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Primer

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Irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is one of the most prevalent disorders of gut–brain interaction, characterized by recurrent abdominal pain or abdominal discomfort associated with altered bowel habits in the absence of identifiable structural disease. IBS affects ~4–11% of the global population and is associated with substantial healthcare utilization, impaired quality of life and considerable socioeconomic burden. IBS is increasingly recognized as a heterogeneous condition caused by dysregulated bidirectional communication within the gut–brain axis. Altered gastrointestinal motility, visceral hypersensitivity, epithelial barrier dysfunction, neuroimmune activation, gut microbiome and metabolome changes, central pain amplification, stress and autonomic dysregulation, and sex-related biological influences underlie pathophysiological mechanisms. IBS can develop after a gastrointestinal infection and can frequently co-occur with other disorders of gut–brain interaction, chronic pain conditions, psychological disorders and organic gastrointestinal disorders such as inflammatory bowel disease and coeliac disease. Diagnosis relies on a positive symptom-based approach using the Rome V criteria, supported by clinical assessment and limited testing to exclude differential diagnoses. Management focuses on improving symptoms and quality of life through an individualized, stepwise approach that involves patient education, dietary interventions, pharmacological therapies and gut–brain behaviour therapies. Emerging biomarkers, multi-omics approaches, digital health tools and precision medicine strategies may enable mechanism-based diagnosis and targeted treatment in the future.

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Introduction

Irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain or abdominal discomfort associated with altered bowel habits, including changes in stool frequency and/or stool form[1]. IBS is classified according to the bowel habit subtypes — IBS with predominant constipation (IBS-C), IBS with predominant diarrhoea (IBS-D), IBS with mixed bowel habits (IBS-M) and unclassified IBS (IBS-U)[1,2]. IBS imposes a substantial global burden owing to its high prevalence, chronic course, and impact on quality of life and healthcare utilization[3–5]. IBS can substantially impair the quality of life of affected individuals, with effects extending beyond gastrointestinal symptoms to daily functioning, work productivity, social relationships, food-related quality of life and emotional well-being. These effects contribute to increased healthcare utilization and indirect costs, including absenteeism and presenteeism[6–8].

Substantial advances in neurogastroenterology and systems biology have reshaped our understanding of IBS pathophysiology. Within the Rome Foundation framework, IBS is classified as a disorder of gut–brain interaction (DGBI)[1], reflecting the bidirectional communication between the peripheral gastrointestinal system and the central nervous system (CNS) that underlies symptom generation. The term does not imply that symptoms originate primarily in the brain, nor does it exclude peripheral biological abnormalities. Although the nomenclature remains debated, it was adopted through an international, multidisciplinary expert process and is used here in the Primer as an integrative framework, recognizing that the relative contributions of peripheral versus central mechanisms vary among patients[9,10]. In IBS, the relationship between the gut and CNS is best viewed as a complex system, encompassing the neural, immune and endocrine systems, and microbial, metabolic and stress pathways, that interact to influence motility, visceral sensation, stress responses and symptom perception[1,11] (Fig. 1). At the same time, CNS processes, including stress responsiveness, emotional regulation and cognitive processing of interoceptive input, contribute to symptom perception and illness behaviour. These interacting mechanisms help explain the heterogeneity of IBS symptoms, the co-existence with other DGBI and non-gastrointestinal conditions, and the variability in treatment responses observed among patients[11,12].

IBS is diagnosed using symptom-based criteria — currently the Rome V diagnostic criteria, which emphasize the presence of recurrent abdominal pain or discomfort associated with changes in stool frequency or form[1]. As no single biomarker currently characterizes IBS, diagnosis relies on a positive clinical strategy, which integrates symptom assessment, recognition of alarm features and limited diagnostic testing to exclude alternative organic disease. A positive diagnostic approach has been shown to improve patient satisfaction, reduce unnecessary investigations and facilitate earlier implementation of targeted management strategies[13,14].

Management of IBS focuses on improving symptoms and quality of life through individualized treatment strategies that address the multifactorial mechanisms. The current approach typically integrates a therapeutic patient–clinician relationship, patient education and reassurance, dietary and lifestyle modifications, pharmacological therapies targeting predominant symptoms, such as bowel habits or visceral pain, and brain–gut behaviour therapies aimed at modulating central and peripheral signalling pathways[1]. Owing to the heterogeneous pathophysiological mechanisms, treatment responses vary among patients, and many individuals require a stepwise or multimodal therapeutic approach.

Despite progress in understanding IBS pathophysiology and treatment, major unmet needs remain. IBS is clinically heterogeneous, and it remains unclear whether all forms of IBS represent variations of the same disorder or distinct mechanistic subtypes with different aetiology and treatment needs. Current therapies are largely selected empirically based on predominant symptoms and benefit only a subset of patients, underscoring the need for validated biomarkers, reliable diagnostic tests, mechanistic subtyping and precision treatment strategies. Key research priorities include better defining the mechanisms underlying bowel urgency, abdominal pain, visceral hypersensitivity, altered bowel control and gut–brain dysregulation. In addition, the roles of diet, the gut microbiome, psychological comorbidity, hormonal changes across the menstrual cycle, pregnancy and menopause must be clarified, as well as which dietary changes or behavioural, neuromodulatory, microbiome-directed or gut–brain therapies are most effective for specific patient subgroups[15]. Emerging multi-omics, microbiome, neuroimaging, digital health and systems biology approaches offer new opportunities to move from symptom-based care towards mechanism-informed diagnosis and individualized management.

In this Primer, we summarize the current knowledge regarding the epidemiology, pathophysiology, diagnosis and management of IBS in adults and highlight emerging insights that are reshaping the existing conceptual framework of this common and complex disorder.

Epidemiology

Prevalence

A 2012 systematic review and meta-analysis of 81 population-based cross-sectional surveys estimated the global prevalence of IBS to be 11.2%[3]. However, this estimate was made across multiple diagnostic criteria, including historical definitions of IBS. Hence, prevalence estimates in individual studies varied widely and were probably overestimated. In 2021, the Rome Foundation conducted an internet-based, cross-sectional survey involving >50,000 individuals from 26 countries using standardized methodology, predefined demographic quotas for age and sex, and Rome IV diagnostic criteria[2]. Overall, the survey reported a pooled prevalence of 4.1% globally. However, this study has a few limitations, including the fact that it is unclear how many people were approached to complete the survey but declined, and whether they differed from people who agreed to participate and completed the survey. In addition, there was reliance on self-completed questionnaires without clinical evaluation or diagnostic testing to confirm diagnoses. Thus, some participants may have had a structural disorder causing their symptoms, although individuals self-reporting relevant organic diagnoses were excluded from meeting criteria for IBS. Moreover, geographical coverage was also limited, particularly in Africa and the Middle East.

In addition, using the Rome IV criteria, the prevalence in countries participating in the internet portion of the survey was found to be lowest in South Asian countries, such as Singapore (1.3%), Japan (2.2%) and China (2.3%), and highest in Egypt (7.6%), although prevalence was between 3% and 5% in most other countries participating[2]. Given the uniform methodology used, these relatively minor variations suggest that genetics, cultural factors and dietary habits may influence the prevalence of IBS. In the same survey, prevalence of IBS was similar in low-income countries, such as Egypt (7.6%), Bangladesh (4.6%), Indonesia (3.5%) and Nigeria (2.7%); however, in some of these countries, face-to-face surveys rather than internet-based surveys were

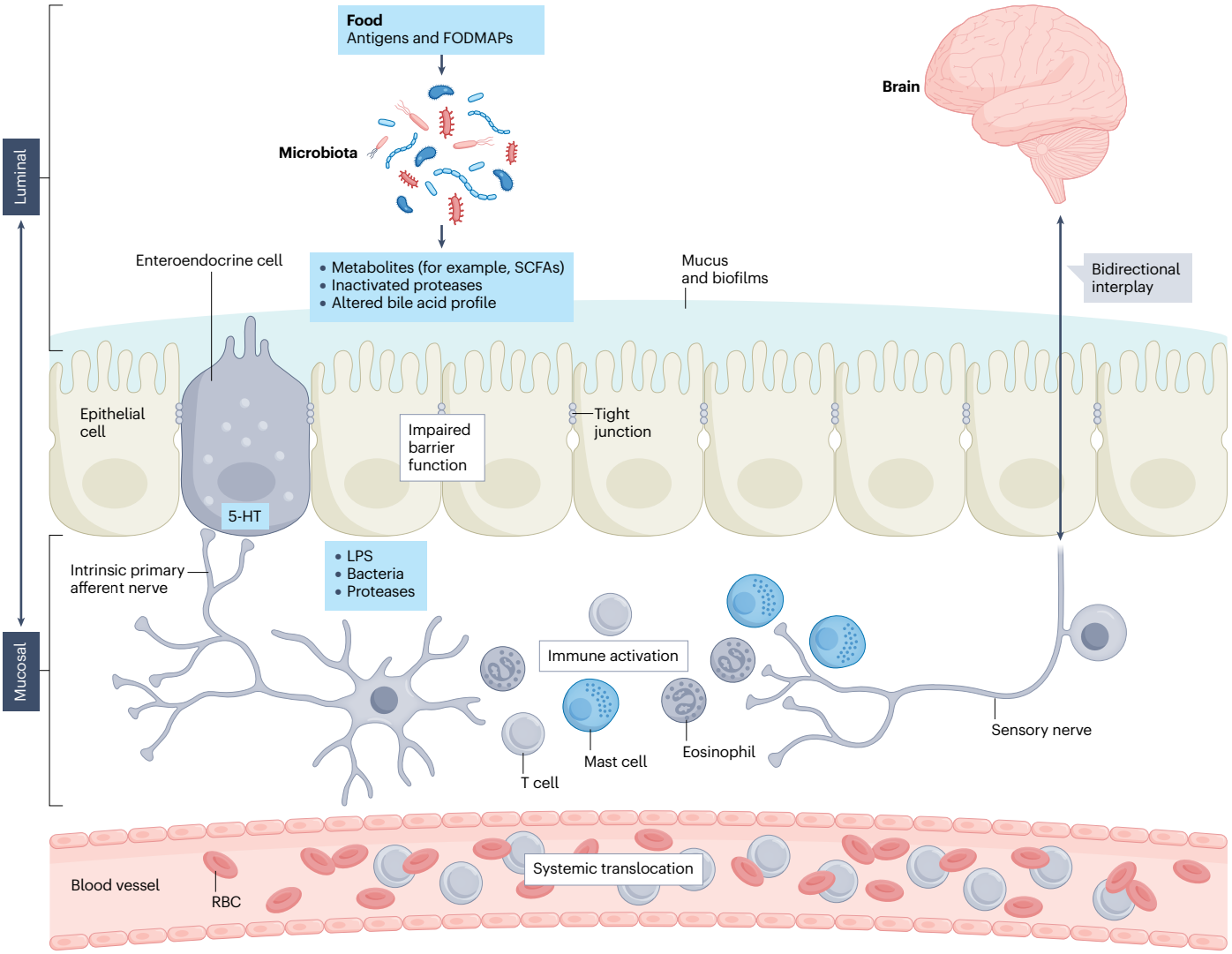


Fig. 1 | Microintestinal environmental factors involved in the pathophysiology of and symptom generation in irritable bowel syndrome. The intestinal microenvironment comprises luminal contents, epithelial barrier properties, microbial activity, immune mediators and bidirectional gut–brain signalling. Dietary factors, including food antigens and fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), influence the luminal environment through interactions with the mucus layer and resident microbiota. Microbial metabolic activity produces bioactive molecules, such as short-chain fatty acids (SCFAs), modifies bile acid pools and can regulate protease activity, thereby affecting epithelial function and sensory signalling. Structural changes in the mucus layer or microbial biofilms may bring microorganisms into closer contact with the epithelium and weaken barrier integrity, allowing luminal components, including lipopolysaccharide (LPS), bacteria and proteases, to interact with epithelial and immune cells. Immune cells, particularly mast cells and enteroendocrine cells, release signalling molecules such as histamine, proteases and serotonin (5-HT), which modulate intestinal secretion, motility and sensory pathways. Through neural and humoral signalling routes, these local processes engage the enteric nervous system and communicate with the central nervous system. Disruption of these interconnected pathways can contribute to visceral hypersensitivity, dysregulated motility and low-grade immune activation, and may participate in the perception of gastrointestinal symptoms characteristic of irritable bowel syndrome. RBC, red blood cell. Reprinted with permission from ref. 61, Elsevier.

conducted owing to a lack of internet access. The epidemiology of IBS in other low-income settings is unclear due to a lack of studies using current diagnostic criteria[3].

The Rome Foundation's internet-based, cross-sectional Rome V survey included 28,771 adults, ~2,000 from each of 15 countries: Argentina, Canada, China, France, Germany, Japan, Mexico, Poland, Romania, South Korea, Spain, Sweden, Turkey, the UK and the USA. The overall prevalence of IBS was 8.5%, including 2.7% with IBS-C, 2.3% with IBS-D, 2.9% with IBS-M and 0.6% with IBS-U[16].

In the USA, 25–50% of individuals with IBS consult with a primary care physician annually, averaging 2–3 visits per year, a rate comparable to that observed in individuals with asthma or migraine[17]. In the UK, IBS accounted for nearly one-third of gastrointestinal presentations in primary care, with approximately one-third referred to

gastroenterologists[18]. One UK study found that almost 50% of individuals with IBS consulted their primary care physician and 25% among these individuals sought gastrointestinal care for their abdominal symptoms in the preceding year[19].

Sex. IBS prevalence varies by sex and shows a predominance in women. The Rome Foundation Global Study estimated that 5.2% of women met Rome IV criteria for IBS compared with 2.9% of men[2,20]. Sex differences in prevalence are also evident across subtypes: for example, IBS-C and IBS-M are approximately twice as prevalent in women as in men (IBS-C, 1.8% versus 0.8%; IBS-M, 1.8% versus 0.9%). By contrast, the sex difference in IBS-D is less marked (1.3% in women versus 1.0% in men)[2], and in some studies using other diagnostic criteria, the prevalence of IBS-D is higher in men than in women[20].

Age. IBS prevalence also varies according to age. In the Rome Foundation Global Study, the prevalence of IBS (according to Rome IV criteria) was highest among individuals aged 18–39 years (5.3%), lower among those between 40 and 64 years (3.7%), and lowest among those ≥65 years (1.7%)[2]. Whether the onset of IBS at different ages represents a biologically distinct disease remains unclear. However, age at symptom onset affects diagnostic evaluation: longstanding, typical symptoms in a younger adult are managed differently than new-onset bowel symptoms in an older adult, in whom colorectal cancer, microscopic colitis, medication effects and differential diagnoses warrant careful consideration. New-onset abdominal symptoms later in life should therefore lower the threshold for investigation to exclude organic disease, without the assumption that the symptoms represent a distinct IBS mechanism.

The natural history of IBS is one of a chronic relapsing and remitting disorder. Extended follow-up in longitudinal studies using the Rome IV criteria suggests that, overall, around two-thirds of people have chronic intermittent symptoms. The remainder one-third either report symptom resolution at the point of follow-up or experience fluctuations in their symptoms, resulting in a diagnosis consistent with another DGBI such as chronic constipation or functional dyspepsia[19]. Despite its chronic nature, large population-based studies demonstrate no convincing evidence that IBS is associated with increased mortality[21,22].

From an epidemiological perspective, IBS is best viewed within a broader landscape of overlapping conditions rather than as an isolated disorder[12]. In the Rome Foundation survey, almost one-third of individuals with any DGBI reported symptoms consistent with at least two different DGBIs in at least two anatomical gastrointestinal regions[23]. Individuals with symptoms overlapping with two or more conditions had higher symptom severity, psychological comorbidity and healthcare utilization, as well as worse quality of life, than those without overlapping symptoms[23]. The gastroduodenal region is the most commonly co-affected region in IBS, with functional dyspepsia overlapping in 17–55% of adults, reaching 55% of individuals in a large cohort with IBS defined by the Rome IV criteria. More broadly, a greater number of overlapping DGBIs was associated with more severe symptoms and increased healthcare use[2,23,24]. IBS-like symptoms can also coexist with organic gastrointestinal disease, including inflammatory bowel disease (IBD) and coeliac disease[25,26].

Risk factors

Studies suggest that the risk of developing IBS arises from complex interactions among biological, psychological, clinical and environmental factors rather than a single cause[27]. However, many reported relationships are associative, and causal effects and modifiable targets require prospective validation.

Biological vulnerability factors include female sex and genetic susceptibility. Female sex is among the most extensively studied risk factors for IBS and is associated with a pooled odds ratio of 1.56 (95% CI 1.4–1.7)[28]. Large-scale biobank studies have identified genetic susceptibility loci associated with common mental disorders and the central and enteric nervous system[29]. However, modest effect sizes suggest that the heritability of IBS is low and can be modified by epigenetic and environmental factors[29,30].

Psychosocial stress and psychological comorbidities are among the strongest risk factors for IBS. Indeed, anxiety and depression are each associated with up to twofold increased risk for developing the condition[31–33]. This relationship is bidirectional – baseline anxiety independently predicts new-onset IBS, whereas existing IBS predicts subsequent development of anxiety and depression[34,35]. Individuals with adverse childhood experiences, including emotional, sexual or physical abuse and exposure to household mental illness or substance abuse, are about twice as likely to develop IBS as those without these experiences[28,36].

Clinical risk factors for IBS include enteric infections, antibiotic exposure, prior intestinal inflammation (for example, diverticulitis), and abdominal or pelvic surgery, whereas environmental factors include diet and chronic stress. Acute infectious gastroenteritis is the strongest established environmental trigger for IBS and provides the clearest model for studying the transition from an acute insult to persistent gastrointestinal symptoms[37,38]. Studies have shown that 10–15% of individuals develop IBS following acute infectious gastroenteritis (that is, post-infection IBS). The risk for developing IBS is further elevated following exposure to pro-inflammatory microorganisms such as *Campylobacter* and SARS-CoV-2 (ref. 38,39). Increased susceptibility to developing post-infection IBS is influenced by the severity and duration of the acute illness, female sex, and psychological distress at or before the infection, including anxiety, somatization or neuroticism, which potentially compromises altered bidirectional gut–brain signalling[38]. Prior antibiotic use has also emerged as an independent risk factor, irrespective of age, particularly with repeated exposures[40,41]. In addition, population-based studies have demonstrated that high diet quality is associated with a reduced incidence of IBS[42].

Financial burden

In a Rome Foundation survey of three nations (Canada, the USA and the UK), individuals with IBS (as per Rome IV criteria) had significantly higher rates of healthcare utilization, including consultations with a physician, medication use and prior abdominal surgery, than those without IBS[6]. Contemporary data concerning the economic impact of IBS on healthcare systems are relatively scarce. However, a UK study estimated that direct healthcare costs attributable to Rome IV IBS exceed £1 billion per year[8]. In the 2024 US study on the burden of gastrointestinal diseases, IBS was estimated to account for ~750,000 office-based physician visits annually[43]. There are also indirect costs that arise from IBS, which result from its effect on the ability to work. Sickness-related absence was reported by 25–30% of individuals with IBS, and presenteeism by >80% of individuals[7,8].

Comorbidities

IBS exists within a broader spectrum of other DGBIs, and its symptoms overlap with conditions such as functional dyspepsia, functional

constipation, functional diarrhoea, bloating and distension, and anorectal disorders. Clinical assessment should therefore include upper and lower gastrointestinal symptoms, with treatment individualized to the contributing symptom domains and mechanisms. A huge number of overlapping DGBIs is associated with increased symptom severity, psychological comorbidity, healthcare utilization and reduced quality of life[12,23]. These graded associations suggest that overlap identifies a clinically important, higher-burden phenotype, which may reflect shared or interacting pathophysiological mechanisms rather than the coincidental presence of separate disorders.

IBS-like symptoms also occur in patients with organic gastrointestinal diseases, including IBD and coeliac disease. Notably, these symptoms can still persist when the underlying disease is in remission or when symptoms cannot be fully explained by objective inflammatory or structural findings[12]. Recognizing this overlap is clinically important to prevent unnecessary escalation of disease-directed therapies and support treatment approaches that target gut–brain mechanisms, visceral hypersensitivity, diet, motility and psychological comorbidity[44].

IBS is also associated with several extraintestinal comorbidities such as chronic pain and psychological disorders. Some of these conditions include fibromyalgia, chronic fatigue, migraine, temporomandibular disorder, interstitial cystitis or bladder pain syndrome, sleep disturbances, anxiety and depression, all of which are reported more frequently in individuals with IBS than in controls[45]. Anxiety and depression were reported in almost 40% and 30% of individuals with IBS, respectively[12,45]. Although the prevalence of IBS among individuals with depression or anxiety is less commonly reported, studies demonstrate a ~1.5–2.4-fold increased risk of IBS among individuals with depression or anxiety, with the relationship confirmed as bidirectional across multiple longitudinal studies[31,46,47]. In addition, endometriosis is also strongly linked with IBS; meta-analyses show twofold to threefold increased risk of IBS in women with endometriosis, and pooled prevalence estimates suggest that IBS affects ~25% of women with endometriosis[48]. Clinically, identifying comorbidities can help explain symptom severity and guide individualized, multidisciplinary management.

Mechanisms/pathophysiology

IBS arises from bidirectional dysregulation across peripheral (Fig. 1) and central pathways within the brain–gut–microbiome system (Fig. 2). Sex-related biological factors, early life and environmental exposures, individual stress responsiveness, and triggers such as infection,

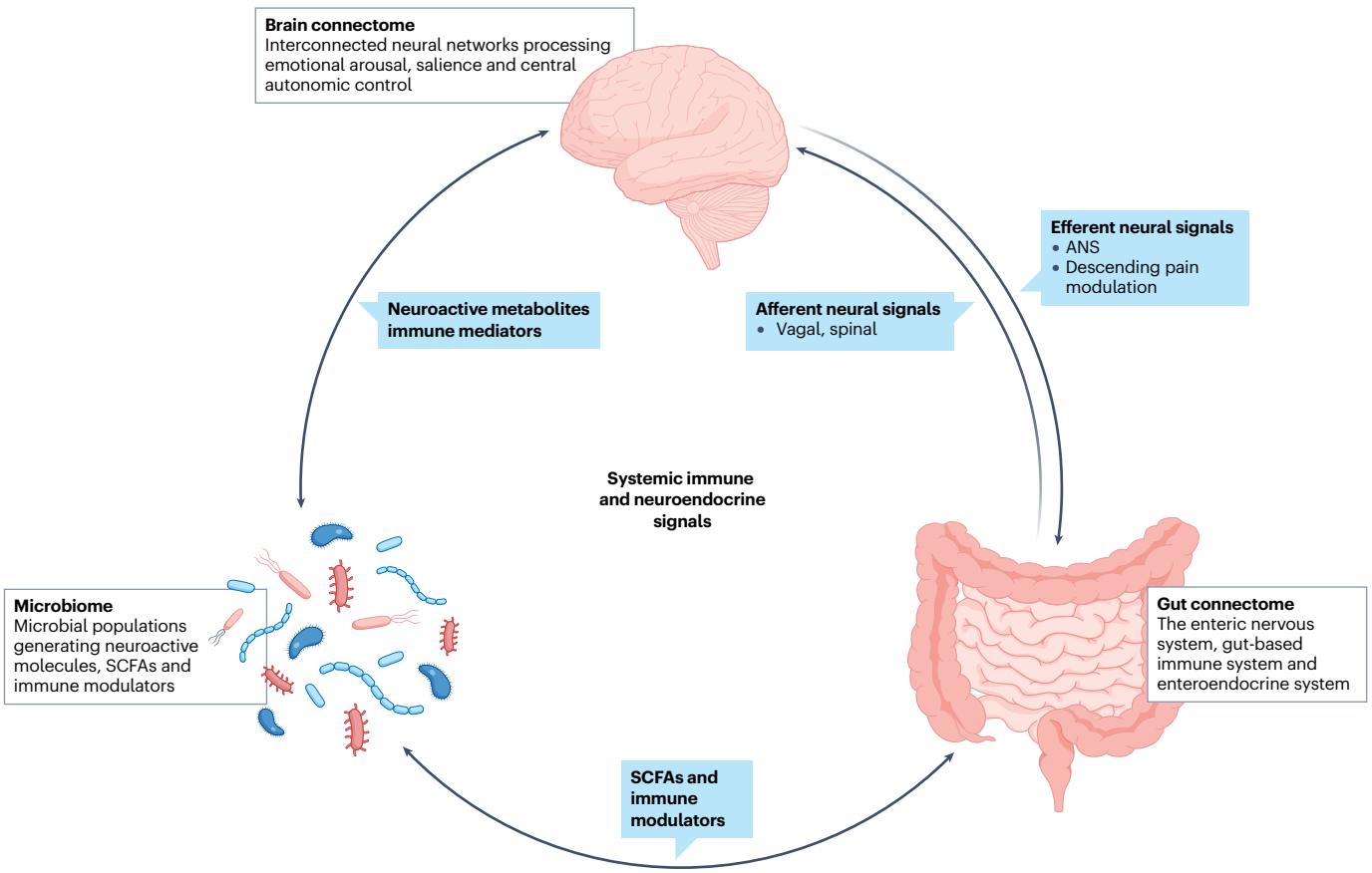


Fig. 2 | Systems biological view of the brain–gut–microbiome system. The brain, gut and gut microbiome are closely interconnected nodes in the brain–gut–microbiome system. This system plays a key role in the maintenance of homeostasis of body and brain in the face of perturbations from the exposome, which includes a wide range of signals from the external environment. The brain connectome is made up of interconnected structural and functional networks involved in the integration, perception and response to signals from the gut connectome, the microbiome and the exposome. The strength of brain–gut–microbiome connections is programmed by genetic factors and early life experiences and is modulated by sex hormones. Its integrated response determines resilience and resistance to diet and psychosocial stress. ANS, autonomic nervous system; SCFAs, short-chain fatty acids.

inflammation or chronic stress, modulate these interactions and contribute to the marked clinical heterogeneity and overlapping phenotypes observed in IBS[49]. Converging evidence supports a model in which visceral hypersensitivity and autonomic nervous system dysregulation are core features of IBS. These abnormalities may arise from altered gut sensory signalling, immune microbial perturbations, and dysregulated central pain processing and stress responses, which collectively amplify gut-derived signals and sustain symptom chronicity[11,50].

