Focus on Pharmacotherapy for Irritable Bowel Syndrome with Constipation

Joy J. Liu, MD, Darren M. Brenner, MD*

KEYWORDS

• Irritable bowel syndrome • IBS-C • Constipation • Treatment • Pharmacotherapy

KEY POINTS

- Irritable bowel syndrome with constipation (IBS-C) is a disorder characterized by abdominal pain associated with the passage of hard, lumpy stools.
- Multiple effective FDA-approved therapies are now available for treating global IBS-C symptoms.
- Some national gastroenterology societies suggest that over-the-counter laxatives should not be used to treat IBS-C given their lack of ability to improve abdominal symptoms.

INTRODUCTION

Irritable bowel syndrome (IBS) with constipation (IBS-C) is a disorder of gut-brain interaction currently defined by the Rome IV criteria as abdominal pain occurring greater than or equal to 1 d/wk associated with alterations in pain perception with defecation, and/or changes in stool form, and/or frequency.[1] IBS is further categorized by predominant stool texture using the Bristol Stool Form Scale (BSFS). Patients with IBS-C report that greater than one-quarter of their stools are BSFS 1 to 2 (hard/lumpy) in texture and less than 25% are BSFS 6 to 7 (loose/watery) (**Fig. 1**). Recent studies suggest that IBS affects 4.6% of the US population and IBS-C accounts for approximately 30% of these diagnoses.[2–4]

IBS-C is distinguished from functional constipation (FC) by the Rome IV definitions because most experts now consider them to be similar disorders along a spectrum of symptoms.[5] Rome IV concedes that individuals with IBS or FC can experience pain; however, pain serves as the sine qua non symptom of the former but is not predominant in the latter. Furthermore, individuals diagnosed with FC should not meet criteria for IBS-C. There is substantial clinical overlap and individuals may alternate between

Division of Gastroenterology/Hepatology, Department of Medicine, Northwestern University, 676 North St Clair Street, Suite 1400, Chicago, IL 60611, USA
* Corresponding author.
E-mail address: darren.brenner@nm.org

Gastroenterol Clin N Am 50 (2021) 639–653
https://doi.org/10.1016/j.gtc.2021.04.004
gastro.theclinics.com

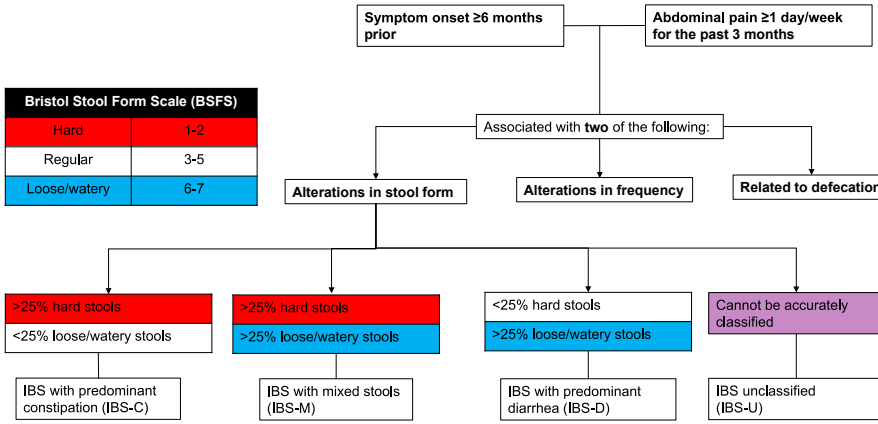

Fig. 1. Classification of irritable bowel syndrome.

IBS-C and FC at different points in their lives.[5] As such, it is not surprising that many recently Food and Drug Administration (FDA)-approved therapeutics for constipation are approved and have proven effective for both disorders.[6]

The methodology used in randomized controlled trials (RCTs) to evaluate the efficacy of pharmaceuticals for treating IBS-C has evolved over the past two decades.[7] More recent trials have consistently used Rome criteria for inclusion, and in 2012, the FDA provided guidance on specific end points. Currently, patients must meet an overall responder end point defined as a weekly average of greater than or equal to 30% improvement in abdominal pain plus an increase of at least one complete spontaneous bowel movement (CSBM) per week compared with baseline during the same week for greater than or equal to 50% of a 12-week trial.[8] Although this end point may seem arbitrary, it correlates well with a positive clinical response.[9,10] Data on primary end points, outcomes, and adverse effects from phase III trials for FDA-approved agents to treat IBS-C are found in **Table 1**.

Multiple over-the-counter (OTC) laxatives are used to treat constipation associated with IBS-C; however, data supporting their efficacy are limited or lacking. Whereas many of these agents may improve bowel function (stool frequency, texture, straining) they have minimal impact on abdominal symptoms, such as bloating and pain. Consequently, major gastrointestinal societies are now suggesting against their use and instead recommending other agents with more robust data.[11,12] These include the secretagogues (lubiprostone, linaclotide, prucalopride, tenapanor) and prokinetics (tegaserod). This article reviews the efficacy, safety, and tolerability profiles for each of these agents with a focus on results from their pivotal trials.

