Case Study Series

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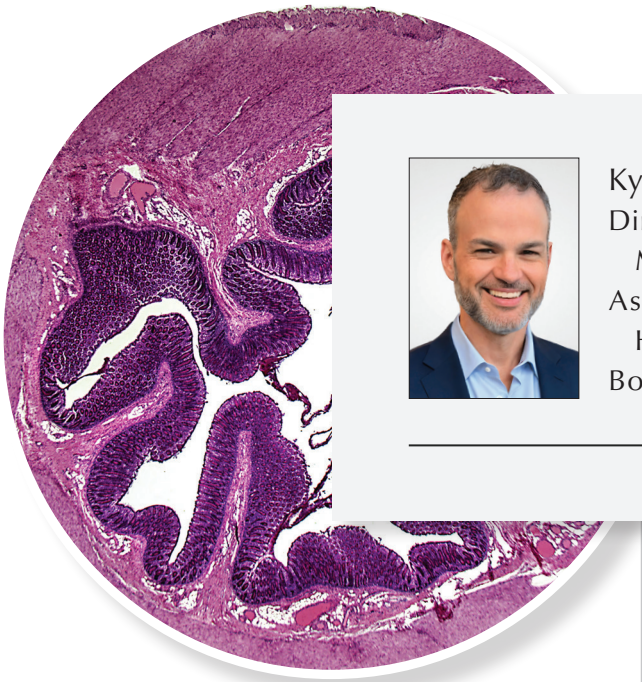
Raising Expectations in IBS-C Management



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Raising Expectations in IBS-C Management

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Patient Case

CF is a 47-year-old female who presents for a second-opinion evaluation of chronic constipation and abdominal pain (Table 1). Her past medical history is significant for generalized anxiety disorder, migraines, temporomandibular joint (TMJ) disorder, depression, and gastroesophageal reflux disease (GERD). She reports a history of hemorrhoids that cause intermittent bleeding.

CF reports experiencing constipation since childhood and remembers having to use mineral oil when younger. Over the years, her symptoms changed such that she experienced several years of diarrhea with abdominal pain. However, her symptoms have returned to consistent constipation, and she estimates having bowel movements every 3 or more days. After seeing a Bristol Stool Form Scale (BSFS), she identifies that most of her stools are types 1 and 2.

In addition to constipation, CF experiences lower abdominal pain concentrated on her left side associated with bowel movements. This pain sometimes improves with defecation. She also has frequent straining during a bowel movement and often requires sitting on the toilet for 10 minutes or longer. Other symptoms that she affirms include a sense of incomplete evacuation and a sense of anorectal blockage. CF notes significant bloating with abdominal distension that typically (although not always) improves with bowel movements.

Over the years, she has relied on frequent use of polyethylene glycol. CF states that she has achieved improved bowel movement frequency (every 1 to 2 days) and consistency (BSFS types 3 and 4) with polyethylene glycol, but that her abdominal pain persists. She has also cycled through docusate (which she found to be ineffective) and senna (which led to abdominal cramping). A few years ago, her primary care physician offered a prescription of linaclotide, to which she experienced no effect until the dose was increased to 290 μg, which led to cathartic diarrhea.

CF has tried a low–fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet on her own, but found it to be too restrictive for her lifestyle; probiotics offered her no perceived benefit and she considered them very expensive. She has also supplemented her diet with fiber and kiwifruit, with little effect.

Her prior workup includes several tests. A small intestinal bacterial overgrowth (SIBO) breath test was positive; thus, she was prescribed rifaximin but experienced no symptom improvement. Laboratory testing included celiac serology and *Helicobacter pylori* stool antigen, both of which were negative. Thyroid-stimulating hormone levels were normal, as was complete blood count and comprehensive metabolic panel. A colonoscopy, ordered with first presentation of symptoms, was normal. Other imaging tests were then conducted, including abdominal ultrasound and computed tomography of the abdomen and pelvis. All imaging was normal.

CF's mental health history is notable for anxiety and depression. After trialing several agents, she is currently treated with a selective serotonin reuptake inhibitor and buspirone. She states that both conditions are well controlled with treatment.

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

Table 1. Patient Case Summary

47-year-old female with medical history significant for generalized anxiety disorder, migraines, TMJ disorder, depression, and GERD who presents for evaluation of chronic constipation and abdominal pain	
Constipation since childhood	• Recalls using mineral oil • Several years of diarrhea and abdominal pain but has returned to consistent constipation
Bowel movements	• Every 3+ days • Primarily BSFS types 1 and 2
Abdominal pain	• Bowel movements associated with left-side lower abdominal pain • Abdominal pain sometimes improves with defecation
Straining	• Frequent straining • Sits on the toilet for 10+ minutes • Sense of incomplete evacuation • Sense of anorectal blockage • History of hemorrhoids with intermittent bleeding
Bloating	• Notes significant bloating with abdominal distension • Bloating somewhat improves with bowel movements
Prior medications	• Frequent use of polyethylene glycol > Result: improved bowel movement frequency and consistency (BSFS types 3 and 4, every 1-2 days) but abdominal pain persists • Docusate > Result: ineffective • Senna > Result: led to abdominal cramping • Linaclotide > No effect until 290 µg dose, which led to cathartic diarrhea
Diet	• Low-FODMAP diet > Found it too restrictive > Ineffective • Also tried fiber, kiwifruit
Probiotics	• No benefit (and very expensive)
Prior workup	• Positive SIBO breath test, took rifaximin without improvement • Celiac serology and *Helicobacter pylori* stool antigen: negative • Colonoscopy with first presentation of symptoms: normal • Abdominal ultrasound: normal • CT of the abdomen/pelvis: normal • TSH: normal
Past medical history	• Mental health history notable for anxiety and depression • Currently treated with SSRI and buspirone • Well controlled after many medication trials
Rectal examination	• External hemorrhoids noted • Decreased perineal descent while bearing down • Normal resting anal pressure with normal anal squeeze pressure • Some dyssynergia noted with stimulated defecation • Decreased rectal pressure with Valsalva maneuver

(Table continues on next page)

Table 1. Patient Case Summary *(Continued from previous page)*

Results of anorectal manometry	
Maximum resting anal pressure	74.8 mm Hg (<50 years old: normal 68-112; ≥50 years old: normal 33-91)
Maximum squeeze anal pressure	200.0 mm Hg (<50 years old: normal 115-209; ≥50 years old: normal 99-248)
Duration of long squeeze	3.1 seconds (normal 3-23)
Rectoanal pressure differential	-45.9 (<50 years old: normal -74-(-1); ≥50 years old: normal -55-32)
Rectal sensation	• First sensation: 30 mL (normal 20-40) • Urge sensation: 60 mL (normal 60-120) • Maximum tolerable volume: 170 mL (normal 182-204)
Balloon expulsion	Able to expel 50 mL balloon in less than 2 minutes
Impression	
Anal tone and contractility	• Findings consistent with normal anal physiology • Normal reflex anal contraction with cough
Rectoanal inhibitory reflex	Normal
Rectoanal coordination	• Inadequate rectal pressure increase with inadequate anal relaxation • Prolonged (≥2 minutes) balloon expulsion • Normal expulsion with poor propulsion and dyssynergia
Rectal sensation	Rectal hypersensitivity (≥1 parameter <LLN)
What was done?	
Change in medication to one with a different MOA	Initiated tenapanor 50 mg twice daily
6-week follow-up	Significant improvement in both bowel and abdominal symptoms

BSFS, Bristol Stool Form Scale; CT, computed tomography; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GERD, gastroesophageal reflux disease; LLN, lower limit of normal; MOA, mechanism of action; SIBO, small intestinal bacterial overgrowth; SSRI, selective serotonin reuptake inhibitor; TMJ, temporomandibular joint; TSH, thyroid-stimulating hormone.

