

Review article: an analysis of safety profiles of treatments for diarrhoea-predominant irritable bowel syndrome

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Summary

Background: Irritable bowel syndrome (IBS) is multifactorial in nature, and a wide range of therapies is available to manage symptoms of this common disorder.

Aim: To provide an overview of the safety of interventions that may be used to manage patients with diarrhoea-predominant IBS (IBS-D).

Methods: Medline and Embase database searches (through 02 May 2018) to identify clinical studies that evaluated treatment safety and/or efficacy in adults with IBS-D.

Results: IBS-D treatments include dietary modification, probiotics, serotonin receptor antagonists, opioid receptor agonists and antagonists, nonsystemic antibiotics, bile acid sequestrants, antidepressants, and complementary and alternative therapies. These treatments vary in administration frequency (eg, daily; short-course therapy) and target various pathophysiologic factors. Safety profiles vary considerably by treatment among IBS-D therapies. The number needed to harm (defined as the number of patients treated to encounter an adverse event) was lowest (worse) for antidepressants (8.5) and highest (best) for probiotics (35), and the number needed to harm (defined as the number of patients who discontinued due to an adverse event) was lowest for tricyclic antidepressants (9) and highest for rifaximin (8971). Notable safety concerns with IBS-D treatments include pancreatitis with eluxadoline, ischaemic colitis and serious complications of constipation with alosetron, and cardiac adverse events with loperamide and tricyclic antidepressants. Treatment decisions need to account for medication risks and adverse events for each patient.

Conclusions: Multiple treatment options are now available for patients with IBS-D. However, the safety profiles of these agents vary widely by number needed to harm value. Providers should consider both safety and efficacy of a specific intervention when determining how best to manage patients' IBS-D symptoms.

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1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder characterised by abdominal pain and altered bowel habits (constipation, diarrhoea, or alternating constipation and diarrhoea) often coupled with abdominal bloating.¹ The diagnosis of IBS, according to the Rome IV criteria, is based on recurrent abdominal pain at least once weekly in the previous 3 months, with the pain associated with at least two of the following: defecation, alterations in stool frequency, and changes in stool form.¹ IBS is further categorised by its predominant bowel habit, including diarrhoea-predominant IBS (IBS-D; >25% Bristol Stool Scale form types 6 or 7 and <25% Bristol Stool Scale form types 1 or 2), constipation-predominant IBS (>25% Bristol Stool Scale form types 1 or 2 and <25% Bristol Stool Scale form types 6 or 7), or mixed form IBS (>25% Bristol Stool Scale form types 1 or 2 and >25% Bristol Stool Scale form types 6 or 7).¹ IBS, including IBS-D, is associated with reduced quality of life^{2,3} and increased healthcare costs.^{4,5}

In one study, 76.5% of 179 patients with IBS reported impaired daily activity (ie, ≥ 5 of 10 domains examined: job/school performance, social activity, physical activity, physical appearance, household activities, sexual activity, leisure activity, travel, eating alone, and eating in groups), with social activity impaired in 80% of patients and job/school performance in 72%.⁶ In the United States, IBS is usually managed on an outpatient basis.^{7,8} For patients with IBS-D included in a US commercially insured population (2013), mean all-cause annual healthcare costs (eg, diagnostic tests and laboratory or radiology services [50.3%], prescriptions [19.5%], inpatient admissions [13.6%], emergency department visits [8.5%], and outpatient office visits [8.1%]) were estimated at \$13 038, an amount \$8768 in excess of that of individuals without IBS-D ($P < 0.001$).⁴

The exact pathophysiology of IBS remains to be elucidated, but it is related in part to alterations in the gut microbiota, changes in gastrointestinal (GI) motility, microscopic inflammation, bile acid malabsorption, and alterations in the enteric nervous system.⁹ Given the multifactorial nature of IBS, no gold standard of treatment exists.⁹ Available treatments for IBS-D include dietary modification, probiotics, serotonin (5-hydroxytryptamine type 3 [5-HT₃]) receptor antagonists (eg, alosetron, ondansetron), opioid receptor agonists and antagonists (eg, loperamide, eluxadoline [Viberzi[®], Allergan, Irvine, CA]), nonsystemic antibiotics (eg, rifaximin [Xifaxan[®], Salix Pharmaceuticals, Bridgewater, NJ]), bile acid sequestrants (eg, cholestyramine, colesevelam), antidepressants (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors), complementary and alternative medicine (eg, herbal therapies, mind-body interventions [eg, cognitive behavioural therapy, hypnotherapy], and mechanical interventions [eg, yoga, acupuncture]). As no validated treatment algorithm exists for patients with IBS and diarrhoea, many treatments are frequently used to manage symptoms.¹⁰ Ideally, the selection of a therapy should be based on a careful assessment of both efficacy and adverse events (AEs). However, many healthcare providers primarily focus on efficacy. This may occur because efficacy

results are reported more widely, and thus are better known, than safety results. As well, many providers tend to focus treatment discussions on benefits of a treatment rather than AEs. However, both types of outcomes are important to discuss and should be given equal weight when evaluating treatment options for a patient. The objective of this article is to provide an overview of the safety of interventions that are used in the management of patients with IBS-D.

2 | METHODS

A search of the Medline and Embase databases for articles available through 02 May 2018 was conducted to identify relevant English-language articles using the following key words: “irritable bowel syndrome,” “diarrhoea-predominant irritable bowel syndrome,” “IBS,” “IBS-D,” “dietary modification,” “probiotic,” “alosecron,” “ondansetron,” “loperamide,” “Lomotil” (Lomotil[®], G.D. Searle LLC, New York, NY, USA), “diphenoxylate and atropine,” “eluxadoline,” “rifaximin,” “bile acid sequestrant,” “antidepressant,” “tricyclic antidepressant,” “selective serotonin reuptake inhibitor,” “complementary and alternative medicine,” “complementary and alternative therapy,” “CAM,” “herbal,” “Iberogast” (Iberogast, Bayer Consumer Care AG, Basel, Switzerland), “STW 5,” “Tongxie Yaofang,” “Tong Xie Yao Fang,” “peppermint oil,” “cognitive behavioral therapy,” “hypnotherapy,” “yoga,” “acupuncture,” “clinical trial,” “adverse event,” and “safety.” Abstracts were reviewed for clinical studies that evaluated treatment safety, efficacy, or both in adults with IBS-D. Additional relevant publications were identified from article reference lists. If number needed to treat data were reported in >1 publication, then results from each publication were included.

