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SYMPOSIUM REPORT

An Evidence-Based Approach to IBS and CIC: Applying New Advances to Daily Practice

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An Evidence-Based Approach to IBS and CIC: Applying New Advances to Daily Practice

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Target Audience

This CME monograph will target gastroenterologists and other healthcare providers involved in the care of patients with irritable bowel syndrome (IBS).

Learning Objectives

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

- Describe approaches for assessing study design and safety, efficacy, and tolerability results for IBS/CIC therapies
- Integrate data from randomized controlled trials (RCTs) with clinical experience to design evidence-based treatment plans for patients with IBS-C/CIC
- Integrate data from RCTs with clinical experience to design evidence-based treatment plans for patients with IBS-D

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An Evidence-Based Approach to IBS and CIC: Applying New Advances to Daily Practice

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Abstract: Many nonpharmacologic and pharmacologic therapies are available to manage irritable bowel syndrome (IBS) and chronic idiopathic constipation (CIC). The American College of Gastroenterology (ACG) regularly publishes reviews on IBS and CIC therapies. The most recent of these reviews was published by the ACG Task Force on the Management of Functional Bowel Disorders in 2014. The key objective of this review was to evaluate the efficacy of therapies for IBS or CIC compared with placebo or no treatment in randomized controlled trials. Evidence-based approaches to managing diarrhea-predominant IBS include dietary measures, such as a diet low in gluten and fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs); loperamide; antispasmodics; peppermint oil; probiotics; tricyclic antidepressants; alosetron; eluxadoline, and rifaximin. Evidence-based approaches to managing constipation-predominant IBS and CIC include fiber, stimulant laxatives, polyethylene glycol, selective serotonin reuptake inhibitors, lubiprostone, and guanylate cyclase agonists. With the growing evidence base for IBS and CIC therapies, it has become increasingly important for clinicians to assess the quality of evidence and understand how to apply it to the care of individual patients.

Evidence-Based Assessment of IBS/CIC Therapies: Setting the Stage

Irritable bowel syndrome (IBS) and chronic idiopathic constipation (CIC) are highly prevalent, heterogeneous functional disorders that are among the most common conditions seen by gastroenterologists.[1-3] Selecting appropriate therapies for patients with these disorders is complicated by the heterogeneity of the pathogenic mechanisms and patient populations, as well as the broad range of nonspecific symptoms that patients may experience.[4,5] Accordingly, a broad range of nonpharmacologic and pharmacologic therapies are available to manage IBS and CIC, and a number of new therapies are currently under investigation. Understanding the current evidence regarding these therapies is important in guiding clinicians to the most appropriate therapy for their individual patients. To that end, several systematic reviews of therapies for IBS and CIC have been conducted.[4,6-8]

The American College of Gastroenterology (ACG) has published a number of reviews on IBS and CIC therapies over the past decade.[6-9] The most recent of these reviews was published by the ACG Task Force on the Management of Functional Bowel Disorders in 2014.[6] The key objective of these reviews was to evaluate the efficacy of therapies for IBS or CIC compared with placebo or no treatment in randomized controlled trials (RCTs). The primary outcome measure assessed for IBS and CIC therapies was any improvement of global IBS or CIC symptoms, respectively, whenever possible. Recommendations regarding treatments were graded using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[6] According to this system, the quality of the evidence is assessed based on study design as well as potential for bias, inconsistency, indirectness, and imprecision.[10] The quality of evidence is rated from very low to high, depending on the extent to which further evidence would change the estimate of the treatment effect (Figure 1).[6] The strength of recommendations is graded as weak to strong based on the quality of evidence as well as its applicability to all patient groups, balance of benefits and risks, patient preferences, and cost.

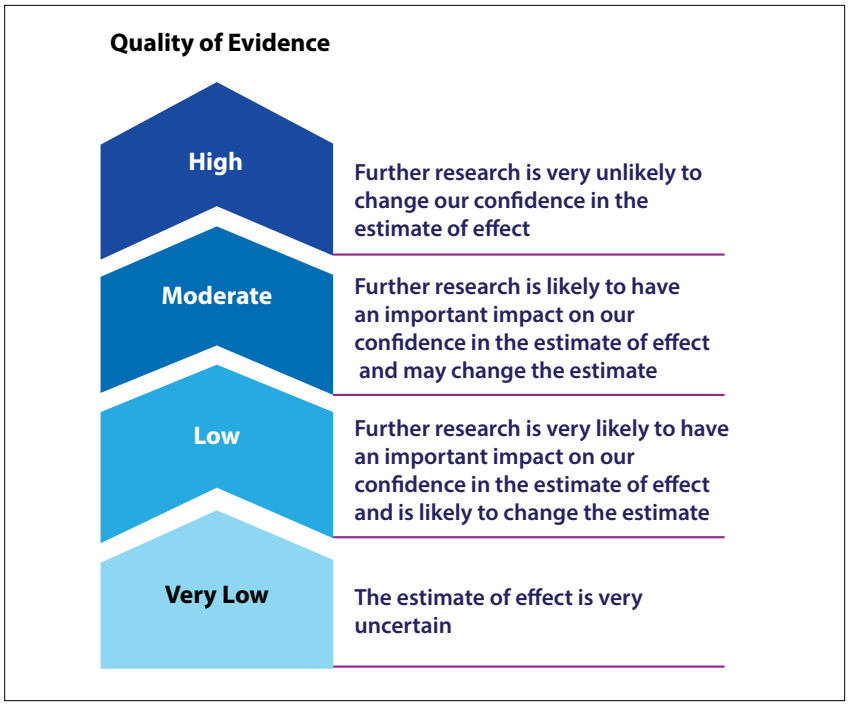

Figure 1. Interpreting the quality of the recommendation. Adapted from Ford AC et al. *Am J Gastroenterol.* 2014;109(suppl 1):S2-S26; quiz S27.[6]

