New and emerging therapies for the treatment of irritable bowel syndrome: an update for gastroenterologists

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***Abstract*:** Irritable bowel syndrome is a functional bowel disorder with gastrointestinal symptoms (e.g. abdominal pain, straining, urgency, incomplete evacuation, nausea, and bloating) that occur alongside bowel function alterations (i.e. constipation, diarrhea, or both). Patients with irritable bowel syndrome may also experience comorbid anxiety and depression. Irritable bowel syndrome is common, with a prevalence estimated between 3% and 28%, affecting patient health and quality of life. Patients with moderate or severe irritable bowel syndrome generally seek medical care, whereas those with milder symptoms may choose self-management. Most patients with irritable bowel syndrome receive outpatient care, but irritable bowel syndrome-related hospitalizations do occur. The pathophysiology of irritable bowel syndrome is multifactorial (i.e. genetics, immune components, changes in the gut microbiota, disturbances in physiologic stress response systems, and psychosocial factors). Management of irritable bowel syndrome can include lifestyle changes, dietary interventions, counseling, psychologic medication, and agents that affect gastrointestinal motility. A number of therapies have emerged in recent years with clinical trial data demonstrating efficacy and safety for patients with irritable bowel syndrome, including agents that target gastrointestinal motility (i.e. linaclotide), gastrointestinal opioid receptors (i.e. asimadoline, eluxadoline), and gut microbiota (i.e. rifaximin). Linaclotide has been shown to significantly improve stool frequency and abdominal pain compared with placebo in constipation-predominant irritable bowel syndrome (number needed to treat, 5.1). Asimadoline shows efficacy in patients with moderate-to-severe irritable bowel syndrome-related pain. Rifaximin provided adequate relief of global irritable bowel syndrome symptoms *versus* placebo for a significantly greater percentage of patients with diarrhea-predominant irritable bowel syndrome ($p < 0.001$). Management that encompasses all aspects of irritable bowel syndrome (gastrointestinal symptoms) and comorbid psychologic symptoms (e.g. anxiety or depression) is important for improving overall patient health and well-being.

Keywords: asimadoline, functional bowel disorder, linaclotide, rifaximin

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by symptoms of abdominal pain or discomfort that occur with changes in bowel function for at least 3 days/month for at least 3 months (Rome III criteria) [Drossman, 2006; Longstreth *et al.* 2006]. Patients with mild IBS have few symptoms, report good health-related quality of life (HRQOL), and generally seek medical care for symptoms approximately once per year, whereas patients with moderate or severe IBS have a greater number of symptoms (e.g. abdominal pain, bloating, dietary restrictions), report fair to poor HRQOL, and typically seek medical care approximately two to seven times per year [Drossman *et al.* 2009b, 2011]. IBS is further classified based on stool consistency, including constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), IBS alternating between constipation and diarrhea (IBS-M), or unsubtyped IBS [Longstreth *et al.* 2006]. Patients

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with IBS often experience a number of additional gastrointestinal (GI)-related symptoms, including straining, urgency, incomplete evacuation, nausea, and bloating [Hungin *et al.* 2005, 2014; Longstreth *et al.* 2006; Ringel *et al.* 2009; Su *et al.* 2014]. Bloating has been considered to be one of the most bothersome IBS symptoms by patients; bloating led patients to seek medical care with significantly greater frequency than when bloating did not occur ($p = 0.01$) [Ringel *et al.* 2009]. Bloating adversely affected energy level, food intake, and the physical function subdomains of the IBS-quality of life (IBS-QOL) scale [Ringel *et al.* 2009]. Some symptoms tend to occur more often in a specific subtype of IBS. For example, a significantly greater percentage of patients with IBS-D and IBS-M reported experiencing urgency compared with patients with IBS-C ($p < 0.001$), while nausea was more commonly reported in patients with IBS-M than in patients with IBS-D or IBS-C ($p = 0.01$) [Su *et al.* 2014].

Epidemiology of IBS

The prevalence of IBS has been estimated between 3% and 28%, with IBS-M more prevalent than IBS-C and IBS-D [Brummond *et al.* 2015; Lin *et al.* 2014; Locke *et al.* 2000; Patel *et al.* 2015; Rasmussen *et al.* 2015; Rey de Castro *et al.* 2015; Ringel *et al.* 2009; Saito *et al.* 2002; Su *et al.* 2014]. IBS is also more prevalent in women compared with men [Lovell and Ford, 2012]. Diagnosis and management of patients with IBS occurs primarily in an outpatient setting; however, IBS accounted for 0.03% of US hospital discharges in 2010, with a mean duration of hospitalization of 3.7 days, accounting for a mean of US$21,153 in hospital costs [Mitchell and Drossman, 1987; Sethi *et al.* 2013]. A 2014 narrative review of studies that examined the cost of IBS reported an annual US cost of US$742–7547 per patient [depending on study year (1992 to 2004), relationship (direct *versus* indirect) to IBS care, and source of cost data] and a total projected annual cost of US$1.35 billion [Canavan *et al.* 2014]. Extraintestinal physical symptoms of IBS include fatigue, sleep problems, and back pain, reported by 69.3%, 47.5%, and 37.3% of patients, respectively [Choung *et al.* 2009; Patel *et al.* 2015]. In one study, patients reported the intensity of 12 different symptoms on a scale from 0 to 2 using the Patient Health Questionnaire (PHQ), with a score of 0 indicating 'no bother at all,' a score of 1 for 'bothered a little,' and a score of 2 for 'bothered a lot,' for a total score ranging between 0 and 24 [Patel *et al.* 2015]. Patients with IBS had greater odds of a medium or high total PHQ score (total score $\geqslant 8$) compared with patients of a GI clinic without IBS [odds ratio (OR) 1.7; 95% confidence interval (CI) 1.2–2.4]. A high total PHQ score (i.e. $\geqslant 13$), indicative of more severe physical symptoms, occurred in 31.7%, 22.5%, and 20.8% of patients with IBS-M, IBS-C, or IBS-D [Patel *et al.* 2015]. Low back pain is more common in patients with IBS-C than IBS-D ($p < 0.01$) [Schmulson *et al.* 1999]. Patients with IBS often experience improvement in pain symptoms after a bowel movement, particularly patients with pain-predominant IBS (i.e. abdominal pain >6 times/year), compared with patients with abdominal pain <6 times/year (50% *versus* 13%, respectively) [Talley *et al.* 1990]. Approximately one-quarter of patients in each of these groups had IBS-C. Patients with IBS who develop pelvic floor dyssynergy may experience worsening of IBS symptoms; interestingly, biofeedback therapy for dyssynergia has been shown to resolve IBS symptoms in some patients [Patcharatrakul and Gonlachanvit, 2011; Prott *et al.* 2010; Wong *et al.* 2010]. Thus, a number of physical symptoms appear to play a role in the overall well-being of patients with IBS and should not be overlooked or marginalized.

Pathophysiology of IBS

The pathophysiology of IBS has not been fully elucidated, but is multifactorial, and may include, but is not limited to, genetic factors, immune components, alterations in the gut microbiota, disturbances in physiologic stress response systems (e.g. hypothalamic–pituitary–adrenal), and psychosocial factors (Figure 1) [Camilleri, 2012]. A genetic component appears to play a role in IBS, as demonstrated by familial association studies and genome-wide association studies [Ek *et al.* 2015; Holliday *et al.* 2014; Levy *et al.* 2001; Locke *et al.* 2000] Genome-wide association studies of IBS have identified putative genetic risk loci for IBS [Ek *et al.* 2015; Holliday *et al.* 2014]. Further, additional genetic polymorphisms have been associated with IBS and specific disease characteristics (e.g. colonic transit) [Camilleri *et al.* 2014; Grasberger *et al.* 2013; Wouters *et al.* 2014].

