more than 25% of bowel movements correspond to BSFS types 1 or 2, and fewer than 25% are types 6 or 7.[3] Additionally, patients must report abdominal pain occurring, on average, at least 1 day per week, accompanied by at least two of the follow-

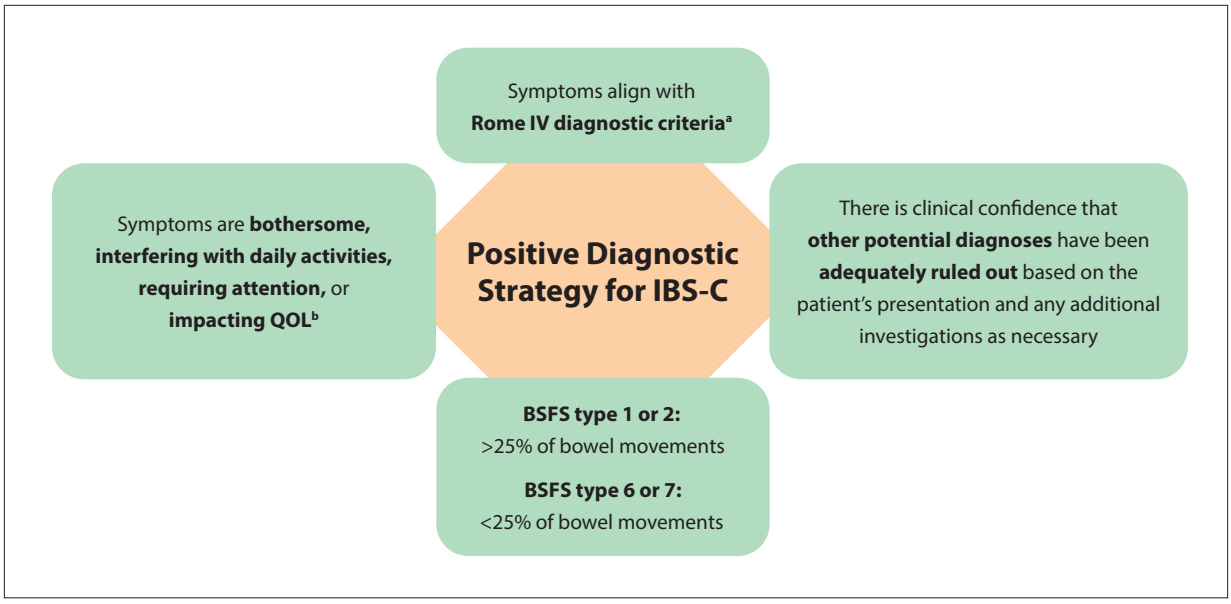

Figure 2. Using a positive diagnostic strategy for IBS-C in the clinic.

BSFS, Bristol Stool Form Scale; IBS-C, irritable bowel syndrome with constipation; QOL, quality of life.

[a]According to the Rome IV criteria, IBS is a disorder of gut-brain interaction in which abdominal pain recurs on average at least 1 day per week 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.

[b]Symptoms are present for at least 8 weeks.

Adapted from Kongara K. *Gastroenterol Hepatol (N Y)*. 2025;21(5)(suppl 3).[5]

Table 1. First Patient Visit: Sample Questions to Ask Your Patients

Questions to aid IBS-C diagnosis
• What is the frequency of your bowel movements?
• What is the character of your bowel on the BSFS scale? *(Share with the patient the BSFS chart)*
• What is the evacuation process? Is there straining associated with your bowel movement?
• Do you feel completely evacuated?
• Do you experience any abdominal symptoms?
• How long have these symptoms persisted? Do you remember any event that triggered your symptoms?
• What have you tried to alleviate these symptoms?
• How do these symptoms impact your QOL?
Questions to rule out alarm features
• Have you experienced unintended weight loss (more than 10% within 3 months) or hematochezia (unrelated to hemorrhoids or anal fissures)?
• Do your symptoms disrupt sleep or awaken you at night?
• Have you experienced any fever, anemia, or rapidly progressing or acute symptoms?
• Do you have any family history of colorectal cancer, polyposis syndrome, celiac disease, or IBD?
Note: Check for any palpable mass, ascites, or lymphadenopathy.

BSFS, Bristol Stool Form Scale; IBD, inflammatory bowel disease; IBS-C, irritable bowel syndrome with constipation; QOL, quality of life.

ing features: pain related to defecation, a change in stool frequency, or a change in stool form or appearance.[2] These symptoms should persist for a minimum of 8 weeks and be perceived as bothersome, interfering with daily activities, requiring attention, or negatively affecting QOL.[3]

In the case of JG, symptoms of abdominal pain, distension, and hard stools (BSFS type 1) began 5 years ago and have remained persistent on a daily basis. Abdominal pain occurs at least 5 times per week, typically in association with the absence of bowel movements. Bloating and distension progressively worsen throughout the day and significantly affect her QOL. Her condition has led to fear of attending social events or dining out and has necessitated missed workdays owing to symptom severity. Prior endoscopy and colonoscopy were unremarkable except for internal hemorrhoids. Combined with a largely benign physical examination and absence of significant personal or family history of gastrointestinal disease, these findings support a confident clinical diagnosis of IBS-C.

Table 1 suggests sample questions for the first patient visit that can aid in IBS-C diagnosis.

