Patient–Provider Communication: The Key to Improving IBS-C Management

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About the Patient

KS is a 34-year-old accountant presenting to the clinic as a new consult for long-standing history of abdominal pain and bloating with irregular bowel habits characterized by constipation. She describes her constipation as days between bowel movements as well as straining with harder stools and a frequent sensation of incomplete evacuation. KS describes nearly daily bloating that worsens as the day progresses and has not responded to trials of dairy- or gluten-free diet in the past. She has fairly significant abdominal pain at least 2 to 3 times per week that can improve with defecation but can be severe enough to affect her focus at work and general activities of daily living. Upon further questioning, KS denied any history of pertinent alarm symptoms.

KS has been evaluated in the past by her primary care physician as well as 2 different gastrointestinal (GI) specialists. Although she has undergone various testing and been told she "likely has irritable bowel syndrome (IBS)", she does not feel confident in that diagnosis and continues to have concerns about her persisting symptoms. She had a colonoscopy at the age of 25 for symptoms of rectal bleeding with straining, and the examination was notable for grade 1 internal hemorrhoids but otherwise normal. Routine laboratory work with her primary care physician has been unremarkable, including thyroid testing, complete blood count, comprehensive metabolic panel, and celiac testing. She reports that her symptoms have been worsening over time, and last year she presented to a local emergency department where a laboratory workup and an abdominal and pelvic computed tomography scan were unremarkable.

In addition to dietary changes including cutting out dairy and gluten, KS has tried various over-the-counter (OTC) therapies for her constipation and bloating including fiber supplementation, polyethylene glycol, and stool softeners along with simethicone, all without significant benefit. The last time she sought care from a GI specialist was 3 years ago, which was a second opinion. The specialist repeated serologic testing and recommended another trial of fiber with polyethylene glycol along with a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet. The GI provider also repeated a colonoscopy, which was unremarkable, and KS did not return for further care out of frustration and a feeling that she must be creating her symptoms due to stress and that it was just all in her head.

Clinical findings at current presentation include:

- Personal medical history: tonsillectomy at age 12, appendectomy at age 18
- Medications: norgestimate 0.25 mg/ethinyl estradiol 0.035 mg
- No pertinent family medical history
- Physical examination: unremarkable
- Vital signs: within normal limits (WNL)
- Abdominal: normoactive bowel sounds on auscultation with minimal distention to palpation and no reported pain/tenderness on examination; no hepatosplenomegaly; rectal examination performed, which was WNL with no physical findings to suggest pelvic floor dysfunction

Treat Your Patient as a Partner: Improving IBS-C Management

#1. Explain the Accuracy of a Positive Diagnostic Strategy

A positive diagnostic strategy, as recommended in the American College of Gastroenterology (ACG) Clinical Guideline for the Management of IBS, is based on the fourth iteration of the Rome Diagnostic Criteria for IBS (Rome IV criteria).[1] These criteria define IBS as a gut-brain interaction disorder. It is characterized by recurrent abdominal pain occurring on average at least 1 day per week and associated with 2 or more of the following criteria: related to defecation; associated with a change in the frequency of stool; or associated with a change in the form (appearance) of stool.[2] In alignment with the Rome IV criteria, to confirm a diagnosis of IBS, these symptoms must have been present for the previous 3 months, with onset at least 6 months prior.

Four IBS subtypes are recognized under the Rome IV criteria, according to the Bristol Stool Form Scale (BSFS).[3] IBS with constipation (IBS-C) is diagnosed with the presence of BSFS types 1 and 2 over 25% of the time, coupled with the presence of BSFS types 6 and 7 in fewer than 25% of bowel movements. In contrast, IBS with diarrhea (IBS-D) is diagnosed when the opposite occurs, with at least 25% of bowel movements of BSFS types 6 or 7, and fewer than 25% of BSFS types 1 or 2. IBS with mixed or alternating bowel habits (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