Alterations in the immune system play a role in IBS, including cytokine imbalances, immune cell activation, inflammation, and increased GI membrane permeability. Results of a meta-analysis indicated that levels of the proinflammatory

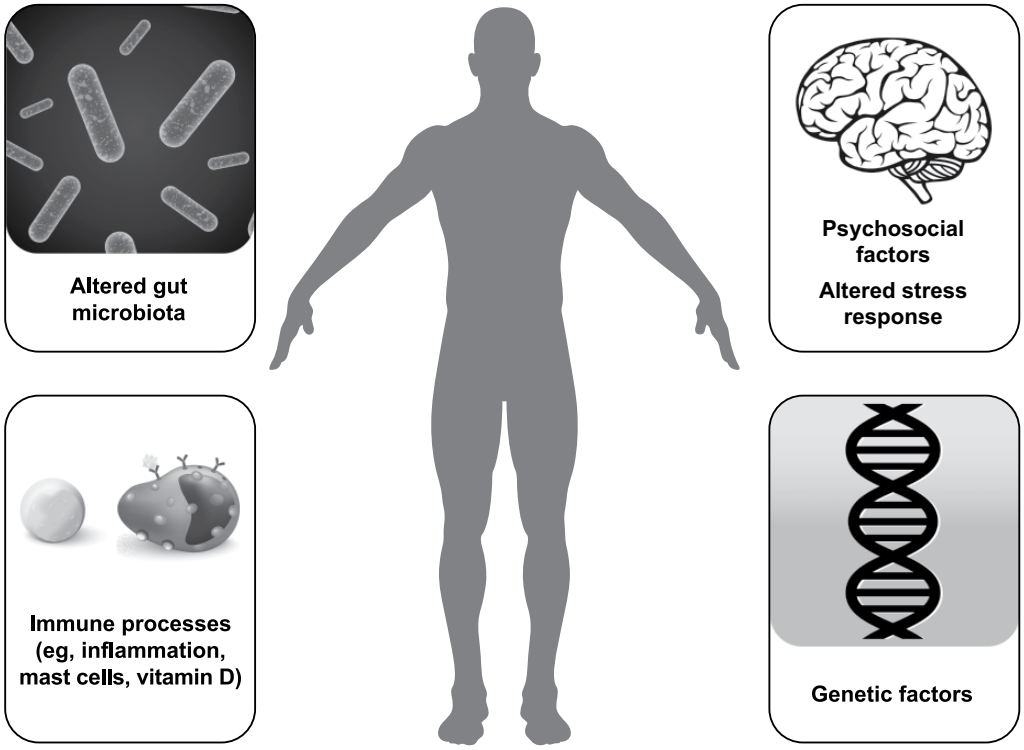

Figure 1. Pathophysiology of IBS.
(Credit: iStock.com/Stefan Alfonso (body silhouette), JDawnInk (DNA helix), and mstay (bacteria); and Shutterstock/maglyvi (brain), and Designua (immune processes artwork).)

cytokine tumor necrosis factor (TNF)-α were significantly increased in patients with IBS-C, IBS-D, and IBS-M, compared with controls ($p \leq 0.03$ *versus* controls for all), while levels of the anti-inflammatory cytokine interleukin (IL)-10 did not differ between patients with either of these three subtypes and controls [Bashashati *et al.* 2014]. Further, serum levels of the proinflammatory cytokine IL-6 were significantly increased in patients with IBS-D compared with controls (32.2 *versus* 7.5 pg/ml, respectively; $p < 0.001$) [Rana *et al.* 2012]. Patients with IBS had increased levels of activated intestinal mucosa immune cells compared with patients of a gastroenterology clinic without IBS, or healthy individuals [Ahn *et al.* 2014; Chadwick *et al.* 2002; Coeffier *et al.* 2010; Guilarte *et al.* 2007; Martínez *et al.* 2012; Vivinus-Nébot *et al.* 2012, 2014]. In patients with IBS-D, the number of daily bowel movements and stool consistency were positively correlated with mucosal levels of activated B-cells and plasma cells [Vicario *et al.* 2014]. Mast cells, which play an important role in innate immunity, release granules containing histamine, serotonin, proteases, lipid mediators, and cytokines upon activation by stress [Barbara *et al.* 2006, 2011]. Indeed, patients with IBS-C and IBS-D had an increased number of duodenal mast cells compared with healthy individuals [Walker *et al.* 2009], and disease severity and abdominal pain were significantly correlated with mast cell counts [Vivinus-Nébot *et al.* 2012].

Vitamin D, which plays a role in inflammatory processes, may also be of relevance in the pathophysiology of IBS [Yin and Agrawal, 2014]. Vitamin D deficiency was significantly associated with depression, a condition not uncommon in patients with IBS [Fond *et al.* 2014; Hoang *et al.* 2011]. Although the role of vitamin D in the pathogenesis of IBS remains to be elucidated, vitamin D supplementation may improve symptoms of IBS, as well as anxiety and depression [Karaahmet *et al.* 2013; Sprake *et al.* 2012]. However, data to support this intriguing hypothesis are sparse and limited to case reports [Sprake *et al.* 2012].

Increased GI membrane permeability is thought to be an important factor in IBS pathogenesis [Martínez *et al.* 2012]. Patients with IBS appear to have increased GI membrane permeability

compared with healthy individuals, with increased severity of disease and abdominal pain significantly associated with membrane permeability ($p = 0.002$ and $p = 0.006$, respectively) [Piche *et al.* 2009; Vivinus-Nébot *et al.* 2014]. Expression of genes related to membrane permeability and mast cell function was altered in patients with IBS-D compared with healthy individuals [Martínez *et al.* 2012]. Expression of the tight junction protein occludin was decreased in patients with IBS compared with healthy individuals [Coeffier *et al.* 2010; Martínez *et al.* 2012; Vivinus-Nébot *et al.* 2014]. Thus, impaired GI membrane permeability appears to play a role in IBS.

The gut microbiota of patients with IBS differs qualitatively and quantitatively compared with that of healthy individuals [Carroll *et al.* 2011; Codling *et al.* 2010; Durbán *et al.* 2012, 2013]. Symptoms of IBS have been associated with specific gut microbiota profiles [Jeffery *et al.* 2012]. Bloating was associated with an increase in GI *Cyanobacteria* in patients with IBS, whereas increased colonic transit time and constipation were associated with 17 different taxa [Jeffery *et al.* 2012]. The GI tract of patients with IBS with depression has a lower concentration of bacteria belonging to the family *Actinomycetaceae* compared with patients with IBS without depression. However, healthy individuals have significantly less *Actinomycetaceae* than patients with IBS without depression ($p = 0.002$); the contribution of this bacterial family to the IBS pathology remains to be elucidated. Although specific symptoms have been correlated with expression of microbiota species in patients with IBS, symptom severity has been associated with instability in the gut microbiota, particularly for patients with IBS-D [Durbán *et al.* 2013]. However, instability of the microbiota was associated with recurrence and remission, with changes to the microbiota profile occurring rapidly (i.e. within days). Further, the microbiota profile differed by symptom severity for a patient with severe IBS-D, with differences between days with mild-to-moderate disease and severe disease. It is still unknown whether alterations in gut microbiota result in the development of IBS symptoms, or occur as a result of IBS.

The bidirectional brain–gut communication axis and brain processing of noxious stimuli appears to play an important role in the pathophysiology of IBS. Patients with IBS may have abnormal colonic transit [Tornblom *et al.* 2012] and visceral hypersensitivity [Camilleri *et al.* 2008; Larsson *et al.* 2012; Posserud *et al.* 2007] potentially related to altered processing of neuronal signals from the GI tract. A meta-analysis of 18 studies that examined brain region activation after rectal distension demonstrated that patients with IBS displayed differences in brain region activity compared with healthy individuals, particularly in brain regions engaged in emotional arousal [Tillisch *et al.* 2011]. Patients with IBS also display alterations in autonomic function [Salvioli *et al.* 2015] and basal levels of stress hormones [Chang *et al.* 2009], suggesting altered function of the hypothalamic–pituitary–adrenal axis.

Psychosocial factors (e.g. physical, sexual, or psychologic abuse; psychiatric conditions) may play a role in the pathophysiology of IBS; psychosocial problems tend to be reported more commonly in patients with more severe forms of IBS [Afari *et al.* 2014; Bradford *et al.* 2012; Chitkara *et al.* 2008; Drossman *et al.* 2011; Halland *et al.* 2014; Knight *et al.* 2015]. Although the exact role of anxiety and depression in the pathophysiology of IBS is currently unknown, both have been associated with increased risk for IBS. Indeed, anxiety and depression occurred in a significantly greater number of patients with IBS compared with individuals without IBS ($p < 0.0001$ for both anxiety and depression) [Koloski *et al.* 2012; Ladabaum *et al.* 2012]. Further, 38% of patients with IBS have reported thoughts of suicide and, although rare, some patients with IBS have also attempted suicide (5%) [Miller *et al.* 2004].

