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REVIEW

Current and Future Therapeutic Options for Irritable Bowel Syndrome with Diarrhea and Functional Diarrhea

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Abstract

Irritable bowel syndrome with diarrhea and functional diarrhea are disorders of gut-brain interaction presenting with chronic diarrhea; they have significant impact on quality of life. The two conditions may exist as a continuum and their treatment may overlap. Response to first-line therapy with antispasmodics and anti-diarrheal agents is variable, leaving several patients with suboptimal symptom control and need for alternative therapeutic options. Our aim was to discuss current pharmacologic options and explore alternative therapeutic approaches and future perspectives for symptom management in irritable bowel syndrome with diarrhea and functional diarrhea. We conducted a search of PubMed, Cochrane, clinicaltrial.gov, major meeting abstracts for publications on current, alternative, and emerging drugs for irritable bowel syndrome with diarrhea and functional diarrhea. Currently approved therapeutic options for patients with first-line refractory irritable bowel syndrome with diarrhea and functional diarrhea include serotonin-3 receptor antagonists, eluxadoline and rifaximin. Despite their proven efficacy, cost and availability worldwide impact their utilization. One-third of patients with disorders of gut-brain interaction with diarrhea have bile acid diarrhea and may benefit from drugs targeting bile acid synthesis and excretion. Further understanding of underlying pathophysiology of irritable bowel syndrome with diarrhea and functional diarrhea related to bile acid metabolism, gastrointestinal transit, and microbiome has led to evaluation of novel therapeutic approaches, including fecal microbiota transplantation and enterobacterial "crapsules". These opportunities to treat disorders of gut-brain interaction with diarrhea should be followed with formal studies utilizing large samples of well-characterized patients at baseline and validated response outcomes as endpoints for regulatory approval.

Keywords Pharmacotherapy · Irritable bowel syndrome · Diarrhea · Fecal transplantation · Microbiota · Bile acid

Abbreviations

5-HT3	Serotonin(5HT)-3 receptors/5-hydroxy-tryptamine-3(5HT-3) receptors
^{75}SeHCAT	75-Selenium homotaurocholic acid retention test
ASBT	Apical sodium-coupled bile acid transporter
BSFS	Bristol Stool Score
C4	7α-Hydroxy-4-cholesten-3-one
CA	Cholic acid
CDCA	Chenodeoxycholic acid
CYP7A1	Cytochrome P450 7A1
DCA	Deoxycholic acid
DGBI	Disorders of gut-brain interaction
FDA	U.S. Food and Drug Administration
FGF-19	Fibroblast growth factor 19
FMT	Fecal microbiota transplantation
FXR	Farnesoid X receptor
IBAT	Ileal bile acid transporter
IBS	Irritable bowel syndrome
IBS-D	Irritable bowel syndrome with diarrhea
IBS-SSS	Irritable bowel syndrome severity score system
LCA	Lithocholic acid
LJN452	Tropifexor
OCA	Obeticholic acid or C-ethyl CDCA
PBC	Primary biliary cholangitis
RCT	Randomized clinical trial
REMS	Risk evaluation and mitigation system
SHP	Small heterodimer partner

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SRMA	Systematic review and meta-analysis
TGR5	Taketa G-coupled receptor 5
UDCA	Ursodeoxycholic acid

Introduction

Chronic diarrhea is a complex condition that affects from 3 to 20% of adults worldwide [1]. Patients describe chronic diarrhea as an increase in frequency of stools, loose consistency, urgency, or a combination of these symptoms; chronicity implies that the diarrhea lasts longer than 28 days [2]. The differential diagnosis includes organic and functional etiologies [3–5]. Disorders of the gut-brain interaction (DGBI), previously known as functional gastrointestinal disorders, presenting with chronic diarrhea are irritable bowel syndrome with diarrhea (IBS-D) and functional diarrhea [2, 4].

Irritable bowel syndrome (IBS) is a chronic disorder characterized by abdominal pain in association with altered bowel function (stool consistency and/or frequency) [6]. Its prevalence varies between 3 and 9% depending on which symptom-based criteria is used for diagnosis [7, 8]. Functional diarrhea is defined as chronic (onset at least 6 months prior, and active during the past 3 months) loose or watery stool corresponding to more than 25% of bowel movements, without predominant abdominal pain or bloating [3, 9]. There is increasing evidence that IBS and functional diarrhea result from peripheral mechanisms in addition to dysfunction of the gut-brain axis [10–13]. Some of those mechanisms can be directly treated if they are identified in the diagnostic workup. These include alterations of gastrointestinal motility and bile acid diarrhea [14, 15]. Thus, whereas diagnosis is clinical, based on symptom criteria in addition to physical examination and limited tests to exclude conditions that can mimic IBS, there is an opportunity to identify underlying pathophysiological mechanisms that can be specifically targeted in IBS-D and functional diarrhea. In addition, epidemiological studies show that both conditions may exist as a continuum rather than in isolation, since patients could present with symptoms of either disorder at the same or non-concomitant times, e.g., reporting abdominal discomfort with the chronic diarrhea [2, 16].

