REVIEW

Current US Food and Drug Administration-Approved Pharmacologic Therapies for the Treatment of Irritable Bowel Syndrome with Diarrhea

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ABSTRACT

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain and alterations in stool form and/or frequency, leading to reduced quality of life. Pharmacologic agents currently approved by the US Food and Drug Administration for treatment of IBS with diarrhea (IBS-D) in adults are the nonsystemic antibiotic rifaximin, the mixed μ- and κ-opioid receptor agonist/δ-opioid antagonist eluxadoline, and the selective serotonin 5-HT_3 antagonist alosetron (the last of which is indicated only in women with severe IBS-D refractory to conventional therapy). Both eluxadoline and alosetron are administered as chronic daily therapies; rifaximin is given as a 2-week course of treatment with repeat courses administered as needed for symptom recurrence. Presumed mechanisms of action of rifaximin include modulation of the gut microbiota, anti-inflammatory activity, normalization of visceral hypersensitivity, and reduction in intestinal permeability. Eluxadoline targets opioid receptors in the gastrointestinal (GI) tract, resulting in decreased GI motility, fluid secretion, and visceral pain perception. Alosetron antagonizes serotonergic afferent neural signals and also slows GI motility. The efficacy and safety of these agents have been investigated in several rigorous clinical trials, and it has been demonstrated that they improve global and individual IBS symptoms. This review highlights the pivotal efficacy and safety data of the three pharmacologic agents currently indicated in the USA for the management of IBS-D in adults.
Funding: Salix Pharmaceuticals.

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Key Summary Points

Irritable bowel syndrome (IBS) is a common disorder associated with abdominal pain and changes in bowel habits (e.g., diarrhea).

IBS negatively impacts health-related quality of life and can be a substantial physiologic and social burden on patients with the disorder.

Rifaximin, eluxadoline, and alosetron are indicated for the treatment of IBS with diarrhea (IBS-D), and their efficacy in treating the totality of IBS-D symptoms has been shown in several well-designed trials.

Frequency of administration (e.g., short-course versus daily therapy) and safety profiles of agents indicated for IBS-D differ and should be taken into consideration when determining a treatment approach.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by recurrent abdominal pain associated with alterations in visceral pain perception, with defecation and/or changes in stool frequency and/or stool form [1]. IBS is a heterogenous condition and is further subclassified by its predominant stool texture [1]. By definition, individuals who have IBS with diarrhea (IBS-D) experience the passage of Bristol Stool Form Scale (BSFS) type 6 or 7 stools (loose, mushy, watery) during more than 25% of bowel movements, and types 1 and 2 stools (hard, lumpy, pellet-like) less than 25% of the time. Current Rome IV diagnostic criteria specify that stool texture should be assessed on days with abdominal pain to enable greater precision in differentiating the IBS subtype [1, 2].

IBS is a common disorder, with worldwide prevalence estimates between 8.8% [3] and 11.2% [4]. In the USA, up to 14.1% of individuals are thought to be affected [5]. Women are almost twice as likely as men to suffer from IBS (14% vs. 8.9%), and the prevalence of IBS-D, at up to 40% of adults, is highest among the IBS subtypes [4]. Although not required for a diagnosis, patients with IBS-D report additional symptoms, including abdominal distention, bloating, increased defecatory urgency, and sensations of incomplete evacuation [1]. IBS-D negatively impacts health-related quality of life, with patients reporting avoidance of planned activities, eating prior to or during social events, and increased absenteeism (missed work or school) and presenteeism (decreased productivity at work or school) in reaction to or for management of their symptoms [6, 7]. Consequently, effective therapies are needed to reduce the substantial physiologic and social burdens of this disorder. In recent years, there has been a shift in the management paradigm from treating isolated symptoms to improving the global symptom profile. The goal of this narrative review is to highlight global efficacy and safety data for current pharmacologic agents approved by the US Food and Drug Administration (FDA) in the USA for IBS-D.

METHODS

A search of the Medline database for all English-language articles published through 31 December 2018 (i.e., no start date used in literature search) was conducted to identify relevant articles using the following keywords: "alosetron", "efficacy", "eluxadoline", "irritable bowel syndrome", "irritable bowel syndrome with diarrhea", "IBS-D", "rifaximin", and "safety". Abstracts that discussed pharmacologic agents approved by the FDA for IBS-D were reviewed for safety and/or efficacy data in individuals with IBS-D. Additional relevant publications were identified from article reference lists. This review article is based on studies previously conducted in humans and references two clinical studies performed by the authors.

