Case Study Series

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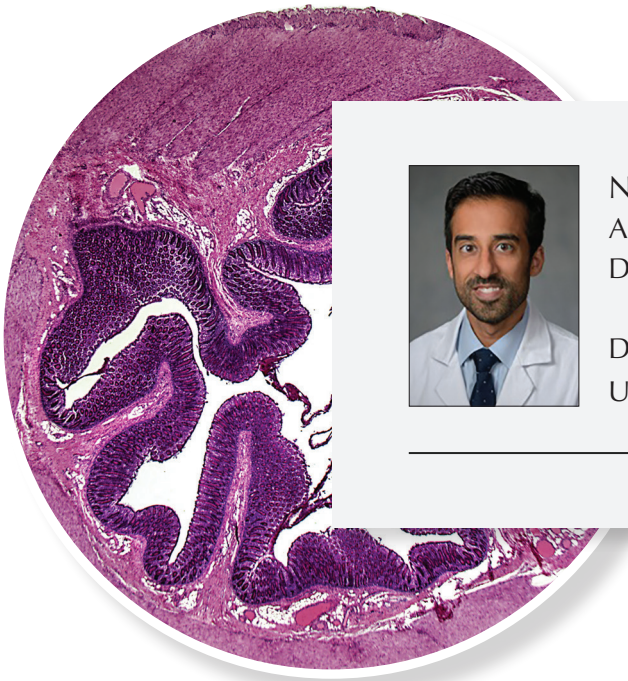
# A Case Study in the IBS-C Management Continuum: Assessing Patient Response and Tailoring Treatment





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# A Case Study in the IBS-C Management Continuum: Assessing Patient Response and Tailoring Treatment

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## Patient Case

A 60-year-old woman presented to the clinic with a chief complaint of constipation (Table 1). She reported that she had been experiencing altered bowel habits for at least 30 years. Her most recent bout of diarrhea was 4 to 5 years earlier, after which she much more consistently experienced constipation with associated gas, bloating, and hypogastric pain that remitted with passage of stool. She reported a reliable sense of incomplete evacuation at least weekly and prior use, albeit rarely, of manual maneuvers to assist with defecation. The patient reported that her symptoms, particularly abdominal pain, inhibited her functionality at work at least once a month.

She endorsed an ample amount of dietary fiber intake. During the preceding few years, she had tried several over-the-counter measures for constipation relief, including bisacodyl, senna, and polyethylene glycol (PEG), which were only partially helpful. She also reported trying magnesium citrate, which was unhelpful.

Her past medical history was otherwise notable only for gastroesophageal reflux disease, which was well controlled on pantoprazole. Her surgical history was notable for a cesarean section and hysterectomy. Family and social history were noncontributory.

A rectal examination performed at her initial visit was normal, with grossly appropriate pelvic excursion by inspection following squeeze and bear-down maneuvers, grossly appropriate baseline tone, grossly adequate squeeze, and grossly appropriate relaxation with bear-down maneuver on digital assessment. A radiopaque marker study ordered by a prior physician demonstrated 1 marker remaining in the distal sigmoid colon on day 5 along with a background of mildly increased colonic fecal burden. A recent complete blood count revealed a normal hemoglobin of 14.7 g/dL. Screening colonoscopy performed 1 year prior demonstrated good preparation quality and normal findings apart from small internal hemorrhoids.

The patient was diagnosed with irritable bowel syndrome with constipation (IBS-C) and offered a prescription for linaclotide 145 µg daily, to be taken before breakfast. Three weeks later, she called the office to report that this dose worked well only for her bowel symptoms for 2 weeks but became "too strong" in the third week. Abdominal symptoms persisted. The patient was then offered a prescription for linaclotide 72 µg daily. At a clinic follow-up 3 months later, she described the effects of the low-dose linaclotide as "hit or miss." Pain and bloating were improved from baseline, but she reported that she did not have a bowel movement every day. After being asked to quantify her response, she judged her overall symptoms to be about 75% improved.

Because of her residual discomfort, she was offered a transition to lubiprostone 8 µg twice daily. At a clinic follow-up another 3 months later, she reported great

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

success with the new medication. She noted that effects of the medication seemed to be more robust with consistent use, judging her overall bowel and abdominal symptoms now to be 95% improved. Following this medication change, she also established care with a dietician because of concern for prediabetes and initiated an exercise regimen 3 times weekly. At a follow-up clinic visit an additional 6 months later, she remained on lubiprostone 8 µg twice daily and reported persistent symptom benefit.

We will now examine evidence-based answers to the following questions to understand this patient's experience in clinical context:

- What in this patient's presentation called for an IBS-C diagnosis?
- How bothersome are abdominal and bowel symptoms for patients with IBS-C?
- How should clinicians assess symptom control in patients with IBS-C?
- Are over-the-counter measures for constipation relief efficacious in IBS-C?
- What are the US Food and Drug Administration (FDA)–approved medications available for IBS-C?
- What is the impact of available FDA-approved agents on bowel and abdominal symptoms?
- Why was the patient's medication eventually changed to an agent with a different mechanism of action (MOA)?

