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Advances in IBS 2016: A Review of Current and Emerging Data

Philip S. Schoenfeld, MD, MSEd, MSc
Professor of Medicine
Director of the GI Epidemiology Training Program
University of Michigan School of Medicine
Ann Arbor, Michigan

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- Discuss current approaches for diagnosing IBS and differentiate IBS from other functional bowel disorders
- Evaluate the role of current therapies, including non-pharmacologic options, for the management of IBS
- Implement evidence-based therapies for the management of IBS
- Discuss new and emerging diagnostic strategies and therapies for IBS

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Advances in IBS 2016: A Review of Current and Emerging Data

Philip S. Schoenfeld, MD, MSEd, MSc

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Abstract: Irritable bowel syndrome (IBS) is characterized by chronic intermittent abdominal pain and associated diarrhea (IBS-D), constipation (IBS-C), or both. IBS can significantly impact patient function and quality of life. The diagnosis of IBS is based on the presence of characteristic symptoms, the exclusion of concerning features, and selected tests to exclude organic diseases that can mimic IBS. The pathophysiology of IBS remains incompletely understood, and new contributing factors have been identified over the past decade. Altered gut immune activation, intestinal permeability, and the intestinal and colonic microbiome may be important factors. Poorly absorbed carbohydrates have been implicated in triggering IBS symptoms. Increasing evidence supports the benefit of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). Although there are several randomized controlled trials of probiotics in IBS, they are typically poorly designed and have not consistently demonstrated efficacy. Until recently, there were few effective treatments for IBS-D. Data from recent clinical trials support the use of rifaximin, eluxadoline, and peppermint oil. Options for the treatment of IBS-C include lubiprostone and linaclotide.

Introduction

Irritable bowel syndrome (IBS) is a common and costly functional gastrointestinal (GI) disorder with profound implications for patient function and quality of life. Characterized by chronic intermittent abdominal pain that is associated with diarrhea (IBS-D), constipation (IBS-C), or both (IBS-M),[1] IBS also represents a major burden in terms of patient quality of life, work productivity, and healthcare costs.[2,3] Considerable advances have been made regarding key pathogenic factors that contribute to IBS symptoms. Further, despite a historical lack of controlled data supporting treatment efficacy, the evidence from randomized controlled trials (RCT) regarding the efficacy, safety, and tolerability of new classes of IBS treatments has grown considerably in the past few years with the investigation and approval of several new classes of drugs for IBS.[4-7] Despite these advances, however, recent surveys of IBS patients indicate that they wait an average of 4 years before a diagnosis of IBS is established, and treatment remains unsatisfactory for most patients.[8,9] The objective of this update is to review key advances in the understanding of the pathophysiology, diagnosis, and treatment of IBS, with the aim of improving the management of the heterogeneous group of patients with this common disorder.

Pathophysiology of IBS

Although the pathophysiology of IBS remains incompletely understood, new contributing factors have been identified over the past decade. Traditional pathogenic concepts have focused on abnormalities in motility, visceral sensation, brain-gut interactions, and psychosocial distress (Figure 1).[3] However, IBS is a heterogeneous disorder, and no single abnormality accounts for IBS symptoms in all patients.[3,10,11]

Altered gut immune activation, intestinal permeability, and the intestinal and colonic microbiome may be important factors in IBS pathophysiology (Figure 1).[3,12-14] Studies have confirmed a strong association between acute enteric infection and subsequent IBS symptoms (ie, post-infectious IBS [PI-IBS]).[15-18] Meta-analyses demonstrate that the risk of developing PI-IBS increases over sevenfold after an acute episode of infectious gastroenteritis.[17] Additional data indicate that IBS symptoms persist for at least 8 years in a minority of these patients.[15] Further, with the advent of culture-independent molecular techniques, quantitative and qualitative changes in the fecal microbiota of IBS patients have been demonstrated.[12]