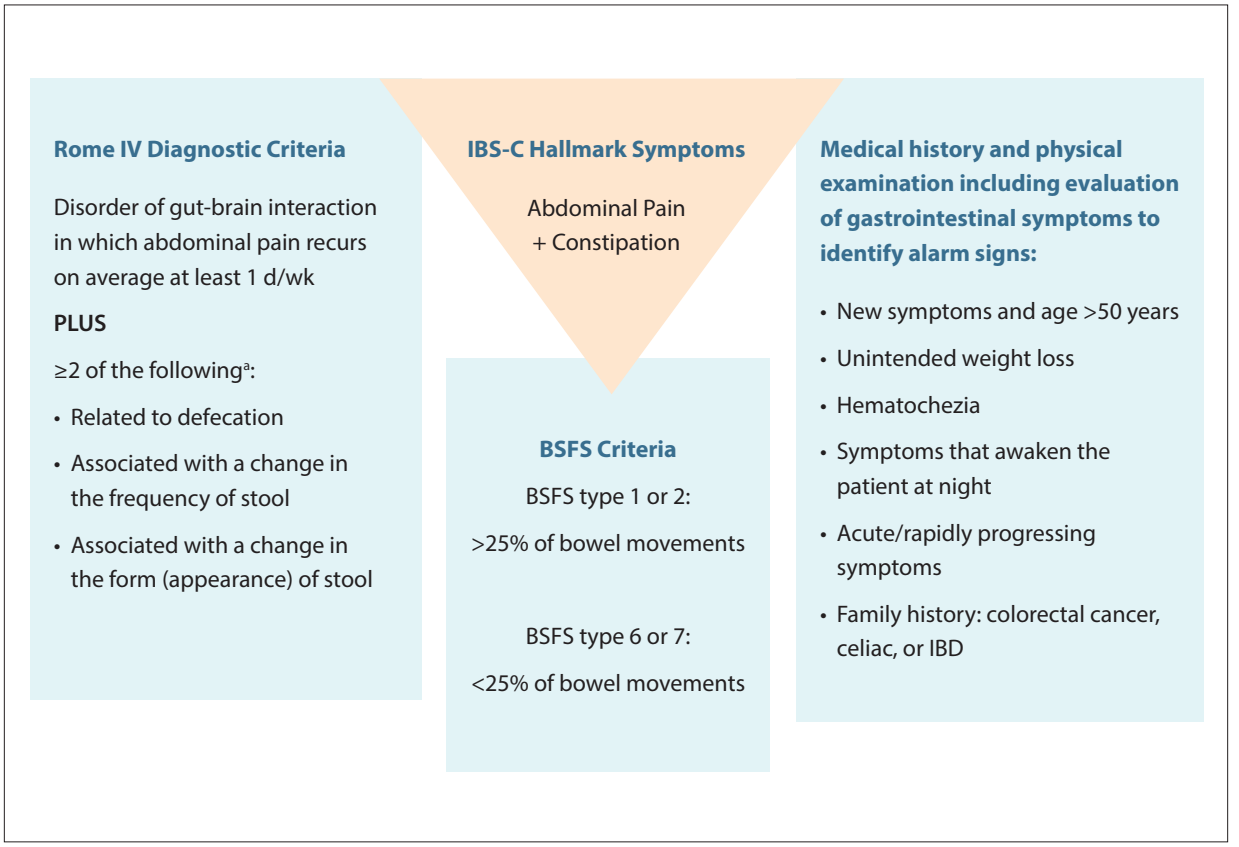

Figure 1. The definitive diagnosis of IBS-C.[1-6]

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

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

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

BSFS types 6 or 7. Finally, IBS without a significant pattern of abnormal stool (IBS-U) is diagnosed in patients who meet the Rome IV criteria for IBS but do not fall into one of the other 3 IBS subgroups.

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). The presence of these symptoms, in conjunction with the Rome IV criteria, is sufficient to support a positive diagnosis without the need for further testing in most patients (Figure 1).[1-6]

Patients who present with alarm features require prompt investigation, further evaluation, and a diagnostic strategy of exclusion as these alarm features may be a sign of a non-IBS disorder.[5,6]. 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 inflammatory bowel disease (IBD).

Patients or clinicians may express concern about the potential for a missed diagnosis with the use of this positive diagnostic strategy, leading some investigators to evaluate the added benefit of colonoscopy in patients with suspected IBS. Chey and colleagues performed a prospective, observational, case–control study that investigated the prevalence of non-IBS lesions or IBD in both healthy controls (asymptomatic persons undergoing screening colonoscopies) and patients with non-constipation-predominant IBS (patients who fulfilled Rome II criteria without alarm features).[7] In this study, the most common lesions in patients with suspected IBS were hemorrhoids (18.2%), polyps (14.6%), and diverticuli (8.8%). The most common lesions in the control group were polyps (34.4%), diverticuli (21.3%), and hemorrhoids (16.4%). Microscopic colitis was identified in 1.5% of the group with suspected IBS. Overall, colonoscopy did not result in a change of the diagnosis

Patient Case and Discussion

After reviewing KS's clinical course and symptoms, which had been occurring over the past 10 to 15 years, I provided a diagnosis of IBS-C using a positive diagnostic strategy. I assured KS that this positive diagnostic strategy is supported by GI societies including the ACG and is associated with an extremely high degree of confidence in a case like hers where there are no other alarm signs.

