Clinical and Experimental Gastroenterology

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REVIEW

Review of the Patient Burden and Therapeutic Landscape of Irritable Bowel Syndrome with Constipation in the United States

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Abstract: Irritable bowel syndrome (IBS) is a common disorder of the gut–brain axis. IBS with constipation (IBS-C) accounts for approximately one-third of IBS cases and is associated with substantial burden of illness and decreased quality of life. This narrative review provides an overview of the current and upcoming treatment options and disease management for IBS-C from a US perspective and discusses the importance of the relationship between patient and health care provider in diagnosis and treatment. A positive diagnostic strategy for IBS-C is recommended, based on clinical history, physical examination, and minimal laboratory tests. An effective communication strategy between patients and health care professionals is essential to ensure early diagnosis and reduce both health care costs and overall disease burden. Treatment typically begins with lifestyle interventions and nonpharmacologic options, such as dietary interventions, fiber supplements, and osmotic laxatives. In patients with inadequate response to these therapies, 4 currently available therapies (lubiprostone, linaclotide, plecanatide, and tenapanor) approved by the US Food and Drug Administration may relieve IBS-C symptoms. These agents are generally well tolerated and efficacious in improving IBS-C symptoms, including constipation and abdominal pain. In patients with persistent abdominal pain and/or psychological symptoms, brain–gut behavioral therapy or neuromodulator therapy may be beneficial.

Keywords: irritable bowel syndrome with predominant constipation, tenapanor, lubiprostone, linaclotide, plecanatide

Introduction

Irritable bowel syndrome (IBS) is a common disorder of the gut–brain axis.[1,2] It is a chronic and often debilitating condition that causes recurrent symptoms of abdominal pain and altered bowel movements,[1,2] as well as abdominal bloating and abdominal distension in many patients.[3] A detailed clinical history is central to the diagnosis of IBS,[4] Rome IV diagnostic criteria for IBS require that a patient has recurrent abdominal pain at least once a week on average in the last 3 months associated with ≥2 of the following: defecation, change in stool frequency, and change in stool form.[5] IBS is classified into 4 main subtypes based on the predominant stool form: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and unclassified IBS (IBS-U).[1,5] IBS-C accounts for approximately one-third of adult IBS cases.[6,7] It is characterized by >25% of stools being hard and lumpy (Bristol Stool Form Scale [BSFS] type 1 or 2) and <25% of stools being mushy or watery (BSFS type 6 or 7).[5] In the United States, the prevalence of IBS according to Rome IV criteria was estimated to be 4.7% in 2015, with IBS-C comprising 29.3% of cases;[7] with Rome III criteria, the estimated prevalence rate was approximately half of that (IBS prevalence 8.6%, including 16.2% IBS-C cases), because of fewer patients meeting the revised IBS thresholds. According to both Rome IV and Rome III criteria, prevalence rates in 2015 were higher in women than men (6.1% for Rome IV vs 3.2% for Rome III; $p<0.0001$) and higher in patients aged <65 years than those aged ≥65 years (5.0–6.4% vs 1.7%; $p<0.0001$).[7] This article reviews current

Received: 17 February 2024
Accepted: 25 June 2024
Published: 2 August 2024

and emerging treatment options and disease management for IBS-C from a US perspective and discusses the importance of the patient–health care provider (HCP) relationship and patient education in diagnosis and treatment.

Pathophysiology

The Pathophysiology of IBS-C is multifactorial, with genetic, environmental, and psychosocial factors contributing to an increased risk of the disorder.[3] Several potential mechanisms have been proposed to explain disease pathogenesis, including changes in gut motility, altered intestinal permeability, visceral hypersensitivity, immune dysfunction, hormonal influences, and changes in gut microbiota (Figure 1).[8–12] In patients with IBS-C, hard and infrequent stools may result from water imbalance and diminished colonic contractions because of changes in gut motility.[11,13] Intestinal permeability may be altered because of the widening of tight junctions between intestinal epithelial cells in response to stress, food antigens, infections, and dysbiosis, leading to inflammation close to afferent nerves in the intestine, which can trigger abdominal pain.[8,9,11,14] Abdominal pain in IBS-C results from visceral hypersensitivity (ie, enhanced pain signaling) caused by alterations in the periphery resulting from injury (ie, from microbial infections, food allergy, and/or inflammation), which then leads to central sensitization compounded by psychological factors such as childhood trauma, anxiety, or depression.[8,11,15–18] Microbial infections alter the production of microbial metabolites such as short-chain fatty acids, which can affect intestinal homeostasis, resulting in abdominal pain, altered intestinal contractility, increased permeability, and inflammation.[8]

Role of Early Life Events and Psychosocial Factors

Individuals' genetics and experiences in early life (eg, trauma, illness) can affect their susceptibility to gastrointestinal (GI) dysfunction and influence their psychological state and coping mechanisms.[21] Results of studies have shown a higher prevalence of IBS in individuals with a history of trauma (eg, sexual abuse[22,23]) or infections (eg, *Salmonella* infection[24]). Later in life, psychosocial factors such as stress, maladaptive coping mechanisms, and comorbid anxiety or depression can influence gut function via brain–gut interaction. These factors can affect patient perception of symptoms and, ultimately,

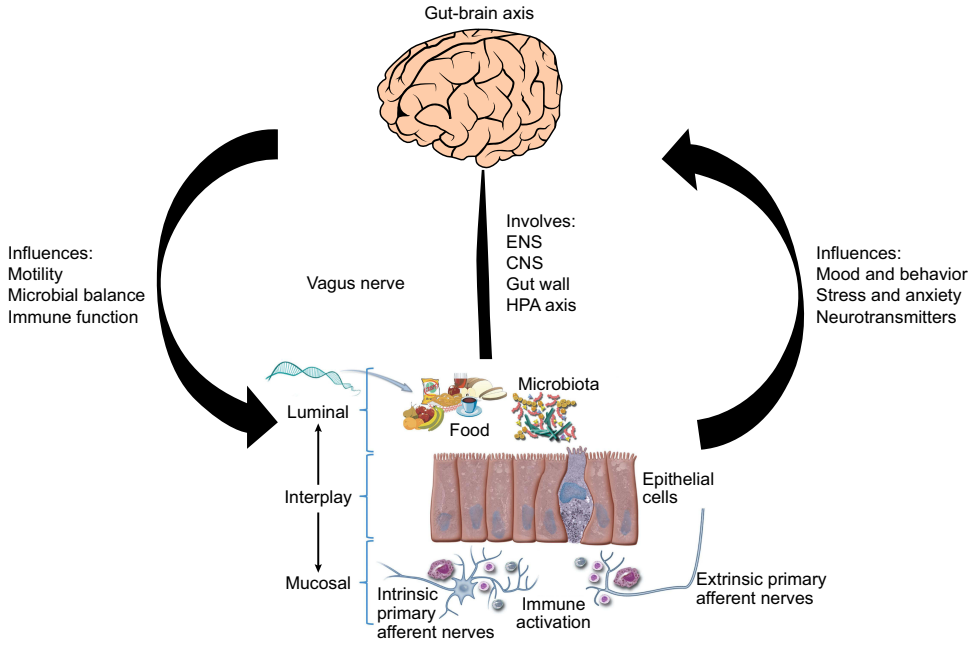

Figure 1 Pathophysiology of IBS-C. Compromised epithelial barrier integrity due to microenvironmental factors (eg, food, microbiota changes) may lead to increased intestinal permeability, which may elicit immune responses that affect signals sent from the gut to the brain and in turn, may alter motility, microbial balance, sensory perception, and immune function. This content was published in *Gastroenterology*, Vol 150, Barbara G, Feinle-Bisset C, Ghoshal UC, et al, The intestinal microenvironment and functional gastrointestinal disorders. 1305–1318, ©AGA 2016. With permission from Elsevier.[19] Used with permission of *Annals of Translational Medicine* from Tang HY, Jiang AJ, Wang XY, et al. Uncovering the pathophysiology of irritable bowel syndrome by exploring the gut-brain axis: a narrative review, Vol 9(14) 2021; permission conveyed through Copyright Clearance Center, Inc.[20]
Abbreviations: CNS indicates central nervous system; ENS enteric nervous system; HPA hypothalamo-pituitary-adrenal; IBS-C, irritable bowel syndrome with constipation.

treatment outcomes.[21] Stress can both produce and exacerbate GI symptoms in susceptible individuals.[25] Psychiatric disorders like depression and anxiety, which are common in patients with IBS,[26] can also amplify symptoms and worsen clinical outcomes.[21,27] In turn, poor clinical outcomes influence symptom severity and illness behavior.[21,27] Therefore, although diagnosis of IBS does not include assessment of psychosocial factors,[21] HCPs need to be aware of their influence, as these patients could benefit from psychological therapies.[25]

Overlapping Conditions

IBS and other disorders of gut–brain interaction often overlap and are believed to exist on a continuum;[21] thus, patients may be diagnosed with more than 1 disorder, or diagnoses may change over time.[21] In a US, web-based survey study conducted in 2010 (N=2641), IBS-C overlapped with gastroesophageal reflux disease (GERD) and functional dyspepsia (FD) in 1% and 5% of respondents, respectively, and overlapped with both GERD and FD in 4% of respondents.[28] IBS also overlaps with extraintestinal conditions, including psychological (eg, anxiety or depression), rheumatologic (eg, fibromyalgia, chronic fatigue syndrome, or chronic back pain), urogynecologic (eg, chronic pelvic pain, endometriosis, or sexual dysfunction), neurologic (eg, migraine or sleep disorders), and pulmonary (eg, asthma or bronchial hypersensitivity) comorbidities.[29,30] Fibromyalgia, a chronic musculoskeletal pain syndrome, is one of the most common comorbidities and like IBS, is more prevalent in women[31] and is often associated with psychological disorders, sleep disturbances, and chronic fatigue.[32] Endometriosis is another extraintestinal condition often occurring in women with IBS. Both are conditions associated with symptoms such as chronic pelvic pain, abdominal pain, and altered bowel movements.[33]

Patients' Experience with IBS-C

Burden of Symptoms

IBS-C symptoms are variable and include abdominal bloating, abdominal discomfort, abdominal pain, and abdominal cramping. In the BURDEN IBS-C online questionnaire study, the prevalences of the most common symptoms experienced by diagnosed respondents at disease onset were 75%, 66%, 65%, 62%, and 54% for difficulty with bowel movement, abdominal discomfort, abdominal bloating/distension, abdominal pain, and stomach cramps, respectively.[34] Overlapping conditions further increase symptom burden, with 1 study showing that abdominal pain, discomfort, and bloating were more than twice as frequent in patients with IBS-C, GERD, and FD as in patients with IBS-C alone.[28] IBS-C symptoms negatively affected productivity and daily activities in ≈50% (≈4 d/mo) and ≈40% (≈3 d/mo) of 1311 patients, respectively, in the BURDEN IBS-C study.[34] Likewise, in the IBS in America survey study, 37% of the 1885 respondents with IBS-C who were employed or in school reported that their productivity was affected on average 8.2 days per month, and reported missing work/school on average 1.7 days per month.[35] About 40% to 60% of patients in these studies found their symptoms to be somewhat or extremely bothersome.[34,35] Results of 1 study indicated that patients with IBS would be willing to sacrifice 25% of their remaining life, which averages to about 15 years, and 14% of patients would risk a 1 in 1000 chance of death associated with the treatment, provided it would relieve them of their IBS symptoms.[36]

Psychological Burden

Individuals diagnosed with IBS frequently have feelings of discomfort and shame and may be required to sacrifice their recreational and social activities to manage their symptoms, resulting in social isolation and difficulty forming meaningful relationships. Patients with frequent symptoms may feel frustration and embarrassment, leading to withdrawal from social situations. In the BURDEN IBS-C study, 43% of individuals with IBS-C were frustrated, 28% were stressed, 22% felt self-conscious, and 21% were embarrassed because of their symptoms.[34] Moreover, some patients express concern regarding how their bowel habits might affect their dating and sexual experiences.[35,37] This further increases social isolation and stigma for patients.