The severity of IBS and the intensity of abdominal pain have been positively correlated with anxiety and depression [Rey de Castro *et al.* 2015]. Patients with IBS-C and IBS-D, but not IBS-M, had significantly greater anxiety compared with healthy individuals ($p = 0.04$, $p = 0.01$, and $p = 0.06$, respectively); only patients with IBS-D had significantly greater incidence of depression than healthy individuals ($p = 0.03$) [Fond *et al.* 2014]. A greater percentage of patients with IBS with anxiety or depression had extraintestinal physical symptoms compared with patients without anxiety (44.8% *versus* 16.8%, respectively; $p < 0.001$) or depression (57.0% *versus* 21.5%, respectively; $p < 0.001$) [Patel *et al.* 2015]. A greater percentage of patients with IBS received anxiolytics and antidepressants compared with healthy controls ($p < 0.0001$ for both comparisons); notably, 62% of patients received these agents prior to receiving a diagnosis of IBS

[Ladabaum *et al.* 2012]. Further, patients with IBS were more likely to have psychiatric conditions than individuals without IBS [Gulewitsch *et al.* 2011; Singh *et al.* 2012]. A significantly greater percentage of patients with severe IBS had at least one psychiatric disorder compared with patients with mild or moderate IBS (94.4% *versus* 35.7% and 76.1%, respectively; $p = 0.003$ and $p = 0.02$) [Singh *et al.* 2012]. Thus, the pathophysiology of IBS is multifactorial in nature.

Management of IBS: established approaches

Patients with IBS may benefit from lifestyle changes (e.g. exercise, dietary modification) [Fukudo *et al.* 2015]. In a study of patients with IBS undergoing military training, 62.9% of patients had improvement from baseline in bowel habits after 9 weeks of lifestyle modification imposed by the training (i.e. no smoking or alcohol consumption, regular meals, physical activity) [Kang *et al.* 2011]. After 9 weeks of training, mean stool frequency decreased from baseline, and the percentage of patients with normal stools (defined as Bristol stool scale score of 3, 4, or 5) increased from baseline ($p = 0.05$). In a randomized, controlled study of patients with IBS, patients in the group with increased physical activity experienced significant improvement from baseline in IBS severity compared with patients who had no change in physical activity after 12 weeks ($p = 0.003$) [Johannesson *et al.* 2011]. Further, patients who increased physical activity had significant improvement from baseline in the emotional ($p = 0.002$), sleep ($p = 0.03$), energy ($p = 0.006$), physical function ($p = 0.001$), social role ($p = 0.001$), and physical role ($p = 0.008$) dimensions of the IBS-QOL instrument after 12 weeks. Thus, increased exercise is a lifestyle change that appears to benefit patients with IBS.

Dietary modification is a therapeutic option preferred by patients with IBS, but may be limited by issues of long-term patient adherence and potential risk of nutritional deficiencies [Gibson *et al.* 2015]. A meta-analysis of four randomized, controlled clinical studies supported the efficacy of a low fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) diet in patients with IBS, with an estimated number needed to treat (NNT) of 2.2 (95% CI 1.9–2.5) [Khan *et al.* 2015]. However, long-term maintenance of a low-FODMAP diet may not be practical [Muir and Gibson, 2013] and its efficacy beyond that of traditionally recommended IBS diet (i.e. regular ingestion of meals and snacks, reduced intake of certain foods such as onions, avoidance of carbonated beverages and artificial sweeteners, and ingestion of fiber) is uncertain [Böhn *et al.* 2015]. Gluten-free diets may be recommended for patients with IBS, although it is unclear how gluten affects IBS symptoms [Vazquez-Roque *et al.* 2013]. In a randomized, controlled study of patients with IBS-D (based on Rome II criteria), those receiving a gluten-free diet for 4 weeks achieved a significant reduction in daily stool frequency compared with patients receiving diets containing gluten ($p = 0.04$). The National Institute for Health and Care Excellence recommends avoidance and exclusion diets (e.g. FODMAP) in patients who have persistent IBS symptoms; however, such patients should be under the care of a dietary management expert. Finally, the efficacy and safety of probiotics, which are one of the most common dietary supplements used for the treatment of GI conditions, are limited by the number of quality clinical studies (e.g. adequate sample size, variability in outcomes examined) supporting their use [Didari *et al.* 2015; Dossett *et al.* 2014; Whelan, 2014] It is currently unclear which probiotic strain might be appropriate for IBS symptoms, and at what daily therapeutic dose [Whelan, 2014]. Probiotics, if used, should be administered in combination with conventional treatments for IBS for best effect [Ringel and Ringel-Kulka, 2011].

Carbohydrate malabsorption is associated with symptoms of IBS (i.e. abdominal pain, constipation, diarrhea), although affected individuals may not have IBS [Goebel-Stengel *et al.* 2014]. In a retrospective study of patients with IBS-like abdominal symptoms, 36% and 64% of patients had symptomatic lactose and fructose malabsorption, respectively, as determined by breath testing. Of patients with diagnosed IBS (by Rome III criteria), 22% had fructose malabsorption as determined by breath testing [Melchior *et al.* 2014]. In these patients, carbohydrate malabsorption can be managed by an elimination diet [Goebel-Stengel *et al.* 2014].

Given the number of patients with IBS with anxiety or depression, patients with IBS may benefit from psychological (psychotropic) therapies [American College of Gastroenterology Task Force on IBS, 2009; Fukudo *et al.* 2015]. Indeed, findings of a systematic review and meta-analysis that evaluated 32 randomized, controlled trials of

psychological therapies found that a greater percentage of patients receiving control therapy (i.e. monitoring of symptoms, physician's 'usual management', supportive therapy, or placebo) reported that their symptoms of IBS did not improve (76.1%), compared with the percentage of patients that did not experience improvement with psychological therapy (i.e. cognitive behavioral therapy, multicomponent psychological therapy, stress management, and relaxation therapy; 51.9%) [Ford *et al.* 2014b]. Thus, results of this meta-analysis suggest that psychological therapies are an effective management option in patients with IBS.

Serotonin is a ubiquitous signaling molecule in the body, primarily produced and stored by enterochromaffin cells in the GI tract [Gershon, 2004; Gershon and Tack, 2007]. Serotonin is important for normal GI motility, secretion, and visceral sensitivity [Bennett and Whitney, 1966; Delvaux *et al.* 1998; Gershon, 1999]. Inactivation of serotonin is mediated by the serotonin reuptake transporter (SERT), which is expressed on GI enterocytes [Gershon, 2004; Wade *et al.* 1996]. Colonic serotonin and SERT levels were decreased in patients with IBS compared with healthy individuals [Coates *et al.* 2004]. Selective serotonin reuptake inhibitors (SSRIs) can increase serotonin levels in patients with IBS by inhibiting the reuptake of this neurotransmitter [Chang *et al.* 2014]. An analysis of pooled data from 7 or 11 randomized, controlled studies of SSRIs or tricyclic antidepressants, respectively, found active treatment was associated with decreased symptoms of IBS compared with placebo (NNT = 4 for both) [Ford *et al.* 2014a]. Although efficacious for patients with IBS, psychotropic medications can be associated with adverse events (AEs) including drowsiness, dry mouth, and lower libido, with a number needed to harm of 9 [Clayton and Montejo, 2006; Ford *et al.* 2014a]. The American College of Gastroenterology weakly recommends the use of SSRIs and tricyclic antidepressants for relief of symptoms and pain in patients with IBS, and the National Institute for Health and Care Excellence notes one could consider them as a second-line therapy [Ford *et al.* 2014a].

Whereas the majority of patients with IBS-C or IBS-D have normal colonic transit times, 12% of patients with IBS-C have slow, and 27% of patients with IBS-D have fast colonic transit times [Tornblom *et al.* 2012]. A number of therapeutic agents that influence colonic transit are available for the treatment of patients with IBS. Lubiprostone, a selective chloride channel activator indicated for the treatment of women with IBS-C, had exhibited a greater degree of efficacy than placebo for relief of global IBS-C symptoms [Takeda Pharmaceuticals America, Inc., 2013; Drossman *et al.* 2009a; Ford *et al.* 2014a]. Results of two phase III clinical studies demonstrated that a significantly larger percentage of patients with IBS-C receiving lubiprostone for 12 weeks achieved overall response (i.e. moderate or significant relief of global IBS symptoms for $\geqslant 2$ of 3 months by patients self-report) compared with placebo (17.9% *versus* 10.1%, respectively; $p = 0.001$) [Drossman *et al.* 2009a]. However, lubiprostone has been associated with mild-to-moderate nausea, which may negatively impact use for some patients [Drossman *et al.* 2009a]. Loperamide, an effective antidiarrheal agent, is not currently recommended for the treatment of patients with IBS, based on insufficient evidence of global IBS symptom relief [Ford *et al.* 2014a]. Alosetron is a selective 5-hydroxytryptamine (5-HT_3) receptor antagonist indicated for the treatment of women with severe, chronic IBS-D refractory to other therapies [Prometheus Laboratories, Inc., 2014]. Early clinical studies of alosetron in patients with IBS included mostly women and failed to demonstrate improved efficacy compared with placebo in men [Bardhan *et al.* 2000; Camilleri *et al.* 1999]. Alosetron provided adequate relief of IBS pain and discomfort, and improvement of stool consistency, in men with IBS-D, but did not improve stool frequency, urgency, bloating, or number of pain-free days compared with placebo [Chang *et al.* 2005]. Because of the risk of severe constipation and ischemic colitis in some patients, prescribing of alosetron is limited to healthcare providers enrolled in a special prescribing program, and patients must sign an acknowledgment form before initiating treatment [Prometheus Laboratories, Inc., 2014; Chang *et al.* 2010; Schiller and Johnson, 2008]. Analysis of postmarketing data acquired after implementation of the risk management program demonstrated that the incidence of ischemic colitis and constipation remained rare and decreased between 2002 and 2011 [Tong *et al.* 2013]. Another 5-HT_3 receptor antagonist, ondansetron, has also been shown to improve symptoms in patients with IBS-D. In a randomized, placebo-controlled crossover trial, patients with IBS-D who received ondansetron 12–24 mg/day for 5 weeks experienced significantly greater

improvement from baseline in mean stool form than placebo ($p < 0.001$) [Garsed *et al.* 2014]. In addition, patients who received ondansetron had reduced mean numbers of days per week with urgency ($p < 0.001$) and mean numbers of days per week with bloating ($p = 0.002$) compared with placebo [Garsed *et al.* 2014]. The most frequent AE with ondansetron was constipation, which occurred in a greater percentage of patients who received ondansetron (9%) than placebo (2%); however, most patients responded to dose reduction and continued with the trial [Garsed *et al.* 2014].

Abnormal contraction of smooth muscle within the GI tract may underlie some IBS symptoms, especially pain; therefore, agents that relax smooth muscles such as antispasmodics and peppermint oil have been evaluated in patients with IBS. A 2014 systematic review of available randomized, placebo- or 'no treatment'-controlled trials for various antispasmodics (23 trials; 2154 patients) demonstrated that antispasmodics significantly improved IBS symptoms to a greater extent than placebo [NNT for antispasmodics 5 (95% CI 4–9)]. However, the effectiveness of individual antispasmodic agents varied, with only otilonium, hyoscine bromide, cimetropium bromide, pinaverium bromide, and dicyclomine hydrochloride showing benefits above placebo. AEs with antispasmodics were more common than with placebo [relative risk (RR) 1.6; 95% CI 1.1–2.4; number needed to harm 20 (95% CI 9.5–333)]; nonserious AEs of dry mouth, dizziness, and blurred vision were commonly reported [Ford *et al.* 2014a]. Two systematic reviews of randomized, placebo-controlled trials of enteric-coated peppermint oil in patients with IBS (5 trials, 482 patients; 9 trials, 726 patients) showed that peppermint oil was more efficacious than placebo for improving IBS symptoms (RR 2.2; 95% CI 1.8-2.8; NNT 3) [Ford *et al.* 2014a; Khanna *et al.* 2014]. Data are somewhat conflicting regarding the incidence of AEs. A pooled analysis study that included 7 randomized, placebo-controlled trials (474 patients) demonstrated a significantly greater risk of experiencing an AE than placebo (RR 1.7; 95% CI 1.3–2.4), whereas a separate study that pooled data from 5 randomized, placebo-controlled trials (482 patients) showed no significant difference from placebo (RR 1.3; 95% CI 0.8–2.1). This dissimilarity may reflect differences in the inclusion of individual studies for the pooled analysis rather than an actual clinical difference in AE occurrence.

The therapies that have been discussed within have been available for patients with IBS for a number of years and, in many cases, much longer. The purpose of this review is to provide gastroenterologists with an update on more recent therapies that have become available (i.e. since 2012), or are currently in development, for the treatment of patients with IBS.

Methods

A PubMed search of English-language articles available through 8 May 2015 was conducted using the following keywords to identify randomized, controlled studies performed in humans: 'irritable bowel syndrome guidelines', 'rifaximin and irritable bowel syndrome', 'linaclotide and irritable bowel syndrome', 'alosetron and irritable bowel syndrome', 'ramosetron and irritable bowel syndrome', 'asimadoline and irritable bowel syndrome', and 'eluxadoline and irritable bowel syndrome'. Reference lists from review articles were used to identify additional studies for inclusion. Further, a ClinicalTrials.gov search of phase III or IV randomized, controlled studies of IBS (primary condition) was conducted on 15 February 2015 to identify additional agents for inclusion in this review.

Newer agents for the treatment of IBS

Targeting GI motility

The prosecretory agent linaclotide is a guanylate cyclase-C agonist indicated for the treatment of patients with moderate-to-severe IBS-C [Forest Laboratories, Inc., 2014; Yu and Rao, 2014]. Linaclotide binding activates guanylate cyclase-C, which leads to phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR). Chloride and bicarbonate ions are secreted through the CFTR, while sodium absorption is decreased, leading to an increase of intestinal fluid into the GI lumen, and a subsequent increase in GI transit time [Layer and Stanghellini, 2014].

Linaclotide was shown to be well tolerated and efficacious for the treatment of patients with IBS-C in 2 randomized, double-blind, placebo-controlled studies, as well as additional post-hoc analyses (Table 1) [Castro *et al.* 2013; Chey *et al.* 2012; Macdougall *et al.* 2013; Quigley *et al.* 2013; Rao *et al.* 2012, 2014]. In one randomized, controlled study, a significantly greater percentage of

Table 1. Summary of randomized, controlled clinical studies of linaclotide in patients with IBS[a].