In the Clinic . . .
Constipation: Not Just About the Number of Bowel Movements

The definition of constipation is very broad and patients and providers may not be on the same page when using the term. Number of bowel movements alone is not a reliable indicator of constipation, as patients may report frequent trips to the restroom because of a persistent sense of incomplete evacuation. Therefore, understanding the **nature of the constipation (character of the stool and evacuation process)** specifically, in addition to the number of bowel movements, is critical.

Clinical aid: *Keep a BSFS chart in your clinic to help patients describe the nature of their stool.*

In the Clinic . . .
Rule Out Alarm Features

Check for the following alarm features during the first patient visit:

- New symptoms in patients over 50 years of age
- Unintended weight loss (more than 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

What you should do: *Start a prompt investigation and initiate treatment in case of any alarm features, as these could indicate an underlying organic GI disorder.*

Table 2. First Patient Visit: Sample Answers to Typical Patient Questions

Patient question	Possible answer
Are you sure I do not need any tests to confirm this diagnosis?	**Assure the patient** that, unlike for other diseases that have markers to test to confirm a diagnosis, IBS diagnosis is straightforward and symptom based. It usually involves debilitating abdominal symptoms accompanied by change in stool form or frequency. There are no valid tests.
Why do I have IBS-C?	**Explain to the patient** that, although the diagnosis of IBS-C is relatively straightforward, its underlying pathophysiology is complex and could involve immune dysfunction, the gut microbiome, dysbiosis, intestinal permeability, viral infection, etc. There is no way to know what is the cause of each patient's underlying symptoms.
Can I make any modifications in my lifestyle to help with my symptoms?	**Emphasize to the patient** that lifestyle modifications work well for some patients but are insufficient in addressing all IBS-C symptoms. I advocate for adequate water and fiber intake along with exercise but caution my patients that these alone will not get them to the improved QOL goal that is possible with FDA-approved treatments. • Fiber such as bran increases bloating • A low FODMAP diet worsens constipation • Osmotic and stimulant laxatives and PEG have no impact on abdominal pain • Stimulants worsen abdominal symptoms • Probiotics have a limited impact on abdominal symptoms
What can you do to cure IBS-C?	**Be up-front with patients** that, although you would like to completely cure their IBS, that is not yet possible with current treatments. Assure them that with the FDA-approved treatment options available, your aim is to achieve a 60% to 80% overall symptom improvement (both bowel and abdominal) and significant QOL improvement.
Why is there a trial-and-error approach to IBS-C management?	**Educate the patient** that because the pathophysiology of IBS-C can be different from patient to patient, a one-size-fits-all approach cannot be applied to IBS-C management. The good news is that various FDA-approved agents target different pathophysiologic pathways, so if one medication does not work well for the patient, then switching to a medication with a different MOA may achieve desired response.

FODMAP, low-fermentable oligo-, di-, monosaccharides, and polyols; IBS-C, irritable bowel syndrome with constipation; MOA, mechanism of action; PEG, polyethylene glycol; QOL, quality of life.

Establish Trust

Establishing trust during the first patient visit is critical. Some patients may have already heard of the term IBS, and others may have had their symptoms dismissed in the past by being told, "It's just IBS. You don't have to worry about it." Although IBS isn't life-threatening or linked to IBD, minimizing patient suffering in this manner can discourage patients from seeking appropriate care, openly discussing QOL concerns, or engaging actively in treatment planning. Clinicians should be empathetic and be prepared to answer all patient questions (Table 2).

A qualitative analysis of online posts of patients' IBS-C experiences with pharmacologic therapies presented at Digestive Disease Week 2025 confirmed the high biopsychosocial burden of IBS-C and reinforced the need for shared decision-making in IBS-C management.[6] This approach is essential in addressing patient perceptions of efficacy, side effects, cost, and personal beliefs, allowing patients and their clinicians to identify the best treatment option for each individual and potentially improving adherence and outcomes.

Acknowledging the complex multifactorial pathophysiology of IBS-C is important, along with clear communication about realistic expectations and therapeutic goals. Establishing significant QOL improvement as the central objective helps orient both clinician and patient toward meaningful outcomes.

An informed, collaborative approach builds trust, validates patient experiences, and lays the groundwork for successful long-term IBS-C management.

In the Clinic . . .
Address ALL Patient Concerns

By the time patients present for their initial consultation, many have endured prolonged symptom burden and frustration. It is essential to dedicate sufficient time during this first patient visit to build confidence and reassure patients that their symptoms are valid, manageable, and deserving of attention, and that with long-term collaborative management QOL improvement is achievable.

Make QOL the Focus of IBS-C Management

A crucial aspect of IBS-C management entails understanding the specific symptoms that most influence each patient's QOL. This assessment can vary widely among individuals. For some, severe abdominal pain is profoundly debilitating; for others, bloating and distension are the most distressing, often leading to embarrassment especially when changing clothes or taking photographs. Beyond these primary complaints, the IBS in America 2024 survey highlights additional burdensome abdominal symptoms, including abdominal fullness, excessive gas or flatulence, fatigue, tenesmus, and gastroesophageal reflux or heartburn.[7] Bowel-related challenges are equally disruptive, with many patients reporting frequent, unproductive visits to the restroom, persistent sensations of incomplete evacuation, and significant straining.

