Managing IBS-C: Focus on Symptom Control

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Patient Case

JP is a 24-year-old man referred for a second opinion in Gastroenterology. He reports a yearlong history of lower abdominal pain and discomfort, bloating, and infrequent stools that are difficult to evacuate. He believes that symptoms began after traveling through Europe when he could not always find a restroom. He noted that the trip was stressful because he broke up with his fiancée during the trip. He reports that he now frequently experiences 2 to 3 days without a bowel movement and that the stool is hard and difficult to evacuate. A review of his diet confirms that he ingests approximately 25 grams of fiber each day.

His primary care provider and then his local gastroenterologist ordered several laboratory tests including a complete blood count (CBC), metabolic profile, liver chemistries, thyroid tests, celiac serologies, and C-reactive protein (CRP); these were normal on both occasions. He tried several over-the-counter products including docusate sodium, senna, and bisacodyl and polyethylene glycol. However, none of these improved his symptoms to any significant degree and some caused abdominal cramps.

Because of his persistent symptoms, his local gastroenterologist performed a colonoscopy, which was grossly normal. He came prepared to this office visit with various questions. These included:

- What is my diagnosis?
- Why did I develop these symptoms?
- Is there anything worrisome in my history?
- How long will I have these symptoms? What will happen if my symptoms go untreated?
- Do I need any further tests?
- Will changing my diet help?
- Are there other ways to treat my symptoms?
- How do these treatments work?
- How effective are these treatments?
- What side effects should I be aware of?
- How long will I have to take the treatment to see any benefit?

We will now examine evidence-based answers to these questions.

What Is My Diagnosis?

With the patient's description of hard stool that is difficult to evacuate, coupled with a yearlong history of abdominal pain associated with changes in stool frequency and consistency, the diagnosis for the patient in this case is IBS-C.

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI; previously called a functional bowel disorder). The Rome IV criteria (Figure 1) define IBS as the presence of abdominal pain recurring on average at least once weekly in conjunction with 2 or more of the following: related to defecation, associated with a change in stool frequency, or associated with a change in stool form.[1] By definition, these criteria are chronic and must be fulfilled at least once weekly on average during the prior 3 months with symptom onset at least 6 months prior to diagnosis.

The Rome IV criteria are used together with the Bristol Stool Form Scale (BSFS) to establish a patient's IBS subtype (Figure 2).[1,2] Irritable bowel syndrome with constipation (IBS-C) is classified by at least 25% of bowel

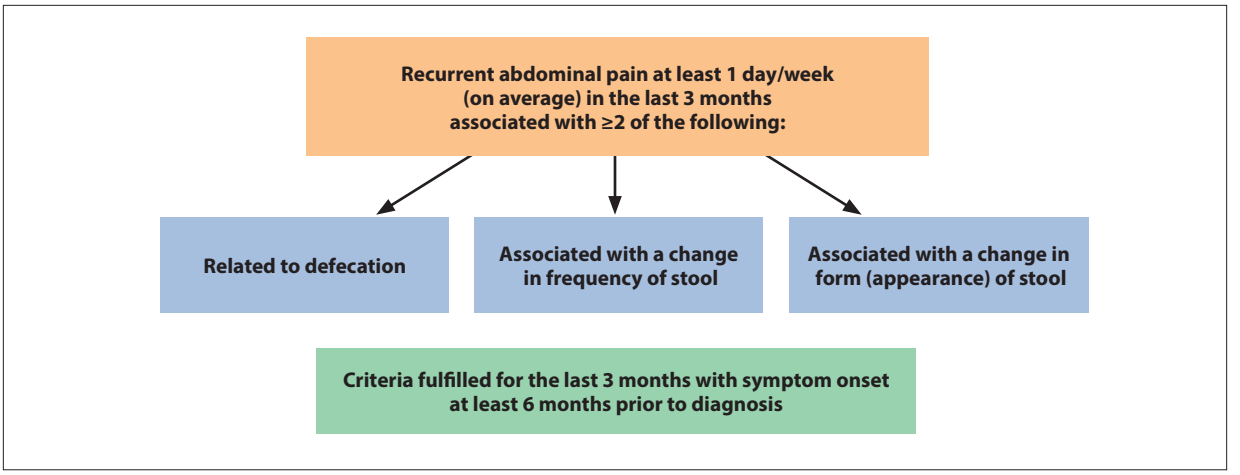

Figure 1. The Rome IV criteria for irritable bowel syndrome.[1]

movements of BSFS types 1 or 2, and less than 25% of BSFS types 6 or 7. In contrast, IBS with diarrhea (IBS-D) is classified by at least 25% of bowel movements of BSFS types 6 or 7, and less than 25% of BSFS types 1 or 2. IBS with mixed or alternating bowel habits (IBS-M) is classified 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. Lastly, IBS unclassified (IBS-U), which is not very prevalent, is used to classify patients who meet criteria for IBS but do not fall into one of the other 3 IBS subgroups according to BSFS type.

The differential diagnosis of IBS (Table 1) supposes that chronic abdominal pain is required to meet the diagnostic criteria for IBS. Therefore, patients with acute abdominal pain should be excluded when the abdominal pain is not associated with defecation or alterations in stool frequency or consistency.[2]

Key Teaching Points

Although there are conditions that mimic IBS, the Rome IV criteria provide straightforward diagnostic criteria for IBS.