Anorectal manometry and rectal examination are performed. External hemorrhoids are visibly noted. CF exhibits decreased perineal descent while bearing down, and normal resting anal pressure with normal anal squeeze pressure. Some dyssynergia is noted with stimulated defecation. There is decreased rectal pressure upon the Valsalva maneuver. However, she is not a candidate for pelvic floor biofeedback therapy with a normal balloon expulsion time.

CF is diagnosed with irritable bowel syndrome with constipation (IBS-C). After a discussion about her treatment expectations and goals of treatment, she initiates treatment with tenapanor 50 mg twice a day. She reports significant improvement in both constipation and abdominal symptoms and her overall quality of life (QoL) at a 6-week follow-up appointment.

In the Clinic . . .

This patient was seen by other providers before she was seen in my clinic. She had undergone unnecessary testing but was never offered a comprehensive explanation of IBS-C. When one kind of therapy did not work completely, she was not offered any other option. Providers often have the approach of, "You have IBS. There's nothing wrong with you. Try some Miralax." And if that does not work, there is no plan B. We need a complete reset in how we approach both diagnosing and managing IBS-C, taking into account how this debilitating chronic condition impacts the QoL of our patients.

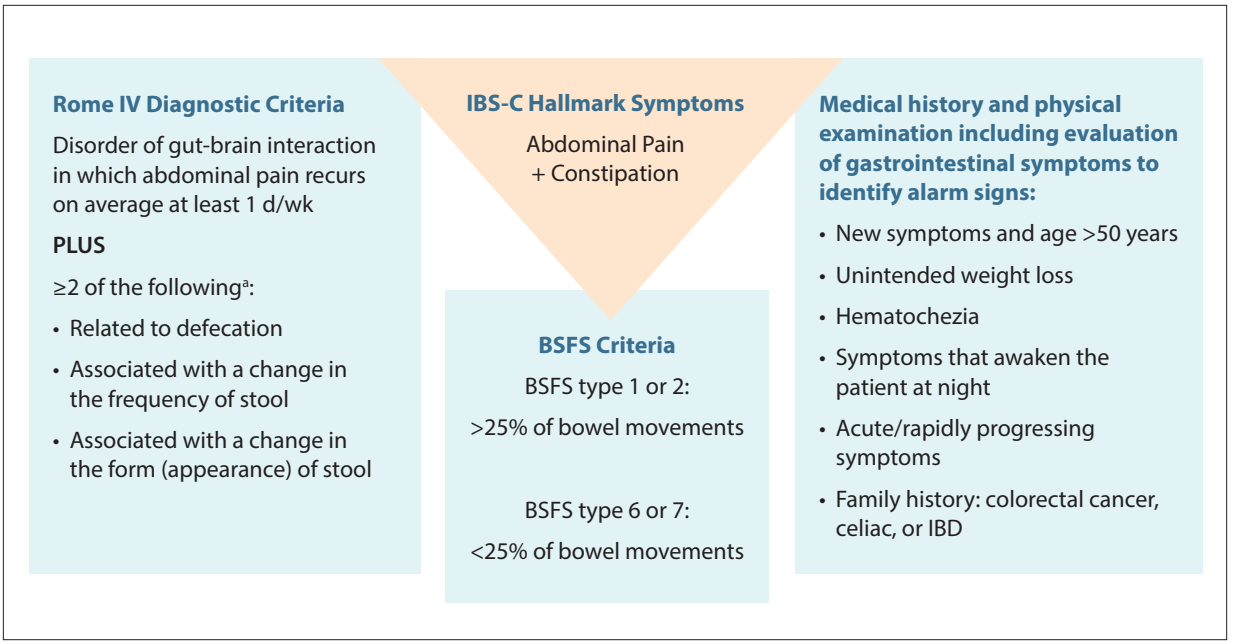

Figure 1. Making a definitive diagnosis of IBS-C.[6]

[a]Criteria met for the previous 3 months with onset of symptoms at least 6 months before the diagnosis.

BSFS, Bristol Stool Form Scale; d, day; IBD, inflammatory bowel disease; IBS-C, irritable bowel syndrome with constipation; wk, week.

Adapted from: Spiegel B. *Gastroenterol Hepatol (N Y).* 2024;20(9)(suppl 7):1-12.

Use a Positive Diagnostic Approach

According to the Rome Diagnostic Criteria for Irritable Bowel Syndrome, fourth iteration (Rome IV criteria), IBS is associated with symptoms of recurrent abdominal pain occurring on average at least 1 day per week and associated with 2 or more of the following: related to defecation; associated with a change in the frequency of stool; or associated with a change in the form (appearance) of stool.[1] Additionally, these symptoms must have been present for the previous 3 months, with onset at least 6 months prior, to confirm a diagnosis of IBS.

The Rome IV criteria were designed for defining patient enrollment in clinical trials. The Rome Foundation has proposed a modification of these criteria for use in clinical practice, whereby an IBS diagnosis can be reached if (1) the nature of the symptoms corresponds to those in the Rome IV diagnostic criteria, and (2) the symptoms are bothersome (interfering with daily activities or requiring attention, causing worry or interference with QoL).[2]

If this is the case, a lower frequency and a shorter duration (8 weeks or more) of symptoms than those required for the Rome IV criteria are allowed, provided that there is clinical confidence that other diagnoses have been sufficiently ruled out based on presentation and additional investigations as needed. An evaluation of the proposed modified criteria found that, when used to diagnose IBS, they were more sensitive but less specific, leading to a much lower positive likelihood ratio than the original Rome IV criteria.[3]

Four IBS subtypes are recognized by the Rome IV criteria: IBS-C, IBS with diarrhea (IBS-D), IBS with mixed or alternating bowel habits (IBS-M), and IBS without a significant pattern of abnormal stool (IBS-U).[4] The classification of IBS subtype is made using the BSFS.[5] A diagnosis of IBS-C is made with BSFS types 1 and 2 (present in more than 25% of bowel movements) together with the presence of BSFS types 6 and 7 (fewer than 25% of bowel movements). The converse is used to classify IBS-D, with at least 25% of bowel movements of BSFS types 6 or 7 coupled with fewer than 25% of BSFS types 1 or 2. IBS-M is defined by at least 25% of bowel movements of BSFS types 1 or 2, and at least 25% of bowel movements of BSFS types 6 or 7, whereas IBS-U is used to identify patients who meet the Rome IV criteria for IBS but do not fall into one of the other 3 IBS subgroups.

Notably, although abdominal pain and hard stools are the hallmark symptoms of IBS-C, many patients report other significant abdominal symptoms (including discomfort and bloating), as well as other bowel-related symptoms (such as infrequent stools, straining, and the feeling of incomplete evacuation). However, of these, only abdominal pain is reflected in the Rome IV criteria.