OVER-THE-COUNTER LAXATIVES

OTC therapies have been a mainstay of treatment of constipation because they are generally safe, well-tolerated, and cost-effective. Multiple classes of OTCs exist including bulking agents (methylcellulose, psyllium, bran), osmotic laxatives (polyethylene glycol [PEG]), magnesium-containing compounds (magnesium oxide, sulfate, hydroxide), stimulant laxatives (senna, bisacodyl, cascara), and stool softeners (docusate). Although there are varying levels of evidence supporting the use of OTC laxatives for FC, data for IBS-C are sparse.

Table 1
Phase III trial data for agents used to treat IBS-C

Drug	Year of FDA Approval for IBS-C	Primary End Points Studied for IBS-C in Phase III Trials	Primary Outcome	Adverse Effects in Treatment Group
Polyethylene glycol	NA	No data to report	NA	NA
Lubiprostone	2008 in women	Moderate relief in 4/4 wk or significant relief in 2/4 wk per mo in $\geq$ 2/3 mo of study	17.9% (8 μg BID lubiprostone) vs 10.1% (placebo) (P = .001)[20]	Nausea (8%), diarrhea (6%), abdominal distention (2%)
Linaclotide	2012	Combined $\geq$30% reduction from baseline in worst abdominal pain + an increase of at least 1 CSBM/wk from baseline during the same week for $\geq$6/12 wk (FDA overall responder end point)	33.7% (290 μg daily linaclotide) vs 13.9% (placebo) (P < .001)[21] 3.6% (290 μg daily linaclotide) vs 21.0% (placebo) (P < .0001)[27] 60% (290 μg daily linaclotide) vs 48.8% (placebo) (P = .001)[28]	Diarrhea (19.7%)[21] Diarrhea (19.5%)[27] Diarrhea (9.4%)[28]
Plecanatide	2018	Combined $\geq$30% reduction from baseline in worst abdominal pain + an increase of at least 1 CSBM/wk from baseline during the same week for $\geq$6/12 wk (FDA overall responder end point)	26% (3 mg daily plecanatide) vs 16% (placebo) ($P \leq$.009)[30]	Diarrhea (4.3%)
Tenapenor	2019	Combined $\geq$30% reduction from baseline in worst abdominal pain + an increase of at least 1 CSBM/wk from baseline during the same week for $\geq$6/12 wk (FDA overall responder end point)	27% (50 mg BID tenapenor) vs 18.7% (placebo) (P = .02)[35] 36.5% (50 mg BID tenapenor) vs 23.7% (placebo) (P < .001)[36]	Diarrhea (14.66%)[35] Diarrhea (16.04%)[36]

(*continued on next page*)

Table 1
(*continued*)

Drug	Year of FDA Approval for IBS-C	Primary End Points Studied for IBS-C in Phase III Trials	Primary Outcome	Adverse Effects in Treatment Group
Tegaserod	2002 in women, 2019 reapproved in women <65 y of age without a history of cardiovascular ischemic events	Subjective global assessment: Some relief 100% of the time or considerable or complete relief ≥ 50% of the time at the end of 1st and 3rd mo ≥ 30% reduction from baseline in worst abdominal pain + ≥50% increase in SBM frequency (≥1/wk) for ≥6/12 wk	End of 1st mo: 34% (6 mg BID tegaserod) vs 21.3% (placebo) ($P < .001$) End of 3rd mo: 44.1% (6 mg BID tegaserod) vs 36.5% (placebo) ($P < .001$)[40] 36% (6 mg BID tegaserod) vs 24.3% (placebo) ($P < .001$)[40]	Headache (14.2%), abdominal pain (12.3%), diarrhea (8.6%)

Abbreviation: SBM, spontaneous bowel movement.

Although not a medication per se, dietary fiber has proven somewhat effective for treating constipation-related symptoms. Specifically, fibers found in such foods as oat bran, kiwifruit, prunes, mangos, and ficus carica, and the supplement psyllium, can increase stool bulk, decrease colonic transit time, and may have prebiotic effects.[13,14] A 2018 American College of Gastroenterology systematic review concluded that soluble fiber provides overall symptom relief in IBS and the recently published American College of Gastroenterology Clinical Guideline on the management of IBS also suggested the use of soluble, viscous, poorly fermentable fibers (psyllium) as first-line agents for IBS-C.[11,15]

PEG is an osmotic laxative that increases intraluminal water content and is FDA-approved for treating occasional constipation. Two RCTs assessing PEG in IBS-C were small (combined n = 181), heterogeneous, and associated with high risks of bias.[16,17] Neither study evaluated a global symptom end point as its primary outcome. Although data from the larger of the two studies revealed that PEG increased spontaneous bowel movement (SBM) frequency and improved stool texture, it did not improve abdominal pain or bloating.[17] In fact, PEG has the potential to worsen bloating and abdominal discomfort in patients with IBS-C.[18] Based on the current evidence, the American College of Gastroenterology and the Canadian Association of Gastroenterology suggest against using PEG to treat global IBS symptoms. The American Gastroenterological Association and the Mexican Association of Gastroenterology continue to recommend its use; however, the American Gastroenterological Association guideline was last updated in 2014 before FDA approval of many the secretagogue and prokinetic agents (**Table 2**).[19,20]