Use clear and concise language while explaining a diagnosis of IBS-C to patients.

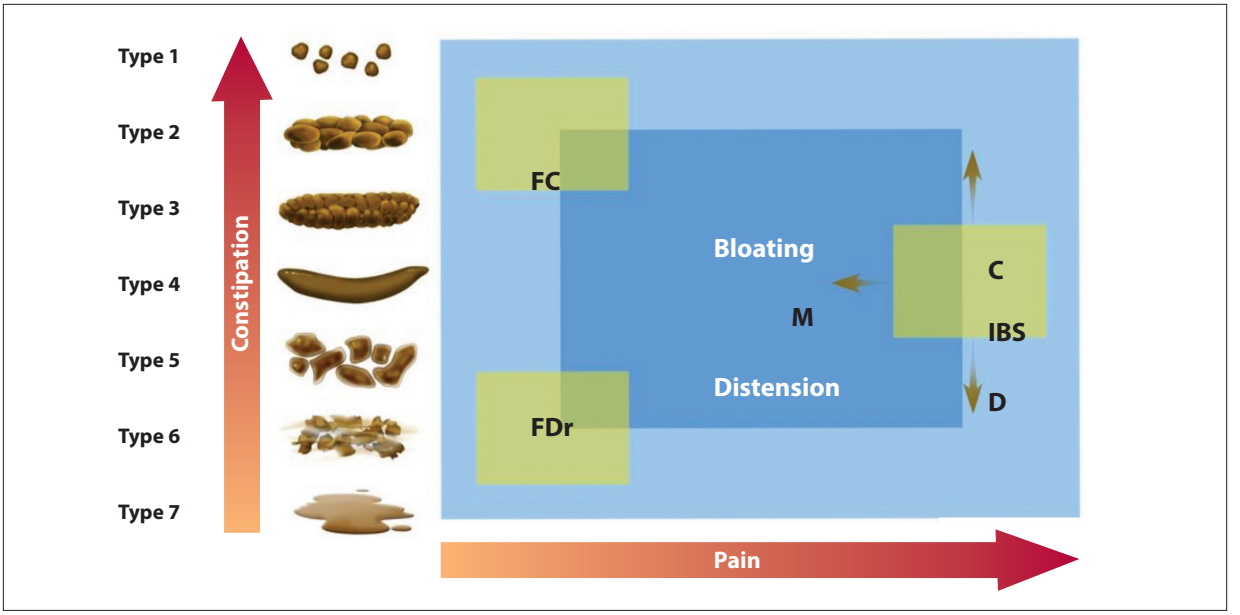

Figure 2. The Rome IV criteria are used in conjunction with the Bristol Stool Form Scale to define the irritable bowel syndrome subtype.[1]

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.

Table 1. Differential Diagnosis of Irritable Bowel Syndrome

Conditions That May Mimic Irritable Bowel Syndrome
Carbohydrate intolerance (eg, lactose, fructose)
Disaccharidase deficiencies (sucrase-isomaltase)
Small intestine bacterial overgrowth
Celiac disease
Nonceliac gluten sensitivity
Inflammatory bowel disease; microscopic colitis
Functional diarrhea
Functional constipation
Rectal evacuation disorders

Why Did I Develop These Symptoms?

The patient was noted to have experienced several stressors immediately prior to first experiencing symptoms—he was traveling (he likely had some issues with stool withholding owing to travel and inability to find a restroom) and he broke up with his fiancée. These may have served as triggers for the development of IBS-C.

IBS is often considered a brain-gut disorder, owing to its high association with psychiatric and psychological conditions, in particular anxiety and depression.[3] However, the pathophysiology of IBS is complex, with several mechanisms contributing to the disease. One model to explain the pathophysiology of IBS includes a genetic predisposition along with negative factors such as adverse events in early life, psychological factors, or a gastrointestinal infection to result in changes in the enteric nervous system (Figure 3).[2-10] Several mechanisms may contribute to IBS pathophysiology, including alterations in gut motility and fluid balance, changes in the gut microbiota leading to aberrant microbiome-immune interactions, and alterations in gut permeability.[4-9]

Acute infectious gastroenteritis resulting from bacterial, viral, or protozoal pathogens such as *Salmonella*, *Campylobacter jejuni*, *Shigella*, *Escherichia coli* 0157:H7, *Giardia*, and norovirus has been identified as a precursor to IBS in 10% to 20% of individuals.[3] A meta-analysis of 8 studies that grouped patients into an infectious gastroenteritis group or a control group reported a median prevalence of IBS of 9.8% and 1.2%, respectively (sign-rank test, P=.01).[10] This resulted in a pooled odds ratio of 7.3 (95% CI, 4.7-11.1) for the development of IBS following infectious gastroenteritis.

Key Teaching Points

Tell patients that they are not unique in developing IBS-C.

This is a common problem with many triggers.

