International Journal of Advances in Medicine
*Mehrotra P. Int J Adv Med. 2025 Jan;12(1):139-146*
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20243824

**Review Article**

# Visceral hypersensitivity and diagnostic markers in functional gastrointestinal disorders: expert opinion

**Puneet Mehrotra***

Department Gastroenterologist and Hepatologist, Aligram Main Rd, Lucknow, Uttar Pradesh, India

**Received:** 18 November 2024
**Accepted:** 10 December 2024

***Correspondence:**
Dr. Puneet Mehrotra,
E-mail: punmel@yahoo.com



## ABSTRACT

Functional gastrointestinal disorders (FGIDs), including irritable bowel syndrome (IBS), present diagnostic challenges due to the absence of specific biomarkers and reliance on symptom-based criteria like the Rome IV classification. IBS, characterized by abdominal discomfort, irregular bowel habits and bloating, affects up to 21% of populations globally, with varying prevalence across regions. Visceral hypersensitivity (VH) is a hallmark of IBS, particularly in diarrhea-predominant IBS (IBS-D), contributing to enhanced pain perception and gut dysmotility. VH involves complex mechanisms integrating peripheral and central nervous system pathways, affecting pain processing and emotional responses. Diagnostic approaches for IBS are hindered by overlapping symptoms with other gastrointestinal disorders and the dynamic nature of gut microbiota. Biomarkers, such as serum and fecal panels, gene expression profiles and psychological assessments, aim to enhance diagnostic accuracy and differentiate IBS subtypes. These biomarkers, including fecal calprotectin, short-chain fatty acids (SCFA), volatile organic compounds (VOCs) in breath tests and specific antibodies against microbial toxins, offer insights into the pathophysiology of IBS and aid in subtype prediction. Considering the scarcity of information on intricacies of VH in IBS and need gap in understanding the precise diagnostic markers for IBS, three physical focus group meetings were conducted with 25 expert gastroenterologists across India. Existing evidence and clinical experience with respect to the diagnosis of IBS, concept of visceral hypersensitivity and its importance in managing IBS, current treatment modalities and the role of various diagnostic biomarkers were discussed in detail by the experts and expert opinions were consolidated and finalized after approval by all participants.

**Keywords:** Biomarkers, Gastrointestinal disorders, Irritable bowel syndrome, Rome IV criteria, Visceral hypersensitivity

## INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are characterized by chronic or recurring gastrointestinal symptoms that are not explained by standard clinical tests such as endoscopy, radiography or blood tests. These disorders are diagnosed using symptom-based criteria, with the Rome IV criteria being the most recent standard. Two common FGIDs are functional dyspepsia (FD) and irritable bowel syndrome (IBS), affecting up to 25% of the general population. IBS is a prevalent functional gastrointestinal disorder marked by abdominal discomfort, irregular bowel habits and bloating. Unlike anatomical or biochemical issues detectable through conventional diagnostic methods, IBS is identified solely by its symptoms. Its prevalence varies globally, affecting 10-15% of the population in North America and Europe, 7% in South Asia and up to 21% in South America. In India, the prevalence is around 15%.

A core feature of IBS is visceral hypersensitivity (VH), which causes gut pain through hyperalgesia (enhanced pain response) and allodynia (pain from non-painful stimuli). This hypersensitivity involves both peripheral and central pathways. Vagal and spinal afferent neurons detect stimuli and transmit information to the spinal cord,

where it is processed and sent to brain regions controlling perception, cognition and emotion.[2] VH is observed in 33% to 90% of IBS patients and is more common in diarrhea predominant irritable bowel syndrome (IBS-D) patients with increased intestinal permeability. These patients often experience more severe IBS complications. Primary investigations indicate that VH is typically confined to the rectum and sigmoid colon.

The diagnostic picture for IBS confronts major challenges, including a lack of clear biomarkers, overlapping symptoms with other gastrointestinal disorders and the diverse symptom profiles and causes of many IBS subtypes. Diagnosis is mainly based on patients' subjective symptom descriptions, which might lead to interpretation disputes.

The lack of standardised diagnostic criteria leads to variable diagnosis between research and physicians. Furthermore, the shifting gut microbiota in IBS patients makes detecting stable microbial markers difficult. The lack of understanding of IBS's underlying processes and pathophysiology further complicates the development of specialised diagnostic tools. These issues underscore the importance of continuous research to improve diagnosis accuracy and provide trustworthy criteria for IBS.

This review summarizes the literature and presents the perspectives of Indian experts on the VH and complexities of diagnosing IBS, aiming to provide a comprehensive understanding of this disorder.

