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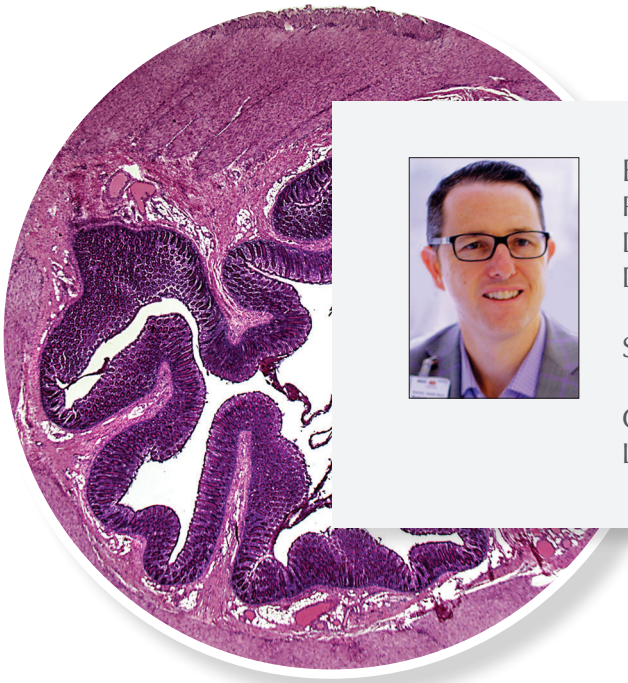
Continuing the Dialogue in IBS-C Management: Importance of Individualizing Care and Tailoring Treatment



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Continuing the Dialogue in IBS-C Management: Importance of Individualizing Care and Tailoring Treatment

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About the Patient

A 28-year-old woman presents to her primary care physician with a history of straining and painful defecation, sense of incomplete evacuation, and bothersome abdominal pain that improves with bowel movements. These symptoms have persisted for a few years and affect her work productivity and overall quality of life. She spends excessive time in the restroom, and experiences significant cramping and pain during work. She reports that her symptoms cause challenges with presenting in meetings, participating on work calls, and constantly being distracted by the discomfort. She reports no rectal bleeding, unintended weight loss, dysphagia, vomiting, fevers, chills, or other gastrointestinal alarm features.

The symptoms affect her not only physically, but also cognitively because she spends a significant portion of her time thinking about her pain, leading to ruminations and distractions. Her symptoms are also affecting her psychologically as she frequently experiences visceral anxiety about her abdominal pain and discomfort.

The patient underwent a series of tests, all of which were normal. She was started on an antidepressant along with fiber. However, these treatments were not effective, causing her to have dry mouth and sleepiness; the fiber caused her to feel even more bloated.

What do you think this patient is suffering from?

In light of the patient's history, including recurrent abdominal pain, constipation that improves with defecation, and lack of alarm symptoms, irritable bowel syndrome (IBS) is likely. IBS is a chronic and sometimes debilitating disorder with the defining symptoms of abdominal pain and disordered defecation.[1] According to the fourth iteration of the Rome Diagnostic Criteria for Irritable Bowel Syndrome (Rome IV criteria), IBS is defined as a gut-brain interaction disorder, with recurrent