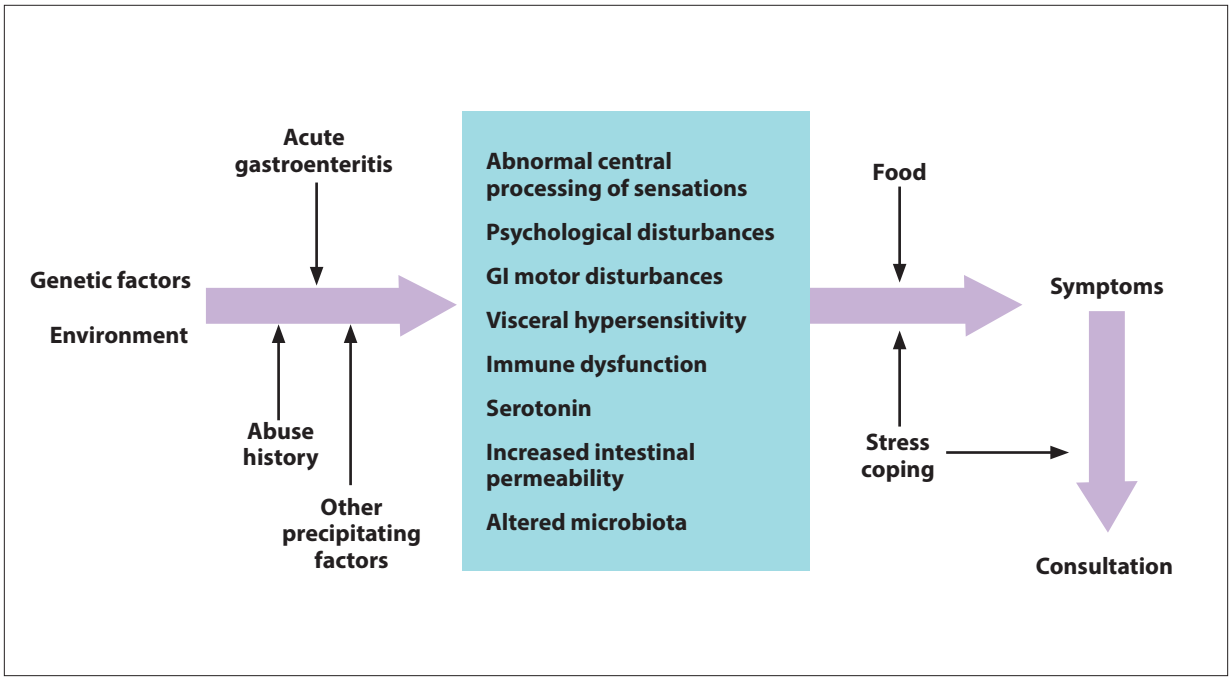

Figure 3. Proposed pathophysiology of irritable bowel syndrome.[2-10]
GI, gastrointestinal.

Is There Anything Worrisome in My History?

The patient in this case is experiencing symptoms that meet Rome IV criteria for IBS and does not exhibit any alarm features that would suggest a differential diagnosis.

It is important to emphasize to patients that IBS is a chronic disorder with a negative impact on quality of life. However, IBS does not alter lifespan (there is no increase in mortality) and does not increase the risk of developing inflammatory bowel disease (IBD). As was demonstrated in a matched, population-based cohort study in Sweden, IBS was not linked to mortality after adjustment for confounders (HR, 0.96; 95% CI, 0.92-1.00).[11] Further, IBS does not increase the risk for developing colorectal cancer, shown in a meta-analysis of population-based studies that found a long-term risk in patients with IBS that was comparable to that of the general population (RR, 1.02; 95% CI, 0.88-1.18; *P*=.813).[12]

However, there is a set of alarm features that should trigger prompt investigation and treatment, as they are not associated with IBS and instead may indicate a sign of an organic gastrointestinal disorder.[1,13] 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, and a family history of colorectal cancer, polyposis syndrome, celiac disease, or IBD. In this patient, no alarm features were present. In addition, CBC, CRP, and celiac serologies were all normal. This information can be used to help reassure the patient that the diagnosis of IBS is correct.

This knowledge of the natural history of IBS coupled with an understanding of the alarm features that suggest a differential diagnosis can provide reassurance to patients with IBS that their disease is unlikely to be life-shortening. Clinicians can then focus their time with the patient on education and effective treatment approaches to achieve optimal management while minimizing impact on the patient's quality of life.

How Long Will I Have These Symptoms? What Will Happen If My Symptoms Go Untreated?

IBS-C is a chronic disorder for many patients. The symptoms of IBS-C can change over time, but prevalence of symptomatic IBS remains stable over the first 1 to 2 years of follow-up.[14] After 10 years, about 50% or more of patients continue to experience persistent symptoms. Although the disorder is not curable presently, IBS-C can be well managed with treatment options currently available. It is important to reiterate to patients that symptoms will persist without treatment and will be bothersome and flare up owing to individual factors. Relating a diagnosis of IBS-C to other chronic and treatable conditions such as hypertension, hypercholesterolemia, or diabetes may help patients understand the importance of treating the IBS-C to effectively manage symptoms.

Key Teaching Points

Discuss with the patient the importance of treating IBS-C in order to manage symptoms and improve quality of life.

Tell the patient with IBS-C,
"You can't expect to get better without treatment."

Do I Need Any Further Tests?

The patient in this case meets the Rome IV criteria for the diagnosis of IBS-C based on symptoms alone. During his clinical journey, laboratory tests were ordered and were normal twice. In addition, a colonoscopy was performed owing to persistent symptoms. In the evaluation of patients with IBS, it is important to understand that extensive testing is not required for most patients. Extensive testing may not change the diagnosis and may potentially cause a delay in diagnosis and treatment.