Interpreting Study Design

A number of aspects are taken into account when evaluating the quality of study design. Randomization is the cornerstone of a clinical trial and is needed to reduce bias by ensuring a balanced distribution of potential confounding factors between treatment groups.[11,12] This in turn helps ensure that differences in outcomes between treatment groups can be attributed to the effect of the treatment. For example, without randomization, the result of an IBS trial could be biased owing to a disproportionate number of patients with severe IBS in either treatment group. Given the subjective nature of functional bowel symptoms, appropriate masking and double-blinding is essential for IBS and CIC trials. For example, patients may be less likely to describe symptom improvement if they or the investigators know that they are receiving placebo treatment. Ensuring complete study follow-up and analyzing data according to intent-to-treat (ITT) principles are also important in ensuring the validity of trial results. ITT analysis avoids overstating the efficacy of an intervention by including every randomized subject regardless of noncompliance, protocol deviations, and/or withdrawal.[13]

Interpreting Key Measures of Treatment Efficacy

The impact of treatments reviewed by the ACG was expressed as a relative risk (RR) of IBS or CIC symptoms *not improving* and reported with 95% confidence intervals (CIs). RR is expressed as the ratio of the risk of symptoms not improving in the 2 groups, with a risk ratio of 1 indicating no difference between treatment groups.[4] The RR reduction, calculated from 1 minus the risk ratio, represents the proportional reduction in risk in one treatment group compared with another.[4] For example, an RR of 0.80 is interpreted as the probability of not achieving global symptom improvement being 20% compared with that without treatment. In other words, patients treated with the active therapy are 20% (100 × [1-RR]%) more likely to achieve symptom improvement compared with patients treated with placebo. The confidence interval (usually 95%) estimates the range of results that might be expected if the study were repeated frequently in the same setting.[12] A narrow 95% CI indicates a more precise estimate of the treatment effect, whereas a wide CI indicates imprecision and can often be attributed to few events or relatively few patients.[4,12]

The number needed to treat (NNT) refers to the number of patients who would need to be treated with an active therapy, over and above the control therapy, for 1 to experience an improvement in symptoms.[6] Although NNT values are helpful when comparing 2 active therapies, they are not as useful when comparing active treatment against placebo. To the contrary, comparing the NNT of treatments that have been evaluated in separate placebo-controlled RCTs can be misleading, as the NNT will vary based on differences in study duration, patient population, endpoint, and other key aspects of the study design.

Applying Evidence-Based Medicine to Practice

In order to critically appraise the evidence, clinicians must understand study limitations, recognize bias, extract information, and reach appropriate conclusions.[14] However, it is important to recognize that the application of evidence-based medicine does not devalue clinical experience. To the contrary, successful evidence-based practice requires that clinicians apply the scientific findings to their clinical decision-making process for *individual* patients.[11] The magnitude of benefit, risk of side effects, patient preferences, and cost for individual patients are all key aspects of clinical decision-making. However, clinical experience guides the clinician's application of data to individual patients. The treatment nuances that clinicians learn over time is invaluable when applying evidence, and is also crucial when useful evidence is absent. Lack of evidence should not be construed as lack of efficacy. For example, the

Table 1. ACG Assessment and Recommendations for IBS-D Treatments[a]

Statement	Evidence			Assessment	
	Clinical Trials	Patients Treated (N)	RR Symptoms (95% CI)	Recommendation	Quality of Evidence
Specialized diets may improve symptoms in individual IBS patients	3	230	NA	Weak	Very low
There is insufficient evidence to recommend loperamide for use in IBS	2	42	0.51 (0.33-0.79)	Weak	Moderate
There is insufficient evidence to recommend antispasmodics available in the United States[b]	23	2154	0.69 (0.59-0.81)	Weak	Low
Peppermint oil[c] is superior to placebo in improving IBS symptoms	5[c]	482[c]	0.51[c] (0.33-0.79)	Weak[c]	Moderate[c]
Recommendations regarding individual species, preparations, or strains cannot be made because of insufficient and conflicting data[d]	23	2575	0.79 (0.70-0.89)	Weak	Low
TCAs are effective in providing symptom relief in IBS. Side effects are common and may limit patient tolerance	11	744	NR	Weak	High
Alosetron is effective in women with IBS-D	8	4987	0.79 (0.69-0.90)	Weak	Moderate
Eluxadoline is superior to placebo for the treatment of IBS-D[e]	2[e]	2427[e]	NR	Strong[e]	High[e]
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D. Rifaximin is superior to placebo for the treatment of IBS-D	6[e]	2879[e]	0.84 (0.78-0.90)	Strong[e]	High[e]

ACG, American College of Gastroenterology; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; NR, not reported; RR, relative risk; TCAs, tricyclic antidepressants.

[a]Does not include data from TARGET 3.

[b]Recommendation revised to reflect evidence for products available in the United States.

[c]Does not include triple-coated peppermint oil.

[d]Recommendation revised to reflect monograph statement for individual products.

[e]New or modified recommendation based on data published since the ACG monograph.

ACG monograph concluded that the quality of evidence for the use of probiotics in IBS is low and that the strength of the recommendation regarding their use is weak.[6] Rather than concluding that all probiotics are ineffective, this indicates that the current evidence is insufficient to identify specific probiotics that are effective. In the future, well-designed research trials may identify effective probiotics or provide more definitive evidence that probiotics are not effective. Until those studies are performed, physicians should use their own clinical experience to decide when to use a probiotic and which probiotic to select. Similar recommendations were made for other therapies in IBS, including loperamide and polyethylene glycol.[6] In scenarios such as these, characterized by a lack of evidence to guide therapy, clinicians must draw on their clinical experience when making treatment decisions.

Evidence-Based Approach to Managing IBS-D

Dietary Approaches

Although many patients with IBS believe that food sensitivity contributes to their symptoms,[15] dietary therapy has not played a key role in IBS management, largely owing to historically poor evidence of its benefit.[7,16] However, there appears to be renewed interest in the role of dietary manipulations in IBS, possibly owing to growing recognition of potential dietary triggers, such as gluten and fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs), in some patients.[5,17]

Of 12 RCTs that evaluated dietary intervention in IBS, only 3 of these trials met the inclusion criteria and were evaluated by the ACG review (Table 1). This evidence was considered to be of very low quality, leading to the weak recommendation that dietary manipulation may improve symptoms in individual patients.[6] Since the ACG review was conducted, however, results of the first RCT of the low FODMAP diet in patients with diarrhea-predom-