The QOL implications of these debilitating symptoms has been reported both anecdotally by patients and in published surveys. The majority of IBS in America 2024 survey respondents experiencing "quite bad" or "very bad" abdominal pain reported significant interference with daily functioning.[8] Moreover, respondents reported some degree of negative impact of IBS-C on several aspects of their overall QOL—including mental and emotional health, sexual health and intimacy, employment or education, sense of independence, relationships with friends or family, and household finances. A separate analysis from the same survey presented at Digestive Disease Week 2025 used a validated financial questionnaire (FACIT-COST) to evaluate the relationship between symptom severity and financial distress.[9] It revealed that patients with greater symptom severity experienced greater financial distress, including concerns about out-of-pocket medical expenses, their ability to work, and their financial future.

This makes it critical to assure the patients that the goal of treatment is to address their most bothersome symptom and significantly improve their QOL.

Educate About the Trial-and-Error Approach to IBS-C Management

IBS, a disorder of gut-brain interaction, has a complex multifactorial pathophysiology.[10-19] Hard stools and decreased defecation could be a result of altered gut motility and water imbalances. Inflammatory and hypervisceral responses could be caused by aberrant microbiome-immune interactions and changes in gut permeability. Other factors that have been implicated in IBS include psychiatric and psychological conditions, particularly anxiety and depression, genetic predisposition, adverse early life events, and GI infections. Note that JG developed IBS-C after a bout of viral gastroenteritis 5 years ago.

Importantly, it is not possible to determine the exact underlying pathophysiology in any individual patient. This is the rationale for the availability of multiple FDA-approved agents with distinct MOAs. Selection of the initial FDA-approved agent is empirical. If a patient fails to respond adequately, then switching to an agent with a different MOA may provide better symptom control by targeting an alternate pathophysiologic pathway.

This makes a structured and thorough assessment at follow-up essential to evaluate efficacy and tolerability and guide further treatment adjustments.

In the Clinic . . .

It is important to acknowledge to the patient that the precise underlying cause of their IBS-C symptoms cannot be definitively determined owing to the complex multifactorial pathophysiology. However, this uncertainty does not change the therapeutic approach. The management of IBS-C inherently involves a degree of trial and error, as the goal is to identify the treatment that provides the greatest symptom relief and QOL improvement for the individual patient.

Reassure the patient that FDA-approved agents offer a range of mechanisms to target different pathways implicated in IBS-C. Emphasize your commitment to working collaboratively to find the option that works best for them. Reiterate that meaningful improvement in QOL is an attainable and a realistic goal.

Encourage Attitude Shift: From a "Cure" to "Long-Term Management" Mindset

Reinforce with the patient that IBS-C is a chronic condition in which the bothersome symptoms wax and wane depending on a host of factors. Sometimes triggers that exacerbate the condition can be identified, but usually actively managing it is the only way to ensure successful outcomes. The chronic nature of this condition necessitates chronic management.

Discuss the MOA of All FDA-Approved Treatment Options

The FDA has approved 5 medications with 3 distinct MOAs for treatment of IBS-C: a 5-hydroxytryptamine type 4 agonist, tegaserod; 3 secretagogues, lubiprostone, linaclotide, and plecanatide; and a retainagogue, tenapanor.[20-24] The first of these, tegaserod, was approved in 2002. Because it is no longer available commercially, it will not be discussed further. This was followed by approval of 3 secretagogues, with the last secretagogue approved in 2017 and then the first-in-class retainagogue, tenapanor, in 2019. Tenapanor was launched in the United States in 2022.

Secretagogues accelerate colonic transit, improve stool consistency, and increase the frequency of bowel

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

FDA-approved agent	IBS-C treatment indication	Dosage and administration
Lubiprostone	Women >18 years of age	8 µg twice daily orally 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		3 mg taken orally once daily with or without food
Tenapanor		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.

movements by increasing the secretion of chloride and bicarbonate ions into the intestinal lumen and hence promoting water secretion.[25] The first-in-class retainagogue, tenapanor, is a locally acting inhibitor of NHE3.[26-29] The NHE3 antiporter is responsible for the absorption of dietary sodium. NHE3 inhibition results in: (1) reduced absorption of dietary sodium; (2) reconstitution of the tight junctions between intestinal epithelial cells; and (3) antagonism of transient receptor potential vanilloid 1 channels. Reduced absorption of dietary sodium causes water retention in the intestinal lumen, accelerating intestinal transit. The latter 2 effects demonstrated reduction in visceral hypersensitivity and improvement in abdominal symptoms in animal models. Assessment of intestinal permeability and visceral hypersensitivity is not available in routine clinical practice.

Of the available agents, plecanatide, linaclotide, and tenapanor are indicated for treatment of IBS-C in adults.[22-24] Note that pediatric studies for linaclotide and tenapanor are ongoing and their preliminary results presented at Digestive Disease Week 2025 are promising.[30-32] Lubiprostone is indicated for the treatment of IBS-C in women at least 18 years of age.[21] Table 3 discusses the dosage and administration of these agents.[21-24]

Discuss the Efficacy and Safety Data of the Available FDA-Approved Treatment Options

Pivotal, large, randomized, and placebo-controlled trials lasting 12 weeks or 26 weeks have evaluated the impact of these FDA-approved agents on both bowel and abdominal symptoms associated with IBS-C.[33-38] They evaluated primary endpoints of overall response or the FDA combined endpoint for IBS-C response. Follow-up analyses evaluated many secondary endpoints—namely, abdominal discomfort or pain, bloating, constipation severity, frequency and stool consistency, and straining.[39-42]