**Table 1.** Key Points of the Patient Case

| | |
|---|---|
| **Chief complaint** | Constipation<br>• Altered bowel habits for at least 30 years<br>• Last bout of diarrhea 4 to 5 years earlier, then consistently constipated with gas, bloating, and hypogastric pain that remitted with passage of stool<br>• Reliable sense of incomplete evacuation |
| **Prior Interventions** | • Ample amount of dietary fiber intake<br>• Over-the-counter measures for constipation relief: bisacodyl, senna, and polyethylene glycol *(only partially helpful)*<br>• Magnesium citrate *(unhelpful)* |
| **Medical history** | • GERD well-controlled on pantoprazole<br>• Cesarean section and hysterectomy |
| **Rectal examination** | Normal<br>• Grossly appropriate pelvic excursion by inspection following squeeze and bear-down maneuvers<br>• Grossly appropriate baseline tone<br>• Grossly adequate squeeze<br>• Grossly appropriate relaxation with bear-down maneuver on digital assessment |
| **Radiopaque marker study** | 1 marker remaining in the distal sigmoid colon on day 5 along with a background of mildly increased colonic fecal burden |
| **Complete blood count** | Normal hemoglobin: 14.7 g/dL |
| **Colonoscopy** | Up to date on age-appropriate screening, good preparation quality and normal findings apart from small internal hemorrhoids |
| **Diagnosis** | IBS-C |
| **Initial treatment** | **Linaclotide 145 µg daily before breakfast**<br><br>Follow-up 3 weeks later:<br>• *Bowel symptoms:* dose worked well only for 2 weeks but became "too strong" in the third week<br>• *Abdominal symptoms:* persisted |
| **Treatment modification** | **Low-dose linaclotide 72 µg daily before breakfast**<br><br>Follow-up 3 months later:<br>• *Bowel symptoms:* effects were "hit or miss" (bowel movement not every day)<br>• *Abdominal symptoms:* pain and bloating improved from baseline<br>• *Self-reported overall symptom improvement:* about 75%<br>• *Dissatisfaction with overall symptom control* |
| **Subsequent treatment** | **Lubiprostone 8 µg twice daily**<br><br>Follow-up 3 months later:<br>• Effects of the medication more robust with consistent use<br>• *Self-reported overall symptom (both bowel and abdominal) improvement:* 95%<br><br>Follow-up 6 months later:<br>Persistent bowel and abdominal symptom benefit |

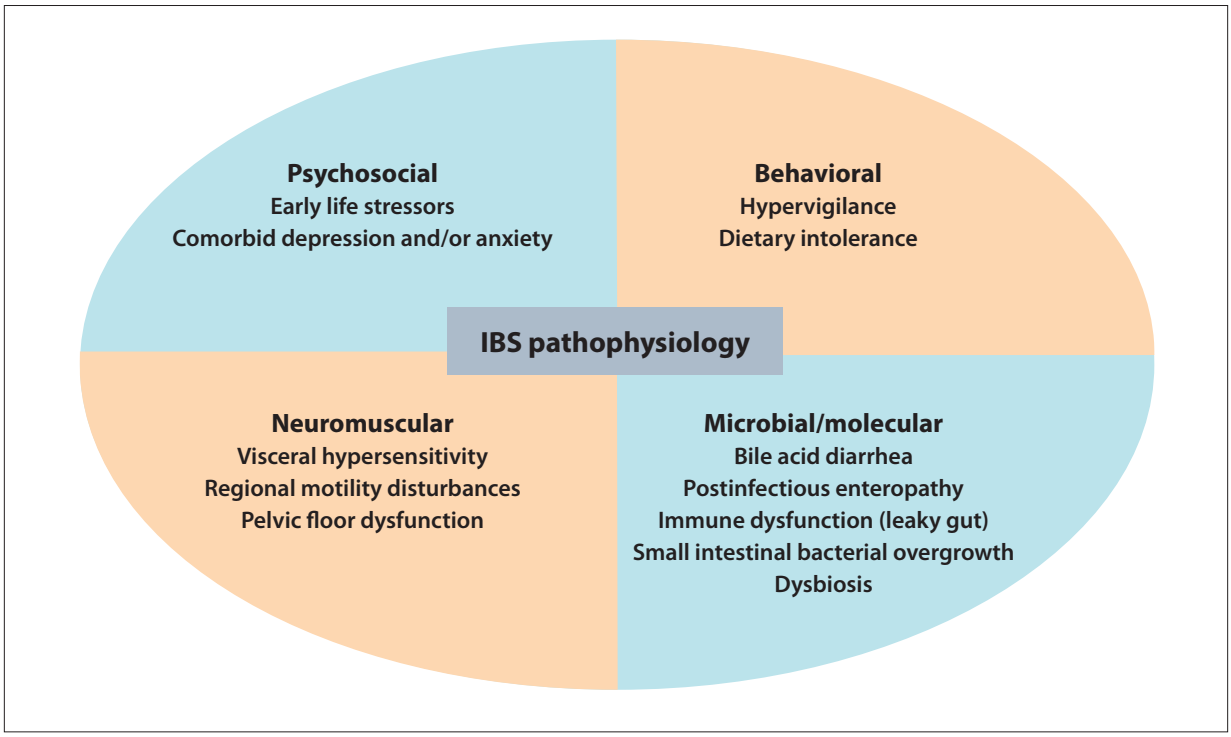


**Figure 1.** Varied and complex pathophysiology of IBS.
IBS, irritable bowel syndrome.

## What in This Patient's Presentation Called for a Diagnosis of IBS-C?

Functional bowel disorders, which are considered a spectrum of overlapping conditions, include multiple chronic disorders of the middle or lower gastrointestinal (GI) tract characterized by abdominal pain, abdominal bloating, abdominal distension, and bowel habit abnormalities (constipation, diarrhea, or mixed constipation and diarrhea).[1] One such disorder is irritable bowel syndrome (IBS), which can be challenging to diagnose owing to its varied and complex pathophysiology (Figure 1).

### *Diagnosing Irritable Bowel Syndrome Using the Rome IV Criteria*

IBS is a diagnosis of shifting borders. To aid in the diagnosis of IBS, the Rome Diagnostic Criteria for Irritable Bowel Syndrome (Rome IV criteria) have been developed to provide clear and concise guidance.[2] Using the Rome IV criteria (Figure 2), IBS is defined as a disorder of gut-brain interaction in which abdominal pain recurring at least 1 day per week on average is associated with two or more of the following: related to defecation; associated with a change in the frequency of stool; and associated with a change in the form (appearance) of stool. The Rome IV criteria further apply a requirement that these criteria must have been met for the previous 3 months with an onset of symptoms at least 6 months before the diagnosis.

