

## Review Article

# Managing irritable bowel syndrome via gut-brain axis modulation and antispasmodic - anxiolytic dual action: an Indian expert panel review

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### ABSTRACT

Irritable bowel syndrome (IBS) is a complex, multifactorial functional gastrointestinal disorder characterized by recurrent abdominal discomfort, altered bowel habits, and a high prevalence of psychological comorbidities, particularly anxiety. In the Indian clinical landscape, IBS remains underdiagnosed, largely due to symptom overlap with other gastrointestinal conditions and the lack of standardized diagnostic protocols. Anxiety significantly contributes to the exacerbation of IBS symptoms, primarily through dysregulation of the gut-brain axis. This manuscript explores the evolving paradigm of IBS diagnosis and management in India, with a particular focus on the therapeutic potential of antispasmodic-anxiolytic combinations. Among these, the fixed-dose combination of clidinium and chlordiazepoxide stands out for its dual mechanism of action, offering both peripheral antispasmodic and central anxiolytic effects. This makes it especially effective in managing IBS cases where psychological stress is a key aggravating factor. Unlike conventional monotherapies, this combination addresses both visceral hypersensitivity and the psychological dimensions of IBS, thereby enhancing symptom control in stress-amplified presentations. The manuscript also explores recent advancements in digital health tools, biomarker discovery, and precision medicine approaches that are reshaping IBS diagnostics and enabling more personalized treatment strategies. Insights from real-world clinical practice and patient profiling underscore the importance of individualized, multimodal management integrating pharmacologic interventions with lifestyle and behavioural therapies.

**Keywords:** Irritable bowel syndrome, Gut-brain axis, Anxiety, Antispasmodic, Clidinium-chlordiazepoxide

### INTRODUCTION

Functional bowel disorders (FBDs) are chronic GI conditions marked by abdominal pain, bloating, and abnormal bowel habits like constipation or diarrhea. It includes irritable bowel syndrome (IBS), functional constipation (FC), functional diarrhea (FDr), functional abdominal bloating/distention, and unspecified FBD.<sup>1</sup> IBS is a common chronic disorder involving disrupted communication between the gut and the brain. It is mainly identified by repeated episodes of abdominal discomfort along with altered bowel habits, in the absence of any detectable structural or biochemical cause.<sup>2</sup> IBS affects about 15% of the Indian population, with a rising trend observed by clinical experts. Approximately 35% of

gastroenterologists' practice involves IBS management, reflecting its growing clinical importance. Nearly 75% of symptomatic individuals actively seek medical care, highlighting increased awareness and healthcare burden.<sup>3</sup> Diagnosing IBS remains a major clinical challenge due to the absence of definitive biomarkers and reliance on symptom-based criteria.<sup>4</sup> The Rome IV criteria define IBS by recurrent abdominal pain with altered stool frequency or form, but in primary care, they are often underused, leading to underdiagnosis, misdiagnosis, and delayed treatment.<sup>5,6</sup>

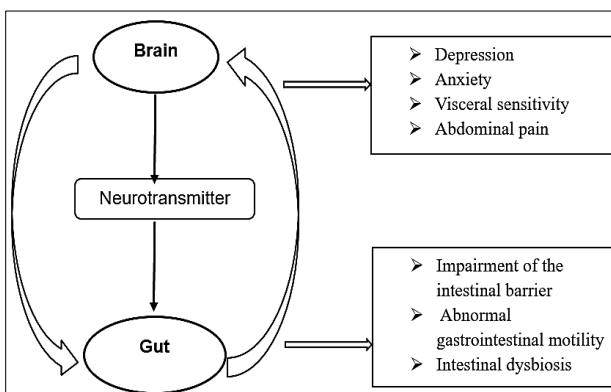
IBS diagnosis is complicated by symptom overlap with IBD, celiac disease, and other functional disorders. Tests like fecal calprotectin and CRP help rule out organic