Study design and patients	Treatment and duration evaluated	Efficacy outcomes	Quality of life	Safety
Primary Analyses				
R, DB, PBO-C [Chey *et al.* 2012] IBS-C (Rome II criteria)	Linaclotide 290 µg qd ($n = 402$) *versus* PBO ($n = 403$) for 26 weeks	Linaclotide *versus* PBO: FDA endpoint[b]: 6 weeks: 33.7% *versus* 13.9%, $p < 0.0001$; 13 weeks: 32.4% *versus* 13.2%, $p < 0.0001$ Decrease from baseline ⩾30% in abdominal pain: for ⩾6 weeks: 48.9% *versus* 34.5%, $p < 0.0001$; for ⩾9 weeks: 38.9% *versus* 19.6%, $p < 0.0001$; for ⩾20 weeks: 36.9% *versus* 17.4%, $p < 0.0001$ Increase from baseline ⩾1 CSBM: for ⩾6 weeks: 47.6% *versus* 22.6%, $p < 0.0001$; for ⩾9 weeks: 18.0% *versus* 5.0%, $p < 0.0001$; for ⩾20 weeks: 15.7% *versus* 3.5%, $p < 0.0001$ Decrease from baseline ⩾30% in abdominal pain and ⩾3 CSBMs and increase from baseline ⩾1 CSBM: for ⩾9 weeks: 12.7% *versus* 3.0%, $p < 0.0001$; for ⩾20 weeks: 12.0 *versus* 2.5%, $p < 0.0001$	Not evaluated	Linaclotide *versus* PBO: AEs: 65.4% *versus* 56.6% Diarrhea: 19.7% *versus* 2.5%
R, DB, PBO-C [Rao *et al.* 2012] IBS-C (Rome II criteria)	Linaclotide 290 µg qd ($n = 405$) *versus* PBO ($n = 395$) for 12 weeks Withdrawal phase: patients receiving linaclotide for 12 weeks randomized to linaclotide ($n = 158$) or PBO ($n = 154$) for 4 weeks; patients receiving PBO for 12 weeks assigned to linaclotide ($n = 335$) for 4 weeks	Linaclotide *versus* PBO: 12-week tx phase: FDA endpoint[b]: 33.6% *versus* 21.0%, $p < 0.0001$ Decrease from baseline ⩾30% in abdominal pain for ⩾6 weeks: 50.1% *versus* 37.5%, $p = 0.0003$ Increase from baseline ⩾1 CSBM for ⩾6 weeks: 48.6% *versus* 29.6%, $p < 0.0001$ Decrease from baseline ⩾30% in abdominal pain for ⩾9 weeks: 34.3% *versus* 27.1%, $p = 0.03$ ⩾3 CSBMs and increase from baseline ⩾1 CSBM for ⩾9 weeks: 19.5% *versus* 6.3%, $p < 0.0001$ Decrease from baseline ⩾30% in abdominal pain and ⩾3 CSBMs and increase from baseline ⩾1 CSBM for ⩾9 weeks: 12.1% *versus* 5.1%, $p = 0.0004$ 4-week withdrawal phase: Re-randomized from linaclotide to PBO: increase in worst abdominal pain and decrease in CSBMs comparable with PBO group in 12-week tx phase Continuation of linaclotide: continued improvement in worst abdominal pain and CSBMs Switch from PBO to linaclotide: improvement in worst abdominal pain and CSBMs comparable with linaclotide group in 12-week tx phase	Not evaluated	Linaclotide *versus* PBO: 12-week tx phase: AEs: 56.2% *versus* 53.0% Diarrhea: 19.5% *versus* 3.5% Abdominal pain: 5.4% *versus* 2.5% Headache: 4.9% *versus* 3.5% Flatulence: 4.9% *versus* 1.5% Abdominal distension: 2.2% *versus* 0.8% 4-week withdrawal phase: Linaclotide-linaclotide: 22.2% Linaclotide-PBO: 22.1% PBO-linaclotide: 30.6%
Post hoc analyses				
R, DB, PBO-C [Castro *et al.* 2013] Post hoc longitudinal responder analysis of patients with IBS-C	Linaclotide 290 µg qd *versus* PBO for 26 weeks (pooled, $N = 805$)	Decrease ⩾30% from baseline in abdominal pain in patients receiving linaclotide Week 3: >50% of patients Week 7: >60% of patients Week 26: ~70% of patients ($p < 0.005$ *versus* PBO for each of 26 weeks)	Not evaluated	Not evaluated

(Continued)

Table 1. (Continued)

Study design and patients	Treatment and duration evaluated	Efficacy outcomes	Quality of life	Safety
R, DB, PBO-C [Quigley *et al.* 2013] *Post hoc* analysis [Chey *et al.* 2012; Rao *et al.* 2012] of patients with IBS-C (Rome II criteria) and mean daily abdominal pain severity score ⩾3.0	Linaclotide 290 µg qd *versus* PBO for 12 weeks	Linaclotide *versus* PBO: EMA endpoint for abdominal pain or discomfort[c]: Trial 31: 54.8% *versus* 41.8%, $p < 0.001$ Trial 302: 54.1% *versus* 38.5%, $p < 0.0001$ EMA endpoint for degree of relief of IBS symptoms[d]: Trial 31: 37.0% *versus* 18.5%, $p < 0.0001$ Trial 302: 39.4% *versus* 16.6%, $p < 0.0001$	Linaclotide *versus* PBO (LS mean change): Improvement in IBS-QOL from baseline to Week 12: Trial 31: 18.4 *versus* 15.2, $p = 0.004$; Trial 302: 16.6 *versus* 11.1, $p < 0.0001$ Improvement in EQ-5D from baseline to Week 12: Trial 31: 0.08 *versus* 0.05, $p = 0.001$; Trial 302: 0.08 *versus* 0.04, $p = 0.0005$ Improvement in EQ-5D VAS from baseline to Week 12: Trial 31: 5.6 *versus* 3.7, $p = 0.06$; Trial 302: 7.1 *versus* 4.4, $p = 0.006$	Not further evaluated
R, DB, PBO-C [Macdougall *et al.* 2013] *Post hoc* analysis [Chey *et al.* 2012; Rao *et al.* 2012] of patients with IBS-C (Rome II criteria)	Linaclotide 290 µg qd *versus* PBO for 12 weeks (pooled, $N = 1602$)	Linaclotide *versus* PBO: FDA endpoint[b]: 33.7% *versus* 17.4%, $p < 0.0001$	Not evaluated	Not evaluated
R, DB, PBO-C [Rao *et al.* 2014] *Post hoc* analysis [Chey *et al.* 2012; Rao *et al.* 2012] of patients with IBS-C (Rome II criteria) and baseline abdominal symptom severity score ⩾7.0) Patients with severe abdominal symptoms: fullness (44%), bloating (44%), discomfort (32%), pain (23%), cramping (22%)	Linaclotide 290 µg qd ($n = 805$) *versus* PBO ($n = 797$) for 12 weeks (pooled, $N = 1602$)	Significant change from baseline in severe abdominal symptoms (pain, discomfort, bloating, fullness, cramping) with linaclotide *versus* PBO at Week 12 ($p < 0.0001$ for all comparisons) Adequate relief of IBS symptoms significantly greater with linaclotide *versus* PBO at Week 12 (59–61% *versus* 28–32%, $p < 0.0001$)	Response by IBS-QOL in 62–68% of patients receiving linaclotide *versus* 45–47% of patients receiving PBO ($p < 0.01$)	Linaclotide *versus* PBO: Diarrhea: 18.3–19.8% *versus* 1.6–2.1% Flatulence: 4.2–5.7% *versus* 1.8–2.5% Abdominal pain: 2.1–4% *versus* 2.2–2.5%

[a]Studies presented are limited to the previous 4 years, due to the large number of clinical studies of linaclotide.
[b]Defined as meeting both an improvement from baseline ⩾30% in mean of daily worst abdominal pain scores and an increase from baseline ⩾1 CSBM for ⩾6 weeks of first 12 weeks of treatment.
[c]Abdominal pain responder defined as patient with improvement from baseline ⩾30% in mean weekly worst abdominal pain score or mean weekly abdominal discomfort score for ⩾6 weeks of first 12 weeks of treatment, with neither score worsening from baseline. Scoring of abdominal pain or discomfort ranged from 0 (none) to 10 (very severe).
[d]Degree-of-relief responder defined as patient with 'considerable' or 'complete' relief of IBS symptoms (i.e. score ⩽2) for ⩾6 of first 12 weeks of treatment. Symptoms were rated weekly on a scale of 1 to 7, with rating of 1 for 'completely relieved', 4 for 'unchanged', and 7 for 'as bad as I can imagine'.
AE, adverse event; CSBM, complete spontaneous bowel movement; DB, double-blind; EMA, European Medicines Agency; EQ-5D, European Quality of Life - 5 Dimensions; EQ-5D VAS, European Quality of Life - 5 Dimensions Visual Analogue Scale; IBS-C, constipation-predominant irritable bowel syndrome; IBS-QOL, Irritable Bowel Syndrome - Quality Of Life questionnaire; LS, least squares; PBO, placebo; PBO-C, placebo-controlled; qd, once daily; R, randomized; tx, treatment.

