

## Mechanism of Action Considerations in the Management of IBS-C



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## Patient Case

A 23-year-old biology PhD candidate presents for further evaluation of her gastrointestinal (GI) symptoms (Table 1). These symptoms have been present for the past 3 years and were not triggered by any specific precipitants. She reports recurrent achy abdominal pain radiating throughout her lower abdomen. This pain usually develops after lunch and is associated with progressive abdominal bloating and distention. She is frustrated that she often appears “9 months pregnant” by dinnertime. She has a daily bowel movement, but the stools are “rock hard” and associated with significant straining and a sensation of incomplete evacuation. There is mild improvement in her pain with passage of minimal amounts of stool, but the pain recurs and is sometimes worse after she consumes her next meal.

The patient was evaluated by her primary care physician, who obtained a complete blood count, comprehensive metabolic panel, and thyroid studies, all of which were normal. She initially attempted to alleviate her symptoms with gluten- and lactose-free diets but found these ineffective. A low fermentable, oligo-, di-, monosaccharides and polyols (FODMAP) diet led to minimal improvement of her abdominal bloating and distention but no improvement in her bowel symptoms.

Fiber worsened her overall symptom profile. Polyethylene glycol (PEG) 3350 up to 3 times per day led to the passage of 5 to 6 liquid bowel movements per day and persistent sensations of incomplete evacuation. PEG also worsened her bloating. At the advice of a friend, she also tried self-guided cognitive behavioral therapy and gut-directed hypnosis via digital applications, but these were unsuccessful. Given her lack of response to these interventions, she was referred to the Gastroenterology department for further recommendations.

Upon initial evaluation she denies any significant acute changes in her symptoms. She is frustrated by her lack of response to—and, in many instances, worsening of symptoms with—previously recommended therapies. She denies nocturnal symptoms, weight loss, bleeding, or a family history of GI disorders. She has no other medical issues and is not taking any medication. On physical examination she does not appear anxious. There is evidence of appropriate diaphragmatic breathing, her abdomen is symmetric yet distended and tympanic, and there is no pain with palpation. There are no other localized findings. Digital rectal examination reveals normal resting tone and squeeze pressures. With Valsalva, there is appropriate perineal descent, relaxation of the anal sphincters, and efficient expulsion of the examination finger.

### On the Cover

Light micrograph of a cross section of a colon.

Credit: Alvin Telser / Science Source

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

<b>Patient History</b>	<p>A 23-year-old female with persistent abdominal pain and constipation over the past 3 years</p> <ul style="list-style-type: none"> <li>• <b>Abdominal symptoms:</b> recurrent achy abdominal pain radiating throughout lower abdomen, usually develops after lunch and is associated with progressive abdominal bloating and distention (“appears ‘9 months pregnant’ by dinnertime”); mild improvement in pain with passage of minimal amounts of stool, but the pain recurs and is sometimes worse after she consumes her next meal</li> <li>• <b>Bowel-related symptoms:</b> daily bowel movements with “rock hard” stools, significant straining, incomplete evacuation</li> <li>• <b>Patient report:</b> no blood in stool, weight loss, or nocturnal symptoms</li> <li>• <b>Previous medical history:</b> none</li> <li>• <b>Family history:</b> no GI disorders</li> <li>• <b>CBC, CMP, and TSH tests:</b> normal</li> <li>• <b>Previous interventions:</b> diets (gluten-free, lactose-free, and low-FODMAP); PEG 3350 up to 3 times daily; self-guided cognitive behavioral therapy and gut-directed hypnosis</li> <li>• <b>Current medications:</b> none</li> <li>• <b>Impact on QoL:</b> difficulty completing experiments in her laboratory because she spends multiple hours each day in the restroom trying to evacuate; missed project deadlines; worried about losing funding</li> </ul>
<b>Initial Clinical Presentation</b>	<ul style="list-style-type: none"> <li>• Moderate abdominal distention and is tympanitic</li> <li>• No pain with abdominal palpation</li> <li>• <b>Digital rectal examination:</b> normal resting tone and squeeze pressures</li> <li>• <b>Valsalva:</b> appropriate perineal descent, relaxation of the anal sphincters, and efficient expulsion of the examination finger</li> </ul>
<b>Diagnosis</b>	IBS-C
<b>Patient Goals</b>	<ul style="list-style-type: none"> <li>• Improved QoL</li> <li>• Improvement in both abdominal and bowel symptoms</li> <li>• Interested in newer therapies</li> </ul>