Among patients with IBS, 4 distinct subtypes are recognized: 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). The Bristol Stool Form Scale (BSFS), measured from type 1 to type 7, can be used to help establish a patient's IBS subtype.[3] According to the BSFS, IBS-C is classified in patients with at least 25% of bowel movements of BSFS types 1 or 2, and less than 25% of BSFS types 6 or 7. IBS-D is classified in patients with at least 25% of bowel movements of BSFS types 6 or 7, and less than 25% of BSFS types 1 or 2. 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. Finally, IBS-U classifies cases that meet the criteria for IBS but do not fall into one of the other 3 IBS subgroups according to BSFS type.

Rome IV criteria were updated in 2016 to reflect improved understanding of IBS pathophysiology. The previous Rome III criteria defined IBS by chronic abdominal pain or discomfort for at least 3 days per month; the updated Rome IV criteria removed the word "discomfort" and increased the frequency of abdominal pain to an aver-

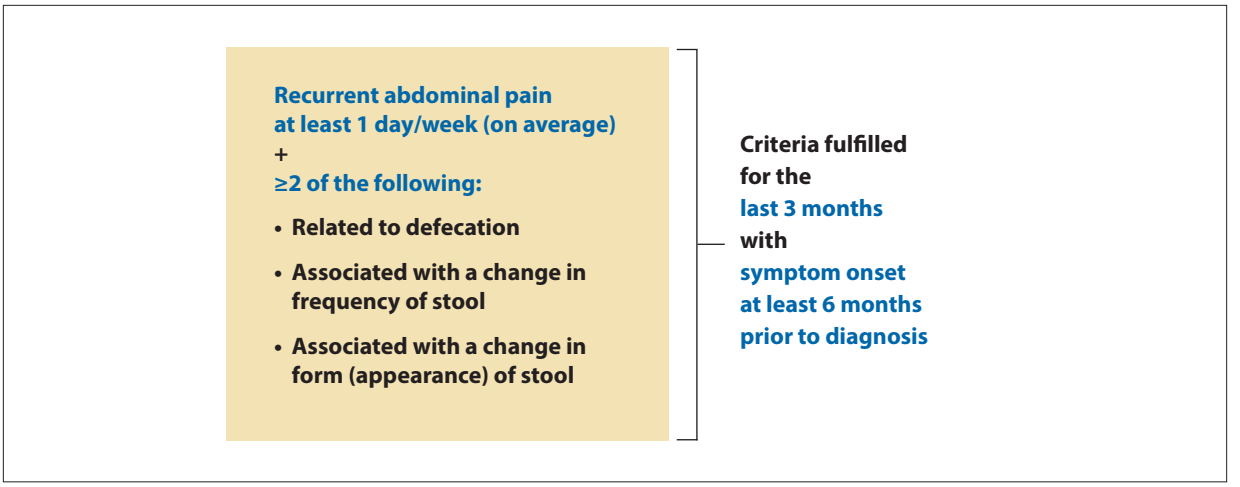


**Figure 2.** The Rome IV criteria for irritable bowel syndrome.[2]

age at least 1 day per week. Rome IV criteria lead to fewer diagnoses of IBS, as demonstrated in a study of 542 Swedish patients with Rome III criteria–defined IBS; of these patients, 85% were found to fulfill Rome IV criteria.[4]

Rome criteria perform only modestly in isolation for a diagnosis of IBS. One study, which used the Rome III criteria in 318 patients, reported a sensitivity of 69.6% (95% CI, 58.3-79.5) and a specificity of 82.0% (95% CI, 76.5-86.7) when used alone.[5] The diagnostic accuracy worsened when combined with the physician's initial impression of whether the patient had IBS, with a sensitivity of 50.0% (95% CI, 33.4-66.6) and a specificity of 79.7% (95% CI, 68.8-88.2).

As such, some patients may benefit from augmenting Rome IV criteria with additional clinical queries. For example, it can be useful to inquire into alarm signs, including new symptoms in patients older than 50 years of age, unintended weight loss, hematochezia, symptoms that awaken the patient at night, fever, acute or rapidly progressing symptoms, and a family history of colorectal cancer or inflammatory bowel disease.[1] In an analysis of 559 patients who met Rome III criteria for IBS, the presence of at least one of these alarm signs made an alternative diagnosis significantly likelier (most frequently Crohn's disease).[6]

Augmenting Rome IV criteria by assessing symptoms of pelvic floor dysfunction may also improve confidence in an IBS diagnosis. An evaluation of anorectal function among 66 patients across different IBS subgroups found that the rates of pelvic floor dysfunction were higher in all IBS subtypes relative to controls (41% vs 5%; $P<.01$).[7] Digital rectal examination is useful for identifying dyssynergia in patients with chronic constipation (sensitivity of 75% and specificity of 87% as compared with formal anorectal physiology testing), providing the potential for an early therapeutic branch-point incorporating pelvic floor physical therapy.[8]

### *Making a Positive Diagnosis*

A positive diagnosis of IBS (made with Rome IV criteria alongside limited, judicious investigation via patient history and physical examination) is optimal for clinical outcomes, cost effectiveness, and patient care. Despite guideline recommendations to this end,[9,10] IBS is often erroneously considered a diagnosis of exclusion. In 2010, a survey-based tool was used to examine the decision-making regarding IBS diagnosis among primary care providers, gastroenterologists, and IBS experts.[11] When these clinicians were given a vignette of a patient with IBS-C, IBS experts were the most likely (72%) to diagnose the patient with IBS on the basis of patient history and physical examination findings alone, with 27% responding they were unsure and needed more information. By comparison, 48% of community gastroenterologists, 17% of general internal medicine physicians, and 12% of nurse practitioners responded with an IBS diagnosis, with 52%, 64%, and 51%, respectively, responding that they needed more information.

Even when a diagnosis of IBS is made, our clinical language can hesitate or hedge. A retrospective review of 207 outpatient department letters written from the gastroenterology unit at a tertiary hospital determined that the diagnostic language used to describe functional bowel disorders tended to be more qualified than the clearer language used to describe organic GI diseases.[12] The use of qualified language occurred in 63% of diagnoses for functional bowel disorders, compared with 13% of diagnoses for organic GI diseases ($P<.001$). Some examples of the

qualified language reported in this study included "may be having," "it is possible that," and "working impression," whereas examples of the clearer language used included "he has," "is suffering from," and "has been diagnosed with."