3 | RESULTS

3.1 | Dietary modification

Dietary modifications (particularly the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [FODMAP] diet or a gluten-free diet) are often used to manage IBS.¹ A low FODMAP diet has been shown to improve symptoms of IBS in both a systematic review of the published literature ($n = 6$ studies)¹¹ and subsequent randomised controlled trials.^{12,13} A gluten-free diet has also been shown to reduce IBS symptoms,^{14,15} but not beyond the improvement obtained with a low FODMAP diet alone.¹⁶ Other dietary modifications for managing IBS include the elimination of specific foods. A Norwegian population-based study reported that 70% of 84 patients with IBS considered their symptoms to be food-related, with 62% of patients reporting the exclusion of specific foods from their diets (mean 2.5 foods; range 0-14).¹⁷ In addition, a survey-based study noted that 73% of 1094 individuals diagnosed with IBS-D reported avoiding foods that they thought would cause stomach upset.¹⁸ The number needed to treat, or the number of patients needed for one patient to achieve improvement of symptoms with

treatment (relative to control), is 5 for the low FODMAP diet compared with an alternative diet ($n = 7$ studies; quality of evidence was considered “very low”); the number needed to treat for a gluten-free diet cannot be calculated accurately.¹⁰

The safety of dietary modification has not been well studied, although 2017 data indicate that 57.4% of US gastroenterologists surveyed ($n = 1562$) usually or almost always recommend a low FODMAP diet to their patients with IBS.¹⁹ A low FODMAP diet markedly alters gut microbiota composition; the long-term effects are unknown and warrant caution.²⁰ In addition, dietary modification, including a low FODMAP diet, may increase the risk of inadequate nutrient intake.²¹ In one study, 20% of 51 patients who limited or excluded specific foods from their diets were considered to have dietary insufficiency (eg, vitamin deficiency, malnourishment).¹⁷ A post hoc analysis of data from a single-centre, randomised clinical study reported that patients following a low FODMAP diet for 4 weeks experienced a significant decrease from baseline in daily consumption of some micronutrients, including retinol, thiamine, riboflavin, calcium, and trans-fatty acids.²² Furthermore, a low FODMAP diet is expensive to maintain and may adversely affect patients’ quality of life related to the burden associated with following such a restricted and complicated regimen.²¹ Patients have reported that the number of foods that can be consumed with a low FODMAP diet is too limited.¹³ Currently, a number needed to harm (based on AEs prompting discontinuation), or the number of patients receiving treatment (relative to control therapy) for one patient to experience an AE,²³ has not been reported for low FODMAP diets.

3.2 | Probiotics

The precise mechanism by which probiotics improve IBS symptoms is unknown; however, some patients may benefit from modulation of gut microbiota.²⁴ A meta-analysis of 37 randomised, controlled studies ($n = 4403$) reported that probiotics were significantly better than placebo for the improvement of IBS symptoms (relative risk of IBS not improving 0.81; 95% CI 0.74-0.88).^{10,25} Combination probiotic products were found to have significantly greater benefit than placebo ($n = 21$ randomised, controlled studies [1931 patients]; relative risk of IBS not improving, 0.79; 95% CI, 0.68-0.91).¹⁰ Although probiotics are generally, albeit mildly, efficacious for the treatment of patients with IBS (number needed to treat, 7), the variability among studies led the American College of Gastroenterology to provide only a “weak” recommendation that probiotics improve global IBS symptoms.^{10,23}

Probiotics have a long history of safety (eg, in food products), but clinical trials of probiotics are inconsistent with regard to safety reporting, particularly in patients who may be at increased risk of AEs (eg, immunocompromised or hospitalised individuals, pregnant women).²⁶ A meta-analysis of 36 randomised, controlled studies that included 4183 patients with IBS found no increased risk of AEs in patients receiving probiotics (relative risk 1.09; 95% CI 0.91-1.29).¹⁰ The number needed to harm for probiotics was 35 and based on patients experiencing an AE.²⁵ Potential AEs of concern with

probiotics include gastrointestinal adverse effects (eg, abdominal cramping, nausea), deleterious metabolic activity (eg, D-lactic acidosis), and a rare risk of systemic infection (ie, fungaemia).²⁶ As safety profiles vary by probiotic strain and dose, rigorous assessment of currently available products is difficult to attain.²⁶

3.3 | 5-HT₃ receptor antagonists

5-HT₃ receptor antagonists have been shown to decrease abdominal pain and slow gastrointestinal transit.^{27,28}

3.3.1 | Alosetron

Alosetron is a selective 5-HT₃ receptor antagonist approved for the treatment of women with severe IBS-D who have failed standard therapy. A meta-analysis of 10 randomised, controlled studies of adults with IBS receiving alosetron (range 0.1-8 mg twice daily), placebo, or mebeverine for ≥ 12 weeks noted global improvement of IBS symptoms ($n = 3$ studies; relative risk 1.58; 95% CI 1.42-1.75), improvement of abdominal pain and discomfort ($n = 8$ studies; relative risk 1.24, 95% CI 1.16-1.33), and improvement of abnormal bowel habits or stool consistency ($n = 3$ studies; relative risk 1.59; 95% CI 1.04-2.41) with alosetron.²⁹ A 2012 clinical study, which did not meet the inclusion criteria for the meta-analysis,²⁹ included 705 women with severe IBS-D and reported that treatment with ≥ 1 alosetron dose (0.5 mg once daily, or 1 mg once or twice daily) for 12 weeks significantly improved all domains of the Irritable Bowel Syndrome Quality of Life instrument (except sexual relations) compared with placebo ($P < 0.05$).³⁰ The number needed to treat for alosetron has been estimated at 6³¹ and 8.^{23,32}

Alosetron is associated with serious AEs³³ and is still marketed under a Risk Evaluation and Mitigation Strategy programme that requires prescribers to complete a training programme. Changes to this Risk Evaluation and Mitigation Strategy programme have made it less onerous for providers to prescribe alosetron than when the Risk Evaluation and Mitigation Strategy was first initiated. The objective of the Risk Evaluation and Mitigation Strategy is to mitigate the risks of ischaemic colitis and serious complications of constipation in patients treated with alosetron. Results of a randomised, placebo-controlled study of women with severe IBS-D ($n = 705$) receiving alosetron 0.5 mg once daily, or 1 mg once or twice daily, for 12 weeks showed that, while the incidence of constipation increased in a dose-related manner (ie, placebo, 5%; alosetron 0.5 mg once daily, 9%; 1 mg once daily, 16%; 1 mg twice daily, 19%), this trend was not observed with ischaemic colitis (one patient receiving alosetron 0.5 mg once daily) or complications of constipation (one patient receiving alosetron 0.5 mg once daily with bowel obstruction; one patient receiving alosetron 1 mg twice daily with faecal impaction).³⁴ Most patients with constipation (75%) reported occurrence of this AE within the first 2 weeks of treatment.³⁴ In one meta-analysis of seven randomised, controlled studies of alosetron ($n = 4607$), constipation was the most common AE compared with placebo, with a number needed to harm of 5 for this individual AE.¹⁰

An adjudicated analysis of an alosetron postmarketing safety database (November 2002 to December 2011) identified 1.03 cases of ischaemic colitis and 0.25 cases of complications of constipation per 1000 patient-years of exposure.³⁵ The number needed to harm for alosetron has been reported to be 10, based on a significantly increased risk of any AE with alosetron compared with placebo (relative risk, 1.19; 95% 1.09-1.30),¹⁰ and 19, based on AEs prompting discontinuation.³²

3.3.2 | Ondansetron

Results of a randomised, double-blind, crossover study showed that ondansetron, a 5-HT₃ receptor antagonist, significantly improved stool form compared with placebo during the last 2 weeks of a 5-week treatment period ($P < 0.001$), although abdominal pain was not improved vs placebo.³⁶ In addition, ondansetron significantly reduced mean faecal urgency scores (range, 0 [none] to 3 [severe]) by 0.3 points vs placebo during the last 2 weeks of treatment ($P < 0.001$).³⁶ The mean frequency of daily bowel movements decreased significantly with ondansetron compared with placebo during the final 2 weeks of treatment (11% decrease; $P = 0.001$).³⁶ For the 98 patients included in the intention-to-treat analysis, constipation was the most common AE with ondansetron (9%; placebo, 2%). Other reported AEs with ondansetron and placebo included headache ($n = 2$ for each treatment), rectal bleeding (not associated with ischaemic colitis; $n = 2$ for each treatment), abdominal pain ($n = 2$ and $n = 1$, respectively), and backache ($n = 1$ for each treatment).³⁶

