Functional Gastrointestinal Disorders 2

Irritable bowel syndrome

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Irritable bowel syndrome is a functional gastrointestinal disorder with symptoms including abdominal pain associated with a change in stool form or frequency. The condition affects between 5% and 10% of otherwise healthy individuals at any one point in time and, in most people, runs a relapsing and remitting course. The best described risk factor is acute enteric infection, but irritable bowel syndrome is also more common in people with psychological comorbidity and in young adult women than in the rest of the general population. The pathophysiology of irritable bowel syndrome is incompletely understood, but it is well established that there is disordered communication between the gut and the brain, leading to motility disturbances, visceral hypersensitivity, and altered CNS processing. Other less reproducible mechanisms might include genetic associations, alterations in gastrointestinal microbiota, and disturbances in mucosal and immune function. In most people, diagnosis can be made on the basis of clinical history with limited and judicious use of investigations, unless alarm symptoms such as weight loss or rectal bleeding are present, or there is a family history of inflammatory bowel disease or coeliac disease. Once the diagnosis is made, an empathetic approach is key and can improve quality of life and symptoms, and reduce health-care expenditure. The mainstays of treatment include patient education about the condition, dietary changes, soluble fibre, and antispasmodic drugs. Other treatments tend to be reserved for people with severe symptoms and include central neuromodulators, intestinal secretagogues, drugs acting on opioid or 5-HT receptors, or minimally absorbed antibiotics (all of which are selected according to predominant bowel habit), as well as psychological therapies. Increased understanding of the pathophysiology of irritable bowel syndrome in the past 10 years has led to a healthy pipeline of novel drugs in development.

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that has a substantial impact on quality of life and social functioning.[1,2] The pathophysiology of IBS is only partially understood.[3] The condition affects between 5% and 10% of the general population,[4] and is characterised by recurrent abdominal pain associated with abnormal stool form or frequency.[5] Treatment aims to improve abdominal pain and bowel habit, but often is targeted towards the most troublesome symptom. First-line therapies include dietary changes, soluble fibre, and antispasmodic drugs. In patients with severe symptoms, treatments include central neuromodulators, including low-dose tricyclic antidepressants, intestinal secretagogues, drugs acting on opioid or 5-HT receptors, antibiotics, and psychological therapies.[6] The annual direct and indirect costs related to IBS are estimated to be up to €8 billion in Europe,[7] ¥123 billion in China,[8] and in excess of US$10 billion in the USA.[9]

Epidemiology

The current symptom-based diagnostic criteria for IBS, the Rome IV criteria, were developed by consensus among experts in functional gastrointestinal disorders. The criteria consist of abdominal pain associated with an alteration in either stool form or frequency, occurring for at least 6 months.[5] Patients are subgrouped according to predominant stool pattern by use of the Bristol Stool Form Scale: IBS with diarrhoea, IBS with constipation, IBS with mixed stool pattern, and IBS unclassified (table 1).[10] It is difficult to obtain precise estimates of prevalence,[11] particularly because, in the absence of universally accepted biomarkers of disease, the diagnosis of IBS relies on self-reported symptom clusters. However, as organic gastrointestinal disease in the community is relatively rare, and a diagnosis of IBS is based on the presence of typical symptoms, population-based epidemiological studies provide a close approximation of true prevalence, which is between 5% and 10% in most geographical regions (figure 1).[4]

Various iterations of these symptom-based diagnostic criteria have resulted in differences in reported prevalence, but disease impact is substantial even in people who believe that they have IBS, but who do not meet such criteria.[14] Additionally, symptom interpretation and

Search strategy and selection criteria

We searched the medical literature using MEDLINE, Embase, Embase Classic, and the Cochrane Central Register of Controlled Trials for articles published during the past 10 years between Jan 1, 2010, and Jan 31, 2020, with the terms "irritable bowel syndrome", "epidemiology", "prevalence", "incidence", "aetiology", "pathophysiology", "diagnosis", "investigation", "management", "therapy", AND "treatment" to identify pertinent articles. Additionally, we searched ClinicalTrials.gov for unpublished trials. We included only publications in English and selected those with findings that were, in our view, of the greatest importance, favouring randomised controlled trials, meta-analyses, and network meta-analyses.

	Diagnostic criteria
IBS	Recurrent abdominal pain, on average for at least 1 day per week in the past 3 months, associated with two or more of the following: related to defaecation, a change in frequency of stool, a change in stool form; criteria must be fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis
IBS with constipation	≥25% of bowel movements of Bristol Stool Form types 1 or 2, and <25% of Bristol Stool Form types 6 or 7
IBS with diarrhoea	≥25% of bowel movements of Bristol Stool Form types 6 or 7, and <25% of Bristol Stool Form types 1 or 2
IBS with mixed stool pattern	≥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
IBS unclassified	Patients who meet criteria for IBS, but do not fall into one of the other three subgroups according to Bristol Stool Form type

Adapted from Mearin and colleagues.[5] IBS=irritable bowel syndrome.

Table 1: **The Rome IV criteria for IBS and its subgroups**

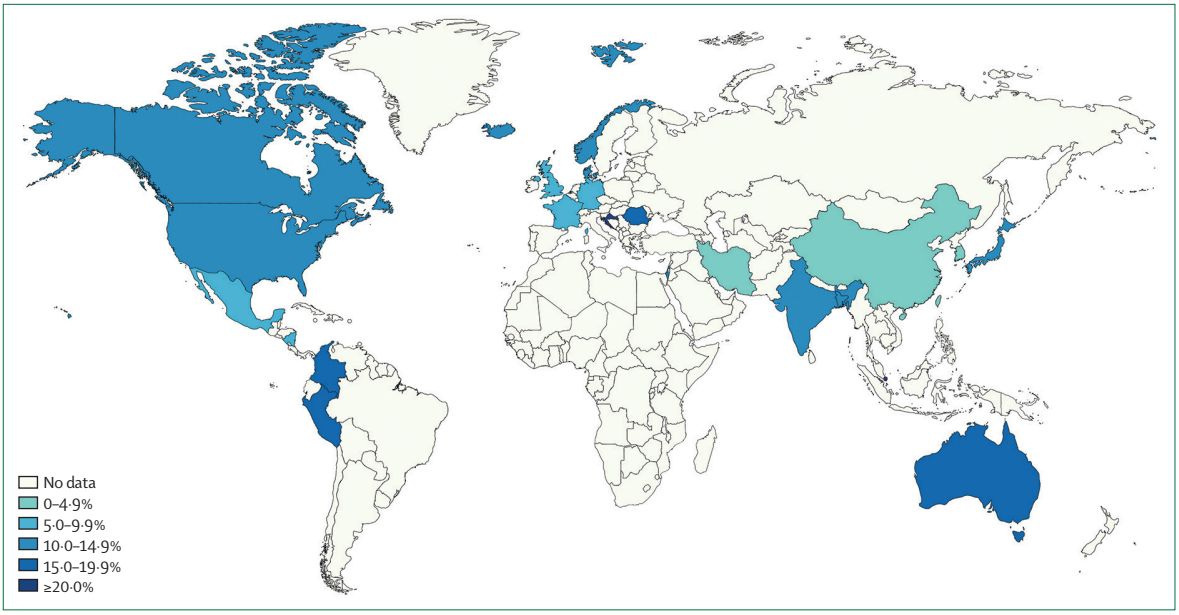

Figure 1: **Global prevalence of IBS according to the Rome III criteria**
Prevalence data taken from studies that used the Rome III criteria for IBS.[4,12,13] IBS=irritable bowel syndrome.