FDA-APPROVED THERAPIES FOR IBS-D

The three pharmacologic agents currently indicated in the USA for treatment of IBS-D in adults have been rigorously analyzed in multiple clinical trials, using standardized trial designs and endpoints from the FDA to examine their efficacy for treating the global symptom profile of IBS. In contrast, loperamide, an over-the-counter therapy for diarrhea, has limited clinical trial data available in IBS, and data supporting its use for overall symptom improvement is lacking. Consequently, the American College of Gastroenterology Monograph authors recently recommended against using it to treat IBS-D [8], but direct comparisons between the FDA-approved agents and loperamide cannot be made, as no head-to-head clinical trials have been published.

Therapies approved for treatment of adults with IBS-D include the nonsystemic antibiotic rifaximin, the mixed μ- and κ-opioid receptor agonist/δ-opioid antagonist eluxadoline, and the selective serotonin 5-HT$_3$ antagonist alosetron (only for women with severe IBS-D who have not responded adequately to conventional therapy) [9–11]. The mechanisms of action of rifaximin are believed to include modulation of the gut microbiota, anti-inflammatory activities, and reductions in intestinal permeability, ultimately improving stool texture and reducing pain [12–16]. Eluxadoline targets opioid receptors in the gastrointestinal (GI) tract, reducing visceral pain and decreasing fluid secretion and GI motility [17, 18]. Alosetron antagonizes serotonergic afferent neural signals and also slows GI motility through selective serotonin inhibition, ultimately leading to improvements in pain and diarrhea [19].

Rifaximin

Rifaximin, an antibiotic that is not absorbed systemically, is administered as a short course of therapy [550 mg three times daily (t.i.d.) for 2 weeks]. The seminal data supporting its efficacy for treating IBS-D comes from two randomized, double-blind, placebo-controlled phase 3 studies (TARGET 1 and 2) and a unique phase 3 retreatment trial (TARGET 3; Table 1) [20, 21]. In TARGET 1 and 2, 1258 individuals with non-constipation IBS received 550 mg of rifaximin t.i.d. for 2 weeks, with a significantly greater percentage of rifaximin-treated patients experiencing adequate relief of their global IBS symptoms (primary efficacy endpoint) for at least two of the first 4 weeks post-treatment compared with placebo [40.7% vs. 31.7%, respectively (pooled); $P < 0.001$] [20]. The 2-week course of rifaximin also provided significant improvement in bloating versus placebo [40.2% vs. 30.3%, respectively (pooled); $P < 0.001$] [20]. Relief of global IBS symptoms and bloating was maintained for at least 12 weeks in a significantly greater percentage of individuals treated with rifaximin compared with placebo (pooled for each endpoint; $P \leq 0.001$), supporting durability of response [20].

The safety profile of rifaximin was comparable to that of placebo in TARGET 1 and 2 [20]. The most commonly reported adverse events (AEs) were headache (6.1% vs. 6.6%, respectively), upper respiratory tract infection (5.6% vs. 6.2%), and abdominal pain (4.6% vs. 5.5%) [20]. Serious AEs were reported in 1.6% of patients in the rifaximin group and 2.4% of patients in the placebo group, and there were no documented cases of Clostridium difficile or ischemic colitis [20]. A 2014 pooled safety analysis including the aforementioned data, as well as data from a phase 2 trial, did not find increased risk of infection or substantial differences in AE rates versus placebo; this adds further credence to the overall safety profile of rifaximin [22].

In the phase 3 IBS-D retreatment study (TARGET 3), all enrollees initially received an open-label course of rifaximin 550 mg t.i.d. for 2 weeks, allowing for a "real-world" assessment of therapeutic effectiveness [21]. A total of 1074 of 2438 participants (44.1%) were considered symptom responders (defined as simultaneously achieving at least 30% decrease from baseline in mean weekly abdominal pain score and at least 50% decrease from baseline in the number of days/week with BSFS type 6 or 7 stool for at least two of the first 4 weeks post-treatment) and were then monitored during an 18-week

Table 1 Efficacy summary of phase 3 clinical trials of rifaximin 550 mg in patients with IBS [20, 21]