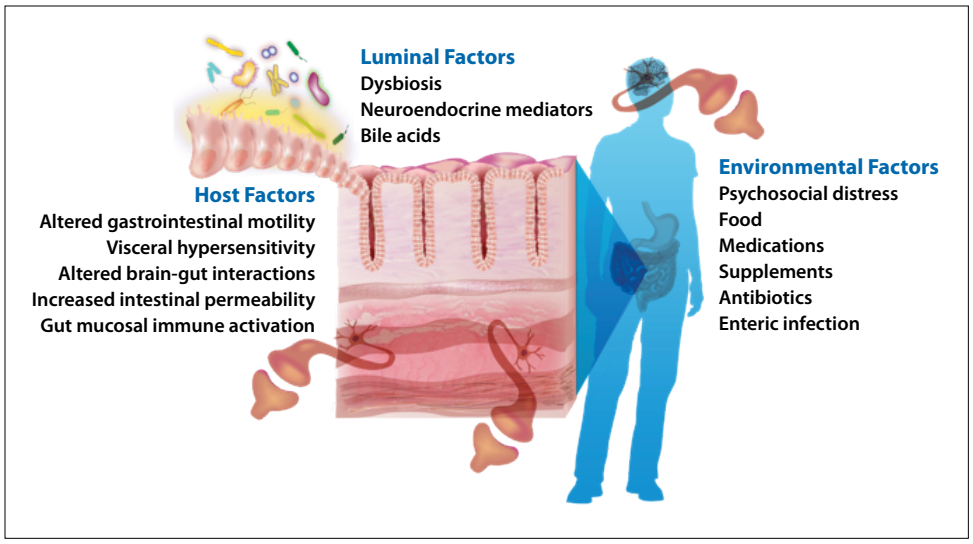

Figure 1. Overview of irritable bowel syndrome pathophysiology. Adapted from Chey WD et al. *JAMA*. 2015;313(9):949-958.[3]

Currently, it is believed that changes in the microbiota may activate mucosal innate immune responses, resulting in increased epithelial permeability, activated nociceptive sensory pathways, and dysregulation of the enteric nervous system.[12]

Bile acid malabsorption may trigger symptoms in some IBS-D patients. Indeed, a systematic review of 17 studies found moderate bile acid malabsorption present in one-third of patients with IBS-D.[19] Excess bile acid can have wide-ranging effects on the colon, including increased water and electrolyte secretion, accelerated colonic transit, and stimulation of enteroendocrine cells.[20,21] Although the precise role of bile acids in IBS-D has not been defined, this finding is driving new therapeutic approaches.[20,22]

Although diet has traditionally been considered of minor importance to IBS pathogenesis, most IBS patients believe that certain foods contribute to their symptoms.[10,23] Indeed, a number of mechanisms by which foods can trigger IBS symptoms have been suggested, including food allergies, food intolerance, exaggerated physiologic responses to food ingestion, and interactions with the microbiota.[11,24] Although the role of food allergies in IBS appears to be small, poorly absorbed carbohydrates have been implicated in triggering IBS symptoms.[3,10] In particular, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) appear to affect colonic function through their osmotic effects on the intestinal lumen, induction of rapid fermentation by gut bacteria to short-chain fatty acids, and associated gas production.[11] Luminal distension by unabsorbed or fermented FODMAPs appears to be associated with pain, bloating, distension, flatulence, and diarrhea.[10] While poorly absorbed carbohydrates exacerbate symptoms in some IBS patients, they rarely cause symptoms in healthy individuals.[3]

Diagnosing IBS

The diagnosis of IBS is based on the presence of characteristic symptoms, the exclusion of concerning features, and selected tests to exclude organic diseases that can mimic IBS (Figure 2).[3,25] The most common conditions to exclude are inflammatory bowel disease (IBD), systemic hormonal disturbances (eg, thyroid dysfunction), enteric infections, colorectal cancer, and diseases associated with malabsorption (eg, celiac disease).[3,26] However, because the prevalence of organic disorders in patients with suspected IBS is low, routine diagnostic testing (eg, thyroid function testing, abdominal imaging, colonoscopies) is not recommended for patients with typical symptoms without "alarm symptoms" for organic disease.[3,26] Such alarm features, or red flags, include rectal bleeding, weight loss, iron deficiency anemia, nocturnal symptoms, and a family history of organic diseases including colorectal cancer, IBD, and celiac disease. Although these features identify patients who may be more likely to have an organic disease, most of these patients will ultimately have negative diagnostic test results.[3]

Given the low probability of organic disease in patients with typical IBS symptoms and the limited value of routine diagnostic testing in such patients, the American College of Gastroenterology (ACG) IBS Task Force recommends the use of symptom-based criteria for diagnosing IBS: "abdominal discomfort associated with altered bowel habits."[26] The Rome Criteria are another symptom-based tool for identifying IBS patients. First developed in 1988, the Rome Criteria for IBS have undergone several revisions,[1,27,28] and updated criteria (Rome IV) have been released in 2016.[29] However, the Rome Criteria are primarily used in research and are infrequently used in clinical practice.

While the yield for testing for organic disease in patients with suspected IBS is low, certain diseases should be considered in the differential diagnosis of such patients. Given data suggesting that patients with IBS symptoms have a higher prevalence

