Understanding the Current Approaches in the Management of IBS-C: A Case Study

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Patient Case

A 36-year-old woman presents with persistent abdominal pain and constipation (Table 1). Upon inquiry, she states that she has experienced abdominal and bowel-related symptoms since she was in college. Her abdominal symptoms include intermittent cramps that typically occur in the left lower quadrant, nearly constant bloating that worsens during menstrual periods, and frequent episodes of constipation. She reports that her hard, small stools are associated with a feeling of incomplete emptying. She typically moves her bowels every other day. She denies seeing blood in her stool, fever, or unexplained weight loss, and she is not awakened at night by her symptoms. She exercises most days and has a normal body mass index (BMI). Her previous medical history includes an appendectomy at the age of 16 years. She reports no prior pregnancies (G0P0). Her family history is notable for breast and lung cancer, but no colorectal or gastric cancer.

The patient has tried to self-manage her symptoms through diet. Specifically, she has separately tried eliminating both gluten and dairy from her diet, with no improvement. Approximately 3 years ago, she tried the low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet at the recommendation of a friend. She reports that the low-FODMAP diet decreased her bloating initially, but over several months the bloating returned. The low-FODMAP diet also worsened her constipation, and she therefore subsequently stopped the diet. Upon inquiry, the patient admits that she limits many social events because of her symptoms and has been sexually inactive for a year. She reports that her symptoms, particularly the pain and bloating, are so debilitating that she calls in sick and skips work about 1 day per month.

She recently started a new job as a clerk at a law firm and expresses concern that she has not accrued enough personal leave to be able to take time off from work. Because she is otherwise healthy, she has not undergone regular physical examinations, and she has no history with this doctor's office. She is now presenting to a primary care physician (PCP) who was recommended to her, and she is inquiring about whether she should see a gastroenterologist.

On physical examination, the patient exhibits mild abdominal distension, and mild tympany is heard during abdominal percussion. Mild tenderness is noted in the left lower quadrant. A complete blood cell (CBC) count, thyroid-stimulating hormone (TSH) test, and comprehensive metabolic panel (CMP) are ordered, which show no abnormalities. The PCP recommends

Table 1. Key Points of the Case

Patient History	• A 36-year-old woman with persistent abdominal pain and constipation has experienced abdominal- and bowel-related symptoms since she was in college. • ***Abdominal symptoms:*** intermittent abdominal cramps (left lower quadrant), nearly constant bloating that worsens during menstrual periods, and frequent episodes of constipation. • ***Bowel-related symptoms:*** hard, small stools and feeling of incomplete emptying; patient typically moves her bowels every other day. • ***Patient report:*** no blood in stool, fever, or unexplained weight loss; patient not awakened at night by symptoms. • Exercises most days. • Normal BMI. • ***Previous medical history:*** appendectomy (at 16 years) and no prior pregnancies (G0P0). • ***Family history:*** breast and lung cancer, but no colorectal or gastric cancer. • ***Self-management through diet:*** elimination of both gluten and dairy with no relief of symptoms; low-FODMAP diet 3 years prior relieved bloating initially but bloating returned over several months and constipation worsened; therefore, patient subsequently stopped the diet**.** • ***Impact on QoL:*** limits social events, not sexually active for a year, calls in sick to work (1 day per month) because of pain and bloating.
Initial Clinical Presentation (PCP)	• Mild abdominal distension • Mild tympany on abdominal percussion • Mild tenderness in left lower quadrant • CBC count, TSH test, and CMP: no abnormalities
PCP Recommendation	• Continue low-fiber diet • Add over-the-counter PEG laxative • Referral to local gastroenterologist
Response (3 months)	• PEG laxative exacerbated bloating, therefore discontinued
Gastroenterologist Examination	• Rectal examination reveals normal relaxation of the pelvic floor, anal sphincter, and puborectalis muscle; proper contraction of the abdominal wall muscles noted when patient asked to simulate defecation
Gastroenterologist Recommendation	• Lubiprostone 8 μg twice daily • Maintain a daily diary of symptoms • Follow-up appointment in 2 months
Response (2 months)	• Tolerated lubiprostone well, with limited decrease in symptoms • Symptom diary review reveals no clear food triggers
Gastroenterologist Recommendation	• Tenapanor 50 mg twice a day • Follow-up appointment in 2 months
Response (2 months)	• Less bloating and abdominal pain • Increased frequency of bowel movements, with bowel movements most days • No noticeable side effects

BMI, body mass index; CBC, complete blood cell; CMP, comprehensive metabolic panel; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; PCP, primary care physician; PEG, polyethylene glycol; QoL, quality of life; TSH, thyroid-stimulating hormone.

that the patient continue her low-fiber diet, additionally recommends an over-the-counter polyethylene glycol (PEG) laxative, and refers her to a local gastroenterologist.