CBC, complete blood count; CMP, comprehensive metabolic panel; FODMAP, fermentable, oligo-, di-, monosaccharides and polyols; IBS-C, irritable bowel syndrome with constipation; PEG, polyethylene glycol; QoL, quality of life; TSH, thyroid-stimulating hormone.

A confident diagnosis of irritable bowel syndrome with constipation (IBS-C) is provided and no further diagnostics are recommended. Upon further discussion, the patient emphasizes that her goals of therapy are improved quality of life (QoL), which she believes can be achieved only if she experiences improvement in both her abdominal and bowel symptoms. She is having difficulty completing experiments in her laboratory because she spends multiple hours each day in the restroom trying to evacuate. She has missed project deadlines and is worried that she may lose funding. She is specifically interested in newer therapies and, as a scientist, wants to discuss the biological plausibility and mechanisms of action of these treatments.

### Overview of IBS-C

Irritable bowel syndrome (IBS) is a chronic and typically debilitating disorder characterized by abdominal pain and disordered defecation.<sup>1</sup> The fourth iteration of the Rome Diagnostic Criteria for Irritable Bowel Syndrome (Rome IV criteria), published in 2016, defines IBS as a gut-brain interaction disorder in which recurrent abdominal pain presents on average at least 1 day per week and is associated with two or more of the following criteria: related to defecation; associated with a change in the frequency of stool; associated with a change in the form (appearance) of stool.<sup>2</sup> These symptoms must have been present for the previous 3 months with onset at least 6 months prior to making a formal diagnosis.

The Rome IV criteria have been recognized to require extended periods of symptom presence and high symptom frequencies, which interfere with their real-world applicability. Consequently, the Rome Foundation recently proposed modified diagnostic criteria more suitable for clinical practice.<sup>3</sup> In the modified criteria, a clinical diagnosis of IBS can be made if the nature of the symptoms aligns with the Rome IV diagnostic criteria, the symptoms are bothersome (evidenced by interfering with daily activities, requiring attention, causing worry, or causing decreased QoL), and the practitioner is confident that other potential diagnoses have been confidently eliminated.

There are 4 recognized 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).<sup>1</sup> The determination of a patient’s IBS subtype occurs with application of the Rome IV criteria in conjunction with the Bristol Stool Form Scale (BSFS).<sup>4</sup> A diagnosis of IBS-C is made when BSFS types 1 and 2 are present more than 25% of the time, whereas types 6 and 7 are present with less than 25% of bowel movements.

**Table 2.** Diagnostic Criteria for IBS-C<sup>1-4</sup>

<b>IBS</b>	<p>Rome IV Diagnostic Criteria</p> <p>Disorder of gut-brain interaction in which abdominal pain recurs on average at least 1 d/wk PLUS</p> <p>≥2 of the following*:</p> <ul style="list-style-type: none"> <li>• Related to defecation</li> <li>• Associated with a change in the frequency of stool</li> <li>• Associated with a change in the form (appearance) of stool</li> </ul>
<b>IBS-C</b>	<ul style="list-style-type: none"> <li>• BSFS type 1 or 2: &gt;25% of bowel movements</li> <li>• BSFS type 6 or 7: &lt;25% of bowel movements</li> <li>• Hallmark symptoms: abdominal pain and constipation</li> <li>• Medical history and physical examination including evaluation of gastrointestinal symptoms to identify alarm signs:                             <ul style="list-style-type: none"> <li>– New symptoms and age older than 50 years</li> <li>– Unintended weight loss</li> <li>– Hematochezia</li> <li>– Symptoms that awaken the patient at night</li> <li>– Acute or rapidly progressing symptoms</li> <li>– Family history of colorectal cancer, celiac, or inflammatory bowel disease</li> </ul> </li> </ul>

\*Criteria met for the previous 3 months with onset of symptoms at least 6 months before the diagnosis.