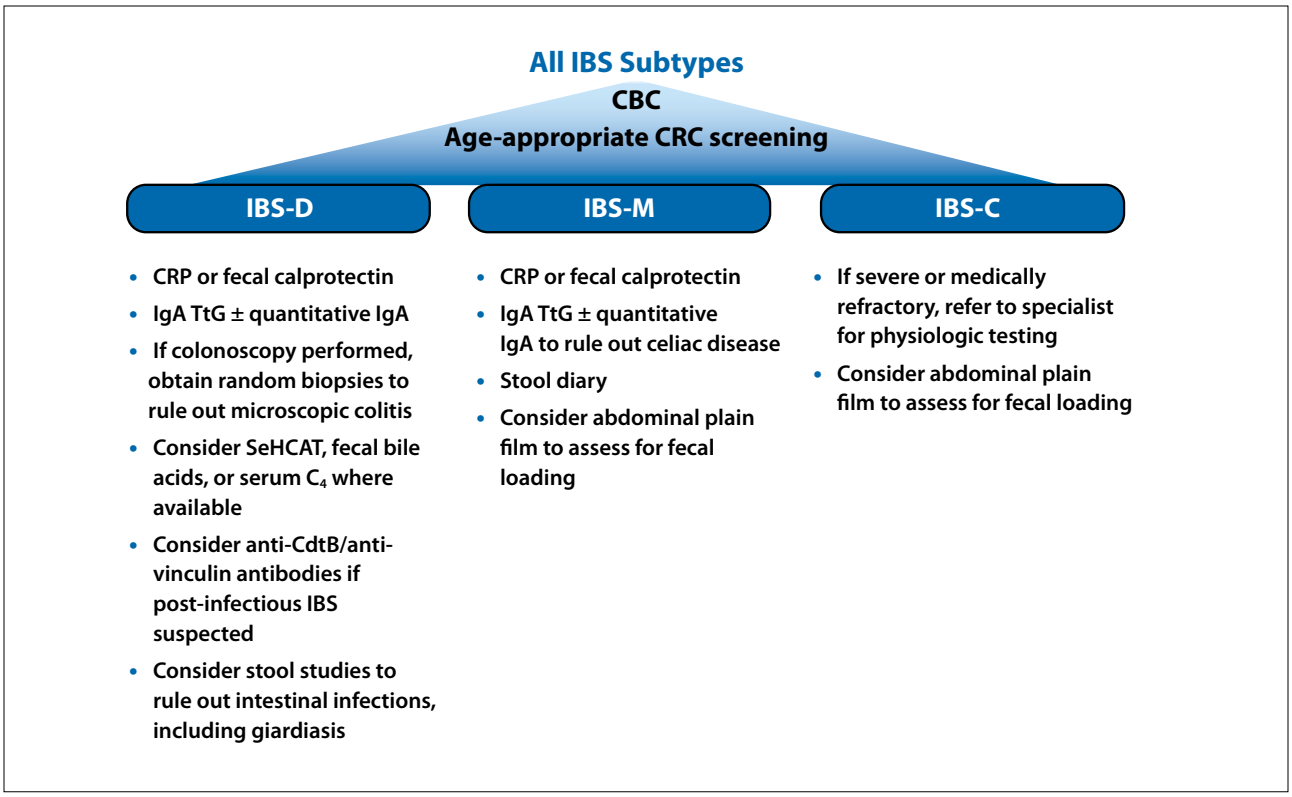

Figure 2. Suggested diagnostic work-up for patients with suspected IBS and no alarm features. Alarm features include age ≥50 years, blood in stool, nocturnal symptoms, unintentional weight loss, change in symptoms, recent antibiotic use, and a family history of organic disease. C, constipation; CBC, complete blood count; CdtB, cytolethal distending toxin B; CRC, colorectal cancer; CRP, C-reactive protein; D, diarrhea; IBS, irritable bowel syndrome; IgA, immunoglobulin A; M, mixed diarrhea and constipation; SeHCAT, selenium homocholic acid taurine; Ttg, tissue transglutaminase. Adapted from Chey WD et al. *JAMA*. 2015;313(9):949-958[3] and Pimentel M et al. *PLoS ONE*. 2015;10(5):e0126438.[35]

of biopsy-proven celiac disease,[30] clinicians should have a low threshold for celiac screening, particularly for patients with IBS-D symptoms.[3] As anemia is an alarm ("red flag") symptom, most patients with IBS symptoms should get a complete blood cell count. Further, a small subset of patients with suspected IBS-D have microscopic colitis.[31] In a case-control study that involved 466 patients with suspected non-constipation–predominant IBS, microscopic colitis was found in 1.5% of patients overall and in 2.3% of those 45 years of age and older.[31] These findings suggest that random colon biopsies are warranted when colonoscopies are performed on patients with suspected IBS-D.[3,31]

Emerging evidence suggests that C-reactive protein (CRP) and fecal calprotectin may be helpful in distinguishing IBS from IBD. Although IBD does not appear to be more prevalent in IBS patients than in controls,[31] symptoms may overlap and, indeed, a considerable proportion of patients with IBD have been found to fulfill the Rome Criteria for IBS.[3,32] Several recent meta-analyses confirm that normal levels of fecal calprotectin and/or CRP can help exclude IBD in patients with IBS symptoms.[33,34] Accordingly, it may be appropriate to perform a colonoscopy to exclude IBD in patients with IBS symptoms with elevated CRP or fecal calprotectin.