Figure 3 discusses the efficacy and safety data of the currently available FDA-approved agents for IBS-C.[25]

Primary Endpoint Significantly more patients achieved the primary endpoint of overall response with lubiprostone and the FDA combined endpoint with linaclotide, plecanatide, and tenapanor compared with placebo:

- Lubiprostone: combined analysis of two 12-week phase 3 trials (17.9% vs 10.1%; *P*=.001; and this increased over the first 3 months of treatment [month 1: 10.8% vs 7.5%; month 2: 18.3% vs 11.4%; month 3: 22.0% vs 14.5%])[33]
- Linaclotide: 26-week (33.7% vs 13.9%; *P*<.0001) and 12-week study (33.6% vs 21.0%; *P*<.0001)[34,35]
- Plecanatide: Study 1 (30.2% [3 mg arm] and 29.5% [6 mg arm] vs 17.8%; *P*<.001) and Study 2 (21.5% [3 mg arm] and 24.0% [6 mg arm] vs 14.2%; *P*=.009)[36]
- Tenapanor: 12-week T3MPO-1 trial (27.0% vs 18.7%; Cochran-Mantel-Haenszel [CMH] *P*=.020) and the 26-week T3MPO-2 trial (36.5% vs 23.7%; CMH *P*<.001)[37,38]

Secondary Endpoints Multiple secondary endpoints were also improved with FDA-approved agents compared with placebo in these trials and their reanalysis.

- Lubiprostone: abdominal discomfort or pain, bloating, constipation severity, stool consistency, and straining significantly improved in overall responders compared with nonresponders[33]
- Linaclotide[34,35]:
  – 12-week study: abdominal pain (48.9% vs 34.5%)

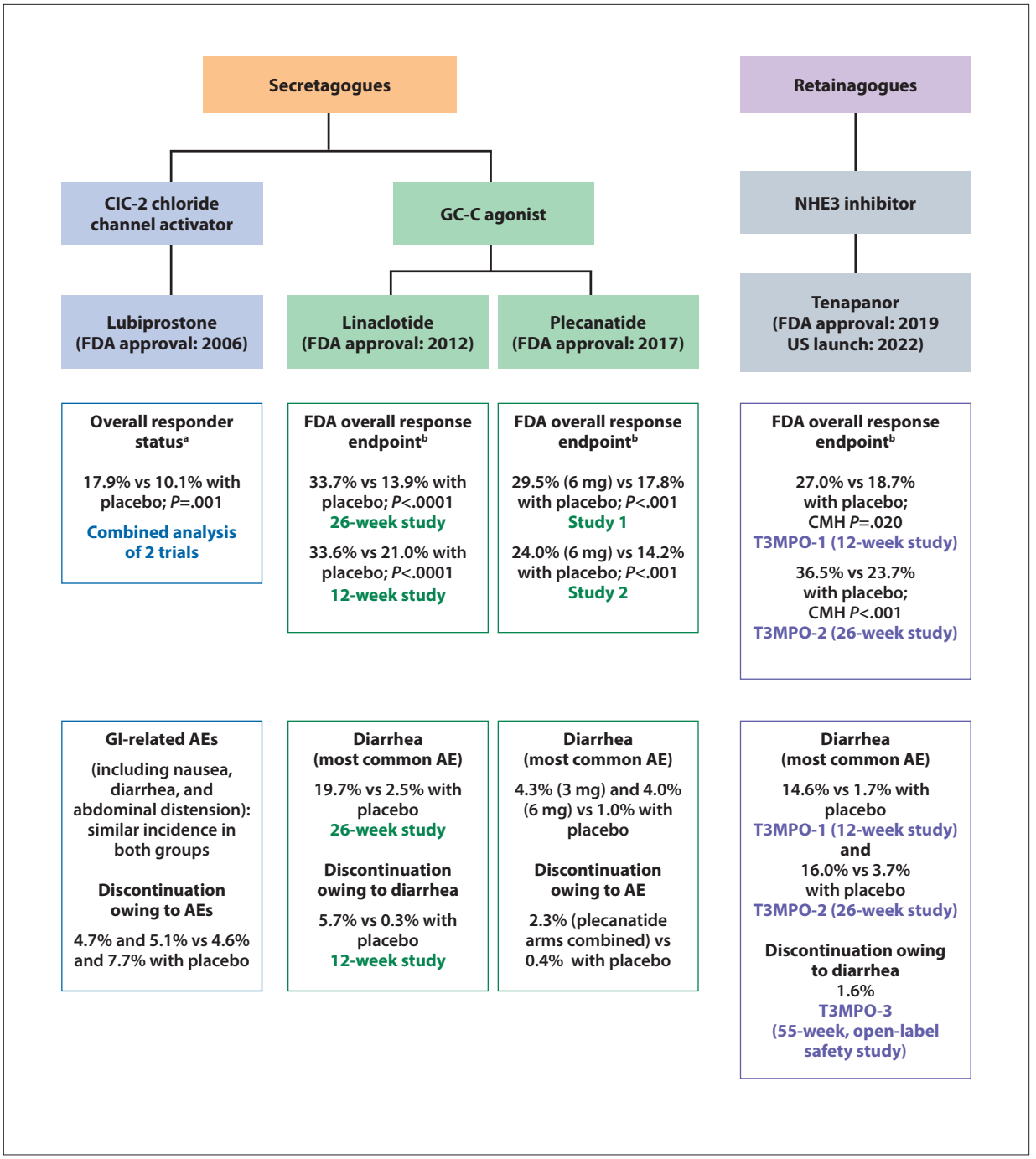

Figure 3. Currently available FDA-approved treatment options for IBS-C and their efficacy and safety data.