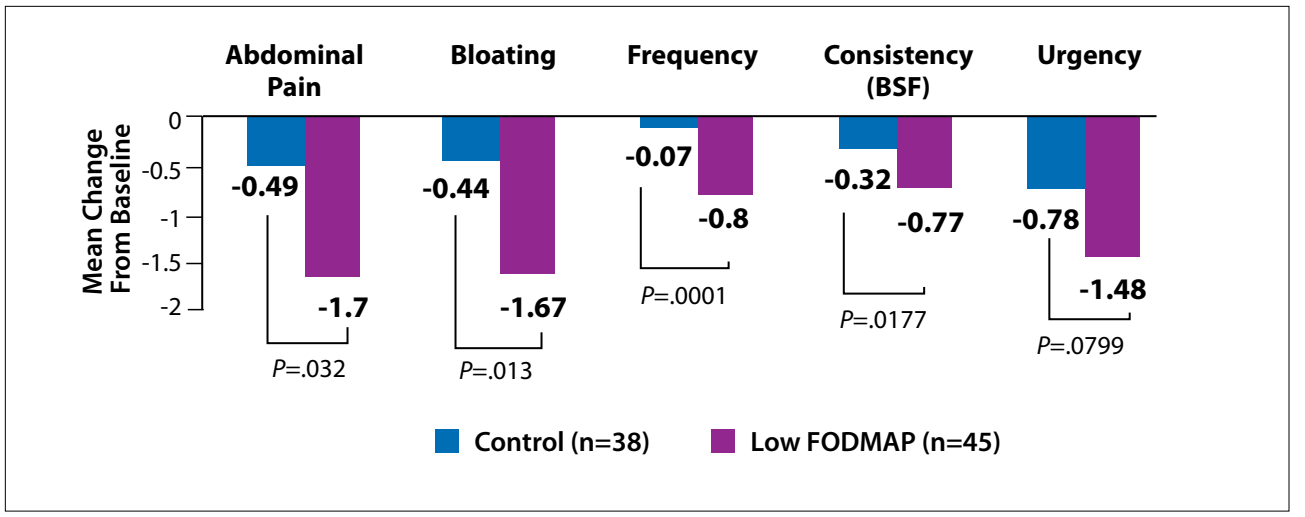

Figure 2. Mean daily symptom scores over treatment weeks 3 and 4. BSF, Bristol Stool Form; FODMAP, fermentable oligo-, di-, and monosaccharides and polyols. Adapted from Eswaran SL et al. *Am J Gastroenterol*. 2016;111(12):1824-1832.[18]

inant IBS (IBS-D) in the United States have been published.[18] In this single-center study, 92 patients were randomized to either a low FODMAP diet or a diet based on modified National Institute for Health and Care Excellence (mNICE) guidelines for 4 weeks. From 40% to 50% of patients reported adequate relief of their IBS-D symptoms with either diet, but the low FODMAP diet was significantly more effective in improving individual symptoms, particularly pain and bloating (Figure 2).

Loperamide

Despite its frequent use in clinical practice, very few controlled trials support the use of loperamide for IBS. Indeed, the evidence reviewed in the ACG monograph included 2 RCTs involving a total of 42 patients.[6] These data were considered to be of very low quality, leading to the strong recommendation that there is insufficient evidence to support the use of loperamide in relieving abdominal pain, bloating, or global IBS symptoms.[6] Despite this conclusion, however, loperamide continues to be used frequently in patients with IBS-D, underscoring the important role of experience-based medicine when there is a lack of evidence to inform clinical decision-making.

Antispasmodics

Antispasmodics have been used for decades for IBS based on their ability to relax smooth muscle in the gut.[5,6] Based on 23 RCTs evaluating 2154 patients with IBS worldwide, the ACG monograph made a weak recommendation that certain antispasmodics can relieve symptoms in the short-term.[6] However, of these studies, only 4 RCTs evaluated antispasmodic drugs that are available in the United States (hyoscine and dicyclomine). Thus, there is insufficient evidence to recommend the use of these particular agents for IBS. As with loperamide, this does not mean that these agents are not effective in individual patients, but rather that the data supporting their use are weak. Further, these agents can cause a number of dose-related anticholinergic adverse effects, such as constipation, fatigue, dry mouth, dizziness, and blurred vision.[5]

Peppermint Oil

Although classified as an antispasmodic based on its calcium channel–blocking properties, peppermint oil and its active ingredient, L-menthol, have a number of other effects that may be relevant to IBS, including normalizing orocecal transit time, κ-opioid antagonism, and 5-HT_3 antagonism.[5,19] In contrast to conventional antispasmodics, a relatively strong body of evidence worldwide supports the use of peppermint oil in IBS. Based on data from 5 RCTs involving 482 patients, the ACG review calculated an RR of 0.51, reflecting a 50% probability of this agent improving IBS symptoms.[6]

A novel triple-coated formulation of peppermint oil was introduced in the United States subsequent to the publication of the ACG monograph. This formulation is designed to promote sustained release of peppermint

> "Clinical practice is the intersection between evidence and clinical experience."
> –William D. Chey, MD

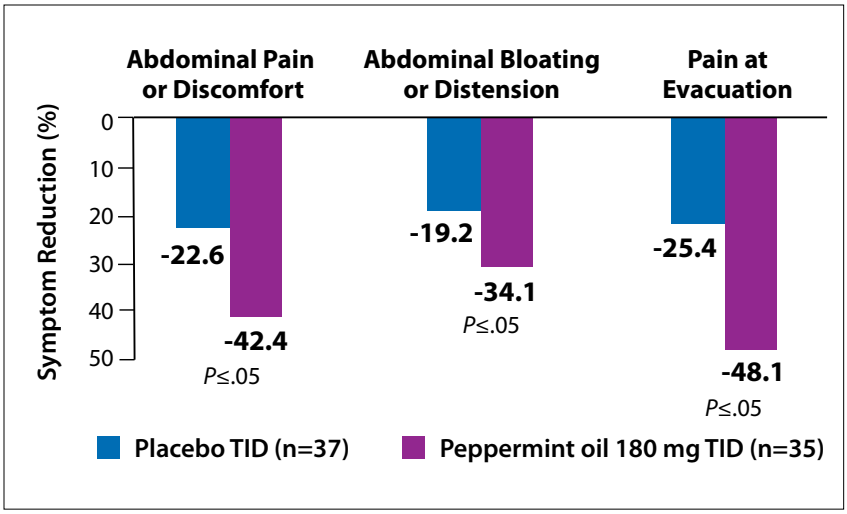

Figure 3. Symptom reduction at day 29 after treatment with triple-coated peppermint oil. TID, 3 times daily. Adapted from Cash BD et al. *Dig Dis Sci*. 2016;61(2):560-571.[19]

