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REVIEW

An evidence-based update on the diagnosis and management of irritable bowel syndrome

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ABSTRACT

Introduction: Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction affecting 5% of the population. The cardinal symptoms are abdominal pain and altered stool form or frequency.

Areas covered: Diagnosis and management of IBS. We searched the literature for diagnostic accuracy studies, randomized controlled trials, and meta-analyses. A positive diagnosis of IBS, alongside testing to exclude celiac disease, is recommended. Exhaustive investigation has a low yield. Patients should be offered traditional dietary advice. If response is incomplete, specialist dietetic guidance should be considered. Probiotics may be beneficial, but quality of evidence is poor. First-line treatment of constipation is with laxatives, with secretagogues used where these are ineffective. Anti-diarrheal drugs should be used first-line for diarrhea, with second-line drugs including 5-hydroxytryptamine-3 antagonists, eluxadoline, or rifaximin, where available. First-line treatment of abdominal pain should be with antispasmodics, with gut-brain neuromodulators prescribed second-line. Low-dose tricyclic antidepressants, such as amitriptyline, are preferred. Brain-gut behavioral therapies are effective and have evidence for efficacy in patients refractory to standard therapies.

Expert opinion: Despite substantial advances, there remains scope for improvement in terms of both the diagnosis and management of IBS. Reinforcement of positive diagnostic strategies for the condition and novel treatment paradigms are required.

PLAIN LANGUAGE SUMMARY

Irritable bowel syndrome (IBS) is a condition where people experience abdominal pain together with abnormalities in either stool frequency or consistency. It affects 1 in 20 people worldwide and, for most people, is a chronic condition. IBS can be diagnosed safely based on the symptoms reported by the patient, but all patients should have testing to rule out celiac disease and those with diarrhea should be investigated to make sure they do not have inflammatory bowel disease. Treatment of IBS is usually with dietary and lifestyle advice initially. Where this does not lead to an improvement in symptoms, then treatment based on the main stool abnormality, or aimed at improving abdominal pain, or both, is usual. This includes laxatives for constipation, anti-diarrheal drugs for diarrhea, and antispasmodics for abdominal pain. If these do not work, there are newer drugs that can treat constipation or diarrhea, and pain-modifying drugs can be used to treat abdominal pain. For people who still experience symptoms despite these measures, treatments such as cognitive behavioral therapy or hypnotherapy, which have been developed specially for IBS, can be considered. In the future, personalized treatment may be achievable by considering the wider impact of symptoms of IBS, not just on the gut, but also on the brain and other organs.

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KEYWORDS
Irritable bowel syndrome; abdominal pain; diarrhea; constipation; diagnosis; randomized controlled trial

1. Introduction

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction [1,2], characterized by abdominal pain associated with a change in stool frequency or form. Patients with IBS are subtyped according to their predominant bowel habit into those with constipation (IBS-C), diarrhea (IBS-D), or mixed bowel habits (IBS-M), or those meeting criteria for none of these three, who have IBS-unclassified. The prevalence of IBS in the community is between 5% and 10%, depending on the criteria used to define its presence, and the condition is commoner in women and younger individuals [3,4]. There is little geographical variation in prevalence [3,4], but data for some regions are sparse. Although the prevalence of IBS remains stable over time [5], the predominant stool pattern reported by the patient may change during longitudinal follow-up in up to one-third of patients [6]. IBS represents a substantial financial burden to society due to the direct costs associated with managing the condition as well as indirect costs arising from absenteeism and presenteeism due to symptoms [7,8]. Quality of life of patients with IBS is impaired to a similar degree to individuals with organic disease, such as stroke or chronic obstructive pulmonary disease [9].

Current guidelines for the management of IBS recommend that, in the absence of red-flag symptoms that may raise concern about serious organic disease, the diagnosis is based on the

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Article highlights

- Although irritable bowel syndrome (IBS) is common, physicians often find it difficult to diagnose.
- Exhaustive investigation to exclude organic gastrointestinal disease is not required in IBS; a positive diagnostic approach with limited testing should be preferred.
- Celiac disease should be excluded in all patients with IBS, irrespective of predominant bowel habit, a fecal calprotectin requested in patients with IBS with diarrhea, and testing for bile acid diarrhea considered in selected patients with IBS with diarrhea.
- Current treatment approaches are based on using drugs to target the predominant abnormality in bowel habit.
- Although efficacious drugs exist, there have been fewer novel drugs brought to market in the last 5 years; repurposing of existing drugs for IBS may, therefore, be useful.
- A new treatment paradigm, which considers the psychological as well as gastrointestinal aspects of IBS, may offer the ability to provide personalized treatment.

clinical history, supplemented by limited judicious investigation [10–14]. This is facilitated by the use of symptom-based diagnostic criteria, with the current gold-standard being the Rome IV criteria [15]. However, in reality, and particularly in primary care where most patients will be managed, many physicians are unfamiliar with these, and few incorporate them into their clinical practice [16]. In addition, despite recommendations that exhaustive investigation is not required to diagnose IBS, a substantial proportion of clinicians still believe it to be a diagnosis of exclusion [17].

The etiology of IBS remains incompletely understood [18]. The most well-recognized trigger for symptoms is an episode of acute gastroenteritis [19], a phenomenon termed post-infection IBS, which is reported by approximately 10% of patients [20]. Genetic factors, altered intestinal barrier function, changes in the intestinal microbiome, abnormal gastrointestinal motility, visceral hypersensitivity, and abnormalities of central pain processing may also be involved in the pathophysiology [18]. However, for most patients there is no single explanation, which means that treating IBS can be difficult, as there is no specific physiological abnormality to target. Conventionally, therefore drugs are targeted at the patient's predominant symptom.

This article will provide an evidence-based update regarding the accuracy of symptom-based diagnostic criteria in making a positive diagnosis of IBS, when to investigate to exclude the organic gastrointestinal diseases that IBS may mimic, and the efficacy of available therapies in the treatment of IBS. As part of this, we searched the literature between 2020 and 2024 inclusive, using MEDLINE and Web of Science, for key updates on the diagnosis and management of IBS, favoring diagnostic accuracy studies, randomized controlled trials (RCTs), and meta-analyses, wherever possible.

2. Diagnosis and investigation of suspected IBS

As in any patient presenting with symptoms for the first time, when consulting with a patient with suspected IBS, the physician needs to take a careful history and perform a physical examination, including digital rectal examination, to exclude organic gastrointestinal disease and identify supportive features for a diagnosis of IBS (Figure 1) [10]. Digital rectal examination is important to identify a rectal mass or dyssynergic defecation [21]. The latter is characterized by paradoxical contraction on rectal examination when the patient strains straining [22]. The symptoms of IBS may mimic some organic gastrointestinal diseases, such as celiac disease, inflammatory bowel disease (IBD), microscopic colitis (MC), bile acid diarrhea (BAD), or even colorectal cancer (CRC). Patients with alarm symptoms, such as weight loss, rectal bleeding, or a recent change in bowel habit to looser stools, require urgent investigation to exclude organic disease, although these perform poorly in predicting a diagnosis of IBD or CRC [23,24].

Current IBS management guidelines advocate the use of symptom-based criteria to make a diagnosis of IBS, in combination with limited investigation [10–14]. Implementing this approach is necessary to avoid over-investigation, which patients with IBS may find anxiety-provoking [25]. Such criteria include the Manning criteria [26], the Kruis scoring system [27], and the current gold standard, the Rome criteria, which were first proposed in 1990 [28]. However, previous studies demonstrated that the Rome criteria did not perform particularly well in terms of predicting a diagnosis of IBS [29,30]. This has led to refinement of the Rome criteria on three subsequent occasions, to date. The current iteration is the Rome IV criteria (Table 1) [15], which consist of abdominal pain occurring on at least 1 day per week over the last 3 months, in association with two or more of the following: related to defecation, associated with a change in stool frequency, or associated with a change in stool form. Symptoms must have been present for at least 6 months to meet these criteria.

In the modifications made to the Rome IV criteria, the term 'abdominal discomfort' was removed from the definition of IBS, as this was felt to be ambiguous in some languages, and the symptom frequency for abdominal pain was increased from a minimum of 3 days per month to 1 day per week [15]. These changes increased the specificity of the Rome IV criteria for a diagnosis of IBS in a validation study conducted by the Rome Foundation [31]. However, this has come at the expense of sensitivity, with a proportion of patients felt by a clinician to have IBS no longer meeting current diagnostic criteria [32]. In addition, the performance of recommended diagnostic criteria should be validated independently to ensure their accuracy if they are to provide reassurance to patients and physicians that the diagnosis of IBS is secure and reduce costs from unnecessary investigation.

An independent validation study examining the performance of the Rome IV criteria compared with Rome III, in over 500 patients referred with suspected IBS to secondary care, confirmed not only that the Rome IV criteria were more specific, but also that they performed better in terms of their agreement with a reference standard of a diagnosis of IBS confirmed by an experienced physician after limited, judicious, investigation [33]. The positive likelihood ratio (LR) of the Rome IV criteria for a diagnosing IBS in this study was 4.82, compared with 2.45 for Rome III criteria. This means a patient with suspected IBS meeting Rome IV criteria is almost five times more likely to have IBS

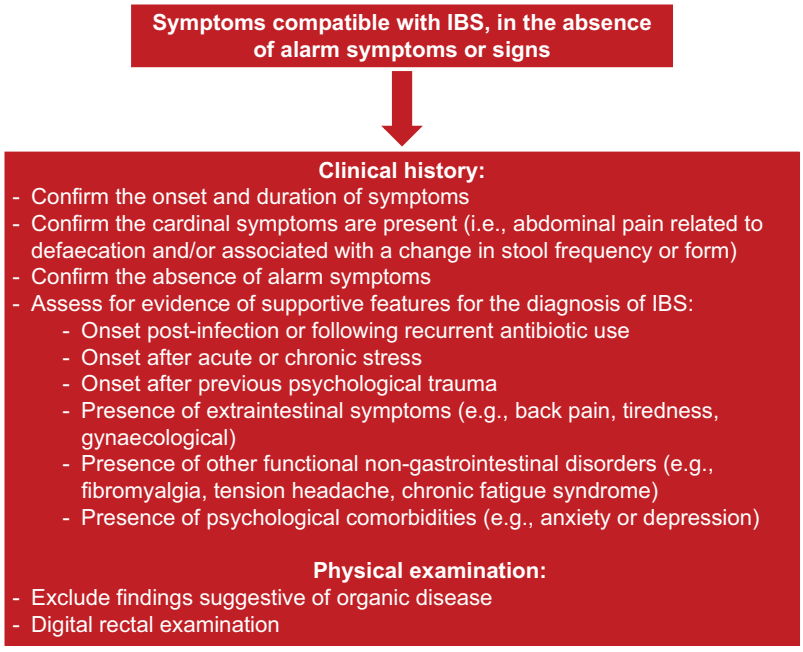

Figure 1. Suggested approach to the initial consultation with the patient with suspected IBS.
Figure adapted from Vasant et al. [10].

Table 1. The Rome IV criteria for irritable bowel syndrome.

Rome IV Diagnostic Criteria for IBS			
1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and associated with two or more or the following: a. Related to defecation; b. Associated with a change in frequency of stool; c. Associated with a change in form of stool. AND 2. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis			
IBS-C	IBS-D	IBS-M	IBS-U
≥25% of bowel movements of Bristol stool form types 1 or 2, and < 25% of Bristol stool form types 6 or 7.	≥25% of bowel movements of Bristol stool form types 6 or 7, and < 25% of Bristol stool form types 1 or 2.	≥25% of bowel movements of Bristol stool form types 1 or 2, and ≥ 25% of bowel movements of Bristol stool form types 6 or 7.	Patients meeting criteria for IBS, but who do not fall into one of the other three subtypes according to Bristol stool form type.

than to have another explanation for their symptoms. The Rome IV criteria performed significantly better in predicting an ultimate diagnosis of IBS-C (positive LR = 25.7) or IBS-M (positive LR = 10.6), compared with IBS-D (positive LR = 2.07). This suggests a missed diagnosis of organic disease is very unlikely in IBS-C or IBS-M. In a 4-year follow-up study of these patients, the miss rate for future organic gastrointestinal disease among those re-referred and re-investigated was only 1%, suggesting a diagnosis of IBS made using the Rome IV criteria after limited investigation was safe and durable, even in those with IBS-D [34].

Despite their improved performance, there is ongoing concern that the Rome IV criteria lead to the selection of a group of patients with both higher gastrointestinal symptom severity and psychological comorbidity [32]. The criteria are due to be updated in 2025 although, at present, it is unclear what changes will be made to them. In a retrospective study examining the diagnostic performance of simple modifications to the Rome IV criteria [35], relaxing the required symptom frequency for abdominal pain back to 3 days per month led to a lower specificity than with the Rome IV criteria, but sensitivity increased, meaning the positive LR remained above 4. Another study applied these modifications to the Rome IV criteria prospectively and their performance was similar [36]. This may, therefore, be a useful change to incorporate in future iterations of the Rome criteria.

In terms of the investigations required to exclude organic gastrointestinal disease in patients with IBS, several studies have examined the role of a panel of blood tests in suspected IBS patients. There are only limited data to support a role for requesting full blood count (FBC), C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR) in all patients [37,38], with only around 1% of patients having an organic gastrointestinal disease detected after investigation based on abnormalities in any of these. However, there is consistent evidence that excluding celiac disease in all individuals with suspected IBS, via serological testing, is worthwhile. In a meta-analysis of observational studies the odds of positive celiac serology were two to three times higher in patients with suspected IBS than in controls without symptoms suggestive of IBS, and the odds of biopsy-confirmed celiac disease was four-fold higher [39].

Fecal calprotectin (FC), which is a noninvasive marker of gastrointestinal inflammation, has enabled the prioritization of

access to colonoscopy for patients with chronic diarrhea in whom IBD is suspected [40]. A normal FC, according to local laboratory values, excludes the possibility of IBD effectively. If elevated, urgent colonoscopy is required to exclude IBD. However, FC can also be elevated in older or obese patients, in infections or malignancy, or by drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPIs). The test should, therefore, be reserved for patients aged less than 45 years. In the patient aged 45 years or over with a new onset change in bowel habit or a features that are suggestive of IBD, a colonoscopy may be unavoidable.

Otherwise, there is a an extremely low yield of colonoscopy in suspected IBS and there is no evidence that a normal colonoscopy reassures patients [25]. In a study performing colonoscopy in 466 patients with IBS-D or IBS-M [41], only two (0.4%) patients were found to have IBD, and only seven (1.5%) patients had MC. The prevalence of the latter increased to 2.3% in patients aged over 45 years. There were no cases of CRC. Although a meta-analysis of observational studies did not demonstrate an increased odds of MC among patients with suspected IBS [42], it is still worthwhile considering colonoscopy to exclude the condition in some patients with chronic diarrhea. In one cross-sectional survey, factors that were associated with MC on random colonic biopsy among patients with suspected IBS-D or functional diarrhea included age over 50 years, coexistent autoimmune disease, nocturnal diarrhea, weight loss, a duration of diarrhea less than 12 months, or recent introduction of a new drug [43]. Potential culprits include NSAIDs, PPIs, statins, or selective serotonin reuptake inhibitors (SSRIs) [44]. In another study, the presence of MC on random colonic biopsy among patients with chronic diarrhea was significantly associated with age of 50 years or more, female sex, NSAID or PPI use, absence of abdominal pain, or weight loss [45]. The authors used these items to construct a scoring system, which was able to predict the presence of MC on colonic biopsy with 90.5% sensitivity. However, whether this scoring system can be used to prioritize access to colonoscopy for patients with a higher degree of suspicion for MC is unclear.

Primary BAD is a condition in which bile acids enter the colon. This leads to accelerated colonic transit, via water and electrolyte secretion. BAD can be diagnosed using 23-seleno-25-homotaurocholic acid (SeHCAT) scanning, with a 7-day threshold of retention of < 15% used to define a positive test. However, SeHCAT may be unavailable in some settings and countries [46]. The treatment of choice is a bile acid sequestrant, such as colestyramine or colesevelam, with response rates to treatment appearing higher at SeHCAT retentions of < 10% or < 5% [47]. Fecal bile acid testing, a serum 7α-hydroxy-4-cholesten-3-one, or a therapeutic trial of a bile acid sequestrant are possible alternatives, although the latter is not recommended because no response to bile acid sequestrants does not exclude BAD and bile acid sequestrants can be tolerated poorly [48]. IBS-D may mimic BAD, with up to one-in-three patients with suspected IBS-D having BAD on diagnostic testing [49,50]. In the aforementioned validation study of the Rome IV criteria for IBS [33], among patients meeting Rome IV criteria the commonest organic gastrointestinal disease detected was BAD, occurring in 14 (3.5%) of the 395 patients when a threshold of < 10% SeHCAT retention at 7 days was used to define its presence. Predictors of primary BAD in patients with IBS-D, other than higher body mass index [51], are lacking. However, the diagnosis should be considered in any patient with suspected IBS-D who reports nocturnal or severe diarrhea, or in anyone who has had a prior cholecystectomy.

It has been proposed that small intestinal bacterial overgrowth (SIBO) may be an organic explanation for a proportion of cases with suspected IBS, and that this condition should be screened for. Studies in patients with IBS have reported a positive test in up to 80% with lactulose-hydrogen breath testing [52], and over 40% with glucose-hydrogen breath testing [53]. However, in a study using jejunal aspirate and culture, which is considered the gold-standard for the diagnosis of SIBO, the prevalence of a positive test was no different in subjects meeting criteria for IBS than among healthy controls [54]. In addition, in another study performing lactulose-hydrogen breath testing and administering a radio-labeled meal simultaneously with the lactulose substrate, the rise in breath hydrogen coincided with the radio-labeled meal entering the cecum in almost 90% of patients with IBS [55]. This suggests that a positive breath test is actually a marker of rapid gastrointestinal transit, rather than a true indicator of SIBO.

In summary, if FBC, C-reactive protein or ESR, celiac serology, and an FC in the patients with suspected IBS-D, are all normal and the Rome IV criteria are met, by far the likeliest diagnosis is IBS. The yield of further investigation to avoid missing an organic gastrointestinal disease will be in the region of 5%, as shown in the previous validation study of the Rome IV criteria [33]. There is no role for testing to exclude SIBO routinely. Further investigation should be dictated by IBS subtype, with the potential for a missed diagnosis highest in those with IBS-D (Figure 2), compared with IBS-C or IBS-M, or older individuals. If there are features or risk factors to suggest the presence of either MC or BAD in a patient with IBS-D, or IBD or CRC in a patient aged 45 years or over, then these should be excluded using the relevant tests. Otherwise, the diagnosis of IBS is secure and is unlikely to change during follow-up or subsequent re-investigation [34]. Irrespective of whether further investigations are required, the patient should be informed that the likeliest diagnosis is IBS and the underlying etiology and natural history should be explained in the context of the gut-brain axis. Treatment can then be directed at the predominant symptom, but it is important to manage expectations by educating the patient that there is no cure for IBS and that treatment is likely to be required in the longer term.

3. Treatment of irritable bowel syndrome

A suggested approach to the treatment of IBS, according to predominant symptom, and line of therapy is provided in Figure 3.

3.1. General measures

3.1.1. Diet and lifestyle

Many patients with IBS identify diet as the main cause of their gastrointestinal symptoms [56], symptoms often occur

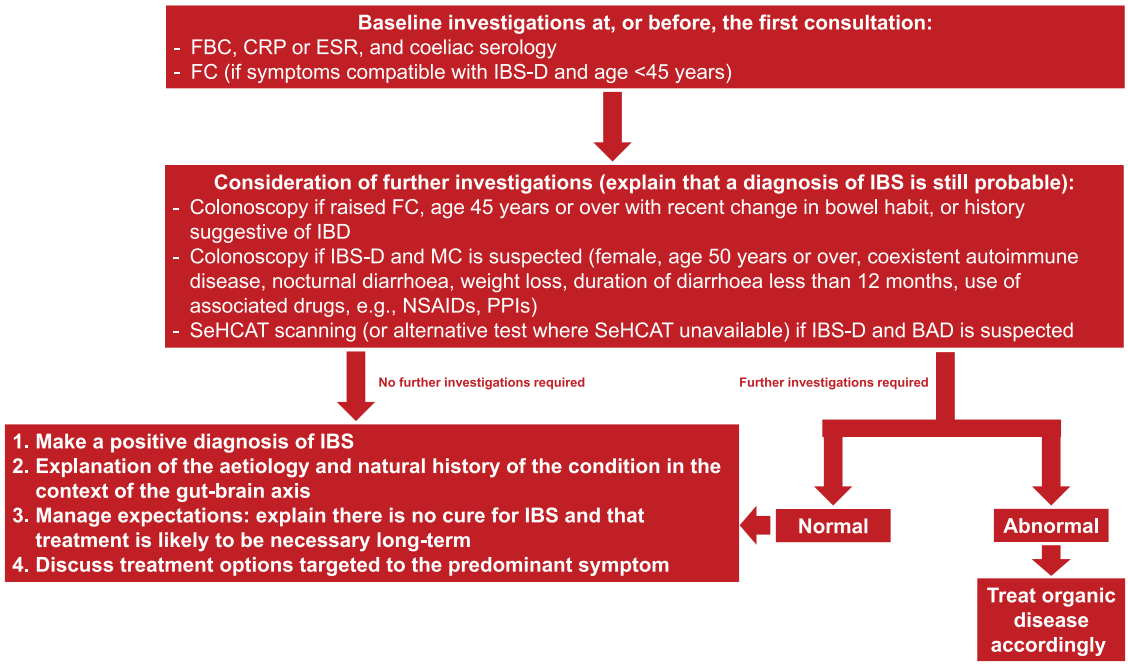

Figure 2. Suggested approach to the investigation of the patient with suspected IBS.
Figure adapted from Vasant *et al.* [10].

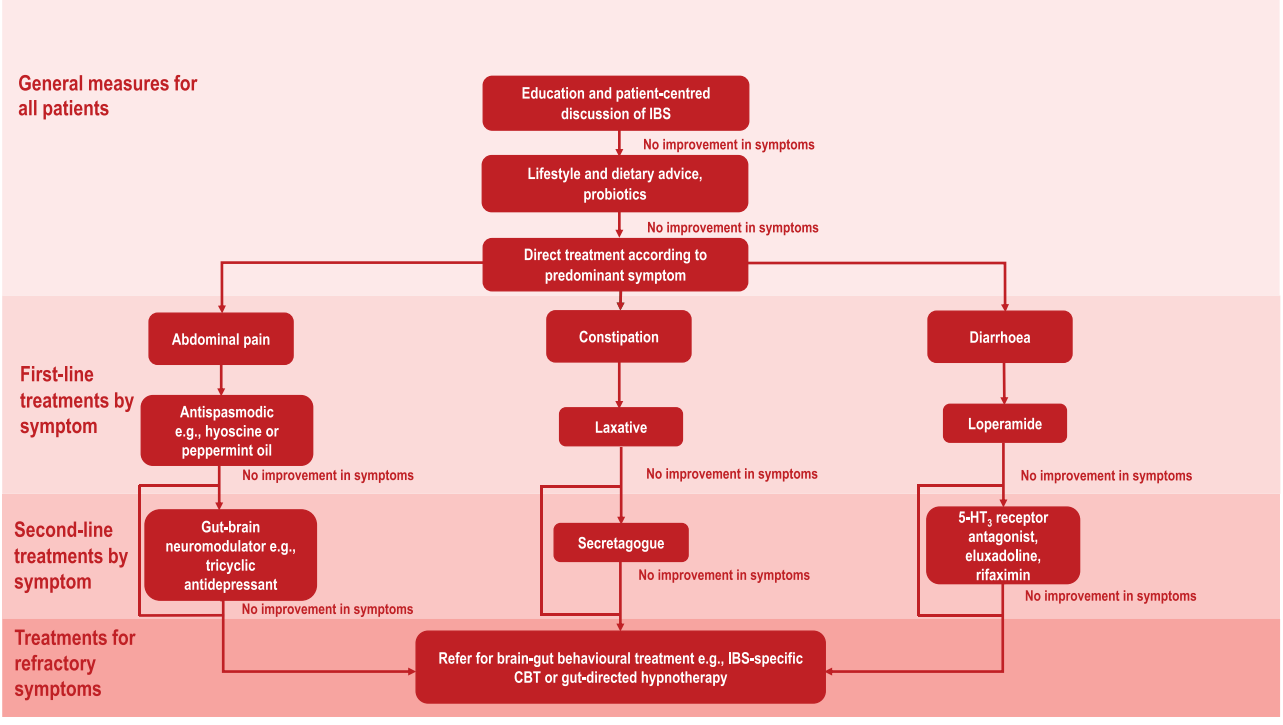

Figure 3. Suggested approach to the treatment of IBS, according to predominant symptom, and line of therapy.
Figure adapted from Vasant *et al.* [10].

postprandially [57], and dietary modification is a cornerstone of managing the condition [10]. Traditional dietary advice provides general recommendations [58], including a focus on eating regular meals, reducing caffeine and alcohol consumption, and maintaining adequate hydration. It offers advice for specific symptoms, such as avoiding sugar-free sweets, gum, and soft drinks containing sorbitol, mannitol, or xylitol in cases of diarrhea, or restricting intake of gas-producing foods like legumes for patients suffering with bloating or flatulence. It also makes recommendations regarding fiber intake, advising patients to increase their consumption if they are constipated, but to reduce it if they have diarrhea.

Fiber can be soluble or insoluble. Insoluble fiber, such as bran, passes through the gut without much in the way of physical transformation, increasing water content and bulking stools, potentially increasing transit times [59]. Soluble fiber, such as ispaghula, forms a gel with water. This may interact with gut bacteria to produce a number of metabolites, such as short-chain fatty acids [60], which may interact with smooth muscle and enteric nerves to influence transit, or have effects via immune-mediated pathways [61]. A previous systematic review and meta-analysis of 14 RCTs containing 906 patients found a benefit in favor of fiber for global IBS symptoms [62]. However, in subgroup analysis, this was confined to trials of ispaghula, with no evidence of efficacy of bran. Fiber can exacerbate abdominal pain, flatulence, and bloating, although these are generally more of an issue with insoluble fiber. Nevertheless, patients should be advised to increase their fiber intake gradually to reduce the likelihood of adverse effects.

If these first-line approaches are ineffective, patients should be referred to a specialist dietitian for consideration of an exclusion diet, of which a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) is the most widely used. These short-chain carbohydrates are slowly absorbed or poorly digested by the small intestine and can cause distension of the intestinal lumen [63]. Restricting their intake might, therefore, improve symptoms of abdominal pain, diarrhea, bloating, and distension, including via mechanisms of reduced colonic fermentation or changes in the gut microbiome [64]. A network meta-analysis identified 13 RCTs of a low FODMAP diet containing 944 patients comparing it with various control interventions, including habitual diet or traditional dietary advice [65]. Regarding improvement in global IBS symptoms, a low FODMAP diet ranked first compared with habitual diet and was superior to all other interventions. A low FODMAP diet ranked first for effects on abdominal pain, abdominal bloating or distention, and bowel habit. It was superior to traditional dietary advice for treating abdominal bloating or distension. Overall, a low FODMAP diet ranked first for all endpoints; however, trials only assessed the effects of FODMAP exclusion and not the subsequent phases of reintroduction and personalization of the diet to tolerance. However, in a study examining blinded FODMAP reintroduction using FODMAP-containing powders, symptom recurrence occurred in 85% of patients with IBS, with fructans and mannitol being the most common triggers [66]. Patterns of symptom recurrence were highly personalized between participants in the study. This highlights the need for further research in this area, and also emphasizes the vital importance of trained dietitians for tailoring the diet to achieve the best outcome for any one individual with IBS [67]. There is emerging evidence that response to a low FODMAP diet might be determined by a patient's microbiome [68], and that microbiome-based artificial intelligence-assisted personalized diets might be more effective than a standard low FODMAP diet [69]. However, as yet, there is little evidence to support the clinical usefulness of microbiome testing in routine practice and warnings have been issued about the potential harms of direct-to-consumer commercialized microbiome tests, which are growing in availability and lack regulatory oversight [70].

A gluten-free diet (GFD) has also been assessed in patients with IBS without celiac disease. In a meta-analysis of two RCTs recruiting individuals who had reported a response to a GFD there was no significant difference between continuing a GFD versus adopting a diet contaminated with gluten [71]. However, these findings might have been influenced by a nocebo effect, where patients anticipated negative consequences with the gluten-challenge, and indeed the importance of this effect has been confirmed in a recent RCT [72]. A Mediterranean diet has also been studied for treatment of IBS and shows some promise [73], although larger studies are needed [74].

A recent RCT compared traditional dietary advice, a low FODMAP diet, and a GFD in non-constipated IBS and found all were similarly efficacious for improving global symptoms [75]. Traditional dietary advice was described as the most patient-friendly intervention with respect to cost and convenience. Another RCT compared 4 weeks treatment with traditional dietary advice in combination with a low FODMAP diet to either a low carbohydrate diet or optimized medical treatment based on predominant IBS symptom [76]. All interventions reduced the severity of IBS symptoms, with larger effects in the dietary intervention groups, although the short duration of the study means that medical therapy was unlikely to have been truly optimized. Overall, the first-line approach for patients with IBS should be traditional dietary advice, with assessment by a specialist dietitian regarding suitability for an exclusion diet reserved as a second-line approach in those with persistent symptoms.

3.1.2. Probiotics

The definition of probiotics encompasses 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [77]. Interest in their use for treating IBS stems in part from some studies demonstrating changes in the intestinal microbiota of IBS patients compared with controls [78,79], and because post-infection IBS occurring after an acute enteric infection is well-recognized and common [19]. Certain probiotics have been shown to attenuate visceral hypersensitivity in mouse models of IBS [80], and others to reduce levels of pro-inflammatory cytokines in patients with IBS [81].

A systematic review and meta-analysis of 82 RCTs, containing 10,332 patients, comparing probiotics with placebo for IBS [82]. Overall, there was evidence of a benefit favoring probiotics compared with placebo for treating global IBS symptoms, abdominal pain, and abdominal bloating or distension. However, the level of certainty in the evidence for each of these endpoints was very low, with significant heterogeneity between studies in each analysis, as well as evidence of possible publication bias. Importantly, of the 82 included studies, there were only 24 at low risk of bias.

Regarding the evidence for specific species or strains, there was a benefit of *Escherichia* strains, with moderate certainty in the evidence, *Lactobacillus* strains and particularly *Lactobacillus plantarum* 299 V, with low certainty, and some combination probiotics or strains of *Bacillus*, with very low certainty, for global IBS symptoms [82]. *Saccharomyces cerevisiae* I-3856 and *Bifidobacterium*

strains had a benefit for treating abdominal pain, with low certainty in the evidence, and there was a benefit of combination probiotics, *Lactobacillus*, *Saccharomyces*, or *Bacillus* strains, but with very low certainty [82]. With respect to abdominal bloating or distension, there was a benefit of combination probiotics or *Bacillus* strains, but with very low certainty in the evidence [82].

Overall, some combination probiotics and specific strains may be beneficial for treating IBS, but confidence in the available evidence is low to very low across all symptom endpoints. Patients wishing to try probiotics for managing IBS symptoms could be advised to do so for up to 12 weeks, but they should be made aware that the underlying evidence for this approach is poor. Larger, rigorously conducted RCTs of probiotics for treating IBS are required.

3.2. Treating constipation

3.2.1. Laxatives

Laxatives are widely available both on prescription and over-the-counter and they are commonly used to treat constipation. However, there are only two small trials of the osmotic laxative polyethylene glycol (PEG) in IBS-C. In one study, 42 patients with IBS-C were randomized to receive either PEG or placebo for 30 days [83]. Both interventions led to relief of IBS symptoms and increased number of bowel movements, with no difference between trial arms. However, in the second study of 139 patients with IBS-C, the number of spontaneous bowel movements increased significantly with 4 weeks of PEG compared with placebo, although there was no benefit for abdominal pain or bloating [84]. Overall, there is more evidence for laxatives in studies of chronic idiopathic constipation (CIC) [85,86]. CIC is a DGBI which, like IBS-C, is defined by the presence of hard or infrequent stools. The two conditions differ only in the frequency of abdominal pain, which occurs at least one day per week with IBS-C, and less frequently than this in CIC [15]. It is, therefore, reasonable to extrapolate available data from CIC to make a stronger case for the use of laxatives in IBS-C. When considered alongside the fact that laxatives are safe and relatively inexpensive, their use as a first-line treatment for IBS-C is appropriate, with second-line agents reserved for patients reporting a suboptimal response to laxatives.

3.2.2. Secretagogues

Secretagogues activate ion channels within the epithelium of intestinal mucosa. This increases electrolyte concentrations and water content within the gut lumen. This softens stools and accelerates gastrointestinal transit to relieve constipation. Lubiprostone was one of the first secretagogues to be developed. It is a prostaglandin E_1 derivative activating chloride type-2 channels, which are found on the apical surface of the intestinal enterocyte. Two placebo-controlled trials evaluating the efficacy of lubiprostone 8 mcg twice daily for IBS-C have been conducted, recruiting a total of 1,171 patients [87]. There was a significantly higher proportion of patients reporting moderate or significant relief of IBS symptoms with lubiprostone in both trials. However, nausea was common, reported by 8% of patients.

Linaclotide and plecanatide are agonists of the guanylate cyclase-C receptor. Their efficacy has been evaluated in trials using the FDA-recommended composite endpoint for treatment trials in IBS-C of an improvement in both abdominal pain and stool frequency. Two North American RCTs demonstrated that both 12 weeks and 26 weeks of linaclotide 290 mcg once daily were superior to placebo [88,89]. Plecanatide 3 mg and 6 mg once daily were also both superior to placebo for IBS-C, with no difference in efficacy between doses, in two RCTs recruiting a total of 2,189 patients [90]. Diarrhea was the most commonly reported adverse event for both drugs.

Tenapanor inhibits sodium uptake from the intestine selectively via the sodium-hydrogen-exchanger-3. A 12-week trial compared tenapanor 50 mg twice daily with placebo in 629 patients with IBS-C and assessed efficacy according to the FDA-recommended composite endpoint [91]. Tenapanor was significantly more efficacious than placebo and, again, diarrhea was the main adverse event reported in the trial.

None of these secretagogues have been compared head-to-head, but their relative efficacy has been assessed in a network meta-analysis [92]. Overall, efficacy was similar for most drugs and doses, and all were superior to placebo, but linaclotide ranked first for efficacy based on the FDA-recommended composite endpoint, and endpoints evaluating abdominal pain response, and increase in complete spontaneous bowel movements, separately. Secretagogues should be used in patients with IBS-C who report inadequate relief following first-line treatment with laxatives, although these drugs are not universally available.

3.3. Treating diarrhoea

3.3.1. Opioid receptor drugs

Anti-diarrhoeals, such as loperamide, are relatively safe and available over the counter. However, their use in individuals with IBS-D or those with an alternating bowel habit has not been well-studied. There have been only two RCTs, conducted in Scandinavia, containing less than 50 patients [93,94]. There was a statistically significant improvement in both frequency and form of stool following therapy but, unfortunately, loperamide did not appear to have any effect on global IBS symptoms in one RCT [94]. In the other study there was a statistically significant improvement in abdominal pain following 13 weeks of loperamide therapy [93]. Pooled analysis of trial data from demonstrated no significant benefit of loperamide for global IBS symptoms over placebo [95]. Despite the fact that available data are conflicting, these drugs may still be useful to improve diarrhea in individuals with IBS, although patients may be dissatisfied with the results [96].

Eluxadoline is a mixed opioid receptor drug. Like loperamide, eluxadoline is an agonist of μ-opioid receptors in the intestine, reducing gut motility and chloride secretion to treat diarrhea, but it also antagonizes δ-opioid receptors thereby treating abdominal pain, whilst minimizing the risk of constipation as a side effect [97]. Eluxadoline has been evaluated in two placebo-controlled trials recruiting over 2400 patients [98]. The primary endpoint was an FDA-recommended composite of improvement in both abdominal pain and stool consistency. Eluxadoline 75 mg twice daily and 100 mg twice

daily were superior to placebo in both trials, although the clinical difference between response rates was modest overall. Eluxadoline has also been shown to be significantly more efficacious than placebo in a cohort of patients with IBS-D who reported inadequate symptom relief with loperamide [96]. Eluxadoline should be considered for those patients who do not respond to first-line treatments for diarrhea, including loperamide, but its availability is limited having been withdrawn in many countries, due to safety concerns including sphincter of Oddi spasm. However, in a network meta-analysis comparing the efficacy of licensed drugs for IBS-D and IBS-M, eluxadoline ranked in third place behind 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists, such as alosetron, which might therefore be the preferred second-line drug for diarrhea in IBS, where available [99].

3.3.2. 5-HT_3 receptor antagonists

5-HT, or serotonin, is involved in both motility and sensation in the gastrointestinal tract. Some studies have shown abnormal levels of 5-HT in patients with IBS [100,101]. Drugs that antagonize the 5-HT_3 receptor, such as alosetron, were first tested in IBS-D in the 1990s. Alosetron was effective, particularly in women, but was associated with a small excess of serious adverse events, including cases of ischemic colitis or severe constipation [102]. The drug was, therefore, withdrawn by the manufacturer, but is now available at a lower dose on a restricted use basis in the U.S.A., although only for women with severe IBS-D. Observational data from almost 2000 patients treated with alosetron 1 mg twice-daily since it was reintroduced suggest it is safe and effective [103], and rates of ischemic colitis and severe constipation have been estimated at 1.03 per 1000 patient years [104], and 0.25 per 1000 patient years [105], respectively.

A systematic review and meta-analyses examining the efficacy of alosetron pooled the results of eight placebo-controlled trials, containing almost 5000 patients with IBS [106]. Alosetron was more effective than placebo, although there was statistically significant heterogeneity between trial results. Side effects occurred more commonly with alosetron than with placebo. In addition, constipation was significantly more likely in those receiving alosetron. There were four cases of ischemic colitis reported in these trials.

Ramosetron, another 5-HT_3 receptor antagonist, is also effective for treating IBS-D [107], and does not have the safety concerns associated with alosetron. However, it is unavailable outside Japan and selected Southeast Asian countries, including India. In a systematic review and meta-analysis of six RCTs of ramosetron, encompassing 2552 patients with IBS [107], ramosetron was more effective than control interventions for improving global symptoms and there was no significant difference in adverse event rates.

Compared with alosetron and ramosetron, ondansetron, which is another 5-HT_3 antagonist, is available in many countries and has a good safety record. Results from three RCTs, involving 327 patients, confirm ondansetron is an effective treatment for diarrhea in IBS, improving stool consistency and reducing days with loose stools and urgency, although it does not appear to improve abdominal pain [108].

In a network meta-analysis of drugs for IBS-D or IBS-M that compared 5-HT_3 antagonists with eluxadoline and rifaximin, all drugs were more effective than placebo, but alosetron and ramosetron appeared to be the most effective [99]. Alosetron 1 mg twice-daily ranked first for efficacy, based on the FDA-recommended composite endpoint of improvement in abdominal pain and stool consistency, effect on global symptoms, and effect on stool consistency. Ramosetron 2.5 mcg once-daily ranked first for effect on abdominal pain and second for both the FDA composite endpoint and global symptom endpoint. The addition of the FDA composite endpoint data from trials of ondansetron saw it rank third for this endpoint, suggesting a class effect of 5-HT_3 antagonists for treating IBS-D [109]. Where available, these drugs should be reserved for patients who do not respond to first-line treatments.

3.3.3. Rifaximin

Rifaximin, which is a minimally absorbed antibiotic, has been evaluated in IBS-D or IBS-M. Its use is based on the premise that an abnormal gut microbiome and SIBO might be involved in the etiology of symptoms in some patients [110]. However, evidence for the latter is generally of poor quality and the SIBO hypothesis in IBS has lately been called into question [111], with positive breath tests often reflecting rapid small intestinal transit and fermentation of the test meal in the cecum by normal colonic bacteria [55].

The efficacy of rifaximin for treating IBS has been demonstrated in two large RCTs, each recruiting almost 600 patients [112]. The primary endpoint was adequate relief of global symptoms of IBS for 2 out of the first 4 weeks after a 2-week course of the drug at a dose of 500 mg three times daily. Rifaximin was more efficacious than placebo. However, the therapeutic gain over placebo was only modest, at around 8%. A re-treatment trial was subsequently conducted and 2,579 patients with IBS-D received open-label rifaximin for 2 weeks [113]. Of these, 636 patients responded but relapsed. They were then randomized to receive up to two further 2-week courses of rifaximin or placebo, 10 weeks apart. Following the first 2-week course, 33% responded with rifaximin compared with 25% with placebo. After the second course the difference in response rates was similar but, in both cases, the therapeutic gain of rifaximin over placebo was, again, modest. Rifaximin is only licensed for the treatment of IBS in North America and in the aforementioned network meta-analysis of drugs for IBS-D or IBS-M it ranked in last place behind 5-HT_3 receptor antagonists and eluxadoline [99].

3.4. Treating abdominal pain

3.4.1. Antispasmodic drugs and Peppermint oil

Abdominal pain in IBS is thought to result from a combination of dysmotility and visceral hypersensitivity [114,115]. Consequently, medications that relax intestinal smooth muscle, such as antispasmodic drugs, might relieve gastrointestinal spasm and improve pain. A systematic review and meta-analysis identified 22 placebo-controlled trials of 12 different antispasmodics in IBS [116]. When data were pooled, there

was a beneficial effect of this class of drugs on global IBS symptoms or abdominal pain, but there was significant heterogeneity between studies. Adverse events, including dizziness, dry mouth, and blurred vision were significantly more common with antispasmodics. Some drugs included in the analysis, such as otilonium and pinaverium, are unavailable in many countries. However, the best evidence appeared to exist for the use of hyoscine, which is widely available, in three RCTs containing over 400 patients, with no heterogeneity between studies [116]. Of note, neither mebeverine nor alverine, which are commonly used treatments, were more efficacious than placebo, although conclusions were based on data from a single small trial for each drug.

Peppermint oil may have similar effects to antispasmodics by antagonizing calcium receptors in the smooth muscle of the gastrointestinal tract, thereby reducing contractility. A recent systematic review and meta-analysis pooled data from 10 RCTs of peppermint oil for IBS [117]. Peppermint oil was more efficacious than placebo for improving both global symptoms and abdominal pain. Adverse events were more common with peppermint oil, although most were mild and included symptoms of dyspepsia, gastro-esophageal reflux, and flatulence. Overall, the quality of included evidence was low and there was heterogeneity in the analyses with wider uncertainty around effect sizes compared with a previous meta-analysis [116]. This primarily reflected the inclusion of two newer trials [118,119], conducted using more rigorous endpoints and more stringent definitions of IBS, neither of which showed a difference in efficacy between peppermint oil and placebo.

Therefore, although current evidence continues to support the use of antispasmodics and peppermint oil as first-line treatments for abdominal pain in IBS, the quality of available evidence is low and newer trials of peppermint oil raise questions about its efficacy in IBS.

3.4.2. Gut-brain neuromodulators

Visceral hypersensitivity is one of the key features of IBS [18], with patients reporting pain in response to balloon dilatation of the rectum at lower thresholds than individuals without IBS [120]. Gut-brain neuromodulators, such as tricyclic antidepressants (TCAs) or SSRIs, have been shown to be effective for treating IBS in individual RCTs. It is likely that these drugs act via the gut-brain axis, although their precise mechanism of action is unclear. They may act peripherally to reduce visceral hypersensitivity in the gut, thereby ameliorating pain responses [121,122]. They might also act centrally to alter pain perception and processing. Most neuromodulators are antidepressants and so these effects might be mediated by improvements in psychological symptoms and mood [123].

A systematic review and meta-analysis from 2019 found a significant benefit in favor of gut-brain neuromodulators for treating IBS based on data from 18 RCTs that compared either TCAs or SSRIs with placebo and recruiting 1127 patients [124]. Heterogeneity between studies was significant; however, this was confined to studies of SSRIs. There was an overall benefit of TCAs over placebo for treating IBS. However, there was considerable variation in which specific drug and dose of TCA was used. Effects on bowel habit are less clear. TCAs can often cause constipation as a side-effect which might be serendipitous in patients with IBS-D, although only one study has investigated this, reporting a positive effect on diarrhea [125].

More recently, a large RCT of titrated low-dose amitriptyline in IBS has been conducted. 463 participants in primary care with IBS, irrespective of stool subtype, were randomized to receive low-dose amitriptyline or placebo for 6 months [126]. Doses were titrated over 3 weeks from a starting dose of 10 mg once daily up to a maximum of 30 mg once daily according to symptoms and tolerability. Low-dose amitriptyline was superior to placebo at 6 months with significantly greater improvements in global IBS symptoms and abdominal pain. Adverse event rates were similar between arms. Interestingly, there was no difference between low-dose amitriptyline and placebo with respect to psychological symptom scores at 6 months. This might suggest that improvements in IBS symptoms are mediated via peripheral, rather than central, mechanisms of action.

There are few RCTs examining the efficacy of serotonin norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, for IBS. However, SNRIs have benefits in other chronic painful disorders, like fibromyalgia [127], and they appear to be efficacious in some patients with IBS, especially if psychological co-morbidity is present [128]. SNRIs could, therefore, be considered in patients with IBS who do not respond to other gut-brain neuromodulators. Overall, however, low-dose TCAs should be the preferred neuromodulator for those patients with IBS in whom first-line treatments prove ineffective.

3.5. Treating refractory symptoms

A number of brain-gut behavioral therapies (BGBT), including cognitive behavioral therapy (CBT), gut-directed hypnotherapy, and various forms of relaxation therapy, have all been tested in IBS. These approaches are primarily designed to treat gastrointestinal symptoms, by focusing on psychological and cognitive factors that influence gastrointestinal symptom perception [129], rather than to address psychological health needs *per se*, although it is recognized that mental health is an important factor in contributing to, and maintaining, gastrointestinal symptoms in IBS. A meta-analysis of observational studies reported a higher prevalence of anxiety and depression in subjects with IBS compared with healthy controls [130]. Patients with a concomitant mood disorder are likely to require specific treatment with an anti-depressant drug and may require review by a psychiatrist or a general psychologist for community-based psychotherapy before embarking on a BGBT for their IBS symptoms [129].

Early trials of CBT for IBS were positive [131], and a previous meta-analysis found a benefit in favor of CBT for IBS compared with control interventions when pooling data from nine trials containing 610 patients [124]. Unfortunately, access to CBT can be limited, not least because it requires face-to-face sessions with a skilled practitioner over a number of weeks. Consequently, studies have evaluated minimal-contact approaches, or CBT delivered over the telephone or via the

internet [132]. These methods, all of which have demonstrated efficacy for improving IBS symptoms, can improve availability of CBT because therapist input is required less frequently. In addition, the benefits of internet or telephone CBT have been shown to persist for up to 24 months in one study [133]. A digital, self-guided program of gut-directed CBT delivered via an app has also been shown to improve IBS symptoms in an uncontrolled study of 843 patients with IBS, although only 19% completed the full 8-week course [134].

Gut-directed hypnotherapy has also demonstrated efficacy for treating IBS symptoms in small studies [135,136], but it may be less beneficial when delivered in a non-expert center [137]. Uncontrolled data show that remote delivery can be successful and this might improve access for individuals [138], although sessions remain therapist-delivered and one-to-one meaning there is no beneficial impact on service capacity. Patient satisfaction with remote hypnotherapy is generally good [139]. Group hypnotherapy might help more patients to access hypnotherapy for IBS and in one multicentre RCT, group hypnotherapy was non-inferior to individual hypnotherapy in a per protocol analysis [140]. These findings are supported by another study comparing individual and group hypnotherapy in 119 patients [141]. More recently, a 42-session daily digital program of gut-directed hypnotherapy for IBS has been compared with an active control in a randomized trial [142]. 81% of those receiving digitally-delivered hypnotherapy achieved a ≥ 50 point decrease in their IBS symptom severity scale compared with 63% in the active control group and this difference reached statistical significance. There were also statistically significant improvements in quality of life with digitally-delivered hypnotherapy.

In a network meta-analysis of 41 RCTs assessing the relative efficacy of BGBTs for treating IBS, several approaches were found to be efficacious compared with control interventions, in terms of improvement in global IBS symptoms [143]. CBT-based techniques and gut-directed hypnotherapy were the interventions with the most available evidence. These were the most efficacious approaches in the long term and were also found to be beneficial when only considering data from trials recruiting patients with IBS with refractory symptoms. However, overall, no BGBT was superior to any another. A subsequent network meta-analysis has examined the effect of these treatments on abdominal pain, specifically, in IBS using data from 42 RCTs [144]. Several BGBTs were shown to be efficacious, with CBT-based interventions and gut-directed hypnotherapy predominating; however, once again, no BGBT was superior to any other.

BGBTs can be recommended for the treatment of gastrointestinal symptoms, including abdominal pain, in IBS. Traditionally, guidelines have positioned these interventions as a last resort, reserving them for those patients whose symptoms are refractory to dietary and medical treatments. This has been, primarily, because access to BGBTs has been poor and there has been insufficient capacity to offer them more widely. However, innovations in group therapy, as well as minimal-contact, virtual, or self-guided approaches, have the potential to widen access so that more patients with IBS can benefit from BGBTs as part of multi-disciplinary care [145].

4. Conclusion

Application of symptom-based criteria, with limited judicious investigation including FBC, CRP or ESR, and celiac serology, along with FC in a patient aged <45 years with IBS-D, is the preferred approach to the diagnosis of IBS, with no role for exhaustive investigation. The potential for a missed diagnosis of organic disease is highest in those with IBS-D or older individuals. If there are features or risk factors to suggest the presence of either MC or BAD in a patient with IBS-D, or IBD or CRC in a patient aged 45 years or over, then these should be excluded. This has shown to be a safe and accurate approach, and even during extended follow-up the diagnosis of IBS is unlikely to be revised if this strategy is applied.

Patients with IBS should be provided with traditional dietary advice, including the role of soluble fiber for managing symptoms, and those who do not respond can be referred to a specialist dietitian to consider trying a low FODMAP diet. Probiotics many benefit some patients but the quality of evidence underpinning this is of low to very low quality.

Laxatives should be prescribed first-line for managing constipation. Patients who fail to respond can be treated with a secretagogue, such as linaclotide. Anti-diarrheal drugs, such as loperamide, should be recommended first-line for the treatment of diarrhea. If this approach is inadequate, a range of second-line drugs can be utilized, such as the 5-HT_3 antagonist alosetron, eluxadoline, or rifaximin. Unfortunately, these treatments remain unavailable or unlicensed for IBS in many countries.

Abdominal pain should be treated, initially, with antispasmodic drugs, such as hyoscine or peppermint oil. Where these are unsuccessful, patients should be prescribed a gut-brain neuromodulator, and a low-dose tricyclic antidepressant, such as amitriptyline, should be first-choice. Finally, BGBT, such as CBT or gut-directed hypnotherapy are effective for managing gastrointestinal symptoms and abdominal pain in IBS, including in those patients refractory to medical treatments. Overall, treatment of IBS should emphasize a multidisciplinary approach to care.

5. Expert opinion

There have been substantial advances in both the diagnosis and management of IBS over the last 20 years. Although a specific diagnostic test, or biomarker, for IBS remains elusive, symptom-based diagnostic criteria have been further refined. When used in conjunction with tests to exclude the limited number of organic gastrointestinal conditions that IBS can mimic, they are more accurate for diagnosing IBS than previous iterations [33,35,36], meaning once a diagnosis of IBS has been made it is unlikely to be changed [34]. This reduces uncertainty for both the patient and the clinician. In addition, multiple new drugs, which act in a variety of ways, have become available for the treatment of IBS, based on predominant bowel habit. Finally, there have been numerous, and are ongoing, efforts to synthesize the available evidence for the efficacy of dietary interventions, probiotics, drugs, and BGBTs.

Despite these advances, there remains scope for improvement in terms of both the diagnosis and management of IBS.

Many physicians still view IBS as a diagnosis made after exclusion of organic gastrointestinal disease [17], and view it as being, primarily, a psychological disorder [146]. In fact, some studies even demonstrate that doctors may hold pejorative views of the condition [147]. This is despite there being evidence of an organic basis for IBS in a subset of patients [148], and it having a similar impact on social functioning and quality of life to IBD [149]. This means that patients themselves, or their friends, relatives, and colleagues may view IBS as being a less legitimate diagnosis than other organic gastrointestinal diseases, leading to a sense of stigmatization [150]. There is, therefore, a need for improved awareness and understanding among doctors in both primary and secondary care that IBS is a genuine disorder, together with education stressing that IBS can be diagnosed positively via the clinical history and examination. This is important to enable institution of appropriate therapy in a timely manner, reduce unnecessary investigation, and thereby minimize direct costs to the health service and indirect costs to wider society.

Nevertheless, the Rome IV criteria may be too restrictive for clinical practice and their use has been shown to lead to higher gastrointestinal symptom severity and psychological comorbidity among patients with IBS [32]. Minor modifications to these criteria appear to perform with similar accuracy but are less restrictive [35,36]. Therefore, future iterations of the Rome criteria could consider relaxing the required frequency for abdominal pain back to 3 days per month from 1 day per week.

Although new drugs continue to be developed for IBS, the pace of this has slowed in recent years. IBS is a condition with no biomarker and endpoints in clinical trials are, therefore, patient-reported and subjective. This means placebo response rates in the condition are high [151]. Thus, the costs involved in developing a drug, only for it to prove to be ineffective, may deter pharmaceutical companies from investment in this field. Other than the drug classes already discussed in this article, in the last 5 years olorinab, a cannabinoid receptor-2 agonist [152], and vibegron, a β_3-adrenergic receptor agonist [153], have been tested in phase 2 trials. However, neither of these drugs met their primary endpoint and, at the time of writing, they have yet to be the subject of definitive phase 3 trials. Re-purposing of existing drugs, which could have beneficial effects in IBS, may be an alternative approach. Recent RCTs demonstrating the efficacy of ondansetron [108,154], amitriptyline [126], and ebastine [155], a histamine receptor-1 antagonist, in IBS are all testament to this, but further efforts in this regard are required.

Finally, despite the advent of new drug classes for the treatment of IBS, these have not led to any incremental increase in the likelihood of success of therapy. The therapeutic gain of most drugs over placebo is modest, and only around one-third of patients with IBS will respond to any particular drug. This suggests that other approaches are needed. In the absence of biomarkers to predict which patient will respond to which drug, a novel treatment paradigm is required. There is increasing evidence that patients with IBS can be subclassified not only according to the severity of gastrointestinal symptoms, but also degree of psychological comorbidity [156–161]. This could offer new opportunities to treat IBS based on a combination of these factors, allowing a more nuanced and personalized management of the condition [162]. Such an approach could include the use of education, lifestyle advice, and general dietary advice in those with mild gastrointestinal symptoms and low levels of psychological comorbidity, drugs targeting only peripheral mechanisms in those with moderate to severe gastrointestinal symptoms and low levels of psychological comorbidity, and combination approaches with both peripherally-acting drugs, gut-brain neuromodulators, and BGBTs in those with gastrointestinal symptoms and high levels of psychological comorbidity [162]. However, further research is needed before this approach can be implemented in usual care. Studies that examine the efficacy of first- and second-line drugs and BGBTs according to the severity of gastrointestinal symptoms and degree of psychological comorbidity would be useful to assess whether their efficacy varies depending on whether gastrointestinal or psychological symptoms are predominant. RCTs assessing whether a treatment approach according to the severity of both gastrointestinal symptoms and degree of psychological comorbidity is superior to one based on conventional management according to predominant bowel habit are also required.

Abbreviations

5-HT_3	5-hydroxytryptamine-3
BAD	Bile acid diarrhea
BGBT	Brain-gut behavioral therapy
CBT	Cognitive behavioral therapy
CIC	Chronic idiopathic constipation
CRC	Colorectal cancer
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
FODMAP	Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
FC	Fecal calprotectin
GFD	Gluten-free diet
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome with constipation
IBS-D	Irritable bowel syndrome with diarrhoea
IBS-M	Irritable bowel syndrome with mixed bowel habits
LR	Likelihood ratio
MC	Microscopic colitis
NSAID	Non-steroidal anti-inflammatory drug
PEG	Polyethylene glycol
PPI	Proton pump inhibitor
RCT	Tandomized controlled trial
SeHCAT	23-seleno-25-homotaurocholic acid
SIBO	Small intestinal bacterial overgrowth
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

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• **Perspective piece offering a hypothesis as to how personalised therapy in IBS could be offered.**