SECRETAGOGUES

Lubiprostone

Lubiprostone was the first secretagogue approved by the FDA (8 μg twice daily) for the treatment of IBS-C in women greater than or equal to 18 years of age. Lubiprostone is a locally acting prostaglandin E_1 derivative that activates type 2 chloride channels on intestinal epithelial cells resulting in increased intestinal fluid secretion and peristalsis.[21] Animal studies have further suggested that lubiprostone improves visceral hyperalgesia via restoration of the intestinal epithelial barrier and reductions in intestinal permeability, but the precise mechanism of its analgesic effects remains unknown.[22–24]

The most robust data supporting the use of lubiprostone for patients with IBS-C comes from two large phase III studies.[25] In aggregate, 1171 patients who met Rome II criteria for IBS-C were randomized to receive lubiprostone (n = 783), 8 μg, or placebo (n = 388) twice daily for 12 weeks. The primary end point was a predecessor to the current FDA-recommended end point for IBS-C studies. Specifically, to be considered a responder, patients had to endorse either significant or moderate relief of their IBS symptoms for 2/4 or 4/4 weeks of a month, respectively, and maintain this response through at least 2 months of the 3-month study. Furthermore, responders could at no time endorse more than mild worsening of symptoms, discontinue treatment because of a lack of efficacy, or increase consumption of rescue laxatives beyond the amount received at baseline. Overall, a significantly higher percentage of patients consuming lubiprostone met this rigorous primary end point (17.9%) compared with placebo (10.1%) ($P = .001$). There was a delay, however, in achieving this significance until the second (Study 0431; $P = .016$) and third months (Study 0432; $P = .026$) of the individual studies. Lubiprostone also significantly improved multiple secondary outcomes including abdominal pain/discomfort, bloating, stool frequency,

Table 2
Comparison of guidelines for the treatment of IBS-C from North American gastrointestinal societies

	American College of Gastroenterology (2020)	American Gastroenterological Association (2014)	Asociación Mexicana de Gastroenterología (2016)	Canadian Association of Gastroenterology (2019)
Polyethylene glycol	Conditional recommendation against use, low-quality evidence	Conditional recommendation for use, low-quality evidence	Strong recommendation for use, moderate-quality evidence	Conditional recommendation against use, very low-quality evidence
Lubiprostone	Strong recommendation for use, moderate-quality evidence	Conditional recommendation for use, moderate-quality evidence	Strong recommendation for use, moderate-quality evidence (not available in Mexico for IBS-C)	Conditional recommendation for use, moderate-quality evidence
Linaclotide	Strong recommendation for use, high-quality evidence	Strong recommendation for use, high-quality evidence	Strong recommendation for use, high-quality evidence	Strong recommendation for use, high-quality evidence
Plecanatide	Strong recommendation for use, strong-quality evidence	NA	NA	NA
Tenapenor	NA	NA	NA	NA
Tegaserod	Strong/conditional recommendation for use, low-quality evidence (for women <65 y and <1 cardiovascular risk factor who have not responded to secretagogues)	NA	NA	NA

and constipation severity compared with placebo ($P < .001$ for all secondary outcomes). There was a trend toward improvement in overall quality of life (Irritable Bowel Syndrome-Quality of Life; $P = .066$) with significant improvements identified in the subcategories of "body image" and "health worry" by Week 12 ($P \leq .025$). The most common treatment-emergent adverse event (TEAE) reported by patients in the lubiprostone cohort was nausea (8% vs 4% placebo) and serious adverse events were rare. Because more than 90% of the subjects in the pivotal studies were female, FDA approval was only granted for females greater than or equal to 18 years of age.

A subsequent 36-week open-label extension study validated the durability of response and safety profile of lubiprostone.[26] Using the same primary responder definition, response rates to lubiprostone were maintained or increased over time to a maximum 37% to 44% after 10 to 13 months. The significant improvements in secondary end points were also maintained. Lubiprostone remained safe and tolerable with diarrhea (11%) and nausea (11%) most commonly leading to cessation of therapy. No serious adverse events were reported during this extension period.

For purposes of comparisons with other secretagogues, a post hoc analysis was more recently completed, defining "responders" as those experiencing an average weekly pain reduction of greater than or equal to 30% and an increase of at least one SBM per week compared with baseline for greater than or equal to 6 of 12 treatment weeks.[27] This end point is slightly less rigorous than the current FDA-recommended CSBM end point because the latter also accounts for the sensation of incomplete evacuation. However, when the lubiprostone data were collected more than a decade ago, CSBM responses were not recorded. Of the 505 participants included in this analysis (n = 325 lubiprostone, n = 180 placebo), a significantly greater percentage of individuals receiving lubiprostone met the composite end point compared with placebo (26.3% vs 15.3%, respectively; $P = .008$). There were also significant improvements in abdominal pain (36.7% vs 25.5%; $P = .005$) and bloating (32.0% vs 20.4%; $P = .012$), but changes in stool features were not reported.

