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Management of Irritable Bowel Syndrome With Diarrhea

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Abstract: Irritable bowel syndrome (IBS) with diarrhea (IBS-D) affects ~1% of the general population and is characterized by abdominal pain associated with diarrhea. IBS-D symptoms significantly impact the quality of life of patients. Major uncertainties remain regarding the optimal management of these patients. Several therapies have been investigated over the years for the treatment of IBS-D. In the initial management, commonly prescribed approaches with an effect on global IBS symptoms include a low Fermentable Oligo-, Di-, Mono-Saccharides and Polyols diet and probiotics, while antispasmodics are used for targeting abdominal pain and loperamide for diarrhea only. Additional therapeutic options for the relief of global IBS symptoms include rifaximin, 5-HT_3 antagonists, gut-directed psychological therapies, and eluxadoline, while tricyclic antidepressants can target abdominal pain and bile acid sequestrants diarrhea. Promising evidence exists for the use of mesalazine and fecal microbiota transplantation in IBS-D, although further evidence is needed for definitive conclusions regarding their efficacy.

Key Words: irritable bowel syndrome, diarrhea, disorders of gut-brain interaction, probiotic, rifaximin

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Disorders of gut-brain interaction are chronic conditions characterized by persistent and recurring gastrointestinal symptoms.[1,2] Among these, one of the most frequently reported is the irritable bowel syndrome (IBS).[2] IBS affects up to about 3% to 5% of the Western population.[3] Its prevalence changes among different geographical regions due to variations in symptom interpretation and reporting.[4] IBS development, likely in genetically predisposed subjects,[5] can be triggered by a number of events, such as antibiotic exposure or other disruptors of gut physiology and microbiota such as an acute bout of gastrointestinal infection,[6–10] menses, diet, and psychological factors.[11] The pathophysiology of IBS includes several factors such as dysbiosis, increased intestinal permeability, mucosal immune activation, altered intestinal motor function, visceral hypersensitivity, and altered processing of information in the central nervous system.[2,12–16] IBS is defined by symptom-based diagnostic criteria, known as the "Rome criteria," derived by consensus from a multinational group of experts, currently in their IV update which is reported in Table 1.[2] Patients are categorized according to predominant stool pattern by the use of the Bristol Stool Form Scale. These include IBS with diarrhea (IBS-D), IBS with constipation, IBS with mixed stool pattern, and IBS unclassified.[2] Patients may also complain of defecation straining, feeling of incomplete bowel movement, urgency, passing mucus, and bloating. IBS is often associated with mood problems, other gastrointestinal symptoms such as functional dyspepsia or gastroesophageal reflux disease, and extra-intestinal symptoms such as fibromyalgia, headache, back pain, and genitourinary symptoms.[17,18] In a recent multinational online survey of 54,127 individuals from 26 countries promoted by the Rome Foundation,[3] the prevalence of Rome IV confirmed that IBS ranged between 1.3% and 7.6%, with a pooled prevalence of 4.1% using Rome IV criteria, while the prevalence of IBS-D was 1.2% (1.1% to 1.3%). Moreover, a recent meta-analysis showed a pooled prevalence of Rome IV–defined IBS-D of 1.4% (95% CI: 0.9%-1.9%).[19] Although IBS-D is not a life-threatening condition, it heavily impacts the quality of life of the patients affected and places a considerable burden on health care systems.[20] Despite its high prevalence, IBS-D is associated with major uncertainties, especially regarding the optimal diagnostic workup and management. Consequently, we aimed to review the current knowledge regarding the management of patients with IBS-D, to optimize clinical outcomes. With this manuscript, we also aimed to provide a critical point of view on treatments outside international guidelines and other promising treatments whose efficacy should be further tested in clinical practice.

SEARCH STRATEGY

Identification of papers on IBS-D for this narrative review was carried out with a literature search up to June 30,

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TABLE 1. The Rome IV criteria for IBS and Its Subgroups (adapted from Lacy et al[2])

IBS	Recurrent abdominal pain, on average for at least 1 d per week in the past 3 mo, associated with 2 or more of the following: related to defecation, a change in frequency of stool, a change in stool form. Criteria must be fulfilled for the past 3 mo, with symptom onset at least 6 mo before diagnosis
IBS with constipation	< 25% of Bristol Stool Form Types 6 or 7 and ≥ 25% of bowel movements of Bristol Stool Form Types 1 or 2.
IBS with diarrhea	< 25% of Bristol Stool Form Types 1 or 2 and ≥ 25% of bowel movements of Bristol Stool Form Types 6 or 7.
IBS with mixed stool pattern	≥ 25% of bowel movements of Bristol Stool Form Types 6 or 7 and ≥ 25% of bowel movements of Bristol Stool Form Types 1 or 2.
IBS unclassified	Patients with IBS criteria outside subgroups according to Bristol Stool Form type.

IBS indicates irritable bowel syndrome.

2023, with MEDLINE via PubMed, Ovid Embase, and Scopus using the following medical subject heading (MESH) terms "irritable bowel syndrome" OR "diarrhea" OR "abdominal pain" performed by 2 authors. Articles more relevant to the topic of this clinical review were selected by the author without language or time restriction; references of selected articles and systematic reviews were also evaluated, when of interest. Disagreements on the relevance of studies selected for inclusion in the review were resolved by a third independent reviewer.

DIAGNOSIS

Since no specific biomarkers of IBS are currently available, the diagnosis of IBS-D is mainly based on the assessment of the symptoms complained by the patients using validated questionnaires, instead of using several diagnostic tests to exclude the multitude of gastrointestinal diseases (Fig. 1). The Rome IV questionnaires and the Bristol stool form scale are the most commonly used tools employed for IBS-D diagnosis.[2,21] A sufficient positive diagnostic strategy for IBS-D should include a careful clinical history, focused on key abdominal symptoms, combined with a physical examination and minimal diagnostic testing.[21] The diagnostic workup should also exclude alarm features such as unintentional weight loss, nocturnal diarrhea, tenesmus, hematochezia, high-volume diarrhea, a very high number of bowel movements, suggestion or evidence of malnutrition, or a family history of colorectal neoplasia, celiac disease, or inflammatory bowel disease, which may require further investigations.[21] Personalized additional investigations are indicated in selected cases to exclude other gastrointestinal diseases able to mimic IBS-D symptoms such as celiac disease, Crohn's disease, food allergies, carbohydrate maldigestion, bile acid diarrhea, small-intestinal bacterial overgrowth, and hyperthyroidism.[21].

The Rome IV criteria recommend making a positive clinical diagnosis of IBS aided by limited diagnostic testing.[2] A complete blood count should be performed to identify alarm features such as anemia or leucocytosis deserving further investigation,[2,22] while C-reactive protein should be used to exclude inflammatory bowel diseases. A recent systematic review and meta-analysis showed that a C-reactive protein level ≤0.5 mg/dL was able to exclude inflammatory bowel diseases in IBS-D.[23] Serological screening for celiac disease, including immunoglobulin A (IgA) tissue transglutaminase and quantitative IgA levels, should be performed while eating a gluten-containing diet, particularly in case of first-line treatment failure.[2,24] Indeed, several prospective case-control studies,[25–27] systematic reviews, and meta-analyses[24,28–31] have examined the clinical utility and the cost-effectiveness of testing for celiac disease in patients with IBS-D, since these patients were reported with an increased likelihood of having positive IgA tissue transglutaminase or biopsy-proven celiac disease.[24] Fecal calprotectin should also be analyzed[2] to rule out inflammatory bowel diseases given its high negative predictive value, while a positive result requires further investigation.[31] Using a cutoff of 50 mcg/mg, fecal calprotectin yielded a sensitivity of 0.81 (96% CI, 0.75-0.86) and a specificity of 0.87 (95% CI, 0.78-0.92).[31] However, in clinical practice higher values are used to rule out organic disease; as an example, in a recent review of the literature,[31] values between 100 and 164 mcg/mg were able to correctly identify 90% of patients without organic diseases (sensitivity, 0.64; specificity 0.90). Personalized additional investigations may include colonoscopy, which should be performed in selected patients aged more than 40 or 50 years respectively with or without alarm features, in this latter case according to colorectal cancer screening program indications.[32] When performed, biopsies should be obtained from both the right and left colon to rule out microscopic colitis.[21] However, most of the structural lesions found during colonoscopy in patients with suspected non-constipation–predominant IBS are not the cause of diarrhea (adenomas, angiodysplasia).[33] Among other tests, routine thyroid tests can be assessed in case of suspicion of hyperthyroidism.[2] Bile acid diarrhea may account for up to one-fourth of presumed cases of IBS-D[34] and can be diagnosed through the ^{75}Se-homocholic acid taurine (SeHCAT) or 7-alpha-hydroxy-E-cholesten-3-one (C4) plasma level determination, which are unfortunately not available in some countries. Breath tests for bacterial overgrowth can also be considered in selected cases with strong clinical suspicion based on the presence of predisposing conditions.[35] Video capsule endoscopy may be considered among the small group of patients with suspect IBS-D who experience persistent severe or aggravating symptoms, or symptoms refractory to standard medical therapy. On the other hand, it may be considered useful to use device-assisted enteroscopy in patients with suspected IBS-D only for targeted lesions identified by small bowel imaging or video capsule endoscopy, which would therefore require further endoscopic diagnostic or therapeutic intervention.[13]

TREATMENT

Several therapies have been investigated over the years for the treatment of IBS-D, mainly targeting diarrhea and abdominal pain (Fig. 2). The first-line tier is often composed of the following treatments targeting global IBS symptoms or only abdominal pain or diarrhea, which can be used alone or in combination, such as low Fermentable Oligo-, Di-, Mono-Saccharides and Polyols (FODMAPs) diet,

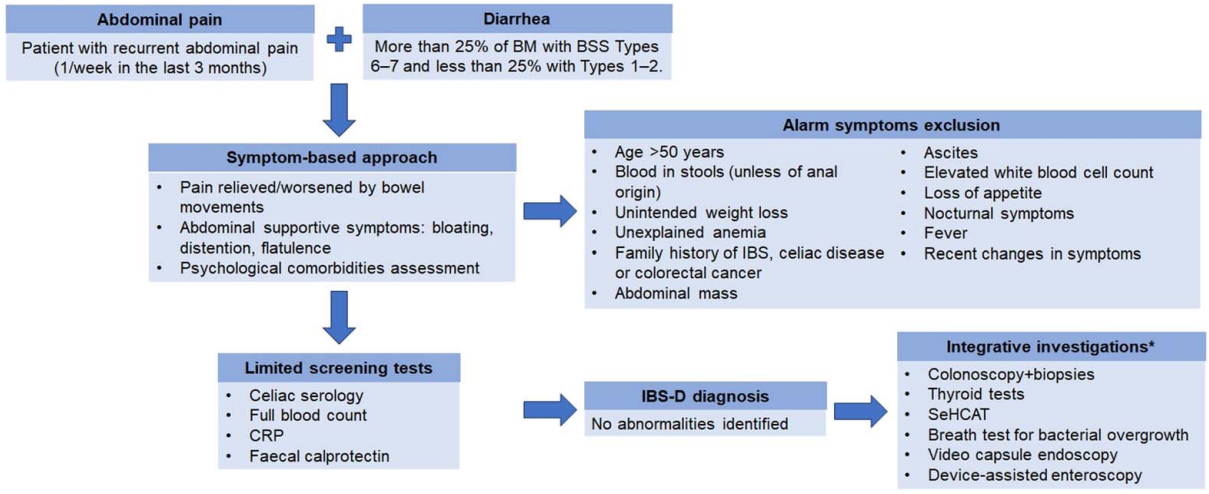

FIGURE 1. Diagnostic flowchart for irritable bowel syndrome with diarrhea. BM indicates bowel movements; CRP, C-reactive protein; IBS-D, irritable bowel syndrome with diarrhea; SeHCAT, 75-selenium homocholic acid taurine test. *Only in selected cases according to clinical suspicion.

probiotics, antispasmodics, and loperamide. Other less common therapies, which are not widely available, sometimes used with an off-label indication and mainly employed as a second-line treatment of IBS-D, include rifaximin, bile acid sequestrants, gut-directed psychological therapies, eluxadolinetricyclic antidepressant, and 5-HT_3 antagonists. Evidence exists for the use of mesalazine and fecal microbiota transplantation (FMT), although additional studies are needed for definitive conclusions regarding their efficacy.

GLOBAL IBS SYMPTOMS

Diet

Most patients with IBS consider their symptoms to be related to food and often automatically avoid some foods. FODMAPs are short-chain carbohydrates that are incompletely absorbed and consequently fermented in the colon where they increase the luminal content of fluids, finally leading to abdominal pain, diarrhea, flatulence, and bloating.[36] Several pooled data analyses have demonstrated the efficacy of a low FODMAP diet in improving global symptoms in IBS patients, especially IBS-D.[37–39] As an example, in the meta-analysis by van Lanen et al,[39] considering studies reporting only patients with IBS-D (n = 6), the irritable bowel syndrome severity scoring system (IBS-SSS) standardized mean difference was −0.62 (95% CI, −0.84 to −0.39, $P = 0.001$) in favor of the low FODMAP diet.

A number of foods have a considerable amount of FODMAPs such as garlic, onions, cow's milk, yogurt, rye, cauliflower, apples, etc. In a systematic review and meta-analysis comparing the efficacy of a gluten-free diet and a low FODMAPs diet in treating symptoms of IBS,[38] there was a significant effect of the latter when compared with a usual diet, while there was only a trend when compared to traditional dietary advice.[40] A recent prospective study compared a low FODMAP diet, a gluten-free diet, and a Mediterranean diet, confirming the superiority of a low FODMAP diet in terms of relief of abdominal pain and diarrhea.[41] On the contrary, a recent trial comparing traditional dietary advice, gluten-free diet, and low FODMAP diet for nonconstipated IBS concluded that despite similar improvements in IBS-SSS, patients reported that traditional dietary advice was cheaper, less time-consuming to shop, and easier to follow when eating out, thus easier to incorporate in everyday life.[42] Indeed, the FODMAP diet is composed of an initial phase of food restriction followed by a gradual reintroduction of foods containing FODMAPs according to the individual tolerability of each of them.[43] Due to the complexity of this dietary regimen, the involvement of an experienced dietician is advised to avoid nutritional deficiencies triggered by long-term extensive food restrictions, difficulties in adherence, and social difficulties.[43–46] However, most of the above-mentioned trials assessed the efficacy of this diet for up to 6 weeks. Other trials[44,46] highlighted the usefulness of a "modified" version of the low FODMAP diet in the long term to improve the compliance of the patients, showing significant improvements in symptoms and quality of life.[44] As FODMAP reintroduction is concerned, a recent study assessed different strategies for fructose reintroduction (2.5, 5, 10, 15 g), concluding that doses higher than 15 g in low FODMAP diet responders should be used to assess tolerance.[47] Moreover, according to a recent cross-over trial, the assessment of IBS severity before the intervention may predict the clinical response to a low FODMAP diet.[48]

As for another diet, gluten ingestion, which is a complex of proteins of wheat, is often associated with patients with IBS symptoms,[49] although its link with IBS has not been clarified yet.[50] A meta-analysis tried to assess the efficacy of a gluten-free diet in IBS and included only 2 randomized controlled trial (RCTs)[38]; when these studies were pooled, the authors failed to find a statistically significant difference in terms of IBS symptoms improvement (risk ratio (RR), 0.42; 95% CI, 0.11-1.55, $I^2 = 88\%$). In addition, the trials reported about patients with different subtypes and not only patients with IBS-D. Other studies suggest that the possible benefits of a gluten-free diet in IBS can be related to a decrease in fructans, which is a wheat-related FODMAP.[51,52]

Probiotics

Probiotics, which are live micro-organisms that when administered in adequate amounts confer a benefit to the host,[53] taken as a group may improve global and certain specific symptoms of IBS according to a systematic review with meta-analysis.[54,55] Meanwhile, an evidence-based

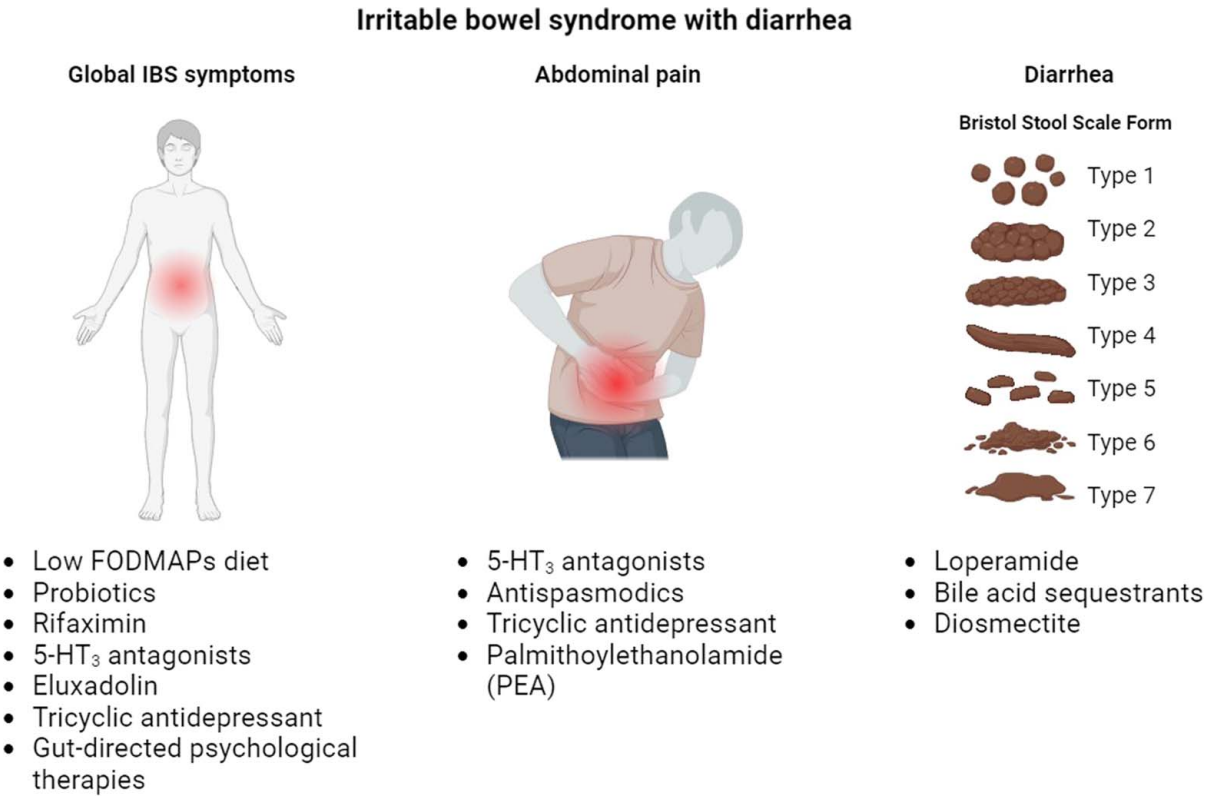

FIGURE 2. Suggested therapies for targeting global symptoms, abdominal pain, and diarrhea in patients with IBS-D.

international consensus reported that probiotics do not improve diarrhea in patients with IBS.[56]

Despite some negative or inconclusive trials with a limited sample size regarding the usefulness of probiotics in IBS-D,[57–59] most of the trials that have been conducted reported their positive effect in this setting. Among studies with a large sample size, only one reported the effect of a specific probiotic formulation (*Lactobacillus acidophilus DDS-1* and *Bifidobacterium lactis UABla-12*) in patients with IBS diagnosed according to Rome IV criteria, concluding that probiotics improved abdominal pain and bowel habits.[60] On the other hand, 4 large studies assessed the effect of probiotics in patients with IBS diagnosed with Rome III criteria, and specifically 2 used live bacteria; a study on 200 patients using a specific probiotic (*Clostridium butyricum*) showed an improvement in overall symptoms, quality of life, and stool frequency,[61] while another study showed an adequate symptom relief by using a multistrain preparation (*Streptococcus thermophilus DSM24731, Bifidobacterium breve DSM24732, Bifidobacterium longum DSM24736, Bifidobacterium infantis DSM24737, L. acidophilus DSM24735, Lactobacillus plantarum DSM24730, Lactobacillus paracasei DSM24733, Lactobacillus delbrueckii* subsp. *Bulgaricus DSM 24734*) as compared with placebo.[62] Among the other 2 large studies, one used a specific strain of heat-inactivated probiotic (*Bifidobacterium bifidum MIMBb75* SYN-HI-001) on 443 patients with IBS (including 178 patients with IBS-D and 34 patients with IBS-M), showing a significant improvement in IBS symptoms according to European Medicines Agency (EMA) endpoints.[63] The second study assessed the effect of a nonviable probiotic lysate (*Escherichia coli DSM17252*and *Enterococcus faecalis DSM16440*), which showed in the posthoc analysis to confer a benefit on patients with IBS-D in terms of abdominal pain response over time and stool consistency, although no differences with placebo have been highlighted for EMA endpoints.[64]

A recent meta-analysis assessing probiotic efficacy in IBS,[65] according to patients with IBS-D included 13 RCTs of combination probiotics that were able to induce an overall improvement of global symptoms (RR, 0.78; 95% CI, 0.67-0.92), while the single strains most studied were all Lactobacillus strains, again with a significant improvement in global symptoms (RR, 0.57; 95% CI, 0.36-0.89).

Therefore, due to the heterogeneity of trials on probiotics in terms of strains used, composition, design, and endpoints,[54,56–63] current guidelines suggest their use in IBS-D taken as a group, without suggesting specific strains or formulations.[11,13]

Rifaximin

Rifaximin is an oral minimally absorbed antibiotic approved by the Food and Drug Administration (FDA) for the treatment of patients with IBS-D. Rifaximin can exert an antibiotic effect through the inhibition of bacterial RNA synthesis,[66] an eubiotic effect promoting commensal bacteria,[67] and an anti-inflammatory effect via a gut-specific activation of pregnane X receptor.[68] Data from the 2 RCTs (TARGET 1 and 2) supporting the use of rifaximin in IBS at a dose of 550 mg 3 times daily for 2 weeks showed an improvement in both abdominal pain and stool consistency in up to 40.8% of patients versus 31.7% for placebo.[69] A subsequent trial assessing the efficacy and safety of rifaximin retreatment in patients' relapsing symptoms of IBS-D

showed that the percentage of responders to FDA-combined primary endpoint was significantly greater with rifaximin than with placebo.[70] Since most patients who initially responded to rifaximin reported symptoms relapse up to 18 weeks after the initial therapeutic course, a subsequent open-label trial confirmed the efficacy of a retreatment of 2 weeks over placebo.[71] A meta-analysis of 5 studies confirmed the efficacy and safety of rifaximin for the treatment of global IBS-D symptoms, with a number needed to treat of 9.[54] As for safety, other studies supported its use due to its negligible systemic absorption and low risk of bacterial infection or development of resistant bacterial strains,[54,72] with a number needed to harm of almost 9000.[73]

5-HT_3 antagonists

5-HT_3 receptors are widely present on intestinal nervous plexuses, sensory, sympathetic, and parasympathetic nerves, and cause smooth muscle contraction and increased intestinal secretion when stimulated. Several 5-HT_3 receptor antagonists have been tested in patients with IBS.[74] Alosetron was first approved by the FDA for the treatment of IBS-D at a dosage of 1 mg b.i.d., since it has been shown to be more effective than placebo in treating both pain and diarrhea, with few side effects such as constipation, nausea, and headache.[75] After reports of ischemic colitis,[76] it was withdrawn from the market and then reintroduced 0.5 mg b.i.d. only for women with severe IBS-D lasting $\geq$6 months.[76] Ramosetron yielded similar positive results on IBS-D, with few reports of constipation as a side effect,[77] and it is licensed only in Asia at a dosage of 2.5 mcg o.d. in women and 5 mcg o.d. in men.[78] A recent network meta-analysis including 3 RCTs assessing the efficacy of alosetron and one for ramosetron concluded that alosetron at 1 mg b.i.d. was more effective than ramosetron, eluxadolin, and rifaximin for the treatment of patients with IBS.[77] However, both 5-HT_3 antagonists were associated with a higher rate of adverse effects compared to placebo, such as constipation.[77] Finally, ondansetron was the first 5-HT_3 antagonist tested in functional bowel disorders and is actually not licensed for IBS-D.[79–81] However, its use has been tested from 4 mg o.i.d. to 8 mg t.i.d or using a 12 mg o.i.d. bimodal release formulation leading to ameliorations in terms of urgency and diarrhea, but not abdominal pain.[82,83] Recently a 12-week parallel group RCT of ondansetron 4 mg o.d. (titrated up to 8 mg t.d.s.) has been carried out on 80 patients with IBS-D.[84] Unfortunately, no differences were highlighted for ondansetron when compared to placebo for the FDA endpoint, while it was able to improve stool consistency (adjusted mean difference, −0.7; 95% CI, −1.0 to −0.3) and increase the whole gut transit time between baseline and week 12 when compared with placebo. Pooling together this trial with other two previous trials, the authors demonstrated that ondansetron was superior to placebo for the FDA composite endpoint (RR of symptoms not responding, 0.86; 95% CI, 0.75-0.98, number needed to treat, 9) and stool response (RR, 0.65; 95% CI, 0.52-0.82, number needed to treat, 5), but not for abdominal pain response (RR, 0.95; 95% CI, 0.74-1.20).[84]

Eluxadoline

Eluxadoline is a μ-opioid receptor agonist, a δ-opioid receptor antagonist, and a κ-opioid receptor agonist.[85] Its efficacy in IBS-D is supported by 2 multicentric double-blind placebo-controlled RCTs (IBS-3001 and IBS-3002) including 2428 patients, where eluxadoline reached FDA and EMA endpoints.[85] These studies consisted of a 26-week study period and 26 weeks of follow-up and showed that only the100 mg eluxadoline formulation was able to have a significant effect in terms of FDA and EMA endpoints, while the 75 mg formulation reached efficacy only for FDA criteria,[85] other than ameliorating stool consistency, frequency, urgency, adequate relief of IBS symptoms, global symptom scores, and scores on IBS-quality of life questionnaires. Besides mild adverse events such as nausea, constipation, and abdominal pain,[85] acute pancreatitis represents a dreaded complication with more than 120 reports to the FDA, occurring mostly in patients with previous cholecystectomy.[86] Therefore, FDA and EMA contraindicate its use in these patients and those with alcoholism, excessive alcohol use, and sphincter of Oddi spasm.[86–88] However, to date, this drug is available only in the United States and Canada and is approved for the treatment of patients with IBS-D who have failed other therapies. Indeed, a posthoc analysis of the above-mentioned trials and a subsequent study confirmed its safety and efficacy up to 52 weeks of treatment in patients with IBS-D not responding to loperamide,[89,90] while a recent study reported its efficacy also on patients with IBS-D with concurrent bile acid diarrhea.[91] Finally, an updated meta-analysis of 42 trials performed a head-to-head comparison of eluxadoline with antispasmodics and concluded that eluxadoline was at least as effective as antispasmodics, but due to the higher amount of adverse events reported, antispasmodics still represent the first choice for the treatment of IBS-D.[92]

ABDOMINAL PAIN

Antispasmodics

Antispasmodic agents can ameliorate abdominal pain through intestinal smooth muscle relaxation.[93] Among antispasmodics, peppermint oil is a well-tolerated and effective therapy for pain and global symptoms in adults with IBS according to a meta-analysis of 12 randomized controlled trials including 835 patients with IBS.[94] Of note, another recent network meta-analysis[95] found that peppermint oil ranked first for efficacy for global symptoms when compared to other therapies for IBS.[95] However, more recently, the trial PERSUADE assessing small-intestinal release or ileocolonic release of peppermint oil showed that using the strict FDA and EMA endpoints, no significant reduction in overall symptom relief or abdominal pain was noted for both the preparations.[96] Recently, other formulations of essential oils were tested for IBS with promising results.[97,98] Otilonium bromide is a calcium channel blocker acting on the smooth muscle cells thus exerting a spasmolytic action. In a pooled analysis, otilonium bromide was more effective than placebo in improving abdominal pain in patients with IBS with a significant therapeutic effect after 10 weeks of treatment and a maximal effect after 15 weeks.[99] However, no significant changes were observed in stool frequency and consistency.[99] Hyoscine butylbromide is an anticholinergic and antimuscarinic agent able to relieve global IBS symptoms according to a pooled analysis including 426 patients.[100] Among antispasmodics showing promising results, pinaverium bromide is a calcium channel blocker able to improve abdominal pain and Bristol stool form scale scores after just 4 weeks of treatment in up to 77.5% of patients according to a randomized trial, although there were no significant differences in stool consistency and frequency when compared with placebo.[101] Alverine citrate is a nonatropinic papaverine-like musculotropic antispasmodic agent that is able to improve abdominal pain in patients with IBS but not stool consistency,[102,103] although an earlier trial failed to show its

efficacy.[104] Finally, mebeverine is another antispasmodic that was shown to be ineffective for the treatment of global symptoms of IBS when compared with a placebo according to a systematic review of 8 randomized trials,[105] and therefore its use is not recommended for patients with IBS.

Antidepressant

Among antidepressants, tricyclic antidepressants (TCAs, amitriptyline, nortriptyline, imipramine, and desipramine) are neuromodulators acting through 5-HT and noradrenaline reuptake inhibition, thus reducing psychological symptoms and improving visceral and central pain.[106,107] In addition, TCAs can slow transit and have antidiarrheal actions due to their anticholinergic effects.[106] The efficacy of TCAs for the treatment of global IBS symptoms and abdominal pain alone has been investigated in several studies which have been pooled in a meta-analysis including a total of 787 patients within 12 RCTs (RR, 0.65; 95% CI, 0.55-0.77).[108] In another more recent network meta-analysis, TCAs were confirmed to be more efficacious than placebo after 4 to 12 weeks of treatment (0.66, 0.53-0.83) and were ranked second compared to antispasmodics and soluble fibers for the global IBS symptoms relief and first for the improvement of abdominal pain alone.[109] A recent large RCT (ATLANTIS trial) performed on 463 patients with IBS (of whom 181 patients with IBS-D and 191 patients with IBS with mixed stool pattern) showed that amitriptyline starting at low-dose and titrated was safe, well-tolerated, and superior to placebo as a second-line treatment for IBS in primary care across multiple outcomes.[110] Limited data are available regarding the effect of TCAs on the stool pattern since many trials were performed regardless of the stool pattern.[111] In the only trial on selected patients with IBS-D,[111] amitriptyline was able to ameliorate the number of loose stools and the feeling of incomplete defecation, as also confirmed by another observational study reporting an inhibition of bowel motility and slow transit due to a prolongation of colonic transit time and an improvement in stool consistency and fecal incontinence.[112] Side effects of this therapy are generally mild and include drowsiness and dry mouth, other than a few cases of insomnia, constipation, urinary retention, flushing, palpitations, and decreased appetite.[108] Among other antidepressants, selective serotonin reuptake inhibitors (citalopram, fluoxetine, paroxetine) increase tissue 5-HT, therefore exerting a prokinetic and prosecretory effect.[106,107] A recent network meta-analysis assessing different therapeutic options for IBS included 6 trials using selective serotonin reuptake inhibitors[109]; it concluded that these drugs have no efficacy over placebo in treating global IBS symptoms and abdominal pain (RR, 0.82, 95% CI, 0.58-1.16), and besides the large heterogeneity between studies included, most of them did not provide details on the effects on diarrhea since they did not provide information on IBS subtypes. Therefore, these drugs are currently not suggested for IBS-D, also due to the significantly greater rate of adverse events over placebo.[108] Selective noradrenaline reuptake inhibitors may be an option for the treatment of abdominal pain in patients with IBS, especially in patients who failed an initial trial of TCAs (ie, duloxetine 30 to 90 mg q.d.).[113,114] However, additional evidence is needed to further support the use of selective noradrenaline reuptake inhibitors in IBS-D.

DIARRHEA

Antidiarrheal Drugs

Antidiarrheal drugs are agents able to decrease stool frequency, improve stool consistency, or reduce stool weight. Loperamide and diphenoxylate are opiate receptor agonists able to bind μ-opioid receptors in the enteric nervous system and sensory afferents leading to the reduction of peristalsis, intestinal transit, and inhibiting intestinal secretion. A meta-analysis of RCTs assessing the effect of loperamide in IBS-D showed no efficacy in improving global IBS-D symptoms,[115,116] while there was an improvement in stool frequency and consistency, as also suggested by another study which additionally highlighted a positive effect on the incidence of urgency.[117] However, according to eluxadoline trials, 61% of patients taking loperamide reported an inadequate control of IBS-D symptoms,[89] other than being associated with side effects such as constipation, abdominal pain, and prolonged QTc.[118] Diosmectite is a natural silicate used as an intestinal adsorbent mainly in the treatment of diarrhea, although in some countries it is used also for IBS-D. Indeed, 2 RCTs using diosmectite 3 g t.i.d. over up to 8 weeks, supported its usefulness over placebo.[119,120] Recently, a cross-over trial reported promising results for the use of xyloglucan and xylo-oligosaccharides in IBS-D in terms of normalization of stool consistency, abdominal pain, and bloating.[121] Xyloglucan is a new agent capable of protecting the epithelial mucosal barrier by forming a film, which unfortunately is available only in some European countries.[122]

Bile Acid Sequestrants

About one-fourth of patients with IBS-D have bile acid malabsorption.[34] Treatments able to target bile acid malabsorption include sequestrants such as colestyramine, colestipol, and colesevelam.[123] As a matter of fact, patients with IBS-D with altered SeHCAT tests more frequently respond to colestyramine,[124,125] with an amelioration of diarrhea directly correlated to the severity of malabsorption,[126] which was reported in up to 70% of the patients.[127] Colestipol and colesevelam are additional therapeutic options alternative to cholestyramine that can be used in patients not responding or reporting side effects such as bloating and constipation, with promising results in terms of efficacy and a better profile in terms of tolerability.[126,128] Unfortunately, these drugs are not available in all countries.[129,130] Moreover, a recent small placebo-controlled trial failed to find significant effects of colesevelam on bowel habits in patients with IBS-D and bile acid malabsorption, probably due to the dose and schedule of colesevelam employed.[131]

OTHER THERAPIES

Gut-directed Psychological Therapies

Since psychological symptoms are common in patients with IBS and may concur with symptom generation,[132] a number of studies assessed the effect of gut-directed psychological therapies in these patients, especially IBS-D.[108,133–135] These therapies can be at least as effective as routine treatments for IBS according to a recent meta-analysis.[108,133] Among the more commonly used gut-directed psychological therapies, cognitive behavioral therapy (CBT) and gut-directed hypnotherapy have been shown to be superior to routine care in terms of improvement of abdominal pain, bowel habit, and quality of life.[108,133] Other therapeutic

options within this field are relaxation, mindfulness-based stress reduction, stress management, and psychodynamic therapy. If on one hand trials assessing these therapies often lack blinding and a valid placebo, the main advantage of these therapies relies on the low number of adverse events reported in these studies.[108,133]

Mesalazine

Patients with IBS often present a low-grade inflammation, according to pathophysiological studies highlighting an increase in inflammatory cells in the intestinal mucosa.[136–138] Mesalazine is an anti-inflammatory drug acting locally on colonic mucosa and reducing inflammation through a variety of anti-inflammatory processes, mainly mediated by the activation of peroxisome proliferator-activated receptor-gamma.[139] Two large RCTs[140,141] including patients with IBS and IBS-D and 1 small trial including patients with IBS-D[142] evaluated the effect of a 12-week course of mesalazine, concluding that this therapy was not superior to placebo for the amelioration of abdominal pain, bloating, or defecation frequency, although patients with postinfection IBS were those most likely responding to mesalazine. However, a recent updated meta-analysis pooling a total of 8 RCTs and 820 patients concluded that mesalazine was more efficacious than placebo for global IBS symptoms (RR of global symptoms not improving, 0.86; 95% CI, 0.79-0.95; number needed to treat, 10; 95% CI, 6-27), but not for abdominal pain or bowel habit or stool frequency; interestingly, subanalyses according to IBS subtype demonstrated efficacy for global IBS symptoms only for IBS-D (RR, 0.88; 95% CI, 0.79-0.99).[65]

FMT

FMT, which is the transfer of the intestinal microbiota from a healthy donor into the gastrointestinal tract of a patient with dysbiosis, has been investigated in the setting of IBS in the last decade,[143] to restore and target dysbiosis associated with IBS.[144] Two different meta-analyses on the use of FMT in IBS reported discordant results: Myneedu and colleagues failed to find a significant effect of FMT over control (RR, 0.93; 95% CI, 0.50-1.75), whereas Ianiro and colleagues confirmed the absence of a significant effect of FMT (RR, 0.98; 95% CI, 0.58-1.66) but also observed that FMT via colonoscopy was superior to placebo, although only 2 trials were included in this subanalysis. This heterogeneity among trials can be explained by the variety of routes of administration, formulations, and the number and type of donors.[145] Recently, another large trial on FMT via the upper gastrointestinal tract using different amounts of feces (30 and 60 g) from a super-donor found that this therapy was more effective than placebo (autologous FMT) according to FDA and EMA endpoints,[146] with a persistent response to therapy after 3 months from FMT in more than 75% of patients. Nevertheless, due to the heterogeneity between studies and the limitations highlighted in trials and their design, further studies are needed to understand the efficacy of FMT in IBS.

Nutraceuticals and Other Antidiarrheal Drugs

Several nutraceuticals and drugs have been preliminary tested in the context of IBS-D or merely to treat diarrhea, with different mechanisms of action, although most of them are not embraced under specific recommendations of international guidelines.[13,55,147] For the treatment of global IBS symptoms, for example, glutamine is an essential amino acid and its depletion has been associated with intestinal hyperpermeability. Glutamine supplementation can restore permeability and decrease bacterial and toxin translocation. In a recent double-blind RCT, patients with postinfection IBS-D were randomized to glutamine (5 g/t.i.d.) or placebo for 8 weeks: 79.6% of patients in the glutamine group and 5.8% in the placebo group achieved the primary endpoint (ie, a reduction of >50 points in the IBS-SSS score). Specifically, the authors found a reduction in daily bowel movement frequency and an amelioration in the Bristol Stool Scale.[148] Another recent double-blind RCT showed that adding glutamine supplementation (15 g/d) to a low FODMAP diet can lead to an amelioration of IBS symptoms compared to diet alone.[149] For the treatment of abdominal pain, palmithoylethanolamide, structurally related to the endocannabinoid anandamide, and polydatin are dietary compounds that act synergistically to reduce mast cell activation. In a double-blind RCT multicenter trial, palmithoylethanolamide/polydatin 200 mg/20 mg b.i.d. was able to improve abdominal pain severity compared with placebo.[150] For the treatment of diarrhea, other small trials have reported a possible role of low doses of clonidine[151,152] and the antisecretory racecadotril,[153] which however should be further confirmed.

CONCLUSIONS

A number of therapeutic options are nowadays available for the treatment of IBS-D. Clinicians should therefore carefully phenotype patients' gastrointestinal and extra-intestinal symptoms to differently target alone or in combination dysbiosis, low-grade inflammation, altered motor function, visceral pain, and overlapping diseases, by combining drugs useful for the global symptom relief or targeting only abdominal pain or diarrhea. Low FODMAPs diet, probiotics, antispasmodic, and loperamide are often used for the initial management of these patients. Additional therapeutic options include rifaximin, 5-HT_3 antagonists, gut-directed psychological therapies, eluxadoline, TCAs, and bile acid sequestrants; these latter when a bile acid malabsorption is confirmed or suspected. Further studies are needed to ascertain the therapeutic role of nutraceuticals, mesalazine, and FMT for the treatment of patients with IBS-D.

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