The American College of Gastroenterology (ACG) Clinical Guideline for the Management of IBS provides recommendations to support a positive diagnostic strategy based on Rome IV criteria instead of a diagnostic strategy of exclusion.[15] In most patients, symptoms are sufficient basis for a diagnosis without the need for further testing. Abdominal pain and hard stools, which are 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).

However, in appropriate patients, some testing strategies may be useful during the initial evaluation, if they have not been recently performed. A simple way to remember these tests is to recall the 4 Cs: CBC, CRP, fecal calprotectin, and celiac serologies. For example, the ACG guidelines recommend serologic testing to rule out celiac disease in patients with IBS and diarrhea symptoms.[15] Further, the ACG guidelines suggest that either fecal calprotectin or fecal lactoferrin and CRP be evaluated in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out IBD. In contrast, the ACG guidelines recommend against routine stool testing for enteric pathogens in all patients with IBS. Because there is no role for colonoscopy in the diagnosis of IBS,

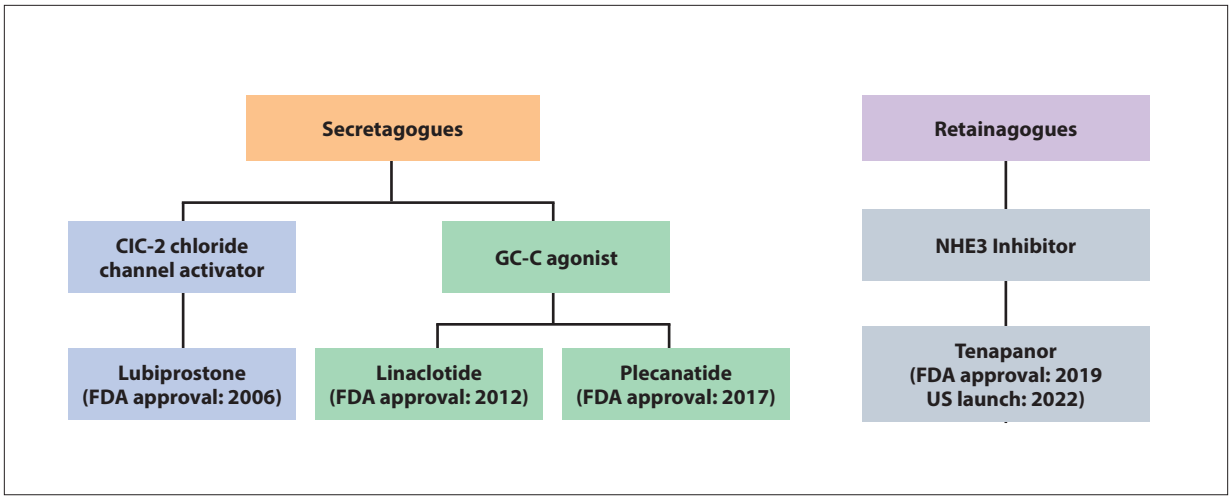

Figure 4. Currently available FDA-approved treatments with a specific indication for IBS-C.[22-26]

FDA, US Food and Drug Administration; GC-C, guanylate cyclase-C; IBS-C, irritable bowel syndrome with constipation; NHE3, sodium/hydrogen exchanger isoform 3.

the ACG guidelines recommend against routine colonoscopy in patients with IBS symptoms but with no alarm features who are under the age of 45 years.

Key Teaching Points

Excessive testing does not reassure patients, and instead exposes them to unnecessary risks, worry, and costs.

Make a positive diagnosis based on symptoms (Rome IV criteria) and limited testing to initiate treatment, ideally at the first visit.

Will Changing My Diet Help?

With a diagnosis of IBS-C, the patient in this case may not benefit from dietary therapy. He is already consuming normal fiber. Adding more fiber will not help and will likely worsen bloating symptoms. Although frequently recommended, a low-FODMAP diet may worsen symptoms of constipation. Also, chronic use of a low-FODMAP diet may lead to vitamin and micronutrient deficiencies.

Over the years, multiple dietary interventions have been proposed for patients with IBS. These include diets incorporating low histamine, immunoglobulin G elimination, low carbohydrates, low fructose/fructans, and low gluten, as well lactose-free diets and the Paleo diet. In general, there are only limited data to support the use of any of these dietary therapies.

Perhaps the most well-studied dietary therapy for IBS is the low-fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) diet. However, as this diet requires a significant reduction in the consumption of fermentable foods, it may exacerbate constipation if followed strictly. As a result, the low-FODMAP diet is a better treatment option for patients with IBS-D or IBS-M, particularly those who experience abdominal bloating and distension. Further, adhering to a low-FODMAP diet can be difficult and frustrating, and its long-term use can result in vitamin and micronutrient deficiencies.

One dietary intervention that is often overlooked, but particularly important for patients with IBS-C, is ensuring adequate fiber intake. The vast majority of Americans fall far short of recommended fiber intake goals, which range from 19 to 38 grams per day, depending on the patient's sex and age.[16,17]

Are There Other Ways to Treat My Symptoms?

The patient in this case has already tried several over-the-counter products with minimal symptom relief. This patient may benefit from an agent that has been specifically tested and proven to be effective in patients with IBS-C. Currently available are 4 medications that are FDA approved for the treatment of IBS-C.

