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Review Article

Irritable bowel syndrome: a multidimensional review of pathophysiology, biomarkers, and tailored interventions

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ABSTRACT

Irritable bowel syndrome is a chronic, functional gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits without identifiable structural or biochemical abnormalities. It significantly impairs quality of life and remains a diagnostic and therapeutic challenge due to its multifactorial pathophysiology and symptom heterogeneity. This review synthesizes evolving evidence on the epidemiology, Rome-IV diagnostic criteria, and pathophysiological mechanisms including visceral hypersensitivity, gut-brain axis dysregulation, microbiota alterations, immune activation, and genetic factors. Special focus is placed on the neurobiology of IBS, highlighting structural and functional brain network changes, neurotransmitter involvement, and microbiota-gut-brain interactions. The manuscript also covers the overlap of IBS with other gastrointestinal and extra intestinal disorders, biomarker innovations, and the clinical value of positive diagnosis over exclusionary practices. A comprehensive, symptom-guided management strategy encompassing pharmacologic therapies, microbial modulation, dietary interventions, and psychological approaches is discussed. A structured approach to IBS begins with a confident diagnosis, followed by identification of underlying mechanisms through symptom assessment and pragmatic testing, and tailored treatment- such as probiotics (e.g. Bifidobacterium) for dysbiosis or antispasmodics (e.g. Mebeverine) for motility and pain, while tracking progress and adjusting therapy toward realistic symptom control goals. This integrative model underscores the necessity of personalized treatment to improve outcomes and patient satisfaction.

Keywords: Irritable bowel syndrome, Rome IV criteria, Gut-brain axis, Visceral hypersensitivity, Microbiota, Neurotransmitters, Overlap syndromes, Biomarkers

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, functional gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits, such as diarrhea, constipation, or a mix of both, without any identifiable structural or biochemical abnormality.[1,2] It is classified under disorders of gut–brain interaction (DGBI) and is one of the most prevalent functional abdominal pain disorders (FABD), significantly affecting both adults and children worldwide.[3,4] The global prevalence of IBS is estimated to be up to 10%, though rates vary widely due to differences in diet, culture, and diagnostic criteria.[4] Women are disproportionately affected, with a female-to-male ratio of approximately 2:1, and symptoms typically begin before the age of 45. However, the condition is also seen in elderly populations.[5] In India, IBS prevalence ranges from 0.4% to 7.2%, as shown in various community-based studies. These variations are attributed to methodological factors, diagnostic tools, and socio-cultural influences. Rome IV criteria tend to underdiagnose IBS compared to Rome III. While Western populations show female predominance, Indian data often report a higher proportion of male patients, possibly due to healthcare-seeking behavior. Community studies suggest nearly equal gender distribution in India. Factors such as diet, gut microbiota

composition, and hygiene practices may contribute to the relatively lower reported prevalence in India.[6] The pathophysiology of IBS is multifactorial and not fully understood. Proposed mechanisms include altered gastrointestinal motility, visceral hypersensitivity (VH), psychosocial stressors, increased intestinal permeability, low-grade mucosal inflammation, and disturbances in the gut microbiota. Post-infectious IBS and Small intestinal bacterial overgrowth (SIBO) have also been implicated in certain patients.[7]

IBS significantly affects patients' quality of life (QOL), leading to physical discomfort, emotional distress, reduced work productivity, absenteeism, and limitations in daily activities.[4,8]

It often overlaps with other functional gastrointestinal disorders (FGIDs), complicating diagnosis and management.[1] Despite the availability of diverse therapeutic options, there is no definitive cure. Management traditionally focused on symptom relief, but current best practices advocate a multidisciplinary approach involving medical therapy, dietary interventions, and psychological support, with the goal of empowering patients to self-manage the condition over time.[3] In recent years, increased awareness, advances in gut-brain axis research, and emerging data on the human gut microbiome have deepened the understanding of IBS. However, the absence of standardized treatment protocols continues to result in inconsistent outcomes and suboptimal satisfaction for both clinicians and patients. Continued research is essential to enhance diagnostic accuracy, therapeutic efficacy, and overall patient outcomes in IBS.[7]

Meetings with Indian specialists were convened to gain nuanced insights into the burden of IBS in India, focusing on diagnostic challenges, pathophysiological mechanisms, and current management practices. The objective of this review is to provide a comprehensive, evidence-based overview of IBS, emphasizing its pathophysiology and diagnostic approaches along with experts' suggestions.

ROME III VS. ROME IV CRITERIA FOR THE DIAGNOSIS OF IBS

The diagnosis of IBS has traditionally relied on symptom-based criteria, with the Manning criteria of the 1970s evolving into the more structured Rome criteria in the 1990s.[9,10] The Rome IV criteria, published in 2016, replaced the Rome III criteria (2006) following concerns over diagnostic accuracy and evolving clinical insights into IBS. Key changes include revised symptom thresholds and a redefined diagnostic framework.[11] Rome III defined IBS as recurrent abdominal pain or discomfort occurring ≥3 days/month over 3 months, linked to at least two of: relief with defecation, altered stool frequency, or form. The inclusion of "discomfort" aimed to broaden diagnostic reach.[11,12] In contrast, Rome IV removed "discomfort" due to its ambiguity and now requires abdominal pain ≥1 day/week over 3 months, plus ≥2 Rome III features. These changes aim to improve diagnostic specificity and reduce overdiagnosis.[12] Consequently, the Rome IV criteria are more stringent and identify patients with more severe symptomatology, potentially associated with a higher prevalence of psychiatric comorbidities and a lower QOL.[11] Another key evolution from Rome III to Rome IV was in the subtyping of IBS. Rome III classified IBS into four subtypes using the Bristol Stool Form (BSF) scale, but included normal stool days, often inflating IBS-U cases. Rome IV improved clarity by basing subtypes solely on abnormal stool days (BSF types 1–2 or 6–7), enhancing clinical relevance.[12]