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

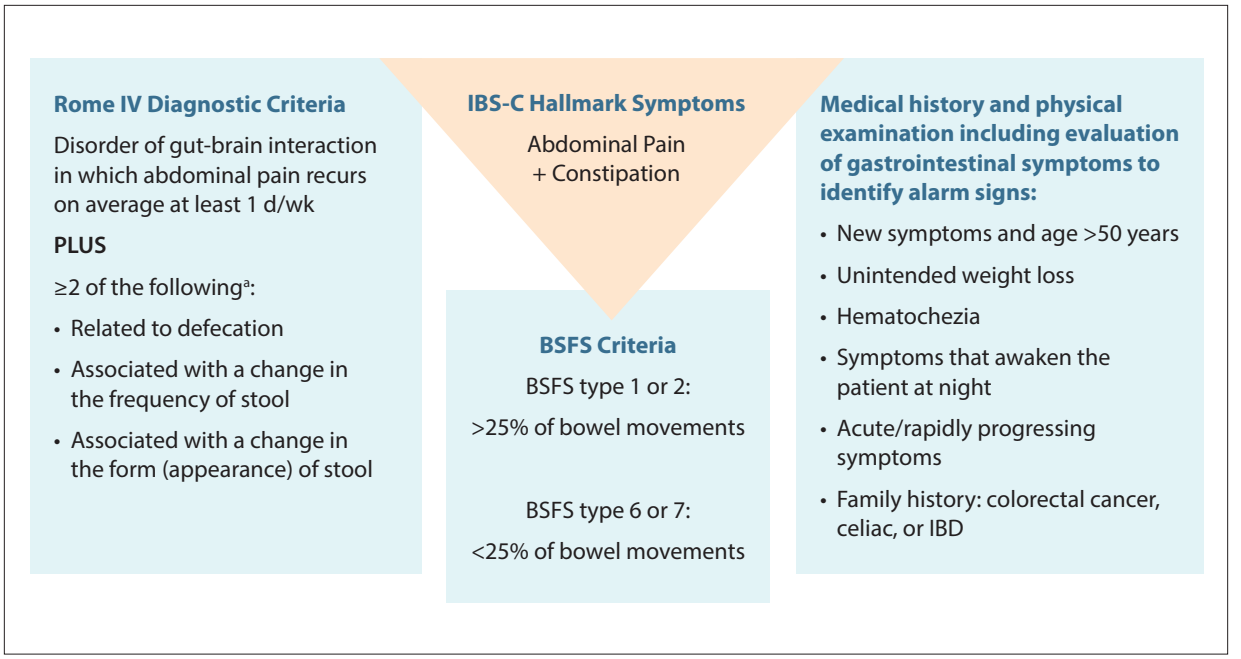

Figure 1. The definitive diagnosis of IBS-C.[1,2]

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.

abdominal pain occurring on average at least 1 day per week and associated with two 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] As defined by 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.

Given the extended periods of symptom presence and high symptom frequencies required to meet the Rome IV criteria, their real-world application can be difficult. Thus the Rome Foundation has proposed modified diagnostic criteria considered more suitable for clinical practice.[3] These modified criteria allow for a clinical diagnosis of IBS if the nature of the symptoms aligns with the Rome IV diagnostic criteria, the symptoms are bothersome (ie, interfering with daily activities, requiring attention, causing worry, or causing decreased health-related quality of life [HRQoL]), and the practitioner is confident that other potential diagnoses have been confidently eliminated.

The Rome IV criteria recognize 4 IBS subtypes: IBS with constipation (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).[1] The IBS subtype is informed by the Bristol Stool Form Scale (BSFS).[4] A diagnosis of IBS-C is made when BSFS types 1 and 2 are present over 25% of the time, coupled with the presence of BSFS types 6 and 7 in fewer than 25% of bowel movements. IBS-D is classified with the opposite findings, with at least 25% of bowel movements of BSFS types 6 or 7, and 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.

Abdominal pain and hard stools are the hallmark symptoms of IBS-C. However, many patients also experience other abdominal symptoms, such as discomfort and bloating, as well as other bowel-related symptoms, including infrequent stools, straining, and the feeling of incomplete evacuation.

How did you arrive at a diagnosis of IBS-C in this patient?

Although there have been many diagnostic tests proposed for diagnosing IBS, there is still no standard biomarker-based approach to rule in IBS. Instead, clinicians must rely on a comprehensive assessment involving medical history, physical examination, and adherence to diagnos-

tic criteria (Figure 1). In most patients, their symptoms of abdominal pain and constipation are sufficient to support a positive diagnosis without the need for further testing. This was certainly true for this patient, who had a history of significant abdominal pain as well as constipation, both of which caused a negative impact on her HRQoL. Guidelines from the American College of Gastroenterology (ACG) include recommendations regarding a positive diagnostic strategy that is based on Rome IV criteria instead of a diagnostic strategy of exclusion.[1]

A set of alarm features can be evaluated for and should trigger prompt investigation and treatment, as they are not associated with IBS but instead may indicate a sign of another gastrointestinal (GI) disorder.[5,6] These alarm features include new symptoms in a patient older than 50 years, unintended weight loss (>10% in 3 months is a good rule of thumb), 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). Notably, the patient in this case exhibited none of these alarm features.

In appropriate patients, some testing strategies may be useful during the initial evaluation to aid in the exclusion of other conditions. For example, serologic testing can be applied to rule out celiac disease in patients with IBS and diarrhea symptoms.[1] Further, checking either fecal calprotectin or fecal lactoferrin and C-reactive protein should be considered to rule out IBD. Routine stool testing or colonoscopy is generally not recommended for patient evaluation except for patients old enough for colon cancer screening, in which case colonoscopy is already indicated.

Why did it take such a long time for a definitive diagnosis?