Guidelines from the American College of Gastroen-

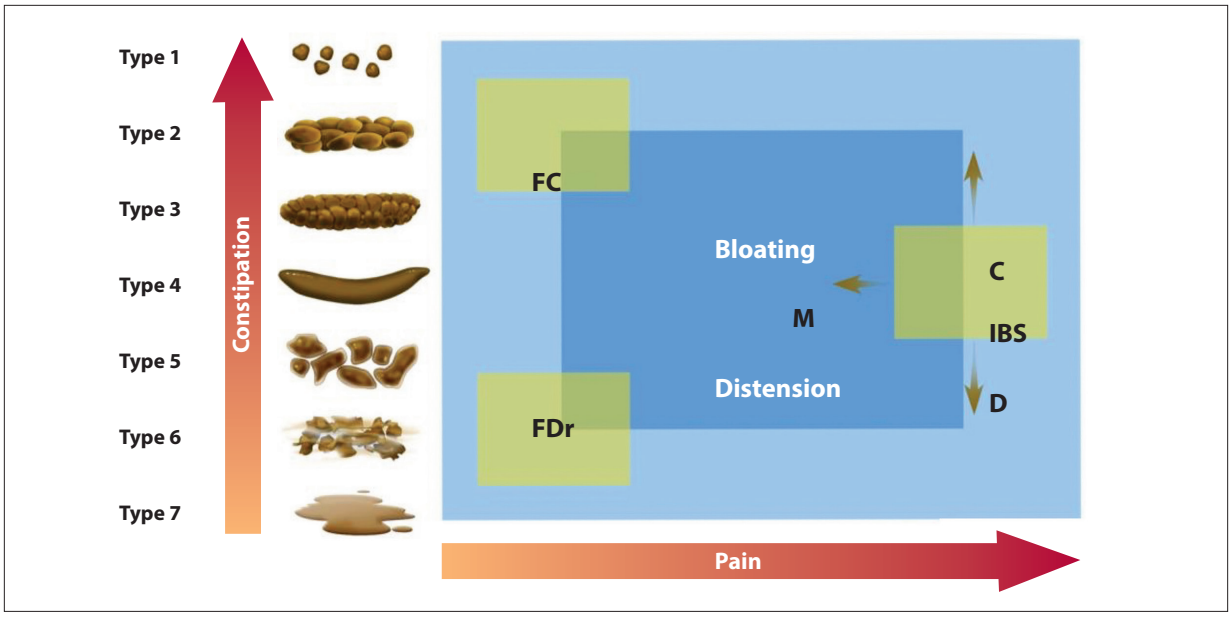

Figure 2. Conceptual framework to explain functional bowel disorders.[7]

FC, functional constipation; FDr, functional diarrhea; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, irritable bowel syndrome with mixed bowel habits.

Adapted from: Lacy et al. *Gastroenterology*. 2016;150(6):1393-1407.

terology include recommendations regarding a positive diagnostic strategy based on Rome IV criteria.[4] This positive diagnosis of IBS involves a comprehensive clinical assessment that considers medical history and physical examination (Figure 1).[6] Findings from this assessment are compared with the Rome IV criteria. The clinical assessment should include evaluation for a set of alarm features that, if present, should trigger immediate investigation and treatment, as they are indicative of another gastrointestinal (GI) disorder.[7,8] These alarm features include new symptoms in a patient older than 50 years, unintended weight loss (>10% in 3 months), hematochezia not caused by hemorrhoids or anal fissures, symptoms that awaken the patient at night, fever, anemia, acute or rapidly progressing symptoms, a palpable mass, ascites, or lymphadenopathy, or a family history of colorectal cancer, polyposis syndrome, celiac disease, or inflammatory bowel disease (IBD).

Abdominal pain and constipation symptoms are enough to meet the Rome IV criteria in most patients, supporting a positive diagnosis without the need for further testing. However, certain testing strategies may aid in the diagnosis in appropriate patients for whom other conditions must be excluded.[4] For example, serology testing may aid in the exclusion of celiac disease for patients with diarrhea symptoms, and fecal calprotectin can be part of a normal workup in IBS-D (as well as colonoscopy in patients for whom there is suspicion for microscopic colitis). Neither is recommended for IBS-C, however.

In the Clinic . . .

There is no workup or biomarker test that can be used to diagnose IBS-C. In this patient, testing for both celiac serology and *H. pylori* stool antigen were negative, the colonoscopy was normal, and cross-sectional imaging and a thyroid study test were negative. Although the SIBO breath test was positive, there is controversy regarding the importance of this for selecting IBS treatments. Notably, none of these tests was necessary to make a definitive IBS-C diagnosis and indeed they delayed the eventual diagnosis. Instead, her long-term symptoms of recurrent abdominal pain related to bowel movements and sometimes improving with defecation were more than sufficient to make a positive diagnosis of IBS-C.

Delay in IBS-C Diagnosis

IBS usually starts at a young age, with about one-half of patients reporting that they first experienced symptoms before they were 35 years old.[9] However, most patients never present for care, and those who do so generally present much later. In my experience, it takes about 4 years after onset for a confident IBS-C diagnosis, an observation supported in the literature.[10,11] There are a multitude of factors responsible for this long diagnostic journey in IBS-C.

Often providers take a rule-out approach to the diagnosis of IBS-C as opposed to a rule-in one. This occurs despite well-established guidelines that point to the

importance of making a positive diagnosis.[4] As a result, the diagnosis of IBS-C can be missed or delayed despite (or in some cases, because of) testing.[12] A survey of 472 gastroenterologists, internists, and family physicians found that the majority of gastroenterologists commonly order laboratory tests, with almost one-third performing flexible sigmoidoscopies or colonoscopies in response to reported IBS symptoms.[13] Another study found that physicians who consider IBS a diagnosis of exclusion ordered an average of 1.6 more diagnostic tests than physicians who use a positive IBS diagnostic strategy.[14]

Another important reason for delayed diagnosis is the stigma associated with IBS-C.[15,16] Providers often worry about disappointing a patient with a diagnosis of IBS-C and are unsure about the existence and/or efficacy of available treatment options. In practice, this often translates to giving patients the message of "It's just IBS. There's not much that we can do for you." Friends often advise to "just stress less and relax and you will be fine." Then patients often internalize this stigma and, because it is a condition that gets worse under stress, they believe that "this isn't something that I should be bothering my physician or my family with" even though it has a monumental impact on their QoL.

One other factor that is responsible for delayed diagnosis is that the symptoms wax and wane over time. Hence patients often do not present to the gastroenterologist until they have reached their breaking point, with symptoms causing a debilitating impact on their QoL.

In the Clinic . . .

Realize that your patient has likely suffered a long time prior to being seen in your clinic.

Educate the Patient: What Is IBS-C?

Education is a critical component of the management of a patient with IBS-C. Patients should be informed that IBS is a functional bowel disorder (Figure 2)[7] now referred to as a disorder of gut-brain interaction.[17-19] The gut may be sending abnormal signals of pain and discomfort to the brain, and/or the brain may be sending abnormal signals back to the gut that can lead to worsening symptoms.

The pathophysiology of IBS-C is considered to be multifactorial.[20-25] Changes in gut motility and water imbalances are thought to account for the development of hard stools and decreased defecation.[22,23] Aberrant interactions between the gut microbiome and the immune system may explain alterations observed in gut permeability (arising from loss of intercellular tight junctions and reduced transepithelial electrical resistance). These dysregulated interactions may also account for the induction of inflammatory responses localized to nerve fibers throughout the gut epithelium and resulting in changes to microbiome-immune interactions.[24,25] Changes in the gut microbiome can exacerbate gut inflammation and immune activation.[24,25] Finally, visceral hypersensitivity can explain the enhanced sensitization of afferent nerve pathways within the intestines.[24,26]

Patients frequently switch IBS subtypes over time.[27,28] A prospective assessment of 317 female patients with IBS found that, within 1 year, 75% of patients changed subtypes, and 29% switched between constipation-predominant IBS and diarrhea-predominant IBS.[29] It can be helpful and reassuring for patients to learn that switching between IBS-D to IBS-C over time is not uncommon.

In the Clinic . . .

Establish a patient–provider relationship, which has been shown to be an independent predictor of the likelihood of success in IBS-C management. Explaining the nature of IBS-C can itself be therapeutic as well as aid in making a positive diagnosis.

Realize that Abdominal Symptoms Are as Debilitating as Constipation

As a result of the complex and multifactorial pathophysiology underlying IBS-C, patients with IBS-C experience a range of symptoms beyond constipation. Indeed, abdominal pain and hard stools, considered the hallmark symptoms of IBS-C, may be accompanied by other abdominal symptoms (discomfort, bloating) and bowel-related symptoms (infrequent stools, straining, sensations of incomplete evacuation). Although these symptoms are not specifically included in the Rome IV criteria, they are recognized as important by patients and providers. However, few of these have been included in any primary study endpoints in the pivotal clinical trials of the agents approved for IBS-C; they are included in many of the secondary endpoints of these trials.