3.4 | Opioid receptor agonists and antagonists

Mu-opioid receptor agonists (eg, loperamide, diphenoxylate, eluxadoline) exert antidiarrhoeal effects by binding to opioid receptors found in the gastrointestinal tract. Drugs of this class slow gastrointestinal motility and may decrease pain perception.^{9,37}

3.4.1 | Loperamide

Loperamide, a peripheral mu-opioid receptor agonist, is an over-the-counter antidiarrhoeal product indicated for acute nonspecific diarrhoea.^{38,39} The recommended initial adult dose for loperamide is 4 mg, followed by 2 mg after each unformed stool, not to exceed 16 mg/d.³⁹ AEs are limited when loperamide is used as directed.⁴⁰ Postmarketing drug safety surveillance showed that cardiotoxicity may occur with excess loperamide use; 48 cases were reported to the US Food and Drug Administration between December 1976 and December 2015, with more than half of cases reported after 2010.⁴⁰ Of the reported cases, 17 (35%) were serious cardiac events associated with treatment of diarrhoea, and five of those involved the misuse of loperamide (ie, excess dosing).⁴⁰ The median daily dosing for the five cases of misuse of loperamide (ie, use exceeding the recommended daily maximum of 16 mg/d) was 80 mg (range 16-100 mg).⁴⁰ Cardiac AEs associated with the excess dosing of loperamide in the management of diarrhoea included torsades de

pointes ($n = 2$), ventricular tachycardia ($n = 2$), syncope ($n = 1$), and cardiac arrest ($n = 1$). Cardiac AEs associated with therapeutic doses in diarrhoeal treatment included syncope ($n = 9$) and ventricular tachycardia ($n = 2$).⁴⁰ In January 2018, the US Food and Drug Administration issued a safety alert for loperamide and noted that higher than recommended doses of loperamide may cause serious cardiac AEs (eg, QT interval prolongation, torsades de pointes or other ventricular arrhythmias, syncope, and cardiac arrest). Pancreatitis has been reported with loperamide use, albeit infrequently (0.3%)⁴¹; in at least one instance, it was associated with loperamide overdose.⁴² However, one case study reported pancreatitis in a patient using loperamide at the recommended dose.⁴³ Currently, neither the number needed to treat nor the number needed to harm for loperamide has been published.

3.4.2 | Diphenoxylate/atropine

Diphenoxylate/atropine, which consists of the mu-opioid receptor agonist diphenoxylate in combination with a subtherapeutic quantity of atropine (to discourage the misuse or excessive dosing of diphenoxylate), is indicated for the management of diarrhoea.^{37,44} The recommended initial adult dose of diphenoxylate/atropine is 20 mg/d (administered as two tablets or 10 mL four times daily).⁴⁴ If improvement is not observed within 10 days at this dosage, continued administration is unlikely to prove beneficial.⁴⁴ Adherence to the recommended dosing is of paramount importance, as overdosage of diphenoxylate (which enters the systemic circulation) is associated with severe respiratory depression, which may lead to brain damage or mortality.⁴⁴ Diphenoxylate/atropine was associated with more frequent central nervous system AEs (eg, nausea and vomiting, drowsiness, dizziness, depression) but lower efficacy compared with loperamide in a double-blind crossover study based on information from 25 patients with chronic diarrhoea.⁴⁵ The number needed to treat and number needed to harm for diphenoxylate/atropine have not been assessed at this time.

3.4.3 | Eluxadoline

Eluxadoline, a mixed mu-opioid receptor agonist/delta-opioid receptor antagonist administered twice daily, is indicated in the United States for the treatment of adults with IBS-D.^{46,47} Pooled results of one 26-week and one 52-week (clinical response compared with placebo through week 26 and safety up to week 52) phase 3, randomised, double-blind, placebo-controlled study of patients with IBS-D ($n = 2425$) showed that a significantly greater percentage of patients were classified as treatment responders (primary efficacy endpoint; defined as a decrease from baseline $\geq 30\%$ in daily average score for worst abdominal pain on $\geq 50\%$ days evaluated, and on the same days, a daily stool consistency score < 5 [score range from 1, hard stool, to 7, watery diarrhoea]) with eluxadoline 75 mg or 100 mg twice daily vs placebo (weeks 1-12, 26.2% and 27.0%, vs 16.7%, respectively [$P < 0.001$, vs placebo]; weeks 1-26, 26.7% and 31.0%, vs 19.5% [$P < 0.001$, vs placebo]).⁴⁸ Eluxadoline 75 mg

TABLE 1 Pooled summary of adverse events with eluxadoline⁴⁹

Adverse events (AEs), n (%)	Eluxadoline 75 mg twice daily (n = 807)	Eluxadoline 100 mg twice daily (n = 1032)	Placebo (n = 975)
AEs			
Any AE ^a	486 (60.2)	575 (55.7)	533 (54.7)
Nausea	65 (8.1)	73 (7.1)	49 (5.0)
Constipation	60 (7.4)	84 (8.1)	24 (2.5)
Abdominal pain	33 (4.1)	47 (4.6)	25 (2.6)
Nasopharyngitis	33 (4.1)	31 (3.0)	33 (3.4)
Headache	32 (4.0)	44 (4.3)	44 (4.5)
Vomiting	32 (4.0)	43 (4.2)	12 (1.2)
Upper respiratory tract infection	27 (3.3)	53 (5.1)	38 (3.9)
Sinusitis	27 (3.3)	27 (2.6)	35 (3.6)
Bronchitis	26 (3.2)	30 (2.9)	21 (2.2)
Gastroenteritis viral	22 (2.7)	14 (1.4)	18 (1.8)
Dizziness	21 (2.6)	33 (3.2)	21 (2.2)
Flatulence	21 (2.6)	33 (3.2)	17 (1.7)
Abdominal distension	21 (2.6)	28 (2.7)	15 (1.5)
Fatigue	21 (2.6)	20 (1.9)	23 (2.4)
Hypertension	20 (2.5)	14 (1.4)	16 (1.6)
Alanine transaminase increased	17 (2.1)	26 (2.5)	14 (1.4)
Urinary tract infection	17 (2.1)	18 (1.7)	17 (1.7)
Any serious AE	34 (4.2)	41 (4.0)	25 (2.6)
Pancreatitis ^b	3 (0.4)	4 (0.4)	0
Major adverse cardiac events	1 (0.1)	2 (0.2)	3 (0.3)
Mortality	0	0	0
Sphincter of Oddi spasm	2 (0.2)	8 (0.8)	0
AEs leading to treatment discontinuation ^c			
Any AE	67 (8.3)	80 (7.8)	42 (4.3)
Constipation	9 (1.1)	15 (1.5)	3 (0.3)
Abdominal pain	9 (1.1)	11 (1.1)	3 (0.3)
Nausea	5 (0.6)	0	4 (0.4)
Abdominal pain upper	3 (0.4)	4 (0.4)	0
Pancreatitis ^d	3 (0.4)	3 (0.3)	0
Headache	3 (0.4)	1 (0.1)	1 (0.1)

(Continues)

has number needed to treat values of 10-15, while eluxadoline 100 mg has number needed to treat values of 9-13.⁴⁸ The most commonly reported AEs in the pooled eluxadoline population (n = 1666) were constipation (8.0%), nausea (7.7%), and abdominal

TABLE 1 (Continued)

Adverse events (AEs), n (%)	Eluxadoline 75 mg twice daily (n = 807)	Eluxadoline 100 mg twice daily (n = 1032)	Placebo (n = 975)
Abdominal distension	2 (0.2)	5 (0.5)	1 (0.1)
Diarrhoea	1 (0.1)	0	3 (0.3)

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AE: adverse event.