## VH IN IBS

VH in IBS involves an increased perception of stimuli, manifesting as both allodynia (pain triggered by ordinarily non-painful stimuli) and hyperalgesia (heightened response to painful stimuli). Patients with VH experience abdominal pain attributed to factors such as intraluminal retention of gas or solid contents and mechanical stress on the gut wall. This visceral pain is often characterized by its vague, diffuse nature, poor localization and frequent association with referred pain.

Within the GI tract, extrinsic nociceptors respond to stimuli such as stretch, pH, bacterial products, immune cell substances and neurotransmitters.

These nociceptors have nerve endings in the mucosal, submucosal and muscular layers, with their cell bodies in the dorsal root ganglion. The first synapse occurs in the dorsal horn of the spinal cord and the nociceptive signal crosses to the contralateral side, traveling to the brain via the spinothalamic tract.

Recent evidence indicates that vagal afferents also transmit anti- and pro-nociceptive signals, bypassing the spinal cord. In the brain, these signals are relayed to cortical areas for pain localization and to limbic areas for the emotional response. Descending inhibitory pathways from the brainstem release inhibitory neurotransmitters in the dorsal horn. Chronic pain mechanisms likely depend on the initiating stimulus and can involve local mediators in the GI tract, remodeling of ascending afferents in the dorsal horn, hyperactivity of central pain circuits and/or loss of descending inhibition.

## MECHANISM INVOLVED IN VH

VH can arise from either peripheral or central causes. Vagal and spinal afferent nerves detect mechanical, thermal and chemical events and transfer them to the spinal cord. Vagal afferents connect to second-order neurons in the brainstem, whereas spinal afferents connect to those in the spinal cord's dorsal horn. These secondary neurons rise to the thalamus via the spinothalamic tract after crossing the spinal cord's midline. Signals are conveyed from the thalamus to brain areas involved in somatosensory perception, as well as cognitive and emotional regulation, including the somatosensory and insular cortex, the anterior cingulate cortex and the limbic system. The ipsilateral dorsal columns also help to transport sensory information to the thalamus.

The central nervous system (CNS) regulates pain transmission via descending channels that can either impede or promote signal transduction. Dysfunctional pain regulation at any of these levels can cause VH.

## FACTORS CONTRIBUTING TO VH IN IBS

Psychological factors such as depression and anxiety significantly influence bowel motility and visceral sensation. Inflammation and disturbances in the immune system within the gastrointestinal tract can alter nociceptive transmission, contributing to VH. Microbial infections and the intestinal microbiota directly regulate visceral nociception, impacting VH. Alterations in the enteric neuroendocrine system are also significant contributors to changes in intestinal perception, leading to VH. Additionally, microRNAs expressed in the colonic tissue of IBS patients can modulate intestinal pathways, affecting VH.[3]

Intestinal tissue inflammation increases the release of inflammatory mediators, which stimulate sensory nerve endings and cause VH. Sensitization of distal peripheral afferents, particularly mesenteric and serosal afferents, plays a crucial role in the pathophysiology of VH in IBS. Furthermore, factors such as diet, brain-gut communication and genetic predisposition also contribute to the manifestation of gastrointestinal symptoms, including VH, in IBS patients.[3]

## PATHOGENESIS OF VH

### *Peripheral factors*

VH can result from peripheral factors, including the sensitization of afferent nerves by immune cells and other

mechanisms. Immune cells in the mucosal wall, such as mast cells and enterochromaffin cells, release mediators that sensitize afferent nerves, contributing to VH.[9]

Mast cells (MCs) play a significant role in VH, with studies indicating that treatment with the MC stabilizer ketotifen can increase the pain threshold and decrease abdominal pain in IBS patients. Histamine, a key mediator released by MCs, acts on specific histamine receptors (H1-H4) and has been implicated in the pathogenesis of IBS. Blocking these receptors may offer a new therapeutic strategy for VH.[9]

Tryptase, another MC mediator, binds to proteinase-activated receptors (PARs) and is believed to contribute to VH. Inhibiting tryptase activity may have anti-nociceptive effects, as demonstrated in preclinical studies. Research has shown that tryptase contributes to increased rectal permeability in IBS and the use of a tryptase inhibitor, nafamostat, can reduce this elevated permeability in rectal biopsy specimens from IBS patients.[9]

### *Central factors*

Central factors contributing to VH include alterations in the brain-gut axis, increased vigilance towards intestinal stimuli and changes in brain function and structure. IBS patients often exhibit a higher prevalence of psychiatric comorbidities, such as psychological distress, depression and anxiety, which can influence the perception of visceral stimuli.[9]