Laxatives are commonly employed in the treatment of IBS-C, with the goals of increasing the frequency of stools while improving stool consistency.[18] Two types of laxatives—osmotic and stimulant—are commonly used in clinical practice, with the former promoting colonic fluid and electrolyte secretion, and the latter working to increase gastrointestinal motility by enhancing intestinal contractility. Osmotic agents, such as polyethylene glycol, may improve symptoms of constipation but do not improve the cardinal symptom of IBS: abdominal pain.[19]

Similarly, laxatives may improve constipation symptoms, but the stimulatory effects may worsen abdominal cramps, discomfort, and pain.[20] As a result, patients then use multiple other therapies in an attempt to treat the many symptoms of IBS-C. Further, there is a lack of randomized clinical trials evaluating these agents in patients with IBS-C.[21]

A more global approach to the treatment of IBS-C employs the 4 currently available and US Food and Drug Administration (FDA)–approved treatment options for patients with IBS-C (Figure 4).[22-26] Of these 4 agents, the first to gain FDA approval was lubiprostone in 2006; this indication is limited to treatment of IBS-C in women.[22] This was followed in 2012 with the approval of linaclotide, and then plecanatide in 2017.[23,24] These 3 agents fall in a class of drugs termed secretagogues. The most recently approved drug for IBS-C, tenapanor in 2019, is a first-in-class agent in a class of drugs termed retainagogues; it was launched in the United States in 2023.[25] Of note, tegaserod, a 5-hydroxytryptamine type 4 agonist, was approved for the treatment of IBS-C in 2002 but is no longer commercially available.

Key Teaching Points

Prevent polypharmacy by treating global IBS-C symptoms with FDA-approved agents that have been evaluated in large, randomized, controlled clinical trials with patients meeting the Rome III/IV criteria.

How Do These Treatments Work?

Although their mechanisms of action differ, lubiprostone, linaclotide, and plecanatide are all classified as secretagogues. As a class, these agents increase the secretion of chloride and bicarbonate ions into the intestinal lumen, which leads to water secretion. This accelerates colonic transit, improving stool consistency and increasing the frequency of bowel movements.[21]

The prostaglandin E1 derivative lubiprostone is a CIC-2 chloride channel activator. These chloride channels are found on the apical membranes of epithelial cells lining the intestine; their activation results in an increase in chloride ions into the intestinal lumen.[27] Lubiprostone is indicated for the treatment of IBS-C in women at least 18 years of age; other FDA-approved indications include chronic idiopathic constipation in adults and opioid-induced constipation in adult patients with chronic noncancer pain.[22]

Linaclotide and plecanatide are guanylate cyclase-C (GC-C) agonists.[23,24] The GC-C receptor is located on the apical membranes of the intestinal epithelial cells, and their activation regulates fluid and ion homeostasis and maintenance of the intestinal barrier.[28] Signaling via the GC-C receptor has also been implicated in reducing gut inflammation. GC-C agonists may also play a role in the relief of abdominal pain, via moderation of visceral pain pathways.[29] The activity of linaclotide is pH independent and is thus active throughout the gastrointestinal tract with equivalent affinity for GC-C receptors in the small intestine and colon. In contrast, plecanatide has a pH-dependent conformation and is thus most active in the acidic environment of the small intestine.[21]

Tenapanor is a serotonergic agent sometimes referred to as a retainagogue.[25] Specifically, tenapanor is a locally acting inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3). The NHE3 antiporter, located on the apical surface of the epithelial cells lining the small intestine and colon, is responsible for absorption of dietary sodium.[30] Inhibition of NHE3 results in 3 actions. The first is a decrease in the absorption of dietary sodium, causing retention of water content in the intestinal lumen that leads to acceleration of intestinal transit. The second is a reconstitution of the tight junctions between intestinal epithelial cells, resulting in decreased intestinal permeability. The third is antagonism of transient receptor potential vanilloid 1 channels.[8,9,31] The latter two actions are hypothesized to be responsible for the reduction in visceral hypersensitivity and improvement in abdominal symptoms.

Key Teaching Points

Because of the multifactorial pathophysiology of IBS-C, optimal management includes the use of FDA-approved agents with different mechanisms of action.

If an agent from one class of medications is not effective, a patient may benefit from switching to an agent from another class of medications.

How Effective Are These Treatments?

All 4 currently available FDA-approved agents were evaluated in pivotal, large, randomized controlled trials compared with placebo (Table 2).[32-37] The earliest of these studies, which evaluated lubiprostone, included a primary endpoint of overall responder status, which 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

Table 2. Pivotal Efficacy Data of Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C[32-37]

Agent	Pivotal efficacy data
Lubiprostone[32]	Combined analysis of 2 phase 3 trials[a] 17.9% vs 10.1% with placebo; *P*=.001
Linaclotide[33,34]	26-week phase 3 study[b] 33.7% vs 13.9% with placebo; *P*<.0001 12-week phase 3 study[b] 33.6% vs 21.0% with placebo; *P*<.0001
Plecanatide[35]	Study 1[b] 30.2% (3 mg) and 29.5% (6 mg) vs 17.8% with placebo; *P*<.001 Study 2[b] 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
Tenapanor[36,37]	T3MPO-1 (12-week study)[b] 27.0% vs 18.7% with placebo; CMH *P*=.020 T3MPO-2 (26-week study)[b] 36.5% vs 23.7% with placebo; CMH *P*<.001

CMH, Cochran-Mantel-Haenszel; CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation.

