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Abbreviations:

5-HT	5-hydroxytryptamine
CBT	cognitive behavioural therapy
CI	confidence interval
CRC	colorectal cancer
cGMP	Cyclic GMP
EMA	European Medicines Agency
FDA	Food and Drug Administration

FODMAPs	fermentable oligo-, di-, and mono-saccharides and polyols
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 stool pattern
IBS-U	irritable bowel syndrome unclassified
MC	microscopic colitis
OR	odds ratio
PI-IBS	post-infection IBS
RCT	randomised controlled trial
RR	relative risk
SeHCAT	23-seleno-25-homotaurocholic acid
SSRI	selective serotonin reuptake inhibitor
SIBO	small intestinal bacterial overgrowth
TCA	tricyclic antidepressant

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ABSTRACT

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder whose symptoms include abdominal pain associated with a change in stool form or frequency. The condition affects between 5% and 10% of otherwise healthy individuals in the community 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 IBS is also more common in people with psychological co-morbidity, and in young adult females. The pathophysiology of IBS remains 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 central nervous system processing. Other less reproducible mechanisms may include genetic associations, alterations in gastrointestinal microbiota, and disturbances in mucosal and immune function. In most people the diagnosis can be made based on the clinical history, with limited, 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 those with more severe symptoms; these include central neuromodulators, intestinal secretagogues, drugs acting on 5-hydroxytryptamine or opioid receptors, or minimally absorbed antibiotics (all of which are selected according to predominant bowel habit), and psychological therapies. The increased understanding of the pathophysiology of IBS in the last 10 years has led to a healthy pipeline of novel drugs in development.

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] It affects between and 5% and 10% of the general population, [4] and is characterised by recurrent abdominal pain in association with abnormal stool form or frequency. [5] Treatment aims to improve both 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 more severe symptoms, treatments include central neuromodulators, including low-dose tricyclic antidepressants (TCAs), intestinal secretagogues, drugs acting on opioid or 5-hydroxytryptamine (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 $10 billion in the USA. [9]

SEARCH STRATEGY AND SELECTION CRITERIA

We searched the medical literature using MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials during the last 10 years with the terms “irritable bowel syndrome”, “epidemiology”, “prevalence”, “incidence”, “aetiology”, “pathophysiology”, “diagnosis”, “investigation”, “management”, “therapy”, and “treatment” in order to identify pertinent articles. In addition, we searched clinicaltrials.gov for unpublished trials. We included only publications in English, and selected those articles whose findings were, in our view, of the greatest importance, favouring randomised controlled trials, meta-analyses, and network meta-analyses.

EPIDEMIOLOGY

The most recent 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, using the Bristol stool form scale: [10] IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), IBS with mixed stool pattern (IBS-M), and IBS unclassified (IBS-U) (Table 1). Methodological limitations make it difficult to obtain reliable estimates of prevalence, [11] particularly because, in the absence of universally accepted biomarkers of disease, the diagnosis relies on self-reported symptom clusters. However, as organic gastrointestinal disease in the community is relatively rare, and a diagnosis of IBS is made 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 felt to have IBS, but not meeting such criteria. [12] In addition, both symptom interpretation and reporting are influenced by cultural factors, and can vary among ethnic groups.[11] Prior to publication of the Rome IV criteria in 2016, [5] two systematic reviews examining global prevalence of IBS were conducted. [4,13] The first reported a pooled prevalence of 11.2% (95% confidence interval (CI) 9.8% to 12.8%), [13] ranging from 1.1% in Iran, using the Rome III criteria, to 45% in Pakistan using Rome II. The second review reported a global prevalence of 8.8% (95% CI 8.7% to 8.9%). [4] Prevalence varied widely, from 1.1% in France using the Rome II criteria, and Iran using Rome III, to 35.5% in Mexico using Rome II. [14] Thus,

despite commonly accepted prevalence ranges, variation in estimates between studies is large, partly due to methodological heterogeneity.

Findings from a Rome Foundation 33-nation cross-sectional survey, examining worldwide prevalence and burden of functional gastrointestinal disorders in over 73,000 individuals in 26 countries, were published in 2020. [15] Using Rome IV criteria, prevalence rates ranged between 2% and 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% for Rome IV. However, there remains a dearth of prevalence data from Africa, Eastern Europe, and the Middle East.

RISK FACTORS

In two systematic reviews, rates of IBS were significantly higher in females [4,13] and, when 14 studies were pooled, prevalence was lower in those aged ≥50 (odds ratio (OR) 0.75; 95% CI 0.62 to 0.92) compared with those aged <50 years. [13] There are no reliable data on IBS and socio-economic status. IBS is more common in patients with functional somatic syndromes, such as fibromyalgia and chronic fatigue. [16] Many other psychosocial, biological, and environmental factors are associated with IBS, and may influence symptom severity (Figure 2). However, it is unclear if these are genuine risk factors; most studies are cross-sectional, and lack the temporal element needed to determine cause and effect.

Perhaps the best-recognised risk factor for IBS, observed in approximately 10% of patients, [17] is prior acute enteric infection. This is termed post-infection IBS (PI-IBS), and can occur after bacterial, viral, or protozoal infection. [18] In one retrospective cohort study, even non-specific gastrointestinal infections, which comprised the vast majority of cases, were associated with an equally high risk of PI-IBS to culture-confirmed bacterial or viral infections. [19] A meta-analysis of 45 observational studies reported a four-fold increase in

odds of developing IBS in exposed individuals 12 months post-infection (OR 4.2; 95% CI 3.1 to 5.7). [18] Risk factors for development of PI-IBS included female sex, antibiotic exposure, psychological distress preceding the illness, and severity of infection. [18] Prognosis may be better than in those with a non-infectious cause although, in one longitudinal follow-up study, 15% of those with PI-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, where adverse events in early life, psychological factors, or gastrointestinal infections then trigger alterations in the enteric nervous system, which controls gastrointestinal motor, sensory, mucosal barrier, and secretory responses (Figure 3). [21]

"Traditional" Mechanisms: The Brain-gut Axis, Stress, Visceral Hypersensitivity, and Altered Motility

In addition to the psychological component of IBS, [22] gut-brain communication is bidirectional. Prospective longitudinal studies demonstrate that a subset of patients experience gastrointestinal symptoms first, [23,24] and psychological distress later. Gastrointestinal infection and psychological disorders appear to be distinct risk factors, contributing additively to the development of both PI-IBS and the extra-intestinal 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. [25] On average, about 60% of patients exhibit increased

sensitivity of the gut to different physiological stimuli. [26,27] Disordered motility in IBS is manifested by abnormal colonic myoelectric activity, [28] repetitive contractions of the small intestine and colon, associated with abdominal pain, and alterations in gastrointestinal or colonic transit. [29,30] Accumulation of different mechanisms (psychological, sensory, and motor) increases both gastrointestinal and non-gastrointestinal symptom severity, as well as impairments in quality of life. [31,32]

The Gut Microenvironment

As many IBS patients report that their symptoms are associated with eating, or eliminating, certain foods, [33] it has been assumed that diet and, more recently, gastrointestinal microbiota are involved in pathophysiology.

Dietary FODMAPs and Disaccharide Maldigestion

Fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) are present in high levels in some fruits, artificial sweeteners, legumes, and green vegetables, and are poorly absorbed in all individuals. They have fermentative and osmotic effects, which may contribute to symptoms in some patients. [34] Although randomised controlled trials (RCTs) have confirmed that dietary modification can affect IBS symptoms, so far, they have not confirmed symptom generation by a specific food. Patients with IBS exhibit comparable increases in small intestinal water content and colonic volume to FODMAPs to those seen in healthy individuals, but symptomatic responses are greater in IBS, supporting the role of visceral hypersensitivity. [35] Dietary disaccharide maldigestion may induce symptoms secondary to osmotic diarrhoea and gas production following fermentation of unabsorbed sugars, [36,37] due to disaccharidase deficiency, classically lactase or, as more recently

demonstrated in 4% of patients with IBS, [38,39] sucrase-isomaltase, which digests sucrose and starch.

The Microbiome

Although some studies demonstrate that patients with IBS have a different gastrointestinal microbiome, compared with healthy controls, [40,41] the role of the microbiota is still questioned, particularly because what constitutes a "healthy" microbiome remains unclear. A systematic review demonstrated few consistent findings in IBS (possibly because age, sex, race, diet, and antibiotic intake were not controlled for in included studies), and certainly no microbiome signature differentiating IBS subgroups. [42] Antibiotics change the intestinal microbiome, and have been associated with development of IBS. [43] Small intestinal bacterial overgrowth (SIBO), has also been implicated, [44] but its role is controversial due, in large part, to limitations of available diagnostic tests, such as glucose and lactulose breath tests [45] and culture of jejunal aspirates. [46]

Bile Acids

Up to 25% of patients who meet criteria for IBS-D have idiopathic bile acid diarrhoea, demonstrated by abnormal retention following 23-seleno-25-homotaurocholic acid (SeHCAT) scanning, [47] or total 48-hour faecal bile acid levels. [48] The latter correlated with stool number and form, and colonic transit, in one case series of patients. [49] Excess faecal bile acids in IBS-D appeared to be associated with dysbiosis, specifically a Clostridia-rich microbiota, in a case-control study. [50]

Barrier Function and Immune Activation

Acute gastrointestinal infections induce changes in intestinal permeability and the microbiome. [51] This may promote activation of immune cells, including T-lymphocytes and mast cells, in the gastrointestinal epithelium, [52] 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 PI-IBS neuronal signalling remained sensitised 2 years after the infection. [53] Other investigators have reported increased gastrointestinal permeability and elevated immune cell counts, even in patients with IBS without an infective aetiology. [54,55]

Genetics

Although research into the genetics of IBS lags behind other conditions, like 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, [56] and mutations in the sucrase-isomaltase gene, [38,39] as previously discussed. In addition, approximately 2% of IBS patients carry missense mutations in *SCN5A*, [57] which alters the function of the voltage-gated mechanosensitive Na^+ channel $Na_v1.5$, and affects smooth muscle function and mechanical sensitivity. In twin studies, concordance of a diagnosis of IBS is commoner in monozygotic, compared with dizygotic twins; however, having a parent with IBS is a stronger predictor, suggesting that environmental factors such as learned illness behaviour are more important. [58]

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Although IBS is a multifactorial and heterogeneous disorder, there are some typical features. The condition is most common among females aged 20 to 40 years, [4,13] although in

some countries appears more prevalent in males. [59] It can occur at any age; [15] the average age of participants in clinical trials of novel drugs in IBS is around 45 years, illustrating the broad age range of patients. Coexistent mood problems and extra-intestinal symptoms, including back pain, gynaecological and bladder symptoms, headache, and fatigue are common, [60,61] 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. Firstly, as IBS is a chronic disorder, causes of acute abdominal pain are ruled out. Secondly, the pain is recurrent, but it is intermittent rather than continuous. Thirdly, pain is usually in the lower abdomen, although Asian patients may report upper abdominal pain. [63] Finally, and most critically, pain in IBS is associated with defaecation, and occurs at the time when the patient experiences alterations in stool frequency or consistency. [5] Although IBS is subgrouped according to predominant stool pattern, [5] this 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. It is often accompanied by visible abdominal distension. [65]

In order to understand the precise meaning of terms such as diarrhoea or constipation, as well as the impact 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, which is discussed later. A detailed history helps differentiate between IBS and other disorders characterised by abdominal pain in association with altered bowel habit, including coeliac disease, IBD, colorectal cancer (CRC), and microscopic colitis (MC). These are considered below.

INVESTIGATIONS

Although there is no universally accepted biomarker for IBS, exhaustive investigation to exclude an organic cause for the symptoms is discouraged, as this 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 extended follow-up. [67] Guidelines recommend a "positive" diagnosis using 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%, and positive and negative likelihood ratios 3.35 and 0.39, respectively. [68] The addition of other features from the clinical history, including absence of nocturnal stools, presence of anxiety, depression, or extra-intestinal symptoms, and a normal full blood count and C-reactive protein enhances the diagnostic performance of the Rome III criteria. [69]

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% in most Western countries, and is an important differential diagnosis. A meta-analysis demonstrated an almost three-fold higher odds of positive coeliac serology in patients with symptoms suggestive of IBS (OR 2.75; 95% CI 1.35 to 5.61), compared with healthy controls, irrespective of predominant stool pattern. [70]

Whether any further investigations are required in a patient with new onset symptoms depends, to some extent, on bowel habit, unless alarm symptoms or signs (Table 2) are present. [71] The latter are an indication for urgent colonoscopy. Colonoscopy should also be performed if the patient is aged ≥50 years and has not already had age-related CRC screening. In addition, unexplained rectal bleeding or iron-deficiency anaemia needs investigation, regardless of age. A family history of coeliac disease, IBD, or CRC is also relevant. In a patient with IBS-C, 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, [72] which is the result of incoordination of the normal functions required for rectal evacuation. If present, anorectal manometry with balloon expulsion testing may be helpful, as the treatment of choice for these conditions is biofeedback, [73] rather than dietary or drug therapy.

In a patient with diarrhoea, there may be greater concern for a missed organic diagnosis. Faecal calprotectin, which is a cytosol protein released by neutrophils, can differentiate between IBS and IBD, [74,75] avoiding the need for colonoscopy, for which the yield is low. In a cross-sectional survey of almost 500 patients with IBS, only 0.4% of patients were found to have IBD at colonoscopy, 1.5% MC, and there were no cases of CRC. [76] MC is more common in females over the age of 45 years. There are other clues to MC as a cause of symptoms, rather than IBS, which should lead to consideration of colonoscopy to obtain colonic biopsies. These include the fact that the presence of abdominal pain is variable, duration of symptoms tends to be shorter, and patients often have coexistent autoimmune disease, report nocturnal diarrhoea and weight loss, or are taking drugs, such as a non-steroidal anti-inflammatory drug or a proton pump inhibitor. [77,78]

Bile acid diarrhoea is another important differential in patients presenting with IBS-D, as its estimated population prevalence is 1%. It can be diagnosed using SeHCAT scanning, a fasting serum 7α-hydroxy-4-cholesten-3-one, fibroblast growth factor-19, or 48-hour faecal bile acid excretion, [79] but these are not universally available. A therapeutic trial of a bile acid sequestrant as a surrogate diagnostic test is an alternative, although it is unclear what dose should be used, and problems with medication compliance may compromise its utility. [80]

The reported association between SIBO and IBS is contentious. [44] Investigations to exclude SIBO should only be considered in patients with clear risk factors, such as previous gastric or intestinal surgery, or known structural abnormalities, including jejunal

diverticulosis. Hydrogen breath tests may be falsely positive, as they are a marker for rapid transit. [45] Instead, culture of jejunal aspirates should be considered if SIBO is suspected. [81]

NATURAL HISTORY AND IMPACT

The typical course in IBS consists of fluctuating symptoms, in terms of bowel habit. [64] Incidence of new-onset IBS was approximately 1.5% to 2.5% per year, over 10 to 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 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]

It also impacts work productivity, [1,2] social integration, and psychosocial factors, such as general and gut-related anxiety, depression, and somatisation. [60,87] Some of these associations are bidirectional, [23,24] so that psychosocial factors can exacerbate IBS symptoms, and the illness experience, and vice versa. One cross-sectional survey showed the impact on daily activity differs according to stool pattern; those with IBS-D avoided travel or leaving the house, due to concerns about toilet access, and those with IBS-C avoided sexual intercourse and reported difficulty concentrating. [88] Associations with severity include overlap with other functional gastrointestinal disorders, [62] and consulter status. [89] However, those who consult with symptoms also have poorer 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

As no medical therapy is proven to alter the natural history of IBS, and the majority of RCTs are only conducted over a 12-week period meaning that their long-term efficacy is unknown, an empathetic approach is key. This 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 fact, structured patient education about the condition led to a significantly greater improvement in symptoms, compared with written information, in one RCT. [94] Treatment is directed towards the predominant symptom, with a realistic discussion of the limitations of available therapies, in order to manage expectations, as most improve symptoms in only 25% to 30% of patients (Table 3), and have only been tested in referral populations. The final decision as to the choice of treatment should be the patient's, after they receive full information on available options in a dialogue with the doctor.

Lifestyle, Diet, and Probiotics

The effect of lifestyle changes in IBS has not been well studied; in a small RCT of physiotherapist-administered exercise, symptoms improved significantly, compared with a control arm with no changes to physical activity. [95] Traditionally, patients with IBS were told to increase dietary fibre intake. However, bran may exacerbate symptoms, [96] although ispaghula husk was more efficacious than placebo in a meta-analysis of seven RCTs (relative risk (RR) of remaining symptomatic 0.83; 95% CI 0.73 to 0.94). [97] Several RCTs demonstrate that FODMAP restriction leads to an improvement in IBS symptoms, compared with habitual diet. [98,99] However, other RCTs 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 may lead to

384 deleterious alterations in the microbiome. [102] FODMAPs should, therefore, be reintroduced to
385 tolerance after a limited period of restriction, but RCTs conducted to date only examine the
386 effect on symptoms during FODMAP elimination. There is little evidence to support benefit
387 of a gluten-free diet in IBS. [103] However, as wheat contains fructans, which is a FODMAP, it
388 incorporates elements of a low FODMAP diet; some patients may, therefore, adapt a low
389 FODMAP diet to one that instead avoids gluten. [104] There have been numerous RCTs of
390 probiotics in IBS but, although some trials show positive results, ability to make
391 recommendations as to which combination, species, or strain is effective is limited due to the
392 wide variety of products studied, and the conflicting results among individual trials. [105]
393
394 **First-line Medical Therapies**
395 Laxatives, antidiarrhoeals, and antispasmodics are all used first-line in IBS. Most
396 RCTs of these drugs are old, and are hampered by suboptimal methodology and
397 heterogeneous patient selection, meaning that efficacy according to predominant stool pattern
398 is uncertain. In addition, efficacy endpoints do not meet current recommendations from the
399 Food and Drug Administration (FDA) or European Medicines Agency (EMA). Although
400 osmotic and stimulant laxatives are efficacious in chronic constipation, [106] there is little
401 evidence for their use in IBS. A placebo-controlled trial of polyethylene glycol in 139
402 patients with IBS-C demonstrated an increased number of bowel movements, but no
403 improvement in abdominal pain. [107] Similarly, there are only a few small RCTs of
404 antidiarrhoeals, such as loperamide. [6] Nevertheless, some patients find laxatives or
405 antidiarrhoeals useful. Antispasmodic drugs were more efficacious than placebo in a meta-
406 analysis of 26 trials (RR of remaining symptomatic 0.65; 95% CI 0.56 to 0.76), although side
407 effects were more common (RR 1.60; 95% CI 1.15 to 2.21). [6] In terms of individual drugs,
408 otilonium, cimetropium, pinaverium, and hyoscine had the most evidence for efficacy;

409 availability is an issue in some countries. A 4-week RCT of pinaverium, recruiting 427
410 Chinese patients with IBS-D, and which used FDA-recommended endpoints, demonstrated a
411 significant benefit of the drug over placebo for both abdominal pain and diarrhoea, [108]
412 suggesting antispasmodics may be efficacious in IBS-D. Peppermint oil also appeared
413 superior to placebo in a meta-analysis of seven RCTs (RR of remaining symptomatic 0.54;
414 95% CI 0.39 to 0.76), [6] although a subsequent placebo-controlled trial of small intestinal or
415 ileocolonic-release formulations did not demonstrate efficacy for either FDA or EMA-
416 recommended endpoints. [109]
417
418 **Second-line Medical Therapies**
419 Given the accepted role of the gut-brain axis in IBS, the use of antidepressant drugs
420 and CNS targeted medications, or central neuromodulators, as a potential therapy is logical.
421 There is some evidence for efficacy of TCAs; a meta-analysis of 12 RCTs reported a RR of
422 remaining symptomatic of 0.65 (95% CI 0.55 to 0.77) compared with placebo, but trial
423 quality was low and in most RCTs patients were not recruited according to predominant stool
424 pattern. [110] Adverse events were more common (RR 1.56; 95% CI 1.23 to 1.98). TCAs have
425 neuromodulatory properties and also slow gastrointestinal transit, [111] so may be best for
426 patients with predominant pain and/or diarrhoea. Evidence for efficacy of selective serotonin
427 reuptake inhibitors (SSRIs) in the same meta-analysis was less convincing. [110] A 12-week
428 placebo-controlled trial of pregabalin in 85 patients failed to demonstrate adequate relief of
429 symptoms, but there were significant improvements in global symptoms, pain, diarrhoea, and
430 bloating. [112] All other second-line therapies are licensed and are used based on predominant
431 stool pattern.
432 5-HT_4 receptor agonists accelerate gastrointestinal transit. Tegaserod was more
433 efficacious than placebo in IBS-C, [113] but was withdrawn due to a small excess number of

cerebrovascular and cardiovascular ischaemic events. It was reintroduced in the USA in 2018 for female patients <65 years without existing cardiovascular disease. Prucalopride, another 5-HT_4 agonist, was superior to placebo in chronic constipation; [106] there are no RCTs in IBS-C. Intestinal secretagogues, such as 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 demonstrated efficacy of these drugs in IBS-C; [114-117] there have been no head-to-head trials. A network meta-analysis of 15 RCTs demonstrated similar efficacy for all drugs, but linaclotide was ranked first for improvements in global symptoms, abdominal pain, and stool frequency; tenapanor ranked first for improvement in bloating. [118] Diarrhoea was the most common adverse event with all drugs except lubiprostone, which causes nausea in up to 20% of patients. [118]

Licensed therapies for IBS-D include the 5-HT_3 antagonists alosetron and ramosetron, a peripherally acting mixed opioid receptor agonist/antagonist eluxadoline, and the minimally absorbed antibiotic rifaximin. 5-HT_3 antagonists and eluxadoline slow gastrointestinal transit and reduce visceral hypersensitivity. [119] 5-HT_3 antagonists also alter rectal compliance. [120] Rifaximin has been tested on the basis that alterations in the gastrointestinal microbiota and SIBO may, in part, be responsible for symptoms in IBS; the exact mechanism of action remains uncertain. [121] Although all these drugs have demonstrated efficacy over placebo, [113,122-124] again there have been no head-to-head trials. A network meta-analysis of 18 RCTs demonstrated that 5-HT_3 receptor antagonists ranked first for improvement in global symptoms, abdominal pain, and stool consistency. [125] All drugs, except rifaximin, were more likely to cause constipation than placebo. A crossover placebo-controlled trial of ondansetron, another 5-HT_3 antagonist, in 120 patients with IBS-D demonstrated significant improvements in stool consistency and urgency, but not pain; [126] a large RCT is ongoing. [127]

Figure 5 outlines the spectrum of medications available for pain, constipation, and diarrhoea in IBS, as well as drugs in development. Overall, there is a plethora of choices for diarrhoea or constipation, but still an unmet clinical need for relief of pain.

Psychological Therapies

Similar to central neuromodulators, psychological therapies may 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 RCTs demonstrated that cognitive behavioural therapy (CBT), gut-directed hypnotherapy, relaxation therapy, multi-component psychological therapy, and dynamic psychotherapy were all more effective than a control intervention. [110] Some have evidence for efficacy out to 12 months of follow-up. [130] These may be intensive, in terms of hours of therapist contact, but subsequent RCTs demonstrate that minimal contact CBT, CBT via the telephone, and group gut-directed hypnotherapy are also effective, even for patients whose symptoms are refractory to medical therapy. [131-133] Whether earlier intervention with psychological therapies can change the natural history of IBS, or whether 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, remain uncertain, and prevalence data from certain regions are lacking. Our understanding of the epidemiology is likely to increase as the Rome Foundation global cross-sectional survey database of 73,076 participants is mined further. [15] Despite considerable efforts, a biomarker for IBS remains elusive. A validation study of antibodies to bacterial toxins and host cell adhesion proteins performed only modestly in distinguishing IBS from health. [134] A case-

control study reported distinct faecal and urinary metabolomic profiles in those with IBS, [135] which might allow the development of microbe-based treatments. The efficacy of probiotics and faecal microbiota transplantation is inconsistent, [105,136] although a RCT of faecal microbiota transplantation using a single, healthy, well-characterised donor demonstrated efficacy. [137] However, more than 50% of patients in this trial continued to have moderate to severe symptoms. With the discovery of actionable biomarkers to identify the mechanisms underlying symptoms the hope is that, in the future, IBS therapy will move away from drugs targeting the predominant symptom, or symptoms, towards one where patients are stratified based on underlying pathophysiology, using these biomarkers, in order 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 looser stools. These include mizagliflozin, a sodium-glucose cotransporter-1 inhibitor, and DRAinh-A250, an inhibitor of the solute carrier 26A3. In a phase 2 placebo-controlled trial of mizagliflozin in patients with chronic constipation, response rates were significantly higher with 5mg and 10mg doses, and the medication 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] there are no human studies to date.

Bile acids are physiological laxatives, and are implicated in the pathophysiology of IBS. [48] Inhibition of the ileal bile acid transporter by elobixibat accelerated colonic transit in patients with constipation, [141] and a trial in Japan demonstrated that a 10mg dose was efficacious in patients with constipation, including IBS-C. [142] Although the drug is licensed in Japan, adverse events occurred in 30% of patients, particularly diarrhoea and abdominal pain, and this was only a 2-week trial.

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

When conventional opioids bind to μ-opioid receptors, they induce analgesia through activation of G protein-mediated pathways, but they also activate β-arrestin, which inhibits gastrointestinal motility and depresses central functions, such as 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 comparable analgesic effects to morphine although there are, as yet, no human studies in visceral pain. [147] The cannabinoid type-2 receptor agonist, olorinab, has the potential to alter immune function, as well as sensation, given expression of cannabinoid type-2 receptors in the brain, peripheral nervous system, and gastrointestinal tract. In an open-label trial in patients with quiescent Crohn's disease, it reduced abdominal pain and improved bowel movements. [148] Clinical trials are being conducted in IBS. [149] The histamine-$_1$ receptor antagonist ebastine appears to attenuate visceral hypersensitivity *in vitro* [150] and, in a RCT of 45 patients, led to significant improvements in both global symptoms and abdominal pain compared with placebo; [150] a larger trial is in progress. [151]

In summary, the greater understanding of 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 currently the main approaches. The diverse molecular mechanisms to which

drugs in development are targeted augurs for substantial impact in the management of IBS in the foreseeable future. Nevertheless, a strong doctor-patient relationship with attention to the clinical history, an appreciation of the impact of symptoms on the patient's life, together with an explanation of the condition and its natural history, and shared decision-making, remain key to effective management.

Contributors

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

Declaration of Interests

ACF has no conflicts of interest. ADS has no conflicts of interest. MC has acted as a consultant to Allergan outside the submitted work. MC reports grant from Allergan, grant from Novartis, grant from Takeda, and other from Allergan, Ironwood, Arena, Takeda (consulting with fees going to employer, Mayo Clinic), outside the submitted work.

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FIGURE LEGENDS.

Figure 1. Global Prevalence of Irritable Bowel Syndrome According to the Rome III Criteria*.

***Note, the prevalence data reported here are taken from studies using the Rome III criteria for IBS, summarised in references 4, 13, and 15.**

Figure 2. Factors Affecting Symptom Severity in Irritable Bowel Syndrome.

Figure 3. Pathophysiological Mechanisms Involved in Irritable Bowel Syndrome.

***Genome-wide association studies have demonstrated associations with variants of chromosome 9 (reference 56), and mutations in the sucrase-isomaltase gene (references 37 and 38), and studies have shown approximately 2% of IBS patients carry mutations in *SCN5A* (reference 57), which alters the function of the voltage-gated mechanosensitive Na^+ channel $Na_v1.5$.**

†See references 17 to 20.

±Gastrointestinal symptoms include abdominal pain, abnormal stool form and/or frequency, and bloating (reference 5); non-gastrointestinal symptoms include back pain, gynaecological and bladder symptoms, headache, and fatigue (reference 60).

Figure 4. Suggested Diagnostic Algorithm for Patients with Suspected Irritable Bowel Syndrome.

***Abdominal pain, related to defaecation, associated with change in stool form or stool frequency (reference 5).**

†Full blood count and C-reactive protein/erythrocyte sedimentation rate

±See Table 2.

§Including family history of inflammatory bowel disease, coeliac disease, or colorectal cancer, or features suggestive of microscopic colitis (female, age ≥50 years; co-existent autoimmune disease; proton pump inhibitor or non-steroidal anti-inflammatory drug

use; duration of diarrhoea < 12 months; weight loss; or nocturnal diarrhoea (references 77 and 78)).

‡Consider measuring SeHCAT retention, serum 7α-hydroxy-4-cholesten-3-one, serum fibroblast growth factor-19, or 48-hour faecal bile acid excretion, where available, or a trial of a bile acid sequestrant, to exclude bile acid diarrhoea.

****If the initial faecal calprotectin level is within the abnormal range the suspicion for inflammatory bowel disease is high, proceed to colonoscopy (reference 74); if the initial faecal calprotectin level is indeterminate according to local laboratory values, 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, including obstructive symptoms (such as a feeling of incomplete evacuation or the need to digitate during defaecation) or paradoxical anal contraction on straining during digital rectal examination, are present consider anorectal manometry with balloon expulsion testing.

Figure 5. Current and Emerging Treatment Options for Irritable Bowel Syndrome.

Table 1. The Rome IV Criteria for Irritable Bowel Syndrome*.

Rome IV IBS Diagnostic Criteria			
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 defaecation; b. Associated with a change in frequency of stool; c. Associated with a change in stool form. **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 who meet criteria for IBS, but who do not fall into one of the other three subgroups according to Bristol stool form type.

***Adapted from reference 5.**

Table 2. Lower Gastrointestinal Alarm Symptoms and Signs (Based on the UK's NICE Guidance*).

Definite Referral Criteria
• Aged ≥40 years with unexplained weight loss and abdominal pain. • Aged ≥50 years with unexplained rectal bleeding. • Aged ≥60 years with change in bowel habit, a positive faecal occult blood test, or iron deficiency anaemia.

***Adapted from reference 71.** Regardless of age, adults 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, need investigation to exclude other gastrointestinal disorders, including cancer.

Table 3. Summary of Evidence for Efficacy of Treatment Approaches for Irritable Bowel Syndrome*.

Therapy	Specific Intervention†	IBS Subgroup Studied	Efficacy	Quality of Data	Adverse Events	Limitations of Data
Diet, lifestyle, and probiotics	Soluble fibre (e.g. ispaghula 20 - 30g/day)	No specific IBS subgroup recruited	Effective	Moderate	Total adverse events no more common with soluble fibre 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	May 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; impact of FODMAP reintroduction not studied within the design
	Exercise	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events not reported	Only two RCTs, which were at high risk of bias; inconsistent effects on symptoms
	Probiotics	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events no more common with probiotics 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 (200mg three times daily)	No specific IBS subgroup recruited	Effective	Low	Total adverse events no more common with peppermint oil 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 may be an issue
	Laxatives (e.g. polyethylene glycol 13.8g once daily and titrated)	Patients with IBS-C	Unclear efficacy	Low	Rates of abdominal pain numerically higher with polyethylene glycol in one RCT	Only two RCTs; both RCTs unclear risk of bias; effect on abdominal pain unclear
	Antidiarrhoeals (e.g. loperamide 4mg as required)	Patients with IBS-D and IBS-M	Unclear efficacy	Very low	Total adverse events no more common with antidiarrhoeals in two RCTs	Only two RCTs; both RCTs unclear risk of bias; not all patients met criteria for IBS; no significant effect on IBS symptoms when data pooled; constipation may be an issue

	Antispasmodics (e.g. cimetropium 50mg three times daily, hyoscine 10-20 mg three times daily, otilonium20-40mg three times daily, or pinaverium 50mg three times daily)	No specific IBS subgroup selected, other than one RCT in patients with IBS-D	May be effective	Very low	Total adverse events significantly more common with antispasmodics 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
Second-line therapies	5-HT_4 agonists (e.g. tegaserod 6mg twice daily)	IBS-C	Effective	High	Diarrhoea significantly more common with tegaserod in a meta-analysis of six RCTs	Concerns regarding small excess of cardiovascular and cerebrovascular events led to withdrawal of tegaserod, reintroduced in 2018 but only for specific patients; no RCTs of prucalopride
	Linaclotide (290mcg once daily)	IBS-C	Effective	High	Diarrhoea significantly more common with linaclotide in a meta-analysis of three RCTs	None
	5-HT_3 antagonists (e.g. alosetron 0.5-1mg twice daily, ramosetron 2.5-5mcg once daily, or ondansetron 4mg once daily and titrated)	IBS-D and IBS-M	Effective	High	Constipation significantly more common with alosetron in a meta-analysis of three RCTs	All RCTs of ramosetron conducted in Japan; serious adverse events with alosetron included ischaemic colitis and severe constipation leading to restricted use; ramosetron is safer, although constipation is still more common with active therapy
	TCAs (e.g. amitriptyline 10-30mg at night or desipramine 50mg at night)	No specific IBS subgroup selected, other than one RCT in patients with IBS-D	Effective	Moderate	Total adverse events significantly more common with TCAs 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
	Lubiprostone (8mcg twice daily)	IBS-C	Effective	Moderate	Nausea significantly more common with lubiprostone in a meta-analysis of three RCTs	Only a modest benefit over placebo in published RCTs
	Plecanatide (3-6mg once daily)	IBS-C	Effective	Moderate	Diarrhoea significantly more common with plecanatide in a meta-analysis of two RCTs	Only a modest benefit over placebo in published RCTs

	Tenapanor (50mg twice daily)	IBS-C	Effective	Moderate	Rates of diarrhoea numerically higher with tenapanor	Awaiting publication of all phase 3 trial data
	Eluxadoline (100mg twice daily)	IBS-D	Effective	Moderate	Rates of constipation, nausea, and vomiting numerically higher with eluxadoline 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
	Rifaximin (550mg three times daily)	IBS-D and IBS-M	Effective	Moderate	Total adverse events no more common with rifaximin in a pooled analysis of three RCTs	Only a modest benefit over placebo in published RCTs
	SSRIs (e.g. fluoxetine 20mg once daily)	No specific IBS subgroup selected, other than one RCT in patients with IBS-C	May be effective	Low	Total adverse events no more common with SSRIs	Only one RCT at low risk of bias; heterogeneity between studies
	Pregabalin (225mg twice daily)	No specific IBS subgroup recruited	May be effective	Low	Total adverse events numerically higher with pregabalin, particularly blurred vision, dizziness, and altered sensation	Only one single-centre RCT although global symptoms, abdominal pain, diarrhoea, and bloating improved significantly
Psychological therapies	CBT 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 due to the nature of the interventions studied; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each intervention; time consuming due to need for therapist contact; limited availability in some countries

***Data adapted from reference 6.**

†Most drugs should be trialled for 3 months, with their efficacy then reviewed, with the exception of rifaximin, which is a 2-week treatment course. A low FODMAP diet should not be maintained long-term; the restriction phase in RCTs to date has been a maximum of 3 to 4 weeks.