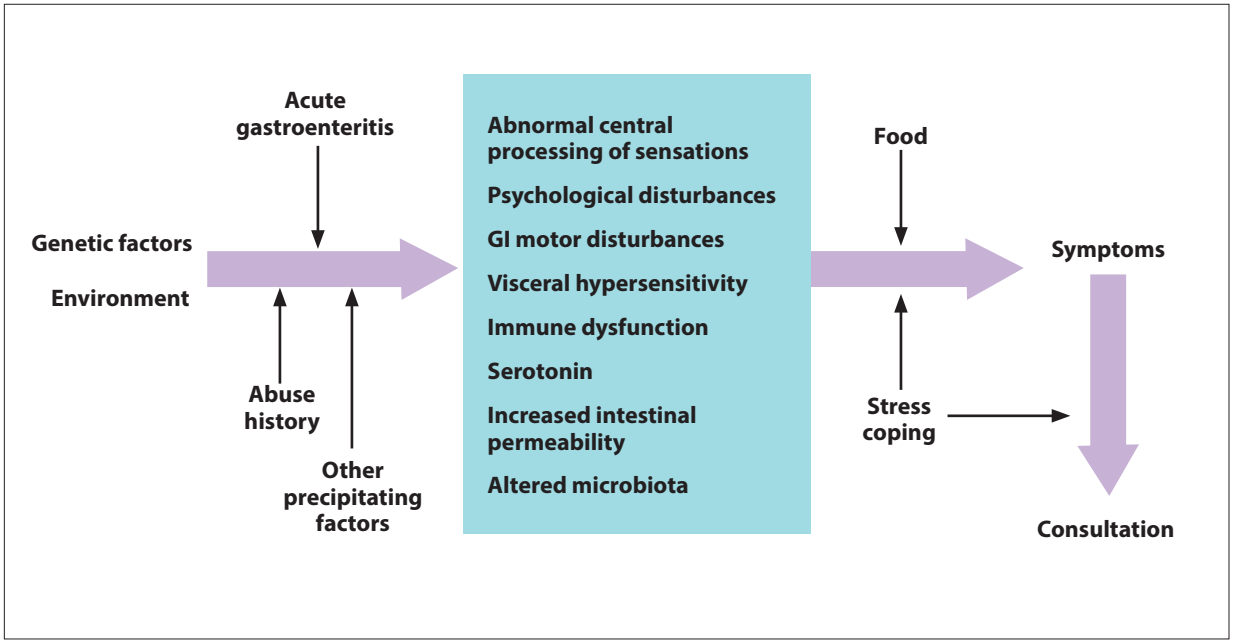

Figure 2. Proposed pathophysiology of irritable bowel syndrome.[8-14,16]

GI, gastrointestinal.

Adapted from: Lacy BE. *Gastroenterol Hepatol (N Y)*. 2024;20(3)(suppl 2):216-222.

to IBS in 98.1% of the 466 patients in that group.

It is critical for health care providers to remember that GI societies including ACG support this positive diagnostic strategy of using Rome IV criteria; and in the absence of alarm features or pertinent family history, this strategy of IBS diagnosis as a primary diagnosis with minimal to no additional testing is associated with a confidence upward of 98%. In most cases, there is no need for a repeat evaluation including colonoscopy unless a patient meets colorectal screening per guidelines or begins to develop those alarm features.

#2. Explain the Natural History and Pathophysiology of IBS-C

Considered a disorder of gut-brain interaction (DGBI), the symptomology of IBS-C is attributed to a complex, multifactorial pathophysiology.[8,9] Changes in gut motility can lead to decreased colonic contractions and water imbalances, ultimately resulting in the hard stools and decreased stool movements characteristic of IBS-C.[10,11] Changes in gut permeability are attributed to a widening of the tight junctions between the intestinal epithelial cells, leading to an inflammatory response localized to nerve fibers throughout the gut epithelium and resulting in microbiome-immune interactions. Changes in the gut microbiome can further gut inflammation and immune activation.[12,13] Finally, visceral hypersensitivity can explain the enhanced sensitization of afferent nerve pathways within the intestines.[12,14]

As a result of this complex pathophysiology, patients with IBS-C can experience a number of symptoms beyond constipation. A recent analysis of the IBS in America 2024 survey showed that, in addition to constipation (94%), several other symptoms were reported among respondents.[15] The most frequent of these were bloating (86%), abdominal cramps and pain (85%), abdominal fullness (73%), excessive gas/flatulence (68%), fatigue (64%), tenesmus (57%), and heartburn/gastroesophageal reflux disease (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 which interfered with their day-to-day activities quite a bit (20%) or very much (9%).

Patient Case and Discussion

In addition to providing a confident diagnosis of IBS-C for KS, I took significant time talking with her about the natural history and pathophysiology of IBS (Figure 2).[8-14,16] Many patients have difficulty accepting a diagnosis of IBS because of the feeling that it is simply a diagnosis of exclusion and because of this, they continue to feel that there must be something else going on to cause their symptoms. Indeed, this belief is often mirrored by health care providers.[17] This is when I took time to dispel myths and misconceptions around a diagnosis of IBS and took a deep dive into explaining the actual pathophysiology of IBS. I validated her concerns that "there must be something going on" and that her symptoms were not just in her head or because of stress or lack of coping. I talked about the relationship between the brain and gut and the dysfunction therein that occurs with IBS, and reviewed potential triggers that may have contributed to the development of IBS-C. We reviewed that, in fact, the pathophysiology of IBS is quite complex and there are multiple pathways contributing to the symptoms KS is experiencing.