disease, but are not specific for IBS.<sup>5</sup> IBS is heterogeneous, with recognized subtypes: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed (IBS-M), and unsubtyped (IBS-U). Psychological factors, including anxiety and depression, are frequently associated, particularly in constipation-predominant and mixed subtypes. These comorbidities complicate patient profiles and management, necessitating a holistic approach that addresses both gastrointestinal and psychological symptoms.<sup>7,6</sup> Current efforts focus on developing noninvasive biomarkers, risk stratification, and improved patient-centered care targeting both GI and psychological symptoms.<sup>8</sup> The purpose of this comprehensive review is to understand current clinical perspectives on IBS diagnosis in India and to assess the role of clidinium-chlordiazepoxide as a targeted therapeutic option, particularly in patients with anxiety-driven IBS symptoms.

## GUT-BRAIN AXIS: ANXIETY MANIFESTATIONS IN PATIENTS WITH IBS

### *The gut-brain axis and its dysregulation in IBS*

The gut-brain axis is a complex, bidirectional communication network connecting the central nervous system (CNS) with the enteric nervous system (ENS) of the gastrointestinal tract, as shown in Figure 1.<sup>10</sup> This interaction is facilitated through neural, hormonal, immune, and microbial signaling pathways. In the context of IBS, dysregulation of the gut-brain axis plays a pivotal role in generating both gastrointestinal symptoms and emotional disturbances, particularly anxiety.<sup>9,10</sup>



**Figure 1: Gut-brain bidirectional communication in IBS.**

Several mechanisms underlie this dysfunctional communication. A hallmark feature of IBS is visceral hypersensitivity, wherein normal gut stimuli are perceived as painful due to exaggerated sensory signaling.<sup>11,12</sup> Additionally, gut microbiota dysbiosis may alter the production of neurotransmitters such as serotonin, a key regulator of both intestinal motility and mood.<sup>9</sup> Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis, alters gut function, and, along with low-grade

inflammation and psychological factors, drives a brain-gut feedback loop that worsens IBS symptoms.<sup>11,12</sup>

### *Expert's opinion*

Common IBS symptoms in India include lower abdominal pain, fullness, and incomplete evacuation. Gut microbiota, neurotransmitter imbalances (especially serotonin), inflammation, and immune dysfunction play key roles in anxiety-associated IBS and gut-brain axis dysfunction. Specific populations (e.g., peri-menopausal women, post-hysterectomy, women with forceps delivery) may have higher IBS prevalence; further research is needed.

### *Anxiety manifestations in IBS: clinical evidence*

A substantial body of evidence links anxiety disorders with IBS. The surveys indicate that up to 50% of IBS patients suffer from anxiety, including gastrointestinal-specific anxiety (GSA), an anticipatory fear and preoccupation with GI symptoms.<sup>9</sup> A study using Hamilton scales showed strong links between IBS and mental health: depression (OR 6.3) and anxiety (OR 7.56). IBS-C and IBS-M patients reported more severe anxiety than IBS-D patients.<sup>13,14</sup> A recent meta-analysis by Mulianda et al highlights a strong link between psychological factors and the risk of developing IBS in Asian populations. The study found that anxiety increases the risk of IBS by 1.53 times, depression by 1.29 times, and poor sleep quality by 1.80 times. These associations were statistically significant, emphasizing the need to integrate mental health and sleep management into IBS prevention and treatment strategies.<sup>15</sup> Long-term studies show that addressing both GI and psychological symptoms in IBS reduces severity and anxiety, with early improvements that strengthen over time, underscoring the value of integrated care.<sup>16</sup>

### *Psychological profile and clinical consequences of anxiety in IBS*

Understanding the psychological and behavioral traits of IBS patients is critical for comprehensive care. Anxiety in this population ranges from generalized worry to panic attacks, social avoidance, and fear of bowel incontinence in public settings.<sup>17,9</sup> Many IBS patients have maladaptive coping styles and negative illness perceptions. Early adverse life events (EALs), particularly childhood trauma, are strongly tied to their onset and severity.<sup>17</sup> Demographic trends suggest a higher prevalence of anxiety in younger individuals and females, though regional variations exist. Certain personality traits, such as neuroticism, perfectionism, and experiences of early-life adversity, may predispose individuals to more severe GI symptoms under chronic psychological stress.<sup>17</sup> IBS often coexists with conditions like depression, fibromyalgia, and dyspepsia. Unmanaged anxiety worsens outcomes, driving higher healthcare use, costs, and treatment resistance, highlighting the need for early screening and multidisciplinary care.