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

IBS is considered a highly prevalent condition, with 4.7% of Americans meeting the Rome IV criteria.<sup>5</sup> In a population-based survey of individuals in the United States meeting Rome IV criteria, approximately 30% met the criteria for IBS-C, approximately 35% met the criteria for IBS-D, and another 30% met the criteria for IBS-M.<sup>5</sup> IBS is more common in women and among individuals younger than 50 years of age.<sup>1</sup>

There are no validated diagnostic tests or biomarkers for IBS-C, but IBS still requires a positive diagnostic strategy rather than a diagnostic strategy of exclusion.<sup>1</sup> The diagnosis is made following a thorough medical history and a physical examination.<sup>6</sup> The presence of alarm signs (eg, new symptoms in a patient older than 50 years, unintended weight loss, hematochezia, symptoms that awaken the patient at night, acute or rapidly progressing symptoms, and a family history of colorectal cancer, celiac, or inflammatory bowel disease) suggest a differential diagnosis (Table 2).<sup>7,8</sup>

Abdominal pain and hard stools are the hallmark

**Table 3.** Multifactorial Pathophysiology of IBS-C<sup>9-14</sup>

<b>Changes in gut motility and water imbalances</b> (resulting in hard stools and decreased defecation)
<b>Aberrant microbiome-immune interactions</b>
<b>Alterations in gut permeability</b> (arising from loss of intercellular tight junctions and reduced transepithelial electrical resistance) inducing inflammatory and hyper visceral responses

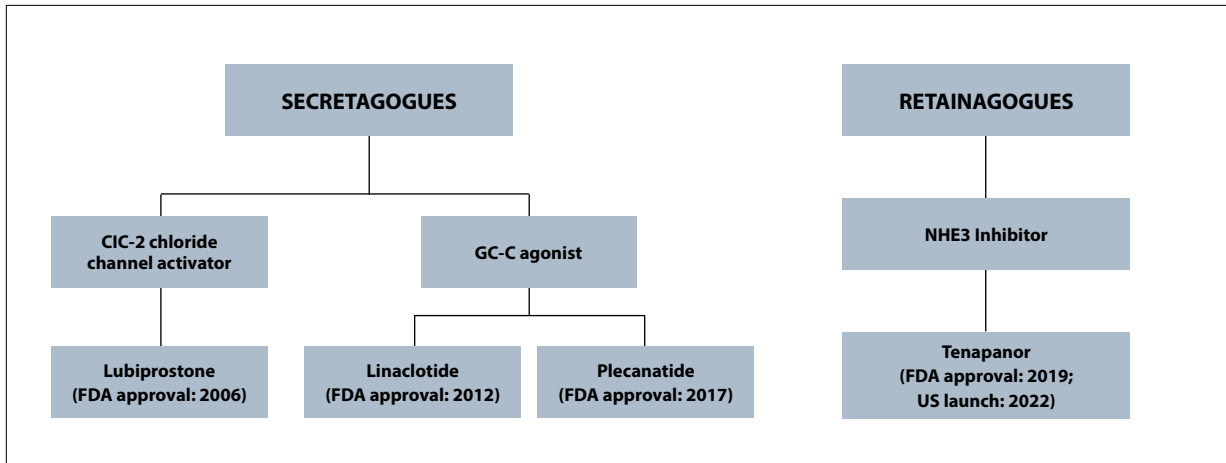
IBS-C, irritable bowel syndrome with constipation.