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

[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.

Adapted from Brenner DM. *Gastroenterol Hepatol (N Y)*. 2023;19(12)(suppl 6):749-756.[28]

and complete spontaneous bowel movement (CSBM) response (47.6% vs 22.6%) for 9 out of 12 weeks
  - 12-week study: reduction in abdominal pain of 30% or greater (50.1% vs 37.5%; *P*=.0003) and an increase of at least 1 CSBM from baseline (48.6% vs 29.6%; *P*<.0001) for at least 6 of the 12 treatment weeks

- Plecanatide[36,39-41]:
  - Pivotal trials: stool frequency/consistency, straining, and abdominal symptoms
  - Reanalysis: novel trisymptom composite endpoint (consisting of abdominal pain, abdominal bloating, and CSBMs)
  - Among patients with IBS-C classified as having moderate-to-severe bloating: reduced bloating severity (least-squares mean change, –1.7 vs –1.3; *P*=.002), reduced abdominal pain (–1.7 vs –1.3; *P*=.006), and increased CSBM frequency (1.4 vs 0.8; *P*<.0001)
  - Systemic review and meta-analysis: abdominal pain (pooled effect size, –0.49; 95% CI, –0.88 to –0.09; *P*=.03); change in BSFS score (pooled effect size, 0.82; 95% CI, –0.53 to 2.18; *P*=.12); change in CSBM (pooled effect size, 0.53; 95% CI, –1.77 to 2.83; *P*=.42); and change in straining score outcome (pooled effect size, 0.39; 95% CI, –1.21 to 1.99; *P*=.40)

- Tenapanor[37,38,42]:
  - T3MPO-1: abdominal pain response (44.0% vs 33.1%; CMH *P*=.008); abdominal discomfort response (29.0% vs 17.1% [CMH *P*<.001]); rate of abdominal bloating response (27.0% vs 16.1% [CMH *P*=.001]); abdominal cramping response (30.6% vs 23.1% [CMH *P*=.044]); and abdominal fullness response (27.4% vs 14.4% [CMH *P*<.001])
  - T3MPO-2: abdominal pain response (49.8% vs 38.3%; CMH *P*=.004) and CSBM (47.4% vs 33.3%; CMH *P*<.001)
  - Post hoc analysis of pooled data from the T3MPO-1 and T3MPO-2 trials: abdominal score (AS; least-squares mean change from baseline: –2.66 vs –2.09; *P*<.0001) and AS response rate for at least 6 out of 12 weeks (44.4% vs 32.4%; *P*<.0001) and for at least 9 out of 12 weeks (30.6% vs 20.5%; *P*<.0001). (AS: average of weekly scores for abdominal pain, discomfort, and bloating symptoms)
  - Note that tenapanor was associated with an improvement in abdominal pain as early as 1 week after treatment initiation and a decrease in other abdominal symptoms including bloating, fullness, discomfort, and cramping.

Safety Side effects with the FDA-approved treatment options are generally mild or moderate in severity. GI-related events were the most frequently occurring adverse events and included nausea, diarrhea, and abdominal distension in both lubiprostone studies.[33] Diarrhea was the most frequently reported adverse event in linaclotide, plecanatide, and tenapanor studies.[34-38] Additionally, tenapanor was well tolerated with no new safety signals and only 1.6% discontinuation owing to diarrhea in a 55-week open-label safety study (T3MPO-3).[43]

In the Clinic . . .

Reiterate that FDA-approved medications for IBS-C are safe and effective across a host of endpoints involving bowel and abdominal symptoms in large, randomized, clinical trials.

Choose the Appropriate Treatment Option for the Patient and Schedule a Follow-up Visit

For patients who have not yet tried an FDA-approved treatment, any FDA-approved agent may serve as an appropriate initial therapy. Current guidelines from the ACG and American Gastroenterological Association do not propose a sequencing algorithm for these agents.[5,44] This is largely owing to the absence of head-to-head clinical trials comparing efficacies of these agents. Nevertheless, 2 network meta-analyses of randomized controlled trials of these agents offer indirect comparisons.[45,46] The first demonstrated similar efficacy of FDA-approved agents across most endpoints and proved their superiority to placebo for the treatment of global IBS-C symptoms. The second also concluded that all agents were superior to placebo and indirect comparisons across agents revealed no significant differences with respect to abdominal bloating.

For patients who have previously tried an FDA-approved treatment without achieving adequate response, it is essential to determine whether the issue was related to insufficient efficacy or poor tolerability. If an agent from one pharmacologic class fails to produce the desired response, then switching within the same class is unlikely to yield improved response. Because IBS-C has a complex multifactorial pathophysiology and different therapeutic classes target distinct pathophysiologic pathways, transitioning to an agent with a different MOA is the more appropriate strategy.