reporting are influenced by cultural factors, and can vary among ethnic groups.[11] Before publication of the Rome IV criteria in 2016,[5] two systematic reviews examined global prevalence of IBS.[4,12] The first review reported a pooled prevalence of 11·2% (95% CI 9·8–12·8),[12] ranging from 1·1% in Iran (with Rome III criteria) to 45% in Pakistan (with Rome II). The second review reported a global prevalence of 8·8% (8·7–8·9).[4] Prevalence varied widely, from 1·1% in France (with Rome II) and Iran (with Rome III) to 35·5% in Mexico (with Rome II). Thus, despite commonly accepted prevalence ranges, estimates between studies vary greatly, partly because of methodological heterogeneity.

Findings from a cross-sectional survey of 33 nations by the Rome Foundation, which examined worldwide prevalence and burden of functional gastrointestinal disorders in over 73 000 individuals in 26 countries, were published in 2020.[13] By use of Rome IV criteria, prevalence rates ranged between 1·3% and 7·6%, with a pooled prevalence of 4·1%. In countries where both Rome III and IV criteria were applied, pooled prevalence fell from 10·1% with Rome III to 3·8% with Rome IV. However, a dearth of prevalence data remains from Africa, eastern Europe, and the Middle East.

Risk factors

In two systematic reviews, IBS prevalence was significantly higher in women than in men[4,12] and, when 14 studies were pooled, prevalence was lower in individuals aged 50 years or older (odds ratio [OR] 0·75; 95% CI 0·62–0·92) than in people aged younger than 50 years.[12] There are no reliable data on IBS and socioeconomic status. IBS is more common in patients with functional somatic syndromes, such as fibromyalgia and chronic fatigue.[15] Many other psychosocial, biological, and environmental factors are associated with IBS, and might influence symptom severity (figure 2). However, it is unclear if these are genuine risk factors because most studies are cross-sectional and do not have the temporal element needed to determine cause and effect.

Perhaps the most well recognised risk factor for IBS, observed in approximately 10% of patients,[17] is previous acute enteric infection. This subtype is termed post-infection IBS and can occur after bacterial, viral, or protozoal infection.[18] In one retrospective cohort study, even non-specific gastrointestinal infections, which comprised most cases, were associated with an equally high risk of post-infection IBS as culture-confirmed bacterial or viral infections.[19] A meta-analysis of 45 observational studies reported that the odds of developing IBS increased by 4 times in exposed individuals 12 months after infection (OR 4·2; 95% CI 3·1–5·7).[18] Risk factors for development of post-infection IBS included female sex, exposure to antibiotics, psychological distress preceding the illness, and severity of infection.[18] Prognosis might be better in patients with post-infection IBS than in individuals with a non-infectious cause; however, one longitudinal follow-up study showed that 15% of patients with post-infection IBS remained symptomatic 8 years later.[20]

Pathophysiology

The biopsychosocial model to explain symptoms of abdominal pain and disordered bowel habit in IBS conceptualised a genetic predisposition, in which adverse events in early life, psychological factors, or gastrointestinal infections trigger alterations in the enteric nervous system, which controls gastrointestinal motor, sensory, mucosal barrier, and secretory responses (figure 3).[26]

Traditional mechanisms: the gut–brain axis, stress, visceral hypersensitivity, and altered motility

In addition to the psychological component of IBS,[27] gut–brain communication is bidirectional. Prospective longitudinal studies show that a subset of patients have gastrointestinal symptoms first,[28,29] and psychological distress later. Gastrointestinal infection and psychological disorders appear to be distinct risk factors, contributing additively to the development of both post-infection IBS and the extraintestinal symptoms frequently linked to IBS, such as chronic fatigue.[19]

Altered visceral sensation in IBS is characterised by central abnormalities in sensory, emotional arousal, and prefrontal cortical regions of the brain. Alterations in the descending pathways modulating sensation and peripheral mechanisms are also involved in the pathogenesis of visceral pain.[30] On average, about 60% of patients exhibit increased sensitivity of the gut to different physiological stimuli.[31,32] Disordered motility in IBS is manifested by abnormal colonic myoelectric activity;[33] repetitive contractions of the small intestine and colon, associated with abdominal pain; and alterations in gastrointestinal or colonic transit.[34,35] Accumulation of different mechanisms (eg, psychological, sensory, and motor) increases the severity of gastrointestinal and non-gastrointestinal symptoms and causes impairments in quality of life.[36,37]

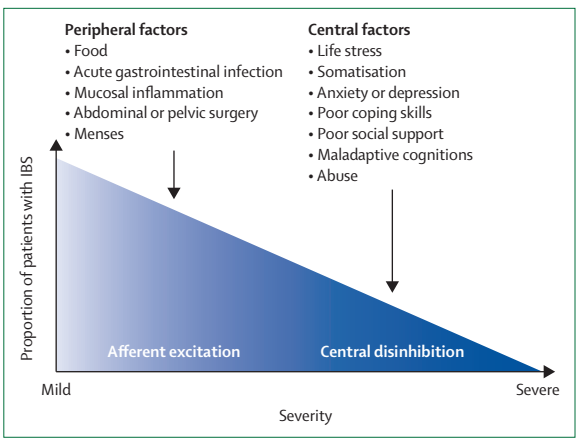

Figure 2: **Factors affecting symptom severity in IBS**
Adapted from Sperber and colleagues.[16] IBS=irritable bowel syndrome.

The gut microenvironment

Because many patients with IBS report that their symptoms are associated with eating or eliminating particular foods,[38] it is assumed that diet and gastrointestinal microbiota are involved in pathophysiology.

Dietary FODMAPs and disaccharide maldigestion

Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are present in high amounts in some fruits, artificial sweeteners, legumes, and green vegetables, and are poorly absorbed in all individuals. FODMAPs have fermentative and osmotic effects, which might contribute to symptoms in some patients.[39] Randomised controlled trials have supported that dietary modification can affect IBS symptoms; however, to date, these trials have not shown that symptoms are generated by a specific food. Although patients with IBS exhibit similar increases in small intestinal water content and colonic volume to FODMAPs to those seen in healthy individuals, symptomatic responses are greater in patients with IBS, supporting the role of visceral hypersensitivity.[40] Dietary disaccharide maldigestion might induce symptoms secondary to osmotic diarrhoea and gas production following fermentation of unabsorbed sugars.[22,41] This maldigestion can be due to disaccharidase deficiency, classically lactase, or as shown in 4% of patients with IBS,[23,42] sucrase-isomaltase, which digests sucrose and starch.

The microbiome

Although some studies show that patients with IBS have a different gastrointestinal microbiome to that of healthy controls,[43,44] the role of the microbiota is still questioned, particularly because what constitutes a healthy microbiome is unclear. A systematic review showed few consistent findings in IBS (possibly because age, sex, race, diet, and antibiotic intake were not controlled for in included studies), and no microbiome signature

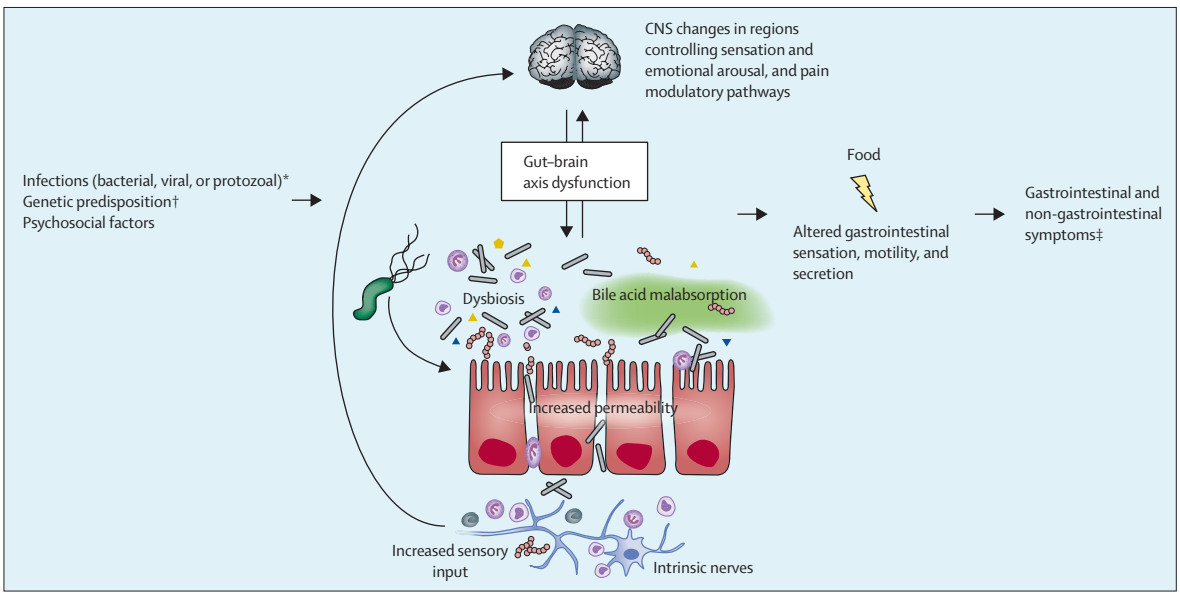

Figure 3: **Pathophysiological mechanisms involved in IBS**
IBS=irritable bowel syndrome. *See references 17 to 20. †Genome-wide association studies have shown associations with variants of chromosome 9 and mutations in the sucrase-isomaltase gene.[21–23] Other studies have shown that approximately 2% of patients with IBS carry mutations in *SCN5A*,[24] which alters the function of the voltage-gated mechanosensitive sodium ion channel NaV1.5. ‡Gastrointestinal symptoms include abdominal pain; abnormal stool form, stool frequency, or both; and bloating.[5] Non-gastrointestinal symptoms include back pain, gynaecological and bladder symptoms, headache, and fatigue.[25]

differentiating between IBS subgroups.[45] Antibiotics change the intestinal microbiome and have been associated with development of IBS.[46] Small intestinal bacterial overgrowth has also been implicated,[47] but its role is controversial largely due to limitations of available diagnostic tests, such as glucose and lactulose breath tests,[48] and culture of jejunal aspirates.[49]

Bile acids

Up to 25% of patients who meet criteria for IBS with diarrhoea have idiopathic bile acid diarrhoea, shown by abnormal retention following SeHCAT scanning,[50] or total 48 h faecal bile acid concentrations.[51] In one case series of patients, faecal bile acids correlated with stool number and form, and colonic transit.[52] In a case-control study, excess faecal bile acids in IBS with diarrhoea appeared to be associated with dysbiosis, specifically a microbiota rich in Clostridia.[53]

Barrier function and immune activation

Acute gastrointestinal infections induce changes in intestinal permeability and the microbiome.[54] These changes might promote activation of immune cells, including T lymphocytes and mast cells, in the gastrointestinal epithelium,[55] leading to cytokine release, which can modify neural control of gastrointestinal motor, sensory, and secretory functions. Pathophysiological alterations can last for years. For example, in post-infection IBS, neuronal signalling remained sensitised 2 years after the infection.[56] Other investigators have reported increased gastrointestinal permeability and raised immune cell counts, even in patients with IBS without an infective cause.[57,58]

Genetics

Although research into the genetics of IBS falls behind that of other conditions (eg, inflammatory bowel disease [IBD]), genome-wide association studies have provided associations with variants on chromosome 9 (9q31·2 locus) that are linked to the functions of diverse ion channels and autonomic dysfunction,[21] and mutations in the sucrase-isomaltase gene.[23,42] Additionally, approximately 2% of patients with IBS carry missense mutations in *SCN5A*,[24] which alter the function of the voltage-gated mechanosensitive sodium ion channel NaV1.5, and affect smooth muscle function and mechanical sensitivity. In twin studies, concordance of a diagnosis of IBS is more common in monozygotic twins than in dizygotic twins; however, having a parent with IBS is a strong predictor, suggesting that environmental factors such as learned illness behaviour are more important than genetic factors.[59]

Clinical presentation and differential diagnosis

Although IBS is a multifactorial and heterogeneous disorder, there are some typical features. The condition is most common among women aged 20–40 years,[4,12] although in some countries it appears more prevalent in younger men (aged 16–30 years).[60] IBS can occur at any age.[13] The average age of participants in clinical trials of novel drugs for IBS is around 45 years, illustrating the broad age range of patients. Coexistent mood problems

and extraintestinal symptoms, including back pain, gynaecological and bladder symptoms, headache, and fatigue are common,[25,61] as is overlap with other functional gastrointestinal disorders.[62] The presence of abdominal pain is essential to the definition of IBS. Accordingly, the differential diagnosis is broad, but other features help narrow this down. First, as IBS is a chronic disorder, causes of acute abdominal pain are ruled out. Second, the pain is recurrent, but it is intermittent rather than continuous. Third, pain is usually in the lower abdomen, although southeast Asian patients might report upper abdominal pain.[63] Finally, and most crucially, pain in IBS is associated with defaecation, and occurs at the time when the patient has alterations in stool frequency or consistency (table 1).[5] Although IBS is subgrouped according to predominant stool pattern,[5] this pattern fluctuates in many patients.[64] Abdominal bloating is not a cardinal symptom but is very common and supports the diagnosis, particularly if it is diurnal. Such bloating is often accompanied by visible abdominal distension.[65]

To understand the precise meaning of terms such as diarrhoea or constipation, as well as the effects of the disorder on social functioning and wellbeing, a thorough history is essential. The Bristol Stool Form Scale is a useful tool to assess stool consistency in the clinic, and can be used to direct treatment. A detailed history helps to differentiate IBS from other disorders characterised by abdominal pain associated with altered bowel habit, including coeliac disease, IBD, colorectal cancer, and microscopic colitis.

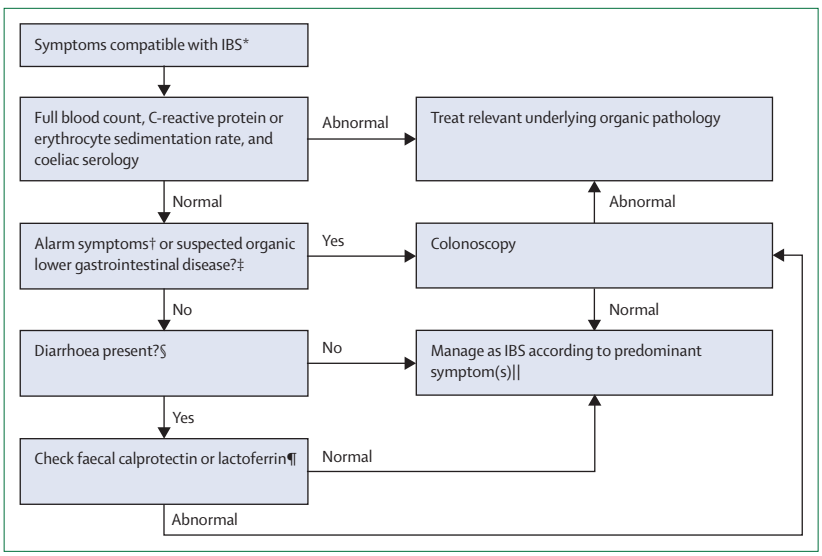

Figure 4: **Suggested diagnostic algorithm for patients with suspected IBS**
IBS=irritable bowel syndrome. *Abdominal pain, related to defaecation, associated with change in stool form or stool frequency.[5] †See panel. ‡Especially if family history of inflammatory bowel disease, coeliac disease, or colorectal cancer, or features suggestive of microscopic colitis (female aged ≥50 years, coexistent autoimmune disease, proton pump inhibitor or non-steroidal anti-inflammatory drug use, duration of diarrhoea <12 months, weight loss, or nocturnal diarrhoea).[68,69] §Consider measuring SeHCAT retention, serum 7α-hydroxy-4-cholesten-3-one, serum FGF19, or 48 h faecal bile acid excretion (where available), or consider a trial of a bile acid sequestrant to exclude bile acid diarrhoea. ¶If the initial faecal calprotectin or lactoferrin concentration is within the abnormal range according to local laboratory values and the suspicion for inflammatory bowel disease is high, proceed to colonoscopy.[70] If the initial faecal calprotectin or lactoferrin concentration is indeterminate, repeat the test off non-steroidal anti-inflammatory drugs and refer for colonoscopy if the repeat test remains indeterminate or is within the abnormal range. ||If features suggestive of a defaecatory disorder are present, including obstructive symptoms (eg, a feeling of incomplete evacuation or the need to digitate during defaecation) or paradoxical anal contraction on straining during digital rectal examination, consider anorectal manometry with balloon expulsion testing.

Investigations

Although there is no universally accepted biomarker for IBS, exhaustive investigation to exclude an organic cause for the symptoms is discouraged because this process is expensive, and many patients are not reassured by such an approach.[66] Once a clinical diagnosis of IBS is made, it is unlikely to be revised, even during long-term follow-up.[67] Guidelines recommend a positive diagnosis by use of symptom-based diagnostic criteria, such as the Rome criteria, and minimising investigations (figure 4).[6] Although the Rome IV criteria have yet to be validated independently, in secondary care, sensitivity of the Rome III criteria was 68·8% (specificity 79·5%), positive likelihood ratio was 3·35, and negative likelihood ratio was 0·39.[71] The addition of other features from a patient's clinical history, including absence of nocturnal stools; presence of anxiety, depression, or extraintestinal symptoms; and a normal full blood count and C-reactive protein enhances the diagnostic performance of the Rome III criteria.[72]

There is little evidence to support a routine panel of blood tests, other than full blood count, C-reactive protein, and serological screening for coeliac disease, which has a prevalence of 1% across most of Europe and North America, and is an important differential diagnosis. A meta-analysis showed an almost three times higher odds of positive coeliac serology in patients with symptoms suggestive of IBS (OR 2·75; 95% CI 1·35–5·61) compared with healthy controls, irrespective of predominant stool pattern.[73]

Whether or not any further investigations are required in a patient with new-onset symptoms depends, to some extent, on bowel habit, unless alarm symptoms or signs are present, necessitating urgent colonoscopy (panel).[74] Colonoscopy should also be done if the patient is aged 50 years or older and has not already had colorectal cancer screening. Additionally, unexplained rectal bleeding or iron deficiency anaemia needs investigation, regardless of age. A family history of coeliac disease, IBD, or colorectal cancer is also relevant. In a patient with IBS with constipation, the diagnosis is secure unless there are obstructive symptoms (excessive straining, sense of incomplete rectal evacuation, or digitation of the anus to facilitate defaecation) or digital rectal examination suggests a defaecatory disorder,[75] which is the result of incoordination of the typical functions required for rectal evacuation. If present, anorectal manometry with balloon expulsion testing might be helpful because the treatment of choice for defaecatory disorders is biofeedback,[76] rather than dietary or drug therapy.

***Panel*: Definite referral criteria for lower gastrointestinal alarm symptoms and signs**

- Aged 40 years or over with unexplained weight loss and abdominal pain
- Aged 50 years or over with unexplained rectal bleeding
- Aged 60 years or over with change in bowel habit, a positive faecal occult blood test, or iron deficiency anaemia

Criteria based on guidance from the UK's National Institute for Health and Care Excellence.[74] Regardless of age, a patient with unexplained rectal bleeding or iron deficiency anaemia (especially if accompanied by abdominal pain, change in bowel habit, or weight loss), or an abdominal or rectal mass, needs investigation to exclude other gastrointestinal disorders, including cancer.

In a patient with diarrhoea, there might be greater concern for a missed organic diagnosis. Faecal calprotectin, which is a cytosol protein released by neutrophils, can differentiate between IBS and IBD,[70,77] avoiding the need for colonoscopy, for which the yield is low. In a cross-sectional survey of 466 patients with IBS, two patients (<1%) were found to have IBD at colonoscopy, seven (2%) had microscopic colitis, and there were no cases of colorectal cancer.[78] Microscopic colitis is most common in women aged 50 years and older. Other clues might suggest microscopic colitis rather than IBS as the cause of symptoms, and lead to consideration of colonoscopy for colonic biopsies. These clues include variable presence of abdominal pain and short duration of symptoms. Additionally, patients often have coexistent autoimmune disease, report nocturnal diarrhoea and weight loss, or are taking drugs (eg, non-steroidal anti-inflammatory drugs or proton-pump inhibitors).[68,69]

Bile acid diarrhoea is another important differential diagnosis in patients presenting with IBS with diarrhoea because its estimated population prevalence is 1%. Bile acid diarrhoea can be diagnosed with SeHCAT scanning, a fasting serum 7α-hydroxy-4-cholesten-3-one, FGF19, or 48 h faecal bile acid excretion,[79] although these diagnostic tests are not universally available. A therapeutic trial of a bile acid sequestrant as a surrogate diagnostic test is an alternative; however, it is unclear what dose should be used, and problems with medication adherence might compromise its utility.[80]

The reported association between small intestinal bacterial overgrowth and IBS is contentious.[47] Investigations to exclude small intestinal bacterial overgrowth should only be considered in patients with clear risk factors (eg, previous gastric or intestinal surgery) or known structural abnormalities (including jejunal diverticulosis). Hydrogen breath tests might be falsely positive because they are a marker for rapid transit.[48] Instead, culture of jejunal aspirates should be considered if small intestinal bacterial overgrowth is suspected.[81]

Natural history and impact

The typical disease course in IBS consists of fluctuating symptoms, in terms of bowel habit.[64] Incidence of new-onset IBS was approximately 1·5–2·5% per year, over 10–12 years, in three longitudinal studies.[82–84] However, prevalence remains stable because the number of people developing new symptoms is matched by the number of individuals whose symptoms disappear or fluctuate to another functional gastrointestinal disorder.[83,84] IBS causes morbidity, but not mortality,[85] and affects quality of life[1] to the same degree as organic gastrointestinal disorders, such as Crohn's disease.[86]

IBS also affects work productivity,[1,2] social integration, and psychosocial factors, such as general and gut-related anxiety, depression, and somatisation.[25,87] Some of these associations are bidirectional,[28,29] so psychosocial factors can exacerbate IBS symptoms and the illness experience, and vice versa. One cross-sectional survey showed that the effect of IBS on daily activity differs according to stool pattern. Individuals with IBS with diarrhoea avoided travel or leaving the house because of concerns about toilet access, and people with IBS with constipation avoided sexual intercourse and reported difficulty concentrating.[88] Factors associated with severity include overlap with other functional gastrointestinal disorders[62] and consulter status.[89] However, people who consult with symptoms also have reduced quality of life, increased rates of psychological symptoms, and reduced coping.[89] There is a direct correlation between number of overlapping functional gastrointestinal disorders, reduced quality of life, and increased health-care utilisation and gastrointestinal surgery.[62] Patients are willing to accept a 1% median risk of sudden death in return for a 99% chance of cure of their symptoms with a hypothetical medication.[90]

Management

Because no medical therapy is proven to alter the natural history of IBS, and most randomised controlled trials are only done over a 12 week period meaning that their long-term efficacy is unknown, an empathetic approach is key. This approach can improve quality of life and symptoms,[91] reduce health-care visits, and enhance adherence to treatment.[92,93] Management should commence with explanation of the disorder, its pathophysiology, and natural history. In one randomised controlled trial, structured patient education about IBS led to a significantly greater improvement in symptoms than did written information.[94] Treatment is directed towards the predominant symptom with a realistic discussion of the limitations of available therapies to manage expectations, given that most therapies improve symptoms in only 25–30% of patients and have only been tested in secondary and tertiary care (table 2). The final decision of the choice of treatment should be the patient's, after they receive full information on available options in a dialogue with the doctor.

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Lifestyle, diet, and probiotics

The effect of lifestyle changes in IBS has not been well studied (table 2). In a small randomised controlled trial of exercise instructed by a physiotherapist, symptoms improved significantly compared with a control group that had no changes to physical activity.[95] Traditionally, patients with IBS were told to increase dietary fibre intake, although bran might exacerbate symptoms.[96] However, in a meta-analysis of seven randomised controlled trials, ispaghula husk was more efficacious than was placebo (relative risk [RR] of remaining symptomatic 0·83; 95% CI 0·73–0·94).[97] Several randomised controlled trials show that FODMAP restriction leads to an improvement in IBS symptoms, compared with habitual diet.[98,99] However, other randomised controlled trials suggest that traditional dietary advice to eat small regular meals, avoid known trigger foods, and reduce alcohol and caffeine is as effective as a low FODMAP diet.[100,101] Long-term FODMAP restriction might lead to deleterious alterations in the microbiome.[102] Therefore, FODMAPs should be reintroduced to tolerance after a limited period of restriction, although randomised controlled trials to date have only examined the effect on symptoms during FODMAP elimination. There is little evidence to support benefit of a gluten-free diet in IBS.[103] However, because wheat contains fructan, a FODMAP, a gluten-free diet incorporates elements of a low FODMAP diet. Therefore, some patients might adapt a low FODMAP diet to one that instead avoids gluten.[104] There have been numerous randomised controlled trials of probiotics in IBS. However, despite some trials showing positive results, the ability to make recommendations on which combination, species, or strain is effective is limited because of the various products studied, and the conflicting results among individual trials.[105]

First-line medical therapies

Laxatives, antidiarrhoeals, and antispasmodics are all used as first-line therapies in IBS. Most randomised controlled trials of these drugs are outdated and are hampered by suboptimal methodology and heterogeneous patient selection, meaning that efficacy according to predominant stool pattern is uncertain. Additionally, efficacy endpoints do not meet current recommendations from the US Food and Drug Administration (FDA) or the European Medicines Agency. Although osmotic and stimulant laxatives are effective in patients with chronic constipation,[106] there is little evidence for their use in IBS. A placebo-controlled trial of polyethylene glycol in

	IBS subgroup studied	Efficacy	Quality of data	Adverse events	Limitations of data
Diet, lifestyle, and probiotics					
Soluble fibre (eg, ispaghula 20–30 g/day)	No specific IBS subgroup recruited	Effective	Moderate	Total adverse events no more common with soluble fibre than with placebo in three RCTs	Only one RCT at low risk of bias; only a small number of patients in existing RCTs
Low FODMAP diet*	No specific IBS subgroup recruited	Might be effective	Very low	Total adverse events rarely reported	All RCTs at high risk of bias; heterogeneity between study designs; imprecision in estimate of effect; effect of FODMAP reintroduction not studied within the design
Exercise	No specific IBS subgroup recruited	Might be effective	Very low	Total adverse events not reported	Only two RCTs; high risk of bias in both RCTs; inconsistent effects on symptoms
Probiotics	No specific IBS subgroup recruited	Might be effective	Very low	Total adverse events no more common with probiotics than with placebo in a meta-analysis of 36 RCTs	Heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each individual probiotic, meaning that it is difficult to know which species or strain is effective
First-line therapies					
Peppermint oil (200 mg three times a day)	No specific IBS subgroup recruited	Effective	Low	Total adverse events no more common with peppermint oil than with placebo in a meta-analysis of six RCTs	Only two RCTs at low risk of bias; heterogeneity between studies; trials used very specific formulations so data cannot be extrapolated to other available products; heartburn might be an adverse effect
Laxatives (eg, polyethylene glycol 13·8 g once a day and titrated)	Patients with IBS with constipation	Unclear efficacy	Low	Rates of abdominal pain numerically higher with polyethylene glycol than with placebo in one RCT	Only two RCTs; unclear risk of bias in both RCTs; unclear effect on abdominal pain
Antidiarrhoeals (eg, loperamide 4 mg as required)	Patients with IBS with diarrhoea and IBS with mixed stool pattern	Unclear efficacy	Very low	Total adverse events no more common with antidiarrhoeals than with placebo in two RCTs	Only two RCTs; unclear risk of bias in both RCTs; not all patients met criteria for IBS; no significant effect on IBS symptoms when data pooled; constipation might be an issue
Antispasmodics (eg, cimetropium 50 mg three times a day, hyoscine 10–20 mg three times a day, otilonium 20–40 mg three times a day, or pinaverium 50 mg three times a day)	No specific IBS subgroup selected, other than one RCT in patients with IBS with diarrhoea	Might be effective	Very low	Total adverse events significantly more common with antispasmodics than with placebo in a meta-analysis of 26 RCTs, particularly dry mouth, dizziness, and blurred vision	Only two RCTs at low risk of bias; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each individual antispasmodic

(Table 2 continues on next page)

	IBS subgroup studied	Efficacy	Quality of data	Adverse events	Limitations of data
(Continued from previous page)					
Second-line therapies					
5-HT4 agonists (eg, tegaserod 6 mg twice a day)	IBS with constipation	Effective	High	Diarrhoea significantly more common with tegaserod than with placebo in a meta-analysis of six RCTs	Concerns regarding small excess of cardiovascular and cerebrovascular events led to withdrawal of tegaserod, which was reintroduced in 2018 but only for specific patients; no RCTs of prucalopride
5-HT3 antagonists (eg, alosetron 0·5–1·0 mg twice a day, ramosetron 2·5–5·0 µg once a day, or ondansetron 4 mg once a day and titrated)	IBS with diarrhoea and IBS with mixed stool pattern	Effective	High	Constipation significantly more common with alosetron than with placebo in a meta-analysis of three RCTs	All RCTs of ramosetron done in Japan; serious adverse events with alosetron included ischaemic colitis and severe constipation leading to restricted use; ramosetron is safer than alosetron, although constipation is still more common with active therapy
Tricyclic antidepressants (eg, amitriptyline 10–30 mg at night or desipramine 50 mg at night)	No specific IBS subgroup selected, other than one RCT in patients with IBS with diarrhoea	Effective	Moderate	Total adverse events significantly more common with tricyclic antidepressants than with placebo in a meta-analysis of six RCTs, particularly dry mouth and drowsiness	Only three RCTs at low risk of bias; possible publication bias; some atypical trials included
Eluxadoline (100 mg twice a day)	IBS with diarrhoea	Effective	Moderate	Rates of constipation, nausea, and vomiting numerically higher with eluxadoline than with placebo in a pooled analysis of two RCTs	Heterogeneity between studies; only a modest benefit over placebo in published RCTs; no benefit over placebo in terms of abdominal pain; serious adverse events include acute pancreatitis and sphincter of Oddi spasm
Antibiotic rifaximin (550 mg three times a day)	IBS with diarrhoea and IBS with mixed stool pattern	Effective	Moderate	Total adverse events no more common with rifaximin than with placebo in a pooled analysis of three RCTs	Only a modest benefit over placebo in published RCTs
Selective serotonin reuptake inhibitors (eg, fluoxetine 20 mg once a day)	No specific IBS subgroup selected, other than one RCT in patients with IBS with constipation	Might be effective	Low	Total adverse events no more common with selective serotonin reuptake inhibitors than with placebo	Only one RCT at low risk of bias; heterogeneity between studies
Pregabalin (225 mg twice a day)	No specific IBS subgroup recruited	Might be effective	Low	Total adverse events numerically higher with pregabalin than with placebo, particularly blurred vision, dizziness, and altered sensation	Only one single-centre RCT, although global symptoms, abdominal pain, diarrhoea, and bloating improved significantly
Intestinal secretagogues					
Linaclotide (290 µg once a day)	IBS with constipation	Effective	High	Diarrhoea significantly more common with linaclotide than with placebo in a meta-analysis of three RCTs	None
Lubiprostone (8 µg twice a day)	IBS with constipation	Effective	Moderate	Nausea significantly more common with lubiprostone than with placebo in a meta-analysis of three RCTs	Only a modest benefit over placebo in published RCTs
Plecanatide (3–6 mg once a day)	IBS with constipation	Effective	Moderate	Diarrhoea significantly more common with plecanatide than with placebo in a meta-analysis of two RCTs	Only a modest benefit over placebo in published RCTs
Tenapanor (50 mg twice a day)	IBS with constipation	Effective	Moderate	Diarrhoea more frequent with tenapanor than with placebo	Awaiting publication of all phase 3 trial data
Psychological therapies					
Cognitive behavioural therapy or gut-directed hypnotherapy	No specific IBS subgroup recruited	Effective	Very low	Adverse events not reported in individual RCTs, precluding their assessment in a meta-analysis of 36 RCTs	All RCTs at high risk of bias because of the nature of the interventions studied; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each intervention; time consuming because of need for therapist contact; minimal availability in some countries

Adapted from Ford and colleagues.[6] Most drugs should be trialled for 3 months, with their efficacy then reviewed (except for rifaximin, which is a 2 week treatment course). IBS=irritable bowel syndrome. RCT=randomised controlled trial. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. *A low FODMAP diet should not be maintained in the long term; to date, the restriction phase in most published RCTs has been a maximum of 3–4 weeks.

Table 2: **Summary of evidence for efficacy of treatment approaches for IBS**

139 patients with IBS with constipation showed an increased number of bowel movements, yet no improvement in abdominal pain.[107] Similarly, there are only a few small randomised controlled trials of antidiarrhoeals, such as loperamide.[6] Nevertheless, some patients find laxatives or antidiarrhoeals useful. In a meta-analysis of 26 trials, antispasmodic drugs were more efficacious than was placebo (RR of remaining symptomatic 0·65; 95% CI 0·56–0·76), although side-effects were more common with antispasmodics (1·60; 1·15–2·21).[6] In

terms of individual drugs, otilonium, cimetropium, pinaverium, and hyoscine had the most evidence for efficacy; however, availability is an issue in some countries. A 4 week randomised controlled trial of pinaverium, which recruited 427 Chinese patients with IBS with diarrhoea and used endpoints recommended by the US FDA, showed a significant benefit of the drug over placebo for abdominal pain and diarrhoea,[108] suggesting that antispasmodics might be efficacious in patients with IBS with diarrhoea. Peppermint oil also appeared superior to placebo in a meta-analysis of seven randomised controlled trials (RR of remaining symptomatic 0·54; 95% CI 0·39–0·76);[6] however, a subsequent placebo-controlled trial of small intestinal or ileocolonic-release formulations did not show efficacy for endpoints recommended by either the US FDA or the European Medicines Agency.[109]

Second-line medical therapies

Given the accepted role of the gut–brain axis in IBS, the use of antidepressant drugs and medications targeting the CNS, or central neuromodulators, as a potential therapy is logical. There is some evidence for the efficacy of tricyclic antidepressants. A meta-analysis of 12 randomised controlled trials reported an RR of remaining symptomatic of 0·65 (95% CI 0·55–0·77) compared with placebo; however, trial quality was low and, in most randomised controlled trials, patients were not recruited according to predominant stool pattern.[110] Adverse events were more common with antidepressants than with placebo (RR 1·56; 95% CI 1·23–1·98). Tricyclic antidepressants have neuromodulatory properties and slow gastrointestinal transit;[111] therefore, they might be best for patients with predominant pain, diarrhoea, or both. Evidence for efficacy of selective serotonin reuptake inhibitors in the same meta-analysis was less convincing.[110] A 12 week placebo-controlled trial of pregabalin in 85 patients did not show adequate relief of symptoms; however, there were significant improvements in global symptoms, pain, diarrhoea, and bloating.[112] All other second-line therapies are licensed and are used on the basis of predominant stool pattern.

5-HT4 agonists accelerate gastrointestinal transit. Tegaserod was more efficacious than was placebo in IBS with constipation;[113] however, the drug was withdrawn because of a small excess number of cerebrovascular and cardiovascular ischaemic events. Tegaserod was reintroduced in the USA in 2018 for female patients who were aged younger than 65 years and did not have existing cardiovascular disease. Prucalopride, another 5-HT4 agonist, was superior to placebo in chronic constipation;[106] however, to date, there are no randomised controlled trials in IBS with constipation. Intestinal secretagogues (eg, lubiprostone, linaclotide, plecanatide, and tenapanor) act on ion channels in enterocytes, leading to water efflux, thereby accelerating gastrointestinal transit and improving stool consistency. Placebo-controlled trials have shown efficacy of these drugs in IBS with constipation,[114–117] although there have been no head-to-head trials. A network meta-analysis of 15 randomised controlled trials showed similar efficacy for all drugs; however, linaclotide ranked first for improvements in global symptoms, abdominal pain, and stool frequency, whereas tenapanor ranked first for improvement in bloating.[118] Diarrhoea was the most common adverse event with all drugs except for lubiprostone, which causes nausea in up to 20% of patients.[118]

Licensed therapies for IBS with diarrhoea include the 5-HT3 antagonists alosetron and ramosetron, a peripherally acting mixed μ-opioid and κ-opioid receptor agonist and δ-opioid receptor antagonist eluxadoline, and the minimally absorbed antibiotic rifaximin. 5-HT3 antagonists and eluxadoline slow gastrointestinal transit and reduce visceral hypersensitivity.[119] 5-HT3 antagonists also alter rectal compliance.[120] Rifaximin has been tested on the basis that alterations in the gastrointestinal microbiota and small intestinal bacterial overgrowth might, in part, be responsible for symptoms in IBS; however, the exact mechanism of action remains uncertain.[121] Although all of these drugs have shown efficacy over placebo,[113,122–124] there have been no head-to-head

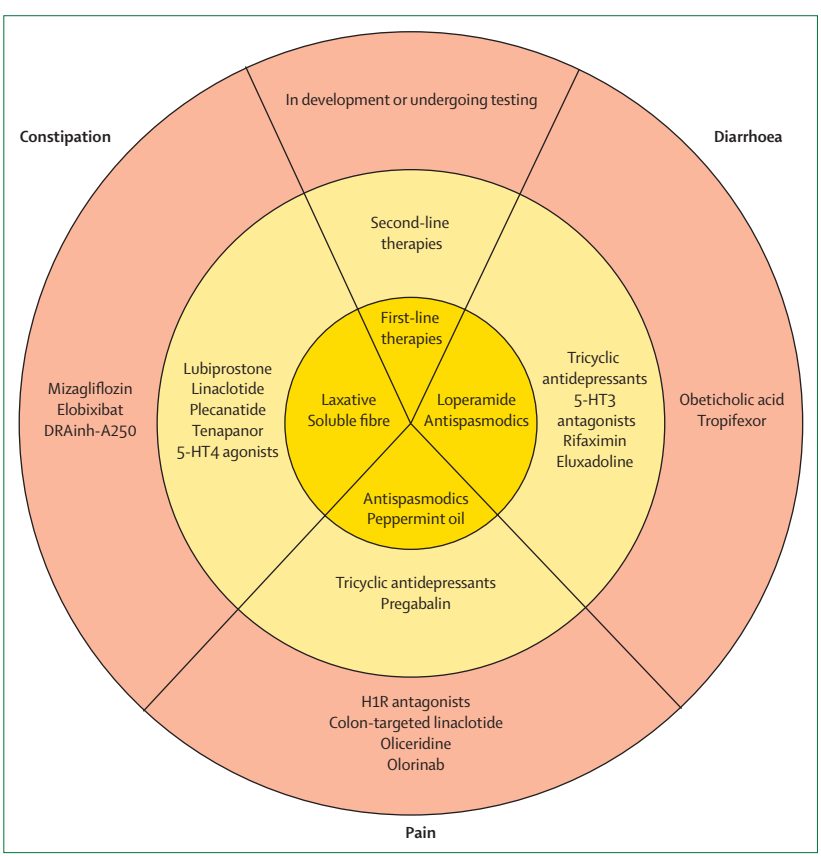

Figure 5: **Current and emerging treatment options for IBS**
IBS=irritable bowel syndrome.

trials. A network meta-analysis of 18 randomised controlled trials showed that 5-HT3 antagonists ranked first for improvement in global symptoms, abdominal pain, and stool consistency.[125] All drugs, except for rifaximin, were more likely to cause constipation than was placebo. A crossover placebo-controlled trial of ondansetron, another 5-HT3 antagonist, in 120 patients with IBS with diarrhoea showed significant improvements in stool consistency and urgency, but not pain.[126] A large randomised controlled trial is ongoing (NCT03555188).[127] Overall, there is a plethora of medication choices for diarrhoea or constipation, but still an unmet clinical need for relief of pain (figure 5).

Psychological therapies

Similar to central neuromodulators, psychological therapies might exert not only central effects on mood, but also peripheral effects on pain perception, visceral hypersensitivity, and gastrointestinal motility.[128,129] A meta-analysis of 36 randomised controlled trials showed that cognitive behavioural therapy, gut-directed hypnotherapy, relaxation therapy, multicomponent psychological therapy, and dynamic psychotherapy were all more effective than was a control intervention.[110] Some trials have evidence of efficacy for up to 12 months of follow-up.[130] These forms of therapy might be intensive, in terms of hours of therapist contact, but subsequent randomised controlled trials have shown that minimal contact cognitive behavioural therapy, cognitive behavioural therapy via the telephone, and group gut-directed hypnotherapy are also effective, even for patients whose symptoms are refractory to medical therapy.[131–133] Whether or not early intervention with psychological therapies can change the natural history of IBS, or whether or not augmentative therapy with a psychological therapy and a central neuromodulator has additive benefit, is unclear.

Future directions and controversies

Reasons for the difference in prevalence of IBS across different countries are uncertain and prevalence data from certain regions are scarce. Our understanding of the epidemiology is likely to increase as the Rome Foundation global cross-sectional survey database of 73 076 participants is analysed further.[13] Despite considerable efforts, a biomarker for IBS remains elusive. A validation study of antibodies to bacterial toxins and host-cell adhesion proteins only modestly distinguished IBS from health.[134] A case-control study reported distinct faecal and urinary metabolomic profiles in individuals with IBS,[135] which might allow for the development of microbe-based treatments. The efficacy of probiotics and faecal microbiota transplantation is inconsistent,[105,136] although a randomised controlled trial of faecal microbiota transplantation with a single, healthy, and well characterised donor showed efficacy.[137] With the discovery of actionable biomarkers to identify the mechanisms underlying symptoms, the hope for the future is that IBS therapy will move away from drugs targeting the predominant symptom, or symptoms, towards one where patients are stratified on the basis of underlying pathophysiology by use of these biomarkers, to facilitate individualised treatment.[138]

Other pharmacological therapies are in development (figure 5). Drugs that reduce uptake of sodium ions from the lumen, via transporters expressed in the intestine, result in water retention in the lumen and loose stools. These drugs include mizagliflozin, a SGLT1 inhibitor, and DRAinh-A250, an inhibitor of DRA. In a phase 2 placebo-controlled trial of mizagliflozin in patients with chronic constipation, response rates were significantly higher with 5 mg and 10 mg doses than with placebo.[139] The medication also appeared safe,[139] albeit after only 1 week of treatment. When administered intraluminally, DRAinh-A250 blocked fluid absorption in mouse colonic loops and reversed loperamide-induced constipation;[140] however, there are no human studies to date.

Bile acids are physiological laxatives and are implicated in the pathophysiology of IBS.[50] Inhibition of the ileal bile acid transporter by elobixibat accelerated colonic transit in patients with constipation,[141] and a trial in Japan showed that a 10 mg dose was efficacious in patients with constipation, including IBS with constipation.[142] Although the drug is licensed in Japan, adverse events occurred in 21 (30%) of 69 patients, particularly diarrhoea and abdominal pain, and this was only a 2 week trial.[142]

Novel analgesic approaches include further refinements of existing secretagogues. Cyclic GMP production in enterocytes is stimulated by some of these drugs, such as linaclotide. When transported into the extracellular space at the basolateral membrane,[143] cyclic GMP leads to decreased conduction of submucosal afferent nociceptive neurons, attenuating visceral pain.[144] A preliminary randomised controlled trial of targeted colonic delivery of linaclotide in patients with IBS with constipation showed pain relief, without effects on constipation,[145] suggesting that cyclic GMP release from enterocytes reduces the function of peripheral visceral afferents.

When conventional opioids bind to μ-opioid receptors, they not only induce analgesia through activation of G protein-mediated pathways, but they also activate β-arrestin, which inhibits gastrointestinal motility and depresses central functions (eg, cognition and respiration). New biased μ-opioid receptor ligands activate the G protein pathway exclusively, leading to analgesia with reduced gastrointestinal dysfunction.[146] Oliceridine is a biased μ-opioid receptor ligand with similar analgesic effects to morphine, although to date there are no human studies in visceral pain.[147] The CB2 agonist, olorinab, has the potential to alter immune function, as well as sensation, given the expression of CB2 in the brain, peripheral nervous system, and gastrointestinal tract. In an open-label trial in patients with quiescent Crohn's disease, olorinab reduced abdominal pain and improved

bowel movements.[148] Clinical trials of olorinab are being done in IBS (NCT04043455). The H1R antagonist ebastine appears to attenuate visceral hypersensitivity in vitro[149] and, in a randomised controlled trial of 45 patients, led to significant improvements in global symptoms and abdominal pain compared with placebo.[149] A trial in 200 participants is in progress (NCT01908465).

In summary, increased understanding of the pathophysiological mechanisms in IBS has ushered in the development of novel treatment strategies to manage patients, particularly the abdominal pain component of IBS, for which central neuromodulators or psychological therapies are the main approaches. The diverse molecular mechanisms to which drugs in development are targeted offer hope for substantial impact in the management of IBS in the foreseeable future. Nevertheless, a strong doctor–patient relationship with attention to the clinical history and an appreciation of the effects of symptoms on the patient's life, together with an explanation of the condition and its natural history, as well as shared decision making, are key to effective management of IBS.

Contributors

ACF, ADS, MCo, and MCa did the literature search, wrote the manuscript, and drafted the figures. ACF and MCa revised the initial manuscript. All authors critically revised subsequent versions of the manuscript and approved the final version.

Declaration of interests

MCo has acted as a consultant to Allergan outside of this Series paper. MCa reports grants from Allergan, Novartis, Takeda; and consulting with fees going to MC's employer, Mayo Clinic, from Allergan, Ironwood, Arena, and Takeda, outside of this Series paper. ACF and ADS declare no competing interests.

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