symptoms of IBS-C; however, many patients tend also to experience other abdominal (discomfort, bloating) and bowel-related (infrequent stools, straining, sensations of incomplete evacuation) symptoms. The pathophysiology of IBS-C is multifactorial (Table 3).<sup>9-14</sup> Hard stools and decreased defecation may be attributed to changes in gut motility and water imbalances.<sup>11,12</sup> Aberrant microbiome-immune interactions may also occur with alterations in gut permeability (arising from loss of intercellular tight junctions and reduced transepithelial electrical resistance) inducing inflammatory and hyper visceral responses.<sup>13,14</sup> Other potential mechanisms, although likely, have yet to be elucidated.

The symptoms experienced by patients with IBS-C can result in a significant QoL burden. In the IBS in America survey, more than one-half of respondents stated that their symptoms were very or extremely bothersome.<sup>15</sup> When asked what they would be willing to give up for 1 month of IBS-C symptom relief, responses included the internet (21%), their cell phones (25%), sex (42%), caffeine (58%), and alcohol (62%). Patients with IBS-C were more likely to report feelings of self-consciousness, sex avoidance, difficulty concentrating, and inability to reach their full potential.

Further data from the IBS in America survey revealed that patients with IBS-C continued to experience symptoms despite an increase in the number of available therapies.<sup>16</sup> Among all patients with IBS-C, approximately 77% reported trying over-the-counter products before presenting to a health care provider. Constipation (77%) and abdominal pain (76%) were the primary symptoms leading patients to seek medical care, but abdominal discomfort (64%), bloating (43%), straining (39%), hard and lumpy stools (36%), and infrequent defecation (37%) were also common indications. Of all IBS-C patients surveyed, only approximately one-quarter reported being very satisfied with treatment. Notably, this survey was conducted in 2015, prior to the approval of multiple currently available therapies by the US Food and Drug Administration (FDA).

Results from the BURDEN IBS-C study published in 2018 echoed that health care providers shared their



**Figure 1.** Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C<sup>22-25</sup>

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

patients' frustrations with available IBS-C treatments.<sup>17</sup> Approximately 79% of health care providers were not satisfied or not completely satisfied with currently available prescription options. Again, note that this survey was conducted in 2016 and early 2017, when fewer FDA-approved agents were available. The top-rated challenges reported by health care providers included inadequate response rates and treatment adherence or compliance issues.

### Laxatives in the Management of IBS-C

The rationale for the use of laxatives to treat the symptom of constipation in IBS-C is twofold: increasing the frequency of stools while improving stool consistency.<sup>18</sup> Although constipation relief has been shown to lead to modest improvement in abdominal pain, patients with IBS-C often continue to experience abdominal symptoms while taking laxatives.<sup>19</sup> Two types of laxatives are commonly used in clinical practice in the management of IBS-C: osmotic and stimulant.

Osmotic laxatives, including PEG, magnesium, and nonabsorbable sugars, promote colonic fluid and electrolyte secretion. As a result, osmotic laxatives induce softer stools and increase bowel movement frequency. However, these therapies have not been validated to improve abdominal symptoms.<sup>20</sup> Given a lack of evidence from randomized clinical trials that PEG derivatives can improve abdominal symptoms, the American College of Gastroenterology (ACG) guidelines recommend against its use for relieving global IBS symptoms.<sup>1</sup> In contrast, the American Gastroenterological Association (AGA) guidelines suggest using PEG laxatives in patients with IBS-C, noting that although PEG has been shown to improve

symptoms of constipation, more studies are needed to better determine the ability of PEG to treat abdominal pain.<sup>21</sup>

Stimulant laxatives work to increase GI motility by enhancing intestinal contractility and promoting fluid and electrolyte secretion into the colon. Stimulant laxatives include anthraquinones (such as senna, cascara, and aloe) and diphenylmethane agents (including bisacodyl and sodium picosulfate). However, although stimulant laxatives improve constipation symptoms, they are predominantly used for acute relief. Further, there is a lack of randomized clinical trials evaluating these agents in patients with IBS-C.<sup>20</sup>