In a recent high-quality systematic review/meta-analysis, lubiprostone proved more effective than placebo for global IBS-C symptom relief with a number needed to treat (NNT) of 12.5 and relative risk of symptom persistence of 0.91 (95% confidence interval [CI], 0.87–0.95).[12] Rates of treatment-emergent nausea have also been analyzed with a significantly greater number of events reported by individuals receiving twice-daily lubiprostone compared with placebo (10.9% vs 6.4%, respectively; $P<.01$). Rates of nausea may be higher when patients do not take lubiprostone with food. Discontinuation because of nausea, however, was similar between groups.[28] Overall, there is current consensus across North American societal guidelines that lubiprostone, 8 μg twice daily, is effective for relieving global IBS-C symptoms (see **Table 2**).

Guanylate Cyclase-C Receptor Agonists

Guanylate cyclase-C receptor agonists represent a second class of secretagogues that are FDA-approved to treat patients with IBS-C. There are currently two therapeutics in this class (linaclotide and plecanatide), and both have similar mechanisms of action. These small peptides target cuanylate cyclase-C receptors found on the brush border membranes of intestinal epithelial cells. Activation of these receptors leads to downstream production of a secondary mediator, cGMP, which functions intracellularly to induce fluid secretion and accelerate intestinal transit and extracellularly (based on animal model data) to reduce the activity of visceral nociceptive neurons.[29,30] Whereas linaclotide is a pH-independent molecule and functions nonpreferentially in the small intestine and colon, plecanatide is a pH-dependent uroguanylin analogue that exerts its primary effects in the acidic environment of the small intestine.

Three North American phase IIb[31] and phase III trials[26,32] and one multinational study (North America, Oceania, China)[33] have substantiated the efficacy of a once-daily 290-μg dose of linaclotide for treating IBS-C. In each of these trials, linaclotide proved superior to placebo for an array of abdominal and bowel symptoms. The most robust data were captured in two parallel North American phase III randomized, double-blind, placebo-controlled studies.[26,32] In these trials, overall responders were defined using the current FDA guidance end point for IBS-C. Specifically, participants were considered weekly responders if they experienced a greater than or equal to 30% reduction in abdominal pain and an increase of greater than or equal to one CSBM during the same week and an overall responder if the weekly response was met for at least 50% of treatment weeks. In the first study, 33.6% of linaclotide-treated patients (n = 405) achieved this response compared with 21% of the 395 patients receiving placebo ($P<.0001$).[32] Patients who completed all 12 weeks were subsequently eligible to enter a 4-week double-blind randomized withdrawal period. The efficacy of linaclotide was further supported because those remaining on linaclotide (n = 158) maintained their initial response, whereas those rerandomized from placebo to linaclotide (n = 335) experienced improvements in abdominal pain and CSBMs, and those rerandomized from linaclotide to placebo (n = 154) experienced recurrence of their symptoms without evidence of rebound. The results of the second study were comparable, with 33.7% of 402 linaclotide-treated patients achieving the FDA responder end point compared with 13.9% of 403 placebo patients receiving placebo ($P<.0001$).[26] In contrast to the first study, patients in this trial were enrolled a priori to continue double-blinded treatment for 26 weeks and there was no evidence of a decay in response over time. Significant improvements were also noted across a spectrum of predefined secondary abdominal (pain, bloating, discomfort, fullness, cramping) and stool (SBMs, CSBMs, straining, and stool consistency) symptoms and an adequate relief assessment, across both studies. Importantly, these changes were maintained throughout the initial 12-week double-blinded periods in both studies and 26 weeks in the second trial.

The benefits of plecanatide have been established in three high-quality phase IIb/III studies.[34,35] In two identical phase III trials, 2189 individuals were randomized to receive placebo (n = 733), 3-mg plecanatide (n = 728), or 6-mg plecanatide (n = 728) once daily for 12 weeks.[35] Given that 3 mg once daily is the FDA-approved dose, the subsequent data focus on those results. The primary end point in these studies was identical to the FDA responder end point used in the linaclotide trials and was met by 26% of patients receiving 3 mg of plecanatide compared with 16% receiving placebo ($P\leq.009$). Furthermore, a sustained efficacy responder end point not assessed in any previous IBS-C therapeutic trials was established a priori. To be considered a sustained responder, individuals had to qualify as overall responders plus experience improvement in the weekly responder end point during greater than or equal to 2 of the last 4 weeks of the trial. Overall, 24.5% and 15.5% of plecanatide- and placebo-treated patients, respectively, were considered sustained responders ($P < .015$). Similar to linaclotide, significant improvements were recognized for multiple abdominal (pain, bloating cramping, discomfort, fullness) and bowel (CSBMs, SBMs, stool consistency, straining) symptoms with significance compared with placebo achieved during weeks 1 to 2 for all end points and maintained through all subsequent weeks of both trials.