The hormonal brain-gut axis is disrupted in IBS, impairing communication between the gut and the brain, leading to abnormal sensory processing and heightened sensitivity to visceral stimuli. Functional and structural changes in brain regions involved in somatosensory perception, cognitive processing and emotional regulation—such as the somatosensory cortex, insular cortex, anterior cingulate cortex (ACC) and limbic system—also play a role in the pathogenesis of VH.[9]

Central sensitization processes in the brain and spinal cord can amplify pain signals from the gut, contributing to the development and maintenance of VH in conditions like IBS.[9]

## DIET-MICROBIOTA INTERACTIONS LEADING TO VH

The gut microbiota, which plays a crucial role in normal gut function, has been identified as a key peripheral factor in the development of VH. Dietary components can stimulate pathways leading to VH, indicating that diet-microbiota interactions play a significant role in this condition. A high intake of fermentable carbohydrates can increase the population of Gram-negative bacteria, resulting in low-grade inflammation and endotoxemia, which contribute to VH. This diet can also induce mast cell activation, increasing colonic permeability and potentially causing VH. Patients with IBS-D have shown increased levels of circulating and fecal lipopolysaccharides, which can be reduced by following a low FODMAP diet, highlighting a direct link between diet, microbiota and VH. Histamine production by gut microbiota can drive mast cell accumulation in the colon, leading to VH through the activation of the histamine 4 receptor.[10]

Interactions between specific dietary components, such as fermentable carbohydrates and histamine-producing bacteria are key factors in the development of chronic abdominal pain in some IBS patients.[10]

## ASSESSING VISCERAL NOCICEPTION IN IBS

Visceral perception is typically assessed through two main methods. Delivering a precisely controlled sensory stimulus. Measuring the resultant nociceptive response.

However, electrical stimulation is generally considered to have limited utility for assessing gastrointestinal sensation due to its non-physiological nature. Alternatively, brain imaging and neurophysiological measurements can, in theory, provide a more objective evaluation of nociceptive responses.

## MECHANICAL STIMULI

### *Rectal distension*

Rectal balloon distension is a commonly employed mechanical stimulus to test visceral perception in IBS patients. Research has demonstrated that a significant percentage of IBS patients exhibit increased sensitivity to rectal distension, suggesting it could serve as a biological marker for IBS.[11]

### *Barostat technique*

The barostat, used in conjunction with polyethylene bags, measures rectal visceral sensitivity by maintaining constant pressure and recording changes in rectal tone during distension protocols.

## NON-MECHANICAL STIMULI

### *Electrical stimulation*

*Transmucosal electric nerve stimulation*

This method activates afferent pathways without targeting specific receptive units, offering a non-mechanical approach to assess visceral sensitivity.

### *Rectal electrical stimulation*

This technique is used to demonstrate altered sensory thresholds in IBS patients. However, it may lead to nonspecific nerve ending activation, potentially affecting the results.

***Cortical evoked potentials***

*Cortical evoked potentials recordings*

Following rectal stimulation, cortical evoked potentials (CEP) recordings have been used to characterize IBS patients based on their neurophysiological profiles, revealing different responses to rectal electrical stimuli.

***Thermal stimuli***

*Intraluminal bags*

Intraluminal bags with recirculating water at controlled temperatures can provide thermal stimuli to the gut.

*Evaluation*

These thermal stimuli can be used to evaluate visceronociceptive responses alongside mechanical and electrical stimuli.

*Observations in IBS*

Like mechanical stimulation, IBS patients exhibit lower thresholds to thermal stimulation of the rectum.

*Chemical stimuli*

Capsaicin: Capsaicin has been effectively used to assess chemical hypersensitivity in functional dyspepsia, as it induces peripheral sensitization of capsaicin-sensitive afferents.

*Drawbacks*

Chemical stimuli have certain drawbacks, such as a relatively long latency time to the onset of effects compared to other stimulation methods and non-reproducibility of these effects.

## EXPERT OPINION

***Diagnostic biomarker***

Biomarkers for IBS can significantly enhance the accuracy of diagnosis, differentiate IBS from other diseases and distinguish between IBS subtypes. Some biomarkers are linked to the underlying pathophysiologic mechanisms of IBS, while others are utilized to differentiate IBS from non-IBS patients. The integration of IBS biomarkers into everyday clinical practice is essential for early diagnosis and effective treatment.