IBS is a symptom-defined disorder with a heterogeneous pathophysiology. In some patients, an identifiable exposure or mechanism, such as prior enteric infection or altered bile acid metabolism, may contribute to symptom development. Other conditions, including bile acid diarrhoea and small intestinal bacterial overgrowth (SIBO), can coexist with IBS or cause a similar symptom phenotype. These relationships cannot always be clearly distinguished as causal, coexistent with IBS, or representing an alternative diagnosis; their clinical relevance lies in identifying potentially treatable mechanisms or overlapping conditions that require targeted management.

The brain–gut–microbiome system

The brain–gut–microbiome system refers to the dynamic, bidirectional communication network linking the CNS, the enteric nervous system, the gastrointestinal tract, the immune system, endocrine pathways, vagal and autonomic signalling, microbial metabolites and the gut microbiota. The gut microbiota can influence gut barrier function, immune activation, neurotransmitter and metabolite signalling, stress responsiveness, brain function and symptom perception[50].

Peripheral mechanisms

Altered gut motility. Increased, decreased or disordered motility is common in IBS, including changes in colonic myoelectric activity and transit time as well as repetitive contractions of the small intestine and colon associated with abdominal pain[4]. Alterations in gastrointestinal transit are often associated with bowel habit abnormalities, particularly in IBS-C and IBS-D, although these changes do not fully account for the broader symptom spectrum, such as abdominal pain[51,52]. For example, <25% of patients with IBS-C have slow colonic transit[51,53]. Disorders of rectal evacuation, particularly dyssynergic defaecation, especially in IBS-C, may contribute to symptom generation[54,55]. IBS is associated with accelerated colonic transit only in subsets of patients, with reported prevalences ranging from 15% to 45%. In most cases, the mechanisms underlying accelerated transit remain unknown[51,53]. When viewed together, objective changes in intestinal transit contribute to altered bowel habits in some patients but do not fully explain the bowel habit disturbances characteristic of IBS.

Neuroimmune activation. A few studies assessing the numbers of immune cells in the mucosa of patients with IBS have reported increased cells in subsets of patients[56]; however, not all studies have confirmed these observations[57–59]. Subsequent studies have shifted the focus towards immune cell activation and mediator release, as well as their impact on gut physiology and symptom perception[60,61]. In particular, mast cell degranulation and release of bioactive mediators, such as histamine and tryptase, have emerged as consistent findings. The spatial proximity between mast cells and mucosal nerves correlates with abdominal pain severity, irrespective of bowel habit type, supporting neuroimmune mechanisms underlying the development of symptoms[62]. Mechanistic studies further support this paradigm. For instance, adoptive transfer experiments demonstrate that induced sensory nerve activation and visceral hypersensitivity are mediated by several mechanisms. These pathways include serine proteases acting on PARs[63], histamine via H1–H4 receptors[64], and polyunsaturated fatty acid metabolites activating TRPV4 channels[65]. Taken together, these findings support the concept that immune activation drives neuroimmune mechanisms, leading to altered gut physiology, visceral perception and symptom generation.

Barrier dysfunction and epithelial–neural crosstalk. The intestinal epithelial barrier represents the largest and most dynamic interface between the external environment and the internal milieu. The barrier consists of the mucus layer, epithelial cells sealed by tight junctions, and an underlying vascular barrier and regulates the systemic diffusion of substances from the intestinal lumen[66]. In IBS, studies have reported structural and functional barrier alterations, including increased epithelial permeability and vascular barrier disruption, particularly in IBS-D and post-infection IBS[67]. Furthermore, increased intestinal permeability is associated with abdominal pain severity[68]. Although less pronounced than in coeliac disease or IBD, these abnormalities may enhance access of luminal antigens and microbial products to the mucosal immune system, promoting immune activation[66]. In vivo studies further confirm this finding and demonstrate increased intestinal permeability and passage of microbiota genetic material in people with IBS compared with controls[69]. Ex vivo, supernatants from IBS mucosal biopsies increase paracellular permeability in Caco-2 monolayers, largely mediated by proteases acting on epithelial PAR2 (ref. 70). These findings indicate that soluble mediators within the IBS mucosal microenvironment can impair epithelial integrity and vascular barrier function, facilitating immune activation and systemic dissemination of potentially harmful luminal factors.

Gut microbiome and metabolome. The gut microbiome and metabolome are interconnected biological systems implicated in IBS pathophysiology. Compositional and functional shifts in gut microbiota have been characterized extensively in IBS, and key microbial metabolites, including short-chain fatty acids (SCFAs), bile acids and biogenic amines, have been identified as potential mediators and putative biomarkers of altered sensorimotor functions, barrier dysfunction, neuroimmune interactions, immune activation, visceral hypersensitivity and disturbed gut–brain signalling[60,71].

Most microbiome studies in IBS have relied on faecal samples and therefore primarily reflect the colonic luminal microbiota[61]. The small intestinal microbiome is less well characterized because of challenges in obtaining representative samples. SIBO can cause bloating, abdominal discomfort and diarrhoea, mimicking IBS, with proposed mechanisms including increased fermentation, bile acid deconjugation and mucosal immune activation[72]. However, estimates of its prevalence in individuals with IBS vary widely owing to inconsistent definitions and the limitations of available diagnostic methods[73]. Although jejunal aspirate culture provides direct evidence of SIBO, reported prevalence in IBS versus controls varies with the diagnostic threshold: 13.9% versus 5.0% at $\geq 10^5$ colony-forming units/millilitre (CFU/ml) and 33.5% versus 8.2% at $\geq 10^3$ CFU/ml (ref. 73). Breath testing is less specific: a scintigraphic study showed that the rise in breath hydrogen during lactulose testing often corresponds to caecal rather than small intestinal arrival of the substrate, suggesting that some positive results may reflect rapid orocaecal transit rather than true SIBO[74]. Moreover, the efficacy of rifaximin in IBS-D does not establish SIBO as its mechanism of action, as rifaximin may act through anti-inflammatory effects

and modulation of the colonic microbiome[75]. Therefore, SIBO is best considered a coexisting or a contributing condition in appropriately selected patients rather than an established cause of IBS.

Although no definitive microbial signature is known in IBS, many studies report reduced diversity and altered abundances of specific taxa (for example, Enterobacteriaceae, Lactobacillaceae, *Bacteroides*, *Faecalibacterium* and *Bifidobacterium*)[76]. Studies have identified contributions of microbial species to specific IBS mechanisms. Bacterial infection can induce adaptive immune responses to dietary antigens, increase mucosal permeability and alter pain signalling through histamine H1 receptor-mediated pathways[77]. Histamine-producing bacteria, such as *Klebsiella aerogenes*, may elicit visceral hypersensitivity[78] through H4 receptor-mediated mast cell activation. Impaired microbial inhibition of host intestinal proteolytic activity in post-infection IBS has been linked to barrier dysfunction and IBS symptom severity[79]. *Ruminococcus gnavus*-driven increases in serotonin biosynthesis underlie accelerated transit and increased colonic secretion in IBS-D[80], with similar effects reported for bacterial production of tryptamine from dietary tryptophan[81].

Microbially derived SCFAs exert diverse intestinal and extraintestinal effects. SCFAs maintain epithelial barrier integrity and modulate gut motility and immune function[82]. SCFAs, particularly butyrate, maintain the intestinal barrier by signalling through G-protein-coupled receptors and histone deacetylase inhibition to regulate tight junction proteins, antimicrobial peptides, epithelial turnover and mucosal immune responses. Butyrate also modulates innate and adaptive immunity by reducing pro-inflammatory cytokine production, enhancing antimicrobial and phagocytic activity, promoting regulatory T cell differentiation and IL-10 production, and shaping immune cell balance within the lamina propria[82]. SCFAs modulate gut motility and secretion by stimulating serotonin synthesis in enterochromaffin cells[83]. Furthermore, butyrate production correlates with improved psychological comorbidities in non-constipated IBS (IBS-D and IBS-M)[84]. Additionally, enrichment of Clostridia bacteria may increase bile acid synthesis and excretion, which is observed in 25–30% of people with IBS-D[85,86]. Conversely, antimicrobial properties of bile acids may further shape the gastrointestinal microbiome reciprocally[87]. Together, these findings highlight the complex host–microorganism interactions underlying IBS pathophysiology.

Bile acid dysregulation. Excess delivery of bile acids to the colon activates GPBAR1 (TGR5) on enterochromaffin cells and enteric neurons, promoting serotonin release and other neurotransmitters, which stimulate secretion, accelerate motility, and may contribute to diarrhoea, urgency and abdominal pain[88]. Evidence of bile acid diarrhoea is found in 25–40% of patients with IBS-D and functional diarrhoea, although the prevalence varies according to the diagnostic test and threshold used[89,90]. Whether bile acid diarrhoea represents a mechanistic IBS-D subgroup or a distinct disorder with an overlapping clinical phenotype remains debated.

Central mechanisms

Central mechanisms may contribute not only to symptom perception but also to the persistence of IBS symptoms. Recurrent gut-derived afferent sensory input, together with stress-related and cognitive-affective influences, might lead to persistent alterations in brain networks involved in processing and modulating visceral signals[91]. In some patients, central amplification may contribute substantially to symptom persistence, potentially explaining the incomplete response to therapies that target peripheral mechanisms alone and providing a rationale for gut–brain neuromodulators and brain–gut behaviour therapies (BGBTs) in IBS.

Functional and structural brain network changes. Functional neuroimaging studies demonstrate aberrant neural activity and altered structural and functional connectivity consistently within large-scale brain networks involved in interoception, emotion regulation and autonomic control[11]. The salience network, anchored by the anterior insula and anterior mid-cingulate cortex, exhibits heightened activation and altered connectivity at rest and during visceral stimulation. As a key detector of interoceptive and environmental threats to homeostasis, hyper-reactivity of the salience network is associated with increased pain perception and symptom severity in IBS[92].

In addition, the emotional arousal network shows reduced prefrontal inhibitory regulation of emotional arousal circuits, including the amygdala, suggesting impaired top-down control. This pattern parallels findings in anxiety disorders and may help explain the high psychological comorbidity in IBS[12]. The default mode network, which supports self-referential processing, demonstrates disrupted intrinsic connectivity, whereas the sensorimotor network shows increased cortical thickness and enhanced connectivity in regions processing visceral afferent input[11,93]. Together, these findings are consistent with central amplification of gut-derived sensory signals. Researchers have yet to determine whether this central amplification leads to exaggerated perpeptual response to normal gut stimuli in all patients or whether symptoms are driven by peripheral changes in some patients and central modulation in different patient subsets. Multimodal imaging further indicates increased coupling among salience, emotional arousal and sensorimotor networks, consistent with widespread network reorganization, which sustains chronic pain[94]. Although convergent evidence supports central amplification of visceral signals in IBS, neuroimaging findings require further validation. Most studies have relied on small, single-centre samples, often including <50 patients and disproportionately representing women in premenopause, with limited inclusion of paediatric, older adult and male populations. Differences in IBS subtypes, imaging protocols and analytical methods have also contributed to inconsistent findings across studies[93]. Large-scale replication using standardized multisite imaging repositories will therefore be essential. For example, a UK Biobank analysis of 171,104 participants showed that IBS symptoms were predominantly associated with reduced volumes of cortical and subcortical regions involved in pain, interoception, emotion regulation and sensorimotor processing, with positive associations limited to select basal ganglia regions[95]. PET scan and MRI provide complementary information. PET assesses cerebral blood flow, metabolism or receptor binding, whereas functional and structural MRI evaluate blood oxygen level-dependent activity, functional connectivity and brain morphology. Although the modalities generally implicate overlapping pain-related and salience-related networks in IBS, the small number of PET studies and methodological heterogeneity preclude firm modality-specific conclusions[93]. Future longitudinal and multimodal studies integrating neuroimaging with microbiome, immune, autonomic and clinical phenotyping will be needed to confirm brain network alterations and identify biologically meaningful subsets of patients with IBS.

Stress and autonomic dysregulation. Dysfunction of central stress systems is a key component of IBS pathophysiology. Stress-responsive brain networks translate perceived or anticipated threats into

autonomic, neuroendocrine, immune and behavioural responses, which can influence gastrointestinal motility, secretion, mucosal barrier function and visceral sensitivity. In IBS, repeated or sustained activation of these pathways may create a reinforcing cycle in which stress amplifies gut signalling and gastrointestinal symptoms, which in turn heighten arousal, hypervigilance and symptom-related anxiety[96]. The hypothalamic–pituitary–adrenal axis shows altered reactivity in IBS, with exaggerated cortisol responses to acute stress and blunted responses under chronic stress conditions[97]. This dysregulation is closely linked to dysfunction within the central autonomic network and related brainstem nuclei that coordinate visceromotor, neuroendocrine and behavioural responses to stress. These regions demonstrate altered engagement during the anticipation and experience of visceral pain, with reduced descending inhibitory control correlating with visceral hypersensitivity[93]. Preclinical models support these observations, showing that alterations in corticotropin-releasing hormone (CRH) signalling within the amygdala and brainstem contribute to enhanced visceral nociception and altered gut motility[98]. However, a causative role for the CRH–CRHR1 signalling pathway in IBS symptoms has not been established.