The presence of circulating antibodies to cytolethal distending toxin B (CdtB) and vinculin may also differentiate IBS-D from IBD patients.[35] CdtB is a toxin produced by *Escherichia coli*, *Shigella, Campylobacter jejuni*, and other gram-negative bacteria that can cause infectious gastroenteritis, while vinculin is a cytoskeleton required for neuron migration. In addition to stimulating production of anti-CdtB antibodies, CdtB appears to stimulate the production of anti-vinculin antibodies. These antibodies appear to be biomarkers of PI-IBS. Animal models demonstrate that the interaction of host antibodies to CdtB in the host gut may produce an IBS-like phenotype.[36,37] In a validation study involving 2375 patients with IBS-D, anti-CdtB and anti-vinculin titers were found to be significantly higher in patients with IBS-D compared with healthy controls, patients with IBD, and those with celiac disease.[35] Optimization demonstrated a likelihood ratio for diagnosing IBS-D vs IBD of 5.2 and 2.0 for anti-CdtB and anti-vinculin, respectively.[35] In addition to validating the presence of anti-vinculin and anti-CdtB as blood-based markers for post-infectious IBS-D, these find-

ings appear to be an important step in determining an organic basis for PI-IBS.

A number of other studies may have a role in assessing patients with suspected IBS. Given the role of bile acid malabsorption in some IBS patients,[19] tests that identify such malabsorption may be helpful in patients with IBS-D.[3] Although not widely available in the United States, the tauroselcholic (selenium 75) acid retention test (SeHCAT), serum C4 measurement, and fecal bile acid measurement may eventually be useful in clinical practice to identify patients likely to benefit from a bile acid sequestrant.[3] Patients with IBS-C symptoms who are unresponsive to therapy may be referred for physiologic testing to evaluate for dyssynergic defecation/pelvic floor dysfunction as the cause of their constipation.[3]

Overview of IBS Management

Non-Pharmacologic Strategies

Dietary Intervention. Many patients with IBS believe that food sensitivity contributes to their symptoms,[23] with 60% of patients in one study reporting worsening of symptoms after meals.[38] In an online survey of 1242 IBS patients, more than half of the patients endorsed eating small meals, avoiding milk products, avoiding fatty foods, and maintaining a high-fiber diet as being beneficial for their symptoms.[23] Despite these trends, dietary therapy has not played a key role in IBS management, largely because of historically poor evidence of its benefit.[39,40] However, there appears to be renewed interest in the role of dietary manipulations in IBS, possibly because of growing recognition of potential dietary triggers in some patients, such as gluten and FODMAPs.

Several studies have investigated the benefit of a low-FODMAP diet. In one controlled, crossover study involving 30 patients with IBS, a low FODMAP diet was associated with lower overall GI symptom scores compared with a typical Australian diet (22.8 vs 44.9, respectively; $P<.001$).[39] Bloating and pain were also reduced ($P<.001$). Other small studies have reported benefit of a low FODMAP diet, but more studies are needed to define the role of this diet in IBS management.[41,42]

Despite increasing evidence supporting low-FODMAP intervention, implementing this diet can be challenging. Clinicians should engage a registered dietician to counsel patients on the various aspects of the low-FODMAP diet and integrate him or her into the healthcare team, if possible.[3,43] This can be essential to successful implementation of the diet, as patients may feel overwhelmed when reading a low-FODMAP diet guide and conclude that adherence to the diet is not possible. In less than an hour, an experienced registered dietician can work with patients to set up a diet plan and provide tips for making the low-FODMAP diet work. Additionally, a registered dietician can help patients who respond well to a strict low-FODMAP diet to identify and gradually reintroduce FODMAP-containing foods that are tolerated, and to identify foods that should be avoided.

Other Interventions. Psychological 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.[41] Structured exercise intervention has also been shown to improve IBS symptoms and some aspects of disease-specific quality of life,[44] leading experts to recommend that patients increase their physical activity.[3]

Managing IBS-D

Conventional therapies. Until recently, there were few effective treatments for IBS-D that were approved and widely available for this indication. Loperamide is an effective antidiarrheal, but there is no controlled evidence supporting its use in relieving abdominal pain, bloating, or global IBS symptoms.[41] While certain antispasmodics are considered effective in providing short-term relief in IBS, particularly from abdominal pain, the antispasmodics available in the United States (eg, dicyclomine, hyoscyamine) are associated with multiple, dose-related anticholinergic adverse effects and have not demonstrated efficacy in appropriately designed RCTs.[41]

Alosetron, a selective serotonin 5-HT_3 receptor antagonist, relieved global IBS symptoms, abdominal pain, urgency, and diarrhea-related complaints in a number of high-quality controlled studies.[41] Despite proven efficacy, however, the use of alosetron has been limited by 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).[45] Accordingly, alosetron is indicated for a narrow population—specifically, women with severe IBS-D who have not responded to conventional therapies—and its use has been restricted under a risk management program.[45,46]

Ondansetron, a 5-HT_3 antagonist used as an antiemetic for decades, has recently been shown to improve symptoms in patients with IBS-D.[47] In a randomized, double-blind, crossover study, 120 patients with Rome III–diagnosed IBS-D received ondansetron 5 mg/day or a placebo for 3 weeks before crossing over to the other treatment.[47] Compared with the placebo, ondansetron therapy significantly improved stool consistency ($P<.001$) and reduced urgency scores ($P<.001$) and bloating ($P=.002$). Unlike alosetron, however, it did not significantly improve abdominal pain. Ondansetron was well tolerated in this study, with constipation being the most commonly reported side effect (reported in 9% of patients receiving ondansetron compared with 2% of patients receiving the placebo).