Hence, the treatment approach to both entities may overlap. First-line therapies include dietary and lifestyle modifications, education and if necessary cognitive behavioral therapy, antispasmodics for abdominal pain, and antidiarrheal agents such as loperamide [6, 17]. However, response to each of these initial approaches is variable, leaving a significant number of individuals with suboptimal symptom control [18]. Alternative therapeutic options have therefore been proposed and approved by regulatory agencies including 5-hydroxytryptamine-3 (5-HT3) receptor antagonists, dual opioid receptor agonists, and the antibiotic rifaximin [6, 18, 19]. Additionally, further testing to rule out concomitant disorders that may account for symptoms is also necessary. For example, about a third of patients with IBS-D and functional diarrhea have been shown to have idiopathic bile acid diarrhea and may benefit from treatment with bile acid sequestrants [14, 15, 20]. Novel therapeutic approaches modulating the microbiome, which is possibly different in IBS-D patients compared to healthy controls, are also in development [21, 22].

The aim of this review is to discuss the current pharmacologic options and explore alternative therapeutic approaches and future perspectives for symptom management in IBS-D and functional diarrhea.

Medications Approved for IBS-D

The treatment for IBS-D and functional diarrhea focuses on control of the diarrhea and abdominal pain. For abdominal pain, the use of antispasmodics and neuromodulators (e.g., tricyclic antidepressants) is often the main approach. For control of chronic diarrhea, the peripheral μ-opioid receptor agonists, loperamide or diphenoxylate, are first-line therapy [6, 19, 23–27]. In many countries, the synthetic opioid, diphenoxylate, is combined with the anticholinergic, atropine, and this may result in adverse effects, especially in elderly patients. In patients who are refractory to these initial approaches, additional therapies have been studied including serotonin (5-HT3) receptor antagonists (e.g., alosetron, ondansetron, and ramosetron), novel combined opioid receptor modulators (e.g., eluxadoline), and selective antibiotics (e.g., rifaximin).

Serotonin (5HT)-3 Receptor Antagonists

Serotonin is an important neurotransmitter involved in motor, secretory, and sensory functions in the gastrointestinal tract [28]. 5-HT3 receptors are present both centrally and peripherally in the gut-brain axis. Antagonists at 5-HT3 receptors slow colonic transit and increase rectal compliance [29–32]. Alosetron and ramosetron are both antagonists of 5-HT3 receptors licensed for IBS-D treatment in different countries. A recent systematic review and network meta-analysis (SRMA) showed that both medications were superior to placebo in achieving the FDA-recommended composite endpoint (pain and altered stool consistency), IBS global score, abdominal pain, and stool consistency responses [33]. Alosetron, 1 mg twice daily, was deemed to be the most efficacious therapy in all categories of IBS-D, except for abdominal pain for which ramosetron, 2.5mcg once daily (RR 0.75, 95% CI 0.65–0.85; *p*-score 0.94), was ranked most efficacious. This study emphasized that the probability of

alosetron, 1 mg, being superior to other competing treatments (ramosetron, eluxadoline, and rifaximin) in achieving FDA-recommended endpoints was 97% (RR 0.69, 95% CI 0.60–0.80; *p*-score 0.97) [33]. On the other hand, when compared to other therapeutic agents (eluxadoline and rifaximin), both 5-HT3 antagonists were associated with a higher rate of adverse effects, notably constipation [33]. These findings were consistent with another study indicating constipation as the most prevalent adverse effect of the treatments for IBS-D (RR 4.28–3, 28–5.60, 95% CI) [28]. Ischemic colitis led to initial withdrawal of alosetron in the USA, and only 0.2% of patients receiving these agents have been shown to develop this complication [28]. However, epidemiological studies subsequently demonstrated that IBS-D itself is a risk factor for ischemic colitis [34]. Alosetron has been approved again by the FDA for treatment of only women with severe IBS-D lasting ≥ 6 months and refractory to conventional therapy. The restrictive requirements of risk evaluation and the mitigation strategy program were lifted in 2016 [6, 33].

Although these agents are efficacious for IBS-D, their availability worldwide is still limited. Thought participants in most trials were predominantly or exclusively women, there is evidence from phase 2B trials as well as meta-analyses that alosetron is also efficacious in men with IBS-D [33, 35, 36]. Ramosetron is only licensed in Japan and some other countries in Asia. Therefore, the 5-HT3 receptor antagonist, ondansetron, which is widely available worldwide, is being studied as a potential therapeutic option in the management of IBS-D. Two trials have shown positive responses of ondansetron, 12 mg daily for 8 weeks, in improving stool consistency, and ondansetron, 4 mg daily for 10 weeks, in improving stool consistency, urgency, and frequency. Constipation was the most common adverse effect with both doses of this medication [27, 37]. However, titrating the dose of ondansetron could effectively avoid the development of constipation while still maintaining control of the IBS-D. In fact, in the multicenter study of 120 patients with IBS-D, dose titration of ondansetron was permitted to avoid constipation [37].