[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]FDA overall response 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.

responder if they were monthly responders for at least 2 of the 3 months of the study. Subsequent studies instead used an FDA-defined endpoint for response in IBS-C, 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.

With a treatment landscape that now includes several different FDA-approved options for patients with IBS-C, an important question is whether one agent is more effective than another. Without head-to-head trials, the comparative efficacies between these agents remains unknown. However, any of these agents is better than no treatment, as was established in a network meta-analysis of randomized controlled trials of these agents. In this study by Black and colleagues, all 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.[38] Another network meta-analysis by Nelson and colleagues, which compared the efficacy of FDA-approved agents for IBS-C with a specific focus on benefit to abdominal bloating, found that all agents were superior to placebo. Indirect comparisons across agents revealed no significant differences.[39]

Lubiprostone

A combined analysis of 2 phase 3 trials compared the efficacy and safety of lubiprostone vs placebo, each administered for 12 weeks.[32] This combined analysis reported a significantly higher percentage of overall responders in the lubiprostone group compared with the placebo group (17.9% vs 10.1%; *P*=.001). The overall response deepened over time with lubiprostone, with an increasing number of patients achieving the primary endpoint over the first 3 months compared with placebo (month 1: 10.8% vs 7.5%; month 2: 18.3% vs 11.4%; month 3: 22.0% vs 14.5%). Importantly, patients classified as overall responders also reported significant improvements in multiple 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

The efficacy and safety of linaclotide vs placebo for the treatment of IBS-C was demonstrated in 2 phase 3 trials. Both studies incorporated the FDA endpoint for IBS-C response. In the first trial, a 26-week study, significantly more patients treated with linaclotide compared with placebo achieved the FDA combined endpoint (33.7% vs 13.9%; *P*<.0001).[33] Several other primary endpoints were also significantly improved in the linaclotide arm compared with the placebo arm, including 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%).

The second trial, conducted over 12 weeks, also randomized patients with IBS-C to receive linaclotide or placebo.[34] The FDA combined endpoint was also significantly improved with linaclotide vs placebo in this study, achieved by 33.6% of patients in the linaclotide arm compared with 21.0% of patients in the placebo arm (*P*<.0001). A number of individual outcomes were also significantly improved with linaclotide 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)

Table 3. Toxicity Profile of Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C[32-37,41]

Agent	AEs/Most common AE	Discontinuation owing to AE/diarrhea
Lubiprostone[32]	GI-related AEs (including nausea, diarrhea, and abdominal distension) Similar incidence in lubiprostone and placebo groups	4.7% and 5.1% (lubiprostone) vs 4.6% and 7.7% (placebo)[a]
Linaclotide[33,34]	Diarrhea 19.7% (linaclotide) vs 2.5% (placebo) in 26-week study	5.7% (linaclotide) vs 0.3% (placebo) in 12-week study[b]
Plecanatide[35]	Diarrhea 4.3% and 4.0% (plecanatide 3 mg and 6 mg, respectively) vs 1.0% (placebo)	2.3% (plecanatide arms combined) vs 0.4% (placebo)[a]
Tenapanor[36,37,41]	Diarrhea T3MPO-1: 14.6% (tenapanor) vs 1.7% (placebo) T3MPO-2: 16.0% (tenapanor) vs 3.7% (placebo)	1.6% in T3MPO-3 (55-week, open-label safety study)[b]

AE, adverse event; FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation.
[a]Discontinuation owing to AE. [b]Discontinuation owing to diarrhea.

and an increase of at least 1 CSBM from baseline (48.6% vs 29.6%; *P*<.0001).

Plecanatide

Two identically designed phase 3 clinical trials evaluated plecanatide or placebo in patients with IBS-C.[35] The same FDA primary endpoint of overall response was used in both studies. In Study 1, a significantly higher percentage of plecanatide-treated patients achieved the primary endpoint vs placebo (30.2% vs 17.8%; *P*<.001). A similar outcome was reported in Study 2 (21.5% vs 14.2%; *P*=.009). Across both studies, all secondary endpoints, including stool frequency/consistency, straining, and abdominal symptoms, were significantly improved with plecanatide compared with placebo.

Tenapanor

The efficacy and safety of tenapanor for the treatment of IBS-C were established in T3MPO-1 (a 12-week trial) and T3MPO-2 (a 26-week trial), 2 placebo-controlled, randomized, phase 3 studies. Both studies used as the primary endpoint the combined FDA endpoint for IBS-C.

Significantly more patients treated with tenapanor than placebo met the primary endpoint in T3MPO-1 (27.0% vs 18.7%; Cochran-Mantel-Haenszel [CMH] *P*=.020).[36] Additionally, the abdominal pain response (44.0% vs 33.1%; CMH *P*=.008) was improved with tenapanor, and the rates of CSBM response were similar between the 2 arms (33.9% vs 29.4%; CMH *P*=.270). Several measures of abdominal symptoms were also improved with tenapanor compared with placebo for at least 9 of 12 weeks, 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). Global IBS treatment measures (including stool consistency, IBS severity, constipation severity, degree of relief from IBS, and adequate relief from IBS) were all significantly improved with tenapanor compared with placebo.