Data from a randomized noninferiority trial demonstrated that a positive diagnostic strategy was noninferior to a strategy of exclusion with regard to patients' health-related quality of life (QoL).[13] The difference between the 2 groups in the change from baseline to 1 year on the physical component summary of the 36-item Short Form Health Survey was 0.64 (95% CI, -2.74 to 1.45). The direct intervention costs associated with a strategy of exclusion were higher than those associated with a positive diagnostic strategy ($5075 vs $3160). Although this difference did not reach statistical significance, it equated to an excess of $863 in costs of investigations per patient in the 1-year follow up.

In similar support of a positive diagnostic approach, a prospective study was conducted among 373 patients meeting the Rome IV criteria for IBS and referred to a single clinic in the United Kingdom.[14] These individuals were followed for a mean of 4.2 years, during which time rates of rereferral, reinvestigation, and missed organic GI disease were assessed. Overall, 62 (16.6%) patients were rereferred with GI symptoms; of these, 35 (56.5%) were rereferred with IBS symptoms and 27 (43.5%) with other GI symptoms (such as rectal bleeding, dysphagia/odynophagia, abdominal pain, and nausea/vomiting). Of the 35 patients who had been rereferred with IBS symptoms, 21 (60%) were reinvestigated. Among these 21 patients, 1 potentially relevant organic GI disease was subsequently diagnosed. Among the 311 patients who were not rereferred, 15.4% underwent further investigations (most frequently, colonoscopy and upper endoscopy) as part of their ongoing care. No cases of organic GI disease were subsequently diagnosed in patients who had repeated investigations. These data demonstrated that, despite 1 in 6 patients undergoing rereferral for GI symptoms together with substantial reinvestigation rates, the rate of missed organic GI disease was only 1%, supporting the validity of the Rome IV criteria for diagnosing IBS.

A positive diagnosis for IBS is also an important step in achieving optimal patient outcomes, as an expeditious diagnosis leads to early initiation of therapy. Findings from an online US survey conducted in 1924 individuals demonstrated a significant proportion (43.1%) meeting the Rome III criteria for IBS but having never received a formal diagnosis.[15] Patients with a formal diagnosis reported a greater mean number of received treatments compared with undiagnosed individuals (4.9 vs 3.4, respectively). Although few diagnosed or undiagnosed individuals reported satisfaction with their overall treatment (20% vs 18%, respectively), patients with a formal diagnosis were more likely to be satisfied with specific treatments. Notably, these data were collected in patients whose diagnosis aligned with IBS-D, but the findings can be extended to IBS-C, for which several FDA-approved agents are available.

Table 2 provides a summary of the findings supporting a positive diagnosis of IBS-C.

The patient in this case reported constipation with associated gas, bloating, and hypogastric pain that remitted with passage of stool and a reliable sense of incomplete evacuation at least weekly. Based on this presentation, and an otherwise unremarkable history and physical examination, the patient was diagnosed with IBS-C.

**Table 2.** Findings Supportive of a Positive Diagnosis of IBS-C[2,10]

| **Diagnostic criteria of IBS-C** | |
|---|---|
| Rome IV diagnostic criteria | Disorder of gut-brain interaction in which abdominal pain recurs on average at least 1 day/week<br>PLUS<br>≥2 of the following[a]:<br>• Related to defecation<br>• Associated with a change in the frequency of stool<br>• Associated with a change in the form (appearance) of stool |
| BSFS | • BSFS type 1 or 2: >25% of bowel movements<br>• BSFS type 6 or 7: <25% of bowel movements |
| Hallmark symptoms | • Abdominal pain<br>• Constipation |
| Medical history and physical examination | Additional targeted history to exclude:<br>• New symptoms at age >50 years<br>• Unintended weight loss<br>• Hematochezia<br>• Symptoms that awaken the patient at night<br>• Acute or rapidly progressing symptoms<br>• Family history of colorectal cancer, celiac, or inflammatory bowel disease<br>Evaluation for the presence of pelvic floor dysfunction |

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

BSFS, Bristol Stool Form Scale; GI, gastrointestinal; IBS-C, irritable bowel syndrome with constipation.

## How Bothersome Are Abdominal and Bowel Symptoms for Patients With IBS-C?

The burden of symptoms associated with IBS-C is significant, as repeatedly demonstrated in patient surveys and analyses of impacts on quality of life. The IBS in America survey was conducted in 3254 individuals who met the Rome III criteria for IBS; of these, 1667 had IBS-C (the remaining had IBS-D).[16] The most commonly experienced symptom reported by respondents with IBS-C was abdominal pain (83%), followed by bloating (78%), straining (75%), infrequent stools (73%), hard lumpy stools (72%), and nausea (46%). More than one-half (53%) considered their symptoms to be at least very bothersome. Further, symptoms experienced by respondents with IBS-C had a marked impact on their daily activities; among employed respondents, symptoms impacted work productivity for an average of 8.2 days, and 37% reported that their symptoms impacted their work productivity on 10 or more days per month. Respondents with IBS-C reported missing an average of 1.7 days of work or school per month. A total of 34% of respondents with IBS-C reported that their symptoms interfered with personal activities (eg, parties, sporting events, family activities) at least 10 days per month. Compared with IBS-D, individuals with IBS-C were more likely to report feelings of self-consciousness, avoidance of sex, difficulty concentrating, and feeling unable to reach their full potential. To the question "What would you be willing to give up for 1 month of IBS-C symptom relief?" responses included the Internet (21%), cell phone (25%), sex (42%), caffeine (58%), and alcohol (62%).