Eluxadoline

Eluxadoline acts as μ- and κ-opioid receptor agonist providing pain relief and reversing diarrhea. In addition, it provides δ-opioid receptor antagonism within the gut which can enhance analgesia while preventing development of tolerance [38]. Eluxadoline, 25 mg and 200 mg, were both more effective than placebo in decreasing at least 30% from baseline the mean daily abdominal pain score and improving stool consistency based on the Bristol Stool Form Scale (BSFS). Normal stool form of 3–4 on the BSFS was observed in 12% and 13.8% of the participants on the 25 mg and 200 mg doses, respectively, compared to 5.7% for the placebo group ($p < 0.05$). Eluxadoline, 100 mg and 200 mg, was also superior to placebo in achieving the FDA-endpoint, that is, reduction of daily worst abdominal pain of ≥ 30% from baseline and either a daily BSFS < 5 or no bowel movement in IBS-D. The proportions of responders were 28% on the 100 mg dose and 28.5% on the 200 mg dose of eluxadoline compared to 13.8% on placebo ($p = 0.002$) [39]. Other studies have shown that eluxadoline was also efficacious and safe over 12 to 52 weeks and in treating patients with IBS-D who were previously partially or completely refractory to loperamide [40, 41]. In a single-center, open-label study, the efficacy and safety of eluxadoline were similar in patients with IBS-D and in patients with bile acid diarrhea [42].

Among adverse effects associated with eluxadoline treatment, nausea, abdominal pain, and constipation were common [39, 40]. Eluxadoline may also increase the risk of sphincter of Oddi spasm and pancreatitis in patients with prior cholecystectomy. The FDA released a warning in 2017 that eluxadoline should no longer be used in patients who do not have a gallbladder [43]. In addition, patients should be monitored for elevation in aminotransferases and episodic abdominal pain following treatment initiation, and eluxadoline should be avoided in patients with a history of pancreatitis, structural diseases of the pancreas, known or suspected sphincter of Oddi dysfunction, and alcohol abuse disorder [40, 44]. There are also post-marketing reports of pancreatitis during treatment with eluxadoline in patients without prior cholecystectomy [45].

Gut-Selective Antibiotics—Rifaximin

Rifaximin is an oral, minimally absorbed, nonsystemic antibiotic that directly targets the gastrointestinal tract and is associated with low risk of development of bacterial resistance [46, 47]. It was approved by the FDA in 2015 for the treatment of adults with IBS-D. Two double-blind, placebo-controlled trials (TARGET 1 and TARGET 2), with 1260 nonconstipated patients with IBS, showed adequate relief of global IBS symptoms, and improvements in bloating, abdominal pain, and stool consistency during the first 4 weeks following treatment with rifaximin, 550 mg three-times daily for 14 days [48]. Similarly, rifaximin, 800 mg daily for 10 days, resulted in significant improvement in global IBS symptoms [49]. Efficacy of rifaximin in improving IBS symptoms in patients with IBS-D was endorsed by two recent SRMAs. The first SRMA involved 1805 nonconstipated patients with IBS who participated in five RCTs. The second SRMA, with a total of 9844 patients, compared rifaximin to other drugs and involved 18 eligible RCTs—two with rifaximin [33, 50].

Since changes in the microbiome are dynamic and a systematic review of the literature suggested that the microbial

changes even within the IBS-D cohorts are inconsistent across studies, as well as the adaptation of microbiota to antibiotics, it is understandable that the durability of effects is limited, with 64.4% of patients relapsing during the first 18 weeks following initial response to rifaximin [17, 51]. When up to three additional treatment courses of rifaximin, 550 mg three times daily for 14 days, were administered, 40% responded to the first course of re-treatment (improvement in abdominal pain and stool consistency during the first 4 weeks of follow-up), and there was prevention of recurrence (13.2%), durable response (17.1%), and reduced bowel movement urgency (48.5%) with rifaximin compared to placebo ($p < 0.05$). Additionally, improvement in IBS symptoms was also observed after second and third rifaximin courses compared to placebo [17]. Developing opportunistic infections such as *Clostridioides difficile* infection and antimicrobial resistance seem unlikely, and rifaximin was ranked first for safety, by an SRMA, of treatments for IBS-D compared to 5-HT3 receptor antagonists and eluxadoline [33, 52].

Rifaximin's mechanism of action remains unclear. Whereas there was no impact on intestinal permeability or fecal bile acid levels, it has been shown that, paradoxically, the drug caused acceleration in ascending colon emptying times and a borderline acceleration in overall colonic transit at 48 h [53]. Indeed, some studies also showed benefit of rifaximin in the treatment of patients with IBS-constipation [54, 55].

Prior infection of the gastrointestinal tract is an important antecedent factor for IBS development [53, 56]. Some studies have shown efficacy of rifaximin in IBS symptoms without significant modification in the microbiome, or even a borderline and transient decrease in richness (number of species) of the microbial community with rifaximin [17, 53, 55–57].