Antidepressant agents have become a widespread treatment for patients with moderate to severe IBS, owing to their effects on pain percep-

tion, mood, and motility.[3,48] Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are considered modestly effective for relieving global symptoms and pain in IBS, although there are conflicting opinions regarding the quality of the evidence base for these agents.[41,49,50] Because TCAs have anticholinergic effects and can cause constipation, their use may be most appropriate in IBS-D patients, while the prokinetic effects associated with SSRIs may be of greater benefit in those with IBS-C.[51] However, the efficacy of antidepressants, according to predominant stool patterns, has not been well studied.[51] SSRIs may also be a good option in IBS patients with concurrent anxiety disorders.[3,48] Antidepressant agents should generally be initiated with low doses in IBS patients and titrated slowly (every 1 to 2 weeks), allowing 4 to 8 weeks for maximal response.[48,52]

Modulation of the gut flora. With growing evidence of the contribution of the gut flora in IBS pathogenesis, strategies aimed at modifying the intestinal microbiota have been increasingly explored.[53-60] Probiotics have been used for decades by IBS patients, although the evidence base for these agents has only recently come under scrutiny.[41] Although there are a number of RCTs of probiotics in IBS, they are typically poorly designed and have not consistently demonstrated efficacy.[41,53] Further, differences in probiotic species, strains, and preparations used in these studies limit recommendations about using specific probiotics.

Rifaximin, an oral, non-absorbable, broad-spectrum antibiotic, is the most extensively evaluated antibiotic in IBS.[41] In 2 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 the placebo for up to 10 weeks after completion of therapy.[61] In a follow-up study, up to 5 rounds of retreatment with rifaximin were found to be successful without reducing the durability of the effect or affecting the rate of adverse events.[62]

Most recently, the randomized, placebo-controlled TARGET-3 trial explored the efficacy of rifaximin retreatment in patients with IBS-D who had received open-label rifaximin for 14 days.[5] The primary endpoint was the proportion of patients with a response as defined by the US Food and Drug Administration (FDA): ≥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 Scale type 6 or 7. Of 2438 patients enrolled in the study, 44% (n=1074) responded to initial treatment. Among these responders, 36% (n=382) did not have recurrence of symptoms during 18 weeks of follow-up, while 59% (n=636) had symptom recurrence and were randomized to the double-blind phase of the study. The median time to recurrence for patients who had responded to open-label rifaximin was 10 weeks. These patients received rifaximin or the placebo for up to 2 additional repeat treatment courses, separated by 10 weeks (Figure 3). There was a significant increase in responders with rifaximin treatment compared to the placebo after the first and second treatment phases (Figure 3).[63]

Based on data from the TARGET clinical program, rifaximin was approved for IBS-D at a dose of 550 mg 3 times daily for up to 3 courses of treatment. Rifaximin is well tolerated, with a safety profile similar to that of the placebo. Further, despite concerns regarding the long-term or repeated use of an antibiotic, rifaximin has demonstrated safety over the time periods in which it has been evaluated.[41]

Eluxadoline. Eluxadoline is an oral agent with mixed opioid effects (μ- and κ-opioid agonist and δ-opioid receptor antagonist) that was approved for IBS-D in 2015.[4,64] The efficacy of this agent was recently demonstrated in 2 pivotal clinical trials involving 2427 patients with IBS-D.[64] Eluxadoline at twice-daily doses of 75 mg and 100 mg achieved the primary FDA endpoint, which 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 a secondary endpoint assessing weeks 1 through 26 (Figure 4). Further, efficacy was sustained for up to 6 months with the 100 mg dose twice daily.

Eluxadoline has been well-tolerated in clinical trials. Constipation is the most frequently reported adverse event, occurring in 8% of patients receiving eluxadoline 100 mg twice daily compared with 2% of placebo-treated patients. Discontinuation of study medication because of constipation occurred in 2% of those receiving eluxadoline 100 mg twice daily compared with <1% of placebo-treated patients.[4] However, several precautions are recommended because of the potential for sphincter of Oddi spasm (<1%) and pancreatitis (<1%), which were frequently associated with excessive alcohol use in clinical trials. Specifically, patients without a gallbladder should receive the lower approved dose (75 mg twice daily).[4] Eluxadoline is contraindicated in individuals with known or suspected biliary duct obstruction or sphincter of Oddi disease/dysfunction, history of alcoholism or tendency to drink more than 3 alcohol beverages per day, history of pancreatitis, severe hepatic impairment, and severe constipation or its sequelae.[4]

Peppermint oil. A new sustained-release formulation of peppermint oil has recently demonstrated efficacy in IBS.[65] Although classified as an antispasmodic because of 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 tran-