Providing details about the pathophysiology of IBS-C and explaining how each of the symptoms KS experiences correlates with a pathway of IBS-C (ie, DGBI leading to disordered motility, increased intestinal permeability, and visceral hypersensitivity) allowed KS to claim her diagnosis more confidently and feel validated regarding the severity of her symptoms and how they affect her day-to-day living. In a manner of level-setting expectations, I discussed with KS that IBS-C can be frustrating to both the provider and the patient as we cannot cure it, and although IBS-C will not affect her lifespan, it can definitely negatively affect her quality of life (QOL) . . . so be validated!

We also discussed that owing to this multifactorial pathophysiology, there is not always a therapy or intervention that can improve all the symptoms she is experiencing. There are periods when symptoms of IBS-C are more stable, and other times when she will have more issues. However, there are many tools in the toolbox and the goal is to get her to the best QOL. Finally, we reviewed the concept of the patient–provider relationship and the focus of patient-centered care, which would be a partnership between the two of us, focusing on all domains of her well-being and sharing in the decision-making process to get KS to her realistic goals in treatment.

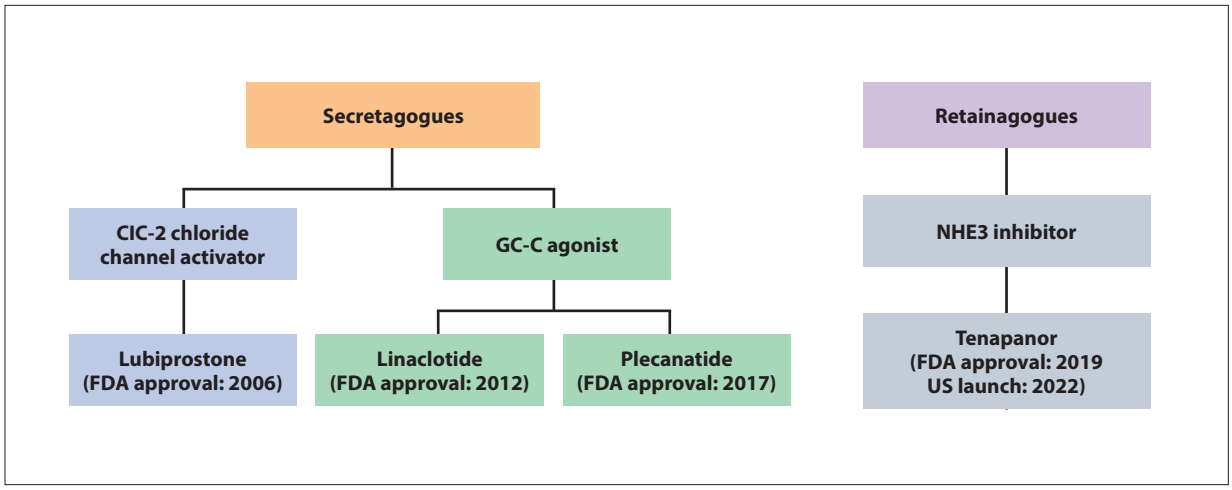

Figure 3. Currently available FDA-approved agents with indications for the treatment of IBS-C.[22-26]

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.

#3. Initiate Treatment With FDA-Approved IBS-C Medication

Two types of OTC laxatives, osmotic and stimulant, are frequently used for IBS-C, although there is a lack of randomized clinical trials demonstrating their effectiveness.[18,19] Osmotic agents can improve symptoms of constipation but have not been shown to improve abdominal pain.[20] Similarly, stimulants can also improve constipation symptoms, but may worsen abdominal cramps, discomfort, and pain.[21] This can lead patients to resort to multiple other treatments in an attempt to relieve the many symptoms of IBS-C.

The availability of 4 medications with US Food and Drug Administration (FDA)–approved indications for IBS-C (Figure 3) now affords patients with multiple treatment options with demonstrated efficacy and safety.[22-26] Three of these agents fall in a class of drugs termed secretagogues as they increase the secretion of chloride and bicarbonate ions into the intestinal lumen, which leads to water secretion accelerating colonic transit and improving stool consistency and frequency.[19] The first of these secretagogues to gain FDA approval, lubiprostone (2006), is limited to treatment of IBS-C in women; the other 2 agents, linaclotide (2012) and plecanatide (2017) are approved in all adult patients with IBS-C. These 3 agents have different mechanisms of action—lubiprostone is an activator of CIC-2 chloride channels while linaclotide and plecanatide are agonists of the guanylate cyclase-C (GC-C) receptor.

The fourth agent, tenapanor (approved in 2019), is a first-in-class agent in a drug class termed retainagogues. Tenapanor is a locally acting inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3). Expressed on the apical surface of epithelial cells lining the small intestine and colon, NHE3 is responsible for absorption of dietary sodium. Thus, NHE3 inhibition by tenapanor is linked to 3 outcomes: (1) decrease in absorption of dietary sodium (leading to retention of water content within the intestinal lumen and acceleration of intestinal transit); (2) reconstitution of the tight junctions between intestinal epithelial cells (resulting in decreased intestinal permeability); and (3) antagonism of transient receptor potential vanilloid 1 channels.[12,13,27,28] The latter two outcomes are thought to reduce visceral hypersensitivity and improve abdominal symptoms associated with tenapanor, as demonstrated in animal models.