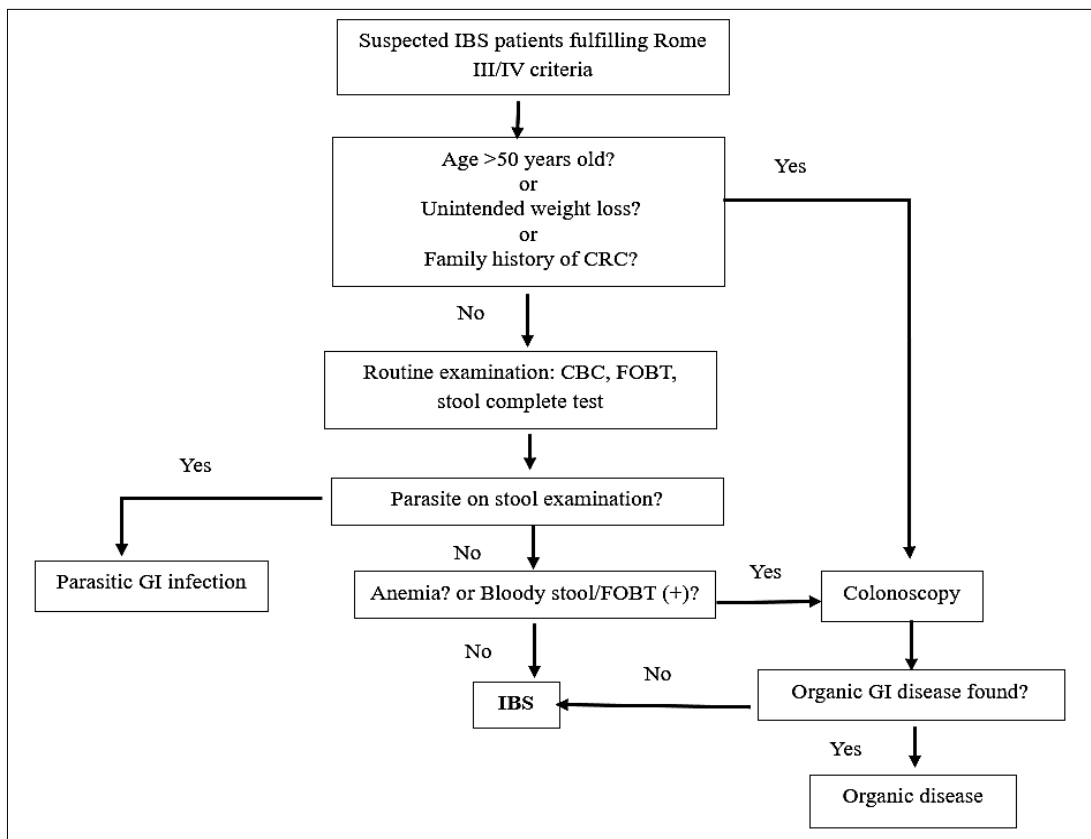
**PRECISION DIAGNOSIS: EXPLORING BIOMARKER ASSAYS AND NEUROIMAGING IN ANXIETY-ASSOCIATED IBS**