Multiple studies have demonstrated the negative effect of symptoms on measures of health-related quality QoL in patients with IBS-C. High levels of absenteeism and presenteeism are common among individuals with IBS.[17-19] QoL measures such as the physical component summary score and mental component summary score are also negatively affected among patients with IBS-C versus a matched comparison group.[20]

Other patient-reported IBS outcome survey instruments have also been evaluated. For example, the IBS-QoL, a condition-specific instrument used to assess the impact of IBS, consists of 34 questions that cover 8 domains including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual health, and relationships.[21] A further study validated the IBS-QoL as responsive to treatment among a referral-based clinical population of patients with functional bowel disorders.[22]

The patient in this case reported that her symptoms, in particular abdominal pain, prevented her from working at least once a month.

## How Should We Assess Symptom Control in Patients With IBS-C?

Assessment of the symptom pattern and severity of symptoms is key to evaluating treatment response. As shown in a retrospective analysis of patients with IBS, visceral hypersensitivity (including allodynia and hyperalgesia), abnormal colonic transit (assessed using radiopaque markers), and psychologic factors (such as anxiety and depression) are all associated with IBS symptoms.[23] Bowel symptom improvement alone is not sufficient for improving the QoL of patients with IBS-C. Too often during a patient follow-up visit, clinicians stop at bowel symptom improvement when asking patients how they are doing with therapy. There remains a need to address abdominal and non-abdominal symptoms during the patient visit, as both can be independently debilitating for patients with IBS-C.

Patient-reported outcomes can be collected using structured symptom assessment questionnaires that allow evaluation of symptom patterns, quantification of symptom severity, and evaluation of response to treatment at follow-up.[24] Patient-reported outcomes are particularly relevant to patients with IBS-C, as there are currently no objective measurable biomarkers to assess GI symptom burden.[25] These assessments are therefore a valuable way to evaluate the presence, impact, and evolution of IBS-C, both in the clinic as well as in clinical trials.

The Chronic Constipation and IBS-C Treatment and Outcomes Real-World Research Platform (CONTOR) is a longitudinal project linking administrative claims data with patient-reported outcomes data among patients with IBS-C or chronic idiopathic constipation.[26] A combination of mailed and online surveys that followed respondents for 1 year was used to determine that over one-half of participants (55.3%) were dissatisfied with management of their condition at baseline. Rates of satisfaction varied by medication use; respondents who reported no current medication use had the lowest satisfaction (68.4% not at all/a little satisfied). In contrast, respondents treated with prescription medications were more likely to be satisfied with treatment. Fewer respondents who were treated with over-the-counter therapies reported satisfaction with treatment (40.6%).

The BURDEN IBS-C study used online questionnaires to survey both patients with IBS-C (N=1311) and health care providers involved in the care of patients with IBS-C (N=331).[27] Survey respondents participated between June 2016 and January 2017. The investigators found that over-the-counter treatments had been used (86%) and/or were currently being used (76%) by the majority of respondents, and 12% were currently on prescription therapy. However, 66% (receiving over-

the-counter treatment) and 63% (receiving prescription therapy) of respondents were not satisfied/completely satisfied, owing primarily to inadequate efficacy (55%) and side effects (39%). Feelings of frustration (43%) and stress (28%) were common. Health care providers were aligned with patients in their impression that patients were frustrated (76%) and stressed, and 79% of health care providers were also not satisfied/completely satisfied with the prescription treatments available to them at the time this study was conducted. Overall, BURDEN IBS-C reinforced the notion that patients with IBS-C may often experience dissatisfaction with their treatment, most notably owing to side effects and lack of efficacy.

In the absence of validated patient-reported outcomes questionnaires specific to abdominal symptoms for patients with IBS-C, clinicians should consider asking their patients more specific questions regarding symptom improvement, quantifying the patient's response. For example, instead of "Are you better?" a clinician might ask, "How much better are you?" regarding each of these symptoms. This paradigm shift is organized around the subjective nature of symptom assessment, insofar as the significance of these symptoms and their impact on QoL are deeply individual.[25]

The patient in this case reported that, after 3 months of initial treatment, her abdominal symptoms were improved but persisted. However, when directly asked to quantify the improvement, she judged her symptoms to be only 75% improved, revealing dissatisfaction with overall symptom control. After switching treatment, her report of 95% improvement in her symptoms indicated that her symptoms were being well managed.

## How Efficacious Are Over-the-Counter Measures for Constipation and Abdominal Symptom Relief in IBS-C?

Patients with IBS-C often first try to self-medicate with over-the-counter treatments to relieve their symptoms of constipation and abdominal pain. Several options are available, including senna, magnesium, and PEG. The American Gastroenterological Association (AGA) guidelines suggest using over-the-counter osmotic laxatives such as PEG while the American College of Gastroenterology (ACG) guidelines recommend against its use for IBS-C, a discordance likely related to the incomplete association between constipation and abdominal pain in this patient population.[9,10] Data for senna (a stimulant laxative), magnesium oxide (an osmotic laxative), and bisacodyl support their use in chronic idiopathic constipation, but not specifically in IBS-C.[28,29] Dietary modification, including an adequate amount of fiber, is often employed to relieve symptoms, and commercially available soluble fibers such as psyllium are recommended. Insoluble fibers such as bran fiber may worsen symptoms and are generally not recommended for the management of IBS-C.

The patient in this case reported having tried several over-the-counter measures for constipation relief in previous years, including bisacodyl, senna, PEG, and magnesium citrate. However, they were only partially helpful or not helpful at all.

## What Are the FDA-Approved Medications Available for IBS-C and How Do They Work?

In recent years the FDA has approved several medications specifically for IBS-C (Figure 3). Both the ACG and AGA provide recommendations for the use of these agents in IBS-C (Table 3).[9,10] These medications, which have been shown to improve both abdominal pain symptoms as well as constipation, possess varying mechanisms of action (MOAs).[30]

The prostaglandin E1 derivative lubiprostone activates the intestinal type 2 chloride channel (CIC-2).[31] Activation of CIC-2, located on the apical surface of small intestinal enterocytes, leads to chloride efflux into the luminal cavity. This process results in fluid secretion into the luminal cavity, which can soften stool and accelerate intestinal transit.