Multiple systematic reviews/meta-analysis have attempted to differentiate the efficacy, safety, and tolerability of these two therapeutics. Compared with placebo, use of linaclotide, 290 μg, yielded a relative risk of failure to respond to therapy of 0.80 (95% CI, 0.76–0.85; NNT = 6)[15,36] and an odds ratio (OR) of response of 2.43

(95% CI, 1.48–3.98; NNT = 6)[37] based on the current FDA composite responder end point. Similarly, plecanatide, 3 mg, had a likelihood of symptom persistence of 0.88 (95% CI, 0.84–0.92; NNT = 10) and an OR of response to treatment of 1.87 (95% CI, 1.47–2.38; NNT = 9).[32,34] Diarrhea was the most common TEAE experienced by patients across the phase III studies. Diarrhea occurred in 20% of individuals receiving 290 μg of linaclotide per day in comparison with 4.3% of those taking 3 mg of plecanatide. There were increased odds of diarrhea with use of either product compared with placebo (linaclotide, 290 μg: OR, 8.02 [95% CI, 5.20–12.37]; plecanatide, 3 mg: OR, 5.55 [95% CI, 1.62–19.00]); however, no significant differences in the rates of diarrhea or withdrawal because of diarrhea have been identified between these two agents.[34] As such, both seem comparably safe, well tolerated, and received strong recommendations for use across US gastrointestinal society guidelines.[11,15,19]

Tenapanor

Tenapanor is a first-in-class sodium-hydrogen ion exchanger-3 receptor inhibitor that reduces sodium absorption from the small intestine and colon secondarily increasing water secretion and decreasing intestinal transit time. In preclinical studies, tenapanor seemed to mediate visceral hypersensitivity via inhibition of TRPV1 receptors. This presumed mechanism requires further validation.[38] Although actively approved for IBS-C it has yet to become commercially available, and clinical trials are ongoing to determine its effect in phosphate management in patients with chronic kidney disease on hemodialysis.

Tenapenor was recently assessed for use in IBS-C in two large phase III studies: T3MPO-1 and T3MPO-2. In both, individuals were randomized to receive 50 mg of tenapanor twice daily or placebo. Similar to the linaclotide trials, patients completing the initial 12-week portion of T3MPO-1 were subsequently transitioned into a 4-week randomized withdrawal period, whereas those enrolled in T3MPO-2 continued to receive blinded therapy for 26 weeks. The primary end point was identical to the FDA end point used in the previous secretagogue studies. In T3MPO-1, 27.0% of those receiving tenapenor (n = 307) achieved this end point compared with 18.7% of those receiving placebo (n = 299) (P = .020).[39] These results were echoed in T3MPO-2 (tenapenor n = 293 [36.5%] vs placebo n = 300 [23.7%]; $P < .001$), with persistence noted at 26 weeks.[40] Durable responder analyses were also reported in both studies with significant improvements favoring tenapanor for individuals meeting the FDA composite weekly end point for greater than or equal to 9 out of 12 weeks plus greater than or equal to 3 of the last 4 weeks of treatment ($P < .001$). During the 4-week randomized withdrawal period of T3MPO-1, expected improvements, reductions, and maintenance of responses were witnessed in the placebo to tenapenor, tenapenor to placebo, and continuation of tenapenor cohorts, respectively. With the exception of straining, significant improvements were achieved in abdominal (pain, discomfort, bloating, cramping, fullness) and bowel symptoms (SBMs, CSBMs, stool consistency) across 12 weeks in T3MPO-1 and 26 weeks in T3MPO-2. Similar to other agents in this class, diarrhea was the most commonly reported adverse event, occurring in 14.6% of tenapanor and 1.7% of placebo-treated patients in T3MPO-1, and 16% and 3.7% of patents in T3MPO-2. One case of diarrhea in T3MPO-2 was defined as serious and believed to be "possibly related" to treatment. T3MPO-3, a single-arm, long-term safety study (52 weeks) comprised of patients from T3MPO-1 and T3MPO-2, validated the initial safety findings with only 2.1% of patients discontinuing therapy for any reason.[41,42]

PROKINETICS

Tegaserod

Tegaserod is the first and only prokinetic agent currently FDA approved for treating IBS-C, specifically women less than 65 years of age with no prior history of cardiovascular ischemic events (angina, myocardial infarction, transient ischemic attack, stroke). It is also the only IBS-C-approved therapeutic with demonstrated symptom improvement in an RCT enrolling individuals with IBS mixed subtype, although it is not approved for this indication.[43]

Prucalopride, a second prokinetic agent, has also been approved, but for the treatment of chronic idiopathic constipation rather than IBS-C.[44] To date, there have been no clinical trials evaluating its efficacy in IBS-C. Tegaserod is a serotonin subtype-4 (5-HT_4) specific agonist that exerts its effects in the enteric nervous system. Activation of 5-HT_4 receptors on neurons in the submucosal and myenteric plexuses directly stimulates secretion and propulsion, and animal studies have suggested that activation of the afferent submucosal neurons may reduce visceral sensitivity. Thus, tegaserod exerts prosecretory and prokinetic effects.