Often patients try to self-medicate to manage their symptoms with over-the-counter agents. This can go on for a long time before they mention their symptoms to their primary care physician; often there is even a longer delay before referral to a gastroenterologist. As reported from a 2-phase community survey, in the United States an estimated 76.6% of individuals with IBS remain undiagnosed, despite its debilitating nature.[7] As reported in the IBS in America survey, about 77% of patients with IBS-C reported first trying over-the-counter products before presenting to a health care provider. The primary symptoms that finally caused them to present to their physician were constipation (77%) and abdominal pain (76%). Other significant symptoms reported included abdominal discomfort (64%), bloating (43%), straining (39%), hard and lumpy stools (36%), and infrequent defecation (37%).[8]

How can IBS-C affect a patient's health-related quality of life (HRQoL)?

IBS-C can have a significant impact on the patient's HRQoL, creating a negative burden carried by the patient. The IBS in America survey is a landmark IBS survey comprising the largest to-date collected information from more than 3200 individuals with IBS (including both IBS-C and IBS-D) and 300 physicians.[8] More than one-half of respondents (53%) with IBS-C ranked their symptoms as "extremely" or "very" bothersome, stating abdominal pain and constipation were their most bothersome symptoms. IBS symptoms were reported to interfere with work or school productivity an average of 9 days per month, and were responsible for missed work or school an average of 2 days per month. IBS-C symptoms were a major reason that prevented respondents from enjoying daily activities (66% "strongly agreed" or "somewhat agreed"). When asked what they would be willing to give up for experiencing 1 month of IBS-C symptom relief, patients reported the Internet (21%), their cell phones (25%), sex (42%), caffeine (58%), and alcohol (62%).

What are the treatment options for this patient?

Laxatives are a common intervention for patients with IBS-C, aiming to increase stool frequency while improving stool consistency.[9] However, although both classes of laxatives—osmotic and stimulant—tend to improve the constipation seen in patients, they have little effect on abdominal pain.[10] In fact, stimulants may worsen abdominal cramps, discomfort, and pain, limiting their utility in patients with IBS-C.[11] Guidelines conflict on the use of the osmotic agent polyethylene glycol, with its use suggested in the American Gastroenterological Association guidelines but suggested against in the ACG guidelines.[1,12] To better address the multiple symptoms experienced by patients with IBS-C, there are 4 US Food and Drug Administration (FDA)–approved treatment options currently available (Figure 2).[13-17]

Three of the FDA-approved agents for IBS-C—lubiprostone, linaclotide, and plecanatide—are classified as secretagogues.[18] This class of agents acts by increasing the secretion of chloride and bicarbonate ions into the intestinal lumen, which in turn causes water secretion. As a result, colonic transit is accelerated, improving both stool consistency and frequency. Within the secretagogue class, the 3 agents have different mechanisms of action.

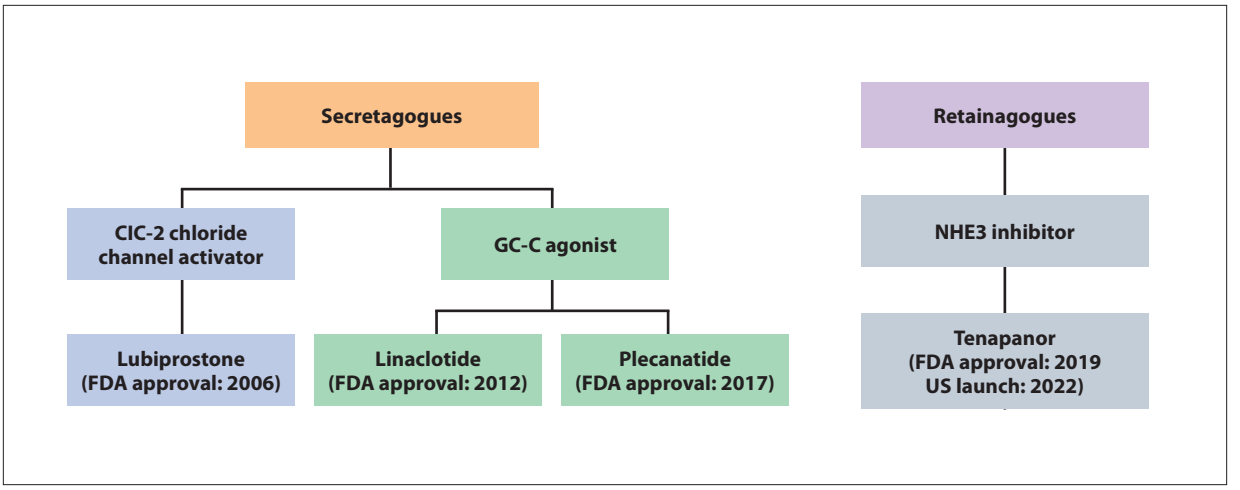

Figure 2. Currently available FDA-approved agents with indications for the treatment of IBS-C.[13-17]

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.