**Role of precision diagnosis in IBS remission**

Precision diagnosis aims to overcome conventional diagnosis limitations by utilizing objective and individualized diagnostic tools. This approach includes advanced biomarker assays and neuroimaging technologies that allow for early detection, subtype classification, and personalized treatment strategies. Recent advances suggest that integrating multi-modal data such as fecal microbiome profiles, serological markers, and neuroimaging findings with artificial intelligence (AI) and machine learning algorithms can significantly improve diagnostic accuracy. This degree of precision helps clinicians identify the underlying pathophysiology of each IBS subtype, thereby improving remission rates, reducing unnecessary treatments, and enhancing patient quality of life.<sup>19</sup>

**Diagnosis criteria guidelines and algorithm**

Globally, the Rome IV criteria continue to serve as the gold standard for diagnosing IBS. These criteria focus on the presence of recurrent abdominal pain and altered bowel habits over a three-month period, excluding alarm features such as weight loss or gastrointestinal bleeding. However, the Rome IV framework does not fully address the biological heterogeneity of IBS, particularly the dysfunction of the brain-gut axis in anxiety-related subtypes. It remains a subjective tool and may miss important physiological and psychological markers.<sup>20,3</sup> In India, clinicians generally follow Rome IV guidelines complemented by exclusion of organic diseases using basic biomarkers and colonoscopy when indicated, though resource constraints limit advanced diagnostics. The American College of Gastroenterology endorses a positive diagnostic strategy using Rome IV, emphasizing detailed history and minimal testing unless alarm signs warrant further evaluation (Figure 2).<sup>3,4,8</sup>



**Figure 2: Proposed diagnostic algorithm for irritable bowel syndrome (IBS) in low- and middle-income countries.<sup>4</sup>** CRC: colorectal cancer; CBC: complete blood count; FOBT: fecal occult blood test; GI: gastrointestinal

**Biomarkers for exclusion of other diseases**

A crucial step in confirming a diagnosis of IBS is ruling out other organic gastrointestinal conditions that present with similar symptoms. Disorders such as IBD, celiac disease, and infectious colitis must be excluded to prevent misdiagnosis and ensure that appropriate treatment is

initiated. Biomarkers play an indispensable role in this exclusion process. Fecal calprotectin is a well-established marker used to identify intestinal inflammation, with a high negative predictive value for IBD. When levels are within the normal range, inflammatory causes can often be ruled out with confidence. Similarly, CRP, a general marker for systemic inflammation, can aid in

differentiating IBS from conditions like Crohn's disease or ulcerative colitis. In cases where celiac disease is suspected, serological tests such as anti-tissue transglutaminase (anti-tTG) antibodies and total IgA levels are recommended. Stool cultures and parasitological testing are also essential in cases with suspected infections, particularly in resource-limited or endemic regions. These biomarkers are valuable in both global and Indian healthcare settings as part of a structured, stepwise diagnostic approach.<sup>21</sup>

### ***Biomarkers specific to IBS with anxiety***

Anxiety-associated IBS involves altered brain activity and neurochemistry. Structural magnetic resonance imaging (MRI), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) reveal hyperactivity in emotional regions (insula, cingulate cortex, amygdala) and reduced activity in frontal and sensorimotor areas. Resting-state fMRI shows abnormal connectivity between limbic and cortical networks. MRS indicates reduced glutamate + glutamine in the insula and hippocampus, and altered gamma-aminobutyric acid (GABA) in the medial prefrontal cortex. These changes suggest disrupted brain-gut signaling in anxiety-related IBS.<sup>22</sup>

IBS patients with anxiety show altered gut microbiota, affecting neurotransmitters like serotonin that regulate gut and mood. While serotonin/norepinephrine levels may not differ, their link to microbiome diversity highlights a complex gut-brain interaction.<sup>23</sup> Additionally, combining gene expression and serological biomarkers with psychological assessments such as anxiety and depression, markedly improves differentiation of IBS patients from healthy individuals, achieving an area under the curve (AUC) of 0.93, which is superior to biological markers alone.<sup>24</sup> Neuroendocrine markers related to visceral hypersensitivity, such as chromogranin A and human beta-defensin 2, and alterations in cortisol regulation via the hypothalamic-pituitary-adrenal (HPA) axis have also been proposed as relevant biomarkers reflecting the anxiety-associated IBS subtype. Collectively, these findings imply that integrated biomarker panels including microbial, neurochemical, immunological, and psychological measures hold the most promise for precise diagnosis of IBS with anxiety.<sup>26</sup>