Small Intestinal Bacterial Overgrowth

An AGA clinical practice update [58] identified that the advent and ready availability of breath tests generated a dramatic expansion in both the rate of diagnosis of small intestinal bacterial overgrowth (SIBO) and the range of associated gastrointestinal and nongastrointestinal clinical scenarios. The update provided several principles on the role of SIBO in the context of functional diarrhea or IBS-D. These principles include controversy concerning the role of SIBO in the pathogenesis of IBS, the importance of identification and correction (where possible) of underlying causes, correction of nutritional deficiencies and, although IBS has been shown to respond to therapy with a poorly absorbed antibiotic, the role of SIBO or its eradication in the genesis of this response warrant further confirmation in randomized controlled trials. There is a limited database to guide the clinician in developing antibiotic strategies for SIBO, in any context. More recently, an authoritative review [59] documented the lack of pathophysiological plausibility that underpins SIBO as a cause of maldigestion/malabsorption in IBS. It was hypothesized that the application of an ever-expanding armamentarium of modern molecular microbiology to the human small intestinal microbiome in both health and disease will resolve this impasse and provide an objective basis for the diagnosis of SIBO. In summary, while rifaximin is approved by the FDA and features prominently in the proposed algorithm for pharmacological choices in a recently published AGA Clinical Guideline [60], there is evidence that 2 weeks of treatment with rifaximin improved gastrointestinal symptoms and quality of life in Chinese patients with IBS-D whether they had SIBO or not [61], and that 2 weeks of treatment with 550 mg rifaximin b.i.d. was not associated with significant improvement in global symptoms, abdominal pain, bloating, stool urgency, frequency, or consistency, or quality of life, and that normalization of SIBO by lactulose-hydrogen breath test was not different between rifaximin- and placebo-treated veterans [62].

Bile Acid Diarrhea

Bile acids are synthesized in the liver and aid fat solubilization and absorption in the small intestine [63]. Bile acid diarrhea results from an excess in bile acids in the colon, resulting in increased colonic secretion and motility [63, 64]. Primary bile acid diarrhea has been reported in 25–33% of patients with chronic diarrhea [15, 20]. Consequently, bile acid diarrhea should be excluded in DGBI patients with diarrhea, especially if there is insufficient response to first-line therapy [65].

There are two categories of bile acids: primary bile acids—cholic acid (CA) and chenodeoxycholic acid (CDCA); and secondary bile acids—the predominant ones being deoxycholic acid (DCA), lithocholic acid (LCA), and ursodeoxycholic acid (UDCA) [66]. Bile acid reabsorption into ileal enterocytes stimulates the nuclear farnesoid X receptor (FXR) to produce fibroblast growth factor 19 (FGF-19), which is transported via the portal circulation to the liver where it induces small heterodimer partner, resulting in reduced levels of the intermediate in bile acid synthesis, 7α-hydroxy-4-cholesten-3-one (C4), and therefore promoting negative feedback for bile acid production. The most potent FXR agonist is CDCA, followed by CA, DCA, and LCA [66, 67].

The remaining 5–10% of bile acids not reabsorbed in the ileum undergo deconjugation in the colon by bacterial bile salt hydrolases and by 7α-dehydroxylating bacteria to form secondary bile acids [66, 68]. In the colon, CDCA and DCA

stimulate intestinal secretion, increase mucosal permeability, and induce high amplitude propagated contractions [66, 69, 70]. Finally, the colon reabsorbs, by passive diffusion, at least 50% of the remaining mass of bile acids reaching that organ, and the rest are excreted in stool [66, 68].

The stool bile acid profile in patients with IBS-D shows increased levels of total and primary bile acids, whereas higher levels of LCA, which is a non-secretory bile acid, are seen in patients with IBS-constipation [71–73]. Increased levels of total, primary, and secretory fecal bile acids have been shown to have a significant correlation with stool frequency and form in patients with IBS-D [74, 75]. Recent advances in screening methods for bile acid diarrhea may lead to a change in clinical practice and guidelines.

Three imaging or biochemical tests can be used to establish the diagnosis of bile acid diarrhea: 75-selenium homotaurocholic acid retention test (^{75}SeHCAT), serum biomarkers of bile acid synthesis, and total or individual fecal bile acid measurements [64, 65, 76].

Since ^{75}SeHCAT is not available in the USA, several criteria have been validated: total fecal bile acid excretion > 2337 µmol/48 h, or primary fecal bile acids > 10%, or combination of total fecal bile acids > 1000 µmol/48 h plus primary bile acids > 4% [63, 77].

Serum biomarkers can directly measure bile acid synthesis by a fasting serum C4 test (> 52 ng/mL) or indirectly by fasting serum FGF-19 (< 61.7 pg/mL) which reflects reabsorption of bile acids in the ileum. The sensitivity and specificity of both serum tests are lower than the gold standard ^{75}SeHCAT or the total 48-h fecal bile excretion test [63, 78–80].

Medications for Bile Acid-Related Diarrhea

The main treatment option for bile acid diarrhea is bile acid sequestrants: cholestyramine, colestipol, and colesevelam [68, 81–85] (Table 1). It is important to ensure at least a 2-h separation from the time of ingestion of other medications to avoid interference with their absorption. Trials documenting efficacy of bile acid sequestrants are of relatively low quality.