Lubiprostone is an activator of CIC-2 chloride channels, which are expressed on the apical membranes of the epithelial cells lining the intestine. CIC-2 channel activation leads to an increase in chloride ions into the intestinal lumen.[19] The other 2 secretagogues, linaclotide and plecanatide, are agonists of the guanylate cyclase-C (GC-C) receptor also expressed on the apical membranes of intestinal epithelial cells.[14,15] Activation of GC-C receptors, which are important in the regulation of fluid and ion homeostasis, increases secretion into the intestinal lumen.[20] GC-C agonists also influence maintenance of the intestinal barrier, reduce intestinal inflammation, and moderate visceral pain pathways.[20,21] The activity of linaclotide is independent of the surrounding pH, and it thus shows equivalent affinity for GC-C receptors in the small intestine as well as the colon. In contrast, plecanatide's active conformation is dependent on pH, causing it to show higher activity in the acidic small intestine.[18]

The fourth FDA-approved agent, tenapanor, has a different mechanism of action and has been described as a "retainagogue."[16] Tenapanor is a first-in-class 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.[22] Thus, NHE3 inhibition by tenapanor is linked to 3 outcomes. First, absorption of dietary sodium is decreased, leading to retention of water content within the intestinal lumen and acceleration of intestinal transit. Second, the tight junctions between intestinal epithelial cells are reconstituted, resulting in decreased intestinal permeability. Third, antagonism of transient receptor potential vanilloid 1 channels has been observed.[23-25] The latter two of these actions are thought to contribute to the reduction in visceral hypersensitivity and improvement in abdominal symptoms associated with tenapanor, as demonstrated in animal models.

What are the clinical data supporting the use of these agents in IBS-C?

Table 1 summarizes the clinical data and current guideline recommendations associated with each of the 4 currently available FDA-approved agents with indications for IBS-C. A prevailing question remains of whether one agent is more effective than another in IBS-C management. However, there are no head-to-head trials between these agents, and thus their comparative efficacies remain unknown. What is clear is that treatment with any of these agents is better than no treatment, as was demonstrated in a network meta-analysis of randomized controlled trials of these agents by Black and colleagues.[26] In this analysis, all FDA-approved agents for IBS-C were superior vs placebo for the treatment of global IBS-C symptoms. Further, the 4 agents showed similar efficacy across most of these endpoints. A second network meta-analysis conducted by Nelson and colleagues also examined the comparative efficacy among the 4 FDA-approved agents. This analysis focused on improvements in abdominal bloating, showing again that all agents were superior to placebo with no significant differences observed in indirect comparisons across agents.[27]

Lubiprostone The efficacy and safety of lubiprostone in patients with IBS-C was established in a combined analysis of 2 phase 3 trials.[28] In both trials, patients were randomized to 12 weeks of treatment with either lubiprostone (8 μg twice daily) or placebo. In both trials as well as in the combined analysis, the primary efficacy endpoint was overall responder status. Overall responders were defined as monthly responders for at least 2 of 3 months, as determined from weekly assessments of symptom relief.

The combined analysis demonstrated a significantly greater number of overall responders over the 12 weeks in the lubiprostone arm as compared with the placebo arm (17.9% vs 10.1%; *P*=.001).[28] Further, lubiprostone was associated with a greater increase in the magnitude of overall response over time, increasing from 10.8% (month 1) to 18.3% (month 2) and 22.0% (month 3) compared with 7.5%, 11.4%, and 14.5% with placebo, respectively. Patients classified as overall responders experienced greater improvements in measures of symptom relief compared with nonresponders. These measures included abdominal discomfort or pain, bloating, constipation severity, stool consistency, and straining (*P*<.001 for all symptoms). Although a trend in improved IBS-QoL at week 12 occurred with lubiprostone vs placebo, this difference did not achieve statistical significance (*P*=.066).

The most common adverse events, reported with similar frequency across the 2 studies, were GI-related, including nausea, diarrhea, and abdominal distension. 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 Two phase 3 trials established the safety and efficacy of linaclotide in patients with IBS-C.[29,30] Both trials evaluated linaclotide at a dose of 290 μg once daily compared with placebo. Both studies had a randomized, double-blind design; the first was 26 weeks in length and the second was 12 weeks in length (followed by a subsequent 4-week randomized withdrawal period). Multiple primary endpoints were evaluated, including the FDA's endpoint for IBS-C response (defined as a patient who reported an improvement of ≥30% from baseline in average daily worst abdominal pain score and an increase of ≥1 complete spontaneous bowel movements [CSBM] from baseline, both in the same week for 6 or more out of 12 weeks).