oil in the small intestine in an effort to overcome unpredictable delivery and tolerability issues (eg, heartburn, nausea) encountered with older, non-coated formulations.[19] In the first RCT evaluating the newer formulation, 72 patients with IBS-D or mixed IBS (IBS-M) were randomized to either the triple-coated formulation or placebo for 4 weeks.[19] At the end of the 4 weeks, patients receiving peppermint oil experienced a 40% reduction from baseline in the Total IBS Symptom Score (primary endpoint) compared with a 24.3% reduction among patients receiving placebo (P=.02), with a significant difference between groups noted as early as 24 hours.[19] Symptoms associated with viscerosensory perception (abdominal pain/discomfort, bloating, pain at evacuation, and urgency) were more responsive to peppermint oil than motility-related symptoms (constipation, diarrhea, and passage of gas or mucus; Figure 3).

Probiotics

Although probiotics have been studied in a large number of RCTs, evaluating their efficacy in IBS is complicated by the heterogeneity of these studies as well as methodologic problems.[6] Further, the large number of preparations included in these studies makes it very difficult to evaluate the efficacy of individual species and strains of probiotics used in IBS. Based on the 23 RCTs evaluated, the ACG monograph made a weak recommendation that probiotics, taken as a whole, improve global symptoms, bloating, and flatulence in IBS.[6] However, recommendations regarding individual species, preparations, or strains cannot be made owing to insufficient and conflicting data across studies. As mentioned previously, these conclusions do not indicate that probiotics are not effective in individual patients, but rather that the evidence supporting their efficacy is weak.

Tricyclic Antidepressants

Antidepressant agents have become a widespread treatment for patients with moderate to severe IBS owing to their effects on pain perception, mood, and motility.[5,20] Because tricyclic antidepressants (TCAs) have anticholinergic effects and can cause constipation, their use may be most appropriate in IBS-D patients, whereas the prokinetic effects associated with selective serotonin reuptake inhibitors (SSRIs) may be of greater benefit in those with constipation-predominant IBS (IBS-C).[21] Although most studies have not differentiated between the various IBS subtypes of the patients recruited, the evidence for the use of TCAs in IBS overall is strong. Based on 11 RCTs involving 744 patients, the ACG monograph concluded that TCAs are effective in relieving IBS symptoms.[6] Despite the high quality of evidence, the recommendation was weak based on the potential for adverse effects with these agents.

Alosetron

Alosetron, a selective serotonin 5-HT_3 receptor antagonist, has been shown to relieve global IBS symptoms, abdominal pain, urgency, and diarrhea-related complaints in a number of high-quality RCTs involving nearly 5000 patients.[6] Despite these robust clinical data, however, the ACG monograph made only a weak recommendation for use of alosetron in female patients with IBS-D based on the potential for adverse events.[6] This includes a small but real risk of ischemic colitis (0.95 cases per 1000 patient-years) and serious complications of constipation (0.36 cases per 1000 patient-years).[22] Accordingly, alosetron is indicated for a narrow population, specifically, women with severe IBS-D who have not responded to conventional therapies.[22,23] Although the use of alosetron continues to be restricted to a risk management program, the program was updated in 2016 to eliminate requirements for a patient attestation form and for affixing prescribing program stickers to alosetron prescriptions.[24]

Eluxadoline

Eluxadoline is an oral opioid receptor modulator that was approved for use in IBS-D in 2015,[25] subsequent to the publication of the ACG monograph on IBS therapies.[6] Eluxadoline has mixed effects on opioid receptors that includes μ- and κ-opioid agonism and δ-opioid receptor antagonism.[26] The benefits of eluxadoline in IBS are attributed to its effects on μ-opioid receptors, which lead to antimotility effects as well as a reduction in visceral hypersensitivity. The ability of eluxadoline to block peripheral δ-opioid receptors governs its effects

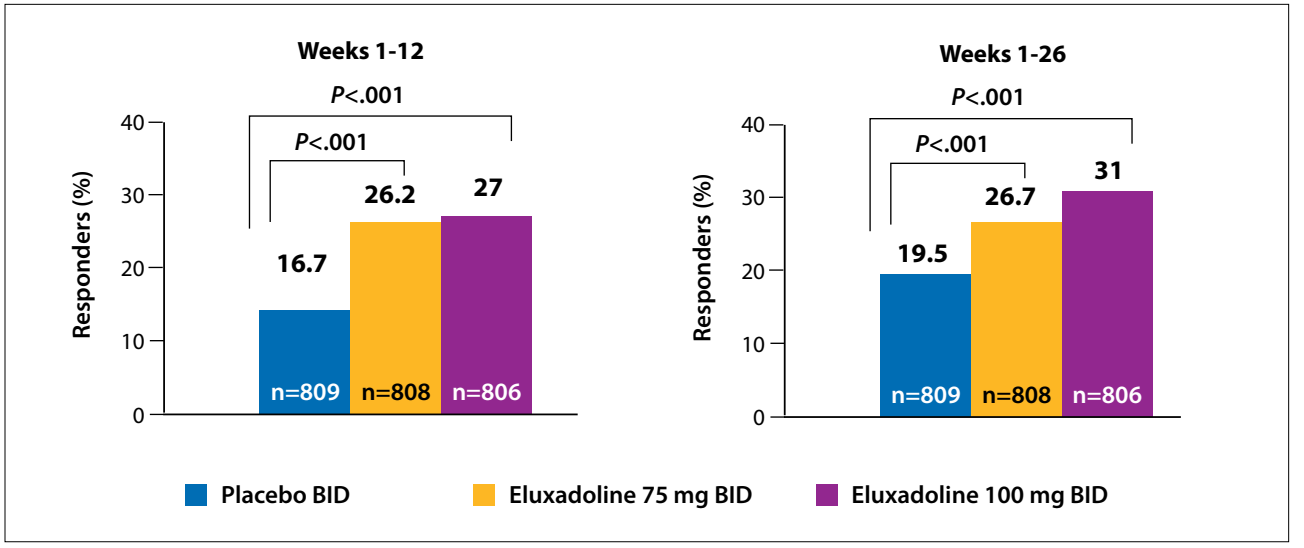

Figure 4. Primary endpoint in eluxadoline pivotal trials. BID, twice daily. Adapted from Lembo AJ et al. *N Engl J Med*. 2016;374(3): 242-253.[26]

on μ-opioid receptors and minimizes development of the constipation that typically results from selective μ-opioid receptor agonists.[26]