The side effect profiles of these 4 FDA-approved medications for IBS-C are comparable, with diarrhea reported as the most frequent adverse event with these agents.[29-35] It is important to discuss this with patients as they initiate treatment so that they can be watchful for symptoms and communicate with their health care providers when these symptoms begin. Notably, diarrhea can be a sign that the medication dosage may need to be adjusted.

All 4 of these FDA-approved agents were evaluated in pivotal, large, randomized and placebo-controlled trials (Table 1).[29-35] In the absence of head-to-head trials, the comparative efficacies between these agents are unknown. What is known is that initiating treatment with any of these agents is better than no treatment, as demonstrated in 2 meta-analyses of randomized controlled trials of these agents. In the first, all the FDA-approved agents for IBS-C were superior to placebo for

Table 1. Pivotal Efficacy and Safety Data of Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C[29-35]

FDA-approved medication	Pivotal efficacy data		Safety data
Lubiprostone	**Overall responder status** was calculated from the weekly assessments of symptom relief. Patients were considered **overall responders** if they were monthly responders[a] 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 due 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 due 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 due to AE:** 2.3% (plecanatide arms combined) vs 0.4% (placebo)
Tenapanor		**T3MPO-1** 27.0% vs 18.7% with placebo; CMH *P*=.020[b] **T3MPO-2 (26-week study)** 36.5% vs 23.7% with placebo; CMH *P*<.001[b]	**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 due to diarrhea:** 1.6% in T3MPO-3 (55-week, open-label safety study)

[a]Monthly responders were defined as patients who rated their IBS symptoms as being at least moderately relieved for all 4 weeks of the month or significantly relieved for at least 2 weeks of the month, with no ratings of moderately or severely worse.
[b]Cochran–Mantel–Haenszel [CMH] P value.
AE, adverse event; CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation.
Adapted from: Brenner DM. *Gastroenterol Hepatol (N Y)*. 2023;19(12)(suppl 6):749-756.

the treatment of global IBS-C symptoms and demonstrated similar efficacy across most endpoints.[36] In the second analysis, the FDA-approved agents for IBS-C were superior to placebo with respect to improvement in abdominal bloating.[37]

Lubiprostone

Lubiprostone was evaluated in a combined analysis of 2 phase 3 trials where it was compared with placebo, each administered for 12 weeks.[29] The primary endpoint of these studies was overall response, 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.

In this combined analysis, the lubiprostone group contained a significantly higher percentage of overall responders vs the placebo group (17.9% vs 10.1%; *P*=.001). These overall responses increased over time with lubiprostone—the percentage of patients achieving the primary endpoint over the first 3 months of treatment with lubiprostone vs placebo were 10.8% vs 7.5% (month 1), 18.3% vs 11.4% (month 2), and 22.0% vs 14.5% (month 3). Patients who achieved an overall response also experienced 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).

The most common adverse events were GI-related (including nausea, diarrhea, abdominal distension) and the rates of discontinuation owing to adverse events were 4.7% and 5.1% with lubiprostone compared with 4.6% and 7.7% with placebo.

Linaclotide

Linaclotide was evaluated for IBS-C in 2 phase 3 trials, both of which incorporated the FDA combined endpoint for IBS-C response. This 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 complete spontaneous bowel movement (CSBM) from baseline, both in the same week for 6 or more out of 12 weeks.

In a 26-week study, a significantly higher percentage of linaclotide-treated patients achieved the FDA combined endpoint compared with placebo-treated patients (33.7% vs 13.9%; *P*<.0001).[30] Linaclotide also resulted in significant improvements compared with placebo in several other primary endpoints, 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%).

In a 12-week study, the FDA combined endpoint was also significantly improved with linaclotide vs placebo (33.6% vs 21.0%; *P*<.0001).[31] 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).

As was examined in a recent post hoc analysis of these studies, linaclotide provided treatment benefits vs placebo by improving multiple symptoms from baseline across body mass index (BMI) subgroups, suggesting no difference in pharmacokinetic and pharmacodynamic properties owing to body weight.[38]

Diarrhea, the most frequently reported adverse event in both phase 3 trials, was the primary reason for discontinuation (5.7% [linaclotide group] vs 0.3% [placebo group] in the 12-week study).

Plecanatide

Plecanatide was also evaluated in 2 identically designed phase 3 clinical trials, where it was compared with placebo using the same FDA combined primary endpoint of overall response. Plecanatide was associated with a significantly higher percentage of patients who achieved the primary endpoint vs placebo in both Study 1 (30.2% [3 mg arm] and 29.5% [6 mg arm] vs 17.8%; *P*<.001) and Study 2 (21.5% [3 mg arm] and 24.0% [6 mg arm] vs 14.2%; *P*=.009).[32] All secondary endpoints evaluated in both studies were significantly improved with plecanatide compared with placebo, including stool frequency/consistency, straining, and abdominal symptoms. Diarrhea, the most common adverse event with plecanatide, was also associated with a higher rate of discontinuation vs placebo (2.3% across both plecanatide doses combined vs 0.4% with placebo).