In the 26-week trial, a significantly higher percentage of patients in the linaclotide arm achieved the FDA combined endpoint compared with placebo (33.7% vs 13.9%; *P*<.0001).[29] Each criterion of the FDA endpoint was also evaluated independently, with both showing considerably improved outcomes with linaclotide vs placebo (48.9% vs 34.5% for the pain responder criterion and 47.6% vs 22.6% for the CSBM responder criterion).

Linaclotide was also associated with significantly improved outcomes in the 12-week trial, with 33.6% of patients in the linaclotide arm achieving the FDA combined endpoint compared with 21.0% in the placebo arm (*P*<.0001)—a clinically meaningful difference.[30] Again, linaclotide was associated with improvements in each individual criterion of the FDA endpoint (50.1% vs 37.5%, *P*=.0003 for the abdominal pain criterion, and 48.6% vs 29.6%, *P*<.0001 for the CSBM responder criterion). During the 4-week withdrawal period of this study, patients remaining on linaclotide continued to demonstrate sustained improvement, and patients who were rerandomized from linaclotide to placebo showed a return of symptoms (but did not worsen from baseline).

In both linaclotide phase 3 studies, diarrhea was the most frequently reported adverse event, and was the primary reason for discontinuation which accounted for 5.7% of patients in the 12-week study.[29,30]

Plecanatide The efficacy and safety of plecanatide in IBS-C was also evaluated across 2 phase 3 trials. Both trials randomized patients in a 1:1:1 fashion to 12 weeks of treatment with plecanatide (3 mg or 6 mg) or placebo.[31] The same FDA primary endpoint of overall response was used in both studies.

In Study 1, a higher proportion of patients in the plecanatide arms achieved the primary endpoint compared with the placebo arm (30.2% and 29.5% of patients in the plecanatide 3 mg and 6 mg arms, vs 17.8% of patients in the placebo arm; *P*<.001 for each dose vs placebo).[31] Study 2 showed similar outcomes, with 21.5% and 24.0% of patients in the plecanatide 3 mg and 6 mg arms, respectively, achieving the primary endpoint (compared with 14.2% of patients in the placebo arm; *P*=.009 compared with the 3 mg dose and *P*<.001 compared with the 6 mg dose).

Across both studies, diarrhea was the most common adverse event with plecanatide, reported in 4.3% of patients treated at the 3 mg dose and 4.0% of patients at the 6 mg dose and compared with 1.0% among placebo-treated patients. Plecanatide was also associated with a higher rate of discontinuation vs placebo (2.3% across both plecanatide doses combined vs 0.4% with placebo).

Tenapanor Tenapanor was evaluated in 2 randomized, phase 3 studies, T3MPO-1 and T3MPO-2.[32,33] Patients in both trials were randomized to treatment with either tenapanor (50 mg twice daily) or placebo. The T3MPO-1 trial had a 12-week duration of treatment followed by a 4-week randomized withdrawal period, whereas the

Table. Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C[1,12,17,28-34]

Agent	MOA	Pivotal efficacy data	Toxicity profile	Guideline recommendations[1,21]
Lubiprostone **(FDA approval: 2006)**	**Secretagogue** CIC-2 chloride channel activator	Combined analysis of 2 phase 3 trials Overall responder status[a]: 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)	**ACG:** chloride channel activators are recommended to treat global IBS-C symptoms (strong recommendation) **AGA:** suggests using in patients with IBS-C (conditional suggestion)
Linaclotide **(FDA approval: 2012)**	**Secretagogue** GC-C agonist	26-week phase 3 study FDA overall response endpoint[b]: 33.7% vs 13.9% with placebo; *P*<.0001 12-week phase 3 study FDA overall response endpoint[b]: 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	**ACG:** GC-C agonists are recommended to treat global IBS-C symptoms (strong recommendation) **AGA:** suggests using in patients with IBS-C (strong recommendation)
Plecanatide **(FDA approval: 2017)**	**Secretagogue** GC-C agonist	Study 1 FDA overall response endpoint[b]: 30.2% (3 mg) and 29.5% (6 mg) vs 17.8% with placebo; *P*<.001 Study 2 FDA overall response endpoint[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	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)	**ACG:** recommended to treat global IBS-C symptoms (strong recommendation) **AGA:** suggests using in patients with IBS-C (conditional suggestion)
Tenapanor **(FDA approval: 2019; US launch: 2022)**	**Retainagogue** NHE3 inhibitor	T3MPO-1 FDA overall response endpoint[b]: 27.0% vs 18.7% with placebo; CMH *P*=.020[c] T3MPO-2 (26-week study) FDA overall response endpoint[b]: 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 due to diarrhea: 1.6% in T3MPO-3 (55-week, open-label safety study)	**ACG:** not reviewed **AGA:** suggests using in patients with IBS-C (conditional suggestion)

ACG, American College of Gastroenterology; AE, adverse event; AGA, American Gastroenterological Association; CIC-2, type 2 chloride channel; CMH, Cochran–Mantel–Haenszel; CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; GC-C, guanylate cyclase-C; GI, gastrointestinal; IBS-C, irritable bowel syndrome with constipation; NHE3, sodium/hydrogen exchanger isoform 3.