### ***Expert's opinion***

IBS diagnosis is primarily clinical and depends on a detailed patient history and physical examination, as no single confirmatory test exists. Colonoscopy is generally recommended only for patients who develop new-onset IBS symptoms after the age of 50 or those who present with alarm features, and it is not routinely indicated for younger individuals without such signs. In Indian patients, the Rome III criteria tend to be more appropriate because abdominal distension and bloating are more prominent than pain; strict application of Rome IV criteria may lead to underdiagnosis, emphasizing the importance of

including distension to improve diagnostic sensitivity. Diagnostic accuracy may be further enhanced by combining symptom assessment with biomarker panels such as cortisol, brain-derived neurotrophic factor, inflammatory cytokines including interleukin-6, tumor necrosis factor-alpha, C-reactive protein, fecal calprotectin, anti-vinculin antibodies, zonulin, and measures of gut microbiota diversity, which together may support more personalized treatment planning. Neuroimaging modalities, including functional magnetic resonance imaging, structural magnetic resonance imaging, and magnetic resonance spectroscopy, have demonstrated altered brain connectivity in IBS patients with anxiety, reinforcing the role of individualized therapies such as cognitive behavioral therapy and neuromodulation. Psychometric assessment tools, including the hospital anxiety and depression scale, IBS quality of life questionnaire, PAC-SYM, and PAC-QOL, complement diagnosis by evaluating psychological comorbidity and overall symptom burden. Targeted investigations, such as lactose-hydrogen breath testing and duodenal biopsy, help exclude overlapping conditions like disaccharidase deficiencies. Although emerging tools such as advanced biomarkers, neuroimaging, rectal manometry, and biofeedback-based assessments show promise in refining diagnosis, their use remains limited by availability and affordability constraints, particularly outside metro and tier-1 cities in India.

### **RECENT ADVANCES IN PRACTICAL IBS MANAGEMENT**

Recent therapeutic advances in IBS emphasize symptom-specific and individualized approaches. For IBS-D, effective options include rifaximin, a non-absorbable antibiotic with good safety for bloating and diarrhea, and fluradoline, a mixed  $\mu$ -opioid agonist/ $\delta$ -antagonist that targets motility and visceral pain. 5-HT<sub>3</sub> antagonists like alosetron and ramosetron also improve stool consistency and reduce pain, though use is limited by side effects.

Bile acid sequestrants such as cholestyramine and colesevelam are beneficial in bile acid malabsorption-associated diarrhea.<sup>27,28</sup> For IBS-C, psyllium, an osmotic laxative like polyethylene glycol, and newer agents like lubiprostone (chloride channel activator) and linaclotide (guanylate cyclase-C agonist) help improve bowel function and pain. Prucalopride, a selective 5-HT<sub>4</sub> agonist, shows promise in patients unresponsive to laxatives.<sup>27</sup>

Abdominal pain, a key symptom across IBS subtypes, is managed using antispasmodics (Clidinium, peppermint oil), trimebutine, or low-dose antidepressants like Tricyclic antidepressants. Nonpharmacologic options such as low-FODMAP diet, probiotics, and psychological therapies are important adjuncts.<sup>29</sup> Emerging treatments like fecal microbiota transplantation (FMT) and symbiotic are under evaluation, though evidence remains mixed. A tailored, multimodal strategy remains essential for effective IBS management.<sup>27</sup>

## COMPARATIVE ANALYSIS: THE CONVENTIONAL, COMPLEMENTARY AND RECENT ADVANCES IN MANAGEMENT OF ANXIETY-ASSOCIATED IBS

The smooth muscle relaxants and antispasmodic-anxiolytic combinations such as mebeverine, clidinium bromide, dicyclomine, