Irritable bowel syndrome and related disorders of gut–brain interaction

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Irritable bowel syndrome, chronic constipation, and functional diarrhoea are disorders of gut–brain interaction, the symptoms of which include abnormal stool consistency or frequency accompanied by varying degrees of abdominal pain, discomfort, bloating, or distension. These conditions affect 20% of the global population with a relapsing and remitting course. Risk factors include female sex, younger age, a history of common mental disorders, and acute enteric infection. The pathophysiology of irritable bowel syndrome, chronic constipation, and functional diarrhoea remain incompletely understood, but are thought to be secondary to aberrant interactions throughout the gut–brain axis, resulting in disordered gut motility and visceral hypersensitivity. These conditions are diagnosed with a combination of clinical history, absence of alarm symptoms—such as weight loss or rectal bleeding—and targeted investigations. An empathetic management approach improves quality of life and symptoms, reduces health-care use, and enhances treatment adherence. Mainstays of treatment include education, dietary and lifestyle advice, modifying fibre intake, and drugs directed towards predominant symptoms. For severe symptoms, other treatments include specific medical devices, biofeedback, or psychological therapies. However, the effectiveness of most treatments is modest and there is an ongoing need to expand available treatments for bowel disorders, with several novel drugs currently in development.

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See **Online** for appendix

Introduction

Irritable bowel syndrome (IBS), chronic constipation, and functional diarrhoea are chronic bowel disorders.[1] Characterised by abnormal stool consistency or frequency and often accompanied by varying degrees of abdominal pain, discomfort, bloating, or distension, bowel disorders are highly prevalent, with substantial effects on quality of life and social functioning.[2,3] There are no structural abnormalities to explain the symptoms and their pathophysiology is only partially understood. Based on an integrated biopsychosocial model of illness (appendix p 1),[4] bowel disorders are thought to result from complex bidirectional gut–brain axis dysregulation. Hence, although previously termed functional gastrointestinal disorders, bowel disorders have been reframed as disorders of gut–brain interaction.[5] Treatment is often targeted towards the most troublesome symptom. Despite advances in knowledge and understanding, bowel disorders are a substantial financial burden to both health-care systems and society.[6–9]

Epidemiology

The most recent symptom-based diagnostic criteria for bowel disorders, the Rome V criteria, were developed by consensus among experts in disorders of gut–brain interaction.[1] The criteria for IBS, chronic constipation, and functional diarrhoea are detailed in panel 1. IBS is subgrouped according to predominant stool pattern, using the Bristol Stool Form Scale, into IBS with constipation, IBS with diarrhoea, IBS with mixed bowel habits, or IBS unclassified.

Prevalence estimates of these disorders globally were hampered, until recently, by methodological variations between the different epidemiological studies conducted separately across multiple countries.[10,11] Methodological differences included use of different diagnostic criteria and variation in the demographics of recruited populations. However, in 2021, a cross-sectional survey by the Rome Foundation[12] simultaneously recruited more than 54 000 adults of similar age and sex distributions from 26 countries, via the internet, using identical methodology. Overall, bowel disorders were the most prevalent group of disorders of gut–brain interaction, affecting 20% of the global population. The pooled prevalence of symptoms compatible with Rome IV IBS was 4·1%, 11·7% for chronic constipation, and 4·7% for functional diarrhoea. Following changes made to diagnostic criteria for bowel disorders with publication of the Rome V process,[1] an updated global survey found pooled prevalences of 8·5% for IBS, 8·9% for chronic constipation, and 5·1% for functional diarrhoea.[13] Prevalence estimates vary slightly across countries, likely reflecting differences in population characteristics, including genetics and dietary intake. Despite these efforts by the Rome Foundation, there remains a dearth of prevalence data from countries in Africa, eastern Europe, and the Middle East.

Search strategy and selection criteria

We searched MEDLINE, Embase, Embase Classic, and the Cochrane Central Register of Controlled Trials for full-text articles published from Jan 1, 2016, to April 30, 2026. We used the terms "irritable bowel syndrome", "chronic constipation", "functional diarrhoea", "epidemiology", "prevalence", "incidence", "aetiology", "pathophysiology", "diagnosis", "investigation", "management", "therapy", and "treatment" to identify relevant articles. We also searched ClinicalTrials.gov for unpublished trials. We included only articles whose findings were, in our view, of the greatest importance, and published in English, favouring randomised controlled trials, meta-analyses, and network meta-analyses.

Panel 1: **Rome V diagnostic criteria for bowel disorders***

Rome V diagnostic criteria for irritable bowel syndrome (IBS)†

1 Recurrent, but not continuous, abdominal pain or discomfort for at least 3 days per month and associated with two or more of the following:
   a Related to defecation
   b Onset associated with a change in frequency of stool
   c Onset associated with a change in form of stool
2 Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis

IBS with predominant constipation
More than 25% of defecations with Bristol stool types 1 or 2 and fewer than 25% with types 6 or 7.

IBS with predominant diarrhoea
More than 25% of defecations with Bristol stool types 6 or 7 and fewer than 25% with types 1 or 2.

IBS with mixed bowel habits
More than 25% of defecations with Bristol stool types 1 or 2 and more than 25% with types 6 or 7.

IBS unclassified
Patients meeting criteria for IBS, but whose bowel habits cannot be accurately categorised into one of the above three groups.

Rome V diagnostic criteria for chronic constipation

1 Two or more of the following:
   a Straining during more than 25% of defecations
   b Lumpy or hard stools (Bristol stool type 1–2) on more than 25% of defecations
   c Sensation of incomplete evacuation on more than 25% of defecations
   d Sensation of anorectal obstruction or blockage on more than 25% of defecations
   e Manual manoeuvres to facilitate more than 25% of defecations (eg, digital evacuation or support of the pelvic floor)
   f Fewer than three spontaneous bowel movements per week
2 Loose stools are rarely present without the use of laxatives
3 Insufficient criteria for IBS
4 Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis

Rome V diagnostic criteria for functional diarrhoea

1 Loose or watery stools occurring in more than 25% of stools
2 Hard stools are rarely present without medication that can cause constipation
3 Insufficient criteria for IBS
4 Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis; patients meeting criteria for IBS with diarrhoea should be excluded

*Adapted from Corsetti et al.[1] †Supportive criteria: abdominal pain or abdominal discomfort should not be only related to menses.

Risk factors

Meta-analyses show a higher prevalence of chronic constipation (odds ratio [OR] 2·32 [95% CI 1·85–2·92]; using Rome III criteria)[14] and IBS (1·46 [1·33–1·59]; using Rome IV criteria)[15] among women compared with men. In the Rome Foundation survey, functional diarrhoea was more common in men than women (5·3% *vs* 4·1%).[12] In general, bowel disorders are less common in individuals aged 65 years and older,[12] although in a meta-analysis, prevalence of chronic constipation appeared to increase with increasing age.[11]

Common mental disorders are strongly associated with bowel disorders. Patients with IBS have approximately three times higher odds of anxiety or depression compared with individuals without IBS.[16] A retrospective study showed that, when diagnosis of a common mental disorder preceded a bowel disorder, the median interval between the common mental disorder and a diagnosis of IBS was 5·5 years (IQR 2·2–10·1), which increased to 7·0 years (2·9–13·4) for a diagnosis of chronic constipation.[17] Conversely, when a bowel disorder diagnosis preceded a diagnosis of a common mental disorder, the median interval was approximately 2 years (1·8 years [0·6–4·2] for IBS and 1·9 years [0·5–4·5] for chronic constipation). A nationwide longitudinal follow-up study reinforced this bidirectional association between IBS and depressive or anxiety disorders. Pre-existing anxiety or depression was associated with a higher risk of subsequently developing IBS (adjusted hazard ratio 1·55 [95% CI 1·42–1·69]; p<0·001), whereas pre-existing IBS was associated with a higher risk of developing anxiety or depression (1·46 [1·37–1·56]; p<0·001).[18]

Post-infection IBS develops in approximately 15% of individuals following infectious enteritis and occurs more frequently with parasitic or bacterial infections.[19] SARS-CoV-2 infection is also associated with an increased risk of IBS (OR 12·92 [95% CI 3·58–46·60]; p<0·001).[20] A population-based study before and after the COVID-19 pandemic reported a modest increase in the prevalence of bowel disorders from 30·1% in 2017, to 32·5% in 2023 (1·12 [1·02–1·23]), with the prevalence of IBS increasing from 4·7% to 6·0% (1·31 [1·08–1·60]) over the same period.[21]

Pathophysiology

Diarrhoea and constipation

The pathophysiology of bowel disorders is incompletely understood but is thought to arise from aberrant gut–brain axis interactions (figure 1).[22] The enteric nervous system—the intrinsic neuronal network in the bowel wall—regulates gut motility and secretion. Extensive sympathetic and parasympathetic projections on to this network provide integration of central autonomic input, modulating gut motility. The effects of stress on gut motility are amplified in disorders of gut–brain interaction, resulting in both diarrhoea and constipation.[23] Abnormal colonic transit times have been shown, with more rapid transit seen in IBS with diarrhoea and functional diarrhoea compared with IBS with constipation and chronic constipation.[24] The postprandial gastrocolic reflex is exaggerated in IBS,[25] resulting in visceral pain in all subtypes, and altered rectal tone in those with diarrhoea.[26]

Serotonin, or 5-hydroxytryptamine (5-HT), is a key enteric neurotransmitter. Changes in serotonin

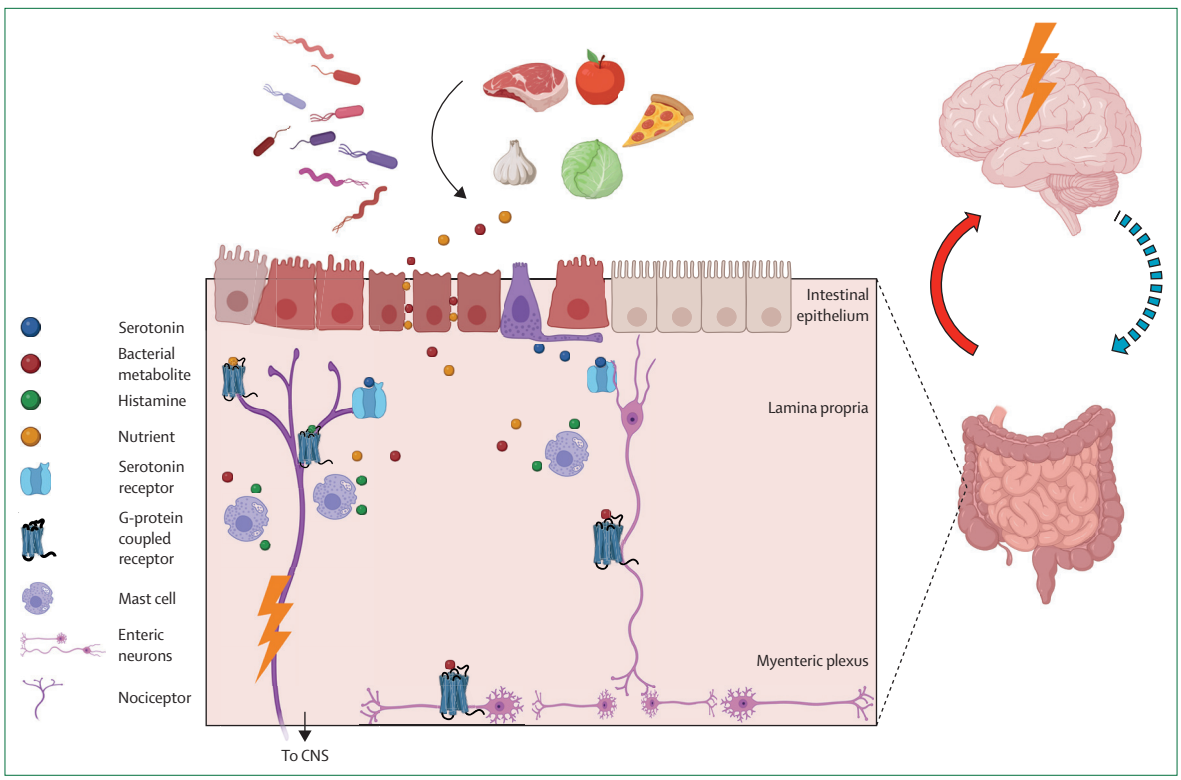

Figure 1: **Pathophysiological mechanisms involved in bowel disorders**
Bowel disorders arise due to aberrant interactions throughout the brain–gut axis. Visceral hypersensitivity is a result of both increased peripheral pain signalling in the ascending pain pathway (red arrow), decreased activity of the inhibitory pain pathway (dashed blue arrow), and changes in central pain processing. At the periphery, impaired intestinal barrier function results in exposure of nociceptors and enteric neurons to luminal antigens, such as nutrients and bacterial metabolites, which can stimulate both nociceptors and enteric neurons. Subsequent infiltration of the lamina propria by mast cells releasing histamine results in visceral hypersensitivity via a histamine-1 receptor dependent mechanism. Increased serotonin release by enterochromaffin cells causes both visceral hypersensitivity and changes in gut motility. Figure created with BioRender.com.

bioavailability via altered enteroendocrine cell numbers, serotonin release, or reuptake, regulate gut motility and visceral pain in IBS.[22,27] Serotonin concentrations are elevated in IBS with diarrhoea compared with IBS with constipation,[28] although this finding is not universal. Genetic polymorphisms in serotonin receptors, synthetic enzymes, and the serotonin reuptake transporter (SERT) are associated with IBS, with different SERT polymorphisms noted in those with IBS with diarrhoea compared with IBS with constipation.[29] Finally, gut microbes synthesise serotonin[30] and some pathogenic species found in IBS with diarrhoea, including *Ruminococcus gnavus,* can increase serotonin bio-availability.[31]

Nutrients and luminal contents also influence gut motility. For example, a significant increase in primary unconjugated faecal bile acids through altered microbial deconjugation, increased synthesis, or decreased absorption is found in patients with IBS with diarrhoea or functional diarrhoea.[32] Bile acids enhance colonic secretion, gut motility, and visceral hypersensitivity.[33,34] Excess colonic carbohydrates, either due to malabsorption from acquired or genetic enzyme deficiency[35] or due to increased colonic load resulting from a diet high in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), also cause diarrhoea secondary to their osmotic effects and contribute to bloating via increased colonic water and gas.[36] Finally, microbial metabolites acting on enteric nerves can cause either diarrhoea or constipation in IBS.[37]

Abdominal pain

In bowel disorders, peripheral and central sensitisation or amplification of pain signalling, either at the level of the gut or the brain or spinal cord, results in hyperalgesia (increased pain in response to mildly painful stimuli) and allodynia (pain in response to non-painful stimuli).[38] Abdominal pain is a key symptom of IBS, driven by visceral hypersensitivity. Painful sensation is transmitted from the gut to the spinal cord via pain-sensing nerves, or nociceptors, residing in the dorsal root ganglia. Thereafter, information is relayed to the brain via ascending pain pathways.[22] Nociceptors express receptors for neurotransmitters, cytokines, chemokines, microbial products, and nutrients.[39] These molecules either stimulate nociceptors directly due to impaired intestinal barrier function, or act indirectly via the epithelium. Nociceptor receptors include the transient receptor potential (TRP)

super family of ion channels (eg, TRP vanilloid-1, the receptor for capsaicin), which are both mechanosensitive and chemosensitive.[40] TRP channels undergo increased channel expression or post-translational modification, resulting in nociceptor sensitisation and increased excitability.[41,42]

Central sensitisation is an equally important contributor to abdominal pain.[43,44] Bowel disorders often coexist with other chronic, painful, non-gastrointestinal disorders, including fibromyalgia, interstitial cystitis, and chronic pelvic pain.[45] This coexistence might reflect the convergence of visceral and somatic inputs at the same level in the spinal cord,[46] causing referred pain to the skin or other visceral organs. Decreased activity of the inhibitory descending pain pathway,[47] increased emotional arousal from comorbid anxiety or depression,[48] and functional and structural changes in brain regions involved in central pain processing are evident in bowel disorders.[44,49] Together, these data indicate that both bottom-up and top-down processes contribute to abdominal pain in bowel disorders.

In the gut, impaired intestinal barrier function is an inciting factor underlying abdominal pain,[50] although it can be secondary to gastrointestinal infection (eg, in post-infection IBS).[51] Compromised barrier function exposes nociceptors to luminal antigens and the subsequent infiltration of the lamina propria by inflammatory cells, including T cells and mast cells.[50,52,53] Mast cells are an important source of neuroactive mediators, such as proteases, tryptase, and histamine; all can stimulate nociceptors.[53] Two mouse model studies from the past 5 years have shown that both water-avoidance stress and infectious enteritis impair barrier function.[50,54] Subsequent exposure to food antigens resulted in mast cell infiltration and degranulation adjacent to neuronal fibres, causing visceral hypersensitivity via a histamine-1-receptor dependent mechanism.[50] These data show that either a central or peripheral event can trigger food sensitivities and mast cell-mediated visceral pain in bowel disorders.

Changes in the gut microbiota, independent of enteric infection, are also associated with visceral hypersensitivity. Altered microbial composition and metabolic activity are seen in IBS.[37,55] Microbes are an important source of neuroactive mediators, including short-chain fatty acids and neurotransmitters.[37,56,57] Such mediators can either stimulate nociceptors directly[58] or indirectly via the epithelium or immune system.[59] Commensal microbes seem to have an antinociceptive role[60] compared with pathogens in IBS,[56,61] suggesting that a balanced luminal microenvironment is necessary to prevent visceral hypersensitivity.

Clinical presentation and differential diagnosis

Bowel disorders are heterogeneous conditions but they have characteristic clinical features, which facilitates a positive, symptom-based approach to diagnosis instead of one based primarily on exclusion of organic gastrointestinal disease.[1] Making such a diagnosis promptly and with an effective physician–patient interaction is associated with reduced health-care use.[62,63] Although the absence of alarm features increases diagnostic confidence, their predictive value for underlying organic disease is only modest.[64] Bowel disorders most commonly affect individuals aged 20 to 40 years, but can occur at any age, with a female predominance for IBS and chronic constipation.[12]

Abdominal pain remains the cardinal symptom of IBS and is essential for diagnosis, although it can occur to a lesser extent in chronic constipation and functional diarrhoea. It is typically recurrent and intermittent, rather than continuous, and usually localised to the lower abdomen, although some Asian patients have reported upper abdominal pain.[65] Pain is characteristically associated with defecation and occurs in conjunction with altered stool frequency, consistency, or both. Although patients with bowel disorders are subclassified by predominant stool pattern, this pattern fluctuates over time.[66] The Rome V criteria refined the symptoms of IBS: reintroducing abdominal discomfort alongside pain, relaxing pain frequency to at least 3 days per month during the preceding 3 months, and specifying that pain should not be continuously present on a daily basis, to distinguish IBS from centrally mediated abdominal pain syndrome.[1] The criteria also emphasised that abdominal pain or discomfort should not be related solely to menses, to discriminate IBS from menstrual-related and gynaecological disorders. As discussed, bowel disorders overlap frequently with painful non-gastrointestinal conditions and with other disorders of gut–brain interaction.[45] This overlap can influence symptom burden, management, and outcomes.

Although abdominal bloating and distension are not incorporated into diagnostic criteria for bowel disorders, both are highly prevalent and support a diagnosis,[1] particularly when symptoms are diurnal and abdominal distension is visible.[67] A detailed clinical history, including use of the Bristol stool form scale, is essential to characterise bowel habits and to distinguish bowel disorders from organic gastrointestinal disease, such as coeliac disease, inflammatory bowel disease, colorectal cancer, or microscopic colitis.

Investigations

To date, no validated biomarkers for bowel disorders exist. Accordingly, a positive symptom-based diagnosis supported by targeted investigations is recommended. Broad exclusionary testing is discouraged because it is costly, low yield, and does not reassure patients or improve quality of life.[68] Therefore, management guidelines recommend the use of symptom-based criteria, such as the Rome criteria, complemented by a focused clinical assessment.[69,70] Diagnostic performance improves when symptom-based criteria are interpreted alongside

supportive features, including the absence of nocturnal symptoms, presence of psychological comorbidity, and normal basic laboratory tests.[71] In a diagnostic accuracy study in 730 patients in secondary care, the Rome V criteria for IBS performed less well than Rome IV (sensitivity 66·1% *vs* 78·9%, specificity 80·1% *vs* 81·0%, positive likelihood ratio 3·33 *vs* 4·16, and negative likelihood ratio 0·42 *vs* 0·26).[72] Validation studies of diagnostic criteria in chronic constipation and functional diarrhoea are scarce.

In most patients, a limited blood panel including full blood count, C-reactive protein, and coeliac serology, is sufficient. C-reactive protein concentrations less than 0·5 mg/dL are associated with a less than 1% probability of inflammatory bowel disease.[73] The global prevalence of biopsy-proven coeliac disease is around 0·7%; it remains an important differential diagnosis in any patient with chronic bowel symptoms.[74] Pooled estimates suggest a prevalence of biopsy-proven coeliac disease of 3·3% among patients with IBS-like symptoms.[75] Screening should include IgA anti-tissue transglutaminase and total IgA concentrations to exclude selective IgA deficiency.[74] Routine faecal testing for enteric pathogens has a low yield in chronic diarrhoea. However, the American Gastroenterological Association recommend consideration of testing for *Giardia lamblia* in the appropriate epidemiological or clinical contexts.[76]

National Institute for Health and Care Excellence guidance now recommends faecal immunochemical testing in the context of lower gastrointestinal symptoms to guide suspected colorectal cancer referral (panel 2),[77] although guidance in other countries varies and direct referral for colonoscopy based on alarm symptoms might still be appropriate elsewhere. Other features, such as a family history of colorectal cancer or inflammatory bowel disease, warrant further evaluation, usually with colonoscopy. Colonoscopy should also be considered in individuals who have not undergone age-appropriate colorectal cancer screening. Overall, the optimal diagnostic strategy for bowel disorders integrates symptom-based criteria, limited targeted investigations, and clinical judgement, with further testing guided by predominant stool pattern, clinical context, and response to initial management (figure 2). Repeated cycles of investigations in people meeting the criteria for a bowel disorder, and in whom the suggested diagnostic algorithm is applied, are of low yield.[78]

In patients with constipation, further testing is usually unnecessary, although selective assessment of thyroid function and serum calcium can be considered. Additional evaluation should be undertaken in patients with symptoms that include excessive straining, a sense of incomplete evacuation, or the need for digital manoeuvres, which suggest a defecatory disorder, or in those with abnormal findings on digital rectal examination.[79] If present, anorectal manometry with balloon expulsion testing is indicated, as defecatory disorders are more appropriately managed with biofeedback than laxatives.[80] Colonic transit testing with radio-opaque markers or scintigraphy can objectively document delayed transit, but regional transit patterns do not reliably distinguish primary slow-transit constipation from delayed transit secondary to a defecatory disorder.[81] Anorectal manometry studies assess evacuation and colonic transit studies assess colonic propulsion, so they are complementary rather than interchangeable tests.[82] Slow-transit disorders and defecatory disorders can coexist and, therefore, presence of one does not exclude presence of the other.[82] Moreover, slow transit can be secondary to a defecatory disorder and can also improve with biofeedback.[83]

In patients with diarrhoea, some additional investigations to exclude organic gastrointestinal disease are usually warranted. A faecal calprotectin investigation is particularly valuable; its negative predictive value in excluding inflammatory bowel disease is 99·8%.[84] Colonoscopy with random colonic biopsies should be considered in patients with features compatible with microscopic colitis,[85] particularly in females older than 45 years or those with coexistent autoimmune disease, nocturnal diarrhoea, weight loss, or exposure to specific medications, such as non-steroidal anti-inflammatory drugs or proton pump inhibitors.[86,87] Bile-acid diarrhoea is another important differential, especially in patients with a higher BMI or nocturnal diarrhoea.[88] The

Panel 2:* Criteria for faecal immunochemical testing in adults to guide referral with suspected colorectal cancer

All patients with faecal immunochemical testing of at least 10 µg of haemoglobin per g of faeces should be referred and patients with a rectal mass should be considered for referral. In other countries, direct referral for colonoscopy based on the presence of these symptoms or signs alone might still be warranted.

Criteria for faecal immunochemical testing:

- Abdominal mass
- Change in bowel habits
- Iron-deficiency anaemia
- Aged 40 years or older with unexplained weight loss and abdominal pain
- Younger than 50 years with rectal bleeding and unexplained:
  - Abdominal pain
  - Weight loss
- Aged 50 years or older and unexplained:
  - Rectal bleeding
  - Abdominal pain
  - Weight loss
- Aged 60 years or older with anaemia even in the absence of iron deficiency

*Criteria adapted from the National Institute for Health and Care Excellence Guidelines.[77]

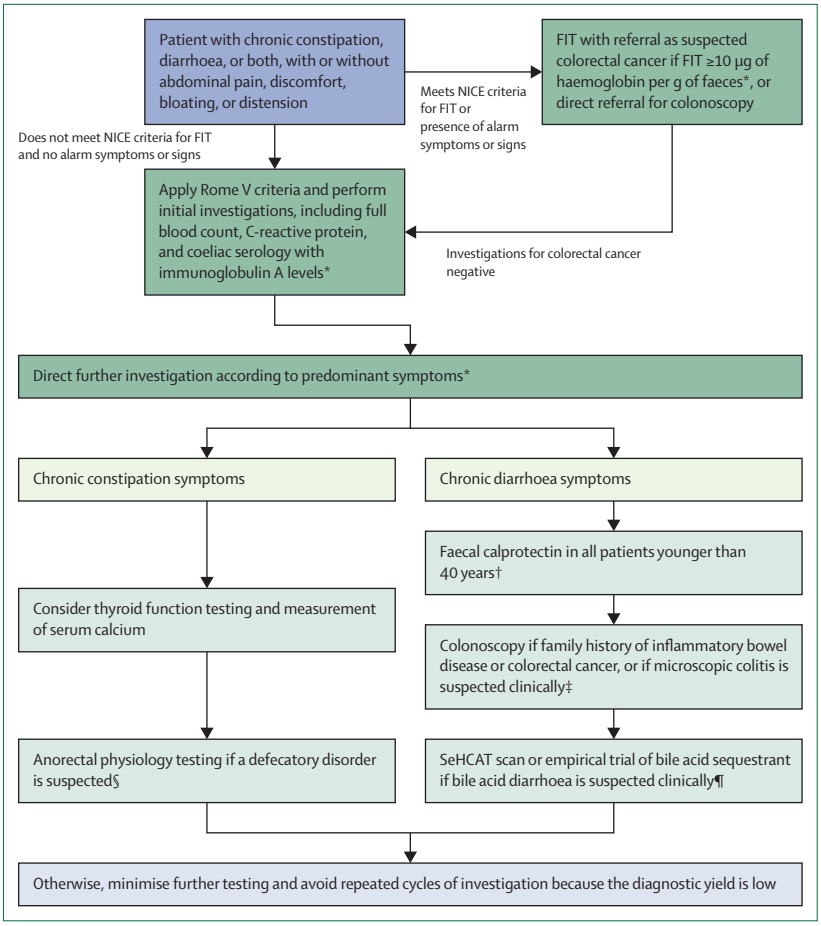

Figure 2: **Diagnostic algorithm for patients with suspected bowel disorders**
FIT=faecal immunochemical testing. NICE=National Institute for Health and Care Excellence. SeHCAT=23-seleno-25-homotaurocholic acid. *Organic disease detected at any point in the algorithm should be treated accordingly. †Referral for urgent colonoscopy to exclude inflammatory bowel disease is required if faecal calprotectin is within the abnormal range according to local laboratory values. If it is indeterminate, repeat the test off non-steroidal anti-inflammatory drugs (if appropriate) and refer for colonoscopy if the repeat test remains indeterminate or is within the abnormal range. ‡Features suggestive of microscopic colitis include female sex, age older than 45 years, coexistent autoimmune disease, nocturnal diarrhoea, weight loss, or proton pump inhibitor or non-steroidal anti-inflammatory drug use. §Features suggestive of a defecatory disorder include excessive straining, a sense of incomplete evacuation, the need for digital manoeuvres, or paradoxical anal contraction on straining during digital rectal examination. ¶Bile-acid diarrhoea is more common in patients with a higher BMI or with nocturnal diarrhoea.

23-seleno-25-homotaurocholic acid retention test remains the gold standard, but availability is limited in many countries. Alternative approaches include measurement of faecal bile acids, serum 7α-hydroxy-4-cholesten-3-one, or FGF19, although their clinical use is less well established.[89] In practice, a therapeutic trial of a bile-acid sequestrant is often used as a pragmatic alternative.[90] Faecal elastase testing is not recommended unless fat malabsorption is suspected clinically.[91]

Other organic gastrointestinal diseases that bowel disorders can mimic include carbohydrate maldigestion, particularly lactose or fructose intolerance,[92] and emerging conditions, such as sucrase-isomaltase deficiency.[35] Although these conditions can generate similar symptoms, including abdominal pain, bloating, or diarrhoea, systematic testing is not supported. Likewise, routine investigation for small intestinal bacterial overgrowth or intestinal methanogen overgrowth is discouraged, unless known risk factors are present, such as previous surgery or structural abnormalities of the small intestine. This recommendation is because of limitations in diagnostic accuracy and uncertain clinical utility.[93] There is no role for routine abdominal ultrasound or cross-sectional abdominal imaging for abdominal pain.

Natural history and impact

Bowel disorders fluctuate over time, although IBS is the most stable of the disorders. In a longitudinal follow-up study, 70·6% of individuals still met criteria for IBS 1 year after baseline compared with 34·1% for those with functional constipation and 35·5% for those with functional diarrhoea.[94] In this study, approximately a third of patients with chronic constipation or functional diarrhoea at baseline fulfilled criteria for IBS at 1-year follow-up. Similarly, switching of IBS subtype occurs frequently, with approximately a third of individuals reporting a change at 1 year,[66] with those with IBS with mixed bowel habits most likely to switch and few people transitioning directly between IBS with constipation and IBS with diarrhoea.

Importantly, bowel disorders are not associated with increased mortality or a higher risk of subsequent organic gastrointestinal disease.[78,95,96] Nevertheless, these conditions impose a substantial burden. Individuals with bowel disorders frequently report somatic and psychological symptoms, reduced quality of life, and greater health-care use, with the greatest impact observed among patients with IBS.[2,3] In IBS, effects on daily activity differ by subtype; those with IBS with diarrhoea might avoid travel or leaving the house due to anxiety about toilet access and those with IBS with constipation might avoid sexual relations.[97] The direct and indirect socioeconomic burden of IBS and chronic constipation, including work absenteeism and reduced productivity, have been well documented,[6–9] but data for functional diarrhoea are scarce. Compared with patients with inflammatory bowel disease, patients with IBS hold more negative illness perceptions, which could contribute to increased symptom reporting, psychological distress, and health-care use.[98]

Management

General measures

Most randomised controlled trials (RCTs) of therapies for bowel disorders extend no longer than 12 weeks, meaning long-term efficacy is unknown. Therefore, an empathetic approach is key to improving symptoms and quality of life, reducing health-care use, and enhancing treatment adherence.[62,99] In addition, because most drug trials are placebo-controlled, the relative efficacy of treatments has to be inferred from network

meta-analyses, and information regarding sequencing of drugs is insufficient.

Management should commence with explanation of the specific bowel disorder, including underlying pathophysiology and natural history. Because bowel disorders exist on a continuum, patients can transition from one to another over time.[66] Thus, treatment is directed towards the predominant symptom, based on best evidence (figure 3; table) and via shared decision making.

Trials of newer drugs in IBS and chronic constipation often use US Food and Drug Administration (FDA)-recommended endpoints to assess efficacy (appendix p 2), whereas trials of older drugs use less stringent endpoints. There are no RCTs in functional diarrhoea, so efficacy must be extrapolated from trials in IBS with diarrhoea. A realistic discussion of the limitations of available therapies is essential to manage expectations, as most treatments will improve symptoms in fewer than 50% of patients.[69] Avoiding opioids is imperative as, in addition to risk of dependence, they exacerbate pain and constipation and can cause narcotic bowel syndrome.[124]

Dietary patterns are associated with symptom severity[125] and healthy lifestyle behaviours, including not smoking, increasing physical activity, and optimising sleep, are associated with a lower incidence of IBS.[126] Although RCTs of lifestyle interventions are scarce,[127] patients should be encouraged to adopt these behaviours for symptom management. Increased fibre intake is recommended routinely for IBS and chronic

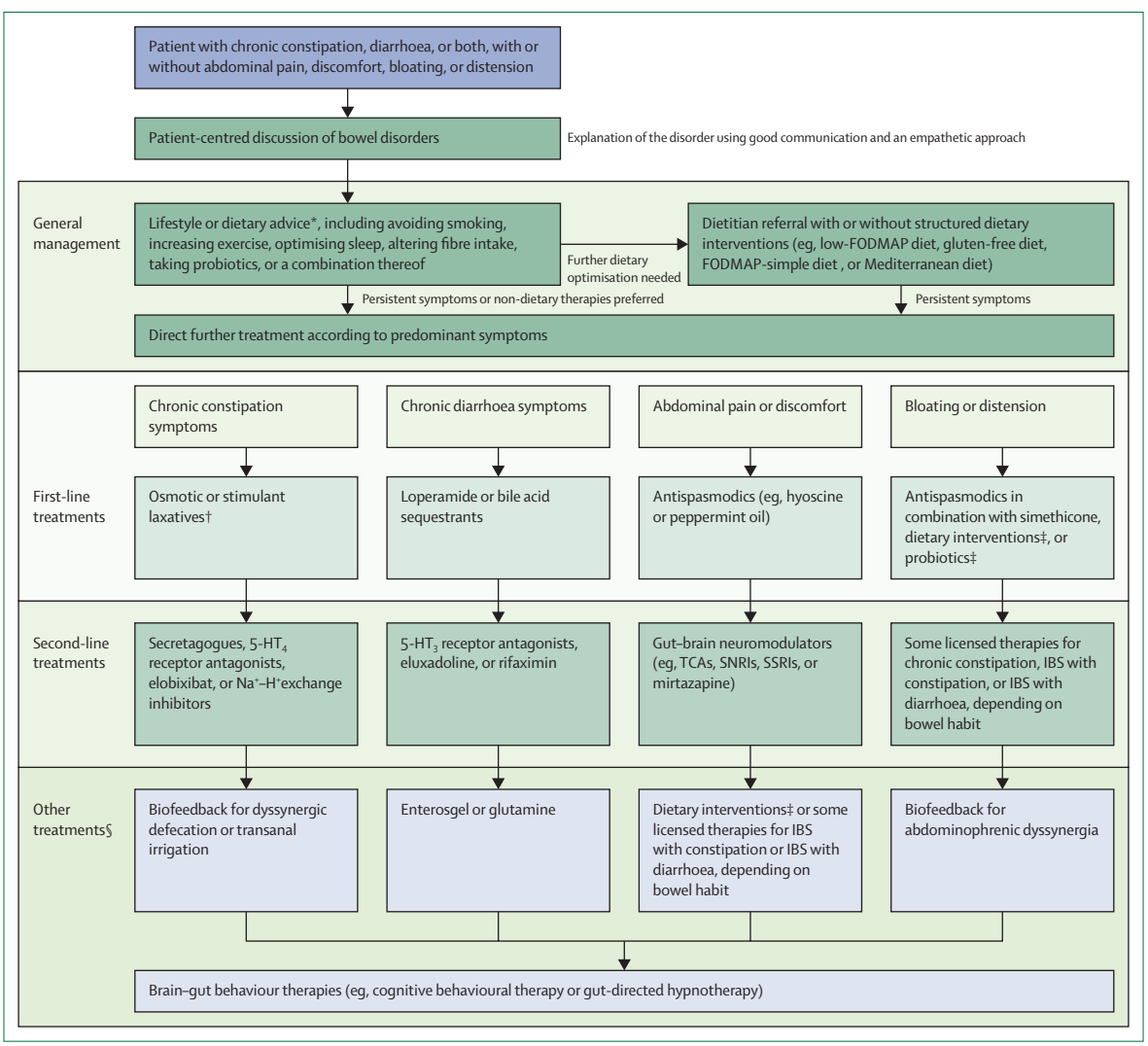

Figure 3: **Treatment algorithm for the management of bowel disorders, including treatment according to the predominant symptom**
5-HT=5-hydroxytryptamine. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. IBS=irritable bowel syndrome. SNRI=serotonin norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant. *Including British Dietetic Association first-line dietary advice for IBS. †Osmotic and stimulant laxatives are effective for chronic constipation, but there are fewer trials in IBS with constipation. ‡Unless already tried without benefit. §Can be implemented alongside the first-line or second-line treatments described in the algorithm, if appropriate.

	Type and number of studies	N and population of RCTs	Reported effect if efficacy was shown	Adverse events	Quality and limitations of data
Ispaghula (soluble fibre) up to 10–30 g/day	Meta-analysis including seven RCTs[100]	499 patients with unselected IBS	RR of persistence of global IBS symptoms or abdominal pain *vs* placebo 0·83 (95% CI 0·73–0·94)	Total adverse events no more common	Low; risk of bias of RCTs and inconsistency; only a small number of patients in existing RCTs
Kiwi fruits	Meta-analysis including three RCTs[101]	192 patients with chronic constipation	Mean difference in stool frequency *vs* ispaghula 0·36 (0·24–0·48)	Adverse events rarely reported	Very low; risk of bias of RCTs and inconsistency; only a small number of patients in existing RCTs
Ryebread	Meta-analysis including two RCTs[101]	48 patients with chronic constipation	Mean difference in stool frequency *vs* white bread 0·43 (0·03–0·83)	Adverse events rarely reported	Very low; risk of bias of RCTs and inconsistency; only a small number of patients in existing RCTs
Low-FODMAP diet	Network meta-analysis including 24 RCTs[102]	1803 patients with IBS (some trials IBS with diarrhoea only)	RR of persistence of global IBS symptoms *vs* habitual diet 0·51 (0·37–0·70); RR of persistence of abdominal pain *vs* habitual diet 0·61 (0·42–0·89); RR of persistence of abdominal bloating or distension *vs* habitual diet 0·55 (0·37–0·80)	Adverse events rarely reported	Moderate; risk of bias of RCTs; effects of FODMAP reintroduction not studied within the design of most RCTs
Starch and sucrose-reduced diet	Network meta-analysis including two RCTs[102]	217 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* habitual diet 0·41 (0·26–0·67); RR of persistence of abdominal pain *vs* habitual diet 0·54 (0·33–0·90)	Adverse events rarely reported	Moderate; risk of bias of RCTs; only a small number of patients in existing RCTs
Gluten-free diet	Network meta-analysis including one RCT[102]	114 patients with non-constipated IBS	RR of persistence of global IBS symptoms *vs* habitual diet 0·45 (0·25–0·81)*	Adverse events rarely reported	Low; risk of bias of RCTs and incoherence; only one RCT
FODMAP-simple diet	Network meta-analysis including one RCT[102]	35 patients with IBS with diarrhoea	RR of persistence of global IBS symptoms *vs* habitual diet 0·56 (0·33–0·96)*; RR of persistence of abdominal bloating or distension *vs* habitual diet 0·35 (0·13–0·96)*	Adverse events rarely reported	Very low; risk of bias of RCT, inconsistency, and incoherence; only one RCT
British Dietetic Association first-line dietary advice for IBS	Network meta-analysis including eight RCTs[102]	710 patients with IBS (some trials IBS with diarrhoea only)	RR of persistence of global IBS symptoms *vs* habitual diet 0·62 (0·43–0·90)*	Adverse events rarely reported	Very low; risk of bias of RCTs, reporting bias, inconsistency, and incoherence
Mediterranean diet	One RCT[103]	139 patients with unselected IBS	Improvement in global IBS symptoms in 61·8% *vs* 42·3% with traditional dietary advice first-line dietary advice (p=0·017); mean difference in improvement in abdominal pain frequency of −1·2 (−2·0 to −0·4) *vs* traditional first-line dietary advice	Adverse events rarely reported	Low; risk of bias of RCT and imprecision; only one RCT, to date, showed a benefit
Combination probiotics	Meta-analysis including 32 RCTs[104]	3369 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·78 (0·71–0·87); RR of persistence of abdominal pain *vs* placebo 0·72 (0·64–0·82); RR of persistence of abdominal bloating or distension *vs* placebo 0·75 (0·64–0·88)	Total adverse events no more common	Very low; risk of bias of RCTs, inconsistency, and publication bias; only a small number of RCTs assessing each combination, so difficult to know which is effective
Lactobacillus-containing probiotic strains	Meta-analysis including 16 RCTs[104]	1498 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·84 (0·72–0·98); RR of persistence of abdominal pain *vs* placebo 0·59 (0·45–0·76)	Total adverse events no more common	Low; risk of bias of RCTs and inconsistency; only a modest benefit over placebo
Escherichia-containing probiotic strains	Meta-analysis including two RCTs[104]	418 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·86 (0·79–0·93); RR of persistence of abdominal pain *vs* placebo 0·87 (0·79–0·95)	Total adverse events no more common	Moderate; risk of bias of RCTs; only a modest benefit over placebo.
Bacillus-containing probiotic strains	Meta-analysis including three RCTs[104]	216 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·44 (0·34–0·57); RR of persistence of abdominal pain *vs* placebo 0·33 (0·23–0·47); RR of persistence of abdominal bloating or distension *vs* placebo 0·41 (0·31–0·56)	Total adverse events no more common	Very low; risk of bias of RCTs and imprecision
Osmotic laxatives (eg, polyethylene glycol [17 g] once or twice a day)	Meta-analysis including five RCTs[105]	573 patients with chronic constipation	RR of not having ≥3 bowel movements per week *vs* placebo 0·52 (0·41–0·65)	Adverse events rarely reported	Low; risk of bias of RCTs and inconsistency
Osmotic laxatives (eg, polyethylene glycol [17 g] once or twice a day)	Two RCTs[106,107]	139 and 47 patients with IBS with constipation	Mean of 2·51 CSBMs per week *vs* 1·74 with placebo (p<0·001); mean stool consistency 1·9 at baseline *vs* 1·1 at follow-up with polyethylene glycol (p=0·047)	Rates of abdominal pain numerically higher with polyethylene glycol in one RCT, total adverse events no more common in the other RCT	Low; risk of bias of RCTs; only a small number of patients in existing RCTs, and effect on abdominal pain unclear.
Stimulant laxatives (eg, bisacodyl 10–20 mg once a day)	Meta-analysis including two RCTs[105]	735 patients with chronic constipation	RR of not having ≥3 CSBMs per week *vs* placebo 0·54 (0·42–0·69)	Adverse events rarely reported	Moderate; inconsistency

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	Type and number of studies	N and population of RCTs	Reported effect if efficacy was shown	Adverse events	Quality and limitations of data
(Continued from previous page)					
Linaclotide 145 µg once a day	Network meta-analysis including four RCTs[108]	2986 patients with chronic constipation	RR of not having ≥3 CSBMs per week and an increase of ≥1 CSBM per week over baseline† *vs* placebo 0·89 (0·86–0·92); ≥30% improvement in abdominal bloating or distension from baseline in 40·5% *vs* 29·2% with placebo in one RCT (p=0·032)[109]	Total adverse events, diarrhoea, and abdominal pain significantly more common with linaclotide	Moderate; risk of bias of RCTs; little availability outside the USA
Linaclotide 290 µg once a day	Network meta-analysis including four RCTs[110,111]	3061 patients with IBS with constipation	RR of persistence of global IBS symptoms† *vs* placebo 0·81 (0·76–0·86); RR of not having an increase of ≥1 CSBM per week† *vs* placebo 0·76 (0·65–0·88); RR of persistence of abdominal pain† *vs* placebo 0·79 (0·73–0·85); RR of persistence of abdominal bloating or distension *vs* placebo 0·78 (0·74–0·83)	Total adverse events and diarrhoea significantly more common with linaclotide	High
Lubiprostone 24 µg twice a day	Network meta-analysis including three RCTs[108]	605 patients with chronic constipation	RR of not having ≥3 bowel movements per week *vs* placebo 0·65 (0·55–0·75)	Total adverse events, diarrhoea, and nausea significantly more common with lubiprostone	Moderate; risk of bias of RCTs; little availability outside the USA
Lubiprostone 8 µg twice a day	Network meta-analysis including two RCTs[110,111]	452 with IBS with constipation	RR of persistence of global IBS symptoms† *vs* placebo 0·87 (0·78–0·96); RR of persistence of abdominal pain† *vs* placebo 0·85 (0·75–0·96); RR of persistence of abdominal bloating or distension *vs* placebo 0·85 (0·76–0·95)	Nausea significantly more common with lubiprostone	High; only a modest benefit over placebo and little availability outside the USA
Plecanatide 3 mg or 6 mg once a day	Network meta-analysis including three RCTs[108]	3504 patients with chronic constipation	RR of not having ≥3 CSBMs per week and an increase of ≥1 CSBM per week over baseline† *vs* placebo 0·91 (0·87–0·94)	Total adverse events and diarrhoea significantly more common with plecanatide	Moderate; risk of bias of RCTs; little availability outside the USA
Plecanatide 3 mg or 6 mg once a day	Network meta-analysis including two RCTs[110]	2922 patients with IBS with constipation	RR of persistence of global IBS symptoms† *vs* placebo 0·87 (0·81–0·94); an increase of ≥1 CSBM per week† in 41·4% *vs* 31·4% with placebo in the RCTs themselves (p<0·001); RR of persistence of abdominal pain† *vs* placebo 0·84 (0·78–0·90)	Total adverse events and diarrhoea significantly more common with plecanatide	High; only a modest benefit over placebo; little availability outside the USA
Tenapanor 50 mg twice a day	Network meta-analysis including three RCTs[110,111]	1428 patients with IBS with constipation	RR of persistence of global IBS symptoms† *vs* placebo 0·85 (0·79–0·92); RR of not having an increase of ≥1 CSBM per week† *vs* placebo 0·81 (0·68–0·96); RR of persistence of abdominal pain† *vs* placebo 0·82 (0·75–0·90); RR of persistence of abdominal bloating or distension *vs* placebo 0·86 (0·80–0·93)	Diarrhoea significantly more common with tenapanor	High; little availability outside the USA
Prucalopride 2 mg once a day	Network meta-analysis including five RCTs[108]	2860 patients with chronic constipation	RR of not having ≥3 CSBMs per week and an increase of ≥1 CSBM per week over baseline† *vs* placebo 0·84 (0·75–0·93); ≥1-point improvement in abdominal bloating score from baseline in 62·1% *vs* 49·6% with placebo in a pooled analysis of six RCTs,[112] p value not reported	Total adverse events, diarrhoea, headache, and nausea significantly more common with prucalopride	Moderate; risk of bias of RCTs
Elobixibat 5 mg once a day	Network meta-analysis including two RCTs[108]	705 patients with chronic constipation	RR of not having ≥3 CSBMs per week and an increase of ≥1 CSBM per week over baseline† *vs* placebo 0·90 (0·84–0·98)	Total adverse events, diarrhoea, and abdominal pain significantly more common with elobixibat	Moderate; risk of bias of RCTs; little availability outside Asia
Biofeedback	Meta-analysis of six RCTs[80]	456 patients with dyssynergic defecation	OR for global chronic constipation symptom improvement *vs* control therapy (including laxatives, botulinum toxin injection, placebo, standard therapy, or sham biofeedback) 3·63 (1·10–11·93)	Adverse events rarely reported	Very low; risk of bias of RCTs and inconsistency
Alosetron 0·5 mg twice a day	Network meta-analysis including seven RCTs[113]	3534 patients with non-constipated IBS	RR of persistence of global IBS symptoms† *vs* placebo 0·69 (0·60–0·80); RR of persistence of loose stools *vs* placebo 0·70 (0·60–0·81); RR of persistence of abdominal pain *vs* placebo 0·83 (0·78–0·88)	Constipation significantly more common with alosetron	Moderate; risk of bias of RCTs; serious adverse events, including ischaemic colitis and severe constipation, and little availability outside the USA
Ramosetron 5 µg once a day	Network meta-analysis including five RCTs[113]	1928 patients with IBS with diarrhoea	RR of persistence of global IBS symptoms† *vs* placebo 0·78 (0·67–0·91); RR of persistence of loose stools *vs* placebo 0·78 (0·71–0·85); RR of persistence of abdominal pain *vs* placebo 0·82 (0·75–0·89)	Total adverse events and constipation significantly more common with ramosetron	Moderate; risk of bias of RCTs; all RCTs conducted in Japan and little availability outside Asia
Eluxadoline 100 mg twice a day	Network meta-analysis including four RCTs[113]	3122 patients with IBS with diarrhoea	RR of persistence of global IBS symptoms† *vs* placebo 0·87 (0·83–0·91); RR of not having a stool consistency score of <5 on 50% of days† *vs* placebo 0·86 (0·81–0·91); RR of persistence of abdominal pain† *vs* placebo 0·89 (0·83–0·96)	Constipation significantly more common with eluxadoline	High; little availability outside the USA, only a modest benefit over placebo, and serious adverse events include acute pancreatitis and sphincter of Oddi spasm

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	Type and number of studies	N and population of RCTs	Reported effect if efficacy was shown	Adverse events	Quality and limitations of data
(Continued from previous page)					
Rifaximin 550 mg three times a day	Network meta-analysis including two RCTs[113]	1260 patients with non-constipated IBS	RR of persistence of global IBS symptoms† *vs* placebo 0·92 (0·86–0·98); RR of persistence of loose stools *vs* placebo 0·78 (0·68–0·89); adequate relief of abdominal bloating or distension in 40·2% *vs* 30·3% with placebo in the RCTs themselves (p<0·001)[114]	Total adverse events no more common with rifaximin	High; only a modest benefit over placebo
Ondansetron 4 mg once a day titrated either up or down	Meta-analysis including three RCTs[115]	327 patients with IBS with diarrhoea	RR of persistence of global IBS symptoms† *vs* placebo 0·86 (0·75–0·98); RR of not having a stool consistency score <5 on 50% of days† *vs* placebo 0·65 (0·52–0·82); RR of not having a ≥30% improvement in urgency *vs* placebo 0·74 (0·59–0·93)	Rates of constipation numerically higher with ondansetron	Moderate; heterogeneity; only a modest benefit over placebo and only a small number of patients in existing RCTs
Enterosgel 15 g twice a day titrated to 30 g twice a day	One RCT[116]	440 patients with IBS with diarrhoea	Improvement in global IBS symptoms† in 37·4% *vs* 24·3% with placebo (p=0·0020); stool consistency score <5 on 50% of days† in 58·4% *vs* 42·5% with placebo (p=0·0007); mean urgency score of 2·51 *vs* 3·08 with placebo (p<0·001)	Total adverse events no more common with enterosgel	Only one RCT
Glutamine 5 g three times a day	One RCT[117]	115 patients with IBS with diarrhoea	Improvement in global IBS symptoms in 79·6% *vs* 5·8% with placebo (p<0·001); mean improvement in stool consistency of −2·64 *vs* 0·02 with placebo (p<0·001)	Total adverse events no more common with glutamine	Only one RCT
Antispasmodics (eg, hyoscine 20 mg three times a day)	Network meta-analysis including 18 RCTs[118]	2131 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·76 (0·64–0·90); RR of persistence of abdominal pain *vs* placebo 0·64 (0·49–0·84)	Total adverse events significantly more common with antispasmodics	Very low; risk of bias of RCTs, inconsistency, and publication bias; small number of RCTs assessing each drug
Peppermint oil 200 mg three times a day	Meta-analysis including ten RCTs[119]	1030 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·65 (0·43–0·98); RR of persistence of abdominal pain *vs* placebo 0·76 (0·62–0·93)	Total adverse events significantly more common with peppermint oil	Very low; risk of bias of RCTs, inconsistency, imprecision, and publication bias; only a modest benefit over placebo, RCTs used specific formulations so data cannot be extrapolated to other products, and heartburn might be an issue
Selective serotonin reuptake inhibitors (eg, fluoxetine 20 mg once a day)	Meta-analysis including eight RCTs[120]	385 patients with unselected IBS	RR of persistence of abdominal pain *vs* placebo 0·74 (0·56–0·99)	Total adverse events no more common with selective serotonin reuptake inhibitors	Very low; risk of bias of RCTs, inconsistency, and imprecision; only a small number of patients in existing RCTs
Serotonin norepinephrine reuptake inhibitors (eg, duloxetine 30 mg once a day)	Meta-analysis including three RCTs[120]	134 patients with unselected IBS	RR of persistence of abdominal pain *vs* placebo 0·22 (0·08–0·59)	Total adverse events no more common with serotonin norepinephrine reuptake inhibitors	Very low; risk of bias of RCTs, inconsistency, and imprecision; only a small number of patients in existing RCTs
Tricyclic antidepressants (eg, amitriptyline 10 mg once a day titrated to 30–50 mg once a day)	Meta-analysis including 14 RCTs[120]	1290 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·70 (0·62–0·80); RR of persistence of abdominal pain *vs* placebo 0·69 (0·54–0·87)	Total adverse events no more common with tricyclic antidepressants	Moderate; publication bias; dry mouth and drowsiness common
Tetracyclic antidepressants (eg, mirtazapine 30 mg once a day)	Meta-analysis including one RCT[120]	67 patients with IBS with diarrhoea	RR of persistence of global IBS symptoms *vs* placebo 0·55 (0·34–0·89); RR of persistence of abdominal pain *vs* placebo 0·49 (0·29–0·80)	Adverse events not reported	Only one RCT
Forms of cognitive behavioural therapy	Network meta-analysis including 19 RCTs[121,122]	1986 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·67 (0·58–0·77); RR of persistence of abdominal pain *vs* placebo 0·75 (0·59–0·94)	Adverse events rarely reported	Very low; risk of bias of RCTs, inconsistency, and publication bias; time-consuming due to need for therapist contact, and little availability in some countries

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constipation,[69,70,128] with evidence supporting soluble fibre supplementation (eg, ispaghula)[100] or specific high-fibre foods (eg, kiwi fruits or ryebread),[101] rather than whole-food, high-fibre diets, for which data are sparse.

Beyond fibre, structured, whole-dietary interventions improve global symptoms in IBS and might influence pathophysiological mechanisms, including altered intestinal permeability or immune activation.[129,130] The

	Type and number of studies	N and population of RCTs	Reported effect if efficacy was shown	Adverse events	Quality and limitations of data
(Continued from previous page)					
Forms of gut-directed hypnotherapy	Network meta-analysis including ten RCTs[121,122]	895 patients with unselected IBS	RR of persistence of global IBS symptoms *vs* placebo 0·80 (0·67–0·95); RR of persistence of abdominal pain *vs* placebo 0·77 (0·61–0·97)	Adverse events rarely reported	Very low; risk of bias of RCTs, inconsistency, and publication bias; time-consuming due to need for therapist contact and little availability in some countries
Correction of thoracoabdominal muscular tone by biofeedback	One RCT[123]	42 patients with abdominal distension	Decrease in abdominal distension score by 66% *vs* 8% with placebo (p<0·001)	Total adverse events no more common with biofeedback	Only one RCT.

CSBM=complete spontaneous bowel movement. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. IBS=irritable bowel syndrome. OR=odds ratio. RCT=randomised controlled trial. RR=relative risk. Most drugs should be trialled for 3 months, with their effectiveness then reviewed, except for rifaximin, which is a 2-week treatment course. A low-FODMAP diet should not be maintained long-term; the restriction phase in RCTs to date has been a maximum of 3–4 weeks. *No direct comparison of the two; estimates derived from indirect evidence from the network meta-analysis. †US Food and Drug Administration endpoint.

Table: **Summary of evidence for treatments for constipation, diarrhoea, abdominal pain or discomfort, and abdominal bloating or distention**

best evidence exists for a low-FODMAP diet. A network meta-analysis showed superiority of a low-FODMAP diet over a habitual diet for global IBS symptoms.[102] Less restrictive diets, including starch and sucrose-reduced, gluten-free, or FODMAP-simple diets, or British Dietetic Association first-line dietary advice for IBS, were also superior to habitual diet for global symptoms. These diets might be particularly appealing because a low-FODMAP diet is not advised long-term due to potential effects on nutritional adequacy and the intestinal microbiome.[131,132] Most RCTs of the low-FODMAP diet only studied the first phase of the diet, the FODMAP exclusion phase, rather than also examining the effectiveness of the subsequent FODMAP reintroduction and personalisation phases. Notably, most trials in the network meta-analysis recruited patients with IBS with diarrhoea or IBS with mixed bowel habits, and no dietary intervention improved bowel habits, specifically, compared with habitual diet. There is also emerging evidence for a Mediterranean diet in IBS.[103]

A meta-analysis showed that some probiotics improve global IBS symptoms, including combination probiotics or *Lactobacillus*, *Escherichia*, or *Bacillus* strains.[104] Confidence in the clinical application of probiotics remains limited by study heterogeneity and insufficient high-quality evidence. However, trials published in the past 3 years have adopted contemporary design standards. In an RCT of patients with IBS with diarrhoea, *Bifidobacterium* quadruple viable tablet improved abdominal pain and stool consistency.[133] By contrast, a trial of a live biotherapeutic containing *Blautia hydrogenotrophica* showed no benefit over placebo in either IBS with constipation or IBS with diarrhoea.[134] These findings underscore the strain-specific effects of probiotics and the need for rigorous RCTs with clinically meaningful endpoints. Evidence for the effectiveness of prebiotics or symbiotics in bowel disorders remains inconclusive.[135]

Treatment of constipation

Constipation symptoms include hard or less frequent stools, straining, and tenesmus. Most treatments aim to improve stool frequency in line with FDA-recommended endpoints, with diarrhoea as a common side-effect. The osmotic laxative polyethylene glycol was effective in a meta-analysis on chronic constipation,[105] but trials in IBS with constipation are scarce.[106,107] Stimulant laxatives, including sodium picosulfate or bisacodyl, are also beneficial for chronic constipation,[105] but there are no RCTs on use for IBS with constipation. There are also no trials of stool softeners (eg, docusate), suppositories, or enemas in chronic constipation or IBS with constipation, but their use can be considered.

Licensed drugs include secretagogues acting on ion channels—such as linaclotide, lubiprostone, or plecanatide—the 5-HT_4 receptor agonist prucalopride, and elobixibat, an ileal bile-acid transporter inhibitor. There have been multiple RCTs in chronic constipation. In a network meta-analysis, all of these drugs were superior to placebo, with prucalopride and linaclotide the highest-ranking at 12 weeks using the FDA endpoint for stool frequency.[108] All three secretagogues and tenapanor (a Na^+–H^+ exchange inhibitor) are also licensed in IBS with constipation and are effective for global symptoms.[110] Using the FDA endpoint for stool frequency for IBS with constipation, linaclotide, plecanatide, and tenapanor were superior to placebo, with linaclotide ranked highest.

For non-drug therapies, there is evidence for biofeedback for the management of constipation in the context of dyssynergic defecation,[80] a condition characterised by impaired pelvic floor relaxation. Finally, transanal irrigation can be considered, although evidence is limited.[136]

Treatment of diarrhoea

Diarrhoea symptoms include loose or more frequent stools and urgency. Most treatments aim to improve stool consistency in line with FDA-recommended endpoints

with constipation being a common side-effect. Although loperamide, a μ-opioid receptor agonist, is often used in IBS with diarrhoea or functional diarrhoea, there is limited evidence supporting its effectiveness[69] and there are no trials of other antidiarrhoeals. Bile-acid sequestrants can be used empirically[90] but there are no RCTs on their use for IBS with diarrhoea or functional diarrhoea.

Licensed drugs for IBS with diarrhoea include 5-HT_3 receptor antagonists, such as alosetron or ramosetron, eluxadoline—a mixed opioid receptor drug—or rifaximin, a non-absorbable antibiotic. In a network meta-analysis, all were superior to placebo for global IBS symptoms.[113] For stool consistency, alosetron and ramosetron ranked highest, but rifaximin performed similarly. In a meta-analysis, ondansetron, another 5-HT_3 receptor antagonist, was superior to placebo for global IBS symptoms, stool consistency, and urgency.[115]

Other approaches include using enterosgel, a device that acts as an intestinal adsorbent, which is postulated to bind intestinal toxins and bile acids. In one RCT, enterosgel was superior to placebo for global symptoms, stool consistency, and urgency.[116] Finally, a trial of glutamine supplementation in patients with post-infection IBS with diarrhoea showed a significant reduction in global IBS symptoms and stool frequency over placebo.[117]

Treatment of abdominal pain or discomfort

Abdominal pain or discomfort is a cardinal feature of IBS but can also occur in chronic constipation and functional diarrhoea, although at a lower frequency than in IBS. Therefore, drugs used to treat pain in IBS can be considered for chronic constipation or functional diarrhoea, provided their other actions will not exacerbate the symptoms. Although mainly studied in small placebo-controlled trials, antispasmodics,[118] peppermint oil,[119] and gut–brain neuromodulators, including tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, or mirtazapine (a tetracyclic antidepressant),[120] can all improve abdominal pain in IBS. In a definitive trial, low-dose amitriptyline was more effective than placebo for both global IBS symptoms and abdominal pain at 6 months.[137]

The relative efficacies of licensed drugs for IBS for abdominal pain have been assessed in network meta-analyses.[110,113] In IBS with constipation, all secretagogues and tenapanor were more effective than placebo for the FDA endpoint for abdominal pain, with linaclotide ranked highest.[110] In IBS with diarrhoea, 5-HT_3-receptor antagonists ranked highest for the FDA endpoint, with eluxadoline also more effective than placebo, but rifaximin had no effect.[113]

If drugs are not preferred or not effective, a low-FOMAP diet, starch or sucrose-reduced diet, or gut–brain behaviour therapies, including cognitive behavioural therapy or gut-directed hypnotherapy, appear to be beneficial for abdominal pain and global IBS symptoms in network meta-analyses.[102,121,122]

Treatment of abdominal bloating or distention

Although few trials evaluate abdominal bloating as a primary endpoint, effective treatments in RCTs include probiotics (eg, combination probiotics or *Bacillus* strains),[104] antispasmodics in combination with simethicone,[138] a low-FODMAP or FODMAP-simple diet,[102] or correction of thoracoabdominal muscular tone.[123] Drugs for constipation or diarrhoea might also alleviate bloating. A network meta-analysis showed that linaclotide, lubiprostone, and tenapanor were superior to placebo for bloating in IBS with constipation.[111] In a trial in patients with chronic constipation with moderate-to-severe bloating, linaclotide was superior to placebo[109] and secondary or post-hoc analyses showed improved bloating with rifaximin in IBS with diarrhoea and prucalopride in chronic constipation.[114,112] Whether symptom improvements reflect effects on mechanisms other than stool abnormalities or pain, such as viscerosensory perception, gas production, microbial dysbiosis, or abdominophrenic dyssynergia, remains unclear.

Future directions and controversies

The clinical implications of the updated Rome V criteria for bowel disorders require further study. Additional analyses from the most recent Rome Foundation global epidemiological study might increase our understanding of the epidemiology of bowel disorders.[13] However, most doctors, particularly in primary care, will not apply the Rome criteria strictly in their practice,[139] preferring to make more pragmatic diagnoses based on patient symptoms. This preference implies that evidence generated from observational studies and treatment trials recruiting patients with bowel disorders using Rome V criteria might not be generalisable to routine clinical care. Treatment of a patient presenting with troublesome constipation, for example, will focus on managing their bowel habit. Whether any accompanying abdominal pain is frequent enough to categorise them as having IBS with constipation, rather than chronic constipation, makes little difference to the patient because if abdominal pain is troublesome, it will also require treatment, although whether abdominal pain is present or absent might influence the clinician's choice of drug.

Consequently, it is debatable if defining bowel disorders as separate entities is helpful, or whether instead they should be viewed as a clinical continuum. Indeed, using discrete diagnostic categories implies differentiation according to distinct underlying pathophysiological mechanisms and validated biomarkers, which is not the case. These disorders share a common construct as disorders of gut–brain interaction and patients move between diagnoses due to symptom fluctuation over

time.[84] IBS and chronic constipation are the most frequently studied, meaning there is less evidence for functional diarrhoea. Designing future trials to target the treatment of specific symptoms across the full spectrum of bowel disorders would widen patient participation and generate an evidence base that, arguably, better reflects real-world clinical practice.

Studies using latent class analysis show that people with bowel disorders separate into distinct subgroups on the basis of combinations of gastrointestinal symptoms, abdominal pain, and psychological symptoms.[140,141] This approach offers the potential to enable more personalised treatment. For example, those with diarrhoea or constipation, with minimal abdominal pain and psychological symptoms, might be best treated with a peripherally acting drug or dietary intervention alone, whereas those with high levels of mixed gastrointestinal and psychological symptoms, together with abdominal pain, might require multidisciplinary management with gut–brain neuromodulators and clinical psychology input.

Unfortunately, drug availability is not universal. Several drugs for bowel disorders are licensed only in specific countries. Elobixibat is only licensed for chronic constipation in Asia. For IBS with diarrhoea, alosetron is only licensed in the USA and rifaximin in the USA and some European, Latin American, and Asian countries. Widening access to existing drugs would enable more patients to benefit, but such expansion is contingent on regulatory approval, with processes and requirements varying between nations. Therefore, there is a need for new pharmacological therapies for bowel disorders, underlining the requirement for pharmaceutical companies to invest in this field.

Mizagliflozin, a sodium-glucose cotransporter-1 inhibitor, reduces sodium absorption from the intestinal lumen, increasing intraluminal water content and loosening stools. It showed promise in phase 2 trials in chronic constipation.[142] However, further development for bowel disorders was abandoned, possibly due to modest efficacy. A vibrating capsule has been tested in chronic constipation and was superior to placebo.[143] Bile acids are physiological laxatives and alterations in their absorption and metabolism are implicated in the pathophysiology of both IBS with diarrhoea and functional diarrhoea.[32] Liraglutide, a glucagon-like peptide-1 receptor (GLP-1) agonist, is effective for treating bile-acid diarrhoea,[144] with its effectiveness thought to result from prolongation of small intestinal transit time.[145,146] Therefore, GLP-1 agonists could be effective for managing diarrhoea and might also be effective for abdominal pain.[147] A study published in 2026 found elevated insulin-like peptide-5, an enteroendocrine hormone released from the distal colon and rectum, in patients with IBS with diarrhoea.[148] Insulin-like peptide-5 release was stimulated by rectal administration of bile acids and concentrations correlated positively with stool consistency. Further study of this hormone might improve understanding of the pathophysiology of chronic diarrhoea, offering new targets for drug development.

Gut–brain neuromodulators, especially tricyclic antidepressants such as amitriptyline, are well established for treating abdominal pain in bowel disorders, particularly IBS.[120] Serotonin norepinephrine reuptake inhibitors, such as duloxetine, have shown efficacy in smaller trials[149] and are efficacious for other chronic painful disorders, such as fibromyalgia.[150] Larger trials of serotonin norepinephrine reuptake inhibitors in bowel disorders should be considered. The cannabinoid type-2 receptor agonist olorinab could alter visceral sensation, given expression of cannabinoid type-2 receptors in the brain, peripheral nervous system, and gastrointestinal tract. However, a 12-week, phase 2, dose-ranging RCT in IBS failed to show a significant change in abdominal pain scores versus placebo.[151] ORP-101 is a novel dimer of buprenorphine that has antidiarrhoeal effects via partial agonism of μ-opioid receptors and treats visceral pain via full antagonism of peripheral κ-opioid receptors only, thereby avoiding CNS effects. However, in a 12-week RCT in IBS with diarrhoea, there was no significant difference between ORP-101 (100 mg once a day) and placebo for the FDA composite endpoint.[152] There was also no difference when abdominal pain and stool consistency response were evaluated individually. Finally, abdominal pain improved significantly with ebastine, a histamine-1-receptor antagonist licensed for allergic rhinitis, versus placebo in a meta-analysis.[153]

Conclusions

In summary, bowel disorders are common, with overlapping symptom profiles that have substantial effects on quality of life for patients. Despite our understanding of underlying pathophysiological mechanisms, no validated biomarker is available. Management relies on making a positive diagnosis based on a careful clinical history and judicious use of investigations, with exhaustive investigation avoided. Treatment is directed according to predominant symptoms. However, the effectiveness of most therapies is modest at best, driving the need to gain further insights into the pathophysiology of bowel disorders, develop new drug therapies, and move towards more personalised care for these common gastrointestinal conditions.

Contributors

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

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References

1 Corsetti M, Shin A, Lacy BE, et al. Bowel disorders. *Gastroenterology* 2026; **170:** 1261–82.

2 Tornkvist N, Palsson OS, Hreinsson J, et al. Global prevalence, characterization and impact of functional bowel disorders. *Am J Gastroenterol* 2025; **121:** 1973–85.

3 Shiha MG, Asghar Z, Thoufeeq M, et al. Increased psychological distress and somatization in patients with irritable bowel syndrome compared with functional diarrhea or functional constipation, based on Rome IV criteria. *Neurogastroenterol Motil* 2021; **33:** e14121.

4 Van Oudenhove L, Crowell MD, Drossman DA, et al. Biopsychosocial aspects of functional gastrointestinal disorders. *Gastroenterology* 2016; **150:** 1355–67.

5 Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut–brain interaction. *Gastroenterology* 2016; **150:** 1257–61.

6 Goodoory VC, Ng CE, Black CJ, Ford AC. Direct healthcare costs of Rome IV or Rome III-defined irritable bowel syndrome in the UK. *Aliment Pharmacol Ther* 2022; **56:** 110–20.

7 Frändemark Å, Törnblom H, Jakobsson S, Simrén M. Work productivity and activity impairment in irritable bowel syndrome (IBS): a multifaceted problem. *Am J Gastroenterol* 2018; **113:** 1540–49.

8 Neri L, Basilisco G, Corazziari E, et al, and the LIRS Study Group. Constipation severity is associated with productivity losses and healthcare utilization in patients with chronic constipation. *United European Gastroenterol J* 2014; **2:** 138–47.

9 Dik VK, Siersema PD, Joseph A, Hodgkins P, Smeets HM, van Oijen MG. Constipation-related direct medical costs in 16 887 patients newly diagnosed with chronic constipation. *Eur J Gastroenterol Hepatol* 2014; **26:** 1260–66.

10 Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10:** 712–21.

11 Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106:** 1582–91.

12 Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation global study. *Gastroenterology* 2021; **160:** 99–114.

13 Sperber AD, Hreinsson JP, Simrén M, et al. Rome V global epidemiology and validation survey: prevalence of disorders of gut–brain interaction and comparison with the Rome IV global epidemiology study. *Gut* 2026; **75:** 1887–97.

14 Barberio B, Judge C, Savarino EV, Ford AC. Global prevalence of functional constipation according to the Rome criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021; **6:** 638–48.

15 Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5:** 908–17.

16 Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2019; **50:** 132–43.

17 Jones MP, Tack J, Van Oudenhove L, et al. Mood and anxiety disorders precede development of functional gastrointestinal disorders in patients but not in the population. *Clin Gastroenterol Hepatol* 2017; **15:** 1014–20.

18 Yu YJ, Huang YC, Weng TH, et al. Bidirectional associations between irritable bowel syndrome and psychological distress: a longitudinal population-based study. *Psychol Med* 2026; **56:** e45.

19 Porcari S, Ingrosso MR, Maida M, et al. Prevalence of irritable bowel syndrome and functional dyspepsia after acute gastroenteritis: systematic review and meta-analysis. *Gut* 2024; **73:** 1431–40.

20 Marasco G, Maida M, Cremon C, Barbaro MR, Stanghellini V, Barbara G. Meta-analysis: post-COVID-19 functional dyspepsia and irritable bowel syndrome. *Aliment Pharmacol Ther* 2023; **58:** 6–15.

21 Palsson O, Simren M, Sperber AD, Bangdiwala S, Hreinsson JP, Aziz I. The prevalence and burden of disorders of gut-brain interaction (DGBI) before vs after the COVID-19 pandemic. *Clin Gastroenterol Hepatol* 2026; **24:** 1151–60.

22 Ford AC, Vanner S, Kashyap PC, Nasser Y. Chronic visceral pain: new peripheral mechanistic insights and resulting treatments. *Gastroenterology* 2024; **166:** 976–94.

23 Posserud I, Agerforz P, Ekman R, Björnsson ES, Abrahamsson H, Simrén M. Altered visceral perceptual and neuroendocrine response in patients with irritable bowel syndrome during mental stress. *Gut* 2004; **53:** 1102–08.

24 Manabe N, Wong BS, Camilleri M, Burton D, McKinzie S, Zinsmeister AR. Lower functional gastrointestinal disorders: evidence of abnormal colonic transit in a 287-patient cohort. *Neurogastroenterol Motil* 2010; **22:** 293–e82.

25 Furgała A, Ciesielczyk K, Przybylska-Feluś M, Jabłoński K, Gil K, Zwolińska-Wcisło M. Postprandial effect of gastrointestinal hormones and gastric activity in patients with irritable bowel syndrome. *Sci Rep* 2023; **13:** 9420.

26 Di Stefano M, Miceli E, Missanelli A, Mazzocchi S, Corazza GR. Meal induced rectosigmoid tone modification: a low caloric meal accurately separates functional and organic gastrointestinal disease patients. *Gut* 2006; **55:** 1409–14.

27 Thijssen AY, Mujagic Z, Jonkers DM, et al. Alterations in serotonin metabolism in the irritable bowel syndrome. *Aliment Pharmacol Ther* 2016; **43:** 272–82.

28 Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005; **3:** 349–57.

29 Pata C, Erdal ME, Derici E, Yazar A, Kanik A, Ulu O. Serotonin transporter gene polymorphism in irritable bowel syndrome. *Am J Gastroenterol* 2002; **97:** 1780–84.

30 Moretti CH, Grasset E, Zhu J, et al. Identification of human gut bacteria that produce bioactive serotonin and promote colonic innervation. *Cell Rep* 2025; **44:** 116434.

31 Zhai L, Huang C, Ning Z, et al. *Ruminococcus gnavus* plays a pathogenic role in diarrhea-predominant irritable bowel syndrome by increasing serotonin biosynthesis. *Cell Host Microbe* 2023; **31:** 33–44.

32 Shin A, Camilleri M, Vijayvargiya P, et al. Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2013; **11:** 1270–75.

33 Duboc H, Rainteau D, Rajca S, et al. Increase in fecal primary bile acids and dysbiosis in patients with diarrhea-predominant irritable bowel syndrome. *Neurogastroenterol Motil* 2012; **24:** 513–20.

34 Li WT, Luo QQ, Wang B, et al. Bile acids induce visceral hypersensitivity via mucosal mast cell-to-nociceptor signaling that involves the farnesoid X receptor/nerve growth factor/transient receptor potential vanilloid 1 axis. *FASEB J* 2019; **33:** 2435–50.

35 Henström M, Diekmann L, Bonfiglio F, et al. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut* 2018; **67:** 263–70.

36 Murray K, Wilkinson-Smith V, Hoad C, et al. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am J Gastroenterol* 2014; **109:** 110–19.

37 Shin A, Kashyap PC. Multi-omics for biomarker approaches in the diagnostic evaluation and management of abdominal pain and irritable bowel syndrome: what lies ahead. *Gut Microbes* 2023; **15:** 2195792.

38 Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nat Med* 2010; **16:** 1248–57.

39 Greenwood-Van Meerveld B, Mawe G, Beyder A, et al. Fundamentals of neurogastroenterology: basic science. *Gastroenterology* 2026; **170:** 1099–113.

40 Basso L, Altier C. Transient receptor potential channels in neuropathic pain. *Curr Opin Pharmacol* 2017; **32:** 9–15.

41 Grover M, Berumen A, Peters S, et al. Intestinal chemosensitivity in irritable bowel syndrome associates with small intestinal TRPV channel expression. *Aliment Pharmacol Ther* 2021; **54:** 1179–92.

42 Wouters MM, Balemans D, Van Wanrooy S, et al. Histamine receptor H1-mediated sensitization of TRPV1 mediates visceral hypersensitivity and symptoms in patients with irritable bowel syndrome. *Gastroenterology* 2016; **150:** 875–87.

43 Caldarella MP, Giamberardino MA, Sacco F, et al. Sensitivity disturbances in patients with irritable bowel syndrome and fibromyalgia. *Am J Gastroenterol* 2006; **101:** 2782–89.

44 Verne GN, Himes NC, Robinson ME, et al. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. *Pain* 2003; **103:** 99–110.

45 Barbara G, Aziz I, Ballou S, et al. Rome Foundation Working Team Report on overlap in disorders of gut–brain interaction. *Nat Rev Gastroenterol Hepatol* 2025; **22:** 228–51.

46 Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; **152** (suppl 3)**:** S2–15.

47 Albusoda A, Ruffle JK, Friis KA, et al. Systematic review with meta-analysis: conditioned pain modulation in patients with the irritable bowel syndrome. *Aliment Pharmacol Ther* 2018; **48:** 797–806.

48 Person H, Keefer L. Psychological comorbidity in gastrointestinal diseases: update on the brain–gut–microbiome axis. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; **107:** 110209.

49 Mayer EA, Labus J, Aziz Q, et al. Role of brain imaging in disorders of brain-gut interaction: a Rome Working Team Report. *Gut* 2019; **68:** 1701–15.

50 Aguilera-Lizarraga J, Florens MV, Viola MF, et al. Local immune response to food antigens drives meal-induced abdominal pain. *Nature* 2021; **590:** 151–56.

51 Balemans D, Mondelaers SU, Cibert-Goton V, et al. Evidence for long-term sensitization of the bowel in patients with post-infectious-IBS. *Sci Rep* 2017; **7:** 13606.

52 Bashashati M, Moossavi S, Cremon C, et al. Colonic immune cells in irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil* 2018; **30:** e13192.

53 Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004; **126:** 693–702.

54 Aguilera-Lizarraga J, Lopez-Lopez C, Jaramillo-Polanco J, et al. Psychological stress-induced local immune response to food antigens increases pain signaling across the gut in mice. *Gastroenterology* 2025; **169:** 104–18.

55 Pittayanon R, Lau JT, Yuan Y, et al. Gut microbiota in patients with irritable bowel syndrome: a systematic review. *Gastroenterology* 2019; **157:** 97–108.

56 Quan R, Decraecker L, Appeltans I, et al. Fecal proteolytic bacteria and staphylococcal superantigens are associated with abdominal pain severity in irritable bowel syndrome. *Am J Gastroenterol* 2025; **120:** 603–13.

57 Petitfils C, Maurel S, Payros G, et al. Identification of bacterial lipopeptides as key players in IBS. *Gut* 2023; **72:** 939–50.

58 Chiu IM, Heesters BA, Ghasemlou N, et al. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* 2013; **501:** 52–57.

59 Bayrer JR, Castro J, Venkataraman A, et al. Gut enterochromaffin cells drive visceral pain and anxiety. *Nature* 2023; **616:** 137–42.

60 Miquel S, Martín R, Lashermes A, et al. Anti-nociceptive effect of *Faecalibacterium prausnitzii* in non-inflammatory IBS-like models. *Sci Rep* 2016; **6:** 19399.

61 De Palma G, Shimbori C, Reed DE, et al. Histamine production by the gut microbiota induces visceral hyperalgesia through histamine 4 receptor signaling in mice. *Sci Transl Med* 2022; **14:** eabj1895.

62 Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician–patient interaction. *Ann Intern Med* 1995; **122:** 107–12.

63 Drossman DA, Chang L, Deutsch JK, et al. A review of the evidence and recommendations on communication skills and the patient-provider relationship: a Rome Foundation Working Team Report. *Gastroenterology* 2021; **161:** 1670–88.

64 Ford AC, Veldhuyzen van Zanten SJO, Rodgers CC, Talley NJ, Vakil NB, Moayyedi P. Diagnostic utility of alarm features for colorectal cancer: systematic review and meta-analysis. *Gut* 2008; **57:** 1545–53.

65 Gwee KA, Wee S, Wong ML, Png DJ. The prevalence, symptom characteristics, and impact of irritable bowel syndrome in an Asian urban community. *Am J Gastroenterol* 2004; **99:** 924–31.

66 Barberio B, Houghton LA, Yiannakou Y, Savarino EV, Black CJ, Ford AC. Symptom stability in Rome IV vs Rome III irritable bowel syndrome. *Am J Gastroenterol* 2021; **116:** 362–71.

67 Houghton LA, Lea R, Agrawal A, Reilly B, Whorwell PJ. Relationship of abdominal bloating to distention in irritable bowel syndrome and effect of bowel habit. *Gastroenterology* 2006; **131:** 1003–10.

68 Begtrup LM, Engsbro AL, Kjeldsen J, et al. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2013; **11:** 956–62.

69 Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology Guidelines on the management of irritable bowel syndrome. *Gut* 2021; **70:** 1214–40.

70 Ford AC, Moayyedi P, Lacy BE, et al, and the Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology Monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 2014; **109** (suppl 1)**:** S2–26.

71 Sood R, Camilleri M, Gracie DJ, et al. Enhancing diagnostic performance of symptom-based criteria for irritable bowel syndrome by additional history and limited diagnostic evaluation. *Am J Gastroenterol* 2016; **111:** 1446–54.

72 Staller K, Goodory VC, Khasawneh M, Black CJ, Ford AC. The Rome V criteria for the diagnosis of irritable bowel syndrome in secondary care: a diagnostic accuracy study. *Lancet Gastroenterol Hepatol* 2026; **11:** 812–20.

73 Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol* 2015; **110:** 444–54.

74 Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: diagnosis and management of celiac disease. *Am J Gastroenterol* 2023; **118:** 59–76.

75 Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol* 2017; **112:** 65–76.

76 Smalley W, Falck-Ytter C, Carrasco-Labra A, Wani S, Lytvyn L, Falck-Ytter Y. AGA Clinical Practice Guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). *Gastroenterology* 2019; **157:** 851–54.

77 National Institute for Health and Care Excellence. Suspected cancer: recognition and referral. National Institute for Health and Care Excellence. 2026. https://www.nice.org.uk/guidance/NG12/ (accessed April 26, 2026).

78 Khasawneh M, Craig OF, Gracie DJ, Black CJ, Ford AC. A diagnosis of irritable bowel syndrome using Rome IV criteria and limited investigations is durable in secondary care. *Clin Gastroenterol Hepatol* 2023; **21:** 3397–404.

79 Brandler J, Camilleri M. Pretest and post-test probabilities of diagnoses of rectal evacuation disorders based on symptoms, rectal exam, and basic tests: a systematic review. *Clin Gastroenterol Hepatol* 2020; **18:** 2479–90.

80 Moore D, Young CJ. A systematic review and meta-analysis of biofeedback therapy for dyssynergic defaecation in adults. *Tech Coloproctol* 2020; **24:** 909–18.

81 Park SY, Burton D, Busciglio I, Eckert D, Camilleri M. Regional colonic transit pattern does not conclusively identify evacuation disorders in constipated patients with delayed colonic transit. *J Neurogastroenterol Motil* 2017; **23:** 92–100.

82 Bharucha AE, Lacy BE. Mechanisms, evaluation, and management of chronic constipation. *Gastroenterology* 2020; **158:** 1232–49.

83 Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. *Gastroenterology* 2005; **129:** 86–97.

84 Dajti E, Frazzoni L, Iascone V, et al. Systematic review with meta-analysis: diagnostic performance of faecal calprotectin in distinguishing inflammatory bowel disease from irritable bowel syndrome in adults. *Aliment Pharmacol Ther* 2023; **58:** 1120–31.

85 Miehlke S, Guagnozzi D, Zabana Y, et al. European Guidelines on microscopic colitis: United European Gastroenterology and European Microscopic Colitis Group Statements and Recommendations. *United European Gastroenterol J* 2021; **9:** 13–37.

86 Macaigne G, Lahmek P, Locher C, et al. Microscopic colitis or functional bowel disease with diarrhea: a French prospective multicenter study. *Am J Gastroenterol* 2014; **109:** 1461–70.

87 Chey WD, Nojkov B, Rubenstein JH, Dobhan RR, Greenson JK, Cash BD. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: results from a prospective, controlled US trial. *Am J Gastroenterol* 2010; **105:** 859–65.

88 Aziz I, Mumtaz S, Bholah H, Chowdhury FU, Sanders DS, Ford AC. High prevalence of idiopathic bile acid diarrhea among patients with diarrhea-predominant irritable bowel syndrome based on Rome III criteria. *Clin Gastroenterol Hepatol* 2015; **13:** 1650–55.

89 Valentin N, Camilleri M, Altayar O, et al. Biomarkers for bile acid diarrhoea in functional bowel disorder with diarrhoea: a systematic review and meta-analysis. *Gut* 2016; **65:** 1951–59.

90 Schiepatti A, Bossert I, Cincotta M, et al. Comparison between SeHCAT test and clinical response to cholestyramine in patients with chronic diarrhea and high suspicion of bile acid malabsorption: a single-center prospective study. *J Dig Dis* 2024; **25:** 279–84.

91 Arasaradnam RP, Brown S, Forbes A, et al. Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. *Gut* 2018; **67:** 1380–99.

92 Rao S, Schultz M, Lesmana E, Oglesbee D, Absah I, Grover M. Clinical insights into disaccharidase deficiency: prevalence, intestinal histology, and outcomes. *Mayo Clin Proc* 2025; **100:** 2267–70.

93 Kashyap P, Moayyedi P, Quigley EMM, Simren M, Vanner S. Critical appraisal of the SIBO hypothesis and breath testing: a clinical practice update endorsed by the European Society of Neurogastroenterology and Motility (ESNM) and the American Neurogastroenterology and Motility Society (ANMS). *Neurogastroenterol Motil* 2024; **36:** e14817.

94 Goodoory VC, Houghton LA, Black CJ, Ford AC. Characteristics of, and natural history among, individuals with Rome IV functional bowel disorders. *Neurogastroenterol Motil* 2022; **34:** e14268.

95 Staller K, Olén O, Söderling J, et al. Mortality risk in irritable bowel syndrome: results from a nationwide prospective cohort study. *Am J Gastroenterol* 2020; **115:** 746–55.

96 Chang JY, Locke GR 3rd, McNally MA, et al. Impact of functional gastrointestinal disorders on survival in the community. *Am J Gastroenterol* 2010; **105:** 822–32.

97 Ballou S, McMahon C, Lee HN, et al. Effects of irritable bowel syndrome on daily activities vary among subtypes based on results from the IBS in America Survey. *Clin Gastroenterol Hepatol* 2019; **17:** 2471–78.

98 MacKrill K, Bass C, Petrie K. Comparing illness perceptions in inflammatory bowel disease and irritable bowel syndrome. *J Psychosom Res* 2025; **196:** 112337.

99 Hulme K, Chilcot J, Smith MA. Doctor–patient relationship and quality of life in irritable bowel syndrome: an exploratory study of the potential mediating role of illness perceptions and acceptance. *Psychol Health Med* 2018; **23:** 674–84.

100 Moayyedi P, Quigley EM, Lacy BE, et al. The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol* 2014; **109:** 1367–74.

101 Van Der Schoot A, Katsirma Z, Whelan K, Dimidi E. Systematic review and meta-analysis: foods, drinks and diets and their effect on chronic constipation in adults. *Aliment Pharmacol Ther* 2024; **59:** 157–74.

102 Cuffe MS, Staudacher HM, Aziz I, et al. Efficacy of dietary interventions in irritable bowel syndrome: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2025; **10:** 520–36.

103 Bamidele JO, Brownlow GM, Flack RM, et al. The Mediterranean diet for irritable bowel syndrome: a randomized clinical trial. *Ann Intern Med* 2025; **178:** 1709–17.

104 Goodoory VC, Khasawneh M, Black CJ, Quigley EMM, Moayyedi P, Ford AC. Efficacy of probiotics in irritable bowel syndrome: systematic review and meta-analysis. *Gastroenterology* 2023; **165:** 1206–18.

105 Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut* 2011; **60:** 209–18.

106 Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol* 2013; **108:** 1508–15.

107 Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. *Colorectal Dis* 2010; **12:** 1131–38.

108 Luthra P, Camilleri M, Burr NE, Quigley EMM, Black CJ, Ford AC. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2019; **4:** 831–44.

109 Lacy BE, Schey R, Shiff SJ, et al. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. *PLoS One* 2015; **10:** e0134349.

110 Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. *Gastroenterology* 2018; **155:** 1753–63.

111 Nelson AD, Black CJ, Houghton LA, Lugo-Fagundo NS, Lacy BE, Ford AC. Systematic review and network meta-analysis: efficacy of licensed drugs for abdominal bloating in irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2021; **54:** 98–108.

112 Staller K, Hinson J, Kerstens R, Spalding W, Lembo A. Efficacy of prucalopride for chronic idiopathic constipation: an analysis of participants with moderate to very severe abdominal bloating. *Am J Gastroenterol* 2022; **117:** 184–88.

113 Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. *Gut* 2020; **69:** 74–82.

114 Pimentel M, Lembo A, Chey WD, et al, and the TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011; **364:** 22–32.

115 Gunn D, Topan R, Barnard L, et al. Randomised, placebo-controlled trial and meta-analysis show benefit of ondansetron for irritable bowel syndrome with diarrhoea: the TRITON trial. *Aliment Pharmacol Ther* 2023; **57:** 1258–71.

116 Howell CA, Kemppinen A, Allgar V, et al. Double-blinded randomised placebo controlled trial of enterosgel (polymethylsiloxane polyhydrate) for the treatment of IBS with diarrhoea (IBS-D). *Gut* 2022; **71:** 2430–38.

117 Zhou Q, Verne ML, Fields JZ, et al. Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. *Gut* 2019; **68:** 996–1002.

118 Black CJ, Yuan Y, Selinger CP, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5:** 117–31.

119 Ingrosso MR, Ianiro G, Nee J, et al. Systematic review and meta-analysis: efficacy of peppermint oil in irritable bowel syndrome. *Aliment Pharmacol Ther* 2022; **56:** 932–41.

120 Khasawneh M, Mokhtare M, Moayyedi P, Black CJ, Ford AC. Efficacy of gut-brain neuromodulators in irritable bowel syndrome: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2025; **10:** 537–49.

121 Goodoory VC, Khasawneh M, Thakur ER, et al. Effect of brain-gut behavioral treatments on abdominal pain in irritable bowel syndrome: systematic review and network meta-analysis. *Gastroenterology* 2024; **167:** 934–43.

122 Thakur ER, Khasawneh M, Moayyedi P, Black CJ, Ford AC. Efficacy of behavioural therapies for irritable bowel syndrome: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2025; **10:** 1075–88.

123 Barba E, Livovsky DM, Accarino A, Azpiroz F. Thoracoabdominal wall motion-guided biofeedback treatment of abdominal distention: a randomized placebo-controlled trial. *Gastroenterology* 2024; **167:** 538–46.

124 Farmer AD, Gallagher J, Bruckner-Holt C, Aziz Q. Narcotic bowel syndrome. *Lancet Gastroenterol Hepatol* 2017; **2:** 361–68.

125 Jaafari H, Houghton LA, West RM, et al. Dietary patterns are associated with variations in the global prevalence and severity of Rome IV irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2026; **24:** 814–23.

126 Ho FF, Sun H, Zheng H, et al. Association of healthy lifestyle behaviours with incident irritable bowel syndrome: a large population-based prospective cohort study. *Gut* 2024; **73:** 922–31.

127 Johannesson E, Simrén M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol* 2011; **106:** 915–22.

128 Dimidi E, van der Schoot A, Barrett K, et al. British Dietetic Association Guidelines for the dietary management of chronic constipation in adults. *Neurogastroenterol Motil* 2025; **37:** e70173.

129 Vazquez-Roque MI, Camilleri M, Smyrk T, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterology* 2013; **144:** 903–11.

130 McIntosh K, Reed DE, Schneider T, et al. FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial. *Gut* 2017; **66:** 1241–51.

131 So D, Loughman A, Staudacher HM. Effects of a low FODMAP diet on the colonic microbiome in irritable bowel syndrome: a systematic review with meta-analysis. *Am J Clin Nutr* 2022; **116:** 943–52.

132 Staudacher HM, Ralph FSE, Irving PM, Whelan K, Lomer MCE. Nutrient intake, diet quality, and diet diversity in irritable bowel syndrome and the impact of the low FODMAP diet. *J Acad Nutr Diet* 2020; **120:** 535–47.

133 Bai T, Xu Z, Xia P, et al. The short-term efficacy of *Bifidobacterium* quadruple viable tablet in patients with diarrhea-predominant irritable bowel syndrome: potentially mediated by metabolism rather than diversity regulation. *Am J Gastroenterol* 2023; **118:** 1256–67.

134 Quigley EMM, Markinson L, Stevenson A, Treasure FP, Lacy BE. Randomised clinical trial: efficacy and safety of the live biotherapeutic product MRx1234 in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2023; **57:** 81–93.

135 Wilson B, Rossi M, Dimidi E, Whelan K. Prebiotics in irritable bowel syndrome and other functional bowel disorders in adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2019; **109:** 1098–111.

136 Knowles CH, Booth L, Brown SR, et al. Non-drug therapies for the management of chronic constipation in adults: the CapaCiTY research programme including three RCTs. *PGfAR* 2021; **9** (suppl 14)**:** 1–133.

137 Ford AC, Wright-Hughes A, Alderson SL, et al, and the ATLANTIS trialists. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023; **402:** 1773–85.

138 Schmulson MJ, Chiu-Ugalde J, Sáez-Ríos A, et al. Efficacy of the combination of pinaverium bromide 100 mg plus simethicone 300 mg in abdominal pain and bloating in irritable bowel syndrome: a randomized, placebo-controlled trial. *J Clin Gastroenterol* 2020; **54:** e30–39.

139 Heidelbaugh JJ, Hungin AP, Palsson OS, et al. Perceptions and practices of primary care providers in Europe and the US in the diagnosis and treatment of irritable bowel syndrome: a multinational survey. *Neurogastroenterol Motil* 2025; **37:** e14967.

140 Polster A, Van Oudenhove L, Jones M, Öhman L, Törnblom H, Simrén M. Mixture model analysis identifies irritable bowel syndrome subgroups characterised by specific profiles of gastrointestinal, extraintestinal somatic and psychological symptoms. *Aliment Pharmacol Ther* 2017; **46:** 529–39.

141 Black CJ, Houghton LA, Ford AC. Latent class analysis does not support the existence of Rome IV functional bowel disorders as discrete entities. *Neurogastroenterol Motil* 2022; **34:** e14391.

142 Fukudo S, Endo Y, Hongo M, et al, and the Mizagliflozin Study Group. Safety and efficacy of the sodium-glucose cotransporter 1 inhibitor mizagliflozin for functional constipation: a randomised, placebo-controlled, double-blind phase 2 trial. *Lancet Gastroenterol Hepatol* 2018; **3:** 603–13.

143 Haghbin H, Zakirkhodjaev N, Gangwani MK, et al. Efficacy and safety of vibrating capsule in treatment of chronic idiopathic constipation: a systematic review and meta-analysis of randomized controlled trials. *Transl Gastroenterol Hepatol* 2024; **9:** 8.

144 Kårhus ML, Brønden A, Forman JL, et al. Safety and efficacy of liraglutide versus colesevelam for the treatment of bile acid diarrhoea: a randomised, double-blind, active-comparator, non-inferiority clinical trial. *Lancet Gastroenterol Hepatol* 2022; **7:** 922–31.

145 Kårhus ML, Brønden A, Røder ME, Leotta S, Sonne DP, Knop FK. Remission of bile acid malabsorption symptoms following treatment with the glucagon-like peptide 1 receptor agonist liraglutide. *Gastroenterology* 2019; **157:** 569–71.

146 Cymbal M, Naseem Z, Hoxha D, Garg S. Impact of GLP-1 receptor agonists on whole-gut gastrointestinal motility using wireless motility capsule: a descriptive single-center case series. *ACG Case Rep J* 2025; **12:** e01789.

147 Hellström PM, Hein J, Bytzer P, Björnssön E, Kristensen J, Schambye H. Clinical trial: the glucagon-like peptide-1 analogue ROSE-010 for management of acute pain in patients with irritable bowel syndrome: a randomized, placebo-controlled, double-blind study. *Aliment Pharmacol Ther* 2009; **29:** 198–206.

148 Bannon CA, Walters JRF, Wu T, et al. Insulin-like peptide 5 is released in response to bile acid in the rectum and is associated with diarrhoea severity in patients with bile acid diarrhoea. *Gut* 2026; **75:** 278–88.

149 Sharbafchi MR, Afshar Zanjani H, Saneian Z, Feizi A, Daghaghzadeh H, Adibi P. Effects of duloxetine on gastrointestinal symptoms, depression, anxiety, stress, and quality of life in patients with the moderate-to-severe irritable bowel syndrome. *Adv Biomed Res* 2023; **12:** 249.

150 Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev* 2018; **2:** CD010292.

151 Chang L, Cash BD, Lembo A, et al. Efficacy and safety of olorinab, a full agonist of the cannabinoid receptor 2, for the treatment of abdominal pain in patients with irritable bowel syndrome: results from a phase 2b randomized placebo-controlled trial (CAPTIVATE). *Neurogastroenterol Motil* 2023; **35:** e14539.

152 Singh P, Nee JW, Ballou S, et al. ORP-101 in irritable bowel syndrome with diarrhea: a phase II randomized, controlled trial. *Clin Gastroenterol Hepatol* 2026; **24:** 2297–304.

153 Khasawneh M, Black CJ, Ford AC. Efficacy of drugs acting on histamine 1 receptors in irritable bowel syndrome: systematic review and meta-analysis. *Gastroenterology* 2024; **167:** 400–01.

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