***Classification of biomarkers in IBS***

Classification of biomarkers includes serologic markers, fecal markers, cellular/molecular markers, breath tests, scintigraphic markers and colonic mucosal immune markers.

***Blood biomarkers for IBS***

A set of 10 blood biomarkers has been investigated for diagnosing IBS, which includes interleukin-1ß (IL-1ß), growth-related oncogene-a, brain-derived neurotrophic factor (BDNF), anti-Saccharomyces cerevisiae antibody (ASCA IgA), antibody against CBir1, anti-tissue transglutaminase (tTG), tumor necrosis factor (TNF)-like weak inducer of apoptosis, anti-neutrophil cytoplasmic antibody, tissue inhibitor of metalloproteinase-1 (TIMP-1) and neutrophil gelatinase-associated lipocalin (NGAL). This biomarker panel showed a positive predictive value of 81%, a negative predictive value of 64% and an overall accuracy of 70% in distinguishing IBS from other GI disorders.[13]

Additionally, other blood biomarkers such as histamine, tryptase, serotonin and substance P, along with 14 gene expression markers, have been incorporated into the original panel. This expanded panel demonstrated a sensitivity of 81% and a specificity of 64% for IBS diagnosis.[13]

***Serum biomarkers for diagnosing IBS***

Lembo AJ et al, studied healthy controls and patients with various GI conditions, including IBS, inflammatory bowel disease (IBD), functional GI disorders and celiac disease, using a biomarker panel. The biomarker panel included IL-1β, growth-related oncogene-α, brain-derived neurotrophic factor, anti-Saccharomyces cerevisiae antibody, anti-CBir1, anti-human tissue transglutaminase, TNF-like weak inducer of apoptosis, anti-neutrophil cytoplasmic antibody, tissue inhibitor of metalloproteinase-1 and neutrophil gelatinase-associated lipocalin. The study found that the panel had a sensitivity of 50% and a specificity of 88% for differentiating IBS patients from non-IBS patients, with an overall accuracy of 70%. However, it is important to note that many of these biomarkers are primarily associated with IBD and were thus categorized as "not IBS.

***Serologic and gene expression biomarkers***

In a study conducted by Jones MP et al, a combination of 34 serologic and gene expression markers, along with psychological measurements, was assessed to differentiate IBS subjects from healthy volunteers. To the original 10-biomarker panel, 10 additional serological markers (including histamine, tryptase, serotonin and substance P) and 14 gene expression markers (such as CBFA2T2, CCDC147 and ZNF326) were added. This expanded panel demonstrated a sensitivity of 81% and a specificity of 64%. The study achieved good discrimination between IBS subtypes, with the best results observed between constipation predominant irritable bowel syndrome (IBS-C) and IBS-D. However, comparisons with other organic

diseases were not provided. Additionally, the definition of healthy adults—without any illness, active infection or significant medical condition—was not validated.

***Biomarkers for IBS related to immune activation***

In patients with IBS, there is observed chronic low-grade immune activation, characterized by elevated levels of inflammatory cytokines such as IL-6, IL-8 and IL-1β in serum and from peripheral blood mononuclear cells compared to healthy controls. While eosinophil levels remain unchanged, mast cells and their mediators are implicated in activating sensory afferent neurons within the gut. Elevated serum cytokine levels, including IL-6, IL-8 and TNF-α, coupled with reduced mucosal expression of IL-10, typically indicate immune activation in IBS. Moreover, mucosal mRNA upregulation of heavy immunoglobulin chains serves as a potential biological marker of humoral activity in these patients. These findings underscore the role of immune dysregulation in the pathophysiology of IBS and highlight the potential for targeted immunomodulatory therapies in managing this complex condition.[13]

***MicroRNA biomarkers***

MicroRNAs (miRNAs) are short noncoding RNA molecules crucial for regulating biological processes like cellular development, differentiation and metabolism.

Dysregulation of miRNAs can lead to various human diseases, including IBS. In IBS, specific miRNAs serve as potential biomarkers, miRNA-24 is upregulated and inhibits the serotonin reuptake transporter, suggesting it as a biomarker for identifying susceptible patients. miRNA-29 increases intestinal permeability, potentially identifying those who may benefit from targeted treatments. Reduced miRNA-199 levels in IBS-D correlate with visceral pain, highlighting its potential as a pain marker and therapeutic target. miRNAs also regulate serotonin receptor genes, implicating them in IBS pathogenesis and emphasizing their role as biomarkers for advancing IBS management.[13]

***Fecal biomarkers***

Fecal markers indicate inflammation of the intestinal mucosa, primarily distinguishing between IBD and IBS. Fecal calprotectin, a protein abundant in neutrophilic granulocytes, monocytes and macrophages, is extensively studied as a marker for intestinal inflammation.