Tegaserod was initially approved in 2002 for treating women with IBS-C but was voluntarily withdrawn from the market in 2007 after it was associated with a small but statistically significant increase in cardiovascular events. It was reapproved in early 2019 at a dose of 6 mg twice daily after two independent adjudications of 29 clinical trials determined that it was safe for use in the currently restricted population.[45]

The initial phase III studies were completed almost two decades ago and based on FDA guidance at that time, the primary end point was a subjective global assessment whereby individuals were considered responders if they rated themselves "considerably" or "completely" relieved greater than or equal to 50% or "somewhat relieved" 100% of the time during the first and last months of the 12-week studies. The results were recently updated post hoc using the same primary outcomes adapted in accordance with the current FDA-approved population.[46] In pooled analyses of four studies, 1386 women less than 65 years of age with no history of cardiovascular ischemic events who received 6 mg of tegaserod twice daily were more likely to experience significant global improvements in symptoms compared with 1366 women who received placebo during both the first 4 weeks and last month of the trials (pooled OR, 1.95 [$P < .001$]; pooled OR, 1.38 [$P < .001$], respectively). In an attempt to draw comparisons with other IBS-C therapies using the current FDA guidance end point, the same data were also reanalyzed using a composite of abdominal pain and stool frequency. Responders were defined as those experiencing a greater than or equal to 30% reduction in weekly abdominal pain intensity and a greater than or equal to 50% increase in stool frequency ($\geq$1/wk) for greater than or equal to 6 of 12 weeks of treatment, and 36.0% of tegaserod-treated patients attained this response in contrast to 24.3% of those receiving placebo ($P < .001$).[45,46]

Given concerns regarding the cardiovascular safety of tegaserod, a pooled safety analysis of 2749 individuals from the aforementioned four trials was also completed.[45] The most common TEAE was headaches occurring in 14.2% of patients receiving 6 mg of tegaserod twice daily compared with 12.1% of control subjects. Importantly, only one (0.1%) patient in the tegaserod cohort experienced a cardiovascular ischemic event TEAE. This patient had preexisting severe three-vessel coronary artery disease and the investigator involved did not believe this event was related to tegaserod. More detailed analyses have further validated the safety of tegaserod. In a population of 9547 tegaserod-treated women less than or equal to 65 years without a history of cardiovascular ischemic disease, the rates of major adverse cardiovascular

Table 3
Prescribing considerations for IBS-C agents

Drug	FDA-Approved Dose for IBS-C	When to Consume
Lubiprostone	8 μg BID	With food and water
Linaclotide	290 μg daily	On empty stomach at least 30 min before first meal of day
Plecanatide	3 mg daily	Any time of day with or without food
Tenapenor	50 mg BID	Immediately before breakfast and dinner
Tegaserod	6 mg BID	At least 30 min before breakfast and dinner

events ranged from 0.1% to 0.3%. In an even more limited population comprised of 7785 of the 9547 women meeting the previous criteria who also had less than or equal to one cardiovascular risk factor (age $\geq$ 55, active tobacco use, body mass index greater than 30 kg/m^2, diabetes mellitus, current hypertension/hyperlipidemia or history of antihypertensive/hyperlipidemic use) the rate of major adverse cardiovascular events approached 0.01%.[47,48]

Tegaserod is currently being marketed as a second-line agent for IBS-C. That said, a high percentage of patients with IBS-C still qualify to use it because a recent US population-based survey revealed that 91% of patients with IBS-C are less than 65 years of age and more than two-thirds are female.[5] Importantly, tegaserod works differently than the secretagogues, affording potential benefits via an alternative mechanism of action for refractory patients.

Comparison of Therapies

Despite the proven efficacy of the agents previously discussed, a paucity of comparative effectiveness trials limits the ability to derive stepwise treatment algorithms. Until such time as these studies are completed, we rely on meta-analyses and clinical guidelines to assist in directing treatment decisions. In a recent meta-analysis of 18 RCTs comparing lubiprostone, linaclotide, plecanatide, tenapanor, and tegaserod with placebo using the current FDA guidance end point, linaclotide, 290 μg once daily, was deemed to be the most effective.[49] However, all of the therapeutics seemed more effective than placebo and no single agent was clearly superior to the others. These findings must still be interpreted with caution because the primary end point in this analysis was consistent with primary end points of the linaclotide, plecanatide, and tenapenor studies but required retrofitting of the data for lubiprostone and tegaserod. Furthermore, the response estimate for tegaserod may have been overestimated because the surrogate end point used in this study, SBM, not CSBMs, is less robust.

The American College of Gastroenterology (2020),[11] American Gastroenterological Association[19] (currently undergoing updating with presumed publication in 2021), Canadian Association of Gastroenterology (2019),[12] and Mexican Association of Gastroenterology (2016)[20] guideline committees have all provided guidance on products available in their respective countries. Overall, there do not seem to be major differences in recommendations (see **Table 2**). Until better comparisons are made, real-world prescribing habits will likely continue to be influenced by prescribing and dosing considerations (**Table 3**), anecdotal success, cost, and third-party payer coverage.