### Mechanisms of Action of the Pharmacologic Agents Used in the Management of IBS-C

Although over-the-counter laxatives can bring patients some relief of their bowel symptoms, they have little effect on abdominal pain, discomfort, or bloating—symptoms that significantly affect the QoL of individuals with IBS-C. Often these are the symptoms ultimately prompting patients to present to clinicians for treatment. There are now several FDA-approved options available for treating IBS-C (Figure 1 and Table 4).<sup>22-32</sup> The first of these to gain FDA approval was lubiprostone in 2006, and this drug was approved specifically for women.<sup>22</sup> This was followed by the approval of linaclotide in 2012 and plecanatide in 2017.<sup>23,24</sup> The most recently approved drug for IBS-C was tenapanor in 2019.<sup>25</sup> Tegaserod, a serotonergic agent, was approved in 2002 but withdrawn because of concerns about potential cardiovascular toxicities, then reintroduced and recently again voluntarily withdrawn from the market in 2022 owing to business decisions and not the safety or efficacy profile of the agent.<sup>33</sup>



**Table 4.** Currently Available FDA-Approved Agents With Indications for the Treatment of IBS-C

Agent	MOA	Pivotal efficacy data	Toxicity profile	Guideline recommendations <sup>1,21</sup>
<b>Lubiprostone<sup>26</sup></b> (FDA approval: 2006)	<b>Secretagogue</b> ClC-2 chloride channel activator	<u>Combined analysis of 2 phase 3 trials</u> Overall responder status <sup>a</sup> : 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)	<b>ACG:</b> chloride channel activators are recommended to treat global IBS-C symptoms (strong recommendation)  <b>AGA:</b> suggests using in patients with IBS-C (conditional suggestion)
<b>Linaclotide<sup>27,28</sup></b> (FDA approval: 2012)	<b>Secretagogue</b> GC-C agonist	<u>26-week phase 3 study</u> FDA overall response endpoint <sup>b</sup> : 33.7% vs 13.9% with placebo; $P<$ .0001  <u>12-week phase 3 study</u> FDA overall response endpoint <sup>b</sup> : 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	<b>ACG:</b> GC-C agonists are recommended to treat global IBS-C symptoms (strong recommendation)  <b>AGA:</b> suggests using in patients with IBS-C (strong recommendation)
<b>Plecanatide<sup>29</sup></b> (FDA approval: 2017)	<b>Secretagogue</b> GC-C agonist	<u>Study 1</u> FDA overall response endpoint <sup>b</sup> : 30.2% (3 mg) and 29.5% (6 mg) vs 17.8% with placebo; $P<$ .001  <u>Study 2</u> FDA overall response endpoint <sup>b</sup> : 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)	<b>ACG:</b> recommended to treat global IBS-C symptoms (strong recommendation)  <b>AGA:</b> suggests using in patients with IBS-C (conditional suggestion)
<b>Tenapanor<sup>30-32</sup></b> (FDA approval: 2019; US launch: 2022)	<b>Retainagogue</b> NHE3 inhibitor	<u>T3MPO-1</u> FDA overall response endpoint <sup>b</sup> : 27.0% vs 18.7% with placebo; CMH $P=$ .020 <sup>c</sup>  <u>T3MPO-2 (26-week study)</u> FDA overall response endpoint <sup>b</sup> : 36.5% vs 23.7% with placebo; CMH $P<$ .001 <sup>c</sup>	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)	<b>ACG:</b> not reviewed  <b>AGA:</b> suggests using in patients with IBS-C (conditional suggestion)

ACG, American College of Gastroenterology; AE, adverse event; AGA, American Gastroenterological Association; 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.

<sup>a</sup>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.

<sup>b</sup>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.