Two guanylate cyclase-C (GC-C) agonists, linaclotide and plecanatide, are approved for the treatment of IBS-C. When activated by its endogenous ligands, the GC-C receptor, located on the luminal surface of intestinal enterocytes, promotes intestinal secretion in response to a meal. Linaclotide and plecanatide are both peptides that mimic these endogenous ligands, acting as selective agonists at the GC-C receptor.[32-34] Binding of these peptides results in increased levels of cyclic guanosine monophosphate, a second messenger that plays a critical role in the regulation and secretion of intestinal fluid into the intestinal lumen.

Tenapanor is a locally acting inhibitor of the sodium/hydrogen exchange transporter isoform 3 (NHE3). Expressed on the apical surface of the small intestine and colon, NHE3 is primarily responsible for the absorption of dietary sodium.[35-37] Tenapanor is understood to impact IBS symptoms via 3 mechanisms.[38-40] First, tenapanor decreases the absorption of dietary sodium, causing luminal water content to be retained, intestinal transit time to be accelerated, and stool to be softened (as distinct from

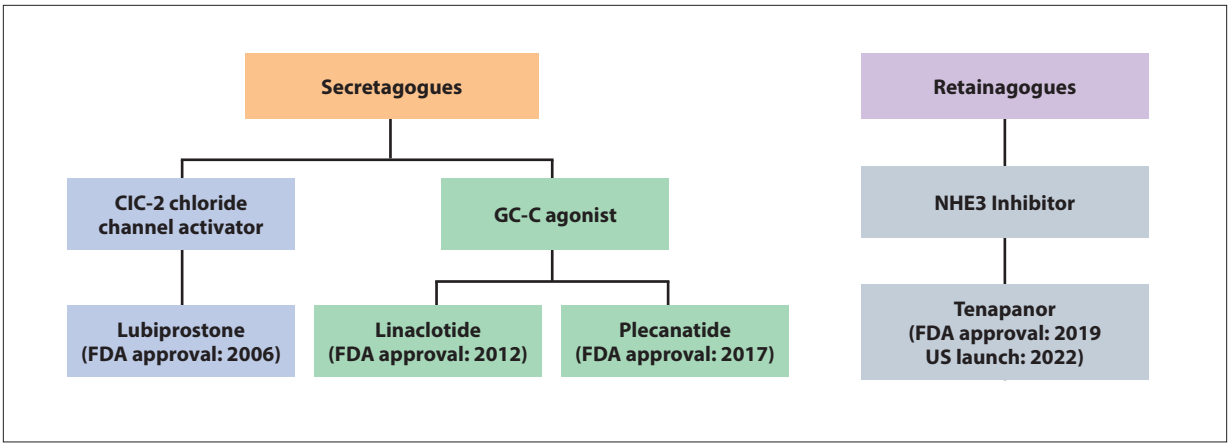


**Figure 3.** Currently available FDA-approved treatments with a specific indication for IBS-C.

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.[30]

the medications discussed above, which are commonly termed colonic secretagogues, tenapanor as an inhibitor of electrolyte resorption has been colloquially dubbed a "retainagogue"). Second, animal models demonstrate that tenapanor narrows the tight junctions between intestinal epithelial cells, resulting in decreased intestinal permeability. Third, animal models have shown that tenapanor reduces visceral hypersensitivity, a common finding in patients with IBS-C.

The serotonin type 4 (5-HT4) receptor agonist tegaserod was FDA approved with an indication for the treatment of IBS-C in women younger than 65 years. However, the manufacturer withdrew tegaserod from the market in 2022 based on a business decision not reflective of the efficacy or safety of this agent.[41] Because it is no longer commercially available, it will not be further discussed here.

## What Is the Impact of Available FDA-Approved Agents on Bowel and Abdominal Symptoms in Patients With IBS-C?

Efficacy and safety data from the pivotal clinical trials of available FDA-approved agents for the treatment of IBS-C are summarized in Table 4.[42-47] Across the different agents, the most frequently reported adverse events were GI related, and in particular diarrhea.

### *Lubiprostone*

A combined analysis of 2 phase 3 trials compared lubiprostone versus placebo over 12 weeks.[42] In these trials, an overall responder was defined as a monthly responder for 2 or more of 3 treatment months; a monthly responder was defined as a patient who experienced at least moderate relief for 4 of 4 weeks or significant relief for 2 of 4

**Table 3.** ACG and AGA Guideline Recommendations for Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C

| Agent | ACG recommendation[10] | AGA recommendation[9] |
|---|---|---|
| Lubiprostone | Chloride channel activators are recommended to treat global IBS-C symptoms (strong recommendation) | Suggests using in patients with IBS-C (conditional suggestion) |
| Linaclotide | GC-C agonists are recommended to treat global IBS-C symptoms (strong recommendation) | Suggests using in patients with IBS-C (strong recommendation) |
| Plecanatide | | Suggests using in patients with IBS-C (conditional suggestion) |
| Tenapanor | Not reviewed | Suggests using in patients with IBS-C (conditional suggestion) |

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; FDA, US Food and Drug Administration; GC-C, guanylate cyclase-C; IBS-C, irritable bowel syndrome with constipation.

weeks. This combined analysis reported a significantly higher percentage of overall responders in the lubiprostone arm compared with the placebo arm (17.9% vs 10.1%; *P*=.001).