In the current case, JG had tried a secretagogue, linaclotide, but experienced intolerable diarrhea and hence stopped taking it. Diarrhea is a common side effect of secretagogues, and although clinical trials suggest a 15% incidence, in clinical practice this may be higher. Moreover, this patient was experiencing severe abdominal pain and bloating. Tenapanor, a first-in-class retainagogue, not only has good clinical data for abdominal pain and bloat-

Table 4. Individualizing Treatment: Key Patient Factors

Key patient factor	What you can do
Reason for failure of prior FDA-approved IBS-C treatment	Investigate if this was an efficacy issue or a tolerability issue.
Timing of medication	In many cases, timing of medication proves to be an issue, especially with linaclotide. Linaclotide cannot be taken too close to the meals, as that results in diarrhea. On the other hand, there are no such restrictions with tenapanor.
Patients on multiple medications for different conditions	This situation can become tricky to navigate, as every medication has a unique side effect profile and specific requirement for administration.

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

ing but is also milder than linaclotide so was deemed a good fit for this patient.

Table 4 discusses some patient factors for consideration in individualizing treatment. Schedule a follow-up visit to assess treatment response and to adapt the treatment plan if necessary.

In the Clinic . . .

Reiterate that IBS-C management is not a one-size-fits-all approach; therefore, what works for one patient may not work for another. This makes it critical to schedule a follow-up visit to assess response.

Follow-up Visit

When to Conduct a Follow-up Visit

Knowing when to conduct a follow-up visit is critical. Most clinical trials with FDA-approved IBS-C medications had at least a 12-week duration and some lasted 26 weeks. Open-label extensions have lasted over 1 year as well. Analysis of these trials show that bowel symptoms improve first, followed by abdominal symptoms.

In a post hoc analysis of pooled data from 3 tenapanor studies (T3MPO-1, T3MPO-2, and a phase 2b study), the median time to CSBM response was 2 weeks, whereas time to abdominal pain response was 4 weeks and time to bloating response was 5 weeks.[47] Moreover, persistence with therapy improved response rates over time—CSBM response probability (52.3%, 72.5%, and 76.7% for weeks 2, 4, and 12, respectively); abdominal pain response (54.6%, 67.9%, and 72.3% for weeks 4, 8, and 12); and abdominal bloating response probability (48.1%, 61.9%, and 67.7% for weeks 4, 8, and 12).

In a post hoc analysis of linaclotide trials, more than one-half of patients with IBS-C in the linaclotide group experienced responses for abdominal pain, discomfort, bloating, or CSBM frequency within 4 weeks of starting treatment, and an additional 8% to 17% showed responses between weeks 5 and 12.[48]

Therefore, patients should persist with treatment for several weeks to experience the full effect of therapy. It is for this reason an ideal follow-up interval is 2 months after therapy initiation.

In the Clinic . . .

Pharmaceutical representatives often leave medication samples, which are subsequently given to patients as a means of initiating treatment. Although this practice may seem pragmatic, it can be particularly counterproductive in IBS-C. Patients often interpret these samples as short-term trials, evaluating the medication's efficacy within the span of 1 week. If symptom relief is not immediate, they may prematurely conclude that the treatment has failed.

This misperception is problematic, given the typical therapeutic timeline of IBS-C pharmacologic agents. Although bowel movements may improve relatively quickly, abdominal symptoms such as pain and bloating (which are often cited by patients as more bothersome) typically require a longer duration of therapy to show meaningful improvement.

A 1-week trial is insufficient to gauge the full therapeutic effect of these agents, and clinicians should proactively counsel patients on expected response timelines and emphasize the importance of sustained treatment before evaluating efficacy.

Define the Goal of IBS-C Management

One of the unique challenges in managing IBS-C is the absence of objective therapeutic endpoints, which distinguishes it from other gastrointestinal disorders such as Crohn's disease or ulcerative colitis, where goals such as mucosal healing, endoscopic remission, or normalized laboratory parameters (eg, liver function tests) guide

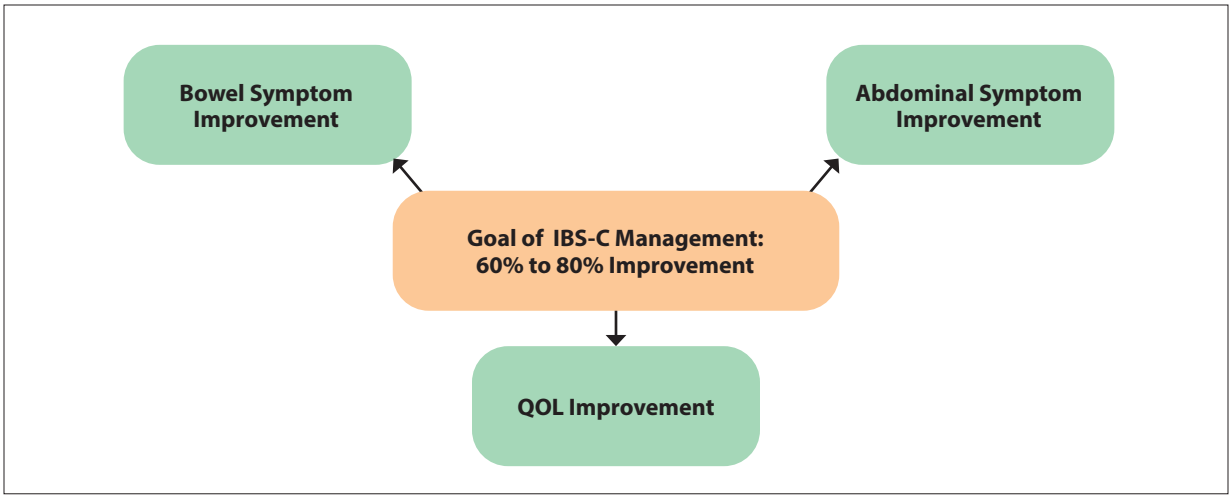

Figure 4. Goal of IBS-C management.