The T3MPO-2 trial reported similar outcomes, with a significantly higher percentage of patients in the tenapanor arm achieving the primary endpoint compared with placebo (36.5% vs 23.7%; CMH *P*<.001).[37] 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 also significantly improved with tenapanor. Among tenapanor-treated patients, improvements in abdominal pain occurred as early as 1 week after beginning treatment. Severe abdominal pain was reduced by 78% from baseline (55%) to week 26 (12%). Over the entire 26-week treatment period, tenapanor-treated patients reported 3.3 CSBMs per week, considered within the healthy range for adults. Tenapanor was also associated with a decrease in other abdominal symptoms (including bloating, fullness, discomfort, and cramping).

A recent post hoc analysis of the T3MPO-1 and T3MPO-2 trials specifically evaluated the efficacy of tenapanor on abdominal symptoms in 1372 patients.[40] Weekly scores were calculated for each abdominal symptom, and an abdominal score (AS) was calculated as the average of weekly scores for abdominal pain, discomfort, and bloating symptoms. The least-squares mean change from baseline in AS was significantly improved with tena-

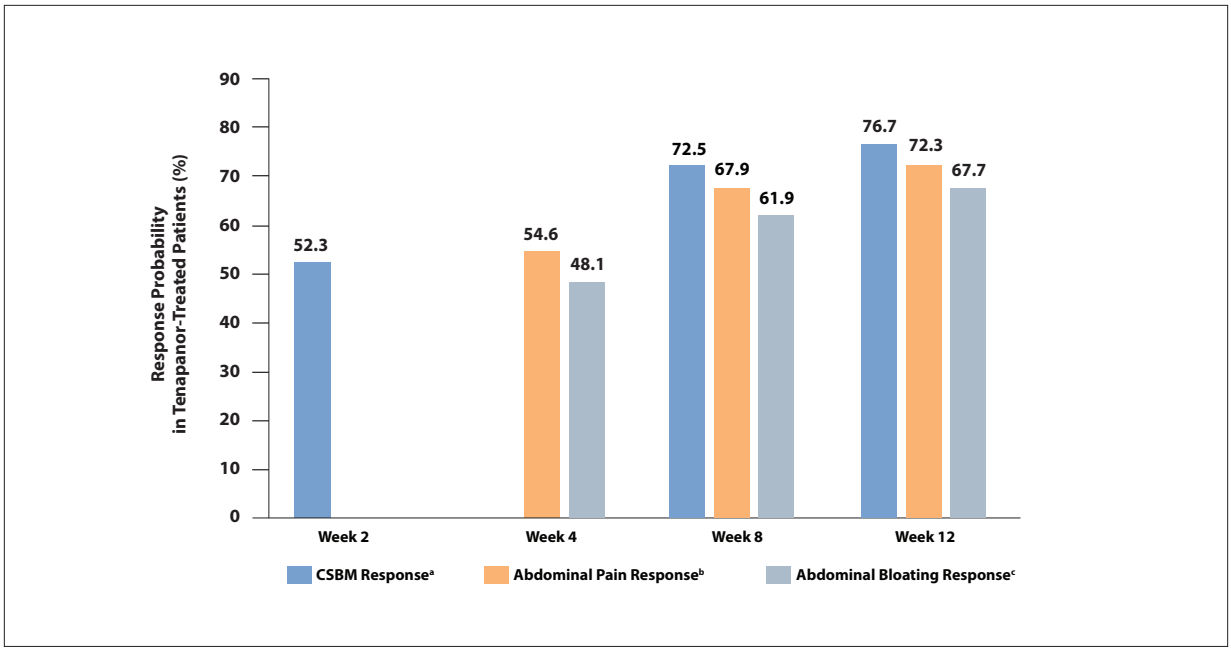

Figure 5. Response probability with tenapanor in a post hoc analysis of patients with IBS-C.[42]

CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation.

[a]CSBM response was defined as an increase of ≥1 in average weekly CSBMs.

[b]Abdominal pain response was defined as a decrease of ≥30% in average weekly abdominal pain score.

[c]Abdominal bloating response was defined as a decrease of ≥30% in average weekly abdominal bloating score.

panor 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).

What Side Effects Should I Be Aware Of?

The side effect profiles of the 4 currently available FDA-approved medications for IBS-C are comparable. Across all studies, diarrhea is the most frequently reported adverse event with any of these agents (Table 3).[32-37,41] It is important to discuss this with patients beginning treatment so that they can be watchful for symptoms and communicate them to the office, as diarrhea may be a sign that the medication dosage may need to be adjusted.

Key Teaching Points

All medications have side effects.

Inform the patients that diarrhea is the most common side effect associated with IBS-C medications and it can be managed.

How Long Will I Have to Take the Treatment to See Any Benefit?

Although many people experience an improvement in symptoms within the first week of treatment, a sizable proportion require longer courses of therapy. Bowel symptoms tend to respond more rapidly than abdominal pain symptoms.

A post hoc analysis recently reported at the ACG 2023 meeting evaluated pooled data from 3 studies (T3MPO-1, T3MPO-2, and a phase 2b study) to determine the time from initiation of tenapanor to improvements in bowel function and abdominal symptoms in 1372 patients with IBS-C.[42] Based on pooled data from the first 12 weeks of the randomized treatment period of each study, Kaplan-Meier estimates were applied to determine the time to CSBM response (defined as achieving an increase of ≥1 in average weekly CSBMs) and time to either abdominal pain response or abdominal bloating response (defined as achieving a decrease of ≥30% in average weekly abdominal pain or abdominal bloating score, respectively).