patients receiving linaclotide had improvement in IBS symptoms as evaluated using the US Food and Drug Administration (FDA) efficacy endpoint [i.e. change from baseline ⩾30% in mean daily worst abdominal pain scores and an increase from baseline ⩾1 complete spontaneous bowel movement (CSBM) for ⩾6 of the first 12 weeks of treatment] compared with placebo (6 weeks, 33.7% *versus* 13.9%, respectively; $p < 0.0001$) [Chey *et al.* 2012]. A greater percentage of patients who received linaclotide *versus* placebo met criteria for the individual components of the combined endpoint [i.e. ⩾30% improvement in abdominal pain (48.9% *versus* 34.5%, respectively) and an increase of ⩾1 in the number of weekly CSBMs from baseline for ⩾6 of 12 weeks (47.6% *versus* 22.6%, respectively)]. Improvement in the FDA efficacy endpoint was sustained for 13 weeks, with 32.4% and 13.2% of patients receiving linaclotide or placebo, respectively, achieving the FDA efficacy endpoint ($p < 0.0001$) [Chey *et al.* 2012]. The percentages of patients who had ⩾30% reduction in average daily worst abdominal pain (36.9 *versus* 17.4% with linaclotide and placebo, respectively; $p < 0.0001$) and ⩾3 CSBMs with an increase of ⩾1 CSBM from baseline (15.7 *versus* 3.5%, respectively; $p < 0.0001$) also remained significantly greater with linaclotide than placebo during an additional 13 weeks of treatment [Chey *et al.* 2012]. These findings were supported by a second randomized, controlled study, which found that 33.6% and 21.0% of patients receiving linaclotide or placebo, respectively, achieved response as defined by the FDA efficacy endpoint ($p < 0.0001$) [Rao *et al.* 2012]. However, in this study, when patients who received linaclotide for 12 weeks were reassigned to receive placebo for 4 weeks, they experienced an increase in mean daily worst abdominal pain and a decrease in CSBMs comparable with that of patients who had received placebo for 12 weeks.

Post hoc analysis of the two randomized, controlled studies [Chey *et al.* 2012; Rao *et al.* 2012] showed that linaclotide significantly improved IBS-QOL from baseline to 12 weeks compared with placebo ($p = 0.004$ and $p < 0.0001$ for the two studies) [Quigley *et al.* 2013]. Indeed, all subscales of the IBS-QOL were significantly improved with linaclotide compared with placebo ($p < 0.05$ for all comparisons), with the exception of the activity interference subscale for patients in the Rao and colleagues study ($p = 0.6$). Although linaclotide improved symptoms of IBS and patient quality of life, this agent was associated with diarrhea [Chang *et al.* 2014; Chey *et al.* 2012; Quigley *et al.* 2013; Rao *et al.* 2012].

Targeting opioid receptors

The μ-, δ-, and κ-opioid receptors expressed in the GI tract are important for the regulation of gut motility and secretion [Bagnol *et al.* 1997; Holzer, 2009; Lamki and Sullivan, 1983]. Expression of the κ-opioid receptor is increased during inflammation and chronic visceral hypersensitivity [Hughes *et al.* 2014a]. In mice, expression of δ-opioid receptors increased under conditions of stress compared with no stress [Wade *et al.* 2012]. Patients with IBS had decreased blood and colonic levels of the endogenous opioid β-endorphin compared with healthy individuals [Hughes *et al.* 2014b].

The mixed μ-opioid receptor agonist and δ-opioid receptor antagonist eluxadoline was approved in May 2015 for the treatment of IBS-D. Patients with IBS-D receiving eluxadoline in a phase II dose-ranging study had greater efficacy compared with patients receiving placebo after 12 weeks [Dove *et al.* 2013]. A significantly greater percentage of patients receiving eluxadoline 25 mg or 200 mg twice daily achieved clinical response (i.e. decrease from baseline in mean worst abdominal pain ⩾30% and ⩾2 points, with a daily Bristol Stool Scale score of 3 or 4 on ⩾66% of daily diary entries within a week) after 4 weeks of treatment compared with placebo (12% or 13.8% *versus* 5.7%, respectively; $p = 0.04$ for 25 mg and $p = 0.02$ for 200 mg *versus* placebo). Clinical response was also significantly greater in patients receiving eluxadoline 100 mg twice daily after 12 weeks of treatment compared with placebo (20.2% *versus* 11.3%, respectively; $p < 0.05$). Eluxadoline improved the number of daily bowel movements and decreased the episodes of urgency and incontinence experienced by patients during the 3-month treatment period. Eluxadoline had an overall favorable safety profile, with nausea, abdominal pain, vomiting, and constipation the most commonly reported AEs. Constipation was most common in the eluxadoline 100 mg group (6%); however, no patients in this group discontinued from the study or rated the intensity of constipation as severe. Three serious incidences of pancreatitis were observed (two within the first two doses of eluxadoline 200 mg twice daily and one within 18 days of 25 mg twice-daily dosing), but all incidences quickly resolved without sequelae. Furthermore,

US prescribing information warns of an increased risk of sphincter of Oddi spasm, resulting in pancreatitis, as well as an increased risk of pancreatitis not associated with sphincter of Oddi spasm [Patheon Pharmaceuticals, Inc., 2015].

Asimadoline is a κ-opioid receptor agonist currently in development for the management of patients with IBS-D with moderate-to-severe pain (Table 2) [Delvaux *et al.* 2004; Mangel *et al.* 2008; Mangel and Hicks, 2012; Szarka *et al.* 2007]. In a phase II, dose-ranging study of patients with IBS with a mean abdominal pain score of 1.5 (on a scale of 0 to 3, with 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain), treatment with asimadoline 0.15, 0.5, or 1 mg twice daily for 12 weeks did not improve response (i.e. number of months with adequate relief of IBS symptoms) compared with placebo [Mangel *et al.* 2008]. However, response was significantly improved in patients with moderate or severe pain (pain score $\geqslant 2$) receiving asimadoline 0.5 and 1 mg, compared with placebo ($p = 0.006$ and $p = 0.005$, respectively). Further, subgroup analysis by IBS type showed that 46.7% and 20% of patients with IBS-D receiving asimadoline 0.5 mg or placebo, respectively, had adequate relief of pain symptoms for $\geqslant 3$ of 4 weeks ($p = 0.01$). A significantly greater percentage of patients with IBS-D receiving asimadoline 0.5 mg achieved a 25% increase in the number of pain-free days during the 12 weeks of treatment compared with placebo (42.9% *versus* 18%, respectively; $p = 0.001$). Bowel function improved in patients with IBS-D after treatment with asimadoline 0.5 mg: the number of daily bowel movements decreased significantly from baseline during month 3 with asimadoline compared with placebo (2.3 *versus* 0.3, respectively; $p < 0.05$) and the number of days with urgency was decreased during the 3 months of treatment at 0.5 or 1.0 mg. Thus, asimadoline may be a potential future therapy for the treatment of patients with IBS-D.

Targeting gut microbiota

The nonsystemic antibiotic rifaximin appears to have anti-inflammatory, host-response, and gut microbiota modulatory activities [Bajaj *et al.* 2013; Brown *et al.* 2010; Cheng *et al.* 2010; Debbia *et al.* 2008; DuPont and Jiang, 2004; Hopkins *et al.* 2014; Jiang *et al.* 2010a, 2010b; Maccaferri *et al.* 2010; Mencarelli *et al.* 2010, 2011; Schrodt *et al.* 2013; Terc *et al.* 2014; Xu *et al.* 2014]. Rifaximin received regulatory approval for the treatment of IBS-D in May 2015; several studies indicated a favorable efficacy and safety profile for rifaximin in IBS-D (Table 3) [Di Stefano *et al.* 2011; Pimentel *et al.* 2006, 2011, 2014]. The identically designed, randomized, placebo-controlled, phase III TARGET 1 and 2 studies examined the safety and efficacy of rifaximin 550 mg 3 times daily for 2 weeks in patients with IBS-D [Pimentel *et al.* 2011]. The primary efficacy endpoint (i.e. percentage of patients with adequate relief of global IBS symptoms for $\geqslant 2$ of the first 4 weeks after the 2-week treatment ended) was achieved by 40.7% and 31.7% of patients receiving rifaximin or placebo, respectively ($p < 0.001$). Further, a significantly greater percentage of patients receiving rifaximin had adequate relief of IBS-related bloating during the first 4 weeks after the 2-week treatment phase compared with placebo (40.2% *versus* 30.3%, respectively; $p < 0.001$). The results of these studies support that rifaximin has a sustained effect in patients with IBS-D, with a 2-week treatment course providing patients with IBS-D benefit for at least 3 months. In addition, three meta-analyses of five randomized, controlled trials of rifaximin for IBS (any subtype) demonstrated significant improvement in overall IBS symptoms with rifaximin compared with placebo (NNT 9–10.6) [Ford *et al.* 2014a; Menees *et al.* 2012; Shah *et al.* 2012]. The safety of rifaximin was favorable and generally comparable with that of placebo; no *Clostridium difficile*–associated diarrhea was reported in the TARGET 1 and 2 studies. Regarding its safety profile, meta-analyses of rifaximin trials showed no difference in the overall incidence of AEs compared with placebo [Ford *et al.* 2014a; Menees *et al.* 2012; Shah *et al.* 2012]. Furthermore, data indicated that 846 patients would benefit from rifaximin treatment for every 1 patient harmed (number needed to harm 8971; NNT 10.6) [Shah *et al.* 2012].

An additional phase III study (TARGET 3) indicated that repeat treatment (up to three 2-week cycles of rifaximin 550 mg three times daily) with rifaximin in patients with IBS-D was significantly more efficacious than placebo in improving IBS symptoms (both abdominal pain and stool consistency) and treatment was well tolerated in patients with IBS-D [Lembo *et al.* 2014]. Rifaximin was not associated with clinically meaningful adverse effects on pathogen emergence or bacterial susceptibility to common antibiotic classes and no sustained disturbance of the overall

Table 2. Summary of randomized, controlled studies of asimadoline in patients with IBS.

Study design and patient population	Treatment	Primary efficacy outcomes	Secondary efficacy outcomes	Safety
R, DB, PBO-C, CO [Delvaux *et al.* 2004] IBS (Rome II criteria) with pain threshold ⩽32 mmHg during first colonic distension attempt	Asimadoline 0.5 mg 1 h prior to colonic distension attempt on Day 1 or 2, alternating with PBO ($n = 20$)	Pain intensity significantly decreased with asimadoline *versus* PBO ($p = 0.04$) Pain thresholds and compliance following colonic distension did not differ between groups ($p = 0.2$)		Not evaluated
R, DB, PBO-C [Szarka *et al.* 2007] Women with IBS (Rome II criteria)	Asimadoline 0.5 mg prn up to 1.0 mg qid ($n = 60$) or PBO ($n = 40$) for 4 weeks	Mean decrease in pain severity from first daily dose to 2 h post-dose when patient had pain level ⩾30 mm on VAS did not differ between groups	Percentage of daily adequate relief of IBS pain and discomfort[a] did not differ between groups and percentage of patients with adequate relief >50% of days with pain was comparable	AEs comparable between groups, except greater percentage of GI-related AEs with PBO
R, DB, PBO-C [Mangel *et al.* 2008] IBS-D, IBS-C, IBS-M (Rome II criteria) with a mean abdominal pain/discomfort severity score ⩾1.5	Asimadoline 0.15 mg ($n = 149$), 0.5 mg ($n = 152$), 1.0 mg ($n = 144$) bid, or PBO ($n = 151$) for 12 weeks	Asimadoline 0.15, 0.5, 1.0 mg, *versus* PBO Total months patients had adequate relief of IBS pain or discomfort[b] during 3 months of tx: 33%, 37%, 37%, 33%, respectively Moderate pain or greater (score ⩾2.0): Asimadoline 0.5 mg and 1.0 mg *versus* PBO, 40% and 40% *versus* 23%, respectively ($p = 0.006$ and $p = 0.005$ *versus* PBO, respectively) Subgroups: IBS-D: 47% and 37% *versus* 20%, respectively ($p = 0.01$ and $p = 0.05$ *versus* PBO, respectively) IBS-M: 50% *versus* 28%, respectively ($p = 0.02$) IBS-C: no benefit with asimadoline	Abdominal pain or discomfort scores[c]: Increase from baseline in pain/discomfort-free days, asimadoline 0.5 mg *versus* PBO, 42.9% *versus* 18% ($p = 0.001$) in patients with IBS-D Stool consistency (Bristol Stool Scale) not improved from baseline in patients with IBS-D or IBS-M Daily stool frequency decreased from baseline to 3 months: asimadoline 0.5 mg *versus* PBO: 2.3 *versus* 0.3, $p < 0.05$ Sense of urgency[d] decreased in patients with IBS-D during 3 months of tx Straining[e] not affected by asimadoline in patients with IBS-D or IBS-M Bloating[f] significantly improved from baseline in patients with IBS-D with asimadoline 0.5 mg and 1.0 mg only during Month 2	Asimadoline 0.15, 0.5, 1.0 mg, *versus* PBO: Diarrhea: 13.4%, 5.9%, 11.1%, *versus* 7.9% Constipation: 12.8%, 10.5%, 7.6%, *versus* 4.6% Headache: 9.4%, 4.6%, 5.6%, *versus* 7.3% Nausea: 5.4%, 8.6%, 2.8%, *versus* 3.3% Sinusitis: 4.7%, 2.6%, 6.3%, *versus* 1.3% Abdominal pain: 5.4%, 4.6%, 4.2%, *versus* 4.0%

[a]Seven-point scale.
[b]Adequate relief of IBS pain or discomfort evaluated by a weekly answer to the question, 'In the past 7 days have you had adequate relief of your IBS pain or discomfort?'. Patients were considered to have adequate relief on a monthly basis if they answered 'yes' ⩾3 of 4 weeks per month. The total number of months that patients had adequate relief was calculated as a percentage of 3 months.
[c]Scoring determined by answer to question, 'Have you experienced abdominal pain or discomfort in the past 24 hours? If yes, how would you rate the maximum severity of abdominal pain or discomfort you have experienced in the past 24 hours? Mild, 1; Moderate, 2; Severe, 3.'.
[d]Evaluated by the answer to the question, 'Have you felt or experienced a sense of urgency in the past 24 hours?'.
[e]Rating determined by the answer to the question, 'Please rate the amount of straining you experienced with your stool in the past 24 hours. 1, no straining; 2, acceptable straining; 3, too much straining.'.
[f]Evaluated by the answer to the question 'Have you experienced bloating or abdominal distension in the past 24 hours?'.
AE, adverse event; bid, twice daily; CO, crossover; DB, double-blind; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, IBS alternating between constipation and diarrhea; IBS-QOL, Irritable Bowel Syndrome - Quality Of Life questionnaire; PBO, placebo; PBO-C, placebo-controlled; prn, as needed; qid, 4 times a day; R, randomized; tx, treatment; VAS, visual analogue scale.

gut (stool) microbiota was observed. Although not indicated for IBS-C, rifaximin has also been examined in patients with IBS-C, specifically in combination with neomycin [Pimentel *et al.* 2014]. Rifaximin plus neomycin significantly improved severity of constipation, and symptoms

Table 3. Randomized, controlled studies of rifaximin in patients with IBS.

Study and design	Patients	Treatment	Primary efficacy outcome(s)	Secondary efficacy outcome(s)	Safety
Rifaximin 550 mg					
R, DB, PBO-C [Pimentel *et al.* 2011]	IBS (Rome II criteria) with abdominal pain and discomfort	Rifaximin 550 mg tid ($n = 624$) *versus* PBO ($n = 634$)[a] for 2 weeks	Adequate relief[b] of global IBS symptoms: rifaximin *versus* PBO: 40.7% *versus* 31.7% ($p < 0.001$)	Adequate relief[b] of IBS-related bloating: rifaximin *versus* PBO, 40.2% *versus* 30.3%, $p < 0.001$	AEs comparable between groups Rifaximin *versus* PBO: Headache: 6.1% *versus* 6.6% Upper respiratory tract infection: 5.6% *versus* 6.2% Abdominal pain: 4.6% *versus* 5.5%
R, DB, PBO-C [Pimentel *et al.* 2014]	IBS-C (Rome II criteria) <3 CSBMs/week and breath methane >3 ppm	Rifaximin 550 mg tid ($n = 16$) or PBO ($n = 16$), both in combination with neomycin 500 mg bid for 2 weeks	Constipation severity 1 week post-tx: rifaximin *versus* PBO: 28.6 *versus* 61.2 ($p = 0.002$)	Baseline to 4 weeks post-tx (rifaximin *versus* PBO): Constipation severity ($p = 0.0007$); bloating ($p = 0.02$); straining ($p = 0.02$); abdominal pain ($p = 0.5$) 4 weeks post-tx: Methane ⩽3 ppm: Rifaximin (67%) PBO (69%)	Rifaximin *versus* PBO: Nausea: 47% *versus* 63% Bloating and distension: 47% *versus* 56% Abdominal pain: 20% *versus* 38% Constipation: 13% *versus* 13% Diarrhea: 1% *versus* 13% Urgency: 0% *versus* 13%
Rifaximin 400 mg					
R, DB, PBO-C [Pimentel *et al.* 2006]	IBS (Rome I criteria)	Rifaximin 400 mg tid ($n = 43$) *versus* PBO ($n = 44$) for 10 days	Global improvement in symptoms favored tx with rifaximin *versus* PBO after 10 weeks (36.4% *versus* 21%, $p = 0.02$)	Bloating significantly improved with rifaximin *versus* PBO after 10 weeks ($p = 0.01$) No significant improvement in VAS scores for abdominal pain ($p = 0.3$), diarrhea ($p = 0.7$), and constipation ($p = 0.07$)	Incidence of AEs comparable between groups Most common AEs: abdominal pain, diarrhea, and bad taste in mouth
R, DB, PBO-C, CO [Di Stefano *et al.* 2011]	IBS-C (Rome III criteria) with moderate-to-severe bloating	Rifaximin 400 mg bid *versus* PBO ($n = 24$) for 7 days; washout of 4 weeks	Symptom severity significantly decreased from baseline with rifaximin, but not PBO: Bloating ($p = 0.002$); abdominal distention ($p = 0.03$); abdominal pain ($p = 0.002$); flatulence ($p = 0.004$); borborygmi ($p = 0.008$); nausea (NS) Cumulative breath hydrogen excretion significantly decreased from baseline with rifaximin ($p < 0.005$), but not PBO (NS)		Not reported

[a]Patients included in modified intention-to-treat analysis.
[b]Defined as relief of symptoms for ⩾2 of first 4 weeks of treatment by self-report.
AE, adverse event; bid, twice daily; CO, crossover; DB, double-blind; CSBM, complete and spontaneous bowel movement; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; NS, not significant; PBO, placebo; PBO-C, placebo-controlled; ppm, parts per million; R, randomized; tid, 3 times daily; tx, treatment; VAS, visual analogue scale.

of bloating, straining, and abdominal pain for up to 4 weeks following 2-week treatment, compared with placebo [Pimentel *et al.* 2014].

Bloating and flatulence in patients with IBS may, in part, be due to bacterial overgrowth, may be diagnosed by breath testing, and is a distinct medical condition from IBS [Saadi and McCallum, 2013; Shah *et al.* 2013]. Antibiotics (e.g. ciprofloxacin, metronidazole) are generally used to treat small intestinal bacterial overgrowth (SIBO), which is thought to affect up to half of patients with IBS [Saadi and McCallum, 2013; Shah *et al.* 2013]. In the rifaximin TARGET 1, 2, and 3 studies, SIBO was not tested as part of the inclusion criteria, and also not included in the diagnosis of IBS. Rifaximin, with its favorable safety profile and demonstrated efficacy, appears to be a viable therapeutic option for patients with IBS with or without comorbid SIBO [Scarpellini *et al.* 2007].

Additional agents for treatment of IBS

The neurokinin-2 receptor antagonist ibodutant is currently in clinical development; however, data from randomized, controlled studies in patients with IBS have not yet been published [Trinkley and Nahata, 2014]. Plecanatide, an analog of the natural peptide uroguanylin, which regulates digestive activity, is currently in phase III trials in patients with IBS-C. Data from a phase II, randomized, controlled trial in patients with IBS-C ($n = 424$) indicated that various doses of plecanatide (including 1.0, 3.0, and 9.0 mg) provided significant improvement in the number of weekly CSBMs *versus* placebo ($p \leqslant 0.05$ for all comparisons) [Miner *et al.* 2014]. The most common AE with plecanatide was diarrhea [Miner *et al.* 2014]. Ramosetron, a selective serotonin receptor antagonist, is currently indicated for the treatment of men with IBS-D in Japan, although efficacy (i.e. improvement in global relief of IBS symptoms by patient report) was also demonstrated in women in one study [Matsueda *et al.* 2008a]. Efficacy was demonstrated in both men and women with IBS-D in a second, phase III study [Matsueda *et al.* 2008b]. In this study, overall response (i.e. global relief of IBS symptoms by patient report) was significantly greater with ramosetron compared with placebo after 1, 2, 3, and 4 months of treatment ($p < 0.001$) [Matsueda *et al.* 2008b], However, when stratified by sex, women reported significant relief of IBS symptoms at month 2 only compared with placebo, whereas men reported significant relief of IBS symptoms *versus* placebo at all time points. Further, the incidence of AEs, including abdominal distension, constipation, hard stool, and decreased white blood cell count, was ⩾3% higher for women than men. Thus, there are apparent differences in response in men *versus* women, but the reasons for these differences are currently unknown. Another treatment being examined for patients with IBS-C is chenodeoxycholic acid (CDC), a bile acid traditionally used for gallstone dissolution [Rao *et al.* 2010]. In a double-blind RCT, patients with IBS-C received placebo, CDC 500 mg, or CDC 1000 mg for 4 days [Rao *et al.* 2010]. CDC significantly accelerated overall colonic transit within 24 hours compared with placebo ($p = 0.005$) [Rao *et al.* 2010]. In addition, among females, CDC significantly improved stool consistency ($p = 0.003$), increased stool frequency ($p = 0.18$), and improved ease of passage ($p = 0.24$) *versus* placebo [Rao *et al.* 2010]. Lower abdominal cramping/pain was the most common AE with CDC and was significantly more prevalent in the CDC groups (42% to 45%) than in the placebo group (0%; $p = 0.01$). Diarrhea (17%-18% with CDC *versus* 0% with placebo) and nausea (9% to 25% *versus* 0%) were also common with CDC and were more prevalent with CDC compared with placebo [Rao *et al.* 2010]. Herbal preparations, such as STW 5 (Iberogast®; Bayer Corporation, Morrisville, NC) may improve IBS symptoms [Madisch *et al.* 2004]; however, clinical data are limited. There is also preliminary evidence that ketotifen, a mast cell stabilizer used in the treatment of asthma, may improve IBS symptoms [Klooker *et al.* 2010], but additional adequately powered studies are needed. Agents that have shown efficacy in other GI conditions [e.g. chronic constipation (elobixibat, or A3309 [Chey *et al.* 2011]), inflammatory bowel disease (AZD9056 [Eser *et al.* 2015] and 5-aminosalicylic acid [Feagan and Macdonald, 2012; Ford *et al.* 2011])] may also be beneficial for patients with IBS, but further research is needed.

Conclusions

IBS is a common condition managed primarily in an outpatient setting. Although patients with moderate-to-severe IBS seek medical care with greater frequency compared with patients with mild IBS, it is important to improve the health and overall well-being of all patients with IBS. Treatment should therefore include identification

and management of psychologic comorbidities, such as anxiety and depression, as appropriate. The pathophysiology of IBS is unclear, but is thought to include genetic, immunologic, microbial, physiologic stress response, and psychosocial components. Management of patients with IBS includes lifestyle changes, dietary modification, use of psychotropic medications, psychological therapies, and over-the-counter agents targeting GI motility. Newer therapies targeting GI motility (i.e. linaclotide for IBS-C), GI opioid receptors (i.e. eluxadoline for IBS-D), and gut microbiota (i.e. rifaximin for IBS-D) have demonstrated efficacy and safety in patients with IBS. Further, additional therapies currently in phase II and III of development appear to show promise for the treatment of patients with IBS.

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A.E.F.-O. has served on the speakers' bureau for Salix, and has received payments for lectures.

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