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

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

[c]Cochran–Mantel–Haenszel [CMH] *P* value.

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

T3MPO-2 trial comprised 26 weeks of continuous treatment. The same FDA combined endpoint utilized in the linaclotide and plecanatide studies was also evaluated as the primary endpoint in both tenapanor trials.

In the T3MPO-1 trial, significantly more patients treated with tenapanor met the FDA combined endpoint compared with placebo (27.0% vs 18.7%; Cochran–Mantel–Haenszel [CMH] *P*=.020).[32] The abdominal pain response criterion was significantly improved with tenapanor vs placebo (44.0% vs 33.1%; CMH *P*=.008); however, CSBM response rates were similar between the 2 arms (33.9% vs 29.4%; CMH *P*=.270). Several abdominal symptoms were improved with tenapanor compared with placebo for at least 9 of 12 weeks. For example, more tenapanor-treated patients were classified as abdominal discomfort responders compared with placebo-treated patients (29.0% vs 17.1%, respectively, CMH *P*<.001). Abdominal bloating response was also significantly improved with tenapanor compared with placebo (27.0% vs 16.1%, respectively, CMH *P*=.001), as was the abdominal cramping response (30.6% vs 23.1%, respectively, CMH *P*=.044), and the abdominal fullness response (27.4% vs 14.4%, respectively, CMH *P*<.001). Compared with placebo-treated patients, those treated with tenapanor experienced significantly greater improvements in global IBS treatment measures which included stool consistency, IBS severity, constipation severity, degree of relief from IBS, and adequate relief from IBS.

The T3MPO-2 trial was associated with similar outcomes, with a greater proportion of patients treated with tenapanor achieving the FDA combined endpoint vs placebo (36.5% vs 23.7%, respectively, CMH *P*<.001).[33] In this second study, patients treated with tenapanor achieved significant improvements in both criteria of the FDA combined endpoint (49.8% vs 38.3%, CMH *P*=.004 for the abdominal pain criterion, and 47.4% vs 33.3%, CMH *P*<.001 for the CSBM response criterion). In T3MPO-2, significant improvements in abdominal pain were observed as early as 1 week after beginning treatment, and abdominal pain was found to have decreased by 54% from baseline at week 26 in the tenapanor arm.

In both trials, diarrhea was the most common adverse event reported, with higher rates in the tenapanor arm compared with the placebo arm (14.6% vs 1.7% in T3MPO-1 and 16.0% vs 3.7% in T3MPO-2).[32,33] Diarrhea onset was reported as rapid, typically occurring within the first week of treatment, and was also classified as transient and mild to moderate in severity. T3MPO-3, a 1-year open-label safety study, has further demonstrated tenapanor to be well tolerated with no new safety signals reported and a 2.1% discontinuation rate owing to adverse events (primarily diarrhea).[34]

A post hoc analysis 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.[35] Among tenapanor-treated patients, the median time to CSBM response was 2 weeks and abdominal bloating response was 5 weeks. The estimated response probabilities also increased with time: CSBM response probability (52.3% by week 2, 72.5% by week 8, and 76.7% by week 12); abdominal pain response probability (54.6% by week 4, 67.9% by week 8, and 72.3% by week 12); and abdominal bloating response probability (48.1% by week 4, 61.9% by week 8, and 67.7% by week 12).

Back to the Patient . . .

Referral

When it became clear that this patient's IBS-C symptoms were not adequately controlled with an antidepressant and fiber, she was referred to my clinic.

What I Did

After her clinical evaluation, a discussion ensued regarding her treatment options. Linaclotide was selected, and the patient began treatment at the recommended dosage of 290 µg once daily.[14]

Did you have any specific instructions for this patient?

During her visit, I spent time with the patient to help set her expectations about beginning a new IBS-C treatment. One of the points we touched on was the importance of adhering to treatment, even if it took some time for her to fully experience symptom relief. The BURDEN IBS-C study, which used an online questionnaire to characterize unmet needs in patients with IBS-C, reported treatment adherence/compliance as a significant issue observed by 58% of health care professionals.[36]

Further, we discussed the variable timing of symptom response to treatment. For example, her bowel symptoms might improve first, even within days, whereas it might take more time to achieve maximal improvements in abdominal pain, discomfort, and bloating—sensory symptoms that are distinguished from defecatory symptoms.[37]

For this reason, an important action for the patient was to carefully monitor her symptoms, noting both her

Back to the Patient . . .