<sup>c</sup>Cochran-Mantel-Haenszel [CMH]  $P$  value.

Each of these approved options has a different mechanism of action (MOA), providing potential alternatives for patients (Figure 1). Because of a lack of head-to-head trials, their comparative efficacies remain unknown. Black and colleagues conducted a network meta-analysis of randomized controlled trials of these agents and found that all were superior to placebo for the treatment of global IBS-C symptoms, with similar efficacy among individual drugs and dosages for most endpoints.<sup>34</sup> Nelson and colleagues conducted a network meta-analysis comparing the efficacy of FDA-approved agents for IBS-C with respect to abdominal bloating and found that all were superior to placebo, also with indirect comparisons revealing no significant differences between drugs.<sup>35</sup> As a result, clinicians continue to face treatment selection decisions that should be individualized, taking into account the patient's predominant symptoms, the safety and tolerability of the therapeutic, as well as cost and coverage considerations.

### Secretagogues

Secretagogues, as their name implies, cause increased secretion of chloride and bicarbonate ions into the intestinal lumen via activation of receptors located in the apical membranes of the epithelial cells lining the intestinal lumen. This increase in the concentration of luminal solutes leads to water secretion, in turn accelerating colonic transit, improving stool consistency, and increasing bowel movement frequency.<sup>20</sup> Three secretagogues are FDA-approved for IBS-C and can be grouped into 2 classes: chloride channel activators (lubiprostone) and guanylate cyclase-C (GC-C) agonists (linaclotide and plecanatide).

**Chloride Channel Activators** Lubiprostone is a prostaglandin E1 derivative that specifically activates CIC-2 chloride channels located on the apical membranes of epithelial cells lining the intestine.<sup>36</sup> Lubiprostone is indicated for the treatment of IBS-C in women at least 18 years of age; other FDA-approved indications include chronic idiopathic constipation (CIC) in adults and opioid-induced constipation in adult patients with chronic noncancer pain.<sup>22</sup>

A combined analysis of 2 phase 3 trials examined the efficacy and safety of lubiprostone in patients with IBS-C. Both trials randomized patients to lubiprostone (8 µg twice daily) or placebo, each administered for 12 weeks.<sup>26</sup> The primary efficacy endpoint for both studies (and the combined analysis) was overall responder status determined from symptom relief assessed weekly and defined as monthly responders for at least two of 3 months.

In the combined analysis, a significantly greater number of overall responders was reported in the lubiprostone group vs the placebo group (17.9% vs 10.1%;  $P=.001$ ).<sup>26</sup> The magnitude of overall response also increased over time

in favor of lubiprostone (10.8%, 18.3%, and 22.0% with lubiprostone in months 1, 2, and 3 vs 7.5%, 11.4%, and 14.5% with placebo, respectively). Compared with non-responders, overall responders achieved greater improvements in symptom relief, including abdominal discomfort or pain, bloating, constipation severity, stool consistency, and straining ( $P<.001$  for all symptoms). There was a trend in improved IBS-QoL with lubiprostone compared with placebo at week 12, but this did not achieve statistical significance ( $P=.066$ ). GI-related events were the most frequently occurring adverse events and included nausea, diarrhea, and abdominal distension. Across the 2 studies these were reported with similar incidence, as were rates of discontinuation due to adverse events (4.7% to 5.1% of lubiprostone-treated patients and 4.6% to 7.7% of placebo-treated patients).