Comprising S100A8 and S100A9 heterodimers, overexpression of S100A8/A9 is linked to inflammatory and neoplastic conditions. Recent analysis shows fecal calprotectin can differentiate IBS from IBD with high sensitivity (93%) and specificity (94%) using a cut-off value of 50 μg/g. However, calprotectin's low cut-off and lack of association with IBS pathogenesis highlight its role primarily in IBD diagnosis rather than in understanding IBS mechanisms.[12]

***Biomarkers for ruling in IBS***

Fecal short-chain fatty acids (SCFAs) and granins are utilized as biomarkers to differentiate individuals with irritable bowel syndrome (IBS) from healthy controls. SCFAs such as acetic acid, propionic acid and butyric acid are produced through gut microbial fermentation of non-digestible carbohydrates. Propionic and butyric acid levels have shown strong diagnostic capabilities, achieving a sensitivity of 92% and specificity of 72% at a cut-off value>0.015 mmol/l.

Granins, including chromogranins (CgB) and secretogranins (SgII, SgIII), present in secretory cells, reflect activity in the enteric neuroendocrine system and exhibit diagnostic validity in identifying IBS patients. For instance, SgII demonstrates a sensitivity of 80% and specificity of 79%. Analysis of volatile organic compounds (VOCs) in breath also holds promise, with specific VOCs elevated in IBS patients compared to controls. A random forest model based on VOC analysis achieves a sensitivity of 89.4% and specificity of 73.3% in distinguishing IBS from healthy controls. Furthermore, methods like rectal barostat testing and a 10-biomarker algorithm have been explored for their potential in discriminating IBS patients from both normal subjects and those with non-IBS conditions, displaying variable sensitivities and specificities.[12]

## BREATH ANALYSIS: A NOVEL NON-INVASIVE METABOLOMIC APPROACH IN THE DIAGNOSIS OF IBS

The investigation conducted by Baranska et al, analyzed a panel of 16 VOCs in patients with IBS compared to healthy controls. Among the hundreds of VOCs examined, elevated levels of n-hexane, 1,4-cyclohexadiene, n-heptane and aziridine were observed in the IBS group. Conversely, butane, tetradecanol, 6-methyloctadecane, nonadecatetraene, methylcyclohexane, 2-undecene, benzyl-oleate, 6,10-emethyl-5,9-undecadine-2-one and 1-ethyl-2-methyl-cyclohexane were increased in healthy controls. Utilizing these VOC profiles, a Random Forest classification model achieved a sensitivity of 89.4% and specificity of 73.3% in distinguishing IBS from healthy subjects. The metabolic pathways of VOCs in the human body and their potential relevance to IBS pathophysiology remain poorly understood, necessitating further research to validate their utility as biomarkers.

## SPECIFIC BIOMARKERS FOR DIARRHEA-PREDOMINANT IBS

Cytolethal distending toxin B (CdtB), produced by bacterial pathogens such as Campylobacter jejuni associated with gastroenteritis, induces post-infectious IBS symptoms akin to those observed in human IBS patients. Host antibodies against CdtB have been linked to small intestine bacterial overgrowth and exhibit cross-reactivity with vinculin, suggesting molecular mimicry.

Anti-CdtB antibodies demonstrate a sensitivity of 43.7% and specificity of 91.6% in distinguishing IBS-D from IBD at a defined cut-off. Similarly, anti-vinculin antibodies show a sensitivity of 32.6% and specificity of 83.8% under specific diagnostic thresholds. Fecal volatile organic metabolites (VOMs), analyzed for their discriminatory potential, achieve a sensitivity of 96% and specificity of 80% in distinguishing IBS-D from active IBD based on a panel of 11 key VOMs. These biomarkers represent a significant advancement in the recognition of IBS-D as an organic disease, offering a pathophysiology-based approach to differentiate it from other organic gastrointestinal disorders.[12]

In a study by Pimentel et al, a total of 2681 subjects were analyzed, comprising 2375 individuals with IBS-D, 43 healthy controls, 121 with celiac disease and 142 with IBD (73 Crohn's disease and 69 ulcerative colitis). Optical density measurements revealed significantly elevated levels of anti-CdtB antibodies in D-IBS subjects (2.53±0.69) compared to healthy controls (1.81±0.73), Crohn's disease (1.72±0.81), ulcerative colitis (1.54±0.68) and celiac disease (2.23±0.70) (P<0.001). No significant differences in anti-CdtB levels were observed between healthy subjects and IBD subjects (p=0.23). Subjects with celiac disease exhibited higher anti-CdtB levels compared to all other non-IBS groups (P<0.001). Anti-CdtB antibodies demonstrated a sensitivity of 43.7% and specificity of 91.6% at a cut-off value of≥2.80, indicating their potential as a biomarker for distinguishing diarrhea-predominant irritable bowel syndrome from inflammatory bowel disease.