Central sensitization. Central sensitization refers to increased responsiveness of central nociceptive pathways, such that normal or subthreshold afferent input may produce amplified or prolonged pain[11]. In IBS, central sensitization may contribute to heightened perception of visceral signals, potentially reinforced by hypervigilance to gastrointestinal sensations in some patients. Evidence for the involvement of central mechanisms in IBS include visceral and somatic hypersensitivity and the frequent overlap of IBS with other chronic pain conditions, including fibromyalgia, migraine, temporomandibular disorder, and interstitial cystitis or painful bladder syndrome[12,45]. Stress-related alterations in emotion-regulating, pain-modulatory and autonomic circuits may further amplify gut-derived sensory signals and contribute to symptom persistence[11]. Recognizing central sensitization may help explain widespread pain and guide the use of centrally acting therapies.

Sex differences

Sex-related differences occur in hormonal regulation, stress reactivity, central pain processing, immune function, gastrointestinal motility and visceral hypersensitivity in IBS, which probably contribute to the increased prevalence of IBS in women of reproductive age[99]. Female sex is a major risk factor for post-infection IBS, with women having a twofold increased odds of developing the condition[27]. Fluctuations in ovarian hormones modulate central and peripheral mechanisms regulating visceral sensitivity and colonic transit[49]. Symptom exacerbations across the menstrual cycle (for example, the late luteal phase when oestrogen and progesterone decline), symptom differences by menopausal status and overlap with gynecological disorders, such as premenstrual syndrome and premenstrual dysphoric disorder, suggest hormonal amplification of gut–brain signalling[12]. Oestrogen upregulates serotonergic pathways and increases epithelial permeability and mast cell activation, contributing to altered nociceptive signalling[49,99,100], whereas low testosterone levels correlate with worse IBS symptoms and slower gastrointestinal transit[101].

Sex differences in stress responsiveness further contribute to IBS pathophysiology. Men with IBS exhibit enhanced cortisol responses to adrenocorticotropin hormone stimulation, whereas women show blunted cortisol responses, suggesting sex-specific hypothalamic–pituitary–adrenal axis dysregulation[97]. The function of the autonomic nervous system also differs according to sex; men with IBS show greater sympathetic activation during visceral stimulation, whereas women with IBS demonstrate altered sympathovagal balance and lower basal parasympathetic activity[102]. Furthermore, neuroimaging studies demonstrate pronounced sex differences in IBS. Women exhibit greater activation of emotional arousal regions (for example, ventromedial prefrontal cortex, anterior cingulate cortex and amygdala) during visceral stimulation, whereas men preferentially engage cognitive-evaluative areas (for example, dorsolateral prefrontal cortex, insula, and dorsal pons or periaqueductal grey)[103]. Resting state analyses show stronger negative functional connectivity in women than in men, suggesting heightened interoceptive–emotional integration[104]. Structural imaging studies show sex differences in cortical thickness and white matter microstructure, which reflect differences in pain sensitivity, stress reactivity and autonomic regulation[105].

Post-inflammatory and post-infection IBS

For many patients with IBS, the initiating trigger is not clearly identifiable and is likely to be heterogeneous, involving variable contributions from genetic susceptibility, early life exposures, psychosocial stress, diet, medications and alterations in the brain–gut–microbiome system[1,28]. However, a substantial proportion of patients with IBS report symptom onset following acute gastroenteritis, termed post-infection IBS[106]. Although its pathophysiology remains incompletely understood, proposed pathophysiological mechanisms largely overlap with those described in non infectious IBS. Altered gut–brain interactions seem central, as both peripheral inflammatory responses and central factors influence the development of persistent symptoms. Limited data suggest colonic and rectal hypercontractility, hyper-reactivity, and visceral hypersensitivity[27]. Studies also report microbiome alterations, characterized by reduced diversity, relative increases in Bacteroidetes, and decreases in Firmicutes and Clostridiales[27,107]. Sustained increases in intestinal permeability after infection may further promote symptom persistence[108]. Immune dysregulation is consistently implicated, including mucosal changes in mast cells, macrophages and T lymphocytes, along with altered systemic and mucosal cytokine profiles[27,60,108]. Genetic susceptibility, particularly in immune-related pathways, can also contribute to the development of post-infection IBS[109,110].

Non-gastrointestinal infections, most notably COVID-19, can similarly increase IBS risk. Proposed mechanisms for post-COVID gut syndromes include ACE2-mediated epithelial and neuromuscular effects, persistent low-grade inflammation, dysbiosis with reduced SCFA production, altered serotonin signalling, barrier dysfunction, and psychosocial stress acting via the gut–brain axis[111].

IBS-like symptoms are also common in patients with organic gastrointestinal diseases despite remission of overt inflammation[12]. The best-studied example is IBD, which has symptoms mimicking those of IBS. Suggested mechanisms include post-inflammatory visceral hypersensitivity, persistent dysbiosis, alterations in the gut–brain axis, increased intestinal permeability with ongoing immune activation, and disturbed bile acid metabolism or malabsorption[12,112–114]. Overall, these mechanisms converge with the broader pathophysiological models of IBS.

Diagnosis, screening and prevention

Diagnostic criteria for IBS

A positive diagnosis of IBS should be established based on characteristic symptoms, clinical context and limited, targeted testing in the absence of alarm features. IBS must no longer be diagnosed based on the

Table 1 | Differential diagnoses of IBS

Condition	Relationship to IBS phenotype	When to consider	Evaluation	Refs.
Bile acid diarrhoea	May mimic or coexist with IBS-D	Watery diarrhoea, urgency, prior cholecystectomy and/or obesity	Faecal bile acids, serum C4 or SeHCAT	1,75,132
Coeliac disease	May produce an IBS-like phenotype	All IBS bowel habit subtypes, particularly IBS-D and IBS-M	IgA tissue transglutaminase and total IgA	1,75,130
Inflammatory bowel disease	Alternative diagnosis or overlap in remission	Alarm features (for example, bloody stools), inflammatory markers, nocturnal symptoms	CRP, faecal calprotectin Colonoscopy with biopsies when indicated	1,75,129,131
Microscopic colitis	May mimic IBS-D	Chronic watery diarrhoea, particularly in older women, with history of autoimmune disease or taking relevant medications (for example, SSRIs, PPIs)	Colonoscopy with biopsies	1,75
Colorectal cancer	May produce an IBS-like change in bowel habits	Rectal bleeding, iron-deficiency anaemia, unintentional weight loss, abdominal mass, new-onset symptoms at an older age, family history of colon cancer	Colonoscopy or other recommended colorectal cancer evaluation tests	75,121,128,136
Giardia or other infection	May mimic IBS-D or trigger post-infection IBS	Travel, exposure, acute onset	Targeted stool testing	1,75,132
Small intestinal bacterial overgrowth	Potential overlapping or alternative condition Relationship to IBS uncertain	Predisposing surgery or motility disorder	Selective breath testing or aspirate culture	72–75,134
Carbohydrate malabsorption or dissacharidase deficiency	May produce or trigger IBS-like symptoms	Reproducible food-related symptoms	Dietary assessment Selective breath testing Duodenal biopsies for dissacharidase enzyme deficiency assays in selected cases	1,75,135

C4, 7α-hydroxy-4-cholesten-3-one; IBS, irritable bowel syndrome; IBS-D, IBS with predominant diarrhoea; IBS-M, IBS with mixed bowel habits; PPIs, proton pump inhibitors; SeHCAT, selenium-75 homocholic acid taurine; SSRIs, selective serotonin reuptake inhibitors.

exclusion of other conditions that require exhaustive testing (Table 1). Alarm features include anaemia, rectal bleeding, unintentional weight loss, nocturnal diarrhoea, new symptom onset after 50 years of age, and a family history of colorectal cancer, IBD or coeliac disease. In patients with typical IBS symptoms and no alarm features, limited testing is generally sufficient to exclude common differential diagnoses. More extensive or targeted evaluation is warranted in the presence of alarm features, abnormal initial test results, atypical symptoms, a marked change in a previously stable symptom pattern, or other clinical findings that raise suspicion of a structural disorder that can present with similar symptoms (Fig. 3). The key clinical features of IBS are recurrent abdominal pain or discomfort and altered bowel habits. The IBS subtypes of IBS-C, IBS-D, IBS-M and IBS-U are defined by the proportion of bowel movements with abnormal stool form using the Bristol Stool Form Scale (BSFS), that is, hard or lumpy stools (BSFS types 1–2) and loose or watery stools (BSFS types 6–7)[1] (Fig. 3). Reduced stool frequency, straining and sensation of incomplete evacuation are clinically important symptoms in IBS and are diagnostic symptoms of chronic constipation; however, these features do not independently determine the IBS bowel habit subtype. As symptoms and subtype may fluctuate over time, bowel habit subtype should be assessed when patients are not taking medications that substantially alter stool form. The Rome V diagnostic criteria (Table 2), informed by data collected after Rome IV implementation, introduced several changes, including the addition of abdominal discomfort, reduction of the required frequency of abdominal pain and/or discomfort to 3 days per month, and clarification that pain or discomfort should not be continuous; pain that is present all day during waking hours, every day should raise consideration of centrally mediated abdominal pain syndrome. A supportive criterion is that symptoms should not occur exclusively during menses[1].

Studies from Japan and China show that some individuals diagnosed with IBS do not consistently report abdominal pain[115,116]. The Rome IV requirement of pain occurring at least weekly identified patients with more severe disease while excluding those with milder symptoms[19,117,118]. Subsequent studies indicate that abdominal pain or discomfort occurring <3 days per month is also reported in the general population, supporting the use of a threshold of ≥3 days per month to distinguish IBS-related symptoms from sporadic gastrointestinal complaints[5]. Clarifying that pain or discomfort should not be continuous nor occur only during menstruation was included to improve diagnostic precision and reduce misclassification.

In clinical practice, the Rome clinical criteria enable greater flexibility: IBS may be diagnosed when the qualitative Rome V features are present, symptoms are sufficiently bothersome to prompt individuals to seek care, or when symptoms interfere with daily activities and alternative diagnoses have been reasonably excluded[119]. Lower symptom frequency is permitted, and the 6-month duration requirement may be shortened (generally to 8 weeks) based on clinical judgement.

Evaluation of IBS symptoms

A thorough clinical history remains central to IBS diagnosis (Fig. 3). Attentive, empathetic listening, symptom validation, a clear explanation of the diagnosis and agreement on treatment goals can strengthen the patient–clinician relationship and have been associated with improved quality of life, reduced healthcare utilization and better treatment adherence[120].

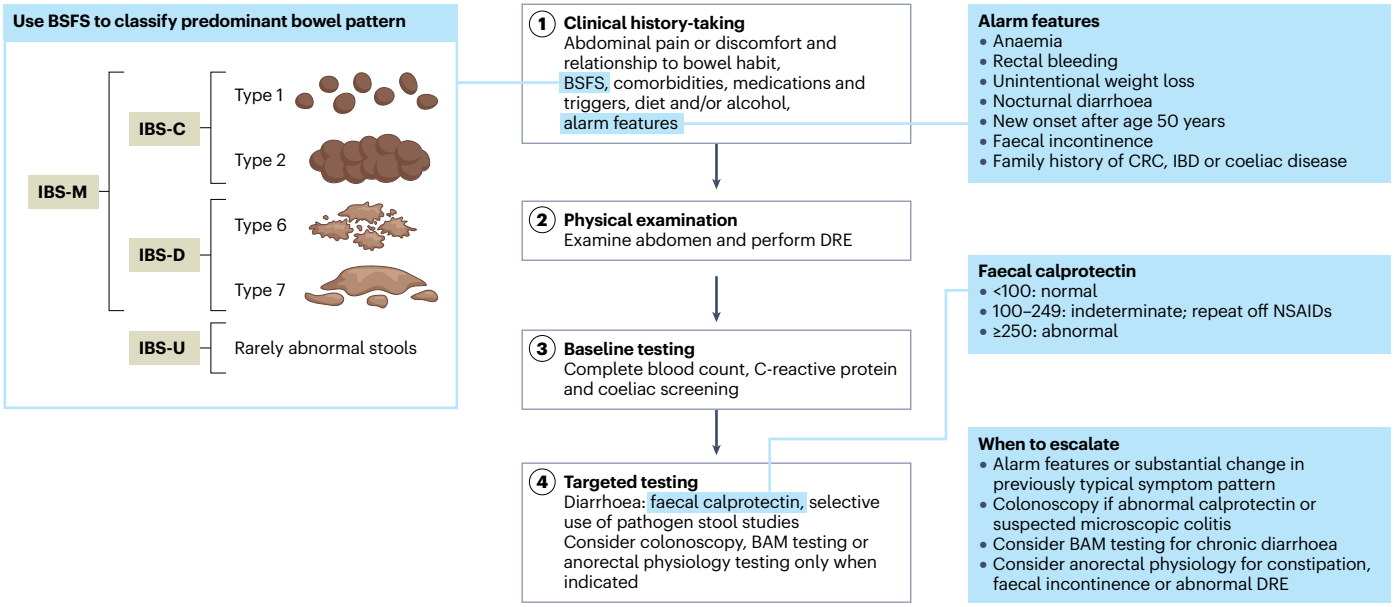


Fig. 3 | Diagnostic approach to IBS. Evaluation begins with a focused clinical history assessing abdominal pain or discomfort related to bowel habits, symptom onset and duration, stool form using the Bristol Stool Form Scale (BSFS), medications, diet and comorbidities, while excluding alarm features. Physical examination includes abdominal assessment and digital rectal examination (DRE). Limited testing may include blood tests (complete blood count, C-reactive protein and coeliac serology) and stool tests, such as faecal calprotectin to exclude inflammatory bowel disease (IBD), and selected pathogen testing when appropriate. Colonoscopy is reserved for patients with alarm features or abnormal findings. Additional testing may be considered based on symptoms, including evaluation for bile acid diarrhoea in people with irritable bowel syndrome (IBS) with predominant diarrhoea and anorectal physiological testing in suspected defaecatory disorders. BAM, bile acid malabsorption; CRC, colorectal cancer; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhoea; IBS-M, IBS with mixed bowel habits; IBS-U, unclassified IBS.

Established symptom-based diagnostic criteria support the diagnosis, but do not independently establish it without accompanying clinical evaluation, particularly in patients with chronic diarrhoea, as active IBD, microscopic colitis and other structural disorders can produce an IBS-like symptom pattern. Use of these criteria must be guided by pretest probability, alarm features and appropriate limited testing. Although alarm features are emphasized during IBS assessment, their predictive value for structural disease seems modest[121].

Clinicians should determine symptom duration and potential triggers such as dietary changes, infection, antibiotics, surgery, stress, psychological trauma or travel. A medical history should confirm whether abdominal pain or discomfort is associated with defaecation and/or changes in stool frequency or form. Stool form should be evaluated using the BSFS[122]. Clinicians should enquire about bloating and distension, which are common and bothersome symptoms in IBS. Bloating refers to the subjective sensation of abdominal pressure or fullness and can be associated with visible abdominal distension, which refers to an increase in abdominal girth[1]. Neither bloating nor distension is required for the diagnosis, as they occur commonly in other disorders. Rectal bleeding and faecal incontinence should also be specifically assessed; incontinence may be under-reported[123].

Coexistent DGBIs, chronic non-gastrointestinal painful conditions (for example, fibromyalgia, interstitial cystitis or migraine) and psychological distress are common comorbidities in patients and can support the diagnosis of IBS. These comorbidities are associated with greater symptom severity, poorer quality of life, functional impairment and increased healthcare utilization[124–126]. Recognition of these associations can guide personalized and multidisciplinary management.

Physical examination helps support a positive diagnosis and exclude differential diagnoses. Abdominal examination should assess for tenderness, distension or masses. A digital rectal examination can identify local causes of bleeding, assess anal sphincter tone (particularly in patients with incontinence) and evaluate for dyssynergic defaecation in patients with constipation.

Symptom-based diagnostic testing

Diagnostic testing should be guided by symptom presentation and disease prevalence. For persistent symptoms, structured follow-up with selective testing may be more cost-effective than exhaustive exclusionary testing[13]. Importantly, negative test results do not always improve reassurance or quality of life, especially in younger patients[127].

For a patient with typical, stable IBS symptoms and no alarm features, initial laboratory evaluation should include a full blood count, CRP and coeliac serologies. Anaemia predicts colorectal cancer in colonoscopy cohorts[128]. A CRP <0.5 mg/dl is associated with a <1% probability of IBD[129]. A systematic review on patients meeting Rome III or IV IBS criteria reported a pooled seroprevalence of coeliac disease of 6% but a biopsy-confirmed prevalence of only 2%. Nevertheless, European data were limited and no studies from the USA were included[26]. Current guidelines recommend IgA anti-tissue transglutaminase testing with total serum IgA levels to exclude selective IgA deficiency, ideally in the setting of a gluten-containing diet[130].

For stool testing, patients with IBS-D or IBS-M should undergo faecal calprotectin measurement. At a prespecified IBD prevalence of 1%, faecal calprotectin has a negative predictive value of 99.8% for distinguishing IBS from IBD, although the positive predictive value is low (9%). A threshold of ≤50 μg/g provided a higher sensitivity than >50 μg/g, with similar specificity[131]. Stool cultures and ova and parasite testing should be reserved for patients with diarrhoea and relevant risk factors such as travel. *Giardia lamblia* (a parasitic protozoan) should be considered where appropriate[132].

Testing for pancreatic insufficiency (faecal elastase), carbohydrate maldigestion, SIBO or dysbiosis are not recommended routinely owing to limited specificity or methodological concerns[74,133,134]. Similarly, routine testing for sucrase–isomaltase deficiency is not recommended as diagnosis requires specialized disaccharidase assays, and performance characteristics of biopsy-based assays are incompletely defined[135]. Bile acid diarrhoea should be considered, particularly after cholecystectomy or in individuals with obesity[132]. Diagnosis can be made by testing faecal bile acids, serum 7α-hydroxy-4-cholesten-3-one (C4) or scintigraphic measurement of selenium-75 homocholic acid taurine, where available[132].

Colonoscopy is not indicated routinely in patients with suspected IBS without alarm features. In a multicentre case–control study, colonoscopy altered the diagnosis in <2% of patients with IBS-D or IBS-M. Microscopic colitis was identified in 1.5%, most commonly in women >45 years of age[136]. Thus, when colonoscopy is performed in suspected IBS-D, mucosal biopsies should be obtained to assess for microscopic colitis. Anorectal function testing should be considered in patients with IBS-C who fail appropriate therapy, when digital rectal examination suggests a defecatory disorder, or in cases of faecal incontinence[1].

Once IBS is diagnosed, clear and confident communication is essential. Describing IBS as a DGBI, rather than emphasizing diagnostic uncertainty, can improve patient understanding and reduce demands for additional testing. Explaining the roles of diet, stress and gut–brain interactions can enhance acceptance and treatment engagement. Educational tools from the Rome Foundation and other gastroenterology societies may further support patient education.

Screening and prevention

Currently, no established primary prevention strategy is available for IBS. However, modifiable lifestyle factors seem to influence risk. One study found that never smoking, adequate sleep, vigorous physical activity, a high-quality diet and moderate rather than high alcohol intake were associated with a reduced risk of incident IBS[42].

Management

Effective management of IBS starts with a strong therapeutic patient–provider relationship, education, reassurance, lifestyle modifications and adequate sleep. Next, treatment should be individualized based on the predominant bowel pattern and symptom drivers such as pain, bloating or urgency. Guidelines recommend employing a stepwise approach, which integrates diet, pharmacological therapies and, when appropriate, behavioural interventions targeting the gut–brain axis[1] (Fig. 4).

Diet

More than 80% of people with IBS report food-related symptoms, and dietary modification is ranked consistently by patients as a preferred strategy for symptom management[137,138]. Accordingly, diet plays a central role in the management of IBS (Box 1). First-line dietary advice

Table 2 | Dietary interventions for IBS

Intervention	Core components	Key evidence and effectiveness	Comments and/or pitfalls
First-line diet	Regular meals, moderate portions, limit fatty meals, moderate caffeine, reduce alcohol, fibre modification, trial probiotic	Indirect evidence that it is superior to habitual diet for global symptoms Foundation of IBS care	One or more components may be implemented depending on diet history Can meaningfully reduce symptoms with lower risk of over-restriction Can be implemented by non-dietitian provider
Low-FODMAP diet	Phase 1 — elimination: short-term (4–6 weeks) restriction of fermentable carbohydrates (fructans, GOS, lactose, fructose, polyols)	~50–70% report global symptom response Mannitol, GOS, fructans identified as commonly causing symptoms Long-term follow-up data confirms sustained benefit in this phase	Not intended as long-term diet
	Phase 2 — reintroduction: systematic dosed challenge of FODMAP subgroups		Important to test individual tolerance and for improving variety in the long term Protocol for implementation varies Important for reducing risk of micronutrient deficiency
	Phase 3 — personalization: liberalize based on phase 2		Aim for healthy and maximal liberalization of diet
Simplified FODMAP diet	Partial FODMAP restriction Two types of approaches: (1) Restrict specific FODMAP subgroups depending on clinical picture (2) Restrict limited high-FODMAP foods from each FODMAP subgroup	Evidence of similar effectiveness to a full low-FODMAP diet in IBS-D	Often used in clinical practice for individuals consuming large concentrations of specific FODMAPs, older individuals, or those with nutritional compromise or mild symptoms Requires larger trials to confirm efficacy
Mediterranean diet	Rich in fruits, vegetables, legumes, nuts and extra virgin olive oil, and low in red meat and processed foods	Growing evidence for IBS symptom improvement	Broad health benefits, for example, cardiometabolic disease May be delivered by non-dietitian provider

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GOS, galacto-oligosaccharides; IBS, irritable bowel syndrome; IBS-D, IBS with predominant diarrhoea. Adapted from ref. 1, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

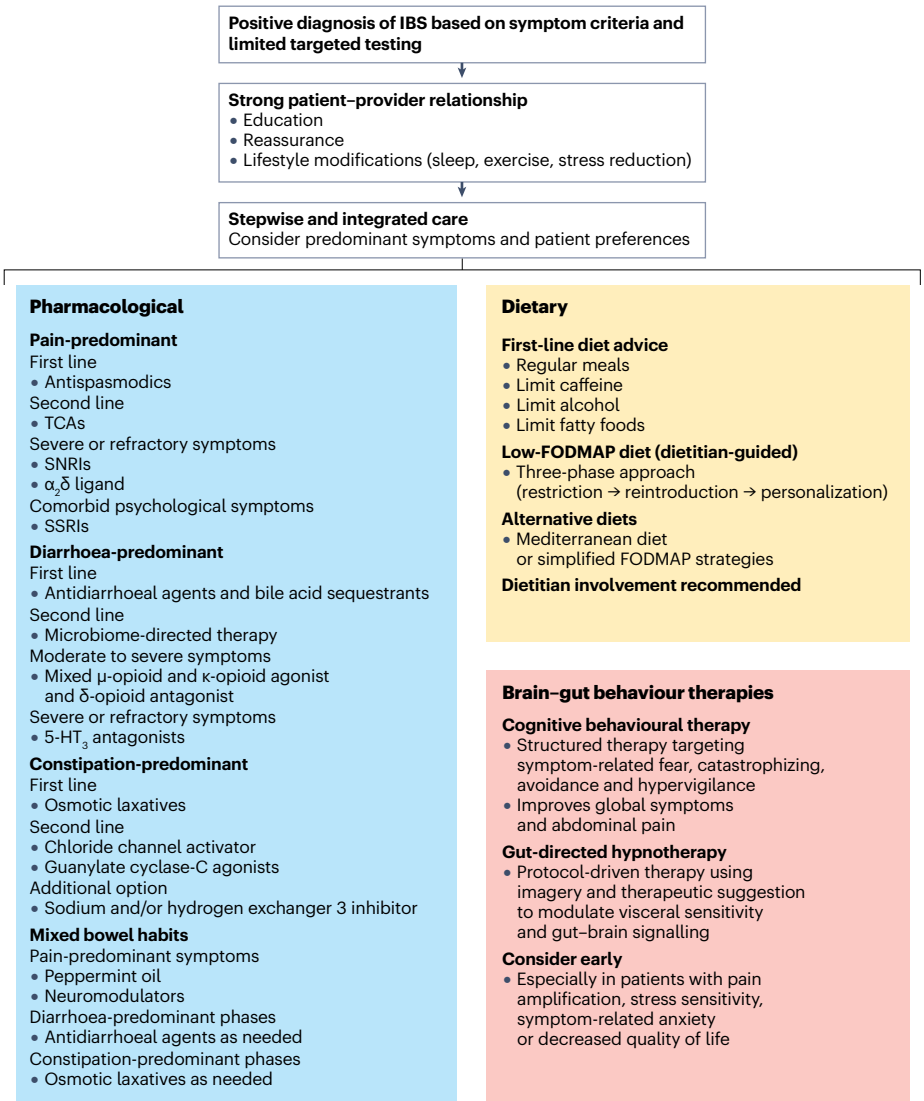


Fig. 4 | Integrated treatment algorithm for IBS. Stepwise, patient-centred management approach following a positive symptom-based diagnosis of irritable bowel syndrome (IBS), clinical assessment and limited targeted testing. Initial care emphasizes a strong patient–provider relationship, education, reassurance and lifestyle modification. Treatment is then guided by predominant symptoms and patient preferences and may include dietary interventions (including dietitian-guided low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) approaches), pharmacological therapy, and behavioural (for example, cognitive behavioural therapy or gut-directed hypnotherapy) or self-management (for example, digital therapeutics) strategies. Pharmacological options are tailored to symptom phenotype, including pain-predominant IBS, diarrhoea-predominant IBS, constipation-predominant IBS and IBS with mixed bowel habits. 5-HT$_3$, serotonin receptor 3; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants. Adapted from ref. 223, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

consists of simple measures such as eating regular meals, limiting caffeine, alcohol and fatty foods, and drinking adequate fluids[138]. Although this set of dietary recommendations has not been evaluated formally, indirect evidence suggests this modified diet may be superior to a habitual diet for improving global symptoms[139].

Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are carbohydrates found in many fruits, vegetables, grains and dairy products, which are not well absorbed and can provoke gastrointestinal symptoms in IBS[140]. Over 20 randomized controlled trials (RCTs), including several sham-controlled trials[139] and a network meta-analysis, evaluated the low-FODMAP diet in IBS and reported superiority over habitual diet for improving global symptoms, abdominal pain and bloating[139]. In clinical practice, a dietitian-supported, structured, three-phase approach is recommended, consisting of a 4–6-week restriction phase followed by systematic reintroduction and personalization[141]. This framework helps minimize unnecessary long-term restriction and reduces the risk of micronutrient deficiency, impaired food-related quality of life and psychological distress. Long-term follow-up data suggest that symptomatic improvement with a low-FODMAP diet can be sustained beyond 6 months[142].

Although the low-FODMAP diet has the strongest evidence, it is not appropriate or effective for all patients. In such cases, alternative dietary strategies, including a Mediterranean diet, a simplified FODMAP approach and other diets, may be considered. One RCT found that more patients with IBS achieved a clinically meaningful improvement in symptoms after 6 weeks on a Mediterranean diet than on standard first-line dietary advice[143]. Smaller studies have reported similar benefits, suggesting that the Mediterranean diet may be a reasonable alternative dietary approach for some patients with IBS[144,145]. A small pilot study in IBS-D demonstrated beneficial effects with a simplified FODMAP diet, which restricts only fructans and galacto-oligosaccharides, rather than all five FODMAP groups[146]; however, larger RCTs are required. Although elimination diets guided by IgG food testing remain controversial, one trial of a novel 18-food IBS-specific IgG ELISA-based elimination diet reported improvement

in global IBS symptoms compared with sham diet[147]. However, further studies are needed.

The majority of trials and real-world studies in IBS involve dietitian-delivered advice, underscoring their central role in successful implementation. Dietitians are uniquely trained to personalize dietary strategies while addressing nutritional and psychosocial challenges inherent to dietary interventions. A more detailed discussion of practical approaches to delivering IBS dietary interventions, including effectiveness of alternative modes of delivery, is available elsewhere[148].

Pharmacological treatments

Pharmacological treatment should be individualized according to predominant symptoms, comorbidities, expected benefit, adverse effects, contraindications and patient preferences. Evidence-based guidelines generally support symptom-directed pharmacotherapy but differ in recommendation strength and certainty because of differences in scope, evidence review and benefit–harm judgements. The American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) recommendations are therefore presented to contextualize the evidence supporting individual therapies[14,149,150]. Across IBS drug trials, <50% of patients typically achieve the prespecified response, with a pooled therapeutic gain over placebo of ~13% using FDA-recommended end points[14,149,150]. Most trials last 12–26 weeks, limiting conclusions about longer-term durability. Furthermore, interpretation of IBS pharmacotherapy trials is complicated by substantial and end point-dependent placebo responses. A meta-analysis reported pooled placebo response rates of 27% for global improvement, 34% for abdominal pain and 18% for the FDA composite end point, with substantial heterogeneity across trials[151]. Accordingly, absolute therapeutic gains over placebo are generally modest, and comparisons across agents using different end points, populations and study durations should be interpreted cautiously.

Pain-predominant IBS. Abdominal pain drives healthcare utilization in IBS[152]. Evidence supporting the usefulness of antispasmodics in IBS is limited. The AGA conditionally suggest antispasmodics based on low-certainty evidence[149], whereas the ACG conditionally recommend against antispasmodics, such as dicyclomine and hyoscyamine, for the treatment of global IBS symptoms but conditionally support peppermint oil, all based on low-quality evidence[14]. Antispasmodics are commonly used as first-line, as-needed therapies for episodic cramping. Peppermint oil has one of the strongest evidence bases among antispasmodics for IBS[14]. It reduces abdominal pain and improves global symptoms, probably through calcium channel blockade and smooth muscle relaxation. Peppermint oil can be used across IBS subtypes as it has minimal effects on stool frequency or consistency[153,154]. Although antispasmodics may reduce abdominal cramping and pain, adverse effects, including dry mouth, constipation, urinary retention and sedation, can limit tolerability, particularly at higher doses and in older adults.

Gastrointestinal society guidelines support the use of tricyclic antidepressants (TCAs) in IBS, although the ACG provide a strong recommendation based on moderate-quality evidence and the AGA a conditional recommendation based on low-certainty evidence[14,149]. An updated meta-analysis subsequently found gut–brain neuromodulators to be efficacious for global IBS symptoms and abdominal pain compared with placebo[155]. The largest body of evidence was available for TCAs, which demonstrated benefit for global IBS symptoms with moderate-certainty evidence[155]. TCAs exert neuromodulatory effects independent of antidepressant activity and are usually prescribed at low doses[149,156]. Tertiary amines (for example, amitriptyline and imipramine) have greater anticholinergic and sedating effects owing to their antihistaminergic properties than secondary amines (for example, nortriptyline and desipramine). Tetracyclic antidepressants, such as mirtazapine, may stimulate

Box 1 | Rome V criteria for IBS

The Rome V criteria for irritable bowel syndrome (IBS) are as follows:

Recurrent, but not continuous, abdominal pain or discomfort on average at least 3 days per month in the last 3 months, associated with two or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Supportive criteria: abdominal pain/discomfort should not be only related with menses.

Predominant bowel habits are based on stool form on days with at least one abnormal bowel movement.[a]

IBS with predominant constipation (IBS-C): >25% of bowel movements with Bristol Stool Form Scale (BSFS) types 1 or 2 and <25% with types 6 or 7.

IBS with predominant diarrhoea (IBS-D): >25% of bowel movements with BSFS types 6 or 7 and <25% with types 1 or 2.

IBS with mixed bowel habits (IBS-M): >25% of bowel movements with BSFS types 1 or 2 and >25% with types 6 or 7.

IBS unclassified (IBS-U): meets IBS criteria but does not meet criteria for IBS-C, IBS-D or IBS-M.

For epidemiological or clinical practice: subtypes may be based on the patient's report that abnormal bowel movements are usually constipation, diarrhoea or both; in IBS-U, abnormal stools are rare.

For clinical trials, subtyping based on at least 2 weeks of daily diary data is recommended, using the '25% rule'.

[a]IBS subtypes related to bowel habit abnormalities (IBS-C, IBS-D and IBS-M) can only be confidently established when the patient is evaluated off medications used to treat bowel habit abnormalities.

Rome V criteria are reprinted from ref. 1 and the bowel habits adapted from ref. 1, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

appetite and promote weight gain. These pharmacological properties may be advantageous in select patients, including those with sleep disturbance, IBS-D or low body weight. Secondary amines may be preferred in older adults or in patients who are more sensitive to anticholinergic effects[157]. A multicentre RCT conducted in the primary care setting demonstrated that low-dose amitriptyline improved multiple symptom-based outcomes, including IBS Severity Scoring System scores (−27.0, 95% CI −46.9 to −7.1) and the proportion of patients reporting relief of global IBS symptoms (OR 1.78, 95% CI 1.19–2.66) compared with placebo across all IBS subtypes at 6 months[156]. Adverse effects, including dry mouth, constipation and drowsiness, may limit tolerability, and withdrawal because of adverse events was more frequent with TCAs than with placebo (RR 1.67, 95% CI 1.08–2.57)[155].

Large, adequately powered RCTs are lacking for non-TCA neuromodulators. However, for refractory pain, other neuromodulators, such as selective serotonin and norepinephrine reuptake inhibitors (for example, duloxetine) or centrally acting $\alpha_2\delta$ ligands, which modulate calcium channels (for example, pregabalin)[155,158], may be considered. Selective serotonin reuptake inhibitors are effective for comorbid psychological symptoms, with limited evidence for abdominal pain relief[155].

Treating comorbid anxiety and depression is important as psychological symptoms are major contributors to long-term impairment of quality of life in IBS. However, standard psychiatric doses of antidepressants do not reliably resolve concurrent IBS, as the neuromodulatory effects of these agents on IBS symptoms seem partly independent of their antidepressant effects[156]. An integrated multidisciplinary approach addressing both gastrointestinal and psychological symptoms is therefore preferred[159].

Despite these options, safe and consistently effective pain-directed therapies remain a major unmet need in IBS. Peripheral visceral afferent pathways, including first-order sensory neurons with cell bodies in the dorsal root ganglia, represent potential targets for future mechanism-based analgesic therapies[160].

IBS with predominant diarrhoea. The management of IBS-D focuses on reducing stool frequency, urgency and incontinence while addressing other coexisting symptoms such as pain and bloating[149,161] (Fig. 5). Loperamide, a peripherally acting μ-opioid receptor agonist, slows intestinal transit and improves stool consistency and urgency but does not always improve abdominal pain or global IBS symptoms. Loperamide should be initiated at low doses, titrated and may be used intermittently. Bile acid sequestrants (for example, cholestyramine and colesevelam) primarily improve stool form rather than global IBS symptoms or abdominal pain[162].

The ACG and AGA support the use of rifaximin for IBS-D; the ACG provide a strong recommendation based on moderate-quality evidence, whereas the AGA provide a conditional recommendation based on moderate-certainty evidence[14,149]. A 2-week course of rifaximin, a minimally absorbed oral antibiotic, produces a modest improvement in global symptoms, bloating and stool consistency compared with placebo, with an absolute therapeutic gain of ~9%[163,164]. Benefits often persist beyond the treatment period, and re-treatment is effective for symptom recurrence for up to two additional courses[163]. Adverse event rates are generally similar to placebo.

Furthermore, the ACG and AGA conditionally recommend eluxadoline based on moderate-certainty evidence[14,149]. Eluxadoline, a mixed μ-opioid and κ-opioid agonist and δ-opioid antagonist, is associated with combined abdominal pain and stool consistency response rates of ~26% versus 17% with placebo, sustained through 26 weeks[165]. Constipation and nausea are common adverse effects. Eluxadoline is contraindicated in patients without a gallbladder, prior pancreatitis, substantial alcohol use, biliary obstruction or severe hepatic impairment due to risk of pancreatitis and sphincter of Oddi dysfunction[166].

Alosetron, a serotonin receptor 3 (5-HT_3) antagonist, improves global symptoms, pain or discomfort, stool frequency and consistency, and urgency. Although the ACG rate the evidence as low-quality, the AGA rate the evidence as moderate-certainty, but societies conditionally recommend alosetron in IBS-D[14,149]. A network meta-analysis found that all FDA-approved medications for IBS-D were superior to placebo for global symptom improvement, with alosetron ranking highest for efficacy in indirect comparisons[167]. However, alosetron is only approved for women with severe IBS-D who have failed standard therapies and has been associated with ischaemic colitis (1:1,000 patients) and constipation. Ramosetron is another 5-HT_3 receptor antagonist that is approved for adults with IBS-D in several countries in Asia[168]. Ondansetron, a widely available 5-HT_3 receptor antagonist used for nausea, seems to improve bowel symptoms and overall IBS-D symptoms but has less effect on pain[169]. The use of 5-HT_3 receptor antagonists is limited by constipation.

Although bile acid diarrhoea is considered a distinct condition from IBS, the AGA and ACG do not recommend testing for it in individuals with IBS-D due to a lack of adequately powered trials. However, a subset of patients meeting IBS criteria may have symptoms partly driven by bile acid-mediated mechanisms. A RCT involving patients with suspected bile acid diarrhoea and those with IBS-D or IBS-M investigated the efficacy of colesevelam, a bile acid sequestrant. The study reported that colesevelam was associated with higher remission rates of bile acid diarrhoea diagnosed by elevated C4 than placebo (OR 11.1, 95% CI 3.5–45.6), with greater benefits observed in those with severe bile acid diarrhoea[170]. Common adverse effects of colesevelam were bloating, stomach ache and nausea; however, none led to treatment discontinuation.

IBS with predominant constipation. Management of IBS-C aims to improve stool frequency and consistency as well as abdominal symptoms, particularly pain and bloating[150,161] (Fig. 6). Polyethylene glycol, an osmotic laxative, improves stool frequency but has limited effects on abdominal pain and global IBS symptoms with low-certainty evidence[171]. It is conditionally suggested by the AGA but not recommended for global symptom relief by the ACG, although both acknowledge its role as an inexpensive, generally well tolerated option for bowel-predominant symptoms. Soluble fibre, particularly psyllium, can improve stool form and global IBS symptoms and is generally better tolerated than insoluble fibre, which may exacerbate bloating[172].

Linaclotide and plecanatide are guanylate cyclase-C agonists that increase intestinal fluid secretion and accelerate transit whilst also improving abdominal pain and global symptoms[173,174]. Lubiprostone, a chloride channel activator, and tenapanor, a sodium–hydrogen exchanger 3 (NHE3) inhibitor, are additional options that improve constipation and abdominal symptoms[175,176]. Evidence is strongest for linaclotide, with high certainty and strong recommendations from both the ACG and the AGA; certainty in evidence for plecanatide, lubiprostone and tenapanor is moderate with conditional recommendations from the AGA[14,150]. Although linaclotide, plecanatide, lubiprostone and tenapanor improve constipation and abdominal symptoms, the

absolute therapeutic gains over placebo are generally modest (ranging from 8% to 20% across pivotal trial end points). Indirect comparisons suggest broadly similar efficacy, although linaclotide consistently ranked highest for most end points[177]. Diarrhoea is the most common adverse effect across these agents, whereas nausea is specifically more common with lubiprostone.

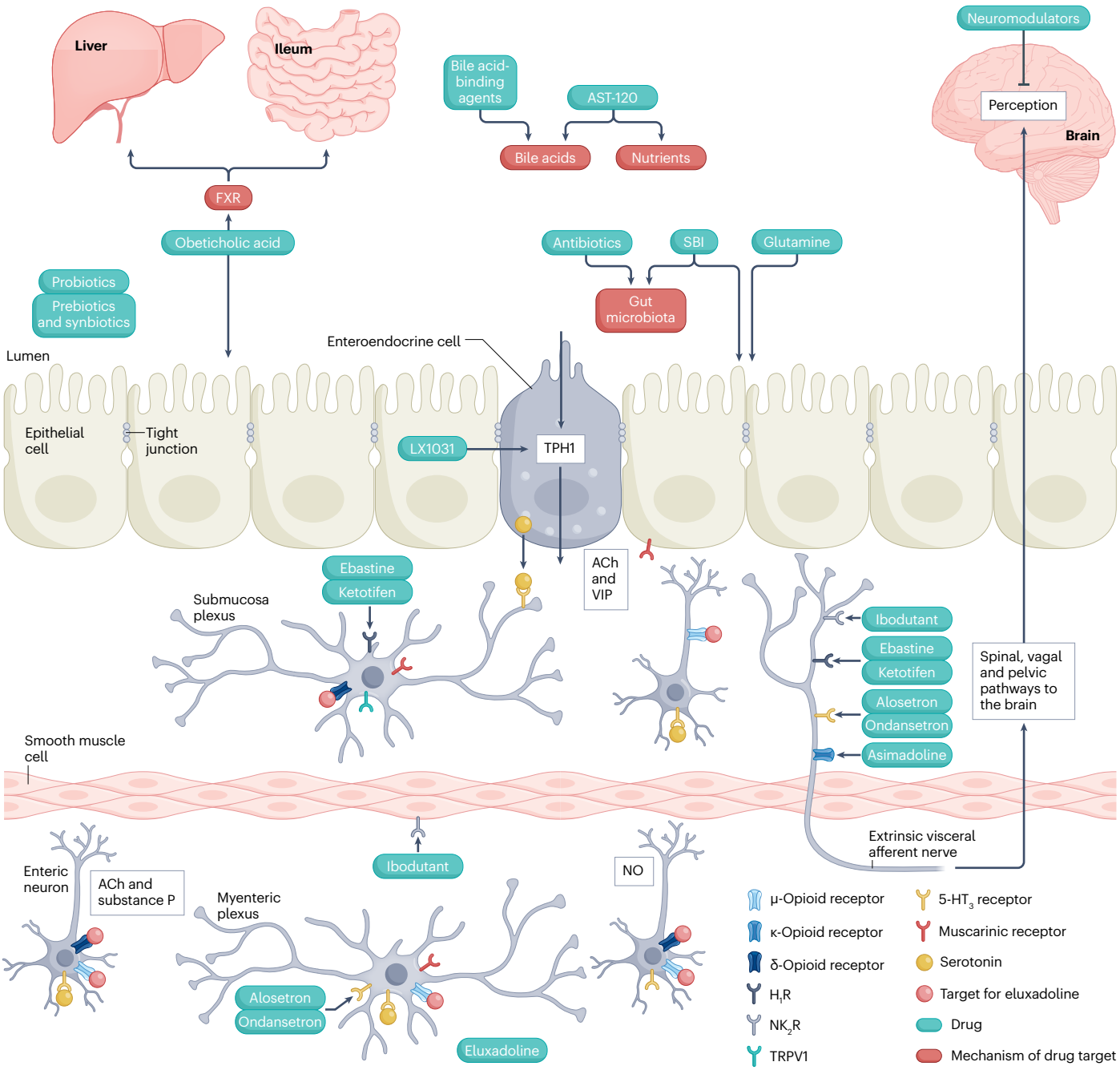


Fig. 5 | Mechanisms and therapeutic targets for irritable bowel syndrome with predominant diarrhoea. Schematic illustrating peripheral and central mechanisms contributing to irritable bowel syndrome with predominant diarrhoea and sites of action of commonly used and other potential therapies. Luminal factors (nutrients, bile acids and microbiota) influence enteroendocrine signalling and serotonin synthesis via tryptophan hydroxylase 1 (TPH1), which modulates enteric neurons within the submucosal and myenteric plexuses. These pathways regulate secretion, motility and visceral afferent signalling to the brain through spinal, vagal and pelvic pathways. Mediators, including serotonin, acetylcholine (ACh), nitric oxide (NO) and substance P, influence smooth muscle activity and sensory signalling. Therapeutic approaches target serotonergic, histaminergic, opioid and neurokinin pathways, bile acid signalling, microbial pathways and epithelial barrier function to reduce diarrhoea, motility disturbances and visceral hypersensitivity. 5-HT_3, serotonin receptor 3; FXR, farnesoid X receptor; H_1R, histamine 1 receptor; NK_2R, neurokinin 2 receptor; SBI, serum-derived bovine immunoglobulin; TRPV1, transient receptor potential vanilloid 1. Adapted from ref. 223, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

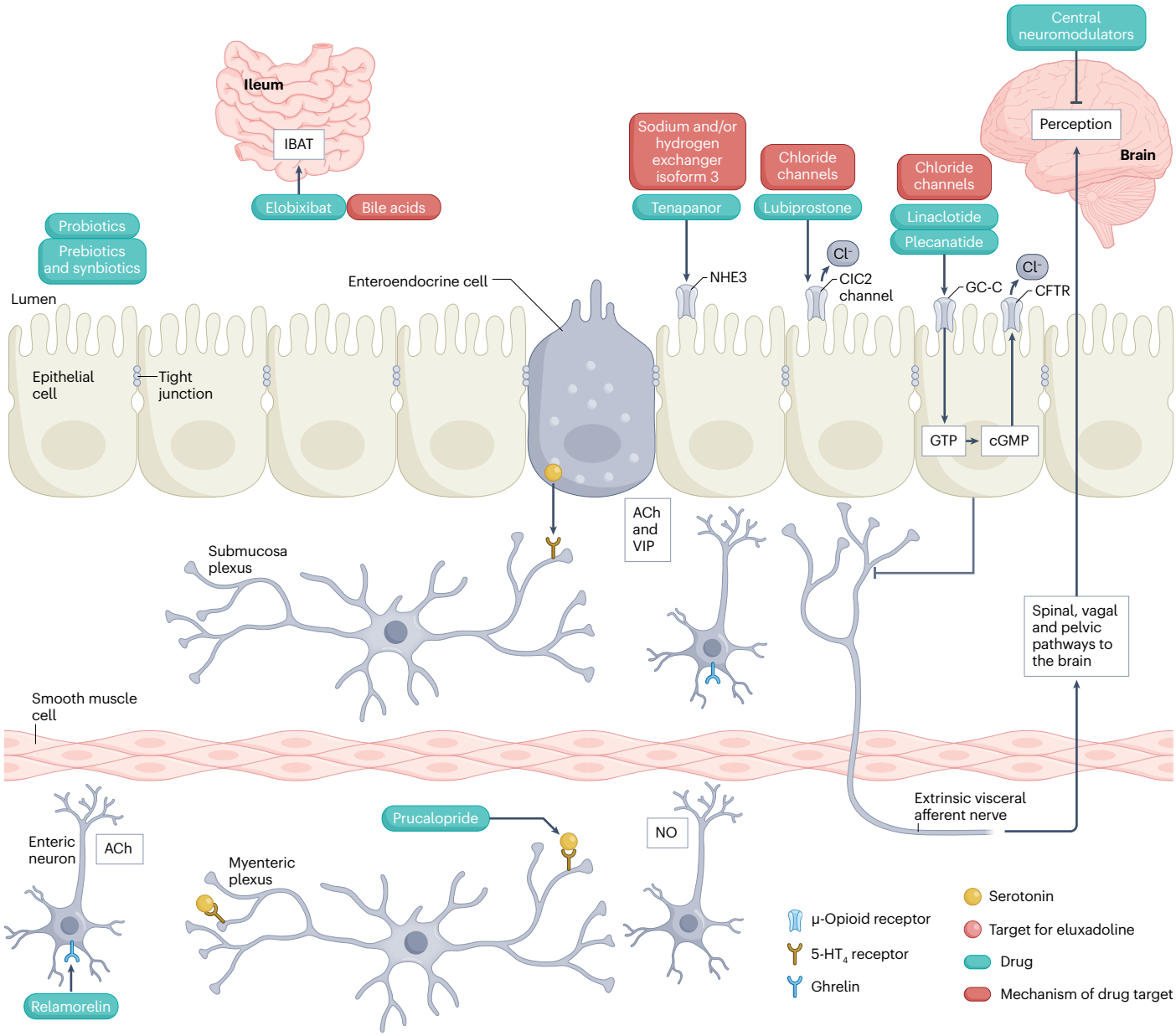


Fig. 6 | Mechanisms and therapeutic targets for irritable bowel syndrome with predominant constipation. Diagram showing key epithelial and neuronal pathways involved in irritable bowel syndrome with predominant constipation and mechanisms of action of major therapies. Luminal signals and microbial metabolites influence enteroendocrine cells and enteric neurons within the submucosal and myenteric plexuses, affecting secretion, motility and visceral signalling. Secretagogues stimulate guanylate cyclase C (GC-C), increasing cyclic guanosine monophosphate (cGMP) and activating cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels to enhance intestinal fluid secretion. Other therapies activate chloride channels, inhibit sodium–hydrogen exchanger 3, stimulate serotonin receptor 4 (5-HT_4) to increase motility, or modulate bile acid signalling and the gut microbiota. These pathways collectively improve intestinal secretion, accelerate transit and alleviate constipation, while central neuromodulators influence symptom perception via brain–gut pathways. ACh, acetylcholine; ClC2, chloride channel 2; IBAT, ileal bile acid transporter; NHE3, sodium–hydrogen exchanger 3; NO, nitric oxide; VIP, vasoactive intestinal peptide.

IBS with mixed bowel habits. IBS-M treatment should be directed by symptoms: peppermint oil, other antispasmodics and neuromodulators may be used for pain, and loperamide might be intermittently used during diarrhoea-predominant phases or osmotic laxatives during constipation-predominant phases. It is conceivable that combination treatments targeting different symptoms may have a potential therapeutic effect. However, RCTs specifically evaluating treatments for IBS-M are lacking.

Brain–gut behaviour therapies

Cognitive behavioural therapy. Cognitive behavioural therapy (CBT) is the most commonly utilized BGBT for IBS, with multiple RCTs supporting its efficacy in improving global symptoms, abdominal pain and quality of life[178–181]. CBT is a structured, time-limited therapy that targets symptom-specific fear, catastrophizing, avoidance behaviours and hypervigilance to visceral sensations, all of which have been associated with increased IBS symptom burden[182]. Core components of CBT typically include psychoeducation, cognitive restructuring, exposure and guided relaxation. CBT is usually delivered by a mental health clinician over 4–12 sessions and has demonstrated durable improvements in abdominal pain, global gastrointestinal symptoms and functional impairment[183]. Evidence also supports manualized CBT programmes focused on teaching and reinforcing CBT skills through nurse-supported[184] and guided self-help formats[179], expanding access to evidence-based care.

Gut-directed hypnotherapy. Gut-directed hypnotherapy (GDH) is a structured, protocol-driven intervention that uses focused attention and therapeutic suggestion to modulate visceral sensitivity, motility and central pain processing. Sessions employ imagery and suggestions designed to normalize gut function and downregulate autonomic arousal, typically paired with daily home practice. RCTs in IBS demonstrate significant and durable improvements in abdominal pain, bowel symptoms and quality of life. GDH protocols typically consist of 7–12 clinician-delivered sessions[183,185,186].

Digital therapeutics. Digital therapeutics are technology-enabled delivery platforms designed to expand access to behavioural interventions, particularly in settings with limited access to trained mental health clinicians[187]. These platforms include app-based CBT and structured online GDH programmes, which have demonstrated efficacy in reducing IBS symptom severity. Patient engagement and sustained use remain important considerations for maximizing treatment effectiveness.

Adjunctive and emerging therapies

Studies have evaluated several adjunctive therapies for use in IBS. A multicentre RCT of patients with IBS-D demonstrated benefit with acupuncture, although durability and efficacy across IBS subtypes remain uncertain[188]. Meta-analyses suggest some probiotics confer modest symptom improvements; however, heterogeneity, limited high-quality evidence and uncertainty regarding optimal strains have led to inconsistent guideline recommendations[189]. Faecal microbiota transplantation trials have yielded mixed results, and responses may vary by donor and recipient microbiome features[190,191]. Hence, faecal microbiota transplantation remains investigational. L-glutamine improved IBS severity scores and intestinal permeability in a single trial in post-infection IBS-D but confirmatory studies are needed[192,193].

Quality of life

Quality of life impairment is a defining feature of IBS and is often disproportionate to objective measures of bowel disturbance[4]. For many patients, the greatest burden extends beyond pain or altered bowel habits to restrictions in daily activities, social participation and emotional well-being. Importantly, quality of life may improve even when gastrointestinal symptoms do not fully resolve. Meta-analyses demonstrate moderate-to-large impairments across physical, emotional and social domains compared with healthy controls, with clinically meaningful improvements following non-pharmacological interventions[194]. Pain and bloating symptoms are independently associated with reduced health-related quality of life and increased anxiety and depression scores[195,196]. In the Rome Foundation Global Epidemiology Study, individuals meeting diagnostic criteria for DGBI had poorer health-related quality of life than those who did not meet the criteria, with IBS particularly showing the most pronounced impairment among bowel disorders[5,197].

Patient experience is a major determinant of quality of life in IBS. Internalized stigma, manifesting as embarrassment, alienation and social withdrawal, explains 25–40% of the variance in quality of life and psychological distress beyond symptom severity[198]. Stigma may also reduce acceptance of neuromodulators and BGBT if patients perceive these treatments as implying that their symptoms are primarily psychological[199]. Clear, culturally sensitive education, which validates symptoms and explains the rationale for centrally acting therapies, can support shared decision-making and adherence. Shame amplifies the relationship between symptom severity and anxiety, depression, and poor quality of life[200]. This suggests that illness perceptions and emotional responses to symptoms reinforce maladaptive coping and impaired well-being. The construct of bothersomeness, that is, the degree to which symptoms are distressing or disrupt daily life, as reported by patients with IBS and functional dyspepsia, captures multidimensional impacts across social, emotional, dietary, occupational and financial domains[201]. Together, these findings underscore empathic communication, clear explanation and collaborative care as core therapeutic elements in IBS.

Among available approaches, BGBTs, particularly CBT, have the most consistent evidence for improving quality of life, often producing larger effects on daily functioning and gastrointestinal symptoms than on mental health[202]. These benefits seem to arise primarily through reductions in symptom-related anxiety, fear-avoidance and maladaptive illness beliefs rather than from direct modulation of gastrointestinal or autonomic physiology[203]. Similar improvements in IBS symptoms are observed when CBT is delivered for comorbid anxiety disorders, particularly among patients with gastrointestinal symptom-related anxiety[204]. Lifestyle interventions, such as physical activity and stress management, may provide additional benefit, although evidence of sustained quality of life improvement remains heterogeneous and of low certainty[205,206]. Food-related quality of life, or the extent to which food, eating and drinking bring enjoyment to people's lives, is lower in people with IBS than in healthy individuals and in persons with IBD[207]. Appropriate dietary support may improve quality of life by restoring confidence in eating and enabling social participation and by improving symptoms in parallel[208].

Outlook

Where we are

The modest gains reported in treatment trials have led some clinicians and patients to question whether available interventions are truly effective. However, such outcomes are consistent with our current empirical treatment paradigm. IBS is not a single disease but a syndrome defined by symptom criteria and limited testing to exclude IBS mimickers. Increasing evidence suggests that IBS represents a shared clinical expression of multiple pathophysiological mechanisms that converge on a similar symptom phenotype. If IBS reflects several mechanistically distinct disorders, empirical therapies targeting a specific pathway will only benefit a subset of patients in whom that pathway is relevant. Novel therapies directed at specific mechanisms but prescribed solely

on the basis of symptoms will probably have similar limitations. In addition, combining therapies that target different levels of the gut–brain axis (for example, peripheral and central mechanisms) may enhance therapeutic efficacy, particularly in patients with multifactorial aetiology. Thus, the central unmet need in IBS is not simply the development of new effective therapeutic interventions but also the identification of validated biomarkers and mechanistic subtypes that can enable precision therapeutic drugs and/or non-pharmaceutical approaches. Treatment trials are of relatively short duration given the chronic course experienced by most patients with IBS. Pharmacological trials typically last 12–26 weeks, and dietary and behavioural intervention periods commonly last 4–12 weeks, although some include longer follow-up. Few controlled studies extend beyond 1 year, limiting conclusions about long-term efficacy and safety.

Important gaps persist — IBS-M, men, paediatric populations and underserved communities remain under-represented in clinical trials, and there are limited data on the outcomes and cost-effectiveness of integrated, multidisciplinary care models. Addressing these inequities is essential for advancing both science and public health.

The way forward

Symptoms will remain foundational to IBS diagnosis and management. Yet symptom-based phenotyping alone lacks the specificity required for precision care. Many clinicians lack the time, training or tools to collect multidimensional data that can guide personalized treatment.

Digital health platforms, artificial intelligence and machine learning can move beyond a predominantly symptom-based approach. Longitudinal symptom tracking integrated with biological and behavioural data, including diet, bowel patterns, physical activity, sleep and stress, can improve phenotypic accuracy[209]. Platforms that capture passive data streams, such as wearable-derived metrics of the autononomic nervous system, actigraphy and sleep staging, may provide objective measures of physiological state. Artificial intelligence-enabled systems can integrate clinical, behavioural and biological data to generate predictive models for treatment response[210]. These platforms can learn over time, enabling iterative personalization, but rigorous validation and equitable implementation is essential to avoid widening disparities.

The exposome

Diet and stress are well-recognized modifiable drivers of IBS symptoms[159], and dietary and behavioural therapies now feature prominently in clinical guidelines[14,211,212]. Integrated, multidisciplinary care, including dietary, behavioural and pharmacological therapies, represents the aspirational standard for IBS[213,214]. Yet access remains uneven, highlighting the need for scalable delivery models, including virtual care and digital therapeutics. Complementary approaches, including acupuncture, herbal therapies, non-invasive vagal nerve stimulation and movement-based interventions, may expand evidence-based options, but further research is needed. Integration of these therapies into mainstream care will depend on clinician training, access to gastrointestinal dietitians and psychologists, quality and safety oversight, and sustainable delivery models.

The broader 'exposome' — the totality of lifetime environmental exposures — extends beyond perturbations of the homeostasis of brain–gut–microbiome interactions by psychosocial and dietary stress to include chemicals, drugs, pollutants and infections. Epidemiological studies link environmental exposures, including air pollution and pesticides, and lifestyle factors, to IBS symptom development or exacerbation[215]. Although causation remains uncertain, plausible mechanisms underlying responses to the exposome include alterations in gut microbiome, impaired gut barrier function, immune modulation and downstream effects on visceral sensitivity and motility. The exposome is also a promising source of modifiable risk factors and biomarkers, but further studies are needed. Microbiome-based and metabolome-based signatures are being explored as predictors of response to the low-FODMAP diet or personalized diets[216,217]. Microbiome engineering, through targeted probiotics, psychobiotics, bacteriophage approaches or metabolite-based interventions, represents an emerging frontier, although robust mechanistic and clinical validation is required.

Host factors and multi-omics integration

Biological abnormalities have been identified in subsets of patients with IBS[218]. None are pathognomonic, underscoring the heterogeneity and the challenge of causal inference. Many studies have focused on isolated abnormalities without fully capturing the complex systems in which they occur. Multi-omics integration, including genomics, transcriptomics, proteomics, metabolomics, metagenomics, epigenomics and even viromics, offers a systems-level framework for mechanistic subtyping[219]. Studies integrating microbial transcripts, host gene expression and metabolite profiles have distinguished IBS subtypes[220] and identified subgroup-specific pathways, including alterations in bile acid and purine metabolism and microbial metabolites such as tryptamine[221]. Longitudinal studies linked to clinical outcomes suggest that mechanistic clusters may predict dietary responses, for example, to a low-FODMAP diet[222], or symptom trajectories, shifting the field towards functional, testable mechanisms.

Understanding sex-specific biology is another priority. IBS exhibits female predominance, yet mechanisms underlying sex differences in pathophysiology and treatment response remain incompletely understood[49]. Future trials should therefore incorporate sex-stratified analyses and consideration of hormonal state.

Research and public health priorities

Progress in advancing clinical care and the scientific understanding of IBS will require standardized end points, harmonized core outcome sets and routine incorporation of validated patient-reported outcomes. Pragmatic trials embedded in real-world settings are needed to evaluate integrated care models, digital therapeutics and combination strategies. Longitudinal cohorts linked to biobanks and digital data streams will be essential for biomarker validation and mechanistic discovery. Public health priorities include expanding access to integrative care, improving global education on DGBI and reducing stigma. Destigmatization can directly increase care-seeking, adherence and research participation.

Future vision

Future progress should build on, rather than replace, evidence-based symptom-directed care. Priorities include prospectively validating candidate biological and behavioural predictors of treatment response and testing whether matching treatments to these features improves outcomes over standard care. Until such predictors are validated, treatment should remain guided by predominant symptoms, evidence, safety and patient preferences.

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Author contributions

Introduction (L.C.); Epidemiology (A.C.F., A.S. and K.T.S.); Mechanisms/pathophysiology (G.B., L.C., E.A.M. and M.S.); Diagnosis, screening and prevention (M.C. and A.S.); Management (S.B., A.J.L., A.S. and H.S.); Quality of life (M.J.S. and K.T.S.); Outlook (W.D.C.); overview of the Primer (L.C.).

Competing interests

L.C. has served as a consultant for AlfaSigma, Ardelyx, Atmo, Food Marble, GlaxoSmithKline, Eli Lilly, Medscape, Nerva, Ono Pharmaceuticals and Vibrant; has been a speaker for Bausch Health; received research grants from AnX Robotica and Ironwood; serves as a member of the Rome Foundation Board of Directors; and has unvested stock options for Food Marble, ModifyHealth, PICO Health and Trellus Health. M.C. has served as a consultant to Sanofi/Opella, Aboca, Biocodex, PROMEDCS, Takeda and Mayoly; has research grants from Sanofi/Opella and Aboca; and serves as a member of the Rome Foundation Board of Directors. W.D.C. has served as a consultant for Ardelyx, Atmo BioSciences, Blueprint Medicines, Comvita, Nestlé, Phathom Pharmaceuticals, Salix Pharmaceuticals and Vibrant; has stock options in Coprata, FoodMarble Digestive Health, Isothrive and ModifyHealth; and serves on the Board of Trustees American College of Gastroenterology, Board of Directors of the Rome Foundation, and International Foundation of GI Disorders. M.J.S. has served as consultant for Daewoong South Korea, Gemelli Biotech, Moksha 8 Mexico, Pro.Med.CS Praha and Promethis Mexico; has been a speaker for Acino Pharma Panamá, Adium Mexico, AlfaSigma Mexico, Arcera/Moksha 8, Biopas Colombia, Daewoong South Korea and Prometis Mexico; and serves as a member of The Rome Foundation Board of Directors. A.S. has served on advisory boards for Gemelli Biotech and Salix Pharmaceuticals; has served as an advisoer or consultant for Ardelyx, Medis Labs, ModernGut and Peterson Health Technology Institute; and is a member of the Rome V Bowel Disorders committee. G.B. has consultancies, business interests or sources of honoraria payments from Aboca, AB Biotics, Agave, AlfaSigma, AGPharma, Bayer, Biocodex, Boeringer, Bromatech, Cadigroup, Danone, Diadema, Falk Pharma, GE Healthcare, Giuliani, Mayoly, Malesci, Sanofy, Sofar and Yakult. S.B. has received research funding from Eli Lilly. E.A.M. has served as a member of scientific advisory board with stock options of Pendulum, Bloom Science, Melius MMB, Tiny Health, Ginger, Salvo, Seed and One Bio. M.S. has served as a consultant for Biocodex, Tillotts, BioGaia, Renapharma and AlfaSigma; has been a speaker for Tillotts, Takeda, Biocodex, Danone, Sanofi, Abbvie, Janssen Immunology, Pfizer, BioGaia, Renapharma, Mayoly and Bromatech; received research grants from BioGaia; and serves as a member of the Rome Foundation Board of Directors. H.S. has received honoraria from Falk Pharmaceuticals and travel funding for an International Scientific Association for Prebiotic and Probiotic Consensus meeting. A.J.L. has served as a consultant for Ironwood, Takeda, Ardelyx, BioAmerica, Pfizer, Viscera Labs, GlaxoSmithKline, Salix and Vibrant; and has stock in Johnson & Johnson, Bristol Myers Squibb and Metaphy Health. The other authors declare no competing interests.

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