**GC-C Agonists** Two GC-C agonists, linaclotide and plecanatide, are FDA approved for the treatment of IBS-C and CIC in adults.<sup>23,24</sup> Signaling through the GC-C receptor on the apical membranes of the intestinal epithelial cells regulates the normal physiological functioning of the GI tract, and its activation is important in fluid and ion homeostasis, maintenance of the intestinal barrier, reducing inflammation, and visceral pain signaling.<sup>37</sup> A role for GC-C agonists in the management of abdominal pain is indeed being further elucidated, as animal models have demonstrated that GC-C activation regulates visceral sensory afferent neurons (colonic nociceptors) located within the intestinal submucosa.<sup>38</sup> The pharmacology of these 2 GC-C agonists differs slightly; the activity of linaclotide is pH-independent and thus active throughout the GI tract with equivalent affinity for GC-C receptors in the small intestine and colon, whereas plecanatide has a pH-dependent conformation and is thus most active in the acidic environment of the small intestine.<sup>20</sup>

Linaclotide (290 µg once daily) was evaluated for the treatment of patients with IBS-C in 2 phase 3 trials. The first was a 26-week, randomized, double-blind, placebo-controlled trial.<sup>27</sup> This study included several primary endpoints, including the FDA's endpoint for IBS-C response. Significantly more patients in the linaclotide arm achieved this FDA combined endpoint compared with the placebo arm (33.7% vs 13.9%;  $P<.0001$ ). When each criterion of the FDA endpoint was evaluated independently, both showed improvement with linaclotide compared with placebo (48.9% vs 34.5% for the pain responder criterion and 47.6% vs 22.6% for the complete spontaneous bowel movement [CSBM] responder criterion). Diarrhea was reported at a higher incidence with linaclotide vs placebo (19.7% vs 2.5%;  $P<.0001$ ) and was the primary reason for discontinuation.

In a second phase 3 study, patients with IBS-C

received linaclotide (290 µg once daily) or placebo over 12 weeks (followed by a subsequent 4-week randomized withdrawal period).<sup>28</sup> The FDA combined endpoint was achieved by more patients in the linaclotide arm (33.6%) than the placebo arm (21.0%;  $P < .0001$ ). Linaclotide-treated patients experienced improvements vs placebo in each individual criterion (50.1% vs 37.5%,  $P = .0003$ , for the abdominal pain criterion; 48.6% vs 29.6%,  $P < .0001$ , for the CSBM responder criterion). Diarrhea was also the most frequently reported adverse event, leading to discontinuation in 5.7% of patients in the linaclotide arm compared with 0.3% of patients in the placebo arm.

Two phase 3 trials were also performed to assess the efficacy and safety of plecanatide for the treatment of IBS-C. In both studies patients were randomized in a 1:1:1 fashion to 12 weeks of treatment with placebo or plecanatide 3 mg or 6 mg.<sup>29</sup> Both studies used the FDA interim endpoint for IBS-C trials. In the first study, 30.2% and 29.5% of patients in the plecanatide 3 mg and 6 mg arms, respectively, achieved the primary endpoint, compared with 17.8% of patients in the placebo arm ( $P < .001$  for each dose vs placebo). In the second study, 21.5% and 24.0% of patients in the plecanatide 3 mg and 6 mg arms, respectively, achieved the primary endpoint, compared with 14.2% of patients in the placebo arm ( $P = .009$  for the 3 mg dose and  $P < .001$  for the 6 mg dose, respectively, vs placebo). Diarrhea was also the most frequently reported adverse event with plecanatide, occurring in 4.3% of patients receiving plecanatide 3 mg and 4.0% of patients receiving plecanatide 6 mg (vs 1.0% in the placebo group). More patients discontinued therapy in the plecanatide arms combined than in the placebo arm (2.3% vs 0.4%).

### ***Retainagogues: Sodium/Hydrogen Exchanger Isoform 3 Inhibitors***

Tenapanor is a first-in-class locally acting inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3), with an MOA distinct from secretagogues. NHE3 is an antiporter responsible for absorption of dietary sodium and is expressed on the apical surface of the epithelial cells lining the small intestine and colon.<sup>39</sup> Tenapanor-mediated inhibition of NHE3 results in 3 actions. The first is a decrease in the absorption of dietary sodium, causing retention of water content in the intestinal lumen that leads to acceleration of intestinal transit. The second is a reconstitution of the tight junctions between intestinal epithelial cells resulting in decreased intestinal permeability, and the third, antagonism of transient receptor potential vanilloid 1 (TRPV<sub>1</sub>) channels.<sup>13,14,40</sup> The latter 2 actions are hypothesized to be responsible for the reduction in visceral hypersensitivity and improvement in abdominal symptoms seen in the phase 3 trials. These changes, however,

are based on data from preclinical animal model studies.