The IBS in America 2024 survey showed that, in addition to constipation (reported by 94% of respondents), many other symptoms were experienced by individuals with IBS-C.[30,31] Among the most frequent of these were bloating (86%), abdominal cramps and pain (85%), abdominal fullness (73%), excessive gas or flatulence (68%), fatigue (64%), tenesmus (57%), and heartburn or GERD (51%). Of the 95% of patients who experienced abdominal pain within the past 7 days, 33% described the pain as quite bad or very bad and interfered with their day-to-day activities quite a bit (20%) or very much (9%).

Overall, these symptoms ultimately mean that patients with IBS-C experience significantly worse QoL

compared with individuals without IBS-C. Several studies have demonstrated that IBS-C symptoms have a negative effect on measures of health-related QoL.[32-35] This was also demonstrated in the IBS in America 2024 survey, as the overwhelming majority of respondents (90%) reported at least some negative (68%) or significant negative (22%) impact of IBS-C on their overall QoL.[36] Mental/emotional health was also negatively affected, with 54% of respondents reporting at least some negative impact and 25% reporting significant negative impact. Other negative impacts on QoL apparent among survey respondents included sexual health and intimacy (40% some negative; 24% significant negative), employment and/or education (31% some negative; 17% significant negative), sense of independence (43% some negative; 16% significant negative), relationships with friends or family (42% some negative; 14% significant negative), and household finances (31% some negative; 12% significant negative).

In the Clinic . . .

Instead of emphasizing to patients that IBS-C is not something that will impact their mortality, acknowledge that this can be a very debilitating condition, and explore specific treatment options that have been proven to impact all symptoms of IBS-C, not just constipation.

Understand the Existence of Common Comorbid Disorders

There is a high degree of association of IBS with psychiatric and psychological conditions, in particular with anxiety and depression.[37] There is an estimated threefold-higher risk of anxiety and depression in individuals with IBS compared with healthy controls.[38] These conditions may present as diagnosed psychiatric disorders or as subclinical symptoms in the patient.[39] A meta-analysis reported that co-occurring anxiety and depressive disorders were prevalent in 23% of individuals with IBS. This same analysis showed that the prevalence of symptoms of anxiety and depression among patients with IBS was 39% and 29%, respectively.[40]

Several studies suggest a causal link between psychological conditions and GI symptoms, at least in subgroups of people with IBS. A systematic review of 11 studies found that individuals with depression had a twofold-higher risk of comorbid IBS and a nearly twofold-higher risk of developing new-onset IBS than individuals without depression.[40] The mechanisms underlying the connection between IBS and mental health are unclear but have been attributed to dysregulation of the hypothalamic-pituitary-adrenal axis, immune activation, or genetic mechanisms.[41] A genome-wide analysis of 53,400 people with IBS identified 6 genetic susceptibility loci for IBS, of which 4 are also associated with mood and anxiety disorders, expressed in the nervous system, or both.[42] This analysis also showed a robust genome-wide association between the risk of IBS and anxiety, neuroticism, and depression. These findings were considered a result of shared pathogenic pathways and not attributed to anxiety-causing abdominal symptoms.

Comorbid chronic pain conditions are prevalent in patients with IBS, most commonly fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain.[43] In a large analysis of a hospitalization database, the prevalence of fibromyalgia (adjusted odds ratio [OR], 5.33; 95% CI, 5.24-5.41; $P<.001$) and chronic fatigue syndrome (adjusted OR, 5.40; 95% CI, 5.04-5.78; $P<.001$) were both significantly higher in patients with IBS vs the general adult population without IBS.[44] A survey of 5650 US adults (of whom 186 met criteria for IBS) reported that IBS was associated with increased odds of headache (adjusted OR, 2.18; 95% CI, 1.41-3.38) and chronic back or neck pain (adjusted OR, 2.74; 95% CI, 1.88-4.00).[45] Note that TMJ disorder, as was experienced by the patient in this case, may also be linked to IBS.[46,47]

IBS-C and defecation disorders can coexist in the same patient; often both need to be addressed. Dyssynergic defecation is a condition in which the pelvic floor and abdominal muscles that are involved in bowel movements do not coordinate properly, leading to difficulty in passing stool. Symptoms of dyssynergic defecation include painful defecation, straining, incomplete evacuation, and a sensation of blocked evacuation.[48] Multiple studies have shown that the positive and negative predictive value of symptoms alone is inadequate for the diagnosis of dyssynergic defecation. Other anorectal symptoms (constipation, fecal incontinence, and anorectal pain) may be present,[49] but they do not correlate with anorectal physiology on testing.

In the Clinic . . .

Be prepared that patients with IBS-C may present with comorbid conditions.

Recognize that Polyethylene Glycol, Fiber, and Probiotics Have a Limited Role in IBS-C

Many drugs that are not specifically approved for IBS-C can have an impact on bowel movements; however, not only do they not address the abdominal pain component of IBS-C, they may worsen these symptoms.

Laxatives are commonly employed in patients with IBS-C (either self-prompted or under clinical advice).[50] However, although both osmotic and stimulant laxatives can improve constipation symptoms, they have little effect on abdominal pain.[51] Further, stimulants can worsen

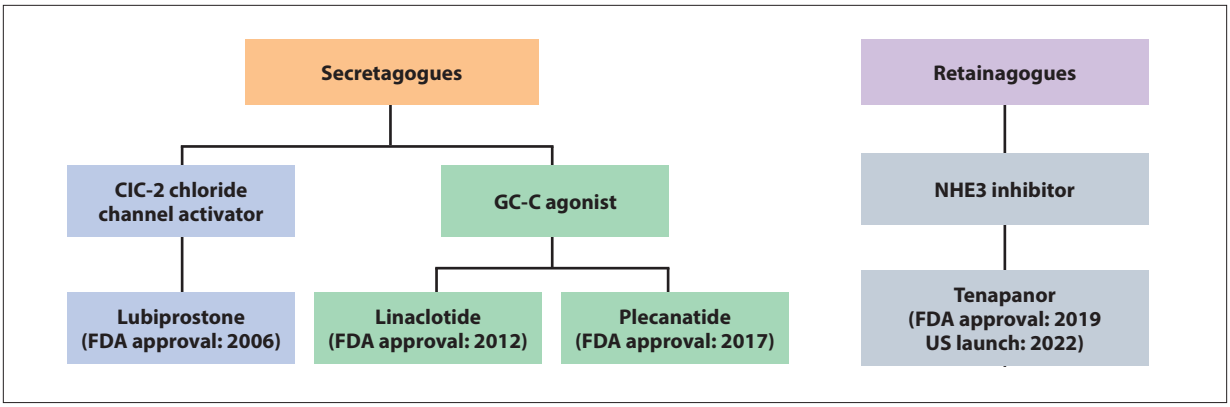

Figure 3. Currently available FDA-approved agents with indications for the treatment of IBS-C.[63]

CIC-2, type 2 chloride channel; FDA, US Food and Drug Administration; GC-C, guanylate cyclase-C; 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.

abdominal cramps, discomfort, and pain.[52] The osmotic agent polyethylene glycol can improve the consistency and frequency of bowel movements. However, it does not alleviate pain, leaving patients with unaddressed IBS-C symptoms. Guidelines offer conflicting views on the use of polyethylene glycol in IBS-C.[4,53]

Fiber has been investigated as an intervention in IBS-C.[54,55] Commercially available soluble fibers such as psyllium are recommended, whereas insoluble fibers such as bran may worsen symptoms and are generally not recommended in patients with IBS-C. Psyllium has the best evidence for use in IBS and constipation, resulting in increases in stool bulk and normalization of colonic transit.[56] Psyllium is slowly fermented and may cause a low degree of bloating. Methylcellulose can be useful in constipation, causing an increase in colonic transit, and is nonfermentable and therefore not associated with bloating.