***Linaclotide and Plecanatide***

Both linaclotide and plecanatide have been evaluated in randomized, controlled phase 3 trials. Compared with placebo, linaclotide showed superior efficacy (33.7% vs 13.9%; *P*<.0001) for the combined primary endpoint of a reduction of 30% or more in worst abdominal pain plus an increase of at least 1 complete spontaneous bowel movement (CSBM) weekly, both for 6 or more of 12 treatment weeks.[43] Plecanatide also showed superiority in comparison with placebo for the same primary endpoint in 2 phase 3 trials (Study 1: 30.2% vs 17.8%, *P*<.001; Study 2: 21.5% vs 14.2%, *P*=.009).[44]

***Tenapanor***

Tenapanor was compared with placebo in 2 randomized phase 3 trials, T3MPO-1 (12 weeks) and T3MPO-2 (26 weeks).[45,46] The primary endpoint of both studies was an overall response for 6 or more of the first 12 weeks of treatment, which was defined as a decrease of 30% or more in average weekly worst abdominal pain score and an increase of at least 1 CSBM from baseline, both in the same week. In T3MPO-1, significantly more patients treated with tenapanor versus placebo met the primary endpoint (27.0% vs 18.7%; Cochran-Mantel-Haenszel [CMH] *P*=.020). Tenapanor-treated patients showed significantly greater improvements in abdominal symptoms (including abdominal discomfort, bloating, cramping, and fullness) as well as global IBS treatment measures (including stool consistency and IBS severity) versus patients treated with placebo. The results of T3MPO-2 were similar, including

**Table 4.** Pivotal Efficacy Data and Toxicity Profile of Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C[42-47]

| Agent | Pivotal efficacy data | AEs/most common AE | Discontinuation owing to AE/diarrhea |
|---|---|---|---|
| Lubiprostone | Combined analysis of 2 phase 3 trials[a]<br>17.9% vs 10.1% with placebo; *P*=.001 | GI-related AEs (including nausea, diarrhea, and abdominal distension)<br>Similar incidence in lubiprostone and placebo groups | 4.7% and 5.1% (lubiprostone) vs 4.6% and 7.7% (placebo)[c] |
| Linaclotide | 26-week phase 3 study[b]<br>33.7% vs 13.9% with placebo; *P*<.0001<br>12-week phase 3 study[b]<br>33.6% vs 21.0% with placebo; *P*<.0001 | Diarrhea<br>19.7% (linaclotide) vs 2.5% (placebo) in 26-week study | 5.7% (linaclotide) vs 0.3% (placebo) in 12-week study[d] |
| Plecanatide | Study 1[b]<br>30.2% (3 mg) and 29.5% (6 mg) vs 17.8% with placebo; *P*<.001<br>Study 2[b]<br>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<br>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)[c] |
| Tenapanor | T3MPO-1 (12-week study)[b]<br>27.0% vs 18.7% with placebo; CMH *P*=.020<br>T3MPO-2 (26-week study)[b]<br>36.5% vs 23.7% with placebo; CMH *P*<.001 | Diarrhea<br>T3MPO-1: 14.6% (tenapanor) vs 1.7% (placebo)<br>T3MPO-2: 16.0% (tenapanor) vs 3.7% (placebo) | 1.6% in T3MPO-3 (55-week, open-label safety study)[d] |

AE, adverse event; 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.

[c]Discontinuation owing to AE.

[d]Discontinuation owing to diarrhea.

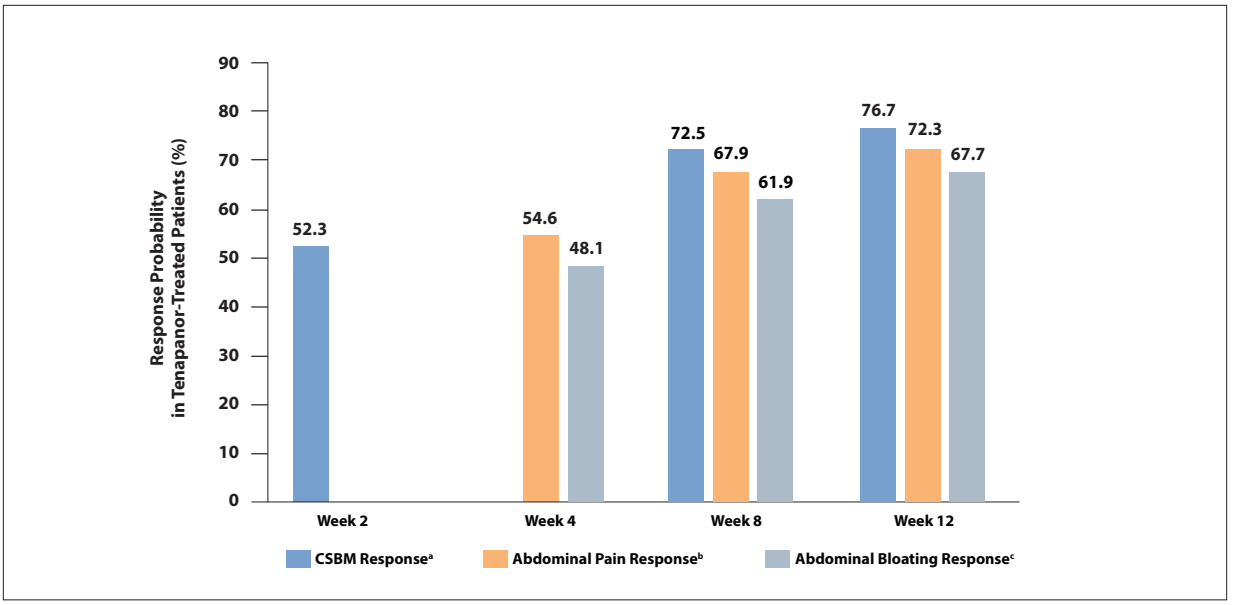


**Figure 4.** Response probability with tenapanor in a post hoc analysis of patients with IBS-C.[48,49]

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.

Adapted from: Lacy BE. *Gastroenterol Hepatol (N Y)*. 2024;20(4)(suppl 2):216-226.

those for the primary endpoint of overall response in 6 or more of the first 12 weeks of treatment with tenapanor versus placebo (36.5% vs 23.7%; CMH *P*<.001). In T3MPO-2, tenapanor was associated with significant improvements in the mean change from baseline in the average weekly number of CSBMs over time; over the 26-week treatment period, the tenapanor arm showed an average of 3.3 CSBMs per week, a frequency that falls within the healthy range for adults. Tenapanor also reduced abdominal symptoms (including bloating, fullness, discomfort, and cramping) over the treatment period, beginning as early as 1 week after the start of treatment.