In individuals with IBS-D, levels of anti-vinculin were markedly elevated (1.34±0.85) compared to those in healthy subjects (0.81±0.59), Crohn's disease (1.05±0.91), ulcerative colitis (0.96±0.77) and celiac disease (1.07±0.98) (p<0.0001). No statistically significant differences in anti-vinculin levels were observed among non-IBS subjects. Anti-vinculin antibodies demonstrated a sensitivity of 32.6% and a specificity of 83.8% at a cut-off value of≥1.68, suggesting their potential utility as a diagnostic biomarker to differentiate diarrhea-predominant irritable bowel syndrome from inflammatory bowel disease.[18]

## SPECIFIC BIOMARKERS FOR CONSTIPATION-PREDOMINANT IBS (IBS-C)

Lactulose breath testing (LBT) involves monitoring methane and hydrogen levels every 15 to 20 minutes following ingestion of 10 g lactulose over a period of at least 2 hours using gas chromatography. Methane producers are identified by a breath methane level≥3 ppm at any point during the test. This testing method serves as a reliable diagnostic tool for predicting irritable bowel syndrome with constipation (IBS-C), exhibiting a sensitivity of 91% and specificity of 81.3%. A meta-analysis involving 1277 subjects confirmed the significant association between methane production and IBS-C. Additionally, research has shown that individuals with methane-producing IBS often experience symptoms such as small bowel movements, straining during defecation, lactose intolerance and weight loss. Furthermore, LBT findings correlate methane production with the severity of constipation, as higher methane levels correspond to decreased stool frequency and lower Bristol stool scores.[12] Novel biomarkers for diagnosing IBS can be categorized into several types aimed at differentiating IBS from healthy controls, identifying specific subtypes such as IBS-D and IBS-C and characterizing the organic basis of the condition. These biomarkers include serum panels, fecal panels, gene expression profiles, psychological assessments and specific markers like fecal calprotectin, SCFA, granins, VOCs in breath tests, measures of visceral hypersensitivity using rectal barostat and evaluations such as colonic transit time, fecal bile acids (BA) and intestinal permeability. Specific antibodies against CdtB and vinculin, fecal VOMs and LBT for methane production also play crucial roles. These biomarkers aim to differentiate IBS as a distinct clinical entity, align with its underlying pathophysiology, establish its organic nature and predict the specific subtype (diarrhea-predominant or constipation-predominant) for more targeted management strategies.

## DRUGS WITH POTENTIAL IN TREATING VH

Drugs like serotonin (5-HT) targeting 5-HT4 receptors, tricyclic antidepressants (TCAs), antispasmodics, plecanatide, pregabalin, eluxadoline and histamine receptor antagonists show potential in treating VH in IBS by modulating GI functions and reducing pain symptoms.

### *Anticholinergic/antimuscarinic antispasmodics*

*Dicyclomine*

One study showed no difference in adverse event rates between dicyclomine and placebo, while another reported higher adverse events (69% vs 16%) with continuous dicyclomine 160 mg/d for 2 weeks compared to placebo. Studies used varying doses and had short treatment durations (10 days–2 weeks).

*Hyoscine*

In three studies lasting 4 weeks to 3 months, hyoscine was more effective than placebo in improving IBS symptoms, but only one study adequately reported adverse events. Studies differed in duration and IBS definitions, with two lacking separate assessments of abdominal pain.

*Hyoscyamine*

A study using hyoscyamine 0.2 mg t.i.d. for 2 weeks showed numerical improvement in IBS symptoms, including pain, compared to placebo, though not statistically significant. Study limitations included short duration and lack of subtype-specific analysis.[19]

***Direct smooth muscle relaxant***

*Mebeverine*

In a study conducted by Kruis et al, a 16-week course of mebeverine 100 mg four times daily was less effective than placebo in alleviating symptoms such as abdominal pain, flatulence and irregular bowel habits in IBS patients, with no significant adverse events reported in either group. Another study indicated that 6 weeks of treatment with mebeverine 135 mg three times daily, with or without the use of a self-management website, did not outperform placebo in improving IBS symptoms and adverse events were not documented.