6-Week Follow-up Visit

The patient reported that linaclotide was very effective and worked for her, but it worked "maybe a little too well." When pressed further, the patient revealed that her abdominal pain and bloating were both much improved. However, she had very loose stools and found herself with urgency rushing to the restroom often while at work. A review of her symptom diary showed she experienced these loose bowel movements up to 2 to 3 times daily.

What I Did

Given the clear improvement this patient experienced with linaclotide, we began to titrate down her linaclotide dose over the subsequent weeks. The goal of this approach is to find the "just right" dose that addressed both her bowel and abdominal symptoms without causing diarrhea. We discussed how loose stools might be acceptable up to a point among people experiencing constipation, an approach I call "therapeutic laxation," but that we also want to avoid excessive diarrhea. Because linaclotide is available in different doses, we discussed finding a dose that works best for her body. Ultimately, we titrated down to the lowest available dosage of linaclotide (72 µg).

Impact of Dose Adjustments

- Weeks 7 and 8 (linaclotide 216 µg): persistent "unpredictable" diarrhea with urgency rushing to the restroom in the middle of any activity.
- Weeks 9 and 10 (linaclotide 145 µg): persistent "unpredictable" diarrhea with urgency rushing to the restroom in the middle of any activity.
- Weeks 11 and 12 (linaclotide 72 µg): persistent "unpredictable" diarrhea with urgency rushing to the restroom in the middle of any activity.

My Analysis

Although many patients do well with secretagogues like linaclotide, this particular patient just could not tolerate the medicine and complained of continued poor HRQoL even after down-titration of the dose.

What I Did

After 3 months of dose adjustments, the patient came in for an office visit. At that point, I discussed with her that we should switch to a different class of medications, explaining that our current understanding of IBS-C does not allow for precise targeting of symptoms because of the multifactorial pathophysiology of IBS-C. For this reason, it can be difficult to predict the most effective treatment among individual patients. However, because of the availability of medications with different mechanisms of action, if a patient proves unresponsive to one therapy there remains the potential for positive outcomes with an alternative approach. Therefore, the patient was switched to tenapanor at a dosage of 50 mg twice daily.[16]

abdominal and bowel symptoms. We discussed how using a diary could be useful to evaluate the impact of treatment, and tailor her therapy if needed.

What made you decide to switch to an agent with a different mechanism of action?

IBS-C is thought to have a multifactorial pathophysiology with a wide range of potential mechanisms underlying the symptoms of abdominal pain and constipation.[38,39] One pathophysiologic component is traced to changes in gut motility, observed as decreased colonic contractions and water imbalances that can lead to hard stools and infrequent defecation.[40,41] Another pathophysiologic component is attributed to intestinal permeability caused by widened tight junctions between the intestinal epithelial cells. This can result in the increased absorption of toxins and bacteria, leading to an inflammatory response that occurs in proximity to nerve fibers throughout the gut epithelium.[23,24] Patients with IBS-C may also experience visceral hypersensitivity, another pathophysiologic component in which there is enhanced sensitization of afferent nerve pathways within the gut.[23,42] A fourth pathophysiologic component may lie within changes in the gut microbiota, which can trigger gut inflammation and immune activation.[23,24]

Why did you not switch the patient to another secretagogue agent?

If the patient showed such a high degree of sensitivity to linaclotide, even at the lowest possible dose, chances are that she would show the same sensitivity to another medication from that same drug class. Given the avail-

- How well are you **tolerating this medicine**?
- Are there any **side effects** that you're experiencing that make taking this medication "not worth it"?
- Can you **predict** when you may have a **flare of IBS**?
- How are your **bowel symptoms**? How much improved?
- How are your **abdominal symptoms**? How much improved?
- Is your **quality of life** substantially better with this medication?
- Would you be interested in **trying a medication from another class with a different mechanism of action**?

Figure 3. Evaluating impact of therapy: sample questions I ask my patients.

ability of multiple FDA-approved therapies, physicians have the choice to proactively switch to another class of agents. This is actually a common practice when we treat other conditions such as IBD, for example, where failure to respond to one drug class leads to switching mechanism of action to another. Sometimes treating patients is a process of trial and error until we find the best fit, because no drug is a panacea.

Back to the Patient . . .

16-Week Follow-up Visit

The patient tolerated tenapanor well. She was able to find a balance where she experienced reduced abdominal pain and bloating while not suffering from fecal urgency. A greater predictability in her bowel movements allowed her to experience a substantial improvement in her quality of life.