T3MPO-1 and T3MPO-2, 2 placebo-controlled, randomized, phase 3 studies, were conducted to investigate the efficacy of tenapanor (50 mg twice daily) vs placebo in patients with IBS-C.<sup>30,31</sup> T3MPO-1 was a 12-week treatment study followed by a 4-week randomized withdrawal period. T3MPO-2 was a 26-week continuous treatment trial. The primary endpoint in both trials was the FDA combined endpoint, which was the same endpoint utilized in the linaclotide and plecanatide studies.

In T3MPO-1, a significantly greater percentage of individuals consuming tenapanor met the FDA combined endpoint compared with placebo (27.0% vs 18.7%; Cochran–Mantel–Haenszel [CMH]  $P = .020$ ).<sup>30</sup> Whereas the abdominal pain response was significantly improved with tenapanor compared with placebo (44.0% vs 33.1%; CMH  $P = .008$ ), the CSBM response rates were similar between the 2 cohorts (33.9% vs 29.4%; CMH  $P = .270$ ).

Similar results for the FDA endpoint were seen in T3MPO-2, with 36.5% of patients treated with tenapanor and 23.7% of patients treated with placebo, respectively, achieving the FDA combined endpoint (CMH  $P < .001$ ).<sup>31</sup> Significant improvements in favor of tenapanor were also identified for both abdominal pain (49.8% vs 38.3%; CMH  $P = .004$ ) and CSBM responses (47.4% vs 33.3%; CMH  $P < .001$ ). In T3MPO-2, significant improvements in abdominal pain occurred as early as 1 week after initiating treatment, and abdominal pain was found to have decreased by 54% from baseline at week 26 in the tenapanor arm.

Diarrhea was the most common adverse event in both studies and was higher in the tenapanor arm than placebo arm (14.6% vs 1.7% in T3MPO-1 and 16.0% vs 3.7% in T3MPO-2).<sup>30,31</sup> Diarrhea onset was characterized as rapid (within the first week of treatment), transient, and mild to moderate in severity. A 1-year open-label safety study (T3MPO-3) revealed that tenapanor was well tolerated with no new safety signals and a 2.1% rate of discontinuation due to adverse events (primarily diarrhea).<sup>32</sup>

### **Conclusion**

A range of FDA-approved agents is now available for the treatment of IBS-C. Differing MOAs may be beneficial for individual patients, but in the absence of diagnostic tests providing insight into the underlying etiology of their symptoms, MOA-focused use remains empirical. In the absence of head-to-head trials, these pharmacologic agents are generally regarded as interchangeable, but different MOAs provide multiple opportunities for symptom relief.<sup>41</sup> Thus practitioners now have the ability to alter treatment by utilizing differing MOAs for unresponsive patients.



## Disclosures

Dr Brenner is a speaker, advisor, and consultant and has participated in educational programs for American Gastroenterological Association (AGA), Anji Pharmaceuticals, Ardeyx, Inc., Continuing Education Alliance, LLC, Continuing Education Company, Inc., Elsevier, Inc., Enova International, Focus Medical Communications, LLC, GI Health Foundation, Gemelli Biotech, Ironwood Pharmaceuticals, Inc., Mahana Therapeutics, Inc., MedForce, Inc., Meetings & Events International, Pri-Med Institute, LLC, Primary Care Education Consortium, RedHill Biopharma Ltd, Salix Pharmaceuticals, Inc., Tactical Advantage Group, University of California, Los Angeles (UCLA), and WebMD, LLC.

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