IBS-C, irritable bowel syndrome with constipation; QOL, quality of life.

clinical decisions. In IBS-C, treatment success is primarily subjective, with response evaluation centered on individualized symptom relief.

The goal of IBS-C management is to achieve a patient-reported improvement of approximately 60% to 80% in the constellation of symptoms that prompted the initial patient consultation (Figure 4). Adequate response is defined by meaningful improvement across multiple symptom domains and overall QOL.

Assess Response and Adapt in Case of Inadequate Response

Improved QOL is the goal of IBS-C management. However, conducting structured QOL assessments commonly employed in clinical trials is not feasible in routine clinical practice. Assessing improvement in IBS-C requires asking very specific, although open-ended, questions (Table 5). These generally revolve around how much progress has been made across key symptom domains such as: What has improved? What remains bothersome? What is worse? By what percentage have you improved? Are there any additional or new concerns? These questions force patients to reflect thoroughly on their experience with the medication.

If significantly improved QOL is not achieved with the initial FDA-approved medication, then it is reasonable to trial an agent with a different MOA rather than an agent within the same drug class. In such cases, achieving a better outcome is far more likely with an agent with a different MOA. If no such agents are available, then trialing with an agent within the same class is reasonable.

This is seen in the case of JG as well. JG had tried linaclotide with significant diarrhea and hence stopped taking it altogether. For this reason I switched from the secretagogue class to the retainagogue class and started JG on tenapanor. At the 10-week follow-up, JG expressed significant improvement in all her symptoms. Her stool consistency improved to BSFS type 3 70% of the time, and straining during defecation was significantly reduced. Abdominal pain and bloating had subsided to the extent that she no longer missed work and had resumed normal social activities, including dining out, without apprehension.

Long-Term Strategies to Maintaining Successful Outcomes in IBS-C

In clinical practice, it is common to encounter patients with IBS-C who initially respond well to pharmacologic therapy but subsequently report a perceived loss of efficacy over time. In such cases, a thorough reassessment of the patient's medical history and lifestyle is essential before attributing symptom recurrence solely to this perceived loss of medication efficacy.

Several extrinsic factors may contribute to diminished therapeutic response. Initiation of medications known to have constipating effects, such as calcium channel blockers, anticholinergics, or certain neurologic agents, should be scrutinized. Surgical interventions, particularly abdominal or pelvic procedures, may alter gastrointestinal motility and exacerbate symptoms. Additionally, lifestyle changes such as reduced physical activity or significant dietary shifts can adversely affect bowel function. Psychosocial stressors also play an amplifying role; although stress does not cause IBS-C, the disorder's underlying gut-brain interaction makes it particularly sensitive to stress. If dyssynergic defecation has not been evaluated and there are symptoms suggestive of pelvic floor dysfunction, then an

Table 5. Follow-up Visit: Sample Questions to Assess Response

Assessment category	Sample questions
Abdominal symptom response	• Has there been any change in your abdominal symptoms? Specify a percentage change. • Are you experiencing less abdominal pain? Specify a percentage change. • Has your bloating improved? Specify a percentage change.
Bowel symptom response	• Has there been any change in the frequency of bowel movements? • Has there been any change in the softness of stools? *Note: Use a BSFS chart to guide the patient.* • Has there been any change in straining during bowel movements? • Has there been any change in the feeling of incomplete evacuation?
QOL response	• How has your QOL been impacted since starting the medication? • Do your symptoms still affect your focus at work? • Are you anxious going out for social gatherings? • Is there any impact on general activities of daily living? • Specify and compare your current QOL with your QOL prior to starting medication.
Additional symptoms	• Are there any new symptoms since starting medication?

BSFS, Bristol Stool Form Scale; QOL, quality of life.

anorectal manometry can be obtained to investigate this.

Careful evaluation of these variables helps differentiate between true pharmacologic waning and secondary factors impacting symptom control. If, after comprehensive review, the loss of efficacy is attributed to the original agent, switching to another medication with a different MOA may be warranted.

Disclosures

Dr Curtin is a consultant/advisor for AbbVie, Ardelyx, Vibrant, and Palette Life Sciences.