The patient immediately makes an appointment but must wait approximately 3 months for her first visit. At the appointment, the gastroenterologist takes a thorough history and performs a rectal examination. This reveals normal relaxation of the pelvic floor, anal sphincter, and puborectalis muscle, and proper contraction of the abdominal wall muscles is noted when the patient is asked

Table 2. Diagnostic Criteria for IBS-C[1-4]

IBS	Rome IV Diagnostic Criteria Disorder of brain-gut interactions in which abdominal pain recurs on average at least 1 d/wk PLUS ≥2 of the following*: • Related to defecation • Associated with a change in the frequency of stool • Associated with a change in the form (appearance) of stool
IBS-C	• BSFS type 1 or 2: >25% of bowel movements • BSFS type 6 or 7: <25% of bowel movements • Hallmark symptoms: abdominal pain and constipation • Medical history and physical examination including evaluation of gastrointestinal symptoms to identify alarm signs: – New symptoms and age older than 50 years – Unintended weight loss – Hematochezia – Symptoms that awaken the patient at night – Fever – Acute or rapidly progressing symptoms – Family history of colorectal cancer or inflammatory bowel disease

*Criteria met for the previous 3 months with onset of symptoms at least 6 months before the diagnosis. BSFS, Bristol Stool Form Scale.

to simulate defecation. When hearing that the addition of the PEG laxative has exacerbated the patient's bloating and that she therefore has discontinued it, the gastroenterologist instead prescribes 8 µg of lubiprostone twice a day and recommends a follow-up appointment in 2 months. The gastroenterologist also recommends that the patient begin a diary of her daily symptoms and diet.

After 2 months, the patient again presents to the gastroenterologist. She reports that she has tolerated the lubiprostone well but that relief of her symptoms has been limited. Review of her symptom diary does not reveal any clear food triggers. The gastroenterologist recommends that she switch to a medication of a different class, and she begins treatment with 50 mg of tenapanor twice a day.

At a follow-up appointment 2 months later, the patient reports less bloating and abdominal pain. She states that the frequency of her bowel movements has increased, and she is now having bowel movements most days. She reports no noticeable side effects from the medication.

Table 3. Multifactorial Pathophysiology of IBS-C[5-11]

Changes in gut motility Decreased colonic contractions and water imbalances leading to hard stools and infrequent defecation
Altered intestinal permeability (widened tight junctions between the intestinal epithelial cells) An inflammatory response in proximity to nerve fibers throughout the gut epithelium
Visceral hypersensitivity Enhanced sensitization of afferent nerve pathways within the gut
Changes in gut microbiota and other triggers of gut inflammation and immune activation

Overview of IBS

In 2016, the fourth iteration of the Rome Diagnostic Criteria for Irritable Bowel Syndrome (IBS; Rome IV criteria) was released (Table 2).[1] Developed by expert consensus, the Rome IV criteria incorporated key changes designed to improve their clinical utility and to reflect an increased understanding of IBS pathophysiology. In the Rome IV criteria, IBS is defined as a disorder of brain-gut interactions in which recurrent abdominal pain on average at least 1 day per week is associated with 2 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. Notably, these criteria must have been met for the previous 3 months with an onset of symptoms at least 6 months before the diagnosis.

Abnormal bowel movements are classified with the Bristol Stool Form Scale (BSFS), which ranges from type 1 to type 7.[2] BSFS types 1 and 2 are associated with constipation, whereas types 6 and 7 are associated with diarrhea. A proper identification of the patient's predominant stool type on days with abnormal stools is important for a correct diagnosis and identification of the subtype of IBS.

The 4 distinct IBS subtypes recognized are the following: 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).[3] Once the pattern of stool type is determined with the BSFS, the Rome IV criteria can be applied to make an appropriate determination of a patient's subtype. For example, IBS-C is diagnosed when more than 25% of a patient's bowel movements are BSFS type 1 or 2 and fewer than 25% are type 6 or 7.