SUMMARY

IBS-C is a common condition that causes significant distress and impairs quality of life. The Rome IV criteria outlined in 2016 provide a more consistent and specific

definition of IBS-C, and trials for IBS-C therapeutics have largely adopted the FDA standardized definition of "responder." OTC laxatives are often used as first-line agents, but they are falling out of favor given their inability to improve abdominal symptoms. Lubiprostone, linaclotide, plecanatide, tenapenor, and tegaserod seem effective for treating abdominal and bowel symptoms. Although gastroenterology societal guidelines (see **Table 2**) provide valuable assessments as to the strength of evidence supporting recommendations, they are of limited utility given the lack of variability separating these products. The choice of appropriate medication depends on patient goals, tolerability of adverse effects, cost, and insurance coverage.

CLINICS CARE POINTS

- Multiple international society guidelines have recommended against PEG as a first-line option for IBS-C, because it does not reduce global IBS symptoms.
- The secretagogues (lubiprostone, linaclotide, plecanatide) are all effective compared with placebo and side effects are generally mild, the two most common of which are nausea (lubiprostone) and diarrhea (linaclotide, plecanatide).
- Tegaserod has been reapproved for treating women with IBS-C less than 65 years with no history of cardiovascular ischemic events.
- There are no head-to-head trials directly comparing IBS-C therapies, but systematic reviews and meta-analyses suggest that all FDA-approved agents are effective.

DISCLOSURE

J.J. Liu does not have any disclosures to report. D.M. Brenner has served as an advisor, consultant, or speaker for the following: Allergan (AbbVie), Ironwood, Salix, Takeda, Alphasigma, Arena, and Alynlam Pharmaceuticals. He is also supported in research by an unrestricted gift from the Irene D. Pritzker Foundation.

REFERENCES

1. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology 2016; 150(6):1393–407.e5.
2. Palsson OS, Whitehead W, Törnblom H, et al. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. Gastroenterology 2020;158(5):1262–73.e3.
3. Ford AC. Commentary: estimating the prevalence of IBS globally—past, present and future. Aliment Pharmacol Ther 2020;51(1):198–9.
4. Shin A, Lembo A. IBS in America. American Gastroenterological Association; 2015. p. 45. Available at: https://www.multivu.com/players/English/7634451-aga-ibs-in-america-survey/. Accessed December 10, 2020.
5. Heidelbaugh JJ, Stelwagon M, Miller SA, et al. The spectrum of constipation-predominant irritable bowel syndrome and chronic idiopathic constipation: US survey assessing symptoms, care seeking, and disease burden. Am J Gastroenterol 2015;110(4):580–7.
6. Cash BD. Understanding and managing IBS and CIC in the primary care setting. Gastroenterol Hepatol 2018;14(5 Suppl 3):3–15.
7. Miller LE. Study design considerations for irritable bowel syndrome clinical trials. Ann Gastroenterol Q Publ Hell Soc Gastroenterol 2014;27(4):338–45.

8. U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry irritable bowel syndrome—clinical evaluation of drugs for treatment 2012. p. 1–14. Available at: www.fda.gov.
9. Lacy BE, Lembo AJ, MacDougall JE, et al. Responders vs clinical response: a critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. Neurogastroenterol Motil 2014;26(3):326–33.
10. Macdougall JE, Johnston JM, Lavins BJ, et al. An evaluation of the FDA responder endpoint for IBS-C clinical trials: analysis of data from linaclotide phase 3 clinical trials. Neurogastroenterol Motil 2013;25(6):481–6.
11. Lacy B, Pimentel M, Brenner D, et al. ACG clinical guideline: management of irritable bowel syndrome. Am J Gastroenterol 2020;116(1):17–44. Available at: https://journals.lww.com/ajg/Fulltext/9000/00000/acg_clinical_guideline__management_of_irritable.98972.aspx. Accessed December 15, 2020.
12. Moayyedi P, Andrews CN, MacQueen G, et al. Canadian Association of Gastroenterology clinical practice guideline for the management of irritable bowel syndrome (IBS). J Can Assoc Gastroenterol 2019;2(1):6–29.
13. Chang C-C, Lin Y-T, Lu Y-T, et al. Kiwifruit improves bowel function in patients with irritable bowel syndrome with constipation. Asia Pac J Clin Nutr 2010;19(4):451–7.
14. Muir J. An overview of fiber and fiber supplements for irritable bowel syndrome. Gastroenterol Hepatol 2019;15(7):387–9.
15. Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology monograph on management of irritable bowel syndrome. Am J Gastroenterol 2018;113(Suppl 2):1–18.
16. Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. Colorectal Dis 2010;12(11):1131–8.
17. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol 2013;108(9):1508–15.
18. Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association Technical Review on Constipation. Gastroenterology 2013;144(1):218–38.
19. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology 2014;147(5):1146–8.
20. Carmona-Sánchez R, Icaza-Chávez ME, Bielsa-Fernández MV, et al. The Mexican consensus on irritable bowel syndrome. Rev Gastroenterol Mex 2016;81(3):149–67.
21. Cuppoletti J, Malinowska DH, Tewari KP, et al. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. Am J Physiol Cell Physiol 2004;287(5):C1173–83.
22. Moeser AJ, Nighot PK, Engelke KJ, et al. Recovery of mucosal barrier function in ischemic porcine ileum and colon is stimulated by a novel agonist of the ClC-2 chloride channel, lubiprostone. Am J Physiol Gastrointest Liver Physiol 2007;292(2):G647–56.
23. Creekmore AL, Hong S, Zhu S, et al. Chronic stress-associated visceral hyperalgesia correlates with severity of intestinal barrier dysfunction. Pain 2018;159(9):1777–89.