Probiotics have been shown to improve overall stool frequency, gut transit time, and stool consistency in patients with IBS.[57] *Bacillus coagulans* strain LBSC (DSM 17654) was demonstrated to improve IBS symptoms such as bloating, abdominal pain, constipation, and diarrhea, and also resulted in improved QoL.[58] However, higher-quality studies have generally demonstrated a very limited effect of probiotics on IBS symptoms, and the American Gastroenterological Association (AGA) guidelines include no role for probiotics in the management of IBS-C.[53]

In the Clinic . . .

Polyethylene glycol, fiber, and probiotics have a limited role in managing IBS-C. Even if they address constipation, they may worsen abdominal symptoms. Using these without addressing abdominal symptoms may increase your patient's frustration with treatment.

Use FDA-Approved Treatment Options for IBS-C

There are now 4 currently available agents approved by the US Food and Drug Administration (FDA) with specific indication for IBS-C: lubiprostone, linaclotide, plecanatide, and tenapanor.[59-62] Of these, lubiprostone is only approved for women 18 years or older with IBS-C. Both lubiprostone and linaclotide have multiple dosing options. FDA-approved dosing options for these agents are 8 µg twice daily for lubiprostone, 290 µg once daily for linaclotide, 3 mg once daily for plecanatide, and 50 mg twice daily for tenapanor.

These agents are classified according to their varying mechanisms of action (MOAs) (Figure 3).[63] Three of these 4 agents are classified as secretagogues (lubiprostone, linaclotide, and plecanatide) and one as a retainagogue (tenapanor).

Lubiprostone is a prostaglandin E1 derivative that activates the intestinal type 2 chloride channel (CIC-2).[64] Located on the apical surface of small intestinal enterocytes, CIC-2 results in chloride efflux into the luminal cavity. This in turn causes fluid secretion into the luminal cavity, leading to stool softening and acceleration of intestinal transit. Two other secretagogues, linaclotide and plecanatide, are peptides that act as agonists to the guanylate cyclase-C (GC-C) receptor.[65-67] Activation of the GC-C receptor, located on the luminal surface of intestinal enterocytes, triggers intestinal secretion that causes stool softening and intestinal transit acceleration.

The fourth FDA-approved agent, tenapanor, is a locally acting inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3), expressed on the apical surface of the epithelial cells lining the small intestine and colon that is primarily responsible for the absorption of dietary sodium.[68-71] Tenapanor is thought to act via 3 mecha-

Table 2. Pivotal Efficacy and Safety Data of Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C[63]

FDA-approved medication	Pivotal efficacy data		Safety data
Lubiprostone[a]	**Overall responder status** was calculated from the weekly assessments of symptom relief. Patients were considered **overall responders** if they were monthly responders[b] for at least 2 of the 3 months of the study.	**Combined analysis of 2 phase 3 trials** Overall responder status: 17.9% vs 10.1% with placebo; *P*=.001	**GI-related AEs (including nausea, diarrhea, and abdominal distension):** similar incidence in lubiprostone and placebo groups **Discontinuation owing to AEs:** 4.7% and 5.1% (lubiprostone group) vs 4.6% and 7.7% (placebo group)
Linaclotide	**FDA overall response combined endpoint** was 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.	**26-week phase 3 study** 33.7% vs 13.9% with placebo; *P*<.0001 **12-week phase 3 study** 33.6% vs 21.0% with placebo; *P*<.0001	**Diarrhea (most common AE):** 19.7% (linaclotide group) vs 2.5% (placebo group) in 26-week study **Discontinuation owing to diarrhea:** 5.7% (linaclotide group) vs 0.3% (placebo group) in 12-week study
Plecanatide		**Study 1** 30.2% (3 mg) and 29.5% (6 mg) vs 17.8% with placebo; *P*<.001 **Study 2** 21.5% (3 mg) and 24.0% (6 mg) vs 14.2% with placebo; *P*=.009 for 3 mg vs placebo and *P*<.001 for 6 mg vs placebo	**Diarrhea (most common AE):** 4.3% and 4.0% (plecanatide 3 mg and 6 mg groups, respectively) vs 1.0% (placebo group) **Discontinuation owing to AE:** 2.3% (plecanatide arms combined) vs 0.4% (placebo)
Tenapanor		**T3MPO-1** 27.0% vs 18.7% with placebo; CMH *P*=.020[c] **T3MPO-2 (26-week study)** 36.5% vs 23.7% with placebo; CMH *P*<.001[c]	**Diarrhea (most common AE):** 14.6% (tenapanor) vs 1.7% (placebo) in T3MPO-1 and 16.0% (tenapanor) vs 3.7% (placebo) in T3MPO-2 **Discontinuation owing to diarrhea:** 1.6% in T3MPO-3 (55-week, open-label safety study)

[a]Lubiprostone is only approved for women 18 years or older with IBS-C. [b]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. [c]Cochran–Mantel–Haenszel [CMH] *P* value.

AE, adverse event; CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; GI, gastrointestinal; IBS-C, irritable bowel syndrome with constipation.

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

nisms.[71] The first of these is by decreasing the absorption of dietary sodium, which causes luminal water content to be retained, intestinal transit time to be accelerated, and stool to be softened; because of these actions, tenapanor is referred to as a retainagogue. Animal models have suggested a second mechanism in which tenapanor narrows the tight junctions between intestinal epithelial cells, resulting in decreased intestinal permeability. The third mechanism, also demonstrated in animal models, involves a reduction of visceral hypersensitivity.

All 4 agents discussed were approved by the FDA based on results from pivotal, large, randomized and placebo-controlled trials (summarized in Table 2).[63] Lubiprostone was compared with placebo in a combined analysis of two 12-week phase 3 trials.[72] A patient was considered an overall responder (primary endpoint) if they were a monthly responder for at least 2 of the 3 months of the study. In this combined analysis, there were a significantly higher percentage of overall responders in the lubiprostone group vs the placebo group (17.9% vs 10.1%; *P*=.001). These overall responses rose over time, with the percentage of patients achieving the primary endpoint with lubiprostone vs placebo increasing 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%). Patients who achieved an overall response also experienced significant improvements

in other symptoms, including abdominal discomfort or pain, bloating, constipation severity, stool consistency, and straining (P<.001 for all symptoms reported in overall responders vs nonresponders).

Linaclotide was compared with placebo in 2 phase 3 trials.[73,74] In both studies, the primary endpoint was the FDA combined endpoint for IBS-C response, defined as an improvement of at least 30% from baseline in average daily worst abdominal pain score and an increase of at least 1 complete spontaneous bowel movement (CSBM) from baseline, both in the same week for 6 or more out of 12 weeks. In the first 26-week study, significantly more patients treated with linaclotide achieved the FDA combined endpoint vs placebo (33.7% vs 13.9%; P<.0001).[73] In the second 12-week study, the FDA combined endpoint was also significantly improved with linaclotide vs placebo (33.6% vs 21.0%; P<.0001).[74] In both studies, linaclotide also resulted in significant improvements compared with placebo across multiple other endpoints. In the 26-week study, these included improved abdominal pain for 9 out of 12 weeks (48.9% vs 34.5%) and CSBM response for 9 out of 12 weeks (47.6% vs 22.6%). In the 12-week study, linaclotide treatment was associated with significant improvements across several other outcomes during at least 6 of the 12 treatment weeks, including 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).

Plecanatide was compared with placebo in 2 identically designed phase 3 clinical trials, both of which used the same FDA combined primary endpoint of overall response.[75] In Study 1, plecanatide was associated with a significantly higher percentage of patients who achieved the primary endpoint vs placebo (30.2% [3 mg arm] and 29.5% [6 mg arm] vs 17.8%; P<.001). Similar results were achieved in Study 2 (21.5% [3 mg arm] and 24.0% [6 mg arm] vs 14.2%; P=.009). All secondary endpoints evaluated in both studies were significantly improved with plecanatide compared with placebo, including stool frequency/consistency, straining, and abdominal symptoms.