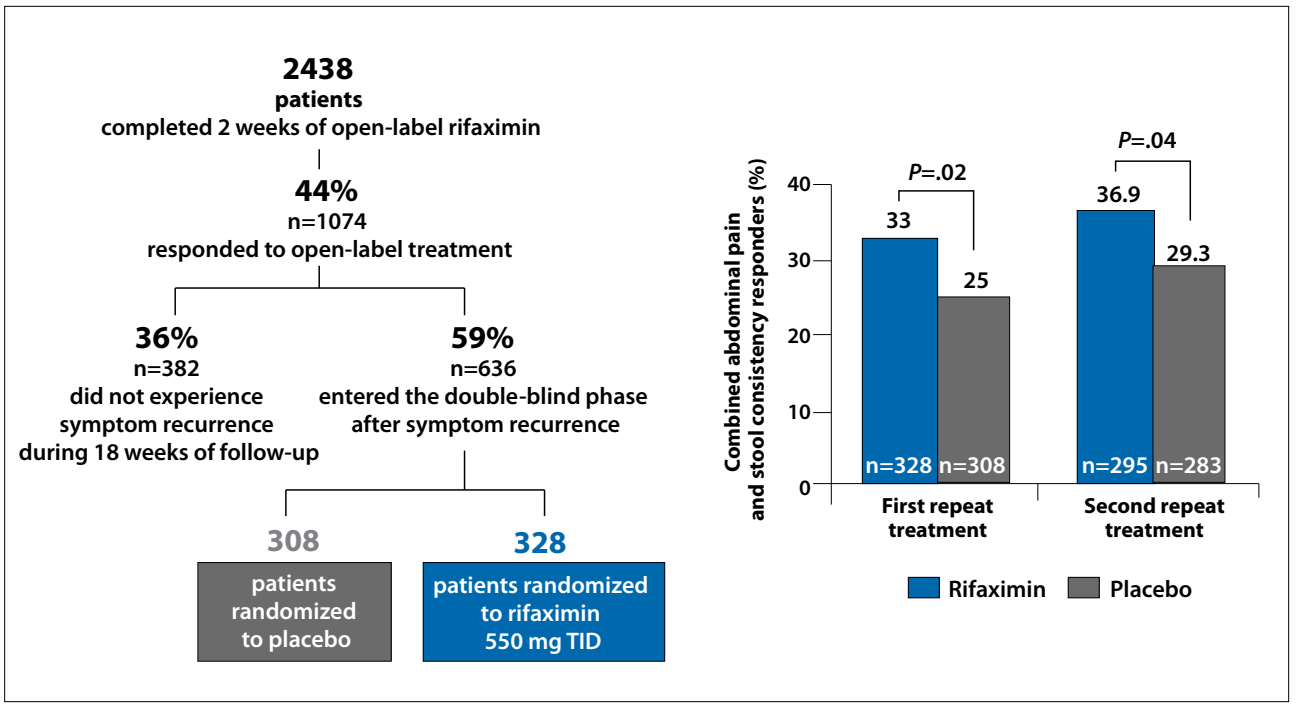

Figure 3. The TARGET-3 study. The left panel shows patient disposition.[5] The right panel shows proportion of composite abdominal pain and stool consistency responders.[63] Response was defined as ≥30% improvement from baseline in the weekly average abdominal pain score and ≥50% reduction in the number of days per week with a daily stool consistency of Bristol Stool Scale type 6 or 7. Adapted from Xifaxan [package insert]. Salix Pharmaceuticals. Bridgewater, NJ; 2015[5] (left panel) and Lembo AJ et al. Abstract 45. Presented at the 2014 Annual Scientific Meeting of the American College of Gastroenterology (right panel).[63]

sit time, κ-opioid antagonism, and 5-HT_3 antagonism.[3,65] In an RCT in 72 patients with IBS-D and IBS-M, patients receiving this formulation of peppermint oil experienced a 40% reduction from baseline in the Total IBS Symptom Score at 4 weeks compared with a reduction of 24.3% with the placebo (*P*=.02). A significant difference between groups was noted as early as 24 hours.[65] 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 5).

Bile acid sequestrants. Increased appreciation for the contribution of bile acid malabsorption to IBS-D symptoms raises the possibility that some patients may benefit from therapy with bile acid sequestrants. One open-label study of 141 IBS patients and control subjects found that 8 weeks of colestipol treatment significantly improved IBS symptoms in patients with evidence of bile acid malabsorption (^{75}SeHCAT ≤20%).[22] Other small, open-label studies have demonstrated benefit of cholestyramine and colesevelam in IBS patients with evidence of bile acid malabsorption.[66,67] In addition, a number of agents that decrease enterocyte bile acid production are currently under investigation.[20,21]