The efficacy of eluxadoline has been demonstrated in 2 pivotal clinical trials involving 2427 patients with IBS-D.[26] The primary endpoint used in both trials was a robust, regulatory endpoint defined as the proportion of patients with a composite response of decrease in abdominal pain and improvement in stool consistency on the same day for at least 50% of days from weeks 1 through 12 and weeks 1 through 26. As depicted in Figure 4, both the 75 mg and 100 mg twice-daily doses of eluxadoline achieved this endpoint.[26] Further, efficacy was sustained for up to 6 months with the 100 mg twice-daily dose. Although not available at the time of the ACG review, this high-quality evidence lends further support to the efficacy of eluxadoline for the treatment of IBS-D.

Eluxadoline was well-tolerated in the pivotal trials, with a relatively low incidence of constipation underscoring the impact of δ receptor antagonism.[26] However, several precautions should be observed when using eluxadoline, based on the potential for an increased risk of sphincter of Oddi spasm and pancreatitis. Importantly, the lower approved dose (75 mg twice daily) should be used in patients without a gallbladder, and these patients should be closely monitored for new or worsening abdominal pain or acute biliary pain with liver or pancreatic enzyme elevations.[25] Further, there are a number of contraindications to eluxadoline use, including 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.[25]

Rifaximin

Rifaximin, an oral, nonabsorbable, broad-spectrum antibiotic, is the most extensively evaluated antibiotic in IBS.[6] In two large phase 3 trials involving 1260 patients with IBS without constipation (TARGET 1 and 2), a 2-week course of rifaximin 550 mg 3 times daily relieved IBS symptoms, bloating, abdominal pain, and loose or watery stools better than placebo for up to 10 weeks after completion of therapy.[27] Based on these data in conjunction with 3 previous RCTs, the ACG monograph made a weak recommendation that rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.[6]

Subsequent to the ACG review, however, results of a third pivotal RCT (TARGET 3) evaluating the safety and efficacy of rifaximin repeat treatment were published.[28] In this trial, patients who initially responded to 2 weeks of open-label rifaximin but lost response were randomized to treatment with rifaximin or placebo for up to 2 additional repeat treatment courses, separated by 10 weeks (Figure 5).[28] The primary endpoint was the proportion of patients who responded according to criteria from the US Food and Drug Administration (FDA), defined as an improvement of 30% or more from baseline in the weekly average abdominal pain score and at least a 50% reduction in the number of days per week with a daily stool consistency of Bristol Stool Scale type 6 or 7. Significant responses to treatment were demonstrated after the first and second treatment phases (Figure 5). Thus, despite the ACG recommendation published in the 2014 monograph, other experts consider the high-quality evidence provided by the complete TARGET clinical program sufficient to support a strong recommendation that rifaximin reduces total IBS symptoms and bloating in IBS-D.

Rifaximin was approved in 2015 for IBS-D at a dose of 550 mg 3 times

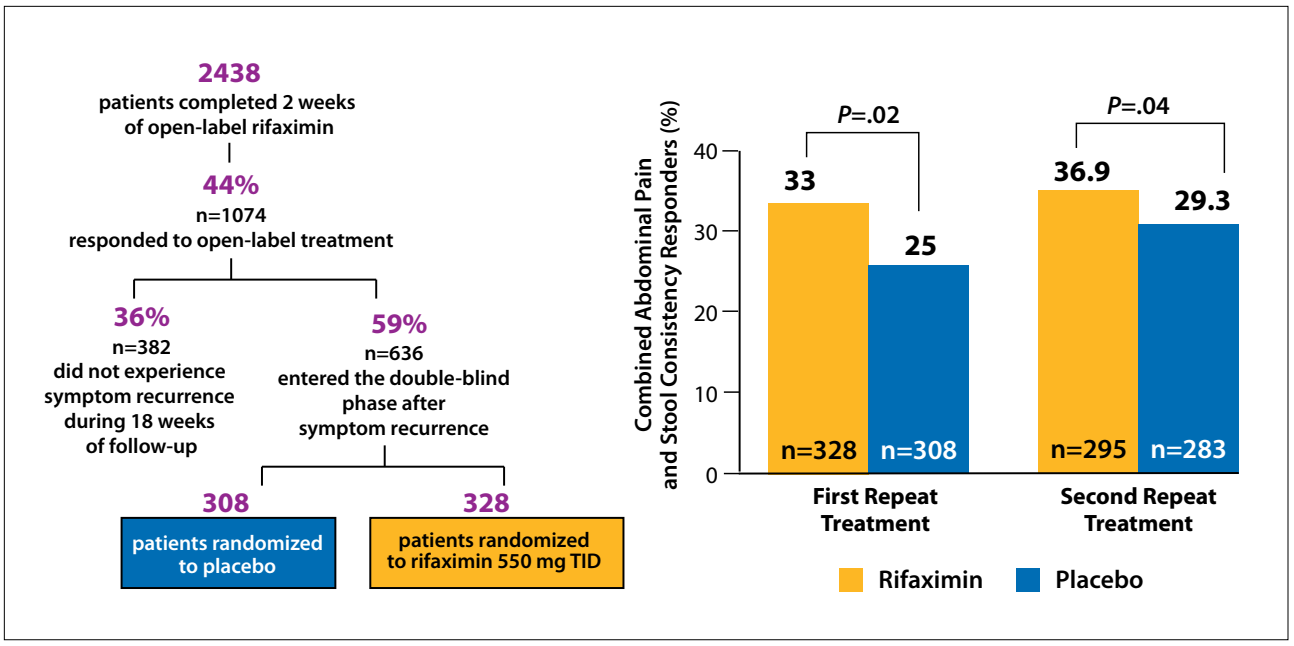

Figure 5. Data from the TARGET 3 trial. Patient disposition (left)[29] and proportion of composite abdominal pain and stool consistency responders (primary endpoint; right).[28] Response was defined as ≥30% improvement baseline in the weekly average abdominal pain score and ≥50% reduction in the number of days per week with a daily stool consistency of Bristol Stool Form Scale type 6 or 7. TID, 3 times daily. Adapted from Lembo AJ et al. 2014 ACG Abstract 45,[28] and Xifaxan [package insert]. Salix Pharmaceuticals: Bridgewater, NJ: 2015.[29]

daily for up to 2 courses of treatment.[29] Rifaximin is well-tolerated, with a safety profile similar to that of placebo. Further, despite concerns regarding the long-term or repeated use of an antibiotic, rifaximin has demonstrated an excellent safety profile throughout the time periods that it has been evaluated.[6]