Several follow-up analyses of these 2 trials focusing on other symptom improvement have been reported. One of these was a reanalysis of data from these studies using a novel trisymptom composite endpoint.[76] This composite endpoint consisted of abdominal pain, abdominal bloating, and CSBMs. Significantly more patients in the plecanatide group achieved this trisymptom composite response compared with the placebo group. In a separate report, plecanatide efficacy was evaluated in patients with IBS-C stratified by bloating intensity.[77] Among patients classified as having moderate-to-severe bloating, plecanatide significantly reduced bloating severity compared with placebo (least-squares mean change [LSMC], –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). A systemic review and meta-analysis of the efficacy and safety of plecanatide assessed 4 outcomes in patients with IBS-C.[78,79] At the FDA-approved dose of 3 mg once daily, the pooled effect size favored plecanatide vs placebo: 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 was evaluated in 2 placebo-controlled, randomized, phase 3 studies: T3MPO-1 (a 12-week trial) and T3MPO-2 (a 26-week trial).[80,81] The primary endpoint of the FDA combined endpoint for IBS-C was significantly improved in both trials. In T3MPO-1, significantly more patients in the tenapanor arm compared with the placebo arm met the primary endpoint (27.0% vs 18.7%; Cochran-Mantel-Haenszel [CMH] P=.020).[80] The T3MPO-2 trial reported similar outcomes in the primary endpoint (36.5% vs 23.7%; CMH P<.001).[81]

In T3MPO-1, the abdominal pain response was improved with tenapanor (44.0% vs 33.1%; CMH P=.008), although the rates of CSBM response were similar between the tenapanor and placebo groups (33.9% vs 29.4%; CMH P=.270).[80] Tenapanor also led to significant improvements across several measures of abdominal symptoms for at least 9 of 12 weeks compared with placebo, including 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).

In T3MPO-2, both the abdominal pain response (49.8% vs 38.3%; CMH P=.004) and improvement in CSBM (47.4% vs 33.3%; CMH P<.001) endpoints were significantly improved with tenapanor compared with placebo.[81] Patients experienced an improvement in abdominal pain with tenapanor as early as 1 week after beginning treatment. Tenapanor was also associated with a decrease in other abdominal symptoms including bloating, fullness, discomfort, and cramping.

A post hoc analysis of pooled data from the T3MPO-1 and T3MPO-2 trials examined the efficacy of tenapanor on abdominal symptoms.[82,83] An abdominal score (AS) was calculated as the average of weekly scores for abdominal pain, discomfort, and bloating symptoms. The LSMC from baseline in AS was significantly improved with tenapanor compared with placebo (–2.66 vs –2.09; P<.0001). The AS response rate was significantly higher for tenapanor 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).

Unsurprisingly, GI-related adverse events are the most frequently reported side effects across all 4 agents. These include nausea, diarrhea, and abdominal distension; are generally mild or moderate in severity; and can be effectively managed.

In the Clinic . . .

FDA-approved IBS-C medications are safe and effective, and positively impact both bowel and abdominal symptoms. They have been evaluated in pivotal, large, randomized controlled trials. Your patient has likely suffered a long time prior to being seen in your clinic. Once you make a positive IBS-C diagnosis, consider starting your patient on an FDA-approved treatment for IBS-C. Prompt initiation of effective therapy is your responsibility.

Defining Treatment Response: Setting Expectations

The first step in setting treatment expectations is understanding the goal of each patient. When I ask my patients their goal for their visit with me, the answers range from "I just want to feel better" to "I just want to know that I do not have cancer." Therein lies the advantage of making a confident positive diagnosis of IBS-C. You can assure your patients that studies have proven no connection between IBS-C and increased risk of mortality.

The next step is defining what "feeling better" would look like for each patient. Data from the US population shows that normal bowel movement frequency is anywhere from 3 times per week to 3 times per day, with BSFS type 3 and 4 for most people.[84,85] So my aim is to get my patients' bowel frequency and consistency in that range.

Then we talk about percentage in overall improvement, which considers abdominal symptoms as well. Unlike IBD, in which a stool-based marker or colonoscopy results indicate the level of inflammation, in IBS-C we are pursuing significant QoL improvement as the goal of therapy. So, although I tell my patients that they may never have a CSBM every single day, they should definitely expect improvement in both the frequency and consistency of their bowel movements along with significant improvement in abdominal pain, straining, and bloating. My goal is to have my patients experience at least 50% or more improvement overall on their IBS-C medication.

To establish these expectations, I encourage my patients to define what "much improved" would mean for them. Often patients identify what is bothering them the most, which usually varies among patients. I ask them to identify the 1 symptom they want to get rid of: Is it pain? Is it constipation? Is it anorectal symptoms like straining and incomplete evacuation? And that is the guide for evaluating significant treatment response for each individual patient.

1. **IBS-C diagnosis is straightforward and does not require extensive testing.**
2. **IBS-C is a chronic condition.**
3. **IBS-C medications are not rescue medications.**
4. **IBS-C treatment is like maintenance therapy.**
5. **The goal of treatment is not immediate bowel movement. It is to improve ALL symptoms of IBS-C and significantly improve patient's QoL.**
6. **There is no way to confirm what is causing the exact set of symptoms in each patient.**
7. **Identifying the optimal medication for a particular patient can be an empirical process. The patient should be prepared for a trial-and-error approach and follow up to evaluate impact of treatment.**
8. **Tailoring therapy could involve changing the medication to one with a different MOA.**
9. **Bowel symptoms will usually improve earlier than abdominal symptoms.**
10. **The symptoms may wax and wane over time. Approach your gastroenterologist to adjust treatment if that happens.**

Figure 4. Educate your patients with IBS-C: what your patients should know.

IBS-C, irritable bowel syndrome with constipation; MOA, mechanism of action; QoL, quality of life.

In the Clinic . . .

Patients with IBS-C have been stigmatized for so long, and as physicians we should acknowledge that and reassure our patients that the aim of treatment is significant QoL improvement, not just bowel frequency improvement.

Setting Expectations: "Chronic Disease Requires Chronic Treatment"

I explain to my patients that, with successful IBS-C treatment, their bowel movements will be more frequent and abdominal symptoms will improve. Overall, there will be significant improvement in their QoL, and they should expect to improve over time. However, equally important is that they realize that IBS-C is a chronic disease that requires chronic treatment. Because of this, patients must remain on daily therapy. IBS-C medication adherence may be influenced by the occurrence of comorbidities, which may predict treatment discontinuation.[86] A common cause of treatment discontinuation is intolerance (primarily diarrhea), which may be effectively managed

via dose adjustment[87] or trial of an alternative agent. Loss of prescription drug coverage and insufficient efficacy derived from therapy are other factors that may trigger treatment discontinuation.

In the Clinic . . .

Educate your patients that IBS-C medications are not rescue medications. The goal of taking IBS-C medication is not an immediate bowel movement. They are maintenance therapies that you take to improve *all* symptoms of IBS-C.

Tailoring Treatment in Case of Inadequate Response: Raising Expectations

IBS-C is a heterogeneous disorder. In some patients, their IBS-C may be more related to peripheral factors such as their bowels; in others, it may be more related to central factors such as psychosocial issues. The multifactorial pathophysiology of IBS-C means that patients may respond completely differently to agents with different MOAs.[21,88] There is currently no way of knowing which specific MOA will work for each patient. Therefore, if one IBS-C medication has not worked well, it does not mean that another will also fail—hence the need for an empirical approach.