Managing IBS-C

Despite their widespread use, fiber and laxatives have not been subjected to large well-designed IBS clinical trials, have not been approved by the FDA for IBS-C, and have received weak recommendations by both the ACG and the American Gastroenterological Association (AGA).[41,49,50] However, recent data from 2 new RCTs have strengthened the evidence for the use of fiber in IBS.[68] The ACG recognizes fiber as effective in providing overall symptom relief in IBS, although the benefit is limited to soluble fibers, most notably psyllium.[41,68] The osmotic laxative polyethylene glycol has been found to improve stool frequency and consistency, but does not consistently relieve abdominal pain or bloating.[3,69]

Multiple large RCTs support the efficacy of prosecretory agents in IBS-C.[70-73] Approved for the treatment of IBS-C in 2006,[6] lubiprostone is a locally acting, bicyclic functional fatty acid derived from prostaglandin E1 that specifically activates CIC-2 chloride channels on the apical aspect of GI cells, eliciting a chloride-rich fluid secretion.[74] Combined analysis of 2 large, 12-week phase 3 trials demonstrated that this agent significantly improved symptoms of IBS-C compared with the placebo (17.9% overall responders vs 10.1%; *P*=.001), as well as abdominal pain.[70] Further, an extension study of patients in these trials demonstrated that initial improve-

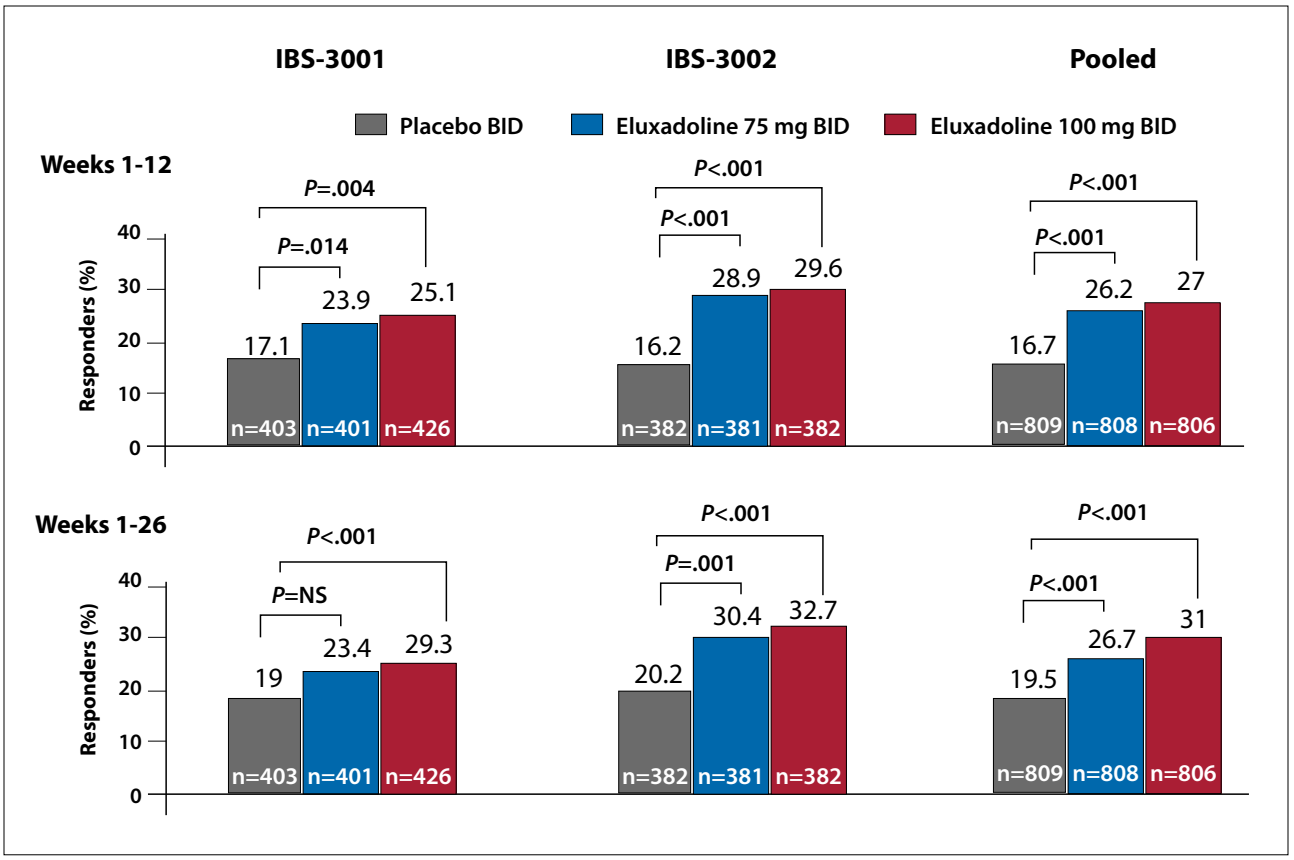

Figure 4. Primary endpoint in eluxadoline pivotal trials. Adapted from Lembo AJ et al. *N Engl J Med*. 2016;374(3):242-253.[64]