Study, design, and treatment	Patient population	Primary efficacy outcome	Key secondary efficacy outcome(s)
Trials 1 and 2 (TARGET 1 and 2) [20] R, DB, PBO-C, MC Rifaximin 550 mg t.i.d. or PBO for 2 weeks, with 10-week treatment-free follow-up	Adults with non-constipation IBS (Rome II; $n = 1258$; rifaximin $n = 624$; PBO $n = 634$) Mean daily abdominal pain and bloating score 2–4.5 (scale range, 0–6) and mean daily stool consistency rating ≥ 3.5 (scale range, 1–5) for past 7 days)	% patients with adequate relief of global IBS symptoms[a] for ≥ 2 of 4 weeks post-treatment Rifaximin vs. PBO: 40.7% vs. 31.7%; $P < 0.001$	% patients with adequate relief of bloating[b] for ≥ 2 of 4 weeks post-treatment Rifaximin vs. PBO (pooled): 40.2% vs. 30.3%; $P < 0.001$
Trial 3 (TARGET 3) [21] R, DB, PBO-C, MC OL phase: rifaximin 550 mg t.i.d. for 2 weeks Responders to OL rifaximin with symptom recurrence entered DB phase: 2 courses rifaximin 550 mg t.i.d. ($n = 328$) or PBO ($n = 308$) for 2 weeks (courses separated by 10-week treatment-free period)	Adults with IBS-D (Rome III; rifaximin $n = 2579$ in OL; rifaximin $n = 328$ in DB; PBO $n = 308$ in DB) Mean daily abdominal pain score ≥ 3 (scale range, 0–10); bloating score ≥ 3 (scale range, 0–6); and BSFS type 6 or 7 stools for ≥ 2 days/week during 7–13 days PBO screening phase	% repeat treatment responders for abdominal pain and stool consistency for ≥ 2 of 4 weeks after first DB repeat treatment Rifaximin vs. PBO: 38.1% vs. 31.5%; $P = 0.03$	Prevention of recurrence (% patients with response to first repeat treatment that continued through end of second repeat treatment phase) Rifaximin vs. PBO: 13.2% vs. 7.1%; $P = 0.007$ Durable response (% patients without recurrence for 6 weeks after first repeat treatment) Rifaximin vs. PBO: 17.1% vs. 11.7%; $P = 0.04$ Bloating response (% patients with decrease from baseline ≥ 1 point in weekly mean bloating score for ≥ 2 of 4 weeks after first repeat treatment) Rifaximin vs. PBO: 46.6% vs. 41.2%; $P = 0.1$

BSFS Bristol Stool Form Scale, *DB* double-blind, *IBS* irritable bowel syndrome, *IBS-D* irritable bowel syndrome with diarrhea, *MC* multicenter, *OL* open label, *PBO* placebo, *PBO-C* placebo-controlled, *R* randomized, *t.i.d.* 3 times daily

[a] Determined by patient response of yes or no to the weekly question, "In regard to all your symptoms of IBS, as compared with the way you felt before you started the study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?"

[b] Determined by patient response of yes or no to the weekly question, "In regard to all your symptoms of bloating, as compared with the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptom of bloating?"

treatment-free phase for assessment of IBS symptom recurrence (loss of abdominal pain or stool consistency response, using the above criteria, for at least 3 weeks in a consecutive, rolling 4-week period) [21]. Patients experiencing symptom recurrence subsequently were randomized in a double-blind manner to receive two 2-week courses of rifaximin (*n* = 328) or placebo (*n* = 308), with each course separated by 10 weeks [21]. A significantly larger percentage of patients in the rifaximin group were responders to repeat treatment (primary efficacy endpoint; assessed using the same abdominal pain and stool consistency composite endpoint) versus placebo (38.1% vs. 31.5%, respectively; *P* = 0.03), and prevention of recurrence and durable response were significantly greater with rifaximin versus placebo [21] (Table 1). As observed in the pivotal trials [20], the rifaximin safety profile during the double-blind phase of TARGET 3 was generally comparable with that of placebo [21]. The most common AEs in the rifaximin and placebo groups during the 22-week double-blind phase were nausea (3.7% vs. 2.3%, respectively), upper respiratory tract infection (3.7% vs. 2.6%), and urinary tract infection (3.4% vs. 4.9%). A similar percentage of patients receiving rifaximin (1.2%) and placebo (1.3%) experienced serious AEs, none of which were considered by investigators to be treatment-related.

Because rifaximin is an antibiotic indicated for two retreatments as needed, after the initial course, some have raised theoretical concerns regarding the risk for development of *C. difficile* infection and induction of bacterial antibiotic resistance. However, no cases of *C. difficile* were reported in TARGET 1 and 2 [20]. In TARGET 3, a single case of *C. difficile* infection was identified 37 days after the completion of a repeat rifaximin treatment; it developed immediately following a course of cefdinir for a urinary tract infection [21]. Furthermore, in a substudy of the TARGET 3 population, 1429 bacterial and yeast isolates were identified in stool samples obtained from substudy participants [23]. Minimum inhibitory concentration analyses revealed no clinically meaningful evidence of bacterial antibiotic resistance to rifaximin or

rifampin, or cross-resistance between rifaximin and other antibiotics [23].