Perceived and internalized stigma are the 2 most-experienced types of stigmas for patients with IBS. Because IBS is considered an "invisible illness", patients may become concerned about how others perceive them and that others hold negative preconceived ideas about them because of their IBS.[38] Patients with high levels of internalized stigma may take

the negative characteristics of the illness and make them a part of who they are. They believe that they are "gross", "unloved or unwanted", "sick", and "unworthy". This contributes to major depression and further isolation.[39,40] Patients may also experience enacted stigma, ie, discriminatory acts and negative attitudes. These attitudes may include the belief that their lifestyle choices or psychological factors are the cause of the condition, leading patients to feel responsible for their illness.[38,39]

Patients can have misconceptions about their condition, which can further add to their anxiety and increase the number of visits to their HCP and requests for additional diagnostic tests.[37] For example, in a survey-based study of 1242 patients with IBS, some of the commonly held misconceptions were that IBS is the result of a lack of digestive enzymes (52%) and that IBS is a type of colitis (43%) or can lead to colitis (43%), malnutrition (38%), or cancer (21%) and will progress with age (48%) and shorten their life (23%).[37,41]

The Importance of Patient–HCP Communication

Patients must first receive a clear diagnosis to build a strong patient–provider relationship. Many patients report not receiving a diagnosis, even after seeing several HCPs. This could be because the HCP used qualified language when communicating the diagnosis (eg, "I think you might have IBS".), which can reduce patients' confidence in treatment recommendations, or because the HCP did not feel comfortable providing a diagnosis of IBS or other disorders of gut–brain interaction because of a lack of knowledge and education on the conditions.[39,42,43]

Patients and HCPs may have a contradictory understanding about the cause of IBS, which can lead to problems meeting expectations during initial patient–HCP interactions. A cross-sectional study of patients (N=5354) with functional GI disorders found that while patients anticipated receiving a somatic (eg, food-related) explanation for their symptoms, HCPs were more likely to consider a psychological component to be the predominant causative factor.[44] Furthermore, while patients often expressed a wish to receive a physical examination (76.2%), further diagnostic investigations (70.8%), and medications (62.4%), their HCP was more likely to converse with the patient than to physically examine them (66.3%) and was less likely to offer further investigations (56.2%) or medications (52.1%).[44] The stigma felt by patients in social settings may also be encountered when interacting with HCPs, leaving patients feeling that IBS is somehow "self-inflicted" and is "all in their head".[45] It is imperative for the medical community and HCPs to play an active role in reducing stigma and shame.[42,46]

Patients and their HCPs can also have differing perspectives on IBS treatment. Patients are increasingly being influenced by information available on the internet, and HCPs can find it very difficult to discuss "fact versus fiction" with them when under time pressure to see as many patients as possible.[37] The evolving health care landscape has reduced face-to-face time for patients and physicians over time and only 33% of HCPs feel they have enough time for their patients with functional GI disorders.[44,47] This leaves patients feeling like their providers are "rushed", "hurried", and "busy".[47] In a small study, outpatients with IBS (N=8) and HCPs (gastroenterologists or general practitioners; N=15) were asked to rank different characteristics of therapy based on level of importance.[48] While HCPs and patients agreed that treatment effectiveness was the most important factor, there were differences in the levels of importance conferred upon other characteristics, such as willingness to pay and therapy location.[48]

Dissatisfaction with Treatment

Despite the substantial burden of IBS-C, patients often do not consult an HCP regarding their symptoms and instead self-treat their symptoms with over-the-counter (OTC) therapies. In the BURDEN IBS-C study, 61% of patients were undiagnosed and had never consulted an HCP. Patients who had discussed their symptoms and had received a diagnosis had previously tried options such as fiber supplementation (39%), dietary changes/home therapies (39%), and stool softeners (24%) for symptom management before consulting an HCP.[34] Overall, treatment satisfaction with OTC medications for IBS-C is low, with <15% of patients with IBS-C reporting being "very satisfied" in the IBS in America survey study.[49]

Among IBS-C patients who had received prescription medications approved by the US Food and Drug Administration (FDA; 18.7%), only 25% of patients were "very satisfied" with their treatment.[49] Reasons for patients discontinuing FDA-approved medications may be attributable to the patient, the treatment, and/or issues with insurance coverage (eg, high copays). A retrospective study that analyzed outpatient data from a cohort of patients with IBS-C

receiving linaclotide (n=225) or lubiprostone (n=492) found that in patients with a chronic overlapping pain condition there was a trend toward increased lubiprostone discontinuation (hazard ratio 1.254; 95% CI 0.997 to 1.576).[50] In a separate retrospective cohort study, the most common reasons cited by patients with IBS-C or chronic idiopathic constipation (n=1612) for discontinuing lubiprostone and linaclotide within 1 year of treatment initiation were intolerance (eg, nausea, abdominal pain, diarrhea, bloating), loss of prescription drug coverage, and insufficient efficacy.[51]

Burden to Health Care Systems and Resources

IBS-C is a considerable burden to the health care system, including inpatient and outpatient visits, diagnostic tests, and treatments (OTC and prescription). Results of a US retrospective cohort study showed that during the 24-month study period (12 months before and 12 months after first diagnosis), patients with IBS-C (N=35,627) had greater health care resource utilization (HCRU) than patients with IBS without constipation, including almost twice as many intestinal-related inpatient admissions (incidence rate ratio [IRR], 1.91; 95% CI 1.84–1.99), more than 3 times as many intestinal-related emergency room (ER) visits (IRR, 3.19; 95% CI 3.08–3.32), and 55% more visits to GI specialists (IRR, 1.55; 95% CI 1.52–1.57).[52] Compared with patients who have IBS without constipation, patients with IBS-C also required more than 3 times as many prescriptions for treating constipation or diarrhea (IRR, 3.42; 95% CI 3.31–3.53) and required more medical procedures and diagnostic tests, including colonoscopy (IRR, 1.42; 95% CI 1.40–1.44), computed tomography (IRR, 1.63; 95% CI 1.59–1.67), ultrasonography (IRR, 1.35; 95% CI 1.32–1.38), and anorectal function testing (IRR, 4.14; 95% CI 3.84–4.46).[52]

IBS-C also imposes significant financial burden on patients and health care systems, both in terms of direct and indirect costs. In a commercially insured population in the United States, patients with IBS-C incurred $3856 more in all-cause health care costs than controls (adjusted mean annual all-cause costs, $8621 vs $4765; $p<0.01$), with medical services accounting for 78.1% and prescription fills for 21.9% of the costs.[53] In another US study, patients with IBS-C, compared with matched controls, had significantly higher outpatient costs ($25,448 vs $21,024; $p<0.05$), ER costs ($6892 vs $3962; $p<0.05$), and imaging costs ($4667 vs $3714; $p=0.02$) over 10 years.[54]

Across IBS subtypes, IBS-C was found to be associated with the highest financial burden to the US health care system. In a retrospective cohort analysis of administrative health claims data, annual health care utilization was compared across subtypes during a 5-year period.[55] The total all-cause and IBS-specific health care costs for patients with IBS-C (N=23,923) were $16,005 (interquartile range [IQR] $6384–$43,972) and $2222 (IQR $511–$7884), respectively. These were higher than the equivalent costs for patients with IBS-D (n=33,947), IBS-M (n=18,052), and IBS-U (n=26,965), which ranged from $11,996 to $13,542 (all-cause costs) and $756 to $1214 (IBS-specific costs). These costs were attributable to the higher number of ER visits/hospitalizations and radiological tests required by patients with IBS-C.[55] Another notable finding, reported by the study investigators and elsewhere, is that many of the direct costs are not actually associated with IBS-related care, but rather with other (non-GI) costs, such as mental health care.[55,56] The data obtained from this study also demonstrated that although the number of available treatment options has increased over recent years, the economic burden of IBS on the US health care system has continued to rise.[55] Furthermore, treatment failure is common in patients with IBS-C, further contributing to the burden of disease.[57] In a retrospective cohort study of 2830 patients with IBS-C (1627 initiated on OTC medications, 1107 on prescription medications, and 96 on both therapies), ≥1 indicator of treatment failure was observed in 46.3% of patients during the 1-year follow-up period. Indicators of treatment failure in this study included switch or addition of IBS-C/constipation therapy, IBS-C or constipation-related inpatient or ER admission, megacolon or fecal impaction, constipation-related surgery or procedure, or aggressive prescription treatments. HCRU was significantly higher in patients with than without treatment failure, particularly in terms of inpatient days (4.77 vs 2.53 days, respectively; IRR, 1.54; $p<0.05$).[57] Treatment failure also adds to the financial burden, with mean total health care costs being significantly higher in patients with than without treatment failure ($18,886 vs $13,897; incremental cost, $4353). In both subgroups, medical costs accounted for most of the total costs ($11,021 vs $7497) and incremental costs associated with treatment failure ($3106).[57]

Diagnosis

The Diagnosis of IBS-C can be challenging because of the overlapping and fluctuating symptoms and lack of disease-specific biomarkers;[58,59] this often leads to frustration among both patients and physicians because of the lack of a clear and confident IBS-C diagnosis.[59] Patients often attend numerous physician visits and undergo varied diagnostic tests before a definitive diagnosis is reached. In the clinical studies leading to the approval of tenapanor for IBS-C, enrolled patients had experienced symptoms for approximately 11 years before study entry.[60,61]

The American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) recommend a positive diagnostic strategy[1,3,62] to shorten the time to appropriate treatment, minimize unnecessary diagnostic testing, and reduce unnecessary costs to health care systems.[1] Diagnosis should be based on clinical history, physical examination, minimal laboratory testing, and, if needed, other appropriate tests (eg, colonoscopy).[1,25,62] Patients presenting with bowel or abdominal symptoms should be evaluated with a detailed clinical history, including psychosocial, dietary, menstrual, gynecologic, and sexual history, and a thorough physical examination.[4,25,58] If alarm features (eg, symptom onset after the age of 45 years, overt GI bleeding, recent change in bowel habit, family history of celiac disease, colon cancer, or inflammatory bowel disease [IBD]) are identified, further testing may be required.[25,58,62] If no alarm features are detected, patients' symptoms should be quantified against Rome IV diagnostic criteria.[25,58] To be diagnosed with IBS-C, according to Rome IV, patients must have abdominal pain and altered bowel habits,[1] with >25% of stools BSFS type 1 or 2, and <25% of stools BSFS type 6 or 7.[5] Limited screening studies can be undertaken, including complete blood count (to rule out conditions such as anemia), C-reactive protein or fecal calprotectin (to exclude IBD), thyroid tests (if deemed appropriate),[3,25] and anorectal physiology testing (to investigate symptoms suggestive of pelvic floor disorder and/or refractory constipation).[1] Screening colonoscopy is recommended for all patients aged >45 years, but routine colonoscopy is not recommended as part of the work-up.[1,25] Testing for food allergies/sensitivities is not recommended unless related symptoms are reproducible.[1]

Management of IBS-C

The aim of treatment in IBS-C is to improve global symptoms and reduce overall severity of the condition, with the choice of treatment guided by the main symptoms.[58] Patient education and a healthy relationship between patient and HCP is critical for the success of therapy;[3,37,58] therefore, current AGA guidelines recommend starting treatment by educating patients and reassuring them about their condition.[63] Recommended treatment options for patients with IBS-C include nonpharmacologic, OTC, and prescription therapies,[1,63] with the choice of treatment dependent on the severity of symptoms (Table 1, Figure 2).[63] The ACG uses global response to IBS symptoms as a basis for their recommendations,[1] whereas the AGA uses a minimal clinically meaningful improvement of ≥10% over placebo as the threshold for determining treatment efficacy.[62]

AGA guidance stratifies treatment by symptom severity (mild or moderate) and makes specific recommendations for first-, second-, and subsequent-line approaches for the treatment of IBS-C.[62] First-line treatment is comprised of nonpharmacologic and OTC therapies and is symptom-led, while later-line therapy may include the use of prescription treatment for IBS-C alone or in conjunction with neuromodulator and brain–gut behavioral therapies.[62,63] The AGA guidelines state that later-line treatment selection should be based on both clinical features and patient needs.[62] In contrast, the ACG guidelines recommend therapies based on their use for the treatment/improvement of global IBS symptoms, and only prescription medications are recommended specifically for the treatment of IBS-C subtype–associated symptoms as they target pain and stool consistency. The ACG provides less guidance for therapeutic sequencing than the AGA, although they do suggest that soluble fiber should be used in first-line treatment and recommend using gut-directed psychotherapies in conjunction with other approaches.

Nonpharmacologic Therapies

Treatment for all patients with IBS should be initiated with lifestyle interventions (eg, exercise, stress reduction, adequate daily fluid intake, and improved sleep) and dietary modifications.[58,63] Adopting healthy eating habits, avoiding long gaps between meals, increasing fiber intake if recommended, and eliminating any medications that can cause or worsen constipation (eg, diuretics or opiates) may improve IBS symptoms.[1,2,4] According to the AGA guidelines, patients who

Table 1 Treatment Recommendations for IBS-C According to Current US Guidelines

Treatment	American College of Gastroenterology guidelines[1]	American Gastroenterological Association guidelines[62,63]
Initial treatment (all IBS)	• Recommend a limited trial of a low-FODMAP diet • Suggest the use of soluble, but not insoluble, fiber	• Provider-patient relationship • Education and reassurance • Lifestyle modifications (exercise, sleep, stress reduction) • Dietary modifications (eg, fiber, low FODMAP)
Polyethylene glycol	Suggest against their use for global IBS-C symptoms	Suggest using as first-line therapy for IBS-C
Antispasmodics	Recommend against their use for global IBS symptoms	Suggest using as first-line therapy for IBS-C
Peppermint oil	Suggest using for global IBS symptoms	Suggest using as first-line therapy for IBS-C
Lubiprostone	Recommended for global IBS-C symptoms	Suggest using as second-line therapy for IBS-C
Linaclotide	Recommended for global IBS-C symptoms	Recommended as second-line therapy for IBS-C
Plecanatide	Recommended for global IBS-C symptoms	Suggest using as second-line therapy for IBS-C
Tenapanor	—	Suggest using as second-line therapy for IBS-C
TCAs	Recommended for global IBS symptoms	Suggest adding or switching to low-dose TCAs, SNRIs, or psychotherapies for persistent IBS-related abdominal pain and/or psychological symptoms despite second-/third-line therapy
SNRIs	—	
Psychotherapies	Suggest using for global IBS symptoms	
Probiotics	Suggest against their use for global IBS symptoms	—
SSRIs	—	Suggest against using SSRIs for IBS

Note: — indicates not reported.
Abbreviations: CV, cardiovascular; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

report symptoms such as abdominal pain and bloating and changed bowel habits after a meal could potentially be more receptive of, and adherent to, dietary modifications.[64]

Elimination of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has been associated with overall symptom improvement in patients with IBS. FODMAPs may exacerbate GI symptoms by increasing GI water secretion and fermentation in the colon, resulting in the production of short-chain fatty acids and gases, which cause bloating; therefore, eliminating FODMAPs may improve symptoms.[1,4] A recent systematic review and network meta-analysis of 13 trials in patients with IBS (n=944) found a low-FODMAP diet to be more effective in improving global IBS symptoms than other diets (Table 2).[65] A low-FODMAP diet also ranked first in improving individual symptoms of abdominal pain, abdominal bloating/distension, and bowel habits, although there were few or no significant differences between the low-FODMAP and other diets.[65] Adhering to low-FODMAP diets can be hard, because they require exclusion of certain grains, fruits, and vegetables and could exacerbate constipation if they are not replaced with alternative fiber sources.[58] Given the benefits observed with dietary exclusion of FODMAPs and the associated difficulties, the ACG recommends a limited trial of a low-FODMAP diet in all patients with IBS and involvement of a GI dietitian if possible to help prevent nutritional deficiencies and the possible development of avoidant/restrictive food intake disorder.[1,66] The AGA guidelines also recommend a FODMAP-elimination diet as the first step in the treatment of IBS.[63] Both guidelines note that the diet consists of 3 phases: restriction (4–6 weeks), reintroduction (6–10 weeks), and personalization,[1,64] and for the clinician to be vigilant in case a patient has an eating disorder and restrictive diets must be avoided.

OTC Treatments

Fiber supplements are often recommended for patients with IBS, with soluble fibers (eg, those in psyllium, oat bran, barley, and beans) found to have laxative properties.[1] Soluble fibers are not fermented in the colon, increase stool water

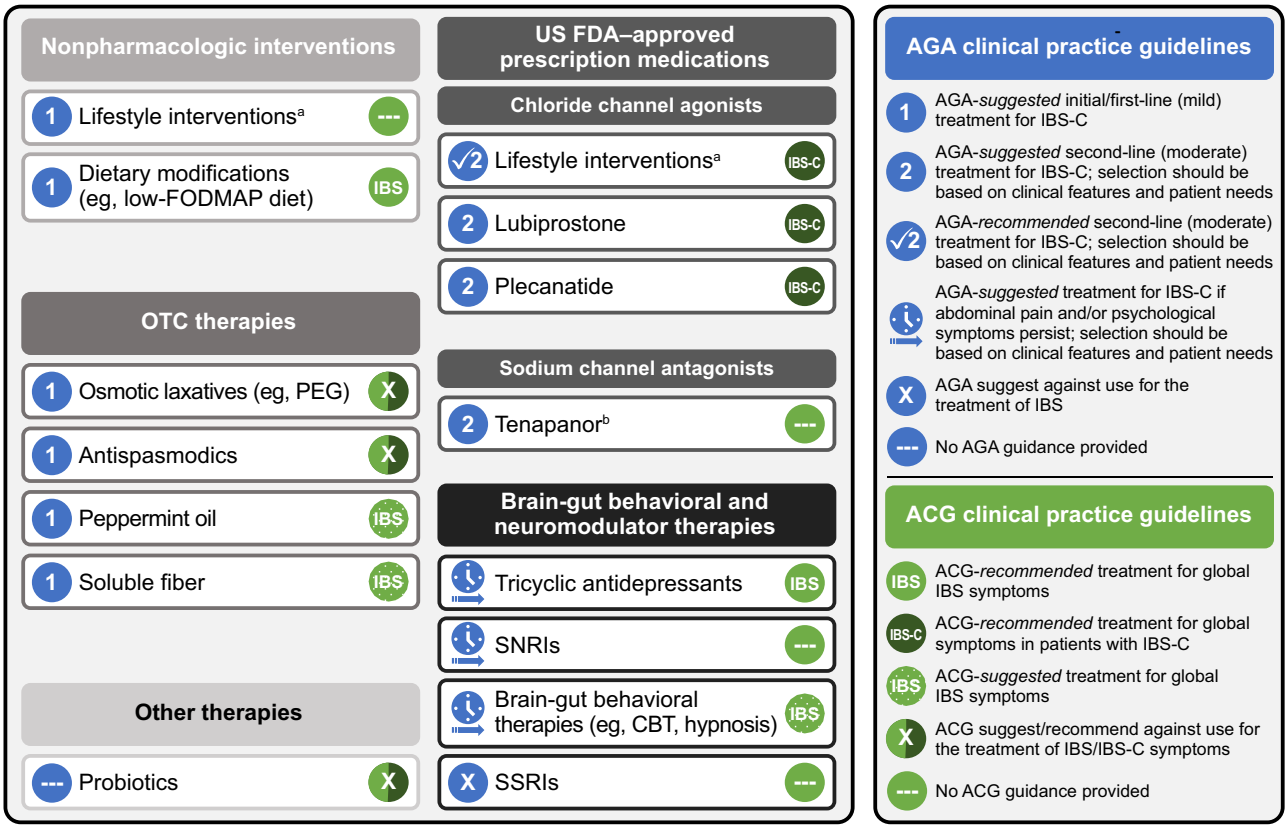

Figure 2 Treatment recommendations for IBS-C according to current US guidelines.[1,62,63] Note that although tegaserod is included in the guidelines, it has been omitted from this figure as it has been withdrawn from the market and is unavailable for prescription. [a]Lifestyle modification suggested by the AGA: exercise, sleep, stress reduction. [b]At the time of preparation of the most recent ACG guidelines, the amount of real-world clinical practice experience with tenapanor available for consideration by the ACG would have been limited (tenapanor received FDA approval for use in 2019).