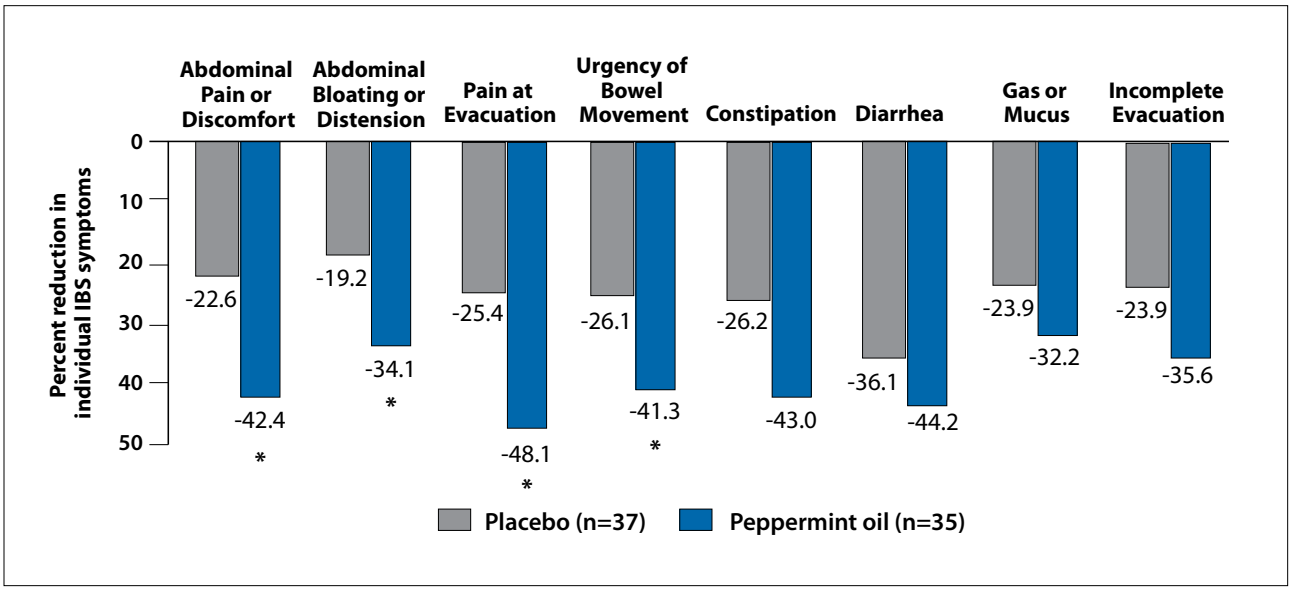

Figure 5. Percent reduction in individual IBS symptoms. **P*<.05. IBS, irritable bowel syndrome. Adapted from Cash BD et al. *Dig Dis Sci*. 2016;61(2):560-571.[65]

ments were maintained over 9 to 13 months of treatment.[75] The most common adverse effect with lubiprostone is dose-related nausea, occurring in 8% of patients receiving 8 µg twice daily in pivotal trials compared with 4% receiving the placebo.[70]

Linaclotide, a first-in-class guanylate cyclase agonist, was approved for the treatment of IBS-C in 2012.[7] The efficacy of this agent is supported by 3 RCTs involving 2028 patients, considered as high-quality evidence by both the ACG and AGA.[41,49,50] These data demonstrate that linaclotide is superior to the placebo in relieving global IBS symptoms, symptoms based on the FDA-responder endpoint, stool frequency, and stool consistency, as well as abdominal pain.[72,73,76] While 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.[3] Additional analyses of the pivotal data have demonstrated that linaclotide significantly improved abdominal pain symptoms, global measures, and IBS-related quality of life in subpopulations of IBS-C patients with severe abdominal pain symptoms.[77] Although diarrhea is reported in up to 20% of patients taking linaclotide, only 5% of patients discontinued linaclotide because of diarrhea.[3,76]

Conclusions

Advances in the understanding of IBS pathophysiology are accompanied by important diagnostic and therapeutic implications. With growing awareness of the contribution of food to symptoms, the low-FODMAP diet is increasingly recognized as a potentially useful therapeutic strategy. The key role of the gut microbiota in IBS has paved the way for new therapeutic targets, reflected in the recent approval of rifaximin for patients with IBS-D,[5] and in the potential utility of anti-CdtB and anti-vinculin antibodies in diagnosing post-infectious IBS-D.[35] Appreciation for the involvement of nociceptive sensory pathways serves as the basis for the use of eluxadoline, another newly approved therapy for IBS-D.[4] The prosecretory agents, lubiprostone and linaclotide, are effective for patients with IBS-C; a number of agents are currently under investigation. Given the heterogeneity of the disorder, further research may provide new treatment strategies and allow clinicians to better target interventions for individual patients.

Disclosure

Dr Schoenfeld is a member of the advisory boards of Ironwood Pharmaceuticals, Allergan, Salix Pharmaceuticals, Synergy Pharmaceuticals, and Daiichi Sankyo. He is a consultant for Ironwood Pharmaceuticals, Allergan, and Salix Pharmaceuticals.

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