Though primary outcomes differ across studies, numbers needed to treat (NNT) or harm (NNH) can be calculated to help gauge the potential benefits and risks of IBS-D therapies [24]. For rifaximin, an analysis of six trials (*n* = 2441) determined an NNT of 10.5 [95% confidence interval (CI) 8–16] [8]. Another analysis, of five rifaximin studies (*n* = 1187 treated patients), yielded a similar conclusion (NNT of 10.6) [24]. Importantly, these five studies yielded an NNH of 8971 (based on discontinuation due to an AE). This indicates that 846 patients will benefit from rifaximin before one AE occurs and leads to treatment discontinuation [24].

Eluxadoline

Eluxadoline, a mixed μ- and κ-opioid receptor agonist/δ-opioid antagonist, is indicated as daily therapy for the treatment of IBS-D [10]. While a dose of 100 mg eluxadoline twice daily (b.i.d.) is recommended for most individuals, a dose adjustment to 75 mg b.i.d. is necessary for those taking concomitant medications that inhibit hepatic organic anion transporting polypeptide 1B1 (OATP1B1) function, or those who have Child–Pugh class A or B hepatic impairment [10]. Eluxadoline 75 mg b.i.d. is also an option for patients who have developed constipation with the 100 mg b.i.d. dosing of the drug [10].

Two phase 3 randomized, double-blind placebo-controlled trials (3001 and 3002) enrolling 2425 patients (*n* = 1280 in the 3001 trial and *n* = 1145 in the 3002 trial) reported significantly greater rates of combined response in patients treated with 75 mg (*P* < 0.001) or 100 mg (*P* < 0.001) of eluxadoline b.i.d. for up to 26 weeks of therapy compared with placebo (pooled; Table 2) [25]. This combined endpoint response to eluxadoline occurred rapidly, within the first month (weeks 1–4) of therapy [75 mg, 22.8%; 100 mg, 24.6%; vs. placebo (pooled), 12.5%; *P* < 0.001 for each dose vs. placebo] [26]. Furthermore, these results were based on the primary endpoint for IBS studies that was

Table 2 Efficacy summary of phase 3 clinical trials of eluxadoline in patients with IBS-D (pooled analysis) [25]

Study, design, and treatment	Patient population	Primary efficacy outcome(s)				Secondary efficacy outcome(s)			
		Eluxadoline 75 mg b.i.d. (n = 806)	Eluxadoline 100 mg b.i.d. (n = 809)	PBO (n = 808)	P value	Eluxadoline 75 mg b.i.d.	Eluxadoline 100 mg b.i.d.	PBO	P value
Lembo et al. [25]	Adults with IBS-D (Rome III; n = 2425[a])	FDA endpoint[b] (% patients)				Pain relief[c,d] (% patients)			
R, DB, PBO-C, MC	Mean daily abdominal pain score > 3 (scale range, 0–10); mean BSFS type ≥ 5.5 (scale range, 1–7); and mean IBS-D global symptom score ≥ 2 (scale range, 0–4) for the weeks before randomization	26.2%	27%	16.7%	P < 0.001 for both vs. PBO	Study 1 (n = 427): 42.4%	Study 1 (n = 426): 43.2%	Study 1 (n = 427): 39.6%	P > 0.05 (NS) for all vs. PBO
Eluxadoline 75 mg or 100 mg b.i.d., or PBO for 52 weeks with 2-week post-treatment follow-up (study 3001), or for 26 weeks with 4-week SB PBO withdrawal period (study 3002)						Study 2 (n = 381): 48%	Study 2 (n = 382): 51%	Study 2 (n = 382): 45.3%	
		EMA endpoint[b] (% patients)				Improvement in stool consistency (BSFS score)[c,e] (% patients)			
		26.7%	31%	19.5%	P < 0.001 for both vs. PBO	Study 1 (n = 427): 30%	Study 1 (n = 426): 34.3%	Study 1 (n = 427): 22%	P ≤ 0.008 for all vs. PBO
						Study 2 (n = 381): 37%	Study 2 (n = 382): 35.6%	Study 2 (n = 382): 20.9%	

b.i.d. twice daily, BSFS Bristol Stool Form Scale, DB double blind, EMA European Medicines Agency, FDA US Food and Drug Administration, IBS-D irritable bowel syndrome with diarrhea, MC multicenter, NS not significant, PBO placebo, PBO-C placebo-controlled, R randomized, SB single blind