While not yet fully validated, Rome IV shows improved specificity (up to 97%) and higher positive likelihood ratios than Rome III, particularly for IBS-C and IBS-M. However, broader studies are needed to confirm its diagnostic superiority.[10] Importantly, the implementation of these diagnostic criteria in real-world practice remains inconsistent. Although the use of Rome criteria is recommended in guidelines, most clinicians possess limited knowledge or fail to apply them, often treating IBS as a diagnosis of exclusion. This discrepancy underscores the need for diagnostic tools that bridge clinical practice with guideline-based approaches.[9] The shift from Rome III to IV reflects a more refined view of IBS as pain-centered with stricter symptom criteria. Yet, without direct comparative studies, it's unclear whether Rome IV defines a stricter subset or a distinct group, leaving key clinical questions unresolved.[10]

PATHOPHYSIOLOGICAL INSIGHTS

IBS is a complex condition with multifactorial pathophysiology.[8] Key mechanisms involved include VH, gut motility disturbances, altered gut-brain axis signaling, microbiota changes, immune activation, and genetic and epigenetic factors. These mechanisms often coexist and interact, contributing to the heterogeneous clinical presentation of IBS.[13]

Visceral hypersensitivity

Visceral hypersensitivity (VHS) is a hallmark of all IBS subtypes, seen in about 61% of patients. It stems from abnormal gut-to-brain signaling, where normal stimuli are perceived as painful. Peripheral factors, like mast cell–derived mediators (e.g., PGE2, COX-2), sensitize gut neurons, while central changes in spinal and brain processing further amplify this sensitivity.[14,16]

Gut-brain axis dysregulation

The gut-brain axis—linking the GI tract and central nervous system—plays a key role in IBS. Dysregulation of this pathway disrupts pain processing, gut motility, and emotional balance. Stress, via corticotropin-releasing hormone (CRH), worsens symptoms by affecting gut sensitivity and barrier function. CRHR1 amplifies, while CRHR2 mitigates stress effects. Emerging therapies like vagal nerve stimulation show potential in easing these stress-driven gut disturbances.[14,16]

Microbiota alterations

Gut microbiota imbalance is central to IBS, marked by fewer beneficial bacteria (e.g., Lactobacillus, Bifidobacterium) and more harmful species (e.g., Enterobacteriaceae, Veillonella). This dysbiosis disrupts motility, increases gas, and promotes low-grade inflammation and visceral pain via immune and gut-brain pathways. Microbial shifts are shaped by genetics, diet, and environment, influencing several key IBS symptoms.[14,17]

Immune activation and post-infectious IBS

Low-grade immune activation is central to IBS, particularly in post-infectious IBS (PI-IBS), seen in 3–36% of individuals after gastroenteritis. Risk factors include prolonged infection, mucosal inflammation, and stress. This leads to persistent immune responses—elevated cytokines, increased mucosal immune cells, and impaired barrier function. Toll-like receptor (TLR) signaling and altered immune gene expression are also involved. Interestingly, stress can trigger similar immune activity, underscoring the link between psychological and immune pathways in IBS.[15,17]

Gastrointestinal motility abnormalities

Altered gastrointestinal motility is another hallmark of IBS, contributing to diarrhea, constipation, or alternating bowel habits. Myoelectric abnormalities, including disrupted slow wave activity and enhanced spike potentials especially postprandially have been documented, particularly in IBS-D.[7] These disturbances affect transit time and contribute to symptoms such as bloating, urgency, and incomplete evacuation.[18] Motility disturbances are closely linked to VH and gut-brain axis dysfunction, forming a vicious cycle. For instance, anxiety or stress can induce motility changes via CRH and autonomic pathways, further aggravating symptoms.[14]

Genetic and epigenetic influences

Genetic and epigenetic mechanisms contribute to the pathophysiology of IBS, though their influence is modest and complex. Mutations in genes like Sodium Voltage-Gated Channel Alpha Subunit 5 (SCN5A) involved in gut motility and associations with Tumor Necrosis Factor Superfamily, Member 15 (TNFSF15) linked to immune response have been observed. Genome-Wide Association Study (GWAS) have identified other candidate genes (KDELR2, GRID2IP), while Single Nucleotide Polymorphism (SNPs) related to serotonin signaling, immune regulation, and barrier function show variable links.[13,18] Epigenetic changes, especially DNA methylation in stress-related genes (NR3C1, CRHR1, BDNF), influence neuroimmune pathways and psychological symptoms. Twin and family studies support a genetic predisposition, with gene-environment interactions playing a key role in IBS development.[13]