Evidence-Based Approach to Managing IBS-C and CIC

IBS-C and CIC are considered distinct disorders, distinguished primarily by the presence of abdominal pain as a primary complaint in IBS-C but not CIC.[30] However, the symptoms of constipation and IBS-C overlap considerably, and increasingly, it is believed that IBS-C and CIC reside on a spectrum of disease as opposed to being 2 separate and distinct entities.[1,31] Accordingly, IBS-C and constipation are often treated similarly,[1] although the current evidence base is not always consistent between the disorders (Table 2).

Fiber

Fiber has long been used as first-line therapy for functional bowel symptoms despite a lack of high-quality evidence supporting its use.[1] Fourteen RCTs included in the ACG review of fiber in IBS were considered to be of moderate quality, supporting the recommendation 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.[1,6] Further, the benefit is limited to soluble fibers, most notably psyllium.[6,32] In the largest study to date, 275 adults with IBS were randomized to soluble fiber (psyllium), insoluble fiber (bran), or placebo once daily for 12 weeks.[33] Psyllium was found to be 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.[33] Importantly, early drop-out was considerable in the bran group, most commonly owing to exacerbation of IBS. This underscores issues of tolerability and the need to initiate therapy with a low dose and

> "There is very good emerging evidence, especially from the United States, supporting a primary role of diet in managing some patients with IBS-D."
> –Brooks D. Cash, MD

Table 2. ACG Assessment and Recommendations for IBS-C and CIC Treatments

Statement	Evidence			Assessment	
	Clinical Trials	Patients Treated (N)	RR Symptoms (95% CI)	Recommendation	Quality of Evidence
IBS-C					
Fiber provides overall symptom relief in IBS. Fiber can cause bloating and abdominal discomfort	14	906	0.86 (0.80-0.94)	Weak	Moderate
Psyllium, but not bran, provides overall symptom relief in IBS	7	499	0.83 (0.73-0.94)	Weak	Moderate
There is no evidence that PEG improves overall symptoms and pain in patients with IBS	2	166	NA	Weak	Very low
SSRIs are effective in providing symptom relief in IBS. Side effects are common and may limit patient tolerance	7	356	NR	Weak	High
Lubiprostone is superior to placebo for the treatment of IBS-C	3	1366	0.91 (0.87-0.95)	Strong	Moderate
Linaclotide is superior to placebo for the treatment of IBS-C	3	2028	0.80 (0.75-0.85)	Strong	High
CIC					
Some fiber supplements increase stool frequency in patients with CIC	3	293	0.25 (0.16-0.37)	Strong	Low
Sodium picosulfate and bisacodyl are effective in CIC	2	735	0.54 (0.42-0.69)	Strong	Moderate
PEG is effective in increasing stool frequency and improving stool consistency in CIC	4	573	0.52 (0.41-0.65)	Strong	High
Lubiprostone is superior to placebo for the treatment of CIC	4	651	0.67 (0.58-0.77)	Strong	High
Linaclotide is superior to placebo for the treatment of CIC	3	1582	0.84 (0.80-0.87)	Strong	High

ACG, American College of Gastroenterology; CIC, chronic idiopathic constipation; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; NA, not available; NR, not reported; PEG, polyethylene glycol; RR, relative risk; SSRIs, selective serotonin reuptake inhibitors.

gradually titrate upwards to improve tolerability.[5] Review of this study and the other 6 RCTs led the ACG to make a weak recommendation for psyllium, but not bran, to provide overall symptom relief in IBS.[6] Although the evidence indicates that symptoms may improve in as few as 6% of patients (based on the upper limit of the 95% CI), psyllium is considered a safe and cost-effective approach for patients with IBS-C.

The evidence for the efficacy of fiber in CIC is less robust than in IBS-C, with only 3 RCTs, involving fewer than 300 patients, reviewed in the ACG monograph.[6] However, the strong RR (0.25) calculated from these studies supports a strong recommendation that fiber can increase stool frequency in patients with CIC.

Stimulant Laxatives

Stimulant laxatives (senna, bisacodyl, castor oil, cascara, rhubarb, and aloe) produce bowel movements by promoting fluid and electrolyte secretion by the colon or by inducing colonic peristalsis.[6] Despite their long history of use in constipation, only 2 RCTs with bisacodyl and sodium picosulfate were evaluated in the ACG monograph.[6,34,35] However, the quality of these data were considered moderate, leading to a strong recommendation that sodium picosulfate and bisacodyl are effective in CIC. Tolerability can be an issue with these agents, particularly with regard to diarrhea and abdominal cramping. There is insufficient evidence to recommend the use of other stimulant laxatives for chronic constipation, and similarly, there are no RCTs of stimulant laxatives in IBS-C.[5,6]