A recent analysis of data from these studies investigated the efficacy of plecanatide among patients with IBS-C using a novel trisymptom composite endpoint, which consisted of abdominal pain, abdominal bloating, and CSBMs.[39] Overall, significantly more patients in the plecanatide group compared with the placebo group achieved a trisymptom composite response. An analysis by baseline bloating intensity revealed that the rates of trisymptom composite response were maintained across baseline bloating intensities.

A recently reported systemic review and meta-analysis of the efficacy and safety of plecanatide assessed 4 outcomes in patients with IBS-C.[40] 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). Two adverse effects were significantly associated with plecanatide: diarrhea (relative risk, 4.11; 95% CI, 2.50-6.77; *P*<.01) and urinary tract infection (relative risk, 1.70; 95% CI, 0.99-2.91; *P*=.05).

Tenapanor

Tenapanor was evaluated in 2 placebo-controlled, randomized, phase 3 studies, T3MPO-1 (a 12-week trial) and T3MPO-2 (a 26-week trial). The primary endpoint in both studies was the FDA combined endpoint for IBS-C.

In T3MPO-1, a significantly greater percentage of tenapanor-treated patients compared with placebo-treated patients met the primary endpoint (27.0% vs 18.7%; Cochran-Mantel-Haenszel [CMH] *P*=.020).[33] The abdominal pain response was improved with tenapanor (44.0% vs 33.1%; CMH *P*=.008), whereas the rates of CSBM response were similar between the tenapanor and placebo groups (33.9% vs 29.4%; CMH *P*=.270). Tenapanor resulted in significant improvements compared with placebo across several measures of abdominal symptoms 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).

The T3MPO-2 trial reported similar outcomes, including in the primary endpoint (36.5% vs 23.7%; CMH *P*<.001).[34] 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 vs placebo. Improvements in abdominal pain were evident 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 the T3MPO-1 and T3MPO-2 trials focused on the efficacy of tenapanor on abdominal symptoms in 1372 patients.[41] 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 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).

Diarrhea, the most common adverse event with tenapanor in T3MPO-1 and T3MPO-2 studies, was associated with rapid onset, typically occurred within the first week of treatment, and was classified as transient and mild to moderate in severity.[33,34] T3MPO-3, a 1-year open-label safety study of tenapanor, reported a 2.1% discontinuation rate owing to adverse events (primarily diarrhea).[35]

Patient Case and Discussion

Because KS had undergone trials of OTC therapies multiples times with mixed results, we discussed the options for prescription therapy, and I spent time reviewing the various medications that are currently FDA approved for IBS-C. After discussing the options, we agreed upon a trial of linaclotide 290 µg once daily and I reviewed proper dosing and safety as well as potential side effects. KS was scheduled for a follow-up appointment in 6 to 8 weeks but was instructed to call or send a portal message in 2 weeks with an update of response. She was also encouraged to reach out at any point if she was having side effects or had other questions or concerns.

#4. Evaluate Impact of Treatment at Follow-up Visit: Understanding Response vs Adequate Response

Although symptom improvement can often be noted within the first week of treatment, most patients require longer courses of therapy before achieving a response. Additionally, bowel symptoms tend to respond more

Table 2. Understanding Response vs Adequate Response to IBS-C Treatment

Scenarios	Response	Adequate response
Abdominal pain and bloating worsen, accompanied with persistent diarrhea	Yes	No
Abdominal pain and bloating improve, but there is no difference in constipation	Yes	No
Abdominal pain and bloating improve, but constipation is replaced by diarrhea	Yes	No
Abdominal pain and bloating and constipation improve, but not to the point of desired impact on quality of life	Yes	No
Abdominal pain and bloating and constipation improve, and there is desired improvement in quality of life	Yes	Yes

IBS-C, irritable bowel syndrome with constipation.

Table 3. Evaluating Response to IBS-C Treatment

Response criteria	Questions I ask my patients
Abdominal response	• Has there been any change in your abdominal symptoms? Specify a percentage change. • Are you experiencing less abdominal pain? Specify a percentage change. • Is your bloating improved? Specify a percentage change.
Bowel response	• Is there any change in the regularity of your bowel movements? Specify. • Has there been any change in your constipation? Specify. • Has there been any change in the softness of your stools? Specify. • Has there been any change in straining during bowel movement? Specify. • Has there been any change in the feeling of incomplete evacuation? Specify.
QOL response	• Are you experiencing any side effects that are bothersome? • How has your quality of life been impacted since starting the medication? • Do your symptoms still affect your focus at work and general activities of daily living? Specify and compare with how this was prior to starting medication.
Overall satisfaction with treatment	• How satisfied are you with the current treatment? Is this treatment achieving all that you were hoping for? • What would you like to ideally achieve with treatment? • Would you consider trying medication from another class to explore achieving your desired response?

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

rapidly than abdominal pain symptoms, so it is important to continue a medication trial for sufficient time to allow the patient to achieve their treatment goals.[16]

This was demonstrated in the post hoc analysis of pooled data from 3 studies (T3MPO-1, T3MPO-2, and a phase 2b study).[42] Kaplan-Meier estimates were used to assess 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). In tenapanor-treated patients, the median time to CSBM response was 2 weeks. By comparison, 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.

The degree of response to treatment should also consider whether the patient has experienced an improvement in their QOL. As was recently reported from the IBS in America 2024 survey, the vast majority of respondents (90%) reported at least some negative (68%) or significant negative (22%) impact of IBS-C to their overall QOL, demonstrating room for treatment-related improvement.[43] The effects on mental health were also apparent, with 54% and 25% reporting at least some or significant negative impact, respectively, on their mental/emotional health. Other QOL impacts included those on sexual health/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/family (42% some negative; 14% significant negative), and household finances (31% some negative; 12% significant negative).

A recent analysis evaluated the potential relationship

Patient Case and Discussion

In follow-up 2 months later, KS described having some improvement in her constipation, with an increase in frequency of stools per week, but continued to experience residual bloating and pain. Within the boundaries of realistic expectations, I discussed with her the difference between "response" and "adequate response" (Table 2) when assessing the efficacy of her medication. Whereas a response suggests a noticeable change in her symptoms, an adequate response indicates a significant and clinically meaningful improvement in IBS-C symptoms, manifesting as substantial reductions in abdominal pain, bloating, and constipation. As a result, achieving an adequate response allows the patient to begin experiencing meaningful improvements in their QOL. Table 3 lists some of the questions I ask patients with IBS-C to evaluate the type of response they are having to treatment. During this discussion, KS voiced her frustration with years of letting these symptoms influence her life and decisions, and her desire to finally achieve an adequate response.

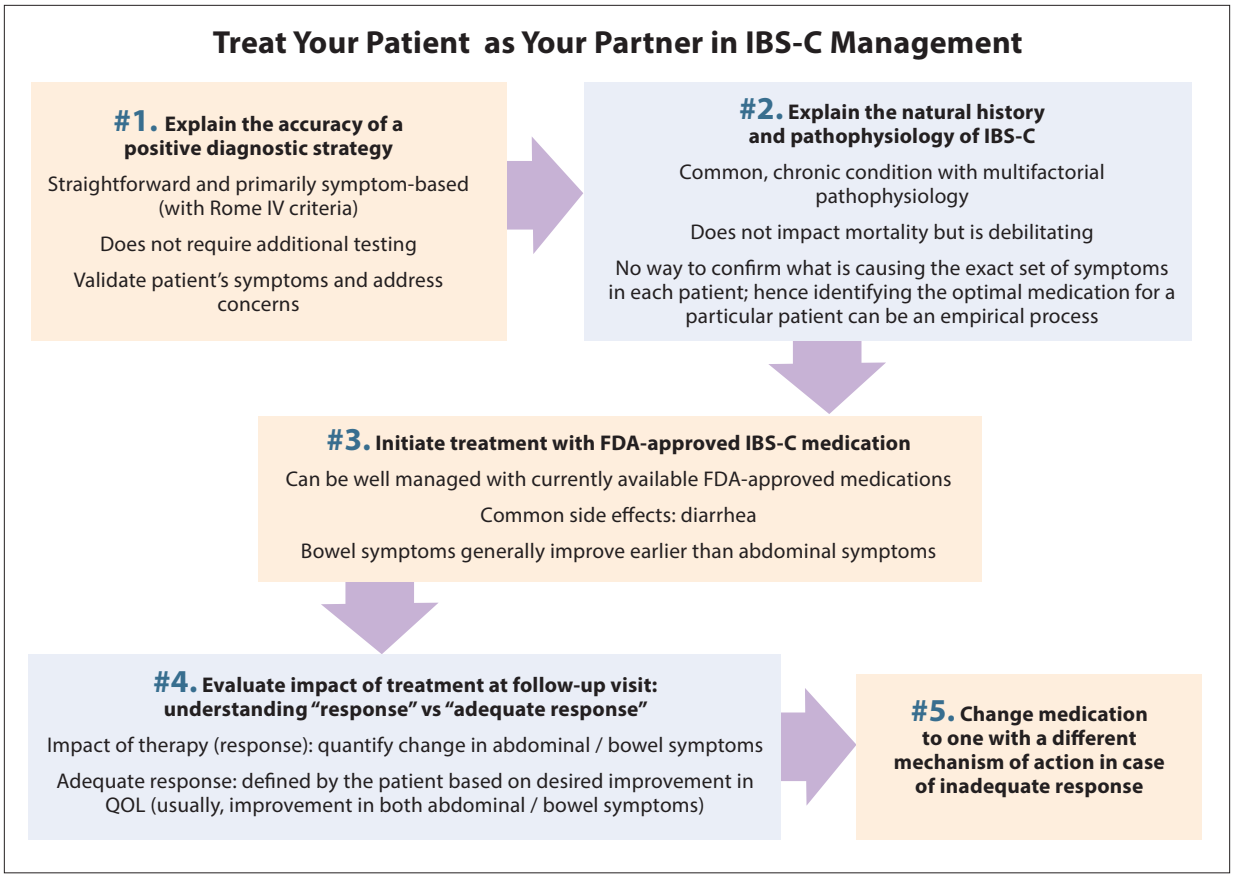

Figure 4. Patient–provider partnership in improving IBS-C management.

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

between IBS-C symptoms and IBS-related QOL and treatment satisfaction.[44] Data from 2 identically designed, randomized, placebo-controlled, phase 3 trials of plecanatide were pooled and analyzed for this evaluation. A positive correlation was observed between the IBS-QOL total score and each of the 3 IBS-C symptoms measured over the 12-week treatment period (abdominal pain weekly mean score, +0.38; bloating weekly mean score, +0.41; and cramping weekly mean score, +0.39). In contrast, a negative correlation was apparent between treatment satisfaction and each of the 3 IBS-C symptoms over the 12-week treatment period (abdominal pain weekly mean score, –0.30; bloating weekly mean score, –0.30; and cramping weekly mean score, –0.27).

#5. Change Medication to One With a Different Mechanism of Action in Case of Inadequate Response

The multifactorial pathophysiology that underlies IBS-C is associated with several potential mechanisms leading to the symptoms of abdominal pain and constipation.[7,8]

Patient Case and Discussion

Knowing that therapeutic interventions may not completely resolve all symptoms of IBS-C, we agreed upon trying a different FDA-approved medication with an alternative mechanism of action. Thus, I switched KS to tenapanor 50 mg twice daily. I also provided further reassurance around KS's diagnosis of IBS-C and validated her concerns, as well as emphasized our long-term partnership in meeting her goals of treatment going forward.

Upon seeing KS in the clinic about 10 weeks later, she now expressed what she felt was adequate response, having more frequent stools and feeling more fully evacuated. She also noted that the episodes of more severe abdominal pain had resolved, and her bloating lessened. Overall, she is satisfied with her current status and understands that we will continue working together to manage her IBS-C in the future, as the need arises.

Accordingly, each of these may be targeted by FDA-approved IBS-C medications with different mechanisms of action, allowing physicians to switch to another class of agents in the setting of an inadequate response. This switching strategy is also employed in other disease states (eg, IBD) where classes of agents with different mechanisms of action are available. It is important to recognize that identifying the optimal medication for a particular patient can be an empirical process owing to the varied multifactorial pathophysiology that is different from patient to patient.

Conclusion

This was a typical IBS-C case where a patient has suffered for many years and undergone unnecessary tests (2 colonoscopies in this case!) before being provided with a definitive diagnosis. Suffering is only one aspect of this delayed diagnosis. Unnecessary testing, loss of productivity, and feeling of helplessness and giving up are other aspects of this debilitating condition. This feeling of helplessness was evidenced when this patient did not seek further help for 3 years after her last GI visit. This patient had visited 2 GI specialists prior to being seen in my clinic and ultimately believed that she must be creating her symptoms due to stress and that it was just all in her head. These aspects could have been avoided by following the strong recommendation of guidelines supporting a positive diagnostic strategy.

After the diagnosis is made, it is important to help patients feel heard and understood, and there are specific steps we can take to instill confidence in our patients, promote patient–provider partnership in IBS-C management, and improve their QOL (Figure 4). As providers it is our responsibility to educate our patients regarding what is possible. While we cannot cure IBS-C, we certainly have FDA-approved medications in our arsenal to help our patients. It is important to tell our patients about the multifactorial pathophysiology of IBS-C and about the possible reasons they have their particular symptoms, and that is what makes it impossible to know which specific medication could help them. This is the reason for FDA-approved medications with different mechanisms of action. Hence patients need to understand and be willing to undergo a potential period of trial and error with respect to their therapy.

Furthermore, we should tell our patients that they need not settle for simply response to therapy, but it is in their power to define what adequate response would look like for them. Follow-up visits with questions that provide a quantitative measure of both abdominal and bowel symptom response are critical. If a particular therapy does not provide adequate response to the patient, as was demonstrated in this case when initial treatment with the secretagogue linaclotide did not provide adequate response, we have FDA-approved medications with different mechanisms of action that may be able to achieve patient-desired responses. In this particular case, KS was moved to the retainagogue tenapanor, finally allowing her to achieve adequate response.

Disclosures

Ms Hanson has served on the advisory board/speakers' bureau of Ardelyx, Gilead, GSK, Intercept Pharmaceuticals, Ipsen Pharma, Madrigal Pharmaceuticals, Phathom Pharmaceuticals, Regeneron Pharmaceuticals, Salix Pharmaceuticals, and Sanofi.

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