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. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150(6):1393-1407.
5. Kongara K. Patient-centered approach in IBS-C management. *Gastroenterol Hepatol (N Y)*. 2025;21(5)(suppl 3).
6. Khalil C, Suchak K, Krut Z, et al. IBS-C patient experiences with pharmacologic therapies: qualitative analysis of online posts from X (Twitter) and e-health forums. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1671.
7. Moshiree B, Ruddy J, Gist B, Stremke E, Williams L, Shah E. Patients with irritable bowel syndrome with constipation from the IBS in America 2024 real world survey experience burdensome symptoms beyond constipation. American College of Gastroenterology 2024 Annual Scientific Meeting & Postgraduate Course; October 25–30, 2024; Philadelphia, PA, USA. Abstract P2335.
8. Shah E, Ruddy J, Gist B, Stremke E, Williams L, Moshiree B. Irritable bowel syndrome with constipation poses a substantial burden to patient overall health status and quality of life: results from the IBS in America 2024 real-world survey. American College of Gastroenterology 2024 Annual Scientific Meeting & Postgraduate Course; October 25–30, 2024; Philadelphia, PA, USA. Abstract P0641.
9. Shah E, Scott L, Ruddy J, et al. Patient-reported IBS-C symptom severity correlates positively with financial burden: IBS in America 2024 real-world survey. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Mo1257.
10. Coss-Adame E, Rao SS. Brain and gut interactions in irritable bowel syndrome: new paradigms and new understandings. *Curr Gastroenterol Rep*. 2014;16(4):379.
11. Mayer EA, Ryu HJ, Bhatt RR. The neurobiology of irritable bowel syndrome. *Mol Psychiatry*. 2023;28(4):1451-1465.
12. Tome J, Kamboj AK, Loftus CG. Approach to disorders of gut-brain interaction. *Mayo Clin Proc*. 2023;98(3):458-467.
13. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol*. 2014;20(22):6759-6773.
14. Camilleri M. Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med*. 2012;367(17):1626-1635.
15. Barbara G, Barbaro MR, Fuschi D, et al. Inflammatory and microbiota related regulation of the intestinal epithelial barrier. *Front Nutr*. 2021;8:718356.
16. 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.
17. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *Lancet*. 2020;396(10263):1675-1688.
18. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med*. 2017;376(26):2566-2578.
19. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome—a meta-analysis. *Am J Gastroenterol*. 2006;101(8):1894-1899.
20. Alfasigma USA, Inc. Press release; June 30, 2022: ZELNORM® (tegaserod) Notice of Withdrawal from Market. Accessed April 11, 2025. https://www.prnewswire.com/news-releases/zelnorm-tegaserod-notice-of-withdrawal-from-market-301578099.html#xd_co_f=MGYwYThkZTktNzU3Yi00NzFhLWEzMTktYTQ0MTAwNmZkNzVl~
21. Amitiza (lubiprostone) [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; August 2023.
22. Linzess (linaclotide) [package insert]. North Chicago, IL: AbbVie, Inc.; June 2023.
23. Trulance (plecanatide) [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; April 2021.
24. Ibsrela (tenapanor) [package insert]. Waltham, MA: Ardelyx, Inc.; April 2022.
25. Brenner DM. Mechanism of action considerations in the management of IBS-C. *Gastroenterol Hepatol (N Y)*. 2023;19(12)(suppl 6):749-756.
26. 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.
27. 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.
28. 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.
29. Li Q, King A, Liu L, et al. Tenapanor reduces IBS pain through inhibition of TRPV1-dependent neuronal hyperexcitability in vivo. Poster P2027 presented at the American College of Gastroenterology Annual Scientific Meeting; October 13–18, 2017; Orlando, FL, US. *Am J Gastroenterol*. 2017;112(suppl):S255.
30. Hyams JS, Saps M, Khlevner J, et al. Efficacy and safety of linaclotide in treating pediatric patients aged 7-17 years with irritable bowel syndrome with constipation (IBS-C): results from a phase 3 study. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract 624.
31. Saps M, Nurko S, Khlevner J, et al. Long-term safety of linaclotide in treating pediatric patients aged 7-17 years with IBS-C: interim results from a phase 3 study. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa2099.
32. Wallach T, Ringheanu M, Cantisano AR, et al. Safety and tolerability of tenapanor in pediatric patients with IBS-C: an analysis of blinded safety data from a phase 3 study and its open-label extension. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1643.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. Brenner DM, Shin AS, Laitman AP, Kunkel DC. Plecanatide is efficacious in patients with irritable bowel syndrome with constipation and bloating: evaluation using trisymptom composite endpoints. American College of Gastroenterology 2024 Annual Scientific Meeting & Postgraduate Course; October 25–30, 2024; Philadelphia, PA, USA. Abstract P2363.
40. Brenner DM, Sharma A, Rao SSC, et al. Plecanatide improves abdominal bloating and bowel symptoms of irritable bowel syndrome with constipation. *Dig Dis Sci*. 2024;69(5):1731-1738.
41. Ahmed S, Ahmad E, Akram U, Albustami I. Efficacy and safety of plecanatide in treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. American College of Gastroenterology 2024 Annual Scientific Meeting & Postgraduate Course; October 25–30, 2024; Philadelphia, PA, USA.
42. Lembo AJ, Chey WD, Harris LA, et al. Abdominal symptom improvement during clinical trials of tenapanor in patients with irritable bowel syndrome with constipation: a post hoc analysis. *Am J Gastroenterol*. 2024;119(5):937-945.
43. 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.
44. Chang L, Sultan S, Lembo A, Verne GN, Smalley W, Heidelbaugh JJ. AGA Clinical Practice Guideline on the pharmacological management of irritable bowel syndrome with constipation. *Gastroenterology*. 2022;163(1):118-136.
45. 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.
46. 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.
47. Lacy B, Yang Y, Rosenbaum D, et al. Tenapanor treatment success for IBS-C symptoms increases with duration of therapy. *Am J Gastroenterol.* 2023;118(10S):S129.
48. 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.


G&H