[a] Intent-to-treat population. Study 1: n = 1280; Study 2: n = 1145

[b] Composite response endpoint: decrease from baseline ≥ 30% in worst abdominal pain for ≥ 50% of the days and, on the same days, a stool consistency (BSFS) score < 5; for patients without a bowel movement, response was limited to improvement in worst abdominal pain. FDA endpoint evaluates response during weeks 1–12 and EMA endpoint assesses response during weeks 1–26

[c] Weeks 1–12

[d] Decrease from baseline ≥ 30% in worst abdominal pain for ≥ 50% of the days

[e] Stool consistency (BSFS) score < 5; for patients without a bowel movement, response was limited to improvement in worst abdominal pain for ≥ 50% of the days

detailed in the most recent FDA guidance (at least 30% reduction in worst abdominal pain compared with baseline, plus a BSFS score less than 5 (or no bowel movement), on at least 50% of treatment days) [27]. Both doses of eluxadoline had significantly greater efficacy for improving individual and global symptoms from baseline, compared with placebo at week 12 [stool consistency: $P < 0.001$ for both doses vs. placebo; stool frequency: $P = 0.002$ (75 mg) and $P < 0.001$ (100 mg) vs. placebo; global symptoms: $P = 0.008$ (75 mg) and $P < 0.001$ (100 mg)] [25]. Improvements in abdominal pain and bloating from baseline were observed with both doses of eluxadoline, but only the 100-mg dose achieved significance versus placebo (abdominal pain, $P < 0.001$; bloating, $P = 0.003$) [25].

The most common AEs reported for eluxadoline 75 mg, 100 mg, and placebo were constipation (7.4% vs. 8.6% vs. 2.5%, respectively), nausea (8.1% vs. 7.5% vs. 5.1%), and abdominal pain (5.8% vs. 7.2% vs. 4.1%); and serious AEs were experienced by 4.2% versus 4.8% versus 3.0% of patients, respectively [25]. Pancreatitis [5/1666 (0.3%)] and sphincter of Oddi spasm [8/1666 (0.5%)] occurred in patients receiving eluxadoline; in nine patients, including all eight individuals experiencing sphincter of Oddi dysfunction spasm, these AEs were associated with the absence of a gallbladder. Another pooled analysis including the two phase 3 studies (3001 and 3002) and a phase 2 study indicated that AEs leading to study discontinuation occurred in a greater percentage of patients receiving eluxadoline 75 mg or 100 mg b.i.d. compared with placebo (8.3% of 807 patients and 7.8% of 1032 patients vs. 4.3% of 975 patients, respectively) [28]. In this pooled safety analysis, a total of seven serious AEs of pancreatitis were reported during clinical trials [28]. On the basis of data from the three aforementioned trials ($n = 3235$), eluxadoline had an NNT of 12.5 (95% CI 8–33) [8], and on the basis of discontinuations due to AEs in the phase 3 trials, eluxadoline 75 mg b.i.d. had an NNH of 25.2, while eluxadoline 100 mg b.i.d. had an NNH of 23.3 [25].

Further, data suggests benefits for eluxadoline in specific subpopulations. A post hoc analysis of the phase 3 studies assessed maintenance of response over time and indicated that global responders (abdominal pain and stool consistency) to eluxadoline during the first 4 weeks of treatment were more likely than nonresponders to maintain response with continued treatment during weeks 1 through 12 and 26 (comparisons with placebo; P values not reported) [26]. This suggests that patients not responding within a month of b.i.d. eluxadoline are unlikely to respond with continued daily therapy, thus limiting the overall time needed to assess eluxadoline's potential efficacy [26].

Another post hoc analysis from the two phase 3 trials evaluated a subpopulation of patients who had previously used loperamide and subjectively experienced an inadequate response to this antidiarrheal [29]. In this subpopulation, a higher percentage of individuals receiving eluxadoline experienced significantly greater improvements in their symptoms compared with placebo (eluxadoline 75 mg and 100 mg b.i.d. for 12 weeks vs. placebo; 26.3% of 198 patients and 27% of 174 patients, respectively, vs. 12.7% of 166 patients; $P \le 0.001$ for both comparisons) [29].

