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Understanding and Managing IBS and CIC in the Primary Care Setting

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Target Audience

This activity has been designed to meet the educational needs of primary care providers, physician assistants, and nurse practitioners involved in the care of patients with irritable bowel syndrome (IBS) and chronic idiopathic constipation (CIC).

Learning Objectives

After completing this activity, participants should be better able to:

- Describe the burden of IBS and CIC on patients and the health care system
- Discuss new and emerging diagnostic strategies and therapies for IBS and CIC
- Describe the evidence base regarding the efficacy and safety of conventional and newer therapies for IBS and CIC
- Differentiate among newer therapies for IBS and CIC with regard to pharmacology, efficacy, safety, and tolerability

Accreditation Statement

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Faculty Disclosure

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Irritable bowel syndrome (IBS) and chronic idiopathic constipation (CIC) are highly prevalent chronic functional gastrointestinal (GI) disorders that are among the most common conditions seen by gastroenterologists and primary care providers.[1-4] IBS is estimated to affect from 7% to 16% of the US population,[5] or nearly 1 in 7 Americans.[6] These disorders represent a major burden in terms of patient quality of life, work productivity, and health care costs.[7-10] A systematic review of studies reported that quality of life among patients with IBS is consistently lower than that of matched controls, and estimated that the total annual cost of IBS care per patient in the United States exceeds $15,000.[9] Results from the "IBS in America" survey indicate that most patients with constipation-predominant IBS (IBS-C) experience symptoms at least 4 to 6 days per week,[11] and in another survey, more than half of patients with diarrhea-predominant IBS (IBS-D) reported experiencing fecal urgency the majority of the time.[12] Another important disease burden of IBS is abdominal pain, which is consistently reported as a key symptom that drives patients to seek care from physicians.[10,11,13] Although practice patterns relating to the diagnosis and management of IBS are not well-described, recent data suggest that many diagnoses of IBS are made by generalists,[14] and approximately 40% of patients with IBS-D are treated by their primary care physicians.[12] To that end, the confidence of primary care providers to diagnose IBS/CIC accurately and utilize evidence-based treatments is important in managing these chronic and costly disorders.

Pathophysiology of IBS

The pathophysiology of IBS is complex and involves multiple mechanisms, with no single abnormality accounting for clinical presentation in all patients.[8,15,16] Traditionally, abnormalities in motility, visceral sensation, brain-gut interactions, and psychosocial processing have been implicated, with alterations in immune activation, intestinal permeability, and the gut microbiome increasingly recognized throughout the past decade.[8,17-20] Many studies have confirmed a strong association between acute enteric infection and subsequent IBS symptoms (ie, postinfectious IBS [PI-IBS]).[21-24] A meta-analysis demonstrated that the risk of developing PI-IBS increases over 7-fold after an acute episode of infectious gastroenteritis,[23] and other data indicate that a significant minority of patients will experience symptoms that persist for at least 8 years.[21] Additionally, data show quantitative and qualitative changes in the fecal microbiota of patients with IBS,[17] with one study correlating IBS severity with a distinct fecal microbiota signature.[25] Bile acid malabsorption also appears to play a role in some patients with IBS. A systematic review of 17 studies showed that moderate bile acid malabsorption was present in up to one-third of patients presenting with IBS-D–type symptoms.[26]

It has long been recognized that patients often associate food intake with their IBS symptoms,[15,27-29] and increasing evidence suggests that foods contribute to the pathogenesis of the disorder in some cases.[28] Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are short-chain carbohydrates that are poorly absorbed, osmotically active, and rapidly fermented by gut bacteria, leading to gas production and luminal distension.[16,30] Other potential diet-related triggers include gluten and wheat, although more data are needed to determine the role of these constituents in causing IBS-like symptoms.[28] It has been shown that ingestion of poorly absorbed or digested carbohydrates such as those mentioned previously are associated with changes in motility patterns, visceral sensation, the microbiome, gut permeability, immune activation, and brain-gut interactions.[16,28,31]

Diagnosing IBS

The diagnosis of IBS can be confidently established without an exhaustive battery of diagnostic tests; a careful history

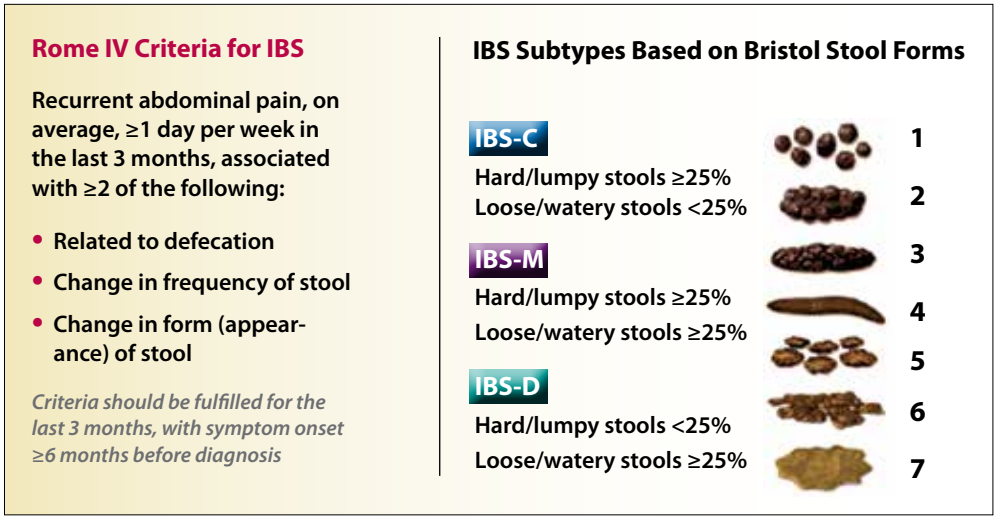

Figure 1. Defining and characterizing IBS. IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; IBS-M, mixed irritable bowel syndrome. Adapted from Mearin F et al. *Gastroenterology.* 2016;150(6):1393-1407.[33]

and physical examination can identify key symptoms and exclude alarm features.[8,20,32,33] Select diagnostic tests may be needed to distinguish IBS from the organic diseases that can mimic it—the most common being inflammatory bowel disease (IBD), systemic hormonal disturbances, enteric infections, and colorectal cancer—and disorders associated with malabsorption, such as celiac disease, bile acid diarrhea, and carbohydrate maldigestion.[8,34] The possibility of obstructive defecation (pelvic-floor dyssynergia) should be considered in patients with constipation-predominant symptoms, and a high-quality digital rectal examination can provide helpful information for that diagnosis.[20] Patients with paradoxical anal contraction on straining should be referred for physiologic testing to confirm the diagnosis.[8,20,35]

Because the prevalence of most organic disorders in patients with suspected IBS is comparable with that of the non-IBS population, expensive or invasive diagnostic testing (eg, abdominal imaging, colonoscopy) is not recommended in patients with typical symptoms but without alarm features for organic disease.[8,20,33,34] Alarm features include rectal bleeding, unintentional weight loss, iron-deficiency anemia, nocturnal symptoms, and a family history of organic diseases, including colorectal cancer, IBD, and celiac disease. Patients with concerning features such as these should be referred to secondary care for further investigation and management.[35] However, although the presence of these features identifies patients who may be more likely to have organic disease, most patients will ultimately have negative test results and be diagnosed with IBS.[8]

Given the low probability of organic disease in patients with typical IBS symptoms, the American College of Gastroenterology (ACG) IBS Task Force recommends the use of symptom-based criteria for diagnosing IBS.[36] According to the Rome IV criteria, abdominal pain must be present to make the diagnosis of IBS (Figure 1).[33] Although abdominal bloating and/or distension are often present, neither is required for diagnosis. Once these symptom-based criteria are met and the diagnosis is established, patients can be subtyped based on their predominant stool pattern into IBS-C, IBS-D, mixed IBS (IBS-M), or IBS unclassified (IBS-U; Figure 2).[37]

The Rome IV diagnostic criteria recognize IBS-C and CIC, or functional constipation, as 2 distinct conditions, with the presence of abdominal pain being the discriminating factor for IBS-C (Table 1).[33] However, considerable symptom overlap and disease burden occurs between the 2 conditions, and many patients tend to migrate between these diagnoses over time, making it difficult to distinguish between them.[36] These similarities have led to the suggestion that these conditions exist along a spectrum of disease, with the presence of abdominal symptoms indicating disease severity rather than defining 2 separate conditions.[10] Additional research in this area is needed.

Although the need for diagnostic testing is minimal in patients with typical IBS symptoms and no alarm features, a complete blood count is recommended to exclude findings warranting further investigation (eg, elevated white blood cell count, anemia).[33] Measurement of C-reactive protein or fecal calprotectin levels should be considered, particularly in patients with diarrhea,[33] as the use of these inflammatory markers to exclude IBD is supported by several recent meta-analyses.[38,39] The presence of circulating antibodies to cytolethal distending toxin B (CdtB) and vinculin has also demonstrated potential in differentiating IBS-D from IBD.[40] The use of these antibodies as biomarkers is predicated on data from a postinfectious animal model demonstrating that host antibodies to CdtB and/or vinculin are associated with an IBS-like phenotype.[41,42] In a validation study involving 2375 patients with IBS-D, anti-CdtB and antivinculin titers were significantly higher in patients with IBS-D compared with

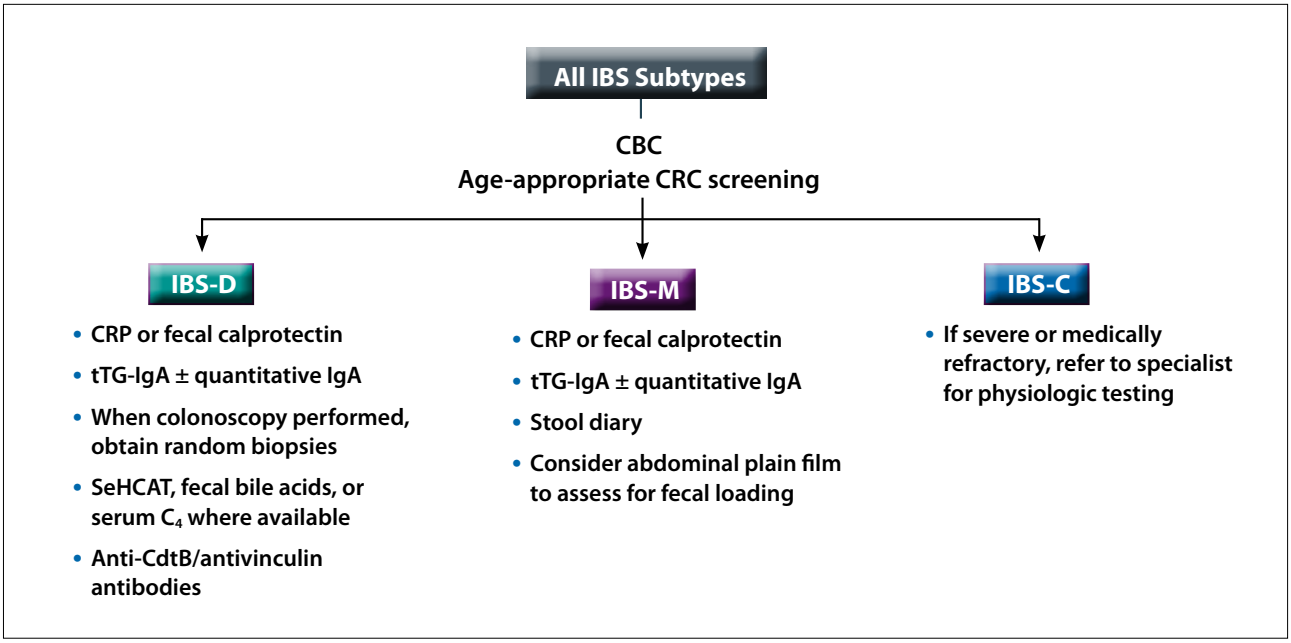

Figure 2. Suggested diagnostic workup for patients with suspected IBS.[8,40] CBC, complete blood count; CdtB, cytolethal distending toxin B; CRC, colorectal cancer; CRP, C-reactive protein; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; IBS-M, mixed irritable bowel syndrome; IgA, immunoglobulin A; SeHCAT, tauroselcholic (selenium 75) acid retention test; tTG, tissue transglutaminase.

healthy controls, patients with IBD, and patients with celiac disease.[40] Optimization of antibody titer levels demonstrated a likelihood ratio for diagnosing IBS-D vs IBD of 5.2 for anti-CdtB and 2.0 for antivinculin.[40]

The US Preventive Services Task Force recommends screening colonoscopy in average-risk patients with IBS symptoms and no alarm features who are ages 50 years or older.[43] Although indiscriminate colonoscopy has a low yield in patients with IBS-like symptoms, a small subset of patients with suspected IBS-D have microscopic colitis.[44] In a case-control study involving 466 patients with suspected nonconstipation-predominant IBS, microscopic colitis was found in 1.5% of patients overall and 2.3% of those ages 45 years and older.[44] These findings suggest that random colon biopsies may have diagnostic value when colonoscopy is performed in patients with suspected IBS-D.[8,44]

The value of screening for celiac disease in patients with suspected IBS, however, remains unclear. Current ACG guidelines recommend that patients with IBS-like symptoms undergo screening for celiac disease with serologic testing.[45] This recommendation is supported by the results of a recent meta-analysis of 36 studies demonstrating a significantly higher prevalence of biopsy-proven celiac disease among patients with all subtypes of IBS compared with healthy controls.[46] However, these findings were no longer significant when the analysis was restricted to North American studies or those derived from the general population, making the value of celiac disease screening in community practice less clear. Despite this conflicting evidence, clinicians are generally encouraged to have a low threshold for celiac disease screening in patients with IBS, particularly those with IBS-D.[8,20,33]

Several other diagnostic tests may have a role in assessing patients with suspected IBS. Breath tests are used in diagnosing various carbohydrate maldigestion syndromes as well as small intestinal bacterial overgrowth, both of which are commonly associated with IBS-like symptoms.[47] Despite significant heterogeneity in test performance, preparations, and indications among current tests, a recent consensus of experts concluded that breath testing can be useful in diagnosing not

Table 1. Rome IV Diagnostic Criteria for Functional Constipation[a]

Must include ≥2 of the following:
• Straining
• Lumpy or hard stools (BSFS 1-2)
• Sensation of incomplete evacuation
• Sensation of anorectal obstruction/ blockage
• Manual maneuvers to facilitate >25% of defecations
• <3 SBMs per week

[a]Criteria should be fulfilled for the previous 3 months, with symptom onset ≥6 months before diagnosis. Loose stools are rarely present without the use of laxatives. These criteria are insufficient for the diagnosis of IBS.

BSFS, Bristol Stool Form Scale; IBS, irritable bowel syndrome; SBMs, spontaneous bowel movements.

Data from Mearin F et al. *Gastroenterology*. 2016;150(6):1393-1407.[33]

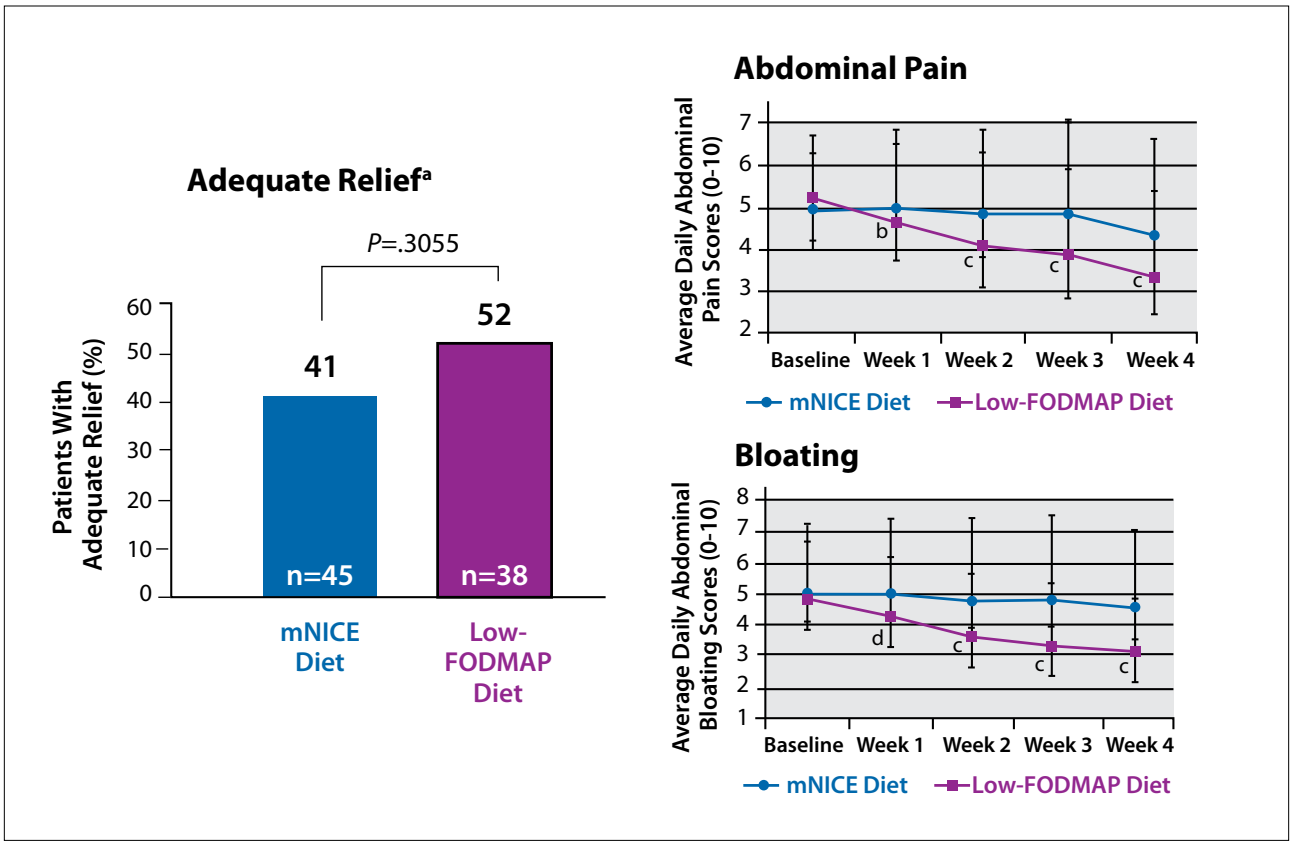

Figure 3. Results of a US-based randomized controlled trial of a low-FODMAP diet compared with an mNICE diet.[30] Patients were instructed to eat small frequent meals, avoid trigger foods, and avoid excess alcohol and caffeine. FODMAP-containing foods were not excluded from the mNICE diet. [a]The proportion of patients reporting adequate relief of gastrointestinal symptoms for ≥50% of weeks 3 and 4. [b]$P \leq .01$. [c]$P \leq .0001$. [d]$P \leq .001$. FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide, and polyol; mNICE, modified National Institute for Health and Care Excellence. Adapted from Eswaran SL et al. *Am J Gastroenterol.* 2016;111(12):1824-1832.[30]

only carbohydrate maldigestion and small intestinal bacterial overgrowth, but also in assessing patients with bloating and methane-associated constipation.[47] Given the role of bile acid malabsorption in some IBS patients,[26] tests that identify such malabsorption may be helpful in patients with IBS-D.[8] The tauroselcholic (selenium 75) acid retention test (SeHCAT), serum C_4 measurement, and fecal bile acid measurement are not widely available in the United States, but these tests may eventually become routinely available in clinical practice to identify patients likely to benefit from bile acid sequestrant therapy.[8]

Treatment of IBS

The treatment of IBS begins with a discussion with the patient that explains the condition, offers reassurance regarding its benign natural history, and provides education about the various therapeutic options.[33] Given the heterogeneity of the disorder, there is no algorithm that suits all patients.[20] Rather, the general approach to management should be tailored to each patient's predominant symptom type and severity.[8,20] Conventional first-line approaches are directed toward improving abdominal pain, cramping, bloating, and bowel symptoms (eg, diarrhea or constipation).

Dietary Modifications

Low-FODMAP Diet Although dietary therapy has not traditionally played a key role in treating IBS, there has been renewed interest in the dietary management of IBS throughout the past decade. The recognition of the physiologic effects of FODMAPs on the GI tract has prompted the use of a low-FODMAP diet in treating IBS. Several small studies have demonstrated benefits of FODMAP restriction on IBS symptoms, although these studies suffer from methodologic weaknesses, and benefits have not been consistent.[48-50] More recently, a US-based, randomized controlled trial compared the effects of a low-FODMAP diet with dietary recommendations based on modified guidelines from the National Institute for Health and Care Excellence (mNICE) in 84 patients with IBS-D.[30] After 4 weeks of dietary intervention, 52% of patients following the low-FODMAP diet reported adequate relief of their IBS-D symptoms (primary endpoint) compared with 41% of the mNICE group

Table 2. Overview of Pharmacologic Therapies for IBS-D[8,20,36]

	Agent(s)	Quality of Evidence	Treatment Benefits	Most Common Adverse Events
Antispasmodics	Various	Low	Some agents improve global symptoms and pain	Dry eyes/mouth, sedation, constipation
	Peppermint oil	Moderate	Improves global symptoms and cramping	Heartburn, dyspepsia, constipation
Antidepressants	TCAs	High	Improve global symptoms and pain	Dry eyes/mouth, sedation, constipation
5-HT_3 Antagonists	Alosetron	Moderate	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D	Constipation, rare ischemic colitis
Opioid Receptor Modulators	Loperamide	Very low	Beneficial for diarrhea, but not for global symptoms or pain	Constipation
	Eluxadoline	High	Improves global symptoms	Constipation, nausea
Antibiotics	Rifaximin	Moderate	Improves global symptoms, pain, and bloating	Similar to placebo
Probiotics	Various	Low	As a class, possible benefits for global symptoms, bloating, and gas, but unable to recommend specific probiotic strains or formulations	Similar to placebo

IBS-D, diarrhea-predominant irritable bowel syndrome; TCAs, tricyclic antidepressants.

(*P*=.31; Figure 3). The low-FODMAP diet led to a higher proportion of abdominal pain responders than the mNICE diet (51% vs 23%; *P*=.008), as well as greater reductions in average daily scores of abdominal pain and bloating, stool consistency, frequency, and urgency. In a subsequent analysis, the low-FODMAP diet was associated with significantly greater improvements in health-related quality of life, anxiety, and activity impairment compared with the mNICE diet.[49]

Despite increasing evidence supporting a low-FODMAP intervention, this diet is not intended to be a long-term solution for IBS.[30] Rather, patients who respond to FODMAP exclusion should gradually reintroduce FODMAP-containing foods to identify the particular foods they can consume to maintain benefit.[8,30] In addition, given the challenges in implementing the diet, clinicians are encouraged to engage a registered dietician to counsel patients on the various aspects of the diet and to integrate these practitioners into the health care team when possible.[8,51]

Gluten Restriction Some patients with IBS have attributed their symptoms to gluten in the absence of celiac disease, a condition known as nonceliac gluten sensitivity or nonceliac wheat sensitivity.[20,28,52] In 2 small randomized controlled trials in patients with IBS in whom celiac disease had been excluded, those following a gluten-containing diet were more likely to experience symptoms than those following a gluten-free diet.[53,54] In contrast, another small randomized controlled trial failed to demonstrate any benefit of gluten restriction in patients with IBS who were following a low-FODMAP diet.[55] Given these inconsistencies, the impact of gluten restriction on IBS symptoms remains unclear, despite its popularity.

Lifestyle Interventions

Psychologic interventions, such as cognitive behavioral therapy, can be effective in improving IBS symptoms, but the use of these modalities is limited by the availability of therapists with expertise in managing this disorder.[36] Structured exercise intervention has also been shown to improve IBS symptoms and some aspects of disease-specific quality of life,[56] leading experts to recommend that patients increase their physical activity.[8]

Pharmacologic Approaches to Managing IBS-D

The pharmacologic therapies for IBS-D include antispasmodics and peppermint oil, serotonergic agents, antidepressants, antibiotics and probiotics, and opioid receptor modulators (Table 2).

Antispasmodics and Peppermint Oil

Antispasmodics have been used for decades to treat the abdominal pain associated with IBS, based on their ability to relax GI smooth muscle.[8,33] The 2014 ACG systematic review on the efficacy of IBS/CIC therapies concluded that antispasmodics as a class are effective in providing short-term relief of IBS.[36] However, few randomized controlled trials have evaluated the antispasmodic drugs that are available in the United States, such as hyoscyamine and dicyclomine. Further, the use of antispasmodic drugs can be limited by dose-dependent anticholinergic adverse events, including constipation, fatigue, dry mouth, dizziness, and blurred vision.[8,36]

A recently developed sustained-release formulation of peppermint oil was found to be effective in IBS.[57] Peppermint oil and its active

ingredient, L-menthol, are classified primarily as antispasmodics based on their calcium channel–blocking properties, but they have several other effects that may be relevant to IBS, including antinociception, carminative properties, κ-opioid antagonism, and 5-HT_3 antagonism.[8,57] In a randomized controlled trial of 72 patients with IBS-D and IBS-M, the sustained-release formulation of peppermint oil was associated with a 40% reduction from baseline in the Total IBS Symptom Score at 4 weeks (primary endpoint), a significant improvement compared with the 24.3% reduction seen with placebo (P=.02). A significant difference between the treatment groups was noted as early as 24 hours.[57] Symptoms associated with viscerosensory perception (eg, abdominal pain/discomfort, bloating, pain at evacuation, urgency) were more responsive to peppermint oil than motility-related symptoms (eg, constipation, diarrhea, passage of gas or mucus).

Serotonergic Agents Based on the physiologic effects of the gut hormone serotonin on GI motility and visceral sensation, 5-HT_3 antagonists have been used to slow colonic transit and improve symptoms in patients with IBS-D.[8,20] Alosetron is a selective serotonin 5-HT_3 receptor antagonist that relieved global IBS symptoms, abdominal pain, urgency, and diarrhea-related complaints in several high-quality, placebo-controlled studies.[36] However, the use of this agent has been limited by the small risk of ischemic colitis (0.95 cases per 1000 patient-years) and serious complications of constipation (0.36 cases per 1000 patient-years), leading to the restriction of its use to women with severe IBS-D who have not responded to conventional therapies.[36,58,59] Although the use of alosetron continues to be subject to a risk management program, requirements for the program were updated in 2016 to eliminate the needs for patients to complete an attestation form and for clinicians to affix prescribing program stickers to alosetron prescriptions.[60]

Antidepressants Antidepressant agents have become a widespread treatment for patients with moderate-to-severe IBS owing to their effects on pain perception, mood, and GI motility.[8,61] Based on the results of 17 randomized controlled trials involving 1084 patients, the ACG systematic review on IBS concluded that tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are effective in providing global symptom relief and reducing pain in IBS.[36] Although the efficacy of using antidepressants according to the predominant stool pattern has not been well-studied, tricyclic antidepressants may be most appropriate in IBS-D given their ability to slow colonic motility and their mildly constipating effects.[61,62] Antidepressant agents should generally be initiated with low doses in IBS patients and titrated slowly (every 1-2 weeks), allowing 4 to 8 weeks for maximal response.[61,63] Given their propensity to cause sedation and orthostasis, tricyclic antidepressants should be administered prior to sleep.[64] Patients should also be counseled regarding the potential for anticholinergic effects, which typically occur early in the course of therapy and become more tolerable with longer duration of use.[64]

Antibiotics and Probiotics The growing evidence implicating dysbiosis of the gut flora in the pathogenesis of IBS suggests that the gut microbiota may be an important target for therapy.

Probiotics have been used for decades by IBS patients, and their efficacy has been evaluated in many randomized controlled trials.[36] However, these studies are typically small and poorly designed, and they have not consistently demonstrated efficacy compared with placebo.[36,65] The ACG systematic review concluded that although probiotics may improve global symptoms, bloating, and flatulence in IBS, the quality of evidence supporting their use is low.[36] Recommendations regarding individual species, preparations, or probiotic strains cannot be made due to insufficient and conflicting data across studies.

Rifaximin is an oral, nonabsorbable, broad-spectrum antibiotic that was approved in 2015 for IBS-D at a dose of 550 mg 3 times daily for 14 days, with up to 2 courses of repeat treatment if necessary.[66] Although the mechanism for its beneficial effects in IBS remains unclear, rifaximin may affect microbial diversity in patients with small intestinal bacterial overgrowth or dysbiosis, and it may decrease host proinflammatory responses to bacterial products.[67]

Rifaximin is the most extensively studied antibiotic in IBS,[36] with efficacy demonstrated in several large randomized controlled trials.[68,69] In 2 large phase 3 trials involving 1260 patients with IBS without constipation (TARGET 1 and 2), a 2-week course of rifaximin relieved IBS symptoms, bloating, abdominal pain, and loose or watery stools better than placebo for up to 10 weeks after completion of therapy.[68] The efficacy of rifaximin retreatment in patients with IBS-D was explored in a subsequent randomized controlled trial (TARGET 3).[69] Before randomization, all patients were treated with open-label rifaximin, and 2438 completed 2 weeks of treatment. A response was reported in 1074 patients. Among the patients with an initial response to treatment, 636 (59%) entered the double-blind phase of the trial after symptoms recurred. The median time to recurrence for patients who had responded to open-label rifaximin was 10 weeks. These patients received rifaximin or placebo for 2 additional repeat treatment courses, separated by 10 weeks. The primary endpoint was the proportion of patients who met the response criteria from the US Food and Drug Administration, which is defined as a 30% or greater improvement from baseline in the weekly average abdominal pain score and a 50% or greater reduction from baseline in the number of days per week with a daily stool consistency of type 6 or 7 on the Bristol Stool Form Scale. Significant improvements in this endpoint were observed with rifaximin vs placebo

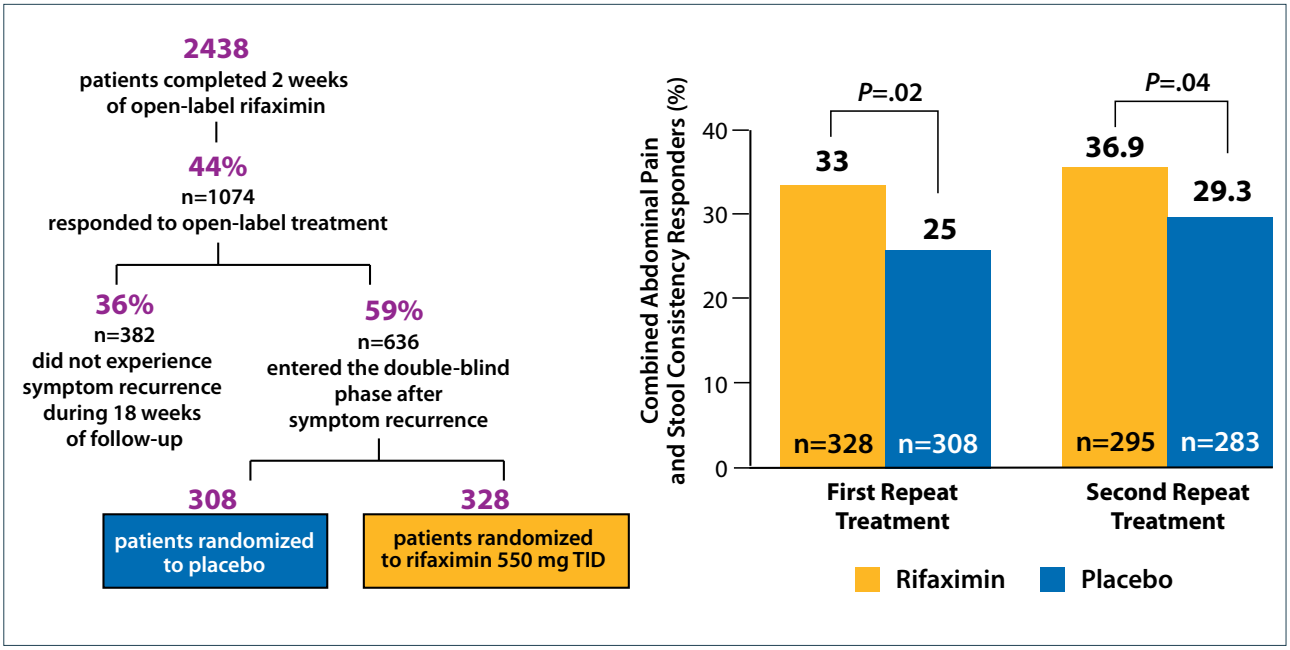

Figure 4. TARGET 3 patient disposition (left)[66] and proportion of composite abdominal pain and stool consistency responders (primary endpoint; right).[69] Response was defined as ≥30% improvement from baseline in the weekly average abdominal pain score and ≥50% reduction from baseline in the number of days per week with a daily stool consistency of type 6 or 7 on the Bristol Stool Form Scale. TID, 3 times daily. Adapted from Xifaxan [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2015,[66] and Lembo A et al. *Gastroenterology*. 2016;151(6):1113-1121.[69]

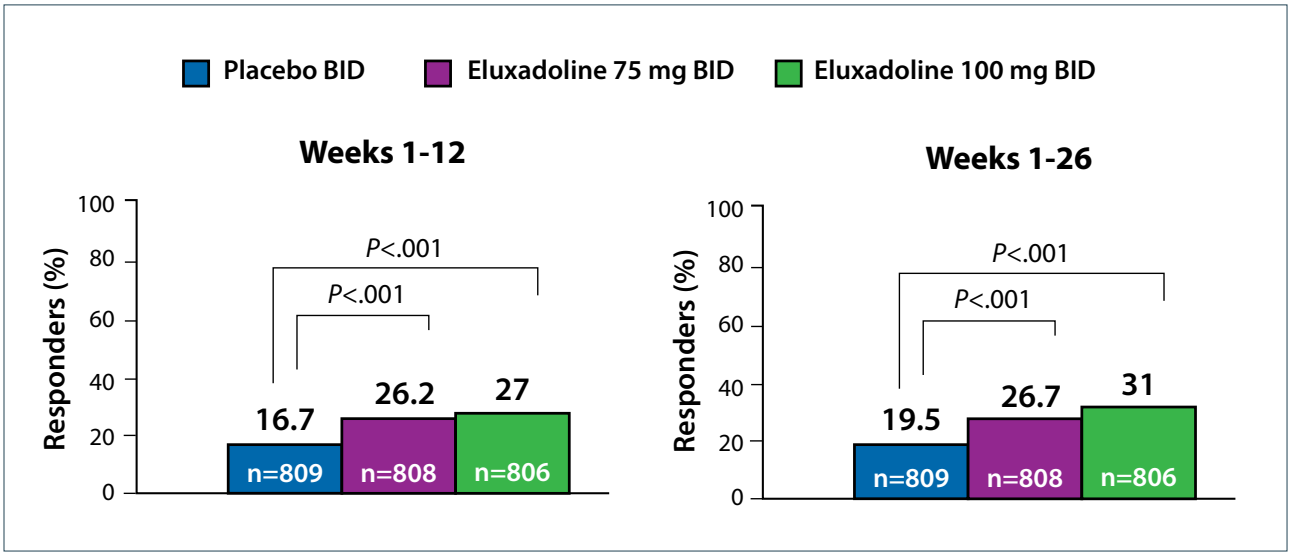

Figure 5. The primary endpoint in eluxadoline pivotal trials was the proportion of patients with a composite response consisting of a decrease in abdominal pain and an improvement in stool consistency on the same day for ≥50% of days from weeks 1 through 12 and weeks 1 through 26. BID, twice daily. Adapted from Lembo AJ et al. *N Engl J Med.* 2016;374(3):242-253.[71]

after each repeat treatment phase (Figure 4).[69]

Rifaximin is well-tolerated, with a safety profile similar to that of placebo. Despite concerns regarding the repeated use of an antibiotic, rifaximin has demonstrated convincing safety throughout the periods that it has been evaluated.[36] In TARGET 3, there was no evidence of clinically relevant effects on GI bacterial susceptibility to other antibiotic classes, pathogenic GI bacterial growth, or overall gut microbiota with up to 3 courses of rifaximin treatment.[67] Moreover, a recent pooled analysis of phase 2b and 3 studies demonstrated that no patients who received a 2-week course

Table 3. Overview of Pharmacologic Therapies for CIC and IBS-C[8,20,36]

	Agent(s)	Quality of Evidence		Treatment Benefits	Most Common Adverse Events
		CIC	IBS-C		
Fiber	Psyllium	Low	Moderate	Improves stool consistency and frequency, and provides overall symptom relief in IBS-C	Bloating, gas, cramping
Laxatives	Stimulants	Moderate	No RCTs	Sodium picosulfate and bisacodyl are effective in CIC	Cramping, diarrhea
	PEG	High	Very low	Improves constipation, but not global symptoms or pain in IBS-C	Bloating, cramping, diarrhea
Antidepressants	SSRIs	High	——	Improve global symptoms and pain; appropriate for patients with prominent anxiety	Nausea, diarrhea, sexual dysfunction
Prosecretory Agents	Lubiprostone	Moderate	High	Improves global, abdominal, and constipation symptoms	Nausea, diarrhea
	Linaclotide	High	High	Improves global, abdominal, and constipation symptoms	Diarrhea
	Plecanatide	High	High	Improves global, abdominal, and constipation symptoms	Diarrhea

CIC, chronic idiopathic constipation; IBS-C, constipation-predominant irritable bowel syndrome; PEG, polyethylene glycol; RCTs, randomized controlled trials; SSRIs, selective serotonin reuptake inhibitors.

of rifaximin developed *Clostridium difficile* colitis.[70]

Opioid Receptor Modulators Opioid receptors are located throughout the GI tract and play a role in regulating motility, secretion, and visceral sensation.[71] Accordingly, agents that act on opioid receptors throughout the GI tract are often used in IBS-D to slow intestinal transit and reduce pain perception.[20] Loperamide, a peripheral μ-opioid receptor agonist, is often used first-line in patients with IBS-D.[8,20] This agent is an effective antidiarrheal and can be used prophylactically when a patient anticipates diarrhea.[8,36] However, there is no evidence from controlled trials supporting its use in relieving abdominal pain, bloating, or global IBS symptoms.[36]

Eluxadoline is an oral, peripherally acting, mixed μ- and κ-opioid agonist/δ-opioid receptor antagonist that was recently approved for IBS-D.[71,72] Unlike pure μ-opioid receptor agonists, this agent reduces visceral hypersensitivity without completely disrupting intestinal motility.[71] In 2 large randomized controlled trials involving 2427 patients with IBS-D, eluxadoline at doses of 75 mg or 100 mg twice daily significantly improved the simultaneous symptoms of abdominal pain and diarrhea during 12 and 26 weeks of treatment as compared with placebo (Figure 5).[71] A subsequent analysis of data from these trials showed that eluxadoline effectively treated abdominal pain and diarrhea in patients who had previously received loperamide, regardless of whether these patients self-reported adequate or inadequate control of their symptoms with the prior treatment.[73]

Eluxadoline was well-tolerated in clinical trials, with a relatively low incidence of constipation (occurring in 8.6% of patients receiving 100 mg).[71] However, several precautions should be observed when using eluxadoline, based on the potential for adverse events. Eluxadoline is contraindicated in patients without a gallbladder and in the setting of known or suspected biliary duct obstruction or sphincter of Oddi disease/dysfunction, alcoholism, history of pancreatitis, severe hepatic impairment, and severe constipation or its sequelae.[72] Additionally, the lower approved dose (75 mg twice daily) should be used in patients who cannot tolerate the higher dose, who have mild or moderate hepatic impairment, or who are receiving concomitant OATP1B1 inhibitors (eg, cyclosporine, antiretrovirals, gemfibrozil).[72]

Pharmacologic Approaches to Managing IBS-C/CIC

Pharmacologic options for IBS-C/CIC include fiber, laxatives, polyethylene glycol, and antidepressants (Table 3).

Fiber Fiber has historically been used as first-line therapy for functional bowel symptoms, but its benefits have not been straightforward, likely owing to the heterogeneity of IBS, confusion regarding various types of fibers, and lack of high-quality evidence supporting its use.[1] Based on 14 randomized controlled trials of moderate quality, the ACG systematic review concluded that fiber provides overall symptom relief in IBS. However, this recommendation is limited by the potential for fiber to exacerbate bloating, flatulence, and abdominal discomfort.[1,36] Importantly, the

benefit observed with fiber is limited to soluble fibers, most notably psyllium.[36,74] In the largest study to date, 275 adults with IBS were randomized to psyllium, insoluble fiber (bran), or placebo once daily for 12 weeks.[75] Psyllium was significantly more effective than placebo in providing adequate symptom relief in the first 2 months of therapy, whereas bran was not more effective than placebo.[75] Importantly, the number of patients who discontinued treatment early was considerable in the bran group; the most common reason was exacerbation of IBS. This finding underscores issues of tolerability and the need to initiate therapy with a low dose and gradually titrate upward to improve tolerability.[8] Current evidence supports the efficacy of fiber in increasing stool frequency in patients with CIC, although the data are less robust than in IBS-C.[36]

Stimulant Laxatives Stimulant laxatives (eg, senna, bisacodyl, castor oil, cascara, rhubarb, aloe) produce bowel movements by promoting fluid and electrolyte secretion by the colon or by inducing colonic peristalsis.[36] Bisacodyl and sodium picosulfate have a long history of use in constipation, but only 2 randomized controlled trials of these agents were evaluated in the ACG systematic review.[36,76,77] However, the quality of these data was considered moderate, leading to a strong recommendation that sodium picosulfate and bisacodyl are effective in CIC. Use of these agents can be limited by poor tolerability, particularly due to diarrhea and abdominal cramping. There is insufficient evidence to recommend the use of other stimulant laxatives for CIC, and similarly, there are no randomized controlled trials of stimulant laxatives in IBS-C.[8,36]

Polyethylene Glycol Although the efficacy of the osmotic laxative polyethylene glycol (PEG) has been well-established in clinical trials in CIC, its effects in IBS-C are less clear.[36] Only 2 randomized controlled trials—one in adolescents in the United States and another in adults in Europe—have studied PEG in IBS-C.[78,79] Both trials demonstrated improvement in stool frequency, but neither demonstrated pain relief or reduction in overall symptoms in IBS. Based on this low-quality evidence, the ACG issued a weak recommendation regarding the use of PEG in IBS-C.[36]

Antidepressants SSRIs are commonly used in IBS-C based on their prokinetic and anxiolytic effects.[8,61] As with tricyclic antidepressants, high-quality evidence supports the efficacy of SSRIs in relieving IBS symptoms.[36] Because they are less potent visceral analgesics compared with tricyclic antidepressants, SSRIs are not considered first-line treatment for painful functional GI disorders, but they are a good option for IBS patients with prominent anxiety.[8,61,64] However, the benefit of these agents can be limited by their adverse events, as well as by the length of time required to achieve an effect. Four to 8 weeks may be needed to observe maximal response with these therapies.[61,63]

Prosecretory Agents for IBS-C and CIC

Lubiprostone and the guanylate cyclase (GC)-C agonists linaclotide and plecanatide are novel drugs that act on intestinal enterocytes to increase fluid secretion into the GI tract and accelerate intestinal transit.[20] Lubiprostone is a locally activating prostaglandin derivative that acts on type-2 chloride channels (ClC-2) to increase secretion of chloride and fluid into the intestinal lumen.[80,81] This activity alters stool consistency and increases intestinal transit, resulting in greater frequency and ease of spontaneous bowel movements.[81]

GC-C agonists activate GC-C receptors, which are located primarily on the luminal side of enterocytes from the duodenum to the rectum.[82,83] Their ability to mimic the endogenous peptides guanylin and uroguanylin activates chloride ion secretion through the cystic fibrosis transmembrane conductance regulator (CFTR), leading to an efflux of electrolytes and water into the lumen and accelerated GI transit (Figure 6).[82-84] In addition, because GC-C pathways are involved in modulating pain fiber activity,[84-86] modulation of these pathways may be effective for treating the abdominal pain and sensory symptoms of patients with IBS-C.[84,87,88]

Lubiprostone Lubiprostone is effective at improving symptoms of both IBS-C and CIC.[36] A combined analysis of 2 large, 12-week phase 3 trials demonstrated that this agent significantly improved symptoms of IBS-C compared with placebo.[89] The rate of overall responders was 17.9% among patients treated with lubiprostone vs 10.1% among those who received placebo (P=.001). Lubiprostone also improved abdominal pain.[89] An extension study of patients in these trials demonstrated that initial improvements were maintained throughout 9 to 13 months of treatment.[90] High-quality evidence also supports the use of lubiprostone in CIC, with efficacy demonstrated in 4 randomized controlled trials involving 651 patients.[36]

Lubiprostone is approved at dosages of 8 µg twice daily for IBS-C and 24 µg twice daily for CIC.[91] In pivotal trials of IBS-C and CIC, the most common adverse event with lubiprostone was dose-related nausea, which occurred in 8% of patients receiving 8 µg twice daily (vs 4% with placebo)[89] and 29% of patients receiving 24 µg twice daily (vs 3% with placebo).[91] Lubiprostone should be taken with food and water to minimize nausea, and treatment can be initiated at lower doses and titrated upward as needed.[8,91]

Linaclotide Linaclotide, the first-in-class GC-C agonist, was approved for the treatment of IBS-C and CIC in 2012.[92] In two phase 3 trials involving 1604 patients, linaclotide was associated with a 33% response rate (defined as a reduction of ≥30% in abdominal pain and an increase

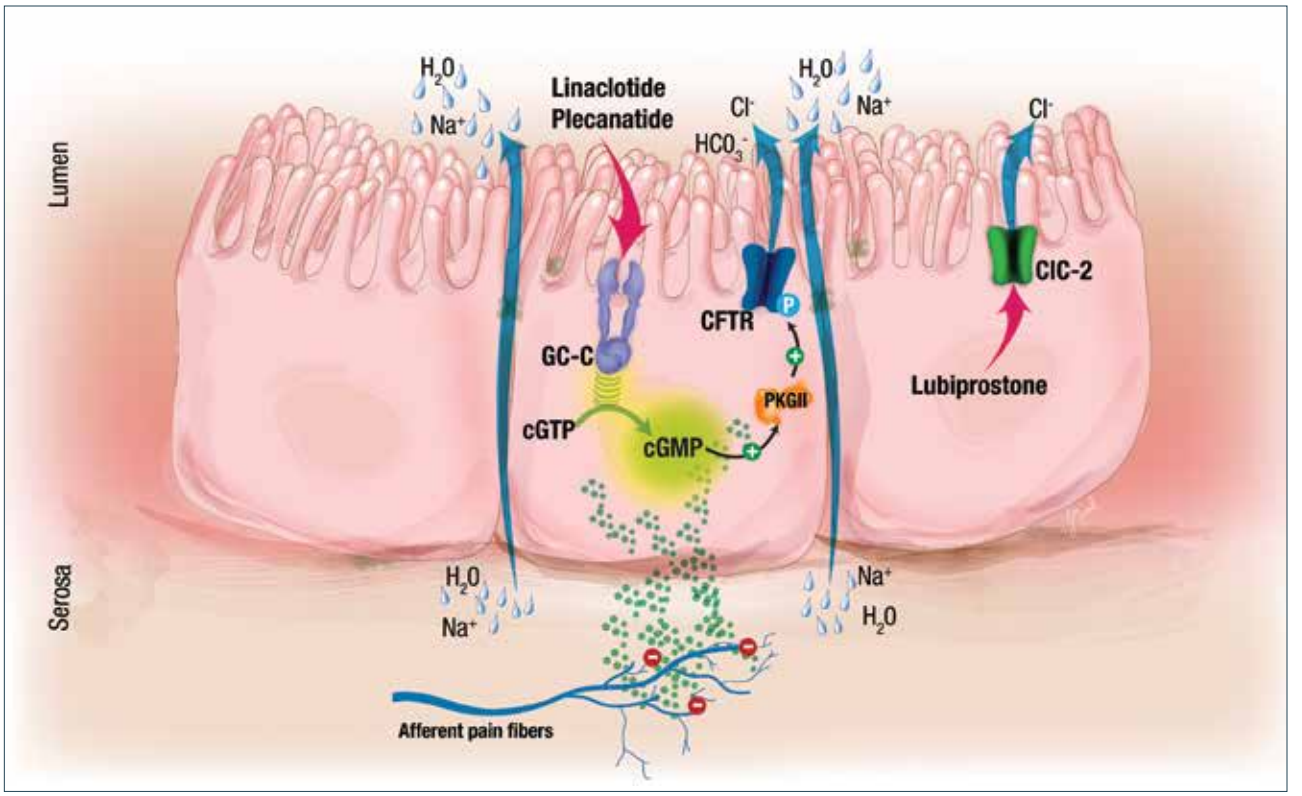

Figure 6. The mechanism of action of prosecretory agents. CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine monophosphate; cGTP, cyclic guanosine triphosphate; ClC-2, type-2 chloride channel; GC-C, guanylate cyclase C.