Abbreviations: ACG indicates American College of Gastroenterology; AGA, American Gastroenterological Association; CBT, cognitive behavioral therapy; FDA, Food and Drug Administration; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome; PEG, polyethylene glycol; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; US, United States.

content, improve stool viscosity and frequency, and are not associated with significant side effects, which make them a reasonable first-choice therapy.[1,2] On the other hand, insoluble fibers (eg, those in wheat bran, whole grains, and some vegetables) can ferment in the colon, lose their water retention capacity, and produce gas, which can exacerbate symptoms of bloating and flatulence.[1] A systematic review and meta-analysis of 14 randomized controlled trials involving 906 patients with IBS showed that soluble fiber is safe and effective in improving global IBS symptoms, whereas no significant benefit was seen with insoluble fiber (Table 2).[76] Given their efficacy and safety, the ACG and AGA guidelines suggest using soluble fiber supplements as initial treatment for IBS.[1,63,64]

Peppermint oil is commonly used to relieve IBS symptoms. Its physiologic effects have been attributed to GI muscle relaxation via calcium channel blockade by L-menthol, antimicrobial and anti-inflammatory activities, effects on visceral sensation by modulation of transient receptor potential voltage channels, and effects on psychosocial distress via its anxiolytic effects.[1,69] In a meta-analysis of pooled data from 835 patients with IBS participating in 12 randomized controlled trials, peppermint oil was found to be safe and effective in improving global IBS symptoms (Table 2).[70] The ACG guidelines suggest that peppermint oil be used for relief from global IBS symptoms,[1] and the AGA guidelines recommend it as first-line therapy for abdominal pain.[63]

Polyethylene glycol (PEG), a long-chain polymer of ethylene dioxide, is an OTC osmotic laxative indicated in the United States for relief from occasional constipation. However, the limited available evidence does not support its efficacy in patients with IBS-C (Table 2).[1,67] Treatment-related adverse events (AEs; abdominal pain and diarrhea) were also reported more frequently with PEG plus electrolytes than with placebo.[67] The AGA guidelines note the need for

Table 2 Nonprescription Therapies for IBS/IBS-C

Treatment	Proposed mechanism of action	Key data in IBS
Nonpharmacologic therapy		
Low-FODMAP diet	• Reduces short-chain fatty acid and gas production via fermentation[1]	Condition and type of study: IBS; meta-analysis[65] Overall no. participants: 944 Efficacy: • No improvement in global IBS symptoms: RR 0.67; 95% CI 0.48–0.91; p=0.99; ranked first and superior to all other interventions (eg, habitual diet) ○ Also ranked first for other "not improving" endpoints: abdominal pain severity (RR 0.72; 95% CI 0.47–1.10; p=0.92), abdominal bloating/distension severity (RR 0.71; 95% CI 0.47–1.06; p=0.82), and bowel habit (RR 0.62; 95% CI 0.37–1.04; p=0.88) Safety: • NA (AEs not assessed in this analysis)
Over-the-counter therapies		
Soluble fiber	• Not fermented in the colon • Increases stool water content; improves stool frequency/viscosity[1,2]	Condition and type of study: IBS; meta-analysis[66] Overall no. participants: 499 Efficacy: • Soluble fiber RCTs (ispaghula husk): RR for not improving IBS symptoms: 0.83; 95% CI 0.73–0.94; p=0.005 • Comparison: bran RCTs: RR 0.90; 95% CI 0.79–1.03; p=0.14 Safety: • No statistically significant increase in AEs with ispaghula husk: RR 1.14; 95% CI 0.94–1.38
Polyethylene glycol	• Osmotic laxative[67]	Condition and type of study: IBS-C; RCT[67] Overall no. participants: 139 Efficacy (PEG+electrolytes vs placebo): • Mean number of SBMs/day (primary end point) at week 4: 4.40 (SD 2.58) vs 3.11 (1.94); 95% CI 1.17–1.95; p<0.0001 • PEG+electrolytes were also superior at week 4 for CSBMs, responder rates, stool consistency, and severity of straining Safety: • No safety concerns; treatment-related AEs reported in 16.4% vs 8.6% of patients receiving PEG vs placebo, respectively

(*Continued*)

https://doi.org/10.2147/CEG.S464375 DovePress

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Table 2 (Continued).

Treatment	Proposed mechanism of action	Key data in IBS
Antispasmodics	• Relax intestinal smooth muscle • Possibly improve visceral hypersensitivity[1,62]	Condition and type of study: IBS-C; systematic review[68] Overall no. participants: 2333 Efficacy (antispasmodics vs placebo): • Improvement of abdominal pain: 58% vs 46% (n=1392); RR 1.32; 95% CI 1.12–1.55; $p<0.001$; NNT=7 • Improvement in global assessment: 57% vs 39% (n=1983); RR 1.49; 95% CI 1.25–1.77; $p<0.0001$; NNT=5 • Improvement of symptom score: 37% vs 22% (n=586); RR 1.86; 95% CI 1.26–2.76; $p<0.01$; NNT=3 Safety: • NA (AEs not assessed in this analysis)
Peppermint oil	• Blockade of calcium channels via L-menthol produces GI muscle relaxation • Antimicrobial and anti-inflammatory activities • Modulation of transient receptor potential voltage channels affects visceral sensation • Anxiolytic effects reduce psychosocial distress[1,69]	Condition and type of study: IBS; meta-analysis[70] Overall no. participants: 835 Efficacy (peppermint oil vs placebo): • Improvement of global symptoms (n=507): RR 2.39; 95% CI 1.93–2.97; NNT: 3 • Improvement of abdominal pain (n=556): RR 1.78; 95% CI 1.43–2.20; NNT: 4 Safety: • No differences in reported AEs for patients using peppermint oil vs placebo: ○ From 8 RCTs: 32 events (9.3%) vs 20 events (6.1%); RR 1.40; 95% CI 0.87–2.26
Neuromodulator and brain–gut behavioral therapies		
Tricyclic antidepressants (TCAs)	• Presynaptic inhibitor of noradrenaline and serotonin reuptake[71] • Affects GI transit and may decrease visceral sensitivity[71]	Condition and type of study: IBS; meta-analysis[71] Overall no. participants: 744 Efficacy (TCAs vs placebo/control): • Persistence of global symptoms: RR favored TCAs: 0.69; NNT=4 • Persistence of abdominal pain: RR favored TCAs: 0.69; 95% CI 0.58–0.82; NNT=3 Safety: • AEs more common with TCA than placebo/control; NNH: 8
Serotonin-norepinephrine reuptake inhibitors	• Presynaptic inhibitor of noradrenaline and serotonin reuptake[71] • Inhibits gastric and colonic tone (less effective than TCAs)[71]	Condition and type of study: not studied adequately in IBS[71] Efficacy • Limited evidence of effect on pain in specific DBGIs (eg, IBS); beneficial effects reported in other pain indications[62,71] Safety: • Fewer side effects than TCAs[71]

Brain–gut behavioral therapies	• Act on central or gut–brain systems to control symptoms[72]	Condition and type of study: IBS; meta-analysis[73] Overall no. participants: 4072 Efficacy (psychological therapy vs control intervention): • Global IBS symptoms after treatment: ○ Self-administered/minimal-contact CBT: 0.61; 95% CI 0.45–0.83; p=0.66 ○ Face-to-face CBT: 0.62; 95% CI 0.48–0.80; p=0.65 ○ Gut-directed hypnotherapy: 0.67; 95% CI 0.49–0.91; p=0.57 Safety: • NA (AEs not assessed in this analysis) Condition and type of study: IBS; meta-analysis[74] Overall no. participants: 2290 Efficacy: • GI symptom severity after psychological therapy: ○ Immediately after therapy: d 0.69; p<0.001; 95% CI 0.52–0.86 ○ Short-term follow-up (1 to 6 months): d 0.76; p<0.001; 95% CI 0.54–0.97 ○ Long-term follow-up (6 months to 1 year): d 0.73; p<0.001; 95% CI 0.43–1.03 Safety: • NA (AEs not assessed in this analysis) Condition and type of study: IBS; meta-analysis[75] Overall no. participants: NA (46 RCTs) Efficacy: • Effect of psychological therapy (compared with active and nonactive controls) on mental health and daily functioning: ○ Mental health: d 0.41; p<0.001; 95% CI 0.29–0.54 ○ Daily functioning: d 0.43; p<0.001; 95% CI 0.30–0.55 Safety: • NA (AEs not assessed in this analysis)

Abbreviations: AE, adverse event; CBT, cognitive behavioral therapy; CSBM, complete spontaneous bowel movement; DGBI, disorder of gut–brain interaction; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; NA, not available; NNH, number needed to harm; NNT, number needed to treat; PEG, polyethylene glycol; RCT, randomized controlled trial; RR, relative risk; SBM, spontaneous bowel movement; TCA, tricyclic antidepressant.

https://doi.org/10.2147/CEG.S464375

additional well-designed studies to evaluate the efficacy of PEG in patients with IBS-C but suggest using PEG to improve symptoms of constipation in these patients.[62] The ACG guidelines, however, do not recommend the use of PEG for relief of global IBS symptoms in patients with IBS-C.[1]

The ACG and AGA guidelines also differ in their recommendations for use of antispasmodics in patients with IBS-C. Antispasmodics, as a drug class, inhibit GI smooth muscle contractions and may lead to constipation, although they improve visceral hypersensitivity.[1,62] The ACG guidelines recommend against the use of antispasmodics available in the United States (dicyclomine, hyoscyamine, and hyoscine) because of insufficient and poor-quality efficacy data in patients with IBS-C.[1] They note that although antispasmodics are frequently used in patients with IBS-C, their efficacy is based on systematic reviews and meta-analyses of the drug class rather than individual agents (Table 2).[1] The AGA guidelines, on the other hand, suggest using antispasmodics to relieve abdominal pain in all patients with IBS,[62,63] based on the efficacy of the drug class in improving abdominal pain and global IBS symptoms.[68]

US FDA–Approved Therapies in Adults

Patients with IBS-C whose symptoms are uncontrolled with nonpharmacologic or OTC medications may need prescription therapies. US FDA-approved therapies include lubiprostone, linaclotide, plecanatide, tenapanor, and tegaserod (Table 3), of which tegaserod is no longer marketed and will not be discussed further. The choice of treatment is dependent on individual patient symptoms and needs.[63]

Lubiprostone

Lubiprostone is an orally administered prostaglandin E1 analog with high selectivity for type 2 chloride channels (CIC-2) present on apical membranes of human intestines.[1,62,77] It activates CIC-2, which increases secretion of chloride-rich fluid into the lumen, resulting in increased intestinal motility and facilitating intestinal transit (Figure 3).[77,78] This prescription laxative is now generic but still cost-prohibitive for many patients. Additionally, dose-dependent risk of nausea may occur with the higher dosage approved for chronic idiopathic constipation.[77]

Lubiprostone approval in the United States was based on the results from 2 identically designed, 12-week, randomized, double-blind, phase 3 studies (NCT00380250 and NCT00399542) in patients with IBS-C, which showed that oral lubiprostone 8 µg twice daily was safe and effective for relieving global symptoms in patients with IBS-C.[77,91] In a combined analysis of the 2 studies, there were significantly more rigorous responders (primary end point) during the 12 weeks of treatment in patients treated with lubiprostone than in those treated with placebo (see Table 4 for definitions and detailed results).[91] In terms of individual symptoms, at month 3, abdominal pain/discomfort, straining, constipation severity, and stool consistency improved from baseline to a greater extent with lubiprostone than with placebo, whereas abdominal bloating and bowel movement frequency did not differ significantly between the 2 groups.[91]

Results of an open-label extension study that enrolled patients who had completed either one of these studies (n=520 evaluable population) showed that the rigorous responder rates increased during 36 weeks of additional treatment with lubiprostone.[96] In addition, results of a post hoc analysis[97] of the 2 phase 3 studies in which data were analyzed using criteria similar to the US FDA guidance issued in 2012[98] showed that lubiprostone improved individual symptoms and composite end points.[97]

Lubiprostone was generally well tolerated in patients with IBS-C, with treatment-related AEs occurring in similar percentages of lubiprostone and placebo recipients in pooled data from the 2 phase 3 studies (Table 5).[91] The most common treatment-related AEs with lubiprostone were nausea and diarrhea, which occurred more frequently with lubiprostone than placebo (Table 5).[91] The tolerability profile of lubiprostone during long-term therapy in the extension study was similar to that observed in the short-term trials.[96]