On the basis of these results, a prospective phase 4, multinational, randomized, double-blind, placebo-controlled trial (RELIEF) was conducted in patients experiencing inadequate IBS-D symptom control with loperamide use in the previous 12 months [30]. In that study's overall population, more than 40% of patients discontinued loperamide because of a perceived lack of improvement of abdominal symptoms, and more than 40% discontinued loperamide specifically because of lack of improvement of bowel symptoms [30]. Primary responders were those meeting criteria defined similarly in the phase 3 trials, except that in the current trial, participants had to experience a more rigorous 40% or more reduction in their worst abdominal pain compared with baseline, plus a BSFS score less than 5 (or no bowel movement), on at least 50% of treatment days [25, 30]. A significantly greater percentage of the 172 patients treated with eluxadoline 100 mg b.i.d. for 12 weeks were combined responders, compared with the 174 patients treated with placebo (22.7% vs. 10.3%, respectively; $P = 0.002$) [30].

In the RELIEF trial, serious AEs of pancreatitis or sphincter of Oddi spasm were not observed in any patients, likely related to careful patient screening and exclusion of post-cholecystectomy patients from the study [30]. Additional postmarketing reports of pancreatitis and sphincter of Oddi dysfunction identified via the Federal Adverse Event Reporting System have been published [31]. In early 2017, the FDA issued a safety announcement about the increased risk of serious pancreatitis in patients without a gallbladder, and eluxadoline is now contraindicated in this population [10].

Alosetron

As noted previously, alosetron has the most restricted indication of the three agents currently FDA-approved for IBS-D, requiring prescription under an FDA modified Risk Evaluation and Mitigation Strategy (REMS) program [32]. It is currently indicated as b.i.d. treatment for women with chronic (less than 6 months) and severe (defined as at least one of the following: painful stomach cramps or bloating, fecal incontinence, and/or severe impact on quality of life) IBS-D symptoms once biochemical and anatomical abnormalities have been excluded and there has been a lack of response to traditional IBS-D therapies [11]. Multiple studies have evaluated alosetron in patients with IBS, but the studies were conducted prior to FDA guidance on appropriate endpoints for IBS-D trials and/or included individuals with the IBS mixed (IBS-M) subtype (Table 3) [33–38]. Only three trials assessed global symptoms [34–36]. In the first of these studies, published by Lembo et al., 801 women with non-constipated IBS (IBS-D, 98%) were randomly assigned to receive alosetron 1 mg b.i.d. or placebo for 12 weeks [35]. Global improvement (defined as moderate or substantial improvement in IBS symptoms) was established a priori as a key secondary endpoint [35]. At week 12, 76% of the patients receiving alosetron endorsed experiencing global improvement, compared with 44% of those receiving placebo ($P < 0.001$) [35]. The second trial, by Krause et al., reported that a significantly greater percentage of women with severe IBS-D ($n = 705$)

who received alosetron 0.5 mg or 1 mg once daily or alosetron 1 mg b.i.d. experienced moderate or substantial IBS global improvement versus placebo at week 12 (50.8% of 177 patients, 48.0% of 175 patients, and 42.9% of 177 patients vs. 30.7% of 176 patients, respectively; $P \leq 0.02$ for all doses vs. placebo) [36]. Finally, in a 2018 open-label prospective study by Lacy et al. using the current FDA composite endpoint (i.e., improvement from baseline of at least 30% in abdominal pain and decrease from baseline of at least 50% in number of days/week with at least one stool with BSFS type 6 or 7 for at least 50% of treatment weeks), 45% of 105 evaluable women with severe IBS-D who received open-label alosetron 0.5 mg b.i.d. (with potential for increase to 1 mg b.i.d. after 4 weeks) were considered responders at week 12 [34].

Despite initial data yielding positive results, the drug was voluntarily commercially withdrawn in November 2000 because of postmarketing increases in the rates of complicated constipation (obstruction or perforation), ischemic colitis, and mortality. It was subsequently reintroduced in November 2002 by the FDA under a REMS program for use in the aforementioned restricted patient population. Subsequent data from 9 years of patient follow-up revealed an adjudicated incidence rate of 1.03 cases/1000 patient-years of exposure for ischemic colitis and a rate of 0.25 cases/1000 patient-years of exposure for constipation [39]. In January 2016, the FDA further reduced the requirements for prescribing this therapy under the REMS program; since then, prescribers are only required to participate in an informational program and complete related forms [32]. In an analysis of eight trials (4987 patients), the NNT for alosetron was 7.5 (95% CI 5–16), whereas its NNH was 10 (95% CI 6–20) [8].