of ≥1 in the number of stools per week) compared with rates of 14%[87] and 21%[93] with placebo. Although improvement in stool frequency occurs within a week of treatment initiation, maximal improvement in abdominal pain and bloating may take 8 to 12 weeks.[8] Additional analyses of these pivotal data have demonstrated that linaclotide significantly improved all abdominal symptoms, global measures, and IBS-related quality-of-life parameters in subpopulations of IBS-C patients with severe abdominal symptoms.[88] High-quality evidence also supports the efficacy of linaclotide in improving bowel symptoms and bloating in patients with CIC.[36]

Linaclotide is approved at a dosage of 72 µg or 145 µg once daily for CIC and 290 µg once daily for IBS-C.[92] The most common adverse event associated with its use is diarrhea, reported in up to 20% of patients taking the higher dose (290 µg).[92] However, fewer than 5% of patients in clinical studies discontinued the drug because of this adverse event. Diarrhea associated with linaclotide can be managed by administering the agent 30 to 60 minutes before breakfast,[8,87] and/or by initiating therapy with the lower dose and titrating upward as needed.

Plecanatide Plecanatide is an oral, locally acting GC-C agonist that is newly approved at a dosage of 3 mg once daily for the treatment of CIC and IBS-C in adults.[94] In 2 pivotal randomized controlled trials in patients with IBS-C, plecanatide was associated with significantly higher responder rates than placebo (Figure 7).[94] A responder was defined in these trials as a patient who met both abdominal pain and stool frequency responder criteria in the same week for at least 6 of the 12 treatment weeks. Similarly, results of 2 large phase 3 trials demonstrated efficacy of plecanatide in increasing bowel movement frequency and stool consistency, changes that were accompanied by significant improvements in straining and abdominal symptoms.[95,96] Like linaclotide, the most frequent adverse event observed with plecanatide is diarrhea, which is typically mild and leads to few treatment discontinuations.[94]

Conclusion

Advances in the understanding of IBS pathophysiology throughout the past several decades have been accompanied by important clinical and therapeutic implications, and the evidence base for IBS management has grown considerably over time. With growing awareness of the potential contribution of certain foods to the development of symptoms, dietary intervention—particularly the low-FODMAP diet—has gained importance as a therapeutic strategy for many IBS patients. Among the common medical therapies for

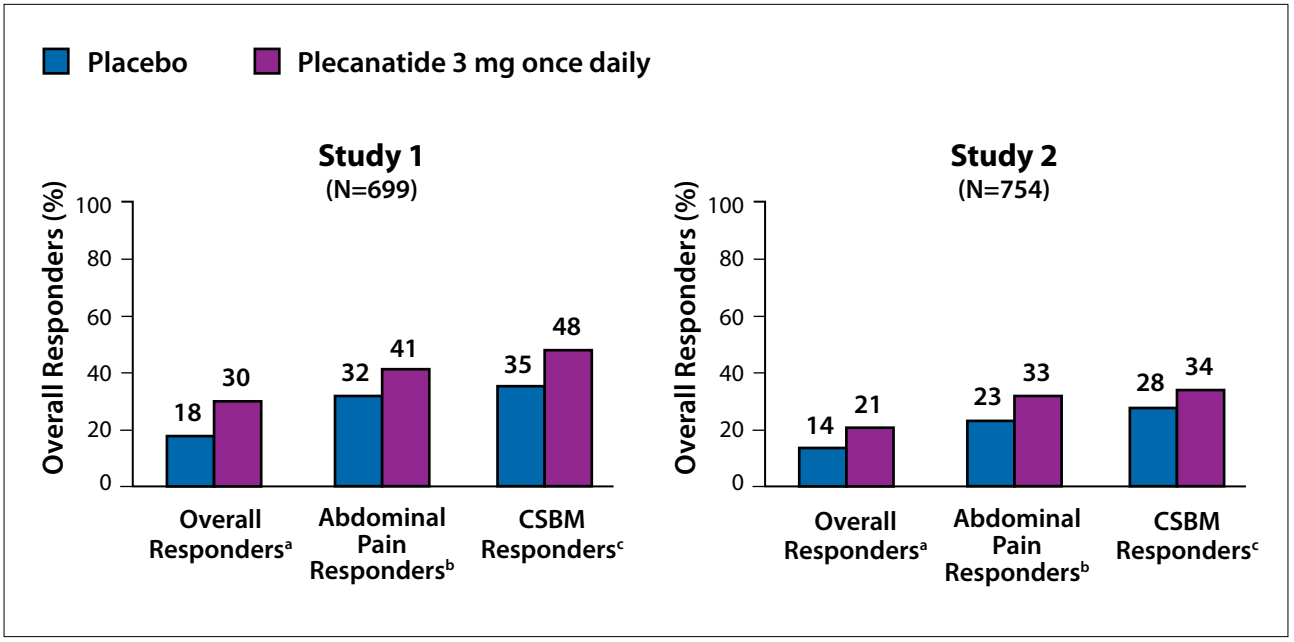

Figure 7. The efficacy of plecanatide in IBS-C in pivotal phase 3 studies. [a]A responder for these trials was defined as a patient who met both the abdominal pain and CSBM weekly responder criteria for at least 6 of the 12 weeks. [b]An abdominal pain responder was defined as a patient who met the criteria of a 30% or greater reduction from baseline in the weekly average of the worst daily abdominal pain for at least 6 of the 12 weeks. [c]A CSBM responder was defined as a patient who achieved an increase in at least 1 CSBM per week from baseline for at least 6 of 12 weeks. CSBM, complete spontaneous bowel movement; IBS-C, constipation-predominant irritable bowel syndrome. Data from Trulance [package insert]. New York, NY: Synergy Pharmaceuticals; 2018.[94]

IBS-D, the best clinical trial evidence supports the use of alosetron, tricyclic antidepressants, peppermint oil, rifaximin, and eluxadoline. Although IBS-C and CIC are often treated similarly, the evidence for various therapies shows some differences between the conditions. PEG and stimulant laxatives are effective nonprescription therapies for CIC, but there is no evidence from randomized controlled trials demonstrating their efficacy in reducing global symptoms in IBS-C. In contrast, high-quality evidence supports the efficacy of lubiprostone, linaclotide, and plecanatide in both CIC and IBS-C. Given the heterogeneity of the disorder, it is hoped that future research will further characterize the utility of various diagnostic and treatment strategies to optimize cost-effective management of individual patients.

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Understanding and Managing IBS and CIC in the Primary Care Setting

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