Given its efficacy and safety in the 2 phase 3 studies and the post hoc analysis, ACG guidelines recommend the use of lubiprostone for the treatment of global IBS-C symptoms.[1] AGA guidelines suggest using lubiprostone in patients with IBS-C[62] based on results of a systematic review of data from the 2 phase 3 studies, which showed significant benefit of lubiprostone over placebo in terms of global response (relative risk [RR], 0.93; 95% CI 0.87–0.96) and abdominal pain (RR, 0.85; 95% CI 0.76–0.95).[99] However, these improvements did not meet the clinically meaningful threshold of ≥10%.[99] Additionally, there was no significant difference between the lubiprostone and placebo groups for improvement

Table 3 US FDA-Approved Medications for IBS-C

Agent	Mechanism of action	Approval year	Indications	Recommended dosage	Use during pregnancy and lactation
Lubiprostone[77,78]	Chloride channel activator; chloride-rich intestinal fluid secretion is increased, thereby increasing motility	2006	• Treatment of IBS-C in women aged ≥18 y • Treatment of CIC in adults • Treatment of OIC in adults with chronic noncancer pain[a]	• 8 µg orally bid • 24 µg orally bid • 24 µg orally bid	• May cause fetal harm • Caution advised when administering to nursing women
Linaclotide[79–81]	Guanylate cyclase-C agonist; increased intestinal chloride and bicarbonate secretion increases fluid secretion and accelerates transit	2012	• Treatment of IBS-C in adults • Treatment of CIC in adults • Treatment of FC in pediatric patients (aged 6–17 y)	• 290 µg orally qd • 145 µg orally qd • 72 µg orally qd	• Maternal use not expected to result in fetal exposure to the drug or active metabolite • Maternal use not likely to result in clinically relevant exposure to the drug or active metabolite in nursing infants
Plecanatide[82,83]		2017	• Treatment of IBS-C in adults • Treatment of CIC in adults	• 3 mg orally qd • 3 mg orally qd	• Maternal use not expected to result in fetal exposure to the drug or active metabolite • Maternal use not likely to result in clinically relevant exposure to the drug or active metabolite in nursing infants
Tenapanor[84–86]	Sodium/hydrogen exchanger 3 inhibitor; reduced sodium absorption increases intestinal water secretion and accelerates intestinal transit	2019	• Treatment of IBS-C in adults	• 50 mg orally bid	• Maternal use not expected to result in fetal exposure • Maternal use not likely to result in clinically relevant exposure to the drug or active metabolite in nursing infants
Tegaserod[87–90]	Agonist of 5-HT4 receptors; stimulates the peristaltic reflex and intestinal secretion, inhibits visceral sensitivity and enhances intestinal transit	Withdrawn in 2022[b]	• Treatment of adult women aged <65 y with IBS-C	• 6 mg orally bid	• Not associated with risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes • Breastfeeding not recommended during treatment because of the potential for serious reactions in nursing infants

Notes: [a]Including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation. [b]Approved initially in 2002 and was then withdrawn in 2007 because of increased risk of cardiovascular events. It was reapproved in 2019 but withdrawn again in 2022 based on a business decision.

Abbreviations: 5-HT4 indicates serotonin type-4; bid, twice daily; CIC, chronic idiopathic constipation; FC, functional constipation; FDA, Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation; qd, once daily; OIC, opioid-induced constipation.

https://doi.org/10.2147/CEG.S464375 DovePress

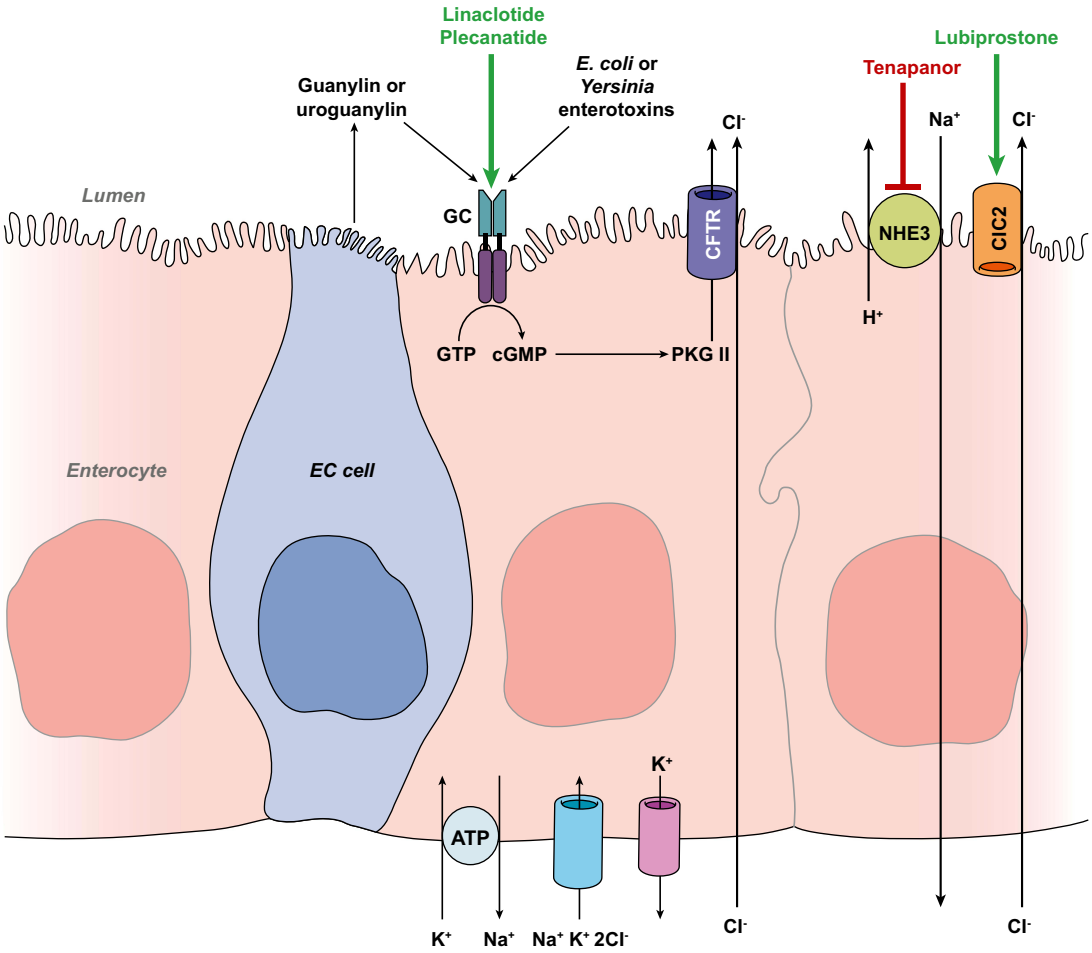

Figure 3 Mechanism of action of drugs approved in the United States for the treatment of IBS-C.[87] These agents increase intestinal water content by inhibiting NHE3 (tenapanor) or acting on chloride channels (lubiprostone, linaclotide, and plecanatide). Reprinted from *Gastroenterology*, volume: 155(6), Pannemans J, Tack J. How effective are secretagogues for irritable bowel syndrome with constipation. Gastroenterology. 1677–1679, Copyright 2018, with permission from Elsevier.[87]
Abbreviations: ATP indicates adenosine triphosphate; ClC2, chloride channel protein 2; CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine 3',5'-monophosphate; EC, enterochromaffin; GC, guanylyl cyclase; GTP, guanosine triphosphate; IBS-C, irritable bowel syndrome with constipation; NHE3, Na^+/H^+ exchanger 3; PKG, cGMP-dependent protein kinase.

in spontaneous bowel movements (SBMs; RR, 0.90; 95% CI 0.75–1.10), and its effect on complete spontaneous bowel movements (CSBMs) is unknown, because it was not assessed in the 2 studies.[99] Because only 8.4% of the study population in the pivotal studies were male patients,[77] lubiprostone is only indicated for adult women (Table 3).

Linaclotide

Linaclotide, an orally administered guanylate cyclase-C (GC-C) agonist, and its active metabolite binds to GC-C receptors on intestinal enterocytes, resulting in an increase in the intracellular concentration of cyclic guanosine monophosphate (cGMP), which regulates secretion of intestinal fluid.[79] Increased intracellular cGMP leads to activation of the cystic fibrosis transmembrane conductance regulator ion channel and secretion of chloride and bicarbonate ions into the intestinal lumen that increase both intestinal fluid secretion and GI transit (Figure 3).[79–81] A cellular study indicated that elevated cGMP could reduce the function of the sodium-hydrogen antiporter (NHE3) by altering its rate of turnover at the plasma membrane.[100] Linaclotide may also reduce visceral pain, as demonstrated by the reduction of abdominal contractions and reduced activation of nociceptors in an animal model of visceral pain.[80,101]

Linaclotide approval in the United States was based on the results of 2 phase 3 studies (NCT00938717[92] and NCT00948818[93]), which showed that oral linaclotide 290 µg once daily was safe and effective for relieving symptoms in

patients with IBS-C.[80,92,93] These were followed by a phase 3b study in which the effect of linaclotide versus placebo was assessed on abdominal symptoms.[94] The 3 studies included a 12-week treatment period, after which, in study 1 (NCT00938717[92]), treatment was continued for 14 additional weeks (total, 26 weeks). In studies 2 (NCT00948818[93]) and 3 (NCT03573908[94]), patients entered a 4-week randomized withdrawal period (RWP), during which patients who initially received linaclotide were rerandomized to linaclotide or placebo, and patients who initially received placebo were switched to linaclotide.

The results of studies 1 and 2 showed that linaclotide significantly improved global and individual symptoms, with significantly more linaclotide than placebo recipients achieving the 6 of 12-week US FDA combined responses and the 9 of 12-week abdominal pain, CSBM, and combined responses (coprimary end points; Table 4).[92,93] Furthermore, treatment benefits with linaclotide were maintained in patients who continued treatment during the RWP of study.[93]

The results of study 3 showed that linaclotide reduced the severity of abdominal symptoms that are important to patients with IBS-C (bloating, discomfort, and pain), as indicated by significant reduction in the Diary for IBS Symptoms-Constipation–derived abdominal score, as well as the abdominal bloating, abdominal discomfort, and abdominal pain scores (Table 4).[94] The percent of patients achieving 6 of 12-week abdominal score response was also higher with linaclotide than with placebo.[94]

Linaclotide was generally well tolerated in these studies, with most treatment-emergent AEs being of mild or moderate severity.[92,93] Diarrhea was the most common treatment-emergent AE with linaclotide, occurring at a higher incidence (3- to 8-fold) than with placebo. It was also the most common reason for treatment discontinuation (Table 5).[93,94]

Given its efficacy and safety, the ACG and AGA guidelines recommend the use of linaclotide to treat global IBS-C symptoms in patients with IBS-C.[1,62] Furthermore, linaclotide was shown to be most effective at relieving abdominal bloating in a meta-analysis comparing US FDA-approved agents for IBS-C.[102]

Plecanatide

Plecanatide is another orally administered GC-C agonist, which, along with its active metabolite, activates GC-C receptors, resulting in increased intestinal fluid secretion and faster GI transit (Figure 3).[82,83] Plecanatide may also reduce visceral pain, as demonstrated by the reduction of abdominal contractions in an animal model of visceral pain.[82,103]

Plecanatide was approved in the United States based on results of 2 identically designed, 12-week, randomized, double-blind, phase 3 studies (NCT02387359 and NCT02493452) in patients with IBS-C, which showed that oral plecanatide 3 mg once daily was safe and effective for relieving global and individual symptoms in patients with IBS-C.[82,95] In both studies, significantly more patients achieved the US FDA combined response (primary end point) with plecanatide 3 mg and 6 mg once daily than with placebo (study 1, 30.2% and 29.5% vs 17.8%; study 2, 21.5% and 24.0% vs 14.2%; all $p<0.01$; Table 4).[95] More plecanatide than placebo recipients also had sustained efficacy responses, and plecanatide was associated with significant improvements in stool consistency and reductions in straining (all $p<0.001$; Table 4). The efficacy results from these studies were supported by an integrated analysis of the 2 studies, which found that patients treated with plecanatide 3 mg or 6 mg had higher US FDA combined response rates (25.6% and 26.7% vs 16.0%), sustained efficacy response rates (24.3% and 25.6% vs 15.6%), US FDA abdominal pain response rates (36.6% and 39.3% vs 27.4%), and CSBM response rates (40.9% and 42.0% vs 31.4%) than placebo recipients (all $p<0.001$). Treatment benefits with plecanatide for individual symptoms were observed as early as week 1 to 2 of treatment and were sustained throughout the study period, as indicated by significant (all $p\leq0.05$) differences in the least-squares (LS) mean changes from baseline between the plecanatide doses and placebo. Benefits for abdominal pain were seen from week 2 and for abdominal discomfort, abdominal fullness, bloating, and cramping, from week 1 through to week 12.[104]

Plecanatide was generally well tolerated in patients with IBS-C, with most treatment-emergent AEs in the 2 studies being of mild or moderate severity.[95] Diarrhea was the most common treatment-emergent AE with plecanatide (incidence <5% with plecanatide 3- and 6-mg groups) and the most common reason for treatment discontinuation (Table 5).

Given its efficacy and safety, the plecanatide 3-mg once-daily dose was approved for use by the US FDA.[82] The plecanatide 6-mg once-daily dose was not associated with additional treatment benefit and appeared to have a higher incidence of AEs; therefore, it is not recommended for use in IBS-C.[82] The ACG guidelines recommend the use of plecanatide to treat global symptoms in patients with IBS-C,[1] and the AGA guidelines suggest using plecanatide in

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Table 4 Key Efficacy Results from Pivotal Trials of US FDA-Approved Treatments for IBS-C

Study	Patient population	Treatment	Demographics	Outcomes
Lubiprostone				
Drossman et al[91] 12-wk, phase 3, r, db, m studies 1 (N=590) and 2 (N=581)	Pts with IBS-C (Rome II criteria); aged ≥18 y; <3 SBMs/wk ≥5% of the time; ≥25% of SBMs with straining of at least moderate severity; ≥25% of SBMs hard or very hard stool consistency	Study 1 and 2 combined LUBI 8 µg bid (N=769) vs PL (N=385)	• Mean age (range), years: LUBI: 46.1 (19.0, 83.0); PL: 47.7 (18.0, 85.0) • Female, n (%): LUBI: 698 (90.8); PL: 359 (93.2) • Race, n (%) ○ White: LUBI: 595 (77.4); PL: 298 (77.4) ○ Black/AA: LUBI: 102 (13.3); PL: 50 (13.0) ○ Other: LUBI: 72 (9.4); PL: 37 (9.6)	• Rigorous responder rate[a] (primary end point): 17.9% vs 10.1%; p=0.001 • Significant (p≤0.05) mean improvements in AD/AP at months 2 and 3, and straining, constipation severity, and stool consistency at months 1, 2, and 3 • Significant mean improvements (p≤0.05) in AB at month 2 and bowel movement frequency at month 1
Linaclotide				
Chey et al[92] 26-wk, phase 3, r, db, m (N=804)	Pts with IBS-C (Rome II criteria); aged ≥18 y; average score of ≥3 for worst daily AP; average of <3 CSBMs/wk and ≤5 SBMs/wk	LINA 290 µg qd (N=401) vs PL (N=403)	• Mean age (range), years: LINA: 44.6 (19, 82); PL: 44.0 (18, 87) • Female, n (%): LINA: 368 (91.8); PL: 352 (87.3) • Race, n (%) ○ White: LINA: 316 (78.8); PL: 311 (77.2) ○ Black: LINA: 70 (17.5); PL: 78 (19.4) ○ Other: LINA: 15 (3.7); PL: 14 (3.5)	4 coprimary end points • 6/12-wk FDA combined response[b] rate: 33.7% vs 13.9%; p<0.0001 • 9/12-wk AP response rate[c]: 38.9% vs 19.6%; p<0.0001 • 9/12-wk CSBM response rate[c]: 18.0% vs 5.0%; p<0.0001 • 9/12-wk combined response: 12.7% vs 3.0%; p<0.0001 Changes from baseline and % responders[d] at weeks 12 and 26: • Worst AP: LS mean −1.9 vs −1.1; −2.1 vs −1.2; both p<0.0001 • AP responders[d]: 48.9% vs 34.5%; 49.1% vs 31.3%; both p<0.0001 • AB: LS mean −1.9 vs −1.0; −2.2 vs −1.2; both p<0.0001 • AB responders[d]: 42.9% vs 23.8%; 42.4 vs 25.1%; both p<0.0001 • CSBM/wk: LS mean 2.2 vs 0.7; 2.2 vs 0.7; both p<0.0001 • CSBM responders[d]: 47.6% vs 2.6%; 43.6% vs 18.6%; both p<0.0001
Rao et al[93] 16-wk,[e] phase 3, r, db, m (N=800)		LINA 290 µg qd (N=405) vs PL (N=395)	• Mean age (range), years: LINA: 43.3 (19, 81); PL: 43.7 (18, 84) • Female, n (%): LINA: 367 (90.6); PL: 357 (90.4) • Race, n (%) ○ White: LINA: 314 (77.5); PL: 301 (76.2) ○ Black: LINA: 78 (19.3); PL: 75 (19.0) ○ Other: LINA: 13 (3.2); PL: 19 (4.8)	4 coprimary end points • 6/12-wk FDA combined response[b]: 33.6% vs 21.0%; p<0.0001 • 9/12-wk AP response rate[c]: 34.3% vs 27.1%; p=0.027 • 9/12-wk CSBM response rate[c]: 19.5% vs 6.3%; p<0.0001 • 9/12-wk combined response rate[c]: 2.1% vs 5%; p=0.0004 Change from baseline and % responders[d] at week 12: • Worst AP: LS mean −1.9 vs −1.1; p<0.0001 • AP responders[d]: 50.1% vs 37.5%; p=0.0003 • AB: LS mean −1.9 vs −1.1; p<0.0001 • AB responders[d]: 43.5% vs 29.9%; p<0.0001 • CSBM/wk: LS mean 2.3 vs 0.7; p<0.0001 • CSBM responders[d]: 48.6% vs 29.6%; p<0.0001

Chang et al[94] 16-wk,[e] phase 3b, r, db, m(N=614)	Pts with IBS-C (Rome III criteria); aged ≥18 y; <3 SBMs/wk for ≥12 wk; average worst AP of ≥3, ≤6 CSBMs/wk, and ≤10 SBMs in the 2 wk prerandomization	LINA 290 µg qd (N=306) vs PL (N=308) (≈22% had prior LINA or PLEC therapy)	• Mean age (range), years: LINA: 46.5 (19, 85); PL: 46.8 (18, 79) • Female, n (%): LINA: 241 (78.8); PL: 255 (82.8) • Race, n (%) o White: LINA: 189 (61.8); PL: 198 (64.3) o Black: LINA: 76 (24.8); PL: 70 (22.7) o Other: LINA: 41 (13.4); PL: 40 (13.0)	Change from baseline to week 12 in: • AS (primary end point[f]): LS mean change −1.9 vs −1.2; $p<0.0001$ • AB: LS mean −1.9 vs −1.1; $p<0.0001$ • AD: LS mean −1.9 vs −1.2; $p<0.0001$ • AP: LS mean −1.9 vs −1.2; $p<0.0001$ Change from baseline and % responders at week 12: • AS: LS mean −1.89 vs −1.18; $p<0.0001$ • 6/12-wk AS responders[g]: 40.5% vs 23.4%; $p<0.0001$ • AP: LS mean: −1.89 vs −1.18; $p<0.0001$ • AP responders[d]: 45.1% vs 28.9%; $p<0.0001$ • AB: LS mean −1.89 vs −1.14; $p<0.0001$ • CSBM/wk: LS mean 2.37 vs 0.96; $p<0.0001$ • CSBM responders[d]: 51.3% vs 33.8%; $p<0.0001$
Plecanatide				
Brenner et al[95] 12-wk, phase 3, r, db, m studies 1 (N=1054) and 2 (N=1135)	Pts with IBS-C (Rome III criteria); aged 18–85 y	Study 1: PLEC 3 mg qd (N=351) and PLEC 6 mg qd (N=349) vs PL (N=354)	• Mean age (range), years: PLEC 3 mg qd: 43.0 (18, 81); PLEC 6 mg qd: 43.2 (18, 78); PL: 43.0 (18, 81) • Female, n (%): PLEC 3 mg qd: 267 (76.1); PLEC 6 mg qd: 266 (76.2); PL: 272 (76.8) • Race, n (%) o White: PLEC 3 mg qd: 220 (62.7); PLEC 6 mg qd: 206 (59.0); PL: 237 (66.9) o Black/AA: PLEC 3 mg qd: 95 (27.1); PLEC 6 mg qd: 118 (33.8); PL: 89 (25.1) o Other: PLEC 3 mg qd: 36 (10.2); PLEC 6 mg qd: 25 (7.2); PL: 28 (8.0)	• 6/12-wk FDA combined response[b] (primary end point): 30.2% and 29.5% vs 17.8%; both $p<0.001$ • Sustained efficacy response[h]: 28.2% and 27.5% vs 17.2%; both $p\leq0.001$ • Improvement in stool consistency at week 12: mean change 1.51 and 1.72 vs 0.98; both $p<0.001$ • Reduction in straining at week 12: mean change −2.23 and −2.44 vs −1.58; both $p<0.001$
		Study 2: PLEC 3 mg qd (N=377) and PLEC 6 mg qd (N=379) vs PL (N=379)	• Mean age (range), years: PLEC 3 mg qd: 44.0 (18, 83); PLEC 6 mg qd: 43.1 (18, 83); PL: 44.8 (18, 81) • Female, n (%): PLEC 3 mg qd: 270 (71.6); PLEC 6 mg qd: 273 (72.0); PL: 272 (71.8) • Race, n (%) o White: PLEC 3 mg qd: 309 (82.0); PLEC 6 mg qd: 312 (82.3); PL: 301 (79.4) o Black/AA: PLEC 3 mg qd: 61 (16.2); PLEC 6 mg qd: 61 (16.1); PL: 73 (19.3) o Other: PLEC 3 mg qd: 7 (1.8); PLEC 6 mg qd: 6 (1.6); PL: 5 (1.3)	• 6/12-wk FDA combined response[b] (primary end point): 21.5% and 24.0% vs 14.2%; both $p<0.01$ • Sustained efficacy response[h]: 20.7% and 23.7% vs 14.0%; $p<0.05$ and $p\leq0.001$, respectively • Improvement in stool consistency at week 12: mean change 1.36 and 1.27 vs 0.84; both $p<0.001$ • Reduction in straining at week 12: mean change −1.85 and −1.82 vs −1.28; both $p<0.001$
		Study 1 and 2 integrated data	NA	Change from baseline to week 12 in: • AP: LS mean −1.6 and −1.6 vs –1.3; both $p<0.0001$ • AB: LS mean −1.5 and −1.6 vs −1.1; both $p<0.0001$ • CSBM/wk: LS mean 1.2 and 1.4 vs 0.7; both $p<0.0001$

(*Continued*)

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Table 4 (Continued).