^aReported in $\geq 2\%$ of patients in any group from phase 2 and phase 3 studies of eluxadoline (pooled safety population).

^bIncludes one AE reported by investigator, but later determined not to meet criteria for pancreatitis.

^cReported in ≥ 3 patients in any group.

^dIncludes all acute pancreatitis and pancreatitis events.

pain (6.5%).⁴⁸ Serious AEs were reported in 4.5% of 1666 patients receiving eluxadoline, with cardiac events (1.7%), spasm of the sphincter of Oddi (0.5%), and pancreatitis (0.3%) reported.⁴⁸

A pooled safety analysis of one phase 2 study and the aforementioned phase 3 studies of patients with IBS-D (n = 2814) receiving eluxadoline 75 mg (n = 807) or 100 mg (n = 1032) twice daily, or placebo (n = 975), for up to 52 weeks reported that the percentage of patients discontinuing treatment related to AEs was greater with eluxadoline 75 mg and 100 mg than with placebo (8.3% and 7.8% vs 4.3%, respectively; Table 1).⁴⁹ Spasm of the sphincter of Oddi occurred in 0.5% of 1839 patients who received eluxadoline (75 mg, 0.2%; 100 mg, 0.8%); all the patients with this AE lacked a gall-bladder.⁴⁹ Constipation, one of the most commonly reported AEs with eluxadoline 75 mg and 100 mg, occurred most frequently within the first 3 months of treatment.⁴⁹ Serious AEs were reported more frequently with eluxadoline 75 mg and 100 mg compared with placebo (Table 1) and occurred most often during the first 2 weeks of treatment.⁴⁹ The most common serious AE with eluxadoline treatment was pancreatitis, with an overall incidence of 0.4%; all patients discontinued treatment at the time of onset, and lipase normalisation occurred within days in all but one patient, who had normalisation after several weeks.⁴⁹ Serious cardiac AEs occurred in 0.2% and 0.3% of patients receiving eluxadoline and placebo, respectively; all patients affected were ≥ 70 years of age and had a history of or were at risk for cardiopulmonary disease.⁴⁹ Colonic ischaemia occurred in one patient, 19 days after receiving the first dose of eluxadoline 100 mg; the patient recovered and had no complications at follow-up.⁴⁹ The number needed to harm values for eluxadoline 75 mg and 100 mg were 25 and 23, respectively, based on AEs prompting discontinuation.⁴⁸

The US Food and Drug Administration issued a safety warning in March 2017 regarding the use of eluxadoline in patients with IBS-D who lack a gall-bladder, given that the increased risk of pancreatitis in this patient population could potentially result in hospitalisation or mortality.⁵⁰ In an analysis of data from the Federal Adverse Event Reporting System (July 2015 to September 2016), pancreatitis

accounted for 98 (16.4%) of 597 reports for eluxadolone, with 53 associated hospitalisations; a history of cholecystectomy was not recorded.⁴¹ By comparison, pancreatitis accounted for <1% of AE reports for other medications evaluated (ie, loperamide, diphenoxylate, oxycodone, rifaximin).⁴¹ Pancreatitis occurred within 1 week after starting eluxadolone (dose range 75-200 mg); dosage was ≤ 75 mg twice daily in 72.3% of patients.⁴¹ A total of 30 cases of sphincter of Oddi dysfunction were reported (5.0%) with nine associated hospitalisations; eluxadolone dosage was ≤ 75 mg twice daily in 92.0% of patients.⁴¹ Eluxadolone is now contraindicated in patients without a gall-bladder in the United States, Canada, and Europe.

Pharmacokinetic data indicate that for patients with mild to moderate hepatic impairment, the lower eluxadolone dose of 75 mg should be administered, given the sixfold and fourfold increases in systemic exposure (ie, mean area under the plasma concentration vs time curve to last measurable concentration) of single-dose eluxadolone in adults with mild and moderate hepatic impairment (ie, Child-Pugh class A and B, respectively).⁵¹ A 16-fold increase in systemic exposure was observed in adults with severe hepatic impairment (Child-Pugh class C); eluxadolone is therefore contraindicated in these patients.^{47,51}

3.5 | Rifaximin

Rifaximin is a nonsystemic antibiotic approved by the US Food and Drug Administration for the treatment of adults with IBS-D.⁵² Based on the results of a meta-analysis of five randomised, double-blind clinical studies (n = 1803), short-course therapy with rifaximin has demonstrated significant improvement of IBS symptoms compared with placebo. Global IBS symptom improvement was reported by 42.2% of patients treated with rifaximin compared with 32.4% in the placebo group (odds ratio 1.57; 95% CI 1.22-2.01; $P < 0.001$).⁵³ In two phase 3, identically designed, placebo-controlled trials, which were included in the meta-analysis publication, a significantly greater percentage of patients with IBS-D treated with a 2-week course of rifaximin 550 mg three times daily (n = 1260) achieved adequate relief of global IBS symptoms during ≥ 2 of the first 4 weeks post-treatment (40.7%) compared with placebo (31.7%; $P < 0.001$ [pooled data]).⁵⁴ In a phase 3, randomised, double-blind, placebo-controlled, multiple short-course treatment trial published in 2016, repeat treatment with a 2-week course of rifaximin 550 mg three times daily in patients with symptom recurrence was significantly more efficacious than placebo.⁵⁵ In that trial, a significantly larger percentage of patients with symptom relapse treated with rifaximin 550 mg three times daily for 2 weeks were responders ($\geq 30\%$ decrease from baseline in mean weekly pain score and $\geq 50\%$ decrease from baseline in number of days per week with Bristol Stool Scale type 6 or 7 stool during ≥ 2 of the first 4 weeks posttreatment) compared with those receiving placebo (38.1% vs 31.5%, respectively; $P = 0.03$).⁵⁵ In addition, two retrospective chart reviews indicated that therapy including up to seven repeat courses of rifaximin was efficacious for the treatment of nonconstipation IBS.^{56,57} The number needed to treat for rifaximin has been estimated to be 8-11.^{10,32}

A pooled safety analysis of one phase 2b and two phase 3 clinical studies⁵⁶ of rifaximin for the treatment of patients with nonconstipation IBS (n = 1008) demonstrated that rifaximin had a safety profile comparable with that of placebo, and that most AEs were mild or moderate (Table 2).⁵⁸ Headache, upper respiratory infection, and nausea were the most commonly reported AEs with rifaximin (rifaximin 550 mg pooled group).⁵⁸ No patients developed *Clostridium difficile* infection during rifaximin therapy (person-years of exposure, 61.3).⁵⁸ The number needed to harm for rifaximin is 8971, based on AEs prompting discontinuation.³² Furthermore, rifaximin 550 mg twice daily, when used to reduce the risk of recurrence of overt hepatic encephalopathy,⁵² has demonstrated long-term safety (≥ 2 years) in patients with cirrhosis with a history of overt hepatic encephalopathy (person-years of exposure, 57.6).⁵⁹