The comparative efficacies between these agents are unknown in the absence of head-to-head trials. However, initiating treatment with any of these agents is clearly better than no treatment, as demonstrated in 2 meta-analyses of randomized controlled trials of these agents. The first of these found that all 4 FDA-approved agents for IBS-C were superior to placebo for the treatment of global IBS-C symptoms and demonstrated similar efficacy across most endpoints.[89] The second analysis found that the FDA-approved agents for IBS-C were superior to placebo with respect to improvement in abdominal bloating.[90]

Although symptom improvement can often be noted within the first week of treatment, most patients require longer courses of therapy before achieving a response. Further, bowel symptoms tend to respond more rapidly than abdominal pain symptoms or bloating, so it is important to continue a medication for sufficient time to allow the patient to achieve their treatment goals.[91]

This was demonstrated in a post hoc analysis of pooled data from 3 studies of tenapanor (T3MPO-1, T3MPO-2, and a phase 2b study).[92] In tenapanor-treated patients, the median time to CSBM response was 2 weeks, whereas the time to abdominal symptom relief was longer. The median time to abdominal pain response was 4 weeks and the median time to abdominal bloating response was 5 weeks. A post hoc analysis of linaclotide trials also suggests that, although over one-half of patients with IBS-C treated with linaclotide experienced response for abdominal pain, discomfort, and bloating or CSBM frequency within 4 weeks of treatment initiation, another 8% to 17% exhibited a response between weeks 5 and 12.[93]

In the Clinic . . .

I explain to my patients that we don't have comparative data of the FDA-approved IBS-C medications. This essentially means that most likely we have to use a trial-and-error method to find the medication that works for them. Reiterate and ensure that your patient understands that this trial-and-error approach is absolutely fine and will ultimately help improve their QoL. Side effects also play a role in this decision. The reality is that many patients go through a variety of different medications before we find one that addresses all their IBS-C symptoms and improves their QoL. So, if we need to persist with treatment or change their treatment to one with a different MOA, we should do so until we find what works for each individual patient. The best medication for any given patient is the one they actually take, meaning it's effective, well tolerated, and not too expensive.

1. **Appreciate that patients are being likely seen in your clinic after years of suffering and internalizing stigma associated with their relentless symptoms.**
2. **Use a positive diagnostic strategy.**
3. **Recognize that, although IBS-C does not impact mortality, it is debilitating. Therefore, the goal of treatment strategy has to be significantly improved QoL.**
4. **Initiate treatment with an FDA-approved medication for IBS-C.**
5. **Evaluate treatment response in 6 weeks—impact on bowel symptoms, impact on abdominal symptoms, impact on QoL.**
6. **Tailor therapy till you achieve significant improvement in QoL—switch to a medication with a different MOA.**

Figure 5. Raising expectations in IBS-C management: physician's approach to a treatment algorithm.

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

Bringing It All Together: Treatment Algorithm for IBS-C

The AGA guidelines include a treatment algorithm for IBS-C.[53] However, this algorithmic approach does have its limitations. The AGA guidelines focus on patient–provider relationship, fiber, a low-FODMAP diet, lifestyle modifications, education, reassurance, laxatives, and pain medication as first-line treatment followed by FDA-approved IBS-C medications as second-line options. Patient education is a significant step in establishing

patient–provider relationship (Figure 4). However, the AGA treatment algorithm provides no guidance on switching MOAs in case of inadequate response with one medication; I believe this is an educational gap.

In the patient we are discussing, linaclotide did not work at all until the 290 µg dose when it worked "too well". Then I switched to tenapanor, which has a unique MOA. The patient responded well, with improvement in both bowel and abdominal symptoms.

We, as physicians, need to educate our patients and ourselves, raise our expectations regarding the outcome of managing IBS-C, and try everything in our toolkit until our patients experience significant improvement in their QoL (Figure 5).

Disclosures

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References

1. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *J Clin Med*. 2017;6(11):99.
2. Drossman DA, Tack J. Rome Foundation clinical diagnostic criteria for disorders of gut-brain interaction. *Gastroenterology*. 2022;162(3):675-679.
3. Black CJ, Ford AC. Assessing the impact of changes to the Rome IV criteria for clinical practice in irritable bowel syndrome. *Gastroenterology*. 2022;162(6):1752-1754.e1.
4. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116(1):17-44.
5. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920-924.
6. Spiegel B. Continuing the dialogue in IBS-C management: importance of individualizing care and tailoring treatment. *Gastroenterol Hepatol (N Y)*. 2024;20(9)(suppl 7):1-12.
7. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150(6):1393-1407.
8. Brenner DM, Domínguez-Muñoz JE. Differential diagnosis of chronic diarrhea: an algorithm to distinguish irritable bowel syndrome with diarrhea from other organic gastrointestinal diseases, with special focus on exocrine pancreatic insufficiency. *J Clin Gastroenterol*. 2023;57(7):663-670.
9. Maxwell PR, Mendall MA, Kumar D. Irritable bowel syndrome. *Lancet*. 1997;350(9092):1691-1695.
10. Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment Pharmacol Ther*. 2005;21(11):1365-1375.
11. Hidayat AA, Waskito LA, Sugihartono T, et al. Diagnostic strategy of irritable bowel syndrome: a low- and middle-income country perspective. *Intest Res*. 2024;22(3):286-296.
12. Burbige EJ. Irritable bowel syndrome: diagnostic approaches in clinical practice. *Clin Exp Gastroenterol*. 2010;3:127-137.
13. Lacy BE, Rosemore J, Robertson D, Corbin DA, Grau M, Crowell MD. Physicians' attitudes and practices in the evaluation and treatment of irritable bowel syndrome. *Scand J Gastroenterol*. 2006;41(8):892-902.
14. Spiegel BM. Do physicians follow evidence-based guidelines in the diagnostic work-up of IBS? *Nat Clin Pract Gastroenterol Hepatol*. 2007;4(6):296-297.
15. Hearn M, Whorwell PJ, Vasant DH. Stigma and irritable bowel syndrome: a taboo subject? *Lancet Gastroenterol Hepatol*. 2020;5(6):607-615.
16. Taft TH, Bedell A, Naftaly J, Keefer L. Stigmatization toward irritable bowel syndrome and inflammatory bowel disease in an online cohort. *Neurogastroenterol Motil*. 2017;29(2):10.
17. 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.
18. Mayer EA, Ryu HJ, Bhatt RR. The neurobiology of irritable bowel syndrome. *Mol Psychiatry*. 2023;28(4):1451-1465.
19. Tome J, Kamboj AK, Loftus CG. Approach to disorders of gut-brain interaction. *Mayo Clin Proc*. 2023;98(3):458-467.
20. Spiller R, Major G. IBS and IBD - separate entities or on a spectrum? *Nat Rev Gastroenterol Hepatol*. 2016;13(10):613-621.
21. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol*. 2014;20(22):6759-6773.
22. Camilleri M. Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med*. 2012;367(17):1626-1635.
23. Camilleri M. Management of the irritable bowel syndrome. *Gastroenterology*. 2001;120(3):652-668.
24. Barbara G, Barbaro MR, Fuschi D, et al. Inflammatory and microbiota-related regulation of the intestinal epithelial barrier. *Front Nutr*. 2021;8:718356.
25. 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.
26. Farzaei MH, Bahramsoltani R, Abdollahi M, Rahimi R. The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments. *J Neurogastroenterol Motil*. 2016;22(4):558-574.
27. Garrigues V, Mearin F, Badía X, et al; RITMO GROUP. Change over time of bowel habit in irritable bowel syndrome: a prospective, observational, 1-year follow-up study (RITMO study). *Aliment Pharmacol Ther*. 2007;25(3):323-332.
28. Chira A, Filip M, Dumitrașcu DL. Patterns of alternation in irritable bowel syndrome. *Clujul Med*. 2016;89(2):220-223.
29. Drossman DA, Morris CB, Hu Y, et al. A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator. *Gastroenterology*. 2005;128(3):580-589.
30. Patients With Irritable Bowel Syndrome With Constipation From the IBS in America 2024 Real-World Survey Experience Burdensome Symptoms Beyond Constipation. *Gastroenterol Hepatol (N Y)*. 2024;20(12)(suppl 9):5-7.
31. 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.
32. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci*. 1993;38(9):1569-1580.
33. Frändemark Å, Törnblom H, Jakobsson S, Simrén M. Work productivity and activity impairment in irritable bowel syndrome (IBS): a multifaceted problem. *Am J Gastroenterol*. 2018;113(10):1540-1549.
34. Paré P, Gray J, Lam S, et al. Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study. *Clin Ther*. 2006;28(10):1726-1735.
35. DiBonaventura M, Sun SX, Bolge SC, Wagner JS, Mody R. Health-related quality of life, work productivity and health care resource use associated with constipation predominant irritable bowel syndrome. *Curr Med Res Opin*. 2011;27(11):2213-2222.
36. 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.
37. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. *N Engl J Med*. 2017;376(26):2566-2578.
38. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*. 2019;50(2):132-143.
39. Staudacher HM, Black CJ, Teasdale SB, Mikocka-Walus A, Keefer L. Irritable bowel syndrome and mental health comorbidity - approach to multidisciplinary management. *Nat Rev Gastroenterol Hepatol*. 2023;20(9):582-596.
40. Nikolova VL, Pelton L, Moulton CD, et al. The prevalence and incidence of irritable bowel syndrome and inflammatory bowel disease in depression and bipolar disorder: a systematic review and meta-analysis. *Psychosom Med*. 2022;84(3):313-324.
41. Koloski N, Holtmann G, Talley NJ. Is there a causal link between psychological disorders and functional gastrointestinal disorders? *Expert Rev Gastroenterol Hepatol*. 2020;14(11):1047-1059.
42. Eijsbouts C, Zheng T, Kennedy NA, et al; 23andMe Research Team; Bellygenes Initiative. Genome-wide analysis of 53,400 people with irritable bowel syndrome highlights shared genetic pathways with mood and anxiety disorders.