Study	Patient population	Treatment	Demographics	Outcomes
Tenapanor				
Chey et al (T3MPO-1)[60] 16-wk,[e] phase 3, r, db, m (N=606)	Pts with IBS-C (Rome III criteria); aged 18–75 y; during the 2-wk screening period: average ≤5 SBMs/wk and <3 CSBMs/wk; BSFS score <3; average weekly AP score ≥3; and no liquid stools for any SBM or mushy stools for >1 SBM, as per BSFS	TENA 50 mg bid (N=307) vs PL (N=299)	• Mean age, (SD), years: TENA: 45.0 (13.4); PL: 44.9 (13.0) • Female, n (%): TENA: 244 (79.5); PL: 249 (83.3) • Race, n (%) ○ White: TENA: 201 (65.5); PL: 186 (62.2) ○ Black/AA: TENA: 88 (28.7); PL: 100 (33.4) ○ Other: TENA: 18 (5.8); PL: 13 (4.4)	• 6/12-wk FDA combined response[b] (primary end point): 27.0% vs 18.7%; p=0.02 • 6/12-wk AP response rate[b]: 44.0% vs 33.1%; p=0.008 • 6/12-wk CSBM response rate[b]: 33.9% vs 29.4%; p=0.270 • 9/12-wk combined response rate[i]: 13.7% vs 3.3%; p<0.001 Change from baseline or % responders at week 12: • AB responders[d]: 37.8% vs 28.1%; p=0.014 • CSBM/wk: 2.2 vs 1.2; p=0.001
Chey et al (T3MPO-2)[61] 26-wk, phase 3, r, db, m (N=593)		TENA 50 mg bid (N=293) vs PL (N=300)	• Mean age (SD), years: TENA: 46.1 (13.1); PL: 44.8 (13.8) • Female, n (%): TENA: 240 (81.9); PL: 247 (82.3) • Race, n (%): ○ White: TENA: 185 (63.1); PL: 192 (64.0) ○ Black/AA: TENA: 92 (31.4); PL: 92 (30.7) ○ Asian: TENA: 12 (4.1); PL: 9 (3.0)	• 6/12-wk FDA combined response[b] (primary end point): 36.5% vs 23.7%; p<0.001 • 6/12-wk AP response rate[b]: 49.8% vs 38.3%; p=0.004 • 6/12-wk CSBM response rate[b]: 47.4% vs 33.3%; p<0.001 • 9/12-wk combined response rate[i]: 18.4% vs 5.3%; p<0.001 • 13/26-wk combined response rate[i]: 35.5% vs 24.3%; p=0.003 Change from baseline or % responders at week 26: • AB responders[d]: 44.7% vs 35.3%; p=0.02 • CSBM/wk: 3.3 vs 1.6; p<0.001

Notes: [a]Defined as a monthly responder for ≥2 of the 3 months of the study, where monthly responders were pts who rated their IBS symptoms as being at least moderately relieved (on a 7-point scale; 1 = significantly worse to 7 = significantly relieved) for all 4 weeks of the month or significantly relieved for ≥2 weeks of the month, with no ratings of moderately or severely worse. [b]US FDA responder defined as a pt who met both of the following criteria in the same week for ≥6 of the first 12 weeks of treatment period: (1) an improvement of ≥30% from baseline in the average of the daily worst abdominal pain scores (abdominal pain response) and (2) an increase of ≥1 CSBM from baseline (CSBM response). [c]At least 30% decrease in average of daily worst AP score (AP response), ≥3 CSBMs and an increase of ≥1 CSBM (CSBM response), and both outcomes in the same week (combined response) for ≥9 of 12 weeks. [d]Pts with ≥30% decrease in AP or AB or CSBM rate increase of ≥1 per week for ≥50% of weeks. [e]Pts completing 12 weeks of the double-blind treatment period could enter a 4-week, double-blind, randomized withdrawal period in which pts initially randomized to LINA were rerandomized to LINA 290 µg or PL, and pts previously randomized to PL received LINA 290 µg qd. [f]Change from baseline in weekly AS (calculated by averaging daily ASs over a week) throughout the treatment period; AS is an end point derived from the DIBSS-C. [g]Defined as a pt who experienced ≥2-point reduction from baseline in weekly AS for ≥6 of the 12 treatment weeks. [h]Defined as an overall responder plus a weekly responder for ≥2 of the last 4 weeks of the 12-week treatment period compared with placebo. [i]At least 30% decrease in average of daily worst AP score and an increase of ≥1 CSBM in the same week (combined response) for ≥9 of 12 weeks or ≥13 of 26 weeks.
Abbreviations: AA indicates African American; AB, abdominal bloating; AD, abdominal discomfort; AE, adverse event; AP, abdominal pain; AS, abdominal score; bid, twice daily; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; db, double blind; DIBSS-C, Diary for IBS Symptoms-Constipation; FDA, Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation; LINA, linaclotide; LS, least squares; LUBI, lubiprostone; m, multicenter; NA, not available; NS, non-significant; PLEC, plecanatide; PL, placebo; qd, once daily; r, randomized; pt, patient; TENA, tenapanor.

Table 5 Tolerability of US FDA-Approved Treatments for IBS-C Based on Results from Pivotal Studies

	Lubiprostone 8 µg bid vs PL	**Linaclotide 290 µg qd vs PL**			**Plecanatide 3 mg and 6 mg bid vs PL**	**Tenapanor 50 mg bid vs PL**	
	Drossman et al[91] (N=779 and 387)[a]	Chey et al[92] (N=402 and 403)	Rao et al[93] (N=406 and 396)	Chang et al[94] (N=306 and 308)	Brenner et al[95] (N=726, 726, 730)[a]	Chey et al (T3MPO-1)[60] (N=309 and 301)	Chey et al (T3MPO-2)[61] (N=293 and 300)
	12 wk	26 wk	12 wk	12 wk	12 wk	12 wk	26 wk
TEAE, %	50 vs 51	65.4 vs 56.6; $p<0.05$	56.2 vs 53.0; $p=0.395$	31.0 vs 26.6	23.8 and 19.8 vs 18.6	35.6 vs 24.6	48.8 vs 41.3
TRAE, %	22 vs 21					18.4 vs 6.0	21.8 vs 9.3
Most common TEAE[b], %		Diarrhea: 19.7 vs 2.5; $p<0.0001$ Flatulence: 3.7 vs 2.2 Viral GE: 3.7 vs 2.2	Diarrhea: 19.5 vs 3.5; $p<0.0001$ AP: 5.4 vs 2.5; $p=0.046$ Flatulence: 4.9 vs 1.5; $p=0.008$	Diarrhea: 4.6 vs 1.6 Headache: 2.6 vs 1.0	Diarrhea: 4.3 and 4.0 vs 1.0	Diarrhea: 14.6 vs 1.7	Diarrhea: 16.0 vs 3.7 AD: 3.4 vs 0.3 Flatulence: 3.1 vs 1.0
Most common TRAE, %	Nausea: 8 vs 4 Diarrhea: 6 vs 4	NR	NR	NR	NR	Diarrhea: 13.3 vs 0.7	Diarrhea: 15.0 vs 2.7
Severe TEAEs	NR	7.7 vs 4.7	6.2 vs 1.9	NR	2.3 and 1.5 vs 1.0	NR	NR
Serious TEAE, %	1[c] vs 0	1[d] vs 1.7[d]	0.5 vs 0.5	1.3[d] vs 0.6[d]	0.8[d] vs 0.8[d,e]	1.3[d] vs 0	1.4[f] vs 2.0
Discontinuations due to AEs, %	5 vs 7	10.2 vs 2.5 (most common: diarrhea 4.5 vs 0.2)	7.9 vs 2.8 (most common: diarrhea 5.7 vs 0.3)	2.9 vs 1.3 (most common: diarrhea 1.6 vs 0)	2.5 and 2.2 vs 0.4 (most common: diarrhea 1.2 and 1.4 vs 0)	7.4 vs 0.7 (most common: diarrhea 6.5)	7.8 vs 1.0 (most common: diarrhea 6.5 vs 0.7)
Deaths, *n*	1[d] vs 0	0 vs 0	0 vs 0	0 vs 0	1[d] and 0 vs 0	0 vs 0	0 vs 0

Notes: [a]Pooled data from 2 studies. [b]Incidence ≥2% and >1% greater than PL. [c]Noncardiac chest pain possibly related to lubiprostone. [d]Unrelated to treatment. [e]Plecanatide-treated patients vs placebo. [f]One SAE (diarrhea) possibly related to treatment.

Abbreviations: AD indicates abdominal distension; AE, adverse event; AP, abdominal pain; bid, twice daily; FDA, Food and Drug Administration; GE, gastroenteritis; IBS-C, irritable bowel syndrome with constipation; NR, not reported; PL, placebo; qd, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

https://doi.org/10.2147/CEG.S464375 DovePress

patients with IBS-C.[62] The AGA guidance is based on the results of a systematic review of data from the 2 phase 3 studies and a phase 2b study,[105] which showed significant benefit with plecanatide relative to placebo in terms of US FDA combined response (RR, 0.87; 95% CI 0.83–0.92), abdominal pain response (RR, 0.86; 95% CI 0.81–0.92), and CSBM response (RR, 0.84; 95% CI 0.79–0.91); however, the results were rated down by the committee, as the 95% CIs crossed the threshold of a clinically meaningful difference of ≥10%.[62]

Tenapanor

Tenapanor is an orally administered, first-in-class, small-molecule inhibitor of the NHE3 antiporter expressed on the apical surface of enterocytes in the small intestine and colon.[60,84,85] Unlike secretagogues that increase stool water content by secreting ions into the lumen, tenapanor-mediated inhibition of NHE3 reduces sodium absorption, leading to increased luminal water, which facilitates accelerated intestinal transit time and softer stool consistency, thereby improving GI motility (Figure 3).[85,86] Tenapanor also reduced visceral hypersensitivity in animal models.[84,106]

The approval of tenapanor 50 mg twice daily in the United States was based on the results of 2 randomized, double-blind, phase 3 studies (T3MPO-1 [NCT02621892] and T3MPO-2 [NCT02686138]) in patients with IBS-C, which showed that oral tenapanor 50 mg twice daily was safe and effective for relieving global and individual symptoms in patients with IBS-C.[60,61,84] The 2 studies included a 12-week treatment period, after which, in T3MPO-2, treatment was continued for 14 additional weeks (total, 26 weeks).[61] In T3MPO-1, patients entered a 4-week RWP, during which patients who initially received tenapanor were rerandomized to tenapanor or placebo, and patients who initially received placebo were switched to tenapanor.[60] Tenapanor significantly improved global and individual symptoms of IBS-C during the 12-week treatment period, as indicated by more patients in the tenapanor group achieving 6 of 12-week US FDA combined response rates, 6 of 12-week abdominal pain and CSBM rates, as well as 9 of 12-week and/or 13 of 26-week combined response rates (Table 4).