How do you judge when it is time to switch a patient to a different therapy?

There are different questions that the clinician might ask to determine if they need to switch a patient to a different therapy (Figure 3). I always ask a few questions starting with, "How satisfied are you with your current therapy?" In this patient case, there was a mixed answer to this question, as linaclotide was certainly working but the patient was not satisfied because it led to persistent

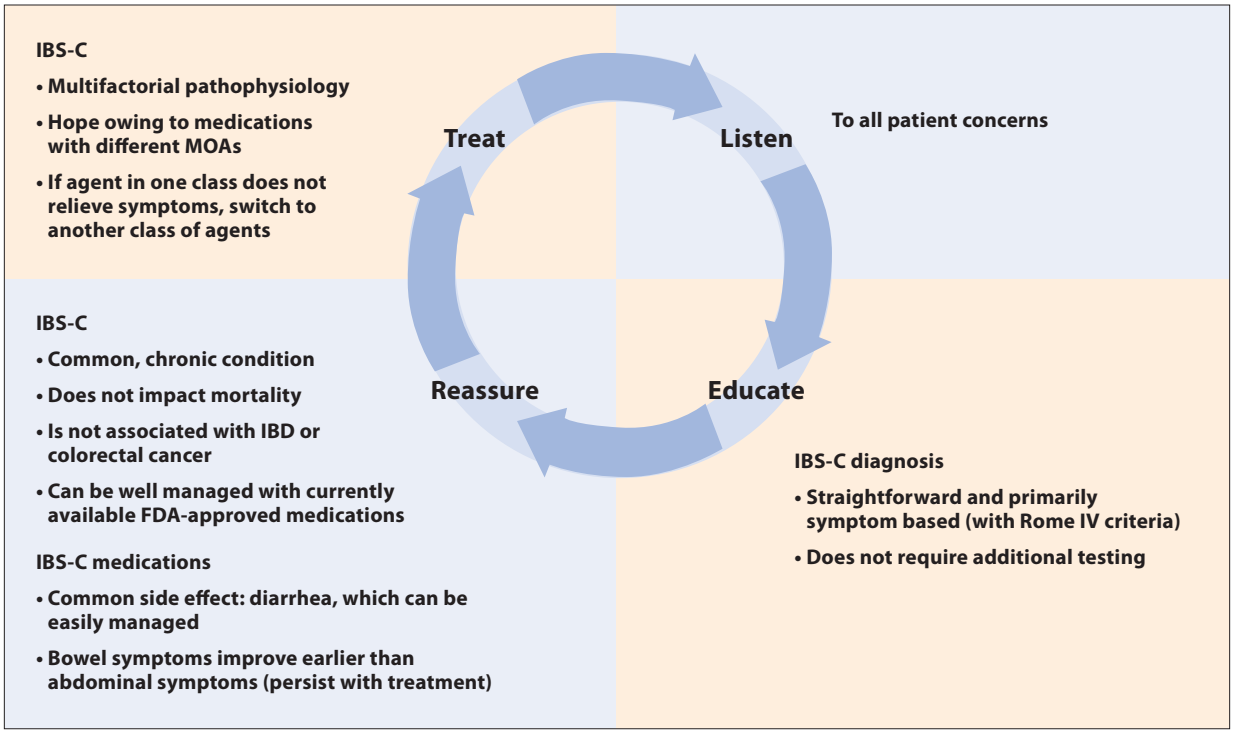

Figure 4. IBS-C management continuum: tips for a successful office visit in the management of a patient with IBS-C.[43]

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

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

diarrhea that impacted her overall HRQoL. Although the medication actually reduced some of the cramping and pain, it replaced constipation with diarrhea, even at a low dose. It is important to consider that if I were to ask her simply, "Is your pain getting better?" she might have simply responded "Yes" without providing the further insight of worsening diarrhea. Thus, there would be a risk that the patient would be continued on that agent and at that dose, with a significant impact on her HRQoL.

What is your take-home guidance from this case study?

This patient case illustrates several important points in the management of IBS-C (Figure 4).[43] First, a dialogue with the patient is extremely important and should be tailored to the individual patient. Points for discussion include answering questions about the diagnosis as well as the multifactorial pathophysiology of IBS-C and why precise targeting of symptoms is not possible and instead treatment is often empirical. This can often lead into a discussion of what the patient should expect with the FDA-approved treatment options, and how to evaluate their therapeutic response with respect to abdominal symptoms, bowel symptoms, and quality of life at follow-up visits. Patients can benefit from being informed early of the availability of FDA-approved therapies with different mechanisms of action in different classes, so that both the clinician and the patient can be proactive in switching therapies in case of incomplete response or intolerability.

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