Nat Genet. 2021;53(11):1543-1552.
43. Riedl A, Schmidtmann M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res*. 2008;64(6):573-582.
44. Tarar ZI, Farooq U, Nawaz A, et al. Prevalence of fibromyalgia and chronic fatigue syndrome among individuals with irritable bowel syndrome: an analysis of United States national inpatient sample database. *Biomedicines*. 2023;11(10):2594.
45. Grover M, Kolla BP, Pamarthy R, et al. Psychological, physical, and sleep comorbidities and functional impairment in irritable bowel syndrome: results from a national survey of U.S. adults. *PLoS One*. 2021;16(1):e0245323.
46. Jones KR, Palsson OS, Levy RL, et al. Comorbid disorders and symptoms in irritable bowel syndrome (IBS) compared to other gastroenterology patients. *Gastroenterology*. 2001;120(suppl 1):A66.
47. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med*. 2000;160(2):221-227.
48. Wald A, Bharucha AE, Limketkai B, et al. ACG Clinical Guidelines: management of benign anorectal disorders. *Am J Gastroenterol*. 2021;116(10):1987-2008.
49. Bharucha AE, Wald AM. Anorectal disorders. *Am J Gastroenterol*. 2010;105(4):786-794.
50. Jin J. JAMA patient page. Over-the-counter laxatives. *JAMA*. 2014;312(11):1167.
51. 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.
52. Patel S, Doerfler B, Boutros K, Ng S, Manuel M, DeSimone E. Review of treatment options for irritable bowel syndrome with constipation and chronic idiopathic constipation. *Int J Gen Med*. 2021;14:1457-1468.
53. 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.
54. Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. *Am J Gastroenterol*. 2013;108(5):718-727.
55. Christodoulides S, Dimidi E, Fragkos KC, Farmer AD, Whelan K, Scott SM. Systematic review with meta-analysis: effect of fibre supplementation on chronic idiopathic constipation in adults. *Aliment Pharmacol Ther*. 2016;44(2):103-116.
56. Purtle BJ, Cash BD. In persons with constipation or IBS-C, kiwifruit vs. psyllium increased spontaneous bowel movements. *Ann Intern Med*. 2023;176(5):JC53.
57. Gupta AK, Maity C. Efficacy and safety of *Bacillus coagulans* LBSC in irritable bowel syndrome: A prospective, interventional, randomized, double-blind, placebo-controlled clinical study [CONSORT Compliant]. [CONSORT Compliant]. *Medicine (Baltimore)*. 2021;100(3):e23641.
58. Le Morvan de Sequeira C, Kaeber M, Cekin SE, Enck P, Mack I. The effect of probiotics on quality of life, depression and anxiety in patients with irritable bowel syndrome: a systematic review and meta-analysis. *J Clin Med*. 2021;10(16):3497.
59. Amitiza (lubiprostone) [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; August 2023.
60. Linzess (linaclotide) [package insert]. North Chicago, IL: AbbVie, Inc.; June 2023.
61. Trulance (plecanatide) [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; April 2021.
62. Ibsrela (tenapanor) [package insert]. Waltham, MA: Ardelyx, Inc.; April 2022.
63. Brenner DM. Mechanism of action considerations in the management of IBS-C. *Gastroenterol Hepatol (N Y)*. 2023;19(12)(suppl 6):749-756.
64. Lacy BE, Levy LC. Lubiprostone: a novel treatment for chronic constipation. *Clin Interv Aging*. 2008;3(2):357-364.
65. Layer P, Stanghellini V. Review article: linaclotide for the management of irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2014;39(4):371-384.
66. Thomas RH, Allmond K. Linaclotide (Linzess) for irritable bowel syndrome with constipation and for chronic idiopathic constipation. *P&T*. 2013;38(3):154-160.
67. Kamuda JA, Mazzola N. Plecanatide (Trulance) for chronic idiopathic constipation and irritable bowel syndrome with constipation. *P&T*. 2018;43(4):207-232.
68. 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.
69. 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.
70. 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.
71. 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.
72. 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.
73. 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.
74. 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.
75. 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.
76. 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.
77. 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.
78. 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.
79. Efficacy and safety of plecanatide in treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. *Gastroenterol Hepatol (N Y)*. 2024;20(12)(suppl 9):7-9.
80. 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.
81. 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.
82. 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.
83. 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.
84. Srinivas M, Srinivasan V, Jain M, Rani Shanthi CS, Mohan V, Jayanthi V. A cross-sectional study of stool form (using Bristol stool chart) in an urban South Indian population. *JGH Open*. 2019;3(6):464-467.
85. Walter SA, Kjellström L, Nyhlin H, Talley NJ, Agréus L. Assessment of normal bowel habits in the general adult population: the Popcol study. *Scand J Gastroenterol*. 2010;45(5):556-566.
86. Shah ED, Brenner DM, Chen VL. Baseline predictors of discontinuation of prescription drug therapy for IBS-C: cohort analysis at an integrated healthcare system. *Dig Dis Sci*. 2022;67(4):1213-1221.
87. Shah ED, Suresh S, Jou J, Chey WD, Stidham RW. Evaluating when and why patients discontinue chronic therapy for irritable bowel syndrome with constipation and chronic idiopathic constipation. *Am J Gastroenterol*. 2020;115(4):596-602.
88. Chey WD, Nojkov B, Rubenstein JH, Dobhan RR, Greenson JK, Cash BD. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: results from a prospective, controlled US trial. *Am J Gastroenterol*. 2010;105(4):859-865.
89. 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.
90. 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.
91. Lacy BE. Managing IBS-C: focus on symptom control. *Gastroenterol Hepatol (N Y)*. 2024;20(4):216-226.
92. 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.
93. 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.


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