CONCLUSIONS

Rifaximin, eluxadoline, and alosetron are indicated for the treatment of IBS-D, and their efficacy for treating the totality of IBS-D symptoms has been proven in multiple well-designed trials with similar NNTs. Comparative data for over-the-counter agents are lacking, and where

Table 3 Efficacy summary of clinical trials of alosetron in patients with IBS-D [33–38]

Study, design, and treatment	Patient population	Primary efficacy outcome	Key secondary efficacy outcome(s)
Camilleri et al. [33] R, DB, PBO-C, MC Alosetron 1, 2, 4, or 8 mg b.i.d. or PBO for 12 weeks, with 2-week treatment-free follow-up	Adults with IBS-D or IBS-M for 6 months (Rome I; $n = 370$; alosetron: 1 mg $n = 72$, 2 mg $n = 74$, 4 mg $n = 76$, 8 mg $n = 68$; PBO $n = 80$) Mean daily abdominal pain 1.5–3.3 (scale range, 0–4); and mean daily stool consistency rating ≥ 2.5 (scale range, 1–5)	% patients with adequate relief of pain and discomfort[a] Alosetron (1 mg and 2 mg) vs. PBO: 60% and 59% vs. 33%; $P \leq 0.02$ for both vs. PBO (only female responders)	Patients with adequate relief of bowel movement urgency, and frequency, and improved stool consistency[b] Alosetron vs. PBO: $P < 0.05$ (only female responders)
Camilleri et al. [38] R, PBO-C, MC Alosetron 1 mg b.i.d. or PBO for 12 weeks, with 4-week treatment-free follow-up	Women with IBS-D or IBS-M for ≥ 6 months (Rome I; $n = 647$; alosetron $n = 324$; PBO $n = 323$) Mean daily abdominal pain 1.0–3.3 (scale range, 0–4); and mean daily stool consistency rating ≥ 2.5 (scale range, 1–5)	% patients with adequate relief of pain and discomfort for ≥ 2 weeks/month[a] Alosetron (1 mg) vs. PBO: All 3 months: 41% vs. 29% Month 1: 52% vs. 42%; $P = 0.02$ Month 3: 56% vs. 47%; $P = 0.02$	Patients with adequate relief of bowel movement urgency, and frequency, and improved stool consistency[b] Alosetron vs. PBO: $P < 0.05$
Camilleri et al. [37] R, DB, PBO-C, MC Alosetron 1 mg b.i.d. or PBO for 12 weeks, with 4-week treatment-free follow-up	Women with IBS-D or IBS-M for ≥ 6 months (Rome I; $n = 626$; alosetron $n = 309$; PBO $n = 317$) Mean daily abdominal pain 1.0–3.3 (scale range, 0–4); and mean daily stool consistency rating ≥ 2.5 (scale range, 1–5)	% patients with adequate relief of pain and discomfort for ≥ 2 weeks/month[a] Alosetron 1 mg vs. PBO: All 3 months: 41% vs. 26%; $P < 0.0001$ Month 1: 50% vs. 39%; $P < 0.05$ Month 3: 60% vs. 41%; $P < 0.001$	Patients with adequate relief of bowel movement urgency, frequency, and improved stool consistency[b] Alosetron vs. PBO: $P < 0.001$ At week 12, alosetron relative to PBO: Urgency decreased by 12.6% Stool frequency decreased by 0.5 stools/day Stool firmness increased by 0.6 points

Table 3 continued

Study, design, and treatment	Patient population	Primary efficacy outcome	Key secondary efficacy outcome(s)
Lembo et al. [35] R, DB, PBO-C, MC Alosetron 1 mg b.i.d. or PBO for 12 weeks, with 2-week treatment-free follow-up	Women with recurrence of non-constipation IBS for $\geq$ 12 weeks in previous 12 months (Rome II; $n = 801$; alosetron $n = 532$; PBO $n = 269$) Abdominal pain/discomfort associated with $\geq$ 2 symptoms: relief of symptoms with defecation, change in stool frequency and/or consistency	% of days patients reported having satisfactory control of IBS-related bowel movement urgency for 12 weeks[c] Alosetron 1 mg vs. PBO: 0.73 days vs. 0.57 days; $P < 0.001$	Patients with moderate or substantial improvement in global IBS symptoms[d] over the previous 4 weeks Alosetron 1 mg vs. PBO: Week 4: 67% vs. 41%; $P < 0.001$ Week 8: 69% vs. 43%; $P < 0.001$ Week 12: 76% vs. 44%; $P < 0.001$
Krause et al. [36] R, DB, PBO-C, MC Alosetron 0.5 mg q.d., 1 mg q.d., or 1 mg b.i.d. or PBO for 12 weeks and 4-week follow-up	Women with severe IBS-D $\geq$ 6 months (Rome II, $n = 705$; alosetron: 0.5 mg q.d. $n = 177$, 1 mg q.d. $n = 175$, 1 mg b.i.d. $n = 177$; PBO $n = 176$) Diarrhea ($\geq$ 50% of days) and mean stool consistency $\geq$ 3 (scale range, 1–5), or mean stool consistency $\geq$ 3.5 plus $\geq$ 1 of the following: frequent and severe abdominal pain/discomfort score $\geq$ 2 (scale range, 0–4); frequent bowel movement urgency or incontinence ($\geq$ 50% of days); and restricted daily activities ($\geq$ 25% of days)	% patients with response on IBS Global Improvement Scale at week 12[e] Alosetron (0.5 mg q.d., 1 mg q.d., and 1 mg b.i.d.) vs. PBO: 51%, 48%, and 43% vs. 31%; $P \leq 0.02$ for all	Adequate relief of IBS pain and discomfort, urgency, and changes in GI symptoms, and normalized bowel pattern Adequate relief of pain and discomfort: alosetron (all doses) treatment differences of 9–16% vs. PBO; $P \leq 0.04$ Stool frequency and consistency: alosetron (all doses) vs. PBO; $P \leq 0.006$ and $P \leq 0.001$, respectively