Polyethylene Glycol

Despite robust evidence for efficacy in CIC, the benefit of the osmotic laxative

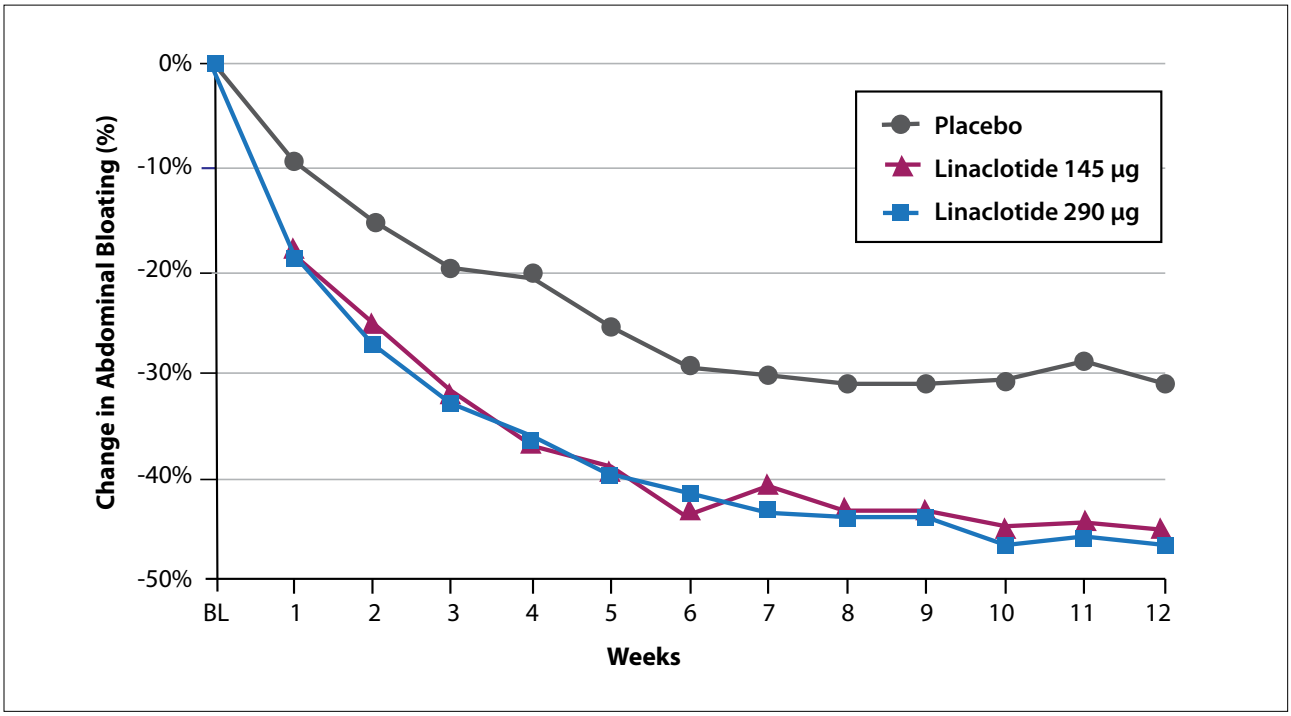

Figure 6. Percent change in abdominal bloating from baseline by week. BL, baseline. Adapted from Lacy BE et al. *PLoS One*. 2015;10(7):e0134349.[47]

polyethylene glycol (PEG) in IBS-C is less clear. Based on 4 high-quality RCTs, the ACG recognizes the efficacy of PEG in increasing stool frequency and consistency in CIC.[6] In contrast, only 2 RCTs, one in adolescents and another in adults in Europe, have studied PEG in IBS-C.[36,37] Although both trials demonstrated improvement in stool frequency, neither study demonstrated pain relief or reduction in overall symptoms in IBS. Based on this low-quality evidence, the ACG has issued a weak recommendation regarding the use of PEG in IBS-C.[6]

Selective Serotonin Reuptake Inhibitors

SSRIs are commonly used in IBS-C owing to their prokinetic effects as well as their visceral analgesic effects (although these effects are less strong than those of TCAs).[5,20] Like TCAs, high-quality evidence supports the efficacy of SSRIs in relieving IBS symptoms.[6] However, the benefit of these agents can be limited by adverse effects, as well as the length of time required to achieve an effect. Indeed, 4 to 8 weeks may be needed to observe maximal response.[20,38]

Lubiprostone

Approved for the treatment of IBS-C in 2006,[39] lubiprostone is a locally acting, bicyclic functional fatty acid derived from prostaglandin E1 that acts by specifically activating CIC-2 chloride channels on the apical aspect of enterocytes, eliciting a chloride-rich fluid secretion.[40] Combined analysis of two large, 12-week, phase 3 trials demonstrated that this agent significantly improved symptoms of IBS-C compared with placebo (17.9% overall responders vs 10.1%; P=.001).[41] It also improved abdominal pain. To determine overall responders at 12 weeks, these trials used a rigorous primary endpoint: at least moderate relief for 4 of 4 weeks or significant relief for 2 of 4 weeks. An extension study of patients in these trials demonstrated that initial improvements were maintained throughout 9 to 13 months of treatment.[42] Based on these data, the ACG issued a strong recommendation regarding the efficacy of lubiprostone for the treatment of IBS-C.[6] High-quality evidence also supports the use of lubiprostone in CIC, with efficacy demonstrated in 4 RCTs involving 651 patients.[6]

Lubiprostone is approved in dosages of 8 µg twice daily and 24 µg twice daily for IBS-C and CIC, respectively.[39] The most common adverse effect with lubiprostone is dose-related nausea, occurring in 8% and 29% of patients receiving 8 µg and 24 µg twice daily, respectively, in pivotal trials of IBS-C and CIC (compared with 4% and 3% of patients receiving placebo).[39,41] Lubiprostone should be taken with food and water to minimize nausea.[5,39] Additionally, therapy can be initiated at lower doses and titrated upward as needed.