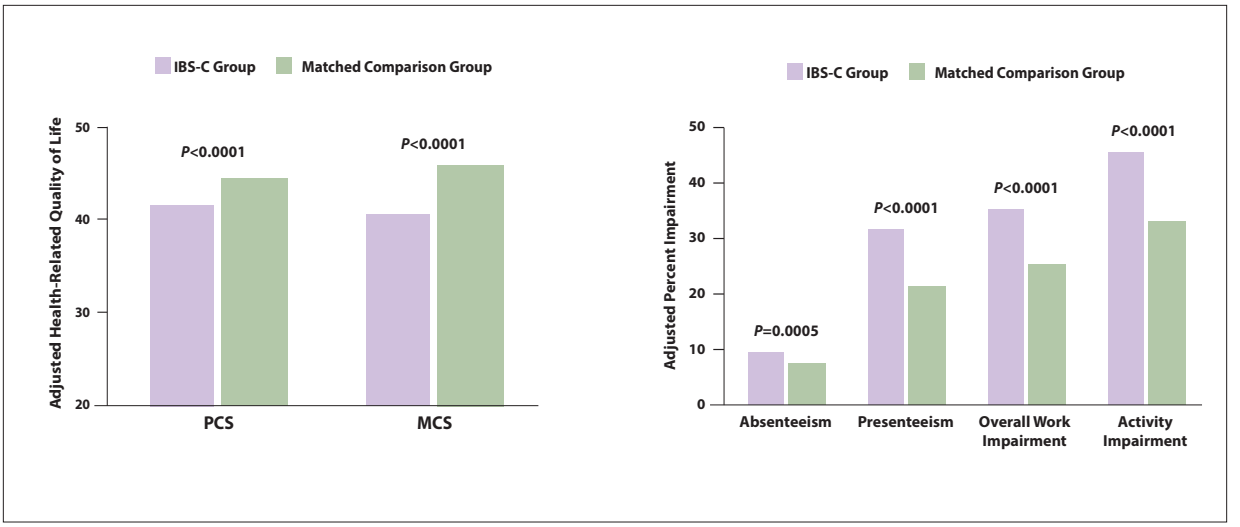

Figure 1. Effect of IBS-C on health-related quality of life and productivity.[13] PCS, physical component summary; MCS, mental component summary.

In contrast, IBS-D is diagnosed when more than 25% of a patient's bowel movements are BSFS type 6 or 7 and fewer than 25% are BSFS type 1 or 2.

With respect to IBS-C in particular, abdominal pain and constipation are considered to be the hallmark symptoms. A diagnosis of IBS-C is based on a medical history and a physical examination that include an evaluation of gastrointestinal symptoms, especially to identify alarm signs (eg, new symptoms in a patient older than 50 years, 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).[4]

A multifactorial pathophysiology has been proposed for IBS-C, with a wide range of potential mechanisms (Table 3).[5,6] Changes in gut motility are thought to lead to decreased colonic contractions and water imbalances, which result in hard stools and infrequent defecation.[7,8] Intestinal permeability may be altered when widening of the tight junctions between the intestinal epithelial cells results in an inflammatory response close to nerve fibers throughout the gut epithelium.[9,10] Patients with IBS-C may also exhibit visceral hypersensitivity—that is, enhanced sensitization of afferent nerve pathways within the gut.[9,11] And finally, changes in gut microbiota and other triggers of gut inflammation and immune activation have been proposed as potential pathophysiologic mechanisms.[9,10]

IBS-C puts a significant burden on patients, as was exemplified by the IBS in America survey of 1667 individuals who met the Rome III criteria for IBS-C.[12] The objective of the survey was to explore the attitudes of patients with IBS-C and better understand their experiences living with IBS-C. More than half of the survey participants reported that their symptoms were very or extremely bothersome. When they were asked, "What would you be willing to give up for 1 month of IBS-C symptom relief?" their responses included the Internet (21%), their cell phone (25%), sex (42%), caffeine (58%), and alcohol (62%). In this same survey, 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.