Stool and staphylococcal skin isolates from a subgroup of patients included in a clinical study of 2-week rifaximin repeat treatment⁵⁵ showed no clinically meaningful bacterial antibiotic resistance to rifaximin or other antibiotics^{60,61}; *C. difficile* isolates from stool

TABLE 2 Pooled summary of adverse events with rifaximin⁵⁸

Adverse events (AEs), n (%)	Rifaximin 550 mg (pooled) ^a (n = 1008)	Placebo (n = 829)
AEs		
Any AE	529 (52.5)	436 (52.6)
Most common AEs ^b		
Headache	55 (5.5)	51 (6.2)
Upper respiratory tract infection	45 (4.5)	47 (5.7)
Nausea	41 (4.1)	31 (3.7)
Abdominal pain	40 (4.0)	39 (4.7)
Diarrhoea	35 (3.5)	26 (3.1)
Urinary tract infection	32 (3.2)	18 (2.2)
Nasopharyngitis	26 (2.6)	39 (4.7)
Sinusitis	23 (2.3)	23 (2.8)
Vomiting	20 (2.0)	12 (1.4)
Back pain	20 (2.0)	19 (2.3)
Any treatment-related AE	124 (12.3)	89 (10.7)
Any serious AE	15 (1.5)	18 (2.2)
Treatment-related serious AEs	1 (0.1)	2 (0.2)
Mortality	0	0
AEs resulting in study discontinuation		
Any AE	19 (1.9)	14 (1.7)
Treatment-related AE	9 (0.9)	7 (0.8)

Adapted with permission from Schoenfeld P, et al. *Aliment Pharmacol Ther.* 2014;**39**:1161-1168.⁵⁸

AE: adverse event.

^aIncludes rifaximin 550 mg or 1100 mg (two 550 mg tablets) twice daily for 2 weeks, rifaximin 550 mg twice daily for 4 weeks, or rifaximin 550 mg three times daily for 2 weeks groups.

^bReported in $\geq 2\%$ of patients in the rifaximin 550 mg (pooled population).

($n = 14$) were considered highly sensitive to treatment with rifaximin.⁶⁰ These findings were consistent with another study that examined the antimicrobial susceptibility of *C. difficile* strains isolated from stool samples in Thailand ($n = 105$ isolates).⁶² In a substudy of the rifaximin repeat treatment trial,⁵⁵ modest, transient changes in the relative abundance of several taxa of the stool microbiota, including Clostridiaceae, were observed in patients treated with rifaximin; however, changes were generally reversed by study end (46 weeks).⁶³

3.6 | Bile acid sequestrants

A meta-analysis of six studies estimated that 28.1% of 908 patients with IBS-D were affected by bile acid malabsorption (7-day selenium homocholic acid taurine retention $<10\%$),⁶⁴ which can occur when the absorption of bile acids in the ileum is disrupted and results in diarrhoea.^{65,66} Similar results were found in a previous meta-analysis that estimated the prevalence of mild (7-day selenium homocholic acid taurine retention $<15\%$) and moderate (7-day selenium homocholic acid taurine retention $<10\%$) bile acid malabsorption as 26% (seven studies, $n = 618$) and 32% (17 studies, $n = 1073$), respectively, in patients with symptoms of IBS-D.⁶⁷ However, clinical studies examining the efficacy and safety of bile acid sequestrants (eg, colesevelam, cholestyramine) for the treatment of patients with IBS-D are limited.^{68,69}

In a small, open-label, single-dose study of 12 patients with IBS-D, the bile acid sequestrant colesevelam (1875 mg administered twice daily) significantly improved mean stool consistency from baseline after 10 days of treatment (Bristol Stool Scale score, 4.8 vs 4.4, respectively; $P = 0.04$).⁶⁸ There were no significant differences from baseline in either the mean number of weekly bowel movements or the ease of stool passage.⁶⁸ An earlier published placebo-controlled IBS-D study that compared 12- to 14-day treatment with colesevelam 1875 mg twice daily ($n = 12$) vs placebo ($n = 12$) also showed a lack of improvement in multiple symptoms, with a significant improvement vs placebo only in the ease of stool passage ($P = 0.048$), but not the number of daily bowel movements (no effect observed) or stool consistency ($P = 0.12$).⁶⁹ The most common AEs with colesevelam compared with placebo were headache (40% vs 33%, respectively), flatulence (24% vs 8%), and nausea (17% vs 24%).⁶⁹

Cholestyramine is a mainstay of treatment for patients with bile acid diarrhoea^{70,71} and may be appropriate for patients with IBS-D and bile acid malabsorption, although clinical studies in this patient population are lacking. In a small, randomised, controlled trial of 26 patients with functional chronic diarrhoea or IBS-D symptoms, the percentage of patients who achieved clinical remission at week 8 (defined as a mean ≤ 3 stools per day, with <1 watery stool per day, for the previous week) was numerically greater, but not significantly different, for cholestyramine (53.8% of 13 patients) compared with hydroxypropyl cellulose (38.5% of 13 patients).⁷² The incidence of AEs was greater with cholestyramine (46.2%) compared with hydroxypropyl cellulose (15.4%).⁷²

Results of a meta-analysis suggest that response to cholestyramine in patients with symptoms of IBS-D was positively related to

the severity of bile acid malabsorption.⁶⁷ An empiric trial of cholestyramine could be considered for patients with IBS-D, given the limited access to selenium homocholic acid taurine testing to assess bile acid absorption.⁷³ However, the use of cholestyramine may be limited by its poor palatability and AEs (eg, constipation, nausea, bloating, flatulence, abdominal pain).^{74,75} In a retrospective study, 12.3% of 171 patients with chronic diarrhoea discontinued cholestyramine treatment because of AEs.⁷⁶ To date, number needed to treat and number needed to harm values have not been reported for cholestyramine in IBS.

3.7 | Antidepressants

Depression and anxiety are common psychiatric comorbidities in patients with IBS,^{6,77} and antidepressants (ie, tricyclic antidepressants, selective serotonin reuptake inhibitors) have been prescribed in patients to help manage IBS symptoms.¹⁸

3.7.1 | Meta-analyses

The overall efficacy of tricyclic antidepressants or selective serotonin reuptake inhibitors (as an overall class) in the treatment of patients with IBS was assessed in a meta-analysis of 18 randomised, controlled trials comprising 1127 patients; the lack of improvement in IBS symptoms after treatment was experienced by fewer patients who received antidepressants compared with placebo (43.5% vs 66.0%, respectively; relative risk 0.66; 95% CI 0.57-0.76).⁷⁸ The number needed to treat for antidepressants was 4.5.⁷⁸ A meta-analysis of eight clinical studies that reported overall AE data for antidepressant medications in the treatment of IBS ($n = 451$ patients) reported that the incidence of AEs was significantly greater with antidepressants compared with placebo (36.4% vs 21.1%, respectively; relative risk 1.56; 95% CI 1.23-1.98); no serious AEs were reported.⁷⁸ The number needed to harm was 8.5 based on a patient experiencing an AE.⁷⁸

3.7.2 | Tricyclic antidepressants

In a meta-analysis of 12 studies that evaluated tricyclic antidepressants ($n = 787$), the lack of improvement in IBS symptoms was experienced by significantly fewer patients who received tricyclic antidepressants compared with those who received placebo (42.7% vs 63.8%, respectively; relative risk 0.65; 95% CI 0.55-0.77).⁷⁸ Likewise, results of another systematic review and meta-analysis ($n = 5$ studies; $n = 428$ patients) showed that tricyclic antidepressants improved global symptoms of IBS relative to placebo (relative risk 1.36; 95% CI 1.07-1.71).⁷⁹ The number needed to treat for tricyclic antidepressants was estimated to be 4.5⁷⁸ and 8,³² based on data from 12⁷⁸ or six³² studies, respectively.