Table 3 continued

Study, design, and treatment	Patient population	Primary efficacy outcome	Key secondary efficacy outcome(s)
Lacy et al. [34][f] OL, MC Alosetron 0.5 mg b.i.d. for 4 weeks; up to 1 mg b.i.d. for 8 additional weeks	Women with severe IBS-D ≥ 6 months (Rome III, n = 192; alosetron evaluable patients n = 105) Frequent and severe abdominal pain/discomfort (scale range, 0–10); bowel movement urgency; fecal incontinence; disability; and restricted daily activities	Composite primary endpoint: ≥ 30% decrease in weekly abdominal pain and ≥ 50% decrease in days/week with BSFS type 6 or 7 stool consistency) 43% patients met responder criteria during the 12 weeks	Overall treatment responder (met composite endpoint for ≥ 6 of 12 weeks) 45% overall responders

b.i.d. twice daily, *BSFS* Bristol Stool Scale, *DB* double-blind, *IBS* irritable bowel syndrome, *IBS-D* irritable bowel syndrome with diarrhea, *IBS-M* irritable bowel syndrome with mixed features, *MC* multicenter, *OL* open label, *PBO* placebo, *PBO-C* placebo-controlled, *q.d.* once daily, *R* randomized

[a] Determined by patient response of yes or no to the weekly question, "In the past 7 days have you had adequate relief of your irritable bowel syndrome pain and discomfort symptoms?"

[b] Determined by patient response regarding their IBS symptoms (pain severity, urgency, stool consistency, stool frequency, bloating, and sense of incomplete evacuation) during the treatment and follow-up phases

[c] Determined by patient response of yes or no to the daily question, "Have you had satisfactory control of your bowel urgency today?"

[d] IBS Global Improvement rating: "Compared to the way you usually felt during the 3 months before you entered the study, are your IBS symptoms over the past 4 weeks substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or substantially improved?" A responder was defined as a patient who reported either moderate or substantial improvement

[e] IBS Global Improvement Scale: "Compared to the way you usually felt during the 3 months before you entered the study, are your IBS symptoms over the past 4 weeks substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or substantially improved?" A responder was defined as a patient who reported either moderate or substantial improvement

[f] This study was designed to evaluate alosetron using Rome III criteria and the FDA composite endpoint for patients who met the inclusion criteria defined in the alosetron package insert

clinical studies are available, there is generally a lack of study rigor or standardization of endpoints. This is in direct contrast to the quality of clinical evidence for rifaximin, eluxadoline, and alosetron. The frequency of administration and safety profiles of the approved agents differ, with both eluxadoline and alosetron indicated for administration as daily therapy, and rifaximin for administration as a 2-week course of therapy with up to two repeat courses to manage symptom recurrence noted in US prescribing information [9]. Reported NNH values for these agents substantially favor rifaximin, owing to its safety profile, which, across three large phase 3 studies, generally was comparable to that of placebo. Eluxadoline overall is well tolerated but has label restrictions in postcholecystectomy patients and those who have other pancreatobiliary risk factors. Alosetron has been associated with greater risks of severe AEs compared with placebo, although the reported rates of ischemic colitis and constipation have declined precipitously, subsequent to implementation of the REMS program. Of the three FDA-approved therapies, alosetron still has the most restrictive indication and remains reserved for the treatment of women with severe IBS-D.

ACKNOWLEDGEMENTS

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