Guanylate Cyclase Agonists

Linaclotide

Linaclotide, a first-in-class guanylate cyclase agonist, was approved for the

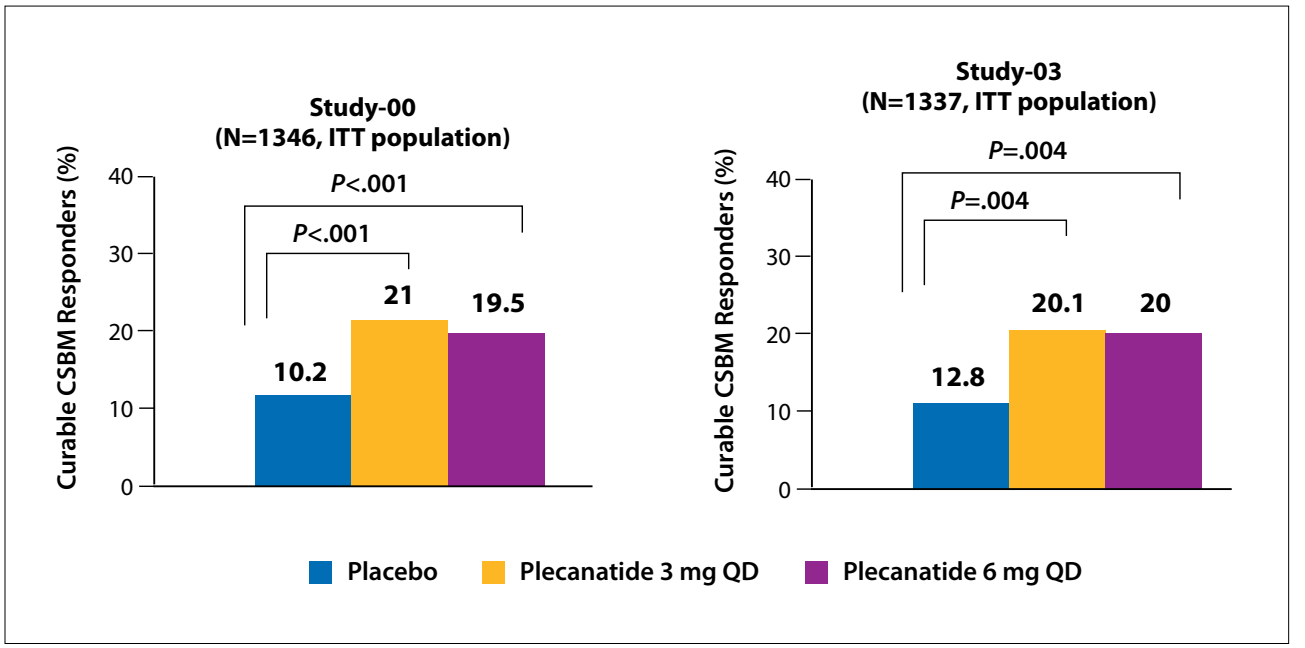

Figure 7. Proportion of durable CSBM responders with plecanatide in CIC. CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movements; ITT, intent-to-treat; QD, once daily. Adapted from Miner PB et al. 2016 DDW abstract SA1440,[49] and Miner PB et al. 2016 DDW abstract SA1444.[50]

[a]Defined as weekly responders for at least 9 of 12 treatment weeks, for at least 3 of the last 4 weeks. Weekly responders had ≥3 CSBMs and an increase of ≥1 CSBM from baseline.

treatment of IBS-C in 2012.[43] The efficacy of this agent is supported by 3 RCTs involving 2028 patients, considered to be high-quality evidence at low risk of bias by the ACG review.[6] The 2 linaclotide pivotal RCTs were the first studies to use the FDA-defined composite endpoint, a rigorous endpoint defined as achieving at least 30% reduction in the worst abdominal pain each week and an increase in 1 or more complete spontaneous bowel movements (SBMs) from baseline for at least 6 of 12 weeks.[44,45] Although improvement in stool frequency occurs within a week of treatment initiation, maximal improvement in abdominal pain and bloating may take up to 8 to 12 weeks.[5] Additional analyses of the pivotal data have demonstrated that linaclotide significantly improved all abdominal symptoms, global measures, and IBS-related quality of life in subpopulations of IBS-C patients with severe abdominal symptoms.[46]

Like IBS-C, the efficacy of linaclotide in CIC is supported by high-quality evidence from 3 RCTs and a strong recommendation from the ACG.[6] Further, results of a phase 3b RCT published subsequent to the ACG monograph demonstrated efficacy of linaclotide in improving abdominal bloating in patients with CIC.[47] In this 12-week study involving 483 patients with Rome II–defined chronic constipation and significant abdominal bloating, linaclotide doses of 145 µg and 290 µg daily significantly improved bowel symptoms and bloating compared with placebo (Figure 6). Given that abdominal bloating is present in a majority of patients with CIC and is considered to be the most bothersome symptom of constipation, the efficacy of linaclotide in improving bloating is important.[47]

Linaclotide is approved at a dosage of 145 µg once daily for CIC and 290 µg once daily for IBS-C.[43] The most common adverse effect associated with its use is diarrhea, reported in up to 20% of patients taking the higher dose (290 µg).[43] This can be managed by administering the agent 30 to 60 minutes before breakfast,[5,45] and/or by initiating therapy with the lower dose and titrating upwards as needed.

Plecanatide

Plecanatide is an oral, locally acting guanylate cyclase agonist that is being studied for use in CIC and IBS-C.[1,17,48] The results of two large phase 3 RCTs have recently demonstrated the efficacy of this agent in improving CIC.[49,50] In these studies, plecanatide doses of 3 mg and 6 mg significantly improved the proportion of durable complete SBM responders, defined as patients who were weekly responders for at least 9 of 12 treatment weeks, including at least 3 of the last 4 weeks (Figure 7). Improvements in complete SBM and SBM occurred within 1 week of therapy and lasted throughout the 12 weeks of the trials. Like linaclotide, the most frequent adverse effect observed with plecanatide is diarrhea, which is

typically mild and leads to few treatment discontinuations. The FDA approved plecanatide for CIC in January 2017.[51]

Conclusions

With the growing evidence base for IBS and CIC therapies, it has become increasingly important for clinicians to assess the quality of evidence and understand how to apply it to the care of individual patients. Emerging evidence supports a primary role of diet, particularly the low-FODMAP diet, in some patients with IBS-D. Of the common medical therapies for IBS-D, the best clinical trial evidence supports the use of alosetron, TCAs, peppermint oil, eluxadoline, and rifaximin. Although IBS-C and CIC are often treated similarly, the evidence for various therapies shows some differences across conditions. Whereas PEG and stimulant laxatives are effective nonprescription therapies for CIC, there is no evidence from RCTs demonstrating their efficacy in reducing global symptoms in IBS-C. In contrast, high-quality evidence supports the efficacy of lubiprostone and linaclotide in both CIC and IBS-C. The successful application of evidence-based medicine requires that clinicians integrate their understanding of the evidence with their own clinical experience in order to balance the magnitude of benefit and risk for individual patients.

Disclosure

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