A meta-analysis of six clinical studies found that AEs occurred at a significantly greater rate with tricyclic antidepressants than placebo (relative risk, 1.59; 95% CI, 1.23-2.06), with AEs of drowsiness and dry mouth occurring most commonly.^{78,80} In a pooled analysis of five

studies of IBS-D (one study did not report AEs in the placebo group), incidence was significantly greater with tricyclic antidepressants relative to placebo for dry mouth (36% vs 15%), insomnia (24% vs 13%), constipation (23% vs 6%), flushing (23% vs 5%), palpitations (9% vs 2%), and decreased appetite (8% vs 1%).³² Overdose of tricyclic antidepressants is associated with cardiac AEs (eg, abnormalities on electrocardiogram, arrhythmias, hypotension).⁸¹ The number needed to harm for tricyclic antidepressants ranged between 9 ($n = 7$ studies),²³ based on patients experiencing an AE, and 18 ($n = 6$ studies), based on AEs prompting discontinuation.³² A Rome Foundation Working Team Report recommended tricyclic antidepressants as the first-line neuromodulators in the treatment of IBS, particularly IBS-D.⁸²

3.7.3 | Selective serotonin reuptake inhibitors

A meta-analysis of seven randomised, controlled clinical studies ($n = 356$) demonstrated the efficacy of selective serotonin reuptake inhibitors for the treatment of IBS, with 45.5% of patients receiving selective serotonin reuptake inhibitors vs 67.2% of patients receiving placebo experiencing no improvement in symptoms after treatment (relative risk, 0.68; 95% CI, 0.51-0.91).⁷⁸ The number needed to treat for selective serotonin reuptake inhibitors was 5.⁷⁸ Another meta-analysis assessed five clinical trials ($n = 799$), including four of the studies included in Ford et al,⁷⁸ and showed no significant improvement in global IBS symptoms compared with placebo (relative risk, 1.38; 95% CI, 0.83-2.28).⁷⁹ This second meta-analysis reported pooled relative risks with selective serotonin reuptake inhibitors for four AEs: headache (relative risk, 0.8; 95% CI, 0.3-2.2), poor sleep (relative risk, 1.0; 95% CI, 0.4-2.5), anxiety (relative risk, 2.0; 95% CI, 0.5-7.6), and nausea (relative risk, 1.0; 95% CI, 0.4-3.0).⁷⁹ No number needed to harm for selective serotonin reuptake inhibitors has been published. A Rome Foundation Working Team Report recommended selective serotonin reuptake inhibitors for patients with IBS with anxiety who did not have abdominal pain and diarrhoea as predominant symptoms.⁸²

3.8 | Complementary and alternative medicine

Of the 13 505 US adults reporting a gastrointestinal condition in the previous year, 42% ($n = 5269$) had used complementary and alternative medicine during the past year, with 3% ($n = 407$) using ≥ 1 complementary and alternative medicine specifically for a gastrointestinal condition.⁸³ However, many complementary and alternative medicine modalities have not undergone rigorous evaluation in randomised, controlled clinical trials to determine efficacy and safety.^{84,85}

3.8.1 | Herbals

STW 5, a preparation comprising nine different herbs, has been evaluated in a single randomised, double-blind, placebo-controlled study.⁸⁶ Results of this study ($n = 208$) showed that STW 5 administered three times daily significantly improved IBS

symptoms compared with placebo after 4 weeks ($P = 0.001$).⁸⁶ No serious AEs were reported in this study; however, one AE of constipation was reported.⁸⁶ No number needed to treat or number needed to harm values have been reported for this treatment. The Chinese herbal medicine Tongxie Yaofang was evaluated in a meta-analysis of 23 randomised clinical studies in patients with IBS-D ($n = 1972$).⁸⁷ Patients with IBS-D receiving Tongxie Yaofang were significantly more likely to experience improvement of clinical symptoms vs other treatments (90.3% vs 72.7%, respectively; odds ratio, 4.0; 95% CI, 3.1-5.3 [ie, pinaverium bromide alone or in combination with a probiotic or montmorillonite powder, glutamine, loperamide, miyarsan, or trimebutine maleate]).⁸⁷ The number needed to treat for Tongxie Yaofang was 5.7.⁸⁷ Safety was evaluated in 12 studies included in the meta-analysis; AEs reported with Tongxie Yaofang included nausea ($n = 3$ in two studies), compared with 16 AEs reported across the other treatments.⁸⁷ A number needed to harm for Tongxie Yaofang was not reported.⁸⁷

Peppermint oil is thought to act as an antispasmodic via the blockade of calcium channels⁸⁸ and is available in various formulations, including as a medical food. A meta-analysis of nine randomised, controlled studies of enteric-coated peppermint oil reported a significantly greater improvement in global IBS symptoms compared with placebo (five studies; $n = 392$; relative risk 2.23; 95% CI 1.78-2.81; number needed to treat = 3) and abdominal pain (five studies, $n = 357$; relative risk 2.14; 95% CI 1.64-2.79; number needed to treat = 4).⁸⁸ A separate meta-analysis of seven randomised, controlled studies ($n = 634$) showed a similar benefit in IBS symptoms for peppermint oil compared with placebo (number needed to treat = 4).¹⁰ Although one meta-analysis found peppermint oil to have an overall incidence of AEs significantly greater than that of placebo (relative risk 1.73; 95% CI 1.27-2.36), the relative risk was no longer statistically significant when one study with an unusually high number of AEs was removed (relative risk 1.65; 95% CI 0.97-2.81),⁸⁸ consistent with the findings of the other meta-analysis (relative risk 1.9; 95% CI 0.81-4.48).¹⁰

A randomised, controlled study of 72 patients with IBS-D or mixed form IBS who received triple-coated microspheres containing a peppermint oil formulation reported a significant improvement from baseline in the overall IBS symptom score, compared with placebo, after 24 hours (19.6% vs 10.3% improvement, respectively; $P = 0.009$) and at 4 weeks (40.0% vs 24.3% improvement, respectively; $P = 0.02$).⁸⁹ Similar to what was seen in the meta-analyses,^{80,88} this formulation of peppermint oil was reported to be generally well tolerated for patients with IBS, with two patients (5.7%) reporting AEs with peppermint oil (ie, dyspepsia [$n = 1$], upper respiratory tract infection [$n = 1$]).⁸⁹ The number needed to harm for peppermint oil has not been published.

3.8.2 | Mind-body interventions

Cognitive behavioural therapy is a type of psychotherapy that can be used to improve mood and IBS symptoms and involves behaviour

modification and alteration of thinking patterns.⁹⁰ The American Gastroenterological Association has provided best practice advice related to the use of brain-gut psychotherapy for patients with gastrointestinal disorders, including those with IBS.⁹¹ Brain-gut psychotherapies differ from traditional psychotherapy in that these modalities are short-term and focused on gastrointestinal symptoms.⁹¹ A meta-analysis of nine clinical studies (n = 610) of cognitive behavioural therapy in IBS showed that 41.5% and 63.6% of patients receiving cognitive behavioural therapy or control, respectively, did not have improvement of IBS symptoms (relative risk, 0.60; 95% CI, 0.44-0.83).⁷⁸ The number needed to treat for cognitive behavioural therapy was 4.⁷⁸ Cognitive behavioural therapy is considered to be safe, but AEs have not been well documented in clinical trials.^{80,91} However, a 2018 clinical study of cognitive behavioural therapy in patients with IBS (n = 436) reported one AE of suicide attempt, which was not considered to be related to treatment.⁹² The number needed to harm for cognitive behavioural therapy has not been published.