***Calcium channel blockers***

*Alverine*

In a study, alverine 60 mg combined with simethicone 300 mg taken three times daily was significantly more effective than placebo in reducing abdominal pain in IBS patients (P=0.047). The safety profile was generally like that of placebo, though the study may have excluded patients with more severe symptoms.

*Otilonium*

Across three studies, otilonium 40 mg taken three times daily reduced the frequency of abdominal pain compared to placebo during weeks 3–4 and at week 15. Mild nausea was reported with otilonium in one study, while no adverse events were noted with placebo. Another study reported prostate disturbance and dizziness with otilonium and a skin rash with placebo, leading to study withdrawal.

*Pinaverium*

The efficacy and safety of pinaverium were evaluated in five randomized, placebo-controlled IBS studies. Three small, single-centre studies published in 1995 or earlier found that pinaverium 50 mg taken three times daily improved abdominal pain in IBS patients. The safety profile of pinaverium in these studies was generally comparable to that of placebo.[19]

***Expert opinion***

Anti-CdtB antibodies help diagnose infectious IBS but lack specificity due to colonic inflammation from infections. Importance of ruling out other allergies before testing for food intolerance; definitive tests should be based on T-cell mediated immune responses. FC is a valuable marker to differentiate IBS from IBD but can be affected by long-term use of PPIs, NSAIDs and other conditions. Micro-RNA profiling is a promising future marker for quantifying serotonin activity, crucial in the pathogenesis of visceral hypersensitivity. ASCA-IgA is useful in diagnosing Crohn's disease, particularly in patients with chronic diarrhea, pain and weight loss.

Anti-tTG antibodies can help diagnose celiac disease and may also appear in pediatric IBS-C patients. Colonoscopy is valuable for patients with chronic symptoms and no improvement, FC should be used for initial assessment before colonoscopy.

Assessing colonic transit time can help differentiate functional constipation, IBS-C, pelvic floor dyssynergia and constipation, though routine practice may be challenging. Future potential markers include fecal markers and fecal short chain fatty acids, which could be effective and non-invasive diagnostic tools Antispasmodics are crucial in VH treatment, helping to mediate colonic motility irregularities that contribute to pain.

Diagnostic approaches include mechanical stimuli like rectal balloon distension, unsedated colonoscopy and chemical tests (e.g., capsaicin), albeit with challenges in standardization and patient variability. Mast cells play a pivotal role in the micro-inflammatory changes of IBS, suggesting a microinflammatory disorder that could benefit from targeted therapies.

Psychological therapies like hypnotherapy and cognitive-behavioral therapy (CBT), combined with pharmacotherapies, show promise in managing VH-related pain. Probiotics and medications like pregabalin and tricyclic antidepressants (TCAs) are also considered in managing symptoms, though their efficacy and optimal duration of use in IBS remain areas of ongoing research and debate.

IBS is a common FGDs affecting millions globally. Characterized by symptoms such as abdominal pain, irregular bowel habits and bloating, IBS lacks definitive biomarkers, complicating diagnosis and treatment. VH, a key feature of IBS, involves heightened sensitivity to gut stimuli and plays a significant role in symptom manifestation. Recent research has identified potential biomarkers, such as blood and fecal markers, that could aid in distinguishing IBS from other gastrointestinal disorders and help identify its subtypes.

## CONCLUSION

IBS remains difficult to diagnose and treat due to its complex nature and absence of clear biomarkers. Advances in understanding IBS pathophysiology, particularly VH, offer hope for more accurate diagnostics and targeted treatments. Drugs addressing VH mechanisms, such as mast cell stabilizers and histamine receptor antagonists, show promise in symptom relief. Continued research is crucial to further elucidate IBS pathophysiology, develop effective diagnostic tools and improve patient outcomes and quality of life.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