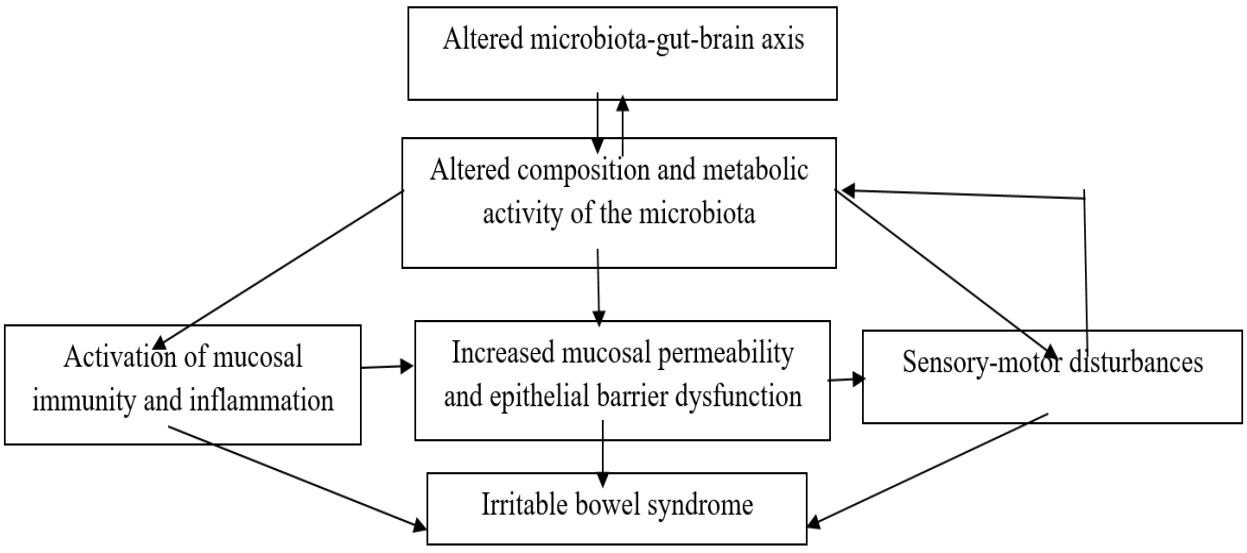

Figure 1: Pathophysiologic role of the microbiota in IBS.[19]

NEUROBIOLOGY OF IBS

Brain connectome alterations in IBS[20]

Neuroimaging studies in irritable bowel syndrome (IBS) consistently demonstrate alterations in key brain networks that underlie pain perception, emotional regulation, sensory integration, and autonomic control, forming the neurobiological basis for its chronic symptoms. The Default Mode Network (DMN) shows reduced connectivity and structural changes, especially in women, correlating with increased symptom burden and emotional reactivity. The Sensorimotor Network exhibits white matter abnormalities and enhanced connectivity, linked to

heightened visceral pain sensitivity. The Salience Network is hyperactive in response to visceral stimuli, with sex-specific connectivity patterns influencing symptom perception. The Emotional Arousal Network is notably hyperactive, contributing to anxiety and symptom anticipation, with serotonin-related genetic factors amplifying this response. Lastly, the Central Autonomic Network displays disrupted CRF and adrenergic signaling, leading to autonomic dysregulation and heightened arousal, mirroring patterns seen in stress-related disorders. Together, these brain connectome alterations highlight the central role of neurobiological dysfunction in the pathophysiology of IBS.[20,21]

Neurotransmitters and the microbiota-gut-brain axis in IBS

IBS arises from the interplay of neurotransmitters (NTs), genetics, and the microbiota-gut-brain axis. Key NTs like serotonin (5-HT), dopamine, and gamma-aminobutyric acid (GABA) regulate gut motility, visceral sensitivity, and mood. Disrupted NT signaling contributes to both GI and psychological symptoms. Notably, these NTs are influenced by the gut microbiota, reinforcing its central role in gut-brain communication.[22]

Serotonin (5-HT), mainly from enterochromaffin cells, regulates gut motility, secretion, and pain. Altered 5-HT signaling is linked to both IBS-D and IBS-C. Gut microbes influence 5-HT via metabolites like short-chain fatty acids (SCFAs). Dopamine, also microbially derived (e.g., from Bacillus subtilis), affects gut permeability, inflammation, and signaling; its dysregulation is tied to motility issues and hypersensitivity. Gamma-aminobutyric acid (GABA), produced by enteric neurons and microbes like Lactobacillus and Bifidobacterium, modulates motility and pain. In IBS-D, reduced GABA levels and receptor expression impair inhibitory control.[22]

OVERLAP SYNDROMES IN IBS

The Rome IV criteria acknowledge that functional gastrointestinal disorders (FGIDs) often overlap, viewing them as a continuum rather than distinct conditions. A global survey of over 54,000 adults found 68.3% had overlapping GI symptoms, with 2.3% spanning multiple regions. IBS commonly coexists with other FGIDs, with shared psychological factors like anxiety and depression underscoring the role of the brain-gut axis.[1]

IBS and functional dyspepsia

Functional Dyspepsia (FD) and IBS are the most common FGIDs and frequently overlap. FD presents with early satiety, postprandial fullness, and epigastric pain, while IBS involves lower abdominal pain with altered bowel habits. Overlap is especially common in IBS-D and IBS-C, with shared symptoms like bloating and fullness. Comorbidity rates range from 30–60%, often with more severe symptoms and gastric hypersensitivity. Both conditions share mechanisms such as delayed gastric emptying, impaired accommodation, visceral hypersensitivity, and post-infectious onset. Despite some anatomical distinctions, symptom overlap and shared pathophysiology call for an integrated diagnostic and treatment approach.[23]

IBS and gastroesophageal reflux disease

IBS and GERD frequently coexist, despite affecting different GI regions. GERD causes heartburn and acid regurgitation, while IBS involves abdominal pain with altered bowel habits. Studies report symptom overlap in 46–47% of cases, likely due to shared mechanisms like visceral hypersensitivity, abnormal motility, and smooth muscle dysfunction.[23] Emerging evidence, including Rome IV data, suggests IBS and GERD often coexist and may lie on a functional GI disorder spectrum. IBS may even raise GERD risk. Reported overlap rates vary widely (3–79%) due to differing diagnostic methods. Recognizing this overlap is key to holistic patient care.[1]

IBS and inflammatory bowel disease

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated condition with a rising global prevalence, now exceeding 0.3%. CD typically presents with chronic or nocturnal diarrhea, abdominal pain, and weight loss, while UC is characterized by bloody diarrhea, rectal urgency, and tenesmus. Despite differing etiologies—IBD being inflammatory and IBS functional—both conditions exhibit overlapping symptoms, particularly abdominal pain and altered bowel habits. This overlap can complicate diagnosis and management, especially in IBD patients in remission who continue to experience IBS-like symptoms.[1,24]

IBS and extra-intestinal disorders

IBS frequently overlaps with non-motility gastrointestinal and somatic disorders, complicating diagnosis. Celiac disease and lactose intolerance mimic IBS symptoms like bloating, pain, and diarrhea, often leading to misdiagnosis or coexistence. While up to 86% of IBS patients report lactose intolerance, true malabsorption is often uncertain. About 20% of celiac patients also report IBS-like symptoms. Beyond GI overlap, IBS is commonly associated with fibromyalgia, chronic fatigue syndrome, temporomandibular joint disorder, and chronic pelvic pain, reflecting shared mechanisms such as visceral hypersensitivity and autonomic dysfunction. Associations with small intestinal bacterial overgrowth (SIBO), non-celiac gluten sensitivity, and serotonin dysregulation further support a multifactorial pathophysiology. Endometriosis-related overlap reinforces the need for careful evaluation to distinguish IBS from other chronic pain conditions.[1,23]

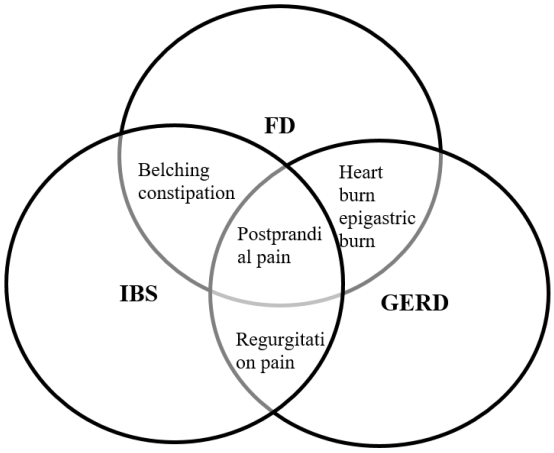

Figure 2: Overlap between symptoms of FD, IBS, and GERD.[25]

DIAGNOSTIC PARADIGMS

Diagnosis of exclusion in IBS

IBS has historically been approached as a diagnosis of exclusion, meaning that it is diagnosed only after other potential organic or structural diseases have been thoroughly ruled out.[26,27] This diagnostic strategy emerged because IBS presents with nonspecific gastrointestinal symptoms such as chronic abdominal pain, bloating, distension, and altered bowel habits such as diarrhea, constipation, or a combination of both, that overlap significantly with various other gastrointestinal conditions. These include IBD, celiac disease, colorectal malignancy, lactose intolerance, and gastrointestinal infections.[27,28] In a diagnosis of exclusion framework, the primary goal of the physician is to eliminate these possibilities through a comprehensive clinical evaluation that includes detailed medical history, physical examination, and a series of diagnostic investigations.[26] These investigations may include complete blood count (CBC) to check for anemia, C-reactive protein (CRP) or fecal calprotectin to rule out inflammation indicative of IBD, thyroid function tests, serologic markers for celiac disease, and stool tests for parasitic or bacterial infections. Imaging studies such as abdominal ultrasound or colonoscopy are often recommended, particularly in patients over the age of 50 or those with red flag symptoms like rectal bleeding, significant unintended weight loss, nocturnal symptoms, or a family history of colorectal cancer.[29] While the diagnosis of exclusion method ensures that serious conditions are not missed, it also carries certain limitations. This approach can be time-consuming, costly, and sometimes psychologically distressing for patients, as they undergo multiple tests without receiving a definitive diagnosis.[30,31] Furthermore, it may lead to delays in initiating treatment, resulting in prolonged patient discomfort and diminished QOL. Additionally, many patients especially in primary care or low-resource settings may not have access to all required diagnostic modalities, leading to underdiagnosis or even misdiagnosis of IBS.[27,32,33] Despite the challenges, diagnosis of exclusion remains important when red flag signs appear or initial treatments fail, warranting further tests to rule out organic disease. However, in the absence of alarming features, the modern approach favors a positive diagnosis based on symptom patterns and established criteria.[34]

Positive diagnosis vs diagnosis of exclusion: a comparative perspective

In current practice, IBS is diagnosed positively rather than by exclusion, using characteristic symptom patterns and the absence of alarm features. The Rome IV criteria define IBS as recurrent abdominal pain at least 1 day per week over the past 3 months.[27,30] This positive approach facilitates earlier diagnosis, reduces unnecessary testing, and fosters improved patient-clinician communication, enhancing patient reassurance and satisfaction. In contrast, the traditional diagnosis of exclusion, while safe and conservative, often leads to delayed treatment initiation, higher healthcare utilization, and greater patient anxiety.[30,29] Moreover, numerous guidelines, including those by the American College of Gastroenterology (ACG) and the National Institute for Health and Care Excellence (NICE), now support making a positive diagnosis based on history and symptomatology, as long as red flags are absent.[27] While the exclusionary approach remains necessary for patients with alarm symptoms or older age, the positive diagnosis model offers a pragmatic, patient-centered strategy. It affirms IBS as a valid functional disorder, promoting timely diagnosis and tailored care—especially crucial in primary care where most IBS cases are managed.[31,32]

Emerging biomarkers in IBS subtypes

Recent advances in biomarker research have enabled a more refined differentiation between IBS subtypes, particularly IBS-D and IBS-C, offering improved diagnostic accuracy and therapeutic guidance. In IBS-D, specific serological markers have shown promise in distinguishing the condition from IBD. Notably, anti-Cytolethal Distending Toxin B (CdtB) and anti-vinculin antibodies have emerged as key biomarkers.[35]

These antibodies, formed after gastrointestinal infections like Campylobacter jejuni, support an autoimmune role in IBS-D via molecular mimicry. A study by Pimentel et al. (n=2,600+) found significantly elevated anti-CdtB and anti-vinculin levels in IBS-D compared to healthy, IBD, or celiac subjects. Anti-CdtB showed 43.7% sensitivity and 91.6% specificity (cut-off ≥2.80), and anti-vinculin 32.6% sensitivity and 83.8% specificity (cut-off ≥1.68). Additionally, fecal volatile organic metabolites (VOMs) can distinguish IBS-D from active IBD with 96% sensitivity and 80% specificity, further supporting an organic basis for IBS-D.[36]

For IBS-C, Lactulose Breath Testing (LBT) detecting methane ≥3 ppm is a reliable diagnostic marker linked to reduced stool frequency, harder stools, and greater symptom severity. A meta-analysis of 1,277 patients confirmed this association. LBT shows high diagnostic accuracy (91% sensitivity, 81.3% specificity) and can guide targeted treatments like antimicrobials or prokinetics for methane-associated constipation.[36] Beyond subtype-specific markers, emerging biomarkers—such as serum and fecal panels, gene expression profiles, fecal calprotectin, SCFAs, granins, VOCs, rectal barostat tests, and assessments of colonic transit, bile acid malabsorption, and gut permeability—are being explored to improve IBS diagnosis and subtyping. These tools reinforce IBS's organic basis and aid in differentiating it from other FGIDs.[35,36]

Investigational tools and tests

Fecal Markers in IBS: Fecal markers such as calprotectin and lactoferrin help distinguish IBS from IBD by indicating intestinal inflammation. Elevated in IBD but normal in IBS and healthy individuals, fecal calprotectin offers high sensitivity and specificity for ruling out IBD. While not diagnostic for IBS, these markers are valuable for excluding inflammation and reducing unnecessary invasive testing.[27]

Serologic Markers in IBS: Serologic markers are being investigated to support IBS diagnosis by reflecting immune, brain-gut, and microbiota-related changes. A validated 10-marker serum panel—including IL-1β (Interleukin-1 beta), BDNF (Brain-Derived Neurotrophic Factor), anti-CBir1, ASCA-IgA, ANCA, anti-tTG, TIMP-1, NGAL, GRO-α, and TWEAK—helps differentiate IBS from IBD and healthy controls. The panel shows 70% diagnostic accuracy (50% sensitivity, 88% specificity), making it more useful for confirming than excluding IBS. While not a standalone tool, it may complement Rome IV criteria to improve diagnostic confidence and limit unnecessary invasive testing.[27,35]

Imaging and Endoscopy in IBS: Routine abdominal imaging and endoscopy are not recommended for IBS patients without alarm features, as they rarely detect structural disease. Studies show <2% diagnostic yield from colonoscopy in such cases. Imaging may be considered for patients >50 years per colorectal cancer screening guidelines. In IBS-D patients with alarm features, colonoscopy with biopsies may help rule out IBD, cancer, or microscopic colitis. IBS-C patients with red flags may be evaluated for mechanical obstruction. Upper endoscopy with biopsies is useful if celiac disease or SIBO is suspected based on labs or stool tests.[27]

Experts' suggestions

IBS is best understood as a disorder of the brain–gut axis rather than a purely "functional" bowel disease. Its pathogenesis is multifactorial, involving gut dysbiosis, low-grade mucosal inflammation, increased permeability, motility disturbance, visceral hypersensitivity and psychosocial stressors. Psychological stress can amplify symptom severity and should be considered a core risk factor in clinical assessment. Bloating is especially common in Indian cohorts, underscoring the need for clearer symptom categorisation. Rome III criteria remain more sensitive for Indian patients than Rome IV, which may under-diagnose IBS; adding Manning criteria and symptom-duration thresholds improves accuracy. The Rome IV pain-frequency requirement risks missing patients whose dominant complaint is discomfort without frank pain; these cases belong under functional diarrhoea/constipation. Diagnosis should rely on symptom criteria, absence of alarm features and a minimal laboratory panel (e.g., CBC, CRP, coeliac serology). Red-flag evaluation must precede the label of IBS, with colonoscopy reserved for age ≥ 50 years or any alarm feature, and fecal calprotectin used when endoscopy is impractical. Fecal calprotectin serves as a first-line screening tool in clinical practice to rule out inflammatory bowel disease, particularly in younger patients without red flag symptoms, by effectively distinguishing IBD from IBS and reducing the immediate need for colonoscopy. Serology for coeliac disease is advisable, whereas routine lactose- or glucose-breath tests add little in typical presentations. Testing for bile-acid diarrhea is valuable when diarrhea persists despite first-line measures, as bile-acid sequestrants can then be deployed. Quality-of-life impact, functional impairment and psychological distress should be documented at baseline to capture true disease burden and guide follow-up.

SYMPTOM-GUIDED MANAGEMENT OF IBS

Symptom-guided management of IBS focuses on tailoring treatment strategies based on the patient's predominant symptoms, such as diarrhea, constipation, bloating, or abdominal pain as shown in figure 3. This personalized approach helps optimize therapeutic outcomes and improve QOL.

Pharmacological management of IBS-D

The treatment of IBS-D remains a clinical challenge due to the heterogeneous nature of the condition and variable patient response to therapies. According to the 2022 ACG guidelines, three drugs with moderate certainty of evidence eluxadoline, rifaximin, and alosetron are recommended for symptom relief in IBS-D. These agents target both abdominal pain and altered bowel habits. However, each comes with specific adverse effects and contraindications that require careful patient selection.[1] Loperamide, a commonly used anti-diarrheal, is often a first-line choice due to its ability to reduce stool frequency by slowing gastrointestinal motility. However, evidence supporting its effectiveness in improving global IBS symptoms or abdominal pain is very limited, and it carries the risk of constipation, especially in patients with alternating bowel habits.[37] When first-line agents are

insufficient, second-line options such as alosetron, ramosetron, rifaximin, and eluxadoline can be considered where available.[3] Alosetron, a 5-HT3 receptor antagonist, is particularly effective in women with severe IBS-D, providing significant improvements in stool consistency, urgency, and abdominal discomfort. Nevertheless, it has been associated with serious adverse events such as severe constipation and ischemic colitis, leading to its restricted availability in the United States under a special prescribing protocol.[17] Ramosetron, also a 5-HT3 antagonist, has shown consistent efficacy in Japanese clinical trials and is available only in selected Asian countries. It offers a safer profile than alosetron. Interestingly, ondansetron, another 5-HT3 antagonist typically used for nausea, has shown preliminary benefit in small IBS-D trials and is currently under investigation in larger studies.[38]

Rifaximin, a minimally absorbed antibiotic, targets dysbiosis and SIBO in IBS. While large trials show modest but significant symptom relief, concerns about repeated use and long-term safety have limited its broader adoption. However, re-treatment studies suggest additional benefit with repeated courses.[37] Eluxadoline, which acts on both μ- and δ-opioid receptors, offers a dual mechanism of action by slowing motility and modulating visceral pain. It has shown efficacy in patients who did not respond adequately to loperamide. However, its use is tempered by the risk of pancreatitis, especially in patients without a gallbladder, and it has been withdrawn in several countries due to safety concerns.[37,38] Low-dose tricyclic antidepressants (TCAs) are used in IBS, particularly for pain and to reduce bowel frequency by modulating visceral hypersensitivity. Selective Serotonin Reuptake Inhibitors (SSRIs) are not recommended due to limited efficacy. Bile acid sequestrants like cholestyramine or colesevelam may help IBS-D patients with bile acid malabsorption, though evidence remains observational. Identifying stress-related triggers is also key; keeping a diary of food, activities, and emotions can aid in tailoring treatment.[17]

Pharmacological management of IBS-C

The first-line pharmacological approach in managing IBS-C typically includes the use of bulking agents and osmotic laxatives.[1] Bulking agents like psyllium, methylcellulose, polycarbophil, and ispaghula husk are safe, affordable options that increase stool bulk by retaining water. Psyllium and ispaghula may help constipation but offer limited relief for pain or bloating. Bran, however, may worsen symptoms. Despite modest evidence and potential bloating, these agents are commonly used first due to their safety.[17] Laxatives, especially osmotic agents like polyethylene glycol (PEG), are commonly used early in IBS-C treatment. PEG improves bowel frequency and is well tolerated, though it offers limited relief for pain or overall IBS symptoms. NICE guidelines support laxatives as first-line therapy—excluding lactulose due to bloating risk. Despite limited long-term data, their affordability and accessibility make them practical initial options.[37]

For patients not responding adequately to bulking agents or laxatives, second-line agents particularly intestinal secretagogues and chloride channel activators are recommended. These include linaclotide, plecanatide, lubiprostone, and tenapanor, which work by enhancing intestinal fluid secretion and improving motility.1 Among these, linaclotide has the most robust evidence base and has been strongly recommended by the ACG based on high-certainty data. It significantly improves both abdominal pain and stool frequency, as demonstrated in multiple randomized controlled trials. Diarrhea is the most common side effect, sometimes leading to discontinuation.[37] Lubiprostone, a prostaglandin E1 derivative, is approved for women with IBS-C and works by activating chloride channels to increase intestinal fluid. Clinical trials show significant symptom relief, though nausea is a frequent side effect. Its efficacy in men remains under study.[17,37] Another guanylate cyclase-C agonist, plecanatide, is effective and well tolerated, while tenapanor also improves IBS-C symptoms but may cause diarrhea. Linaclotide ranks highest in efficacy, though all secretagogues outperform placebo with no clear superior agent. They're best reserved for patients unresponsive to laxatives.[37] Other pharmacological agents considered include TCAs and antispasmodics, though their evidence is weaker. The ACG gives low-certainty recommendations for their use in IBS-C. Conversely, SSRIs are conditionally recommended against due to low-certainty evidence and unclear efficacy in IBS-C.[1]

Management of abdominal pain in IBS

Abdominal pain in IBS is largely due to visceral hypersensitivity (VH), a key symptom requiring targeted treatment. Despite research advances, antispasmodics and select antidepressants remain the mainstays for pain relief and improving quality of life.[17] Antispasmodics with anticholinergic or calcium channel-blocking effects—like dicyclomine, hyoscine, pinaverium, and peppermint oil—are commonly used in IBS to relax gut smooth muscle, easing spasms and pain.[1,17] Meta-analyses have consistently shown a modest but statistically significant benefit of antispasmodics over placebo for both abdominal pain and bloating.[17] A 2008 review found that antispasmodics helped reduce IBS symptoms, though study quality varied. Hyoscine showed the strongest evidence, while mebeverine and alverine lacked clear benefit. Side effects, mainly from anticholinergic action, include dry mouth, blurred vision, dizziness, and constipation.[37] Among the calcium channel blockers, pinaverium provides rapid onset of action but its effectiveness may not sustain beyond the first week. Drotaverine, due to slower onset, is considered more effective in later stages of IBS or chronic presentations.[1]

Peppermint oil, a natural antispasmodic, has shown significant benefit in improving global IBS symptoms, likely by relaxing gut muscles via calcium channel blockade. Efficacy varies by formulation, with sustained-release small intestinal types performing better than

ileocolonic ones.[37,38] For chronic IBS pain, especially with psychological distress, low-dose antidepressants like TCAs and SSRIs offer neuromodulatory benefits by altering pain processing and reducing visceral hypersensitivity. Traditional analgesics are ineffective and may worsen symptoms, so they're not recommended. NICE and other guidelines support using antispasmodics and peppermint oil, with combination therapy appropriate when monotherapy falls short.[17,37]

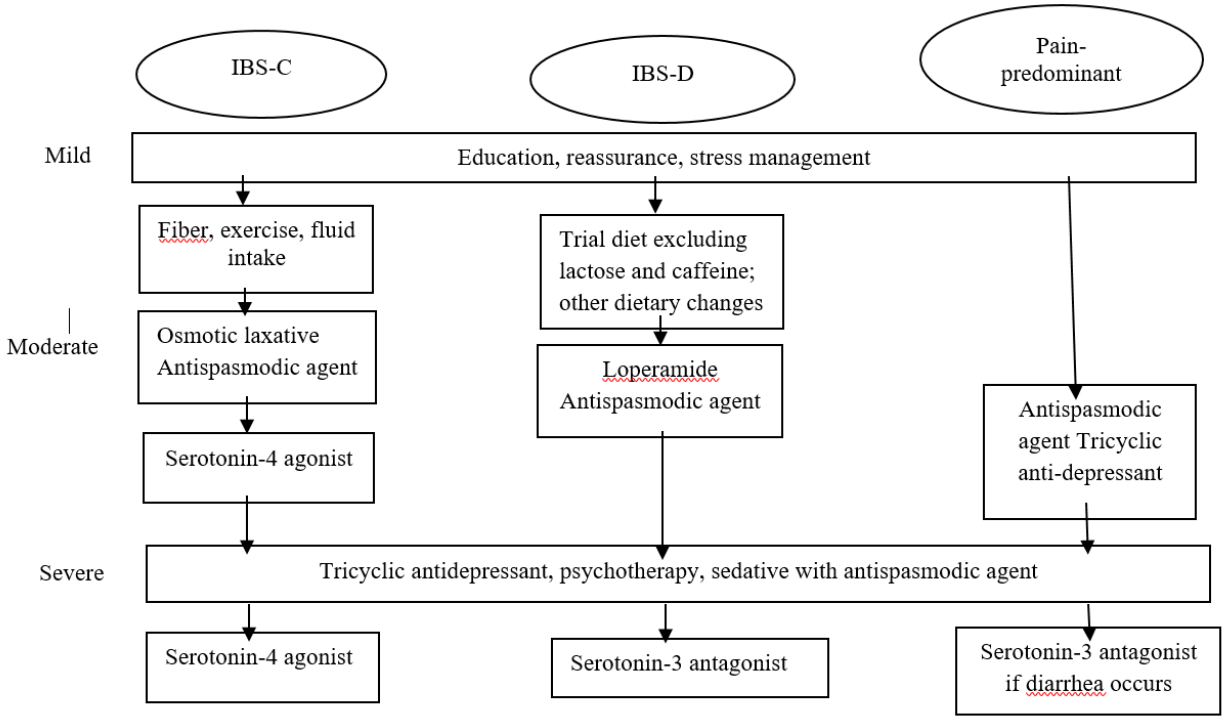

Figure 3: Treatment strategy for IBS.[39]

PATHOPHYSIOLOGY-GUIDED TREATMENT APPROACHES

Microbial therapy in IBS

Probiotics have shown potential in relieving common symptoms of IBS such as bloating, gas, and discomfort, particularly in IBS-D. Strains like Lactobacillus, Bifidobacterium, Escherichia coli, and Streptococcus are commonly studied.[1,4] While some studies report significant symptom improvement, others reveal limited or no benefits, especially when all IBS subtypes are analyzed together. However, subgroup analyses often indicate a better response in IBS-D patients, suggesting that probiotics may be more effective when used in selected populations.[1]

Prebiotics and synbiotics (probiotic–prebiotic combinations) support microbial diversity and gut barrier function. An 8-week trial using Lactobacillus, Bifidobacterium, and fructooligosaccharides showed symptom improvement in IBS. Current guidance suggests a 12-week trial to evaluate their effectiveness.[40] While several randomized control trails have reported positive outcomes compared to autologous stool recipients, other trials have failed to show substantial clinical improvement. Moreover, emerging evidence suggests that FMT may not only alleviate gastrointestinal symptoms in IBS patients but also offer psychological benefits by reducing associated depression and anxiety.[1] Despite promising findings, FMT studies show wide variability in donor selection, dosing, and delivery methods, leading to inconsistent outcomes. Standardized, large-scale randomized trials and meta-analyses are needed to clarify its efficacy, safety, and optimal protocols for IBS treatment.[40]

Pharmacological agents targeting visceral hypersensitivity in IBS

Several drugs target visceral hypersensitivity (VH) in IBS by easing pain and regulating gut function. Antispasmodics like dicyclomine and hyoscine show mixed efficacy, while mebeverine often performs no better than placebo. Calcium channel blockers such as alverine with simethicone, otilonium, and pinaverium show more consistent pain relief with good safety. However, study limitations prevent firm conclusions, underscoring the need for stronger clinical trials.[36]

Experts' suggestions

Effective care demands a multidisciplinary blend of dietary, pharmacologic and psychological strategies tailored to individual needs. Integrating symptom patterns with objective markers yields more accurate, patient-

centred treatment plans than either approach alone. Treatment is symptom-based and guided by the underlying mechanism, involving agents such as antispasmodics, neuromodulators, antibiotics, probiotics, 5-HT3 antagonists, and 5-HT4 agonists. The Rome IV Multi-Dimensional Clinical Profile (MDCP) framework facilitates individualized therapy in irritable bowel syndrome by integrating clinical subtypes, severity levels, psychological and physiological modifiers, and impact assessment. A structured approach to irritable bowel syndrome involves establishing a confident diagnosis by excluding organic pathology, identifying underlying mechanisms through symptom assessment and pragmatic testing, providing an explanatory model to enhance patient understanding, tailoring treatment to specific mechanisms such as probiotics for dysbiosis or antispasmodics for motility/pain, setting review timelines with symptom tracking, and adjusting therapy based on response while setting realistic goals for symptom control. A dietitian-supervised low-FODMAP regimen should be trialled for 4–6 weeks, with re-introduction phases to minimise nutrient deficits common in Indian diets. Direct musculotropic antispasmodics such as mebeverine, pinaverium and otilonium are preferred first-line agents because they relieve pain without anticholinergic side-effects. Mebeverine has demonstrated effectiveness in relieving abdominal pain and bloating in IBS patients, particularly by targeting gut motility without disrupting normal peristalsis. Meta-analyses and clinical trials have shown that Mebeverine is among the most effective antispasmodics for improving bloating, with additional benefits in modulating the gastrocolic reflex and postprandial symptoms. Standard mebeverine therapy is 200 mg sustained-release twice daily for 6–8 weeks, with gradual tapering for longer courses. For IBS-C, combine antispasmodics with bulking agents or osmotic laxatives such as psyllium or PEG; for IBS-D, use episodic loperamide while avoiding prolonged courses for pain control. Secretagogues or prokinetics (prucalopride, lubiprostone, linaclotide) should be introduced when constipation remains refractory to first-line measures. Elobixibat, though officially approved for functional constipation, has been used in clinical practice for IBS-C patients unresponsive to prucalopride or other laxatives, showing improved stool passage with minimal issues related to abdominal pain, and is considered a safe option particularly when pain is not the predominant symptom. Rifaximin 550 mg three times daily for 14 days is an FDA-approved option for IBS-D, with symptom relief often persisting beyond ten weeks. Probiotics containing Bifidobacterium and Lactobacillus should be continued for at least two months; combining Bifidobacterium longum W11 with rifaximin shows added benefit in IBS with suspected SIBO. Probiotics not only modify the gut microbiota but also influence the luminal microenvironment and produce enzymes like lactase, which can help alleviate symptoms such as bloating. Low-dose tricyclics, SSRIs or SNRIs can dampen visceral hypersensitivity and treat co-existing mood disorders, whereas continuous loperamide should be avoided for analgesia. Bile-acid sequestrants are effective when bile-acid diarrhoea is identified through appropriate testing. Ongoing clinician education is essential so that IBS is recognised as a real, positively diagnosable disorder, reducing unnecessary investigations and facilitating timely, personalised therapy. Future management paradigms should jointly target gastrointestinal symptoms and psychological comorbidity to achieve truly individualised care pathways.

CONCLUSION

IBS is a complex, multifactorial disorder involving gut dysbiosis, low-grade mucosal inflammation, increased permeability, motility disturbance, visceral hypersensitivity and psychosocial stressors. While Rome IV offers a more specific diagnostic model, limited clinical uptake highlights the need for practical, symptom-based approaches. A comprehensive understanding of mechanisms like visceral hypersensitivity, gut-brain axis dysfunction, and psychological comorbidities supports holistic, tailored care. Though promising, emerging biomarkers and targeted treatments need further validation. Sustainable symptom relief often requires combining dietary changes, microbiota-directed therapies, psychological support, and pharmacologic options within a personalized, multidisciplinary framework. A structured approach to IBS begins with a confident diagnosis by excluding organic pathology, followed by identification of underlying mechanisms through symptom assessment and pragmatic testing, and provision of an explanatory model to enhance patient understanding. Treatment is then tailored to specific mechanisms—such as probiotics (e.g. Bifidobacterium) for dysbiosis or antispasmodics (e.g. Mebeverine) for motility and pain—while review timelines are set, symptom progress is tracked, and therapy is adjusted based on response with realistic goals for symptom control.

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