Gastrointestinal-focused hypnotherapy is a medical hypnosis modality that involves 7-10 sessions administered over 8-12 weeks in which the hypnotic state is induced in patients and suggestions for mitigating gastrointestinal disease symptoms are presented.⁹³ A meta-analysis of five clinical studies (n = 278) demonstrated that IBS symptoms did not improve in 54.6% of patients with IBS undergoing hypnotherapy vs 77.4% of patients receiving control therapy (relative risk, 0.74; 95% CI, 0.63-0.87).⁷⁸ Based on the findings of this meta-analysis, the number needed to treat of hypnotherapy was 5.⁸⁰ No number needed to harm for hypnotherapy has been published.⁸⁰

3.8.3 | Mechanical interventions

Adequate exercise is an important lifestyle modification for patients with IBS,⁸⁴ although the American College of Gastroenterology weakly recommends exercise, given a lack of randomised, controlled trials examining this modality in IBS.¹⁰ Yoga is a therapeutic modality involving a combination of stretching, breathing exercises, and meditation that patients with IBS may employ for stress reduction.⁹⁴ A systematic review of six randomised, controlled studies of adults and adolescents with IBS (n = 273) reported that yoga improved gastrointestinal symptoms, quality of life, and anxiety compared with no treatment, and was at least as effective as a walking programme for improving patient-reported outcomes.⁹⁵ For the two studies that reported safety specifically in the yoga group, AEs involved slipping during a yoga manoeuvre (n = 1) and temporary lower back pain (n = 3).⁹⁵ No number needed to treat or number needed to harm values has been reported in the literature for yoga as treatment for IBS.

In patients with IBS, acupuncture involves inserting needles at traditional meridian points affecting gastrointestinal function with the intent to alleviate symptoms.^{96,97} A systematic review that included 17 studies (n = 1806) reported that acupuncture significantly improved symptom severity compared with other treatments (ie, pinaverium bromide alone or with loperamide/montmorillonite, sulphasalazine, trimebutine maleate; n = 5 studies [449 patients]; 84%

vs 63%, respectively; relative risk, 1.3; 95% CI, 1.1-1.4) or no treatment (n = 2 studies [181 patients]; 63% vs 34%; relative risk, 2.1; 95% CI, 1.2-3.8).⁹⁷ For studies that reported safety (n = 9), one AE of syncope occurred with acupuncture.⁹⁷ A second meta-analysis of six randomised, controlled studies (n = 664) indicated that acupuncture improved IBS symptoms, although this result was likely driven by positive findings of one large study (odds ratio, 1.8; 95% CI, 1.2-2.5).⁹⁸ A randomised, controlled study that included a subgroup of patients with IBS-D (n = 166) showed that electroacupuncture (16 sessions, with 10 in first 2 weeks, and six in second 2 weeks) or loperamide three times daily for 4 weeks (or until achievement of one bowel movement per day with a Bristol Stool Scale score of 4) reduced weekly stool frequency from baseline to 4 weeks (ie, 16 vs 10.6, respectively).⁹⁶ Overall, 11 patients with IBS-D or functional diarrhoea reported 11 AEs: insomnia (n = 4), fainting (n = 3), abdominal pain (n = 1), cold limbs (n = 1), and weakness (n = 1) with electroacupuncture; and hot flush (n = 1) with loperamide.⁹⁶ However, one study found that improvements in IBS symptoms observed with acupuncture at 3 months were sustained for up to 2 years, although there was no difference between acupuncture and usual care; follow-up data were available for 61% of study participants at 2 years.⁹⁹ Number needed to treat and number needed to harm values for acupuncture as an IBS treatment modality have not been reported.

4 | CONCLUSIONS

IBS is a common gastrointestinal condition, and a number of different treatments, administered either daily or as a short-course of therapy and targeting various pathophysiologic factors, may be considered to manage symptoms of IBS-D. For any IBS-D therapy, both efficacy and safety profiles are critical aspects of the decision-making process for ongoing symptom and disease management (Figure 1).^{10,17,22,23,25,26,32,33,40,41,44,46,47,49,58,60,61,69,74,75,78,81,88,100} A survey study of 182 patients with IBS found that patients were willing to accept substantial medication risk (median 1% risk of sudden mortality with a hypothetical medication for 99% chance of cure).¹⁰¹ These findings highlight both the burden of IBS and the need to emphasise safety considerations in treatment selection. Any direct comparisons across treatments are difficult as patient populations, efficacy endpoints, and safety analyses in clinical trials can widely vary. However, number needed to treat and harm values can help provide some indication of potential clinical benefits and risks among therapies.

The value of a positive patient-provider interaction cannot be underestimated because a positive approach improves the likelihood of treatment response.¹⁰²⁻¹⁰⁷ Just as importantly, providers are often better versed in efficacy data. Response rates, likelihood of improving, and odds ratios for a positive response are strongly favoured in publications and advertising and, thus, offer readily available data for providers to discuss with patients. The number needed to treat is one such piece of information that healthcare providers can use to select appropriate therapies. In this review, a wide range of numbers

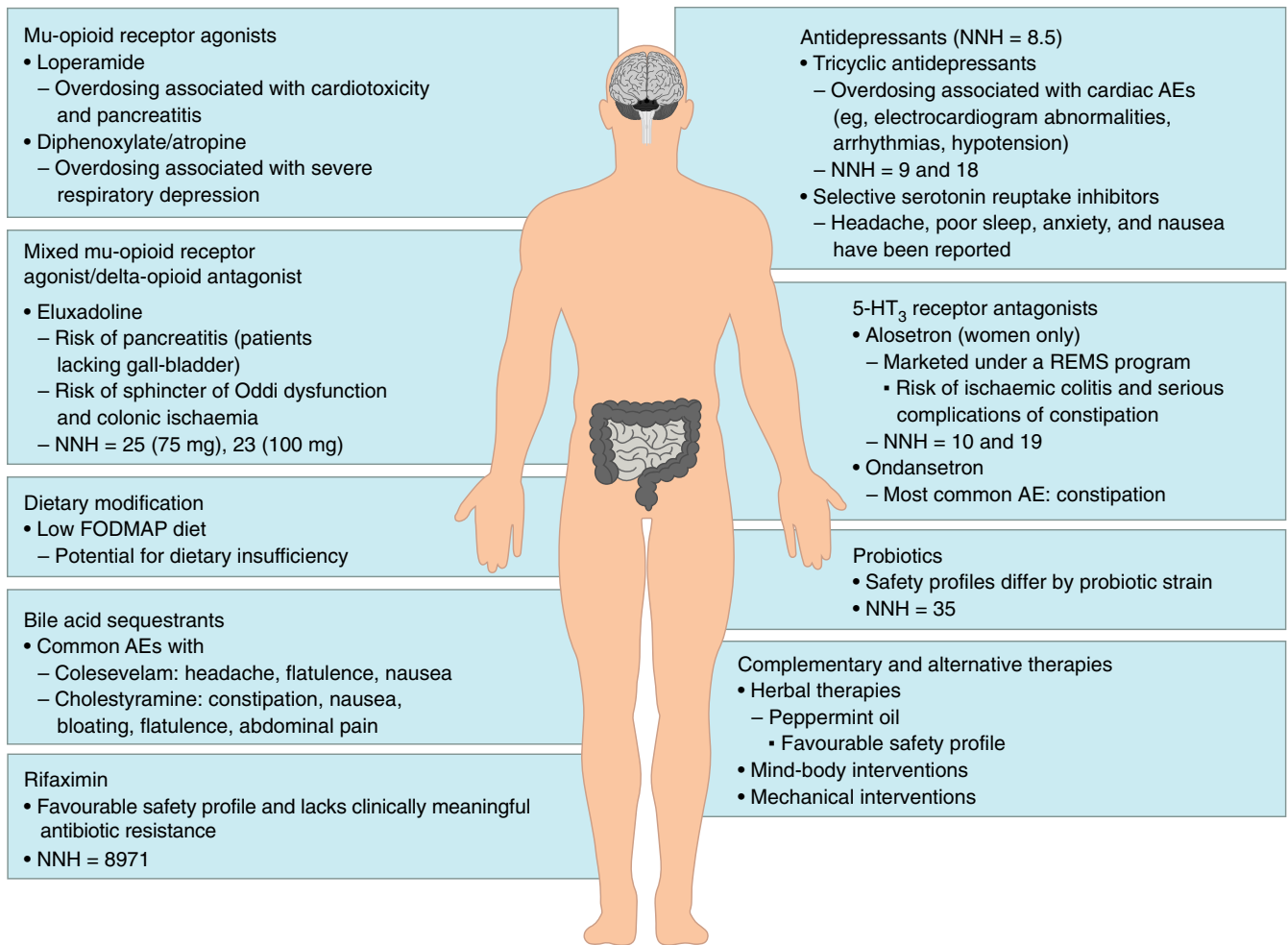


FIGURE 1 Summary of safety profiles for therapies used for the management of IBS-D.^{10,17,22,23,25,26,32,33,36,40,41,44,46,47,49,58,60,61,69,74,75,78,81,88,100,a}
^aNumber needed to harm values have been provided for each therapy for which data are available. 5-HT₃: 5-hydroxytryptamine type 3; AE: adverse event; FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-D, diarrhoea-predominant irritable bowel syndrome; NNH: number needed to harm; REMS: Risk Evaluation and Mitigation Strategy

needed to treat for medications used to treat IBS-D were reported (Table 3)^{10,17,23,31-33,40,42,44,48,50,78,81,87,108} and may be related to the primary endpoint of the studies and other methodologic considerations (patient population).

Discussions about the negative aspects of therapeutic interventions are less important for some healthcare providers,¹⁰⁹ who feel that sharing such information with patients could diminish treatment response (eg, impact adherence)^{109,110} and increase occurrence of perceived AEs,¹¹¹ and also because safety data are often not as well and consistently publicised as efficacy data. However, discussion of potential treatment-related AEs has been considered by patients and some healthcare providers to be beneficial, as related communications may increase awareness and lessen the frequency of AEs.^{110,112,113} Values such as number needed to harm should be considered alongside other information (eg, patient preference, adherence considerations, cost-effectiveness) to help guide patients and healthcare providers. Although definitions varied (patients experiencing an AE vs discontinuing due to an AE), among the IBS-D treatments with available data (Table 3),^{23,32,48} the number needed to

harm values were least favourable for antidepressants (8.5), tricyclic antidepressants (9 and 18), and alosetron (10 and 19) and most favourable for rifaximin (8971).^{10,32,80} In addition to the likelihood of any AE, the risk of serious AEs warrants careful consideration. Notable potential safety concerns with IBS-D treatments include pancreatitis with eluxadoline,⁵⁰ ischaemic colitis and serious complications of constipation with alosetron,³³ cardiotoxicity with loperamide⁴⁰ and tricyclic antidepressants,⁸¹ and abuse/misuse of loperamide.¹⁰⁸ A thoughtful discussion with patients to individualise treatment based on patient-specific characteristics and risk factors (eg, underlying cardiac risk factors; prior trials with antibiotics; presence or absence of a gall-bladder; alcohol use) should occur with a review of number needed to treat and number needed to harm values to shape the discussion with patients of the various treatment options.^{49,50} For agents that target the gut microbiota, safety profiles may differ among probiotic strains and formulations, thus large, well-designed, clinical studies are warranted.^{23,26}

In summary, while numerous treatment options are currently available for patients with IBS-D, providers should carefully consider

TABLE 3 Efficacy (number needed to treat) and safety (number needed to harm) of treatments for IBS-D^{10,23,31,32,48,78,87}

Intervention	Number needed to treat	Number needed to harm	Notable safety concerns
Dietary modification	5 (FODMAP) ^a	NA	Potential for dietary insufficiency ¹⁷
Probiotics	7 ^b	35 ^b	
Alosetron	8 ^{b,c} 6 ^d	10 ^a 19 ^c	Currently marketed under modified Risk Evaluation and Mitigation Strategy programme Ischaemic colitis has been reported ³³
Ondansetron	NA	NA	
Loperamide	NA	NA	Potential for misuse and abuse ¹⁰⁸ Overdosing associated with cardiotoxicity and pancreatitis ^{40,42}
Diphenoxylate/atropine	NA	NA	Overdosing associated with severe respiratory depression ⁴⁴
Eluxadoline	10-15 (75 mg) ^{a,e} 9-13 (100 mg) ^{a,e}	25 (75 mg) ^e 23 (100 mg) ^e	Increased risk of pancreatitis in patients without gall-bladder ⁵⁰
Rifaximin	8 ^a 10.5 ^a 11 ^c	8971 ^c	
Bile acid sequestrants (eg, cholestyramine, colesevelam)	NA	NA	
Antidepressants ^f	4.5	8.5 ^g	
Tricyclic antidepressants	4.5 ^g 8 ^c	9 ^b 18 ^c	Overdosing associated with cardiotoxicity ⁸¹
Selective serotonin reuptake inhibitors	5 ^g	NA	
STW 5 (Iberogast [®])	NA	NA	
Tongxie Yaofang	5.7 ^h	NA	
Peppermint oil	4 ^g	NA	
Cognitive behavioural therapy	4 ^g	NA	
Hypnotherapy	5 ^g	NA	
Exercise	NA	NA	
Yoga	NA	NA	
Acupuncture	NA	NA	

FODMAP: low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-D: diarrhoea-predominant irritable bowel syndrome; NA: not available.

^aAccording to Ford AC, et al¹⁰; number needed to harm based on experiencing an adverse event.

^bAccording to Ford AC, et al²³; number needed to harm based on experiencing an adverse event.

^cAccording to Shah E, et al³²; number needed to harm based on discontinuation due to an adverse event.

^dAccording to Lacy BE, et al³¹

^eAccording to Lembo AJ, et al⁴⁸; number needed to harm based on discontinuation due to an adverse event.

^fTricyclic antidepressants and/or selective serotonin reuptake inhibitors.

^gAccording to Ford AC, et al⁷⁸; number needed to harm based on experiencing an adverse event.

^hAccording to Dai Y-K, et al⁸⁷

the safety in addition to the efficacy of a specific intervention when determining how best to manage IBS-D in an individual patient.

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