### *The Value of Sustained Therapy*

Pivotal trials for these agents showed that many patients can experience an improvement in symptoms as early as the first week of treatment. This is especially notable for bowel symptoms, which tend to respond more rapidly than abdominal pain symptoms. It is worth noting, however, that incremental gains can be observed in other symptom domains with sustained therapy.

A post hoc analysis was conducted using pooled data (1372 patients with IBS-C) from the first 12 weeks of the randomized treatment period of 3 studies of tenapanor (T3MPO-1, T3MPO-2, and a phase 2b study).[48] 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).

In these tenapanor-treated patients, the median time to CSBM response was 2 weeks, and the estimated CSBM response probability increased from 52.3% (week 2) to 72.5% (week 8) and 76.7% (week 12).[48] The median time to abdominal pain response was 4 weeks, and the estimated abdominal pain response probability increased from 54.6% (week 4) to 67.9% (week 8) and 72.3% (week 12). The median time to abdominal bloating response was 5 weeks, and the estimated abdominal bloating response probability increased from 48.1% (week 4) to 61.9% (week 8) and 67.7% (week 12). These results are shown in Figure 4.[48,49]

The patient in this case was first treated with linaclotide 145 µg daily. She experienced the frequent adverse event of diarrhea, reporting that the medication was "too strong" in the third week of treatment, causing the physician to modify the dose to 72 µg daily. However, at a 3-month follow-up, the patient described the effects of the low-dose linaclotide as "hit or miss," judging her overall symptoms to be only 75% improved.

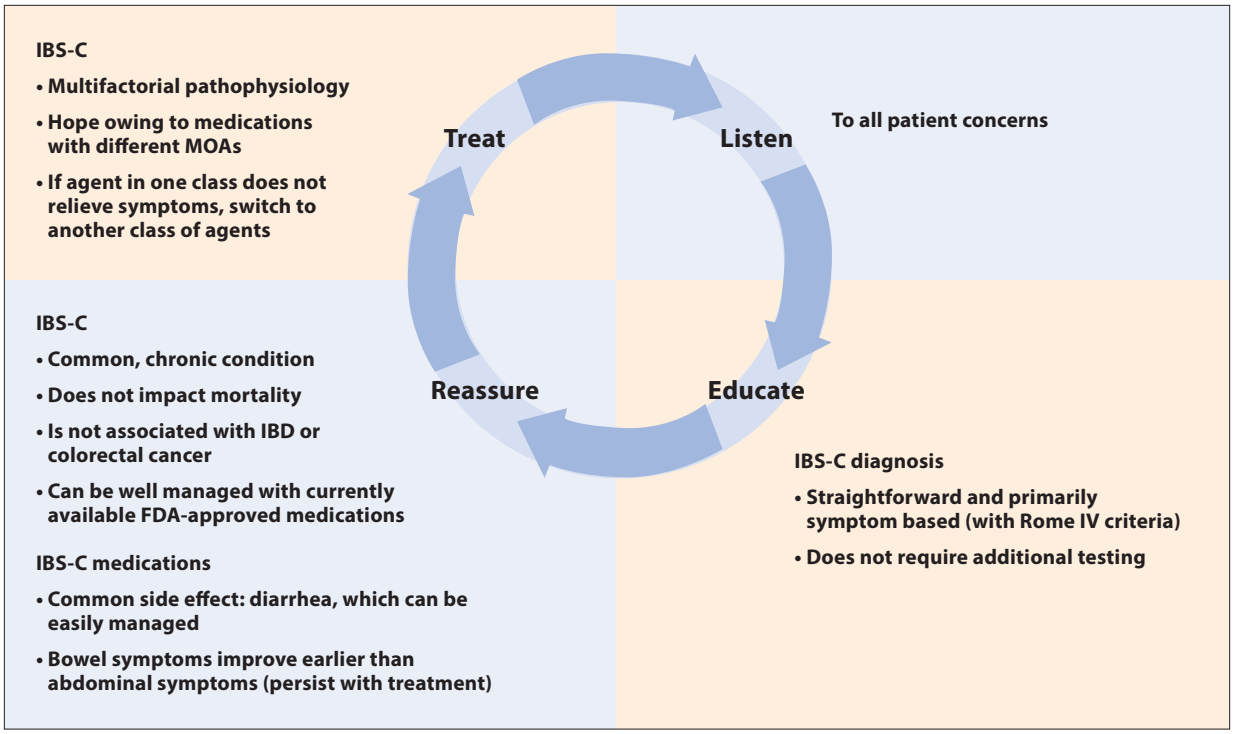


**Figure 5.** IBS-C management continuum: tips for a successful office visit in the management of a patient with IBS-C.[49]

FDA, US Food and Drug Administration; IBD, irritable 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.

## Why Was the Patient's Medication Eventually Changed to an Agent With a Different MOA?

Without head-to-head trials, the comparative efficacies of these agents are not known. However, using any of the FDA-approved treatment options is better than no treatment, which was confirmed in 2 network meta-analyses. A meta-analysis by Black and colleagues evaluated impact of treatment on global IBS-C symptoms and demonstrated similar efficacy across most endpoints.[50] A second meta-analysis by Nelson and colleagues compared the efficacy of treatment with respect to abdominal bloating, finding that all agents were superior to placebo with no significant differences across agents.[51]

Because of the multifactorial pathophysiology of IBS-C, it can be challenging to predict what treatment will be most effective to relieve both stool and abdominal symptoms in individual patients. Identifying the best treatment should be individualized and ideally in partnership with the patient (Figure 5). Payor considerations notwithstanding, the range of FDA-approved agents with different MOAs provides clinicians with several options for interventions in their patients with IBS-C. If an agent with a certain MOA is not providing satisfactory relief of all symptoms, the best approach may be to switch to an agent with a different MOA.

The patient in this case was switched to lubiprostone, a second agent from a different MOA class, after judging her overall symptoms to be only 75% improved with linaclotide. At a 3-month follow-up, she judged her overall bowel and abdominal symptoms to be 95% improved.

***Disclosures***

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