Tenapanor was generally well tolerated in the T3MPO-1 and T3MPO-2 studies (Table 5).[60,61] Diarrhea was the most common treatment-emergent AE with tenapanor (incidence ≈15%) and the most common reason for treatment discontinuation (Table 5).[60,61] Results from T3MPO-2 showed that diarrhea was usually mild or moderate, transient (≤1 week in duration), and occurred within the first week of treatment.[61] During the RWP in T3MPO-1, treatment-related diarrhea occurred in 10.2% of patients in the placebo-to-tenapanor group, 1.6% of patients in the tenapanor-to-tenapanor group (0.8% [1 patient] discontinued treatment), and no patients in the tenapanor-to-placebo group.[60] These results indicate that diarrhea usually occurs early in treatment, and the incidence decreases with continued therapy. Tenapanor was also generally well tolerated during longer-term therapy (≥52 weeks), as demonstrated in the T3MPO-3 extension study in which 312 patients who had completed the T3MPO-1 or T3MPO-2 studies were enrolled.[107] Of the 312 patients, 90 received tenapanor for ≥52 weeks. Treatment-emergent AEs occurred in 37.5% (15.4% treatment related) of patients in the overall population and in 57.8% (20% treatment related) of patients who had received ≥52 weeks of treatment, with the most common AE being mild or moderate diarrhea (10.6% and 11.1% in the respective populations).[107]

The AGA guidelines suggest using tenapanor in patients with IBS-C[62] based on results of a systematic review of data from T3MPO-1 and T3MPO-2 and a phase 2 study (NCT01340053),[108] which showed significant benefit with tenapanor relative to placebo in terms of US FDA combined response (RR, 0.84; 95% CI 0.79–0.90), abdominal pain response (RR, 0.81; 95% CI 0.73–0.88), and CSBM response (RR, 0.83; 95% CI 0.77–0.90); however, the results were rated down by the committee, because the 95% CIs crossed the threshold of a clinically meaningful difference of ≥10%.[62]

Brain–Gut Behavioral and Neuromodulator Therapies

In patients with IBS-C who have persistent abdominal pain and/or psychological symptoms such as symptom-related anxiety, depression, or maladaptive coping behaviors despite treatment with the US FDA-approved prescription medications, the AGA recommends the addition of or switch to low-dose tricyclic antidepressants (TCAs; if not already taking these), serotonin-norepinephrine reuptake inhibitors (SNRIs), and brain–gut behavioral therapy (BGBT) (Table 2).[63] Although the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of IBS-C alone is not recommended, appropriate treatment of concomitant depression and anxiety has led to global improvement in the management of disease in patients with IBS-C. They can be combined with other therapies and are crucial for integrated care of IBS. They typically complement medical treatment but can also be offered as standalone alternatives. BGBTs need not have

condition-specific effects because they act on central or gut–brain systems of symptom control.[72] Several systematic reviews and meta-analyses have shown that BGBTs such as cognitive-behavioral therapy (CBT), gut-directed hypnotherapy (GDH), and relaxation therapy are effective in reducing global IBS symptoms[73,109] and GI symptoms[74] and in improving mental health and daily functioning in patients with IBS,[75] with benefits sustained for up to 1 year after treatment (Table 2).[74] Among the available BGBTs, CBT and GDH have the most evidence supporting their efficacy in improving IBS symptoms.[73] Current ACG guidelines suggest using gut-directed BGBTs along with other IBS therapies in emotionally stable patients with IBS symptoms triggered by cognitive or affective signals.[1]

TCAs are gut–brain neuromodulators that may improve psychological distress in patients with IBS because of their effects on cholinergic, dopaminergic, and norepinephrine receptors. In a systematic review of 8 placebo-controlled trials (N=523) undertaken by the AGA, TCAs (amitriptyline, desipramine, trimipramine, imipramine, and doxepin) were found to improve global symptoms (RR, 0.67; 95% CI 0.54–0.82) and abdominal pain (RR, 0.76; 95% CI 0.61–0.94), with the improvements in global symptoms (but not abdominal pain) being clinically relevant (Table 2).[99] The AGA guidelines suggest adding or switching to TCAs in patients with persistent abdominal and/or psychological symptoms, and the ACG guidelines recommend their use for the treatment of global IBS symptoms.[1,62,63] The AGA guidelines also suggest SNRIs as an option for patients with persistent abdominal and/or psychological symptoms.[63] Although there are no studies in which the efficacy of SNRIs is assessed in patients with IBS, the AGA and the Rome Foundation recommend their use based on the beneficial effects of SNRIs in other pain indications.[62–64,71]

Other Therapies

Probiotic supplements are often used by patients for various conditions, and their use by patients and the population at large has increased in recent years.[110] However, there are no robust data supporting the use of probiotics in patients with IBS.[1,110] Additionally, data suggest that probiotic supplements can lead to negative symptoms, including brain fog in patients with IBS-C.[111] Given the lack of clear benefit with probiotics, ACG guidelines do not recommend the use of probiotics in IBS,[1] and the AGA guidelines make no recommendation for their use in patients with IBS.[110] The ACG guidelines also do not recommend the use of fecal microbiota transplant (FMT) as a treatment for global IBS symptoms.[1] Results of a recent meta-analysis of 8 randomized studies of patients with IBS found no significant difference between FMT and placebo in terms of improving IBS symptom severity.[112]

New and Upcoming Treatment Options for IBS-C

The US FDA requires that any potential therapy for IBS should demonstrate clinical benefits in terms of both abdominal and bowel responses.[98] Among the agents evaluated, ROSE-010, a glucagon-like peptide-1 analog, was shown to improve abdominal pain of IBS[113] and accelerate colonic transit[114] in phase 2 studies. The manufacturer plans to undertake another phase 2 study to further evaluate its efficacy in patients with IBS-C or IBS-M.[115]

Other agents have shown potential in all patients with IBS, regardless of subtype. One such agent is ethosuximide, which is being evaluated in a phase 3 trial (in combination with pentoxifylline) to treat abdominal pain related to IBS (NCT04217733). Also being evaluated is the second-generation histamine-1 receptor antagonist ebastine, the efficacy of which is being assessed in a phase 4 study in patients with IBS (NCT01908465). In an earlier phase 4 study, ebastine was shown to reduce visceral hypersensitivity and abdominal pain and to improve global IBS symptoms (NCT01144832).[116] Nabilone, a synthetic cannabinoid, has been shown to reduce pain as an add-on treatment in other conditions, including cancer pain, chronic noncancer pain, and fibromyalgia, and may be beneficial in relieving IBS abdominal pain.[117] Pregabalin, a second-generation α2δ ligand, was shown to improve IBS-related abdominal pain, bloating, and diarrhea relative to placebo in a phase 2 study in patients with IBS (NCT00977197), but additional trials are needed to confirm these observations.[118]

In addition, a drug-free treatment, the Vibrant capsule, is approved for use in patients with chronic idiopathic constipation,[119] but its efficacy in patients with IBS-C remains to be confirmed. The Vibrant capsule sends out vibrations that act locally in the colon to induce peristalsis and relieve constipation.[120]

The Importance of the Patient–HCP Relationship

Effective clinical interactions between patients and HCPs, built on empathy, transparency, and collaboration, are crucial for the successful management of IBS. When patients are treated with empathy, they feel satisfied with their level of care and empowered; in turn, this reduces their levels of anxiety and, ultimately, improves their clinical outcomes.[45] HCPs may also obtain more professional satisfaction when they employ an empathetic approach, eg, their levels of burnout can be reduced.[45] Empathy can be expressed by simply acknowledging the reality of a patient's symptoms and asking what impact these symptoms have on their daily life and, importantly, listening carefully to the answers.[48,121] Being cognizant of, and responding to, psychosocial cues during office visits can provide additional opportunities for expressing empathy.[121] Another component of positive patient–HCP relationships is having open discussions around bowel symptoms.[58] This is particularly important because diagnoses are symptom-based and receiving a diagnosis aids in the education process critical to patient self-management, reduces health care–seeking behaviors, and increases treatment adherence.

Effective patient education ensures that patients understand their diagnosis, feel involved in treatment decision-making, increase treatment compliance, and address any concerns. Patients should be informed that the disease is chronic, and that treatment aims to improve symptoms rather than achieve complete symptom alleviation.[122] Knowledge can help patients feel in control of their health and encourage them to take care of themselves.[37] Patients' understanding can be assessed by asking them to repeat back what they have heard during their visit.[121]

Effective communication between patients and HCPs is paramount for providing a correct diagnosis and reducing both health care costs and overall disease burden.[25,37,42,58,122] The use of open-ended questioning can elicit helpful information from the patient (eg, symptomatic triggers) that may help with treatment planning and may also enable the HCP to ascertain patient expectations, eg, about the appointment they are attending or the treatment they will be receiving.[121] Treatment options should be discussed with patients so that they can make an informed decision in collaboration with their HCP.[99,122] This approach forms the basis of shared decision-making, a model for making decisions about treatment in which both patients and clinicians participate equally.[123] Shared decision-making is particularly useful in the practice of gastroenterology because conditions such as IBS have no definitive "one-size-fits-all" treatment option. Instead, via effective patient–HCP interactions, the most appropriate management strategies can be identified in accordance with the individual patient's priorities and preferences.[121,123] Engaging multiple clinicians from different specialties (eg, gastroenterologists, trainees, dietitians, psychiatrists, behavioral therapists, hypnotherapists) can also contribute to improved patient outcomes.[124,125]

Conclusion

IBS is a common disorder of the gut–brain axis associated with substantial societal burden in terms of tremendous health care costs, opportunity costs, and decreased quality of life. IBS-C is a common IBS subtype, accounting for approximately one-third of cases. Treatment of IBS-C typically begins with lifestyle interventions and nonpharmacologic options, such as fiber supplements and osmotic laxatives. In patients with inadequate response to these therapies, 4 currently available, US FDA-approved therapies (lubiprostone, linaclotide, plecanatide, and tenapanor) may relieve IBS-C symptoms. These agents are generally well tolerated and efficacious in improving IBS-C symptoms, including constipation and abdominal pain. In patients with persistent abdominal pain and/or psychological symptoms, BGBT or neuromodulator therapy may be beneficial. The future may be brighter for patients with IBS-C if progress is made to increase HCP awareness of the issues with which patients with IBS-C contend and the potential benefits that the totality of the treatment landscape may offer them.

Author Contributions

All authors made a significant contribution to the work reported; participated in the conception, acquisition of data, analysis, and interpretation; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript.

Funding

Medical writing and editorial support were provided by Ashfield MedComms, an Inizio company, and funded by Ardelyx, Inc.

Disclosure

Morgan Allyn Sendzischew Shane reports no disclosures. Michael Cline reports speaker bureau and knowledge leader committees with Ardelyx, Inc, and Evoke Pharma. Baharak Moshiree reports grant funding from Atmo, Restalsis, and Medtronic; advisory committees for Salix, Allergan, Alnylam, Ironwood; speakers' bureau with Salix, Takeda, QOL Medical, Allergan, Bausch Pharmaceuticals; speaking for Salix & Bausch Pharmaceuticals, Allergan Pharmaceuticals, Cairn Diagnostics and AbbVie; speaking and advisory board with Alnylam, Progenity, and Nestle. Johannah Ruddy, David Rosenbaum, and Susan Edelstein are employed by Ardelyx, Inc. The authors report no other conflicts of interest in this work.

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