24. Sweetser S, Busciglio IA, Camilleri M, et al. Effect of a chloride channel activator, lubiprostone, on colonic sensory and motor functions in healthy subjects. Am J Physiol - Gastrointest Liver Physiol 2009;296(2):G295–301.
25. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome: results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther 2009;29(3):329–41.
26. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012;107(11):1702–12.
27. Chang L, Chey WD, Drossman D, et al. Effects of baseline abdominal pain and bloating on response to lubiprostone in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2016;44(10):1114–22.
28. Cryer B, Drossman DA, Chey WD, et al. Analysis of nausea in clinical studies of lubiprostone for the treatment of constipation disorders. Dig Dis Sci 2017;62(12):3568–78.
29. Currie MG, Fok KF, Kato J, et al. Guanylin: an endogenous activator of intestinal guanylate cyclase. Proc Natl Acad Sci U S A 1992;89(3):947–51.
30. Forte LR. Uroguanylin and guanylin peptides: pharmacology and experimental therapeutics. Pharmacol Ther 2004;104(2):137–62.
31. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 2010;139(6):1877–86.e2.
32. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012;107(11):1714–24 [quiz p.1725].
33. Yang Y, Fang J, Guo X, et al. Linaclotide in irritable bowel syndrome with constipation: a phase 3 randomized trial in China and other regions. J Gastroenterol Hepatol 2018;33(5):980–9.
34. Miner P, DeLuca R, La Portilla M, et al. Plecanatide, a novel uroguanylin analog: a 12-week, randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate efficacy and safety in patients with irritable bowel syndrome with constipation (IBS-C): 1831. Off J Am Coll Gastroenterol ACG 2014;109:S541.
35. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. Am J Gastroenterol 2018;113(5):735–45.
36. Atluri DK, Chandar AK, Bharucha AE, et al. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. Neurogastroenterol Motil 2014;26(4):499–509.
37. Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-C agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: a systematic review and meta-analysis. Am J Gastroenterol 2018;113(3):329–38.
38. Li Q, King AJ, Liu L, et al. Tenapanor reduces IBS pain through inhibition of TRPV1-dependent neuronal hyperexcitability in vivo: 484. Off J Am Coll Gastroenterol ACG 2017;112:S255.
39. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of Tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO-1). Am J Gastroenterol 2020;115(2):281–93.

40. Chey WD, Lembo AJ, Yang Y, et al. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 26-week, placebo-controlled phase 3 trial (T3MPO-2). Am J Gastroenterol 2020;115(2):281–93.
41. Lembo A, Chey WD, Rosenbaum DP. An open label long-term safety trial (T3MPO-3) of tenapanor in patients with irritable bowel syndrome with constipation (IBS-C): presidential poster award: 430. Off J Am Coll Gastroenterol ACG 2018;113:S252.
42. Markham A. Tenapanor: first approval. Drugs 2019;79(17):1897–903.
43. Chey WD, Paré P, Viegas A, et al. Tegaserod for female patients suffering from IBS with mixed bowel habits or constipation: a randomized controlled trial. Am J Gastroenterol 2008;103(5):1217–25.
44. Shire US Inc. Motegrity (Prucalopride). U.S. Food and Drug Administration Website. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf. Accessed January 19, 2021.
45. Shah ED, Lacy BE, Chey WD, et al. S0495 The safety profile of tegaserod 6 Mg BID in irritable bowel syndrome with constipation in women <65 years of age without cardiovascular disease history. Off J Am Coll Gastroenterol ACG 2020; 115:S247.
46. Shah ED, Lacy BE, Chey WD, et al. S0492 Tegaserod 6 Mg BID for treating abdominal pain and bloating in women with irritable bowel syndrome with constipation but without cardiovascular risk factors: a pooled analysis of 4 clinical trials. Off J Am Coll Gastroenterol ACG 2020;115:S246.
47. NDA/BLA Multi-Disciplinary review and evaluation: Zelnorm (tegaserod). FDA; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/021200Orig1s015MultidisciplineR.pdf. Accessed December 10, 2020.
48. Zelnorm (tegaserod) [package insert]. Covington, LA: Alfasigma USA, Inc; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021200Orig1s015lbl.pdf.
49. Black CJ, Burr NE, Ford AC. Relative efficacy of tegaserod in a systematic review and network meta-analysis of licensed therapies for irritable bowel syndrome with constipation. Clin Gastroenterol Hepatol 2020;18(5):1238–9.e1.