Among patients treated with tenapanor, the median time to CSBM response was 2 weeks. The estimated CSBM response probability increased from 52.3% by

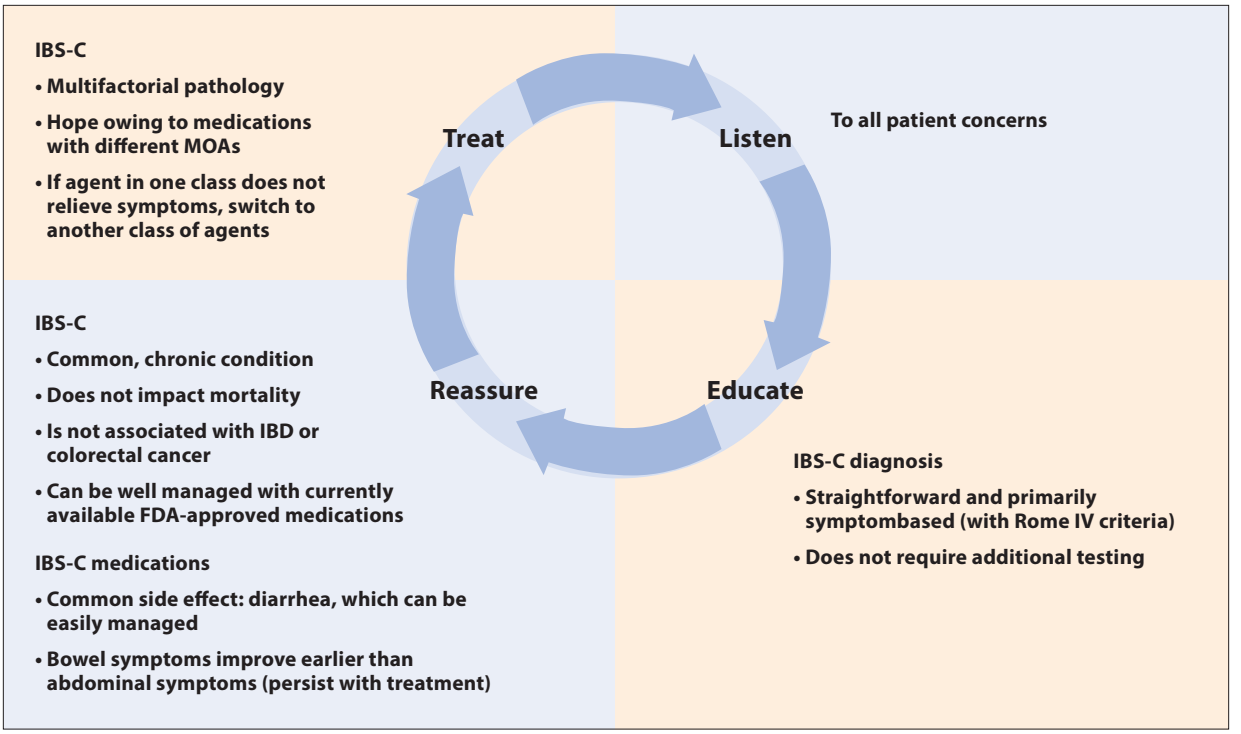

Figure 6. Tips for a successful office visit in the management of a patient with IBS-C.

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

week 2 to 72.5% by week 8 and 76.7% by week 12 (Figure 5).[42] The median time to abdominal pain response in tenapanor-treated patients was 4 weeks. The estimated abdominal pain response probability was 54.6% by week 4, increasing to 67.9% by week 8 and 72.3% by week 12. The median time to abdominal bloating response among tenapanor-treated patients was 5 weeks. The estimated abdominal bloating response probability was 48.1% by week 4, 61.9% by week 8, and 67.7% by week 12.

Key Teaching Points

Don't give up too early! Bowel symptoms consistently tend to respond faster than abdominal symptoms.

Conclusion

A successful office visit follows the paradigm of listen, educate, reassure, and treat (Figure 6). When managing patients with IBS-C, it is essential to listen to the patient and note all their concerns. Then it is important to educate the patient about their diagnosis and how the Rome IV criteria are sufficient and clear on using symptoms to confirm an IBS-C diagnosis. In most cases, there is no need for additional testing, unless otherwise indicated.

The next step is to reassure the patient that although IBS-C can definitely impact their quality of life, it will not lead to early mortality, colorectal cancer, or IBD. Additionally, although IBS-C cannot be cured it can be well managed with FDA-approved treatment options. These treatment options are safe and effective in managing both constipation and abdominal symptoms (pain, discomfort, and bloating). It is also essential to inform the patient that they may experience diarrhea as a side effect that could be managed with dose adjustments in some cases and that abdominal symptoms may take longer to be relieved than constipation itself—therefore, it is essential not to give up but rather persist with the treatment. The last step is to outline a treatment plan and set up a follow-up visit to evaluate how the patient is doing with respect to all IBS-C symptoms, reassuring the patient that improvement of all symptoms is possible with the currently available FDA-approved agents.

It is critical to note that, because of the multifactorial pathophysiology of IBS-C, FDA-approved agents with different mechanisms of action offer hope, and recommending treatment that will work for a particular patient involves some trial and error. Therefore, if an agent in a certain class of medications is not effective, you should switch the patient to an agent in a different class.

Disclosures

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