Studies have also demonstrated the negative effect of IBS-C on measures of health-related quality of life (QoL). When a group of patients who had IBS-C was compared with a matched group of patients who did not have IBS-C, the individuals with IBS-C reported significantly poorer health-related QoL (Figure 1).[13] The physical component summary and mental component summary scores were lower, and overall work and activity impairment was greater, in the patients with IBS-C than in the matched comparison group. Other studies have also reported high levels of absenteeism and presenteeism among individuals with IBS.[14-16]

These studies reflect the significant unmet need of patients with IBS-C, a large proportion of whom reportedly do not respond adequately to treatment. The results of an online questionnaire of more than 1300 people with IBS-C, reported in 2018, found that despite treatment with a prescription IBS-C medication, 77% continued to experience residual abdominal and stool-related symptoms.[17] Abdominal bloating/distension was

Table 4. Pharmacologic Treatments Approved by the FDA[24]

Drug	FDA Approval	What is it?
Tegaserod	2002 (reintroduced in 2019 and withdrawn from the market by manufacturer in 2022)	Serotonin (5-HT_4) receptor agonist
Lubiprostone	2006	Chloride channel type II agonist
Linaclotide	2012	GC-C agonists
Plecanatide	2017	
Tenapanor	2019 (initial FDA approval) 2022 (US launch)	NHE3 inhibitor

FDA, US Food and Drug Administration; GC-C, guanylate cyclase-C; NHE3, sodium/hydrogen exchange transporter isoform 3.

the most frequent of the symptoms. The heterogeneous nature of IBS-C, and the large proportion of patients who continue to suffer despite treatment, point to the need for innovative agents with novel mechanisms of action.

Evidence for the Pharmacologic Management of IBS-C

In the United States, 2 organizations have provided evidence-based guidelines for the management of IBS: the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA). The ACG guidelines, which include topics relevant to the diagnosis and management of both IBS-C and IBS-D, suggest "a positive diagnostic strategy as compared to a diagnostic strategy of exclusion be used to improve time to initiating appropriate therapy."[3] This strategy involves a careful history and physical examination and the use of a standard definition to make a diagnosis, with a limited number of diagnostic tests. The AGA guidelines focus specifically on the pharmacologic management of IBS-C, and a separate guideline focuses on the pharmacologic management of IBS-D.[18,19]

The management of IBS-C encompasses a wide range of interventions, including behavioral modifications, nonpharmacologic approaches, and pharmacologic agents. Behavioral modifications include regular exercise, adequate hydration, and sufficient sleep. [4,20,21] Dietary recommendations include avoiding foods known to trigger gastrointestinal symptoms (eg, sodas, fatty or fried foods, spicy foods, and foods containing artificial sugars). Diets should include regular servings of fruits and vegetables. Ensuring that an adequate amount of fiber is included in the diet is also important; when possible, commercially available fibers such as psyllium, which is primarily a soluble fiber, are recommended. Of note, insoluble fibers such as bran fiber may worsen symptoms and are generally not recommended for the management of IBS-C.[22,23] Changing toileting behavior so that the patient is in more of a squatting position (eg, raising the knees above the hips) and limiting time on the toilet to 10 to 15 minutes are recommended.[4,23] The AGA guideline recommends over-the-counter osmotic (eg, PEG) laxatives and fiber (eg, psyllium) as first-line treatments for IBS-C. For patients whose predominant symptom is pain, neuromodulators such as low-dose tricyclic antidepressants (TCAs) should be considered. Selective serotonin reuptake inhibitors (SSRIs) are generally not recommended, given the limited number of studies showing efficacy.[19]

During the past several years, the US Food and Drug Administration (FDA) has approved several agents for the treatment of IBS-C. These relieve both abdominal pain and constipation. Currently, 5 medications are approved by the FDA for the treatment of IBS-C (Table 4).[24]

Sodium/Hydrogen Exchange Transporter Inhibitor

Tenapanor is an inhibitor of the sodium/hydrogen exchange transporter isoform 3 (NHE3), which is expressed on the apical surface of the small intestine and colon and is primarily responsible for the absorption of dietary sodium.[25-27] NHE3 inhibition acts via 3 mechanisms. First, tenapanor decreases the absorption of dietary sodium, so that luminal water content is retained, intestinal transit time is accelerated, and stool is softened. Second, it has been shown in animal models that tenapanor decreases intestinal permeability by narrowing the tight junctions between intestinal epithelial cells.[9,10] Third, it has also been shown in animal models that tenapanor reduces visceral hypersensitivity, a common finding in patients with IBS-C.[9,28] It is important to note that the relevance to humans of the effects seen in animal models is not known. Importantly, tenapanor is locally acting, with minimal systemic absorption.

The efficacy and safety of tenapanor for the treatment of IBS-C were established in 2 placebo-controlled, randomized phase 3 trials, T3MPO-1 and T3MPO-2.[29,30] Patients with IBS-C were randomized to receive tenapanor (50 mg twice daily) or placebo for 12 weeks, followed by a 4-week randomized withdrawal period in T3MPO-1 (606 adults) and 26 weeks in T3MPO-2 (593 adults). Enrollment was restricted to patients with IBS-C who met the Rome III criteria (which were current at the time of study design) and who, at baseline, reported an average weekly stool frequency of 5 or fewer spontaneous bowel movements (SBMs) and 3 or fewer complete spontaneous bowel movements (CSBMs). Other eligibility criteria included a self-reported average weekly stool

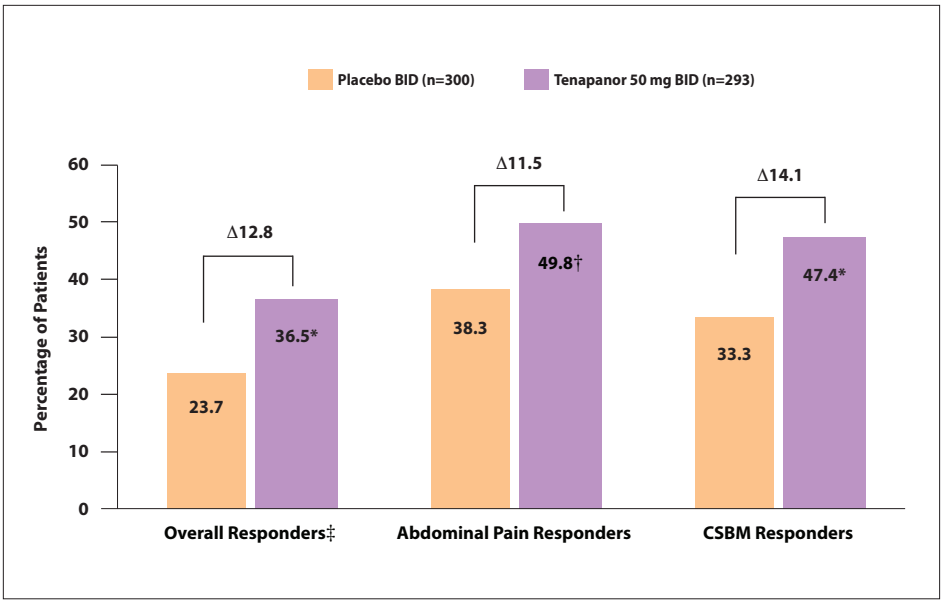

Figure 2. Responder endpoints in T3MPO-2 (26-week trial) with tenapanor.[30]

Primary efficacy endpoint: percentage of overall responders for at least 6 of the first 12 weeks of treatment.

*P<0.001

†P=0.004

‡Overall responder defined as patient with a decrease in average weekly worst abdominal pain of ≥30.0% from baseline AND an increase of at least 1 CSBM from baseline, both in the same week, for at least 6 of the first 12 weeks of treatment.

BID, twice daily; CSBM, complete spontaneous bowel movement.

consistency of BSFS types 1 through 3, an average weekly abdominal pain score of 3 or higher (on a scale of 0 to 10, with 0 indicating no pain and 10 the worst imaginable pain), no liquid stools, and no mushy stools for more than 1 SBM. The primary endpoint was an overall response for 6 or more of the first 12 weeks of treatment; an overall response was defined as a decrease of 30% or more in average weekly worst abdominal pain score and an increase of at least one CSBM from baseline, both in the same week.

In T3MPO-1, a significantly higher percentage of the patients treated with tenapanor than of those who received placebo met the primary endpoint (27.0% vs 18.7%; P=0.020).[29] The percentages of patients with an abdominal pain response and with a CSBM response were also higher in the tenapanor arm than in the placebo arm (44.0% vs 33.1%; P=0.008 and 33.9% vs 29.4%; P=0.270, respectively). The patients treated with tenapanor experienced significantly greater improvements in abdominal symptoms (including abdominal discomfort, bloating, cramping, and fullness) and global IBS treatment measures (including stool consistency and IBS severity) in comparison with the patients treated with placebo.

The results of T3MPO-2 were similar, including those for the primary endpoint of overall response in 6 or more of the first 12 weeks of treatment (36.5% with tenapanor vs 23.7% with placebo; P<0.001) (Figure 2).[30] Considered separately, the abdominal pain responses were 49.8% vs 38.3% (P=0.004), and the CSBM responses were 47.4% vs 33.3% (P<0.001). Reductions in abdominal pain were reported with tenapanor as early as 1 week after the start of treatment, and the tenapanor-treated patients experienced a 54% decrease in abdominal pain from baseline to week 26. Reports of severe abdominal pain showed a 78% reduction from baseline (55%) to week 26 (12%).

In T3MPO-2, a durable response required patients to meet the response criteria for at least 3 of the final 4 weeks of the first 12 weeks of the treatment period. Durable response rates were significantly higher with tenapanor than with placebo; the durable abdominal pain responses were 34.8% vs 26.7% (P=0.028), the durable CSBM responses were 21.2% vs 5.7% (P<0.001), and the durable combined responses were 18.1% vs 5.0% (P<0.001). Tenapanor was associated with significant improvements in the mean change from baseline in the average weekly number of CSBMs over time, as well as in the average weekly abdominal pain score over time. On average, over the 26-week treatment period, the patients treated with tenapanor had 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) as early as 1 week after the start of treatment. Tenapanor was associated with a 41% improvement in the QoL score from baseline to week 26 and with a 3-fold increase in the number of patients reporting the highest QoL scores at the end of treatment.

Diarrhea was more frequently reported with tenapanor than with placebo (14.6% vs 1.7% in T3MPO-1 and 16.0% vs 3.7% in T3MPO-2).[29,30] The onset of diarrhea

was usually within 1 week of the start of treatment and was typically transient and mild to moderate in severity. Other adverse events more frequently reported with tenapanor than with placebo included nausea, abdominal distension, and flatulence.

Guanylate Cyclase-C Agonists

The FDA has approved 2 guanylate cyclase-C (GC-C) agonists, linaclotide and plecanatide, for the treatment of IBS-C. Linaclotide and plecanatide are both peptides that act as selective agonists at the GC-C receptor on the luminal surface of intestinal enterocytes.[31,32] The endogenous ligands for the GC-C receptor promote intestinal secretion in response to a meal, and binding of these peptides results in increased levels of cyclic guanosine monophosphate (cGMP), a second messenger that plays a critical role in the regulation and secretion of intestinal fluid into the intestinal lumen.

Each of the 2 GC-C agonists has been demonstrated to have efficacy in randomized, controlled phase 3 trials. For example, linaclotide showed better efficacy than placebo (33.7% vs 13.9%; $P<0.0001$) in a phase 3 trial in which the primary endpoint was a reduction of 30% or more in worst abdominal pain plus an increase of at least one CSBM weekly, both for 6 or more of 12 treatment weeks.[33] Plecanatide also showed efficacy in comparison with placebo for the same primary endpoint in 2 phase 3 trials (study 1: 30.2% vs 17.8%, $P<0.001$; study 2: 21.5% vs 14.2%, $P=0.009$).[34] Across these phase 3 trials, diarrhea was the most frequently reported adverse event with the 2 peptides (linaclotide and plecanatide).

Chloride Channel Type II Agonist

The prostaglandin E1 derivative lubiprostone activates the intestinal chloride channel type 2 on the apical surface of small intestinal enterocytes, resulting in chloride efflux into the luminal cavity.[35] This process triggers fluid secretion into the luminal cavity, which softens stool and accelerates intestinal transit. In 2 phase 3 trials, the percentage of overall responders was significantly higher in the patients treated with lubiprostone (8 µg twice daily) than in those who received placebo (17.9% vs 10.1%; $P=0.001$).[36] 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 weeks. Nausea (7%) was the most frequently reported adverse event with lubiprostone.

Serotonin (5-HT$_4$) Receptor Agonist

The serotonin (5-HT$_4$) receptor agonist tegaserod is 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; the withdrawal was reportedly based on a business decision and did not reflect the efficacy or safety of this agent.[37]

Conclusion

IBS-C is a common disorder with negative effects on health-related QoL. Currently, 5 agents are approved by the FDA for the treatment of IBS-C, one of which has been withdrawn from the market. Unfortunately, no head-to-head trials have been performed. However, a systematic review and network meta-analysis conducted in 2018 to examine the relative safety and efficacy of FDA-approved agents for the treatment of IBS-C confirmed that each of them was significantly more effective than placebo for decreasing global symptoms.[38] Patients with an inadequate response to fiber and osmotic laxatives (eg, PEG) may benefit from one of the FDA-approved agents that have been shown to relieve both abdominal pain and constipation.

Disclosures

Dr Lembo has performed consulting for Aeon, Ardelyx, Cara Care, Gemelli, Gimoti, Ironwood Pharmaceuticals, Neurogastrx, OrphoMed, Takeda, and Vibrant Pharma; and has stock in Allurion, Bristol Myers Squibb, Johnson & Johnson.

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