Medications in development for BAD are FXR agonist drugs, obeticholic acid (OCA or 6-ethyl CDCA), and tropifexor [68, 86]. OCA is approved for treatment of patients with primary biliary cholangitis (PBC) and advanced cirrhosis [86–88]. In a study to evaluate OCA efficacy in patients with bile acid diarrhea, 25 mg OCA for 2 weeks increased FGF-19, decreased fasting C4, and improved stool frequency, form, and total diarrhea index compared to placebo [89]. However, OCA was associated with increased total cholesterol and LDL-cholesterol, as well as pruritus [68, 89], and there is risk of severe liver injury in the presence of advanced liver fibrosis, questioning its utility for functional diarrhea [90, 91].

Tropifexor (LJN452) is a highly potent non-bile acid FXR agonist that is also being studied for treatment of PBC and nonalcoholic steatohepatitis [92–94]. A small double-blind, placebo-controlled study in patients with bile acid diarrhea showed that 60 µg tropifexor once daily for 14 days demonstrated increased FGF-19 levels, decreased serum C4, and significant slowing in ascending colon transit [95] with no itching observed in these patients or healthy volunteers [95, 96].

Off-Label, Second-Line Medications for Chronic Watery Functional Diarrhea

When Approved First-Line Treatments Fail

Since not all patients respond to first-line and licensed medications to treat functional bowel disorders, it is important to rule out carbohydrate malabsorption and bile acid related diarrhea, and to consider proabsorptive (clonidine) and antisecretory (octreotide) drugs [97].

Clonidine

Clonidine is an α2-adrenergic receptor agonist that increases fluid and electrolyte intestinal absorption, reduces secretion, decreases gastrointestinal motility transit, and increases rectal compliance [98–100]. This drug is most commonly used to treat diarrhea due to narcotic withdrawal and diabetes, typically with evidence of sympathetic neuropathy (adrenergic denervation) [99, 101]. Clonidine seems to decrease on average one litre of stool per day, improving consistency and decreasing frequency of bowel movements, as shown in an SRMA evaluating the benefit of clonidine on treating diarrhea due to variable causes (IBS, diabetes, fecal incontinence, cholera) [99]. The recommended dose is 0.1–0.3 mg three-times/day orally or by weekly patch [101]. Adverse effects include dry mouth, drowsiness, orthostatic hypotension, constipation, and worsening of gastric emptying [99, 100, 102]. Patients rarely can tolerate > 0.2 mg per day, and use of 0.1 mg or 0.2 mg clonidine released by patch over a 24-h period is more tolerable and can avoid hypotension, especially in patients with diabetic diarrhea.

Octreotide

The somatostatin analog, octreotide, has been studied in diverse etiologies of diarrhea including chemotherapy-induced, diabetes, AIDS-associated, short bowel syndrome, and carcinoid diarrhea [97]. Chromogranin A, a protein known to be increased in neuroendocrine tumors as gastrinomas, has been found to be transiently elevated in patients with IBS-D, suggesting it may identify patients

Table 1 Available bile acid sequestrants

Medication	Study design	Study population	Dose/duration of treatment	Outcomes	Results	Additional information	Quality of data	Limitations of data	Ref #
Cholestyramine	Prospective, open-label	BAD	Limited data; median daily dose, 8 g Duration: 34.5 months	Stool consistency, and frequency; full GI transit	Improved: Stool consistency* Stool frequency* prolonged transit in small bowel and transverse colon*	No report on side effects	Low	Study design Small sample size Dose adjustment based on SE, but SE not described	[82]
Colestipol	Prospective, open-label	IBS (Rome II) with ^{75}SeHCAT retention < 20%	Dose: 1 g b.i.d., increased by 1 g every other day if no positive effect Duration: 8 weeks	Clinical symptoms, stool form and frequency	Improved in: IBS-SSS* Stool frequency*	No report on side effects	Low		[81]
Colesevelam	Prospective, unblinded, single-dose	IBS-D and prior evidence of increased BA synthesis or fecal excretion	1875 mg b.i.d. orally Duration: 10 days	Stool 48-h BA Serum C4 Bowel functions, questionnaires daily	Improved: Stool consistency* Increased: Total BA in stool* DCA excretion* Serum C4*	No report on side effects Inverse correlation between stool frequency and BA sequestered in 48-h stool*	Low	Study design Small sample size	[84]
	Single-center, randomized, double-blind, parallel-group, controlled		1875 mg b.i.d. orally Duration: 4 weeks	Same as above Plus: Colonic transit Mucosal permeability mRNA levels in rectosigmoid biopsies	Increased: Total BA in stool* Serum C4* Decreased: FGF-19* Colon mucosal expression of *NR1H4* (gene for FXR protein)*	No serious side effects reported Higher compliance lower rates of SE, notably constipation No differences: stool frequency, consistency, colonic transit, and permeability	Moderate	Small sample size	[83]

75SeHCAT 75-selenium homotaurocholic acid retention test, *b.i.d.* twice daily, *BA* bile acids, *BAD* bile acid diarrhea, *C4* 7α-hydroxy-4-cholesten-3-one, *DCA* deoxycholic acid, *FGF-19* fibroblast growth factor 19, *FXR* farnesoid X receptor, *GI* gastrointestinal, *IBS-D* irritable bowel syndrome with diarrhea, *IBS-SSS* IBS severity scoring system, *Ref* reference, *SE* side effects

*p-value ≤ 0.05

with IBS-D who could benefit from octreotide therapy [103]. This medication increases intestinal absorption, decreases hormone secretion, and inhibits secretion of gastric, pancreatic, and intestinal fluids [97, 104]. A study in patients with chronic idiopathic diarrhea showed an improvement in stool frequency and consistency and quality of life with the longer-acting lanreotide, 120 mg subcutaneously monthly for 3 months. In addition, by the end of the first month, 42% of patients had bowel movement frequency decrease by half [105]. Short-acting octreotide is administered subcutaneously in a dose ranging from 50 to 250 ug, three times daily [100, 101]. Gallstone formation and related complications as well as steatorrhea seem to be most common adverse effects [104, 106]. In a prospective study, 24% of patients with neuroendocrine tumors developed pancreatic exocrine insufficiency [107]. With long-term use, there could be tachyphylaxis in effects of the short-acting octreotide; in clinical use of octreotide for chronic diarrhea, steatorrhea is rarely observed. It is worth noting that octreotide reduced lipase secretion by 27% in formal experimental studies [108].

Herbal Therapies for Chronic Diarrhea

Several studies have reported benefit of herbal medications in the treatment of functional diarrhea or IBS-D. For example:

a. A multicenter, randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy and safety of Chinese medicine (CM) decoction Chang'an I Recipe (I) in the treatment of IBS-D in 216 patients (1:1 ratio) with efficacy rates for IBS-SSS response and adequate relief response for the treatment compared to control groups; however, no differences were noted for IBS-QOL or anxiety and depression scores [109].
b. Xiang-Sha-Liu-Jun-Zi tang (XSLJZT), 3 g t.i.d., was tested in a double-blind, randomized, controlled preliminary study of 28 days' duration in 80 patients with IBS, with improvement in diarrhea (defined as frequent stools) but not in loose stools or urgency [110].
c. Tong-Xie-Yao-Fang (TXYF) granules were tested in a 4-week treatment duration, double-blind, placebo-controlled randomized trial (1:1 ratio) of 160 participants with IBS-D with loose stools (Bristol Stool Form Scale score 5, 6, or 7). There was a significantly higher rate of adequate relief of global symptoms in TXFY group during weeks 1 to 4; however, the effects on stool frequency and consistency were not significant [111].
d. An earlier meta-analysis of Tongxie Yaofang modified decoction and Tongxie Yaofang plus Sini San decoction, Liyiting decoction, and Tongxie yihao capsule showed antidiarrheal effects compared to conventional medicine in patients with IBS-D [112].
e. A more recent meta-analysis [113] of Shenling Baizhu San (SBS), a Chinese medicine herbal formula, assessed 14 RCTs including 1158 participants (54% males) with chronic diarrhea; there was greater patient-reported satisfaction with Shenling Baizhu San combined with or without conventional medicine.
f. Single or combination Chinese herbal medications applied topically to the navel have been used to treat chronic diarrhea. One report included 288 randomized or quasi-randomized controlled trials with a total of 35,706 participants (adults and children) with efficacy rates recorded of 93.5% in adults and 96.6% in children [114].

Overall, the data suggest possible efficacy of herbal medicines, but further definitive proof is required. However, there is evidence that herbal medicine may be as effective as rifaximin in the treatment of SIBO [115].

Future Therapeutics Options

Fecal Microbiota Transplantation

Gut microbiota in patients with IBS differ from healthy individuals due to a lower bacterial diversity. Dysbiosis is considered one of the factors contributing to IBS etiology, though the pathobiological mechanisms are unclear [116–119]. There are conflicting results in the literature regarding efficacy of fecal microbiota transplantation (FMT) in the treatment of IBS. A randomized, double-blind, placebo-controlled study evaluated the impact of different doses (30 g and 60 g) of FMT on IBS symptoms and quality of life in patients with moderate to severe IBS. An improvement of at least 50 points in the IBS Severity Scoring System (IBS-SSS) was seen compared to placebo after 3 months with both doses, particularly in patients who received higher FMT doses (76.9% with 30 g vs. 89.1% with 60 g) [120]. FMT response did not differ between females and males, but women with IBS-D had a significantly higher response rate to treatment and lower IBS-SSS after one and three months of FMT [121]. However, at least a quarter of all patients on either 30 g or 60 g had persistent symptoms within the severe IBS category, and 20% presented with adverse effects such as cramping and abdominal pain when compared to 2% in the placebo group [118, 122]. Conversely, three other recent SRMAs evaluating the efficacy of FMT treatment in IBS observed an improvement in quality of life, but not in IBS symptoms after 3, 6, and 12 months of therapy [123–125].

The mechanism underpinning the therapeutic benefit of FMT in patients with IBS is unclear. FMT efficacy can be affected by many factors including dose, placebo response rate, modality of FMT delivery, and donor selection [125].

Therefore, to explore the heterogeneity of those factors, studies have focused on specific subgroup analysis to interrogate patients who did, as well as those who did not respond to this therapy [123–125]. As expected, it has been highlighted that the characteristics of the stool donor may play an important role in the patient response to FMT. The term "super donor" has been used to refer to an individual who is normobiotic and has a positive microbial signature, thus being more likely to yield positive responses following FMT [119]. Even though it remains unclear which bacterial profile constitutes a positive microbial signature, *Streptococcus, Dorea, Lactobacillus* and *Ruminococcaceae* spp. are four genera of bacteria that have been reported as favorable bacterial profiles for a donor [119, 126, 127]. Several factors have been demonstrated to impact the composition of the intestinal microbiota. European guidelines for FMT suggest that a careful interview with and physical examination of a stool donor are necessary to identify potential positive factors [128]. Early life events such as history of delivery by caesarean section, being formula-fed, smoking or smoking cessation, and chronic use of antibiotics have been shown to reduce intestinal bacterial diversity [129–134]. On the other hand, normal body mass index, regular exercise, and consuming a diet rich in protein, fiber, minerals, and vitamins are known to have positive effects on microbiome composition and, consequently, FMT responses [135–137]. Furthermore, donors should not be first-degree relatives of any of the patients in a trial since gut microbiota may be affected by common genetic or environmental factors [138, 139]. FMT is less beneficial when utilizing frozen stool compared to fresh donor samples [125].

There are three modalities of FMT delivery: enterobacterial capsules, gastroscope or nasojejunal probe into the duodenum, and colonoscopy. Oral capsules are more easily tolerated [125]. Long-term efficacy of FMT has also been evaluated and discordant results have been shown, questioning if FMT should be repeated [140–142]. Nonetheless, there are predicable risks of FMT that should be considered [143–145]. Special features regarding FMT delivery, long-term efficacy, and potential risks are shown in Table 2 [124, 125, 140–147]. In brief, a recent meta-analysis evaluating grade quality of evidence showed very low support in recommending FMT in patients with IBS [125]. Further studies are needed to better understand possible variables that can influence treatment efficacy.

Microbiome-Based Therapy in Relation to Bile Acid Metabolism in IBS-D

The gut microbiota is an indispensable participant in bile acid metabolism including production of secondary bile acids via deconjugation, 7α-dehydroxylation, oxidation, epimerization, desulfation, and esterification reactions [148–151]. Conversely, bile acid metabolism can also contribute to gut microbiome composition [152]. For example, bile acids indirectly influence the gut microbiota by modulation of FXR expression, which results in inhibition of bacterial overgrowth and intestinal mucosal injury [153, 154]. In addition, primary bile acid, particularly the conjugated taurocholic acid (TCA), has been shown to promote the germination of *C. difficile* spores. On the other hand, secondary bile acids have been demonstrated to inhibit vegetative growth and toxin activity of *C. difficile*, as well as inhibit TCA-mediated spore germination [155–157].

A recent study evaluating the correlation between IBS-D, bile acid metabolism, and gut microbiota showed a different microbial profile in patients with IBS-D with excess total bile acid excretion compared to patients with IBS-D with normal fecal bile acid levels and to healthy controls. An increase in Clostridia genera and *Clostridium scindens* species positively correlated with increased total fecal bile acids and serum C4 levels, while negatively impacting FGF-19 levels in patients with IBS-D with increased bile acid excretion. Besides the negative effect on bile acid metabolism in Clostridium genera, *Clostridium leptum* species showed an opposite influence on FGF-19, stimulating the negative biofeedback to bile acid production and, thereby, reducing total fecal bile acids [158]. Our group recently showed that patients with bile acid diarrhea had microbial flora with decreased expression of bile acid thiol ligase, which is involved in the conversion of primary to secondary bile acids and this is associated with higher percentage of stool primary bile acids in patients with bile acid diarrhea. Moreover, a reduction in expression of sulfuric ester hydrolases or sulfatases was identified in the microbiota, and this may be a compensatory effect to reduce the secretory and detergent effects of the bile acids by preserving their sulfation [74].

Given evidence that the interaction of bile acid metabolism and gut microbiota seems to be bidirectional, the therapeutic potential of microbiome products ("crapsules") capable of regulating bile acid synthesis or vice versa to improve diarrhea in functional diarrhea and IBS-D with increased fecal bile acid excretion may be a future target in these populations.

Conclusion

There have been significant advances in the therapeutic opportunities available to treat both irritable bowel syndrome with diarrhea and functional diarrhea. The currently available medications and recommended doses are summarized in Table 3. In the last decade, we have seen the availability of actionable biomarkers [76] that can be used to identify mechanisms that may be causing these clinical presentations including accelerated colonic transit, bile acid

Table 2 Special features of fecal microbiota transplantation mode of delivery, long-term effects, and potential risk factors

Study design	Overall results	Colonoscopy/gastroscope/nasojejunal tube	Capsules	Ref. #
Mode of delivery				
SRMA	No improvement in global symptom in IBS at 12 weeks compared to placebo (RR 0.75, 95% CI 0.43–1.31)	FMT superior to placebo† via colonoscopy (RR 0.70, 95% CI 0.51–0.96) FMT superior to placebo† via gastroscope (RR 0.37, 95% CI 0.14–0.90)	Inferior to placebo via capsule (RR 1.88, 95% CI 1.06–3.35)	[125]
DB, PC RCT	Improved stool frequency in FMT group post-treatment and 1 month follow-up.*		No difference FMT capsules compared to placebo at any time	[147]
SRMA	No improvement in IBS symptom (RR 0.98, 95% CI 0.58–1.66)	FMT via Colonoscopy superior to placebo†: (RR 0.63, 95% CI 0.43–0.93); FMT via nasojejunal tube: non-significant benefit (RR 0.69, 95% CI 0.46–1.02)	Inferior to placebo (RR 1.96, 95% CI 1.19–3.20)	[124]
Randomized, controlled	Improvements in 12 weeks: IBS-SSS* Stool consistency* Anxiety and depression scores*		Superior to placebo in IBS-D patients' comorbid psychological disorders	[146]
Long-term efficacy on IBS symptoms				
SRMA	No improvement in global symptom in IBS at 1-year follow-up (RR 0.90, 95%CI 0.72–1.12)			[125]
Prospective follow-up of RCT	Persistent response to FMT after 1-year (30 g or 60 g of FMT)* Abdominal symptoms and quality of life improved at 1-year compared with after 3 months*			[141]
Single-Center Retrospective	Improvements in: IBS-SSS after 1 month* and persist from 3 to 60 months** Quality of life** and fatigue assessment scale after 3 to 60 months of FMT** Stool frequency and consistency (BSS)** Efficacy of FMT decreases over time (60 months follow-up)			[140]
DB RCT 2nd FMT (retransplantation): open-label	Improvement in IBS symptoms and bloating; and IBS symptom score; and quality of life in 12 weeks* After 1-year follow-up 79% of initial responders had lost FMT effect (median time of 4 months) 2nd FMT offered to: (1) placebo group; (2) non responders from FMT active arm; (3) responders to 1st FMT with loss of response (1): Improve in IBS symptom score and stool frequency* (2): no significative improvement (group resistant to FMT) (3): Improvement in abdominal symptoms*			[142]
Potential risks				
	ESBL-producing *Escherichia coli* bacteremia occurred in two patients after FMT by capsule			[144]
	Both: same stool donor/severe underlying disease and previous use of broad-spectrum antibiotics			[145]
	Alert for potential risk of serious or life-threatening infections with FMT Enteropathogenic Escherichia coli (EPEC) Shigatoxin-producing Escherichia coli (STEC)			[143]

CI confidence interval, *DB* double blind, *ESBL* extended-spectrum beta-lactamase, *FMT* fecal microbiota transplantation, *IBS* irritable bowel syndrome, *IBS-D* irritable bowel syndrome subtype diarrhoea, *IBS-SSS* IBS severity scoring system, *PC* placebo-controlled, *RCT* randomized clinical trial, *RR* relative risk, *SRMA* systematic review and meta-analysis

*p-value < 0.05

**p-value $= 0.05$

†placebo was delivered in the same way of FMT group

Table 3 Summary of drugs used in treatment of diarrhea associated with functional diarrhea or IBS-D

Drug Class	Agent(s)	Targeted mechanism of diarrhea	Dose	Additional comment
Opioid: μ-opioid agonist	Loperamide	Accelerated transit; ↑ intestinal secretion	2–4 mg qid	
μ-opioid agonist and δ-opioid antagonist	Eluxadoline		100 mg bid	Risk of pancreatitis; avoid post-cholecystectomy
5-HT_3 antagonists	Alosetron	Accelerated transit	0.5–1.0 mg bid	FDA warning (< 65 years, female; non-responder to other Rx
	Ondansetron		4-8 mg tid	Off-label use
Non-absorbable antibiotic	Rifaximin	Suspected SIBO	550 mg bid *14 days every 6 months	
Bile acid sequestrants	Cholestyramine	Evidence of ↑ BA synthesis or excretion	4 g daily up to 4 g qid	Risk of interference with absorption of other medication/ nutrients
	Colestipol		1 g bid up to 4 g bid	
	Colesevelam		625–1875 mg bid	
Adrenergic agonist	Clonidine	↑ intestinal secretion	0.1 mg/day by weekly patch	Risk of hypotension
Somatostatin analog	Octreotide SQ	↑ intestinal secretion	50–100 μg tid before meals	Prescribe using multi-draw vials and 1 mL syringes

diarrhea, and possibly SIBO or colonic dysbiosis. Formal studies are now needed to advance the trials targeting these individual mechanisms by utilizing larger samples of well-characterized patients at baseline and by use of validated patient response outcomes as endpoints for regulatory approval.

Author's Contribution MC: guarantor of article. Drs. MC and GPR designed the research study; performed extensive literature research; wrote and revised the manuscript; and approved the final version.

Declarations

Conflict of interest Dr. Camilleri received funding for a single-center study of eluxadoline in bile acid diarrhea and IBS-diarrhea in the past 2 years. Dr. Piovezani Ramos has no conflicts of interest to disclose.

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