## REFERENCES


1. Simrén M, Törnblom H, Palsson OS, Tilburg MAL, Van Oudenhove L, Tack J, et al., Visceral hypersensitivity is associated with GI symptom severity in functional GI disorders: consistent findings from five different patient cohorts. Gut. 2018;67(2):255-62.
2. Lawate P. Expert opinion on current issues and challenges in irritable bowel syndrome. Int J Adv in Med. 2024;11(4):415-22.
3. Farzaei MH, Bahramsoltani R, Abdollahi M, Rahimi R. The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments. J Neurogastroenterol Motil. 2016;22(4):558-74.
4. Gwee KA, Gonlachanvit S, Ghoshal UC, Chua ASB, Miwa H, Wu J, et al. Second Asian Consensus on Irritable Bowel Syndrome. J Neurogastroenterol Motil. 2019;1;25(3):343-62.
5. Pittayanon R, Lau JT, Yuan Y, Leontiadis GI, Tse F, Surette M, et al. Gut microbiota in patients with irritable bowel syndrome-a systematic review. Gastroenterol. 2019;157(1):97-108.
6. Dudzińska E, Grabrucker AM, Kwiatkowski P, Sitarz R, Sienkiewicz M. The importance of visceral hypersensitivity in irritable bowel syndrome—plant metabolites in IBS treatment. Pharmaceuticals. 2023;16(10):1405.
7. Ceuleers H, Van Spaendonk H, Hanning N, Heirbaut J, Lambeir AM, Joossens J, et al., Visceral hypersensitivity in inflammatory bowel diseases and irritable bowel syndrome: The role of proteases. World J Gastroenterol. 2016;22(47):10275-86.
8. Moloney RD, Johnson AC, O'Mahony SM, Dinan TG, Greenwood-Van Meerveld B, Cryan JF. Stress and the microbiota-gut-brain axis in visceral pain: relevance to irritable bowel syndrome. CNS Neurosci Ther. 2016;22(2):102-17.
9. Deiteren A, Wit A, Linden L, De Man JG, Pelckmans PA, De Winter BY. Irritable bowel syndrome and visceral hypersensitivity : risk factors and pathophysiological mechanisms. Acta Gastroenterol Belg. 2016;79(1):29-38.
10. De Palma G, Reed DE, Bercik P. Diet-microbial cross-talk underlying increased visceral perception. Gut Microbes. 2023;15(1):2166780.
11. Keszthelyi D, Troost FJ, Masclee AA. Irritable bowel syndrome: methods, mechanisms and pathophysiology. Methods to assess visceral hypersensitivity in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2012;15;303(2):141-54.
12. Kim JH, Lin E, Pimentel M. Biomarkers of Irritable Bowel Syndrome. J Neurogastroenterol Motil. 2017;30;23(1):20-6.
13. Nakov R, Snegarova V, Dimitrova-Yurukova D, Velikova T. Biomarkers in Irritable Bowel Syndrome: Biological Rationale and Diagnostic Value. Dig Dis. 2022;40(1):23-32.
14. Lembo AJ, Neri B, Tolley J, Barken D, Carroll S, Pan H. Use of serum biomarkers in a diagnostic test for irritable bowel syndrome. Aliment Pharmacol Ther. 2009;15;29(8):834-42.
15. Jones MP, Chey WD, Singh S, Gong H, Shringarpure R, Hoe N, et al. A biomarker panel and psychological morbidity differentiates the irritable bowel syndrome from health and provides novel pathophysiological leads. Aliment Pharmacol Ther. 2014;39(4):426-37.
16. Waugh N, Cummins E, Royle P, Kandala NB, Shyangdan D, Arasaradnam R, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess. 2013;17(55):1-211.
17. Baranska A, Mujagic Z, Smolinska A, Dallinga JW, Jonkers DM, Tigchelaar EF, et al. Volatile organic compounds in breath as markers for irritable bowel syndrome: a metabolomic approach. Aliment Pharmacol Ther. 2016;44(1):45-56.
18. Pimentel M, Morales W, Rezaie A, Marsh E, Lembo A, Mirocha J, et al., Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. PLoS One. 2015;10(5):126438.
19. Brenner DM, Lacy BE. Antispasmodics for Chronic Abdominal Pain: Analysis of North American Treatment Options. Am J Gastroenterol. 2021;1;116(8):1587-600.
20. Kruis W, Weinzierl M, Schüssler P, Holl J. Comparison of the therapeutic effect of wheat bran, mebeverine and placebo in patients with the irritable bowel syndrome. Digestion. 1986;34(3):196-201.
21. Wittmann T, Paradowski L, Ducrotté P, Bueno L, Delestrain MC. Clinical trial: the efficacy of alverine citrate/simeticone combination on abdominal pain/discomfort in irritable bowel syndrome--a randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2010;31(6):615-24.
22. Baldi F, Longanesi A, Blasi A. Clinical and functional evaluation of the efficacy of otilonium bromide: A multicenter study in Italy. Ital J Gastroenterol. 1991;23:60–3.


**Cite this article as:** Mehrotra P. Visceral hypersensitivity and diagnostic markers in functional gastrointestinal disorders: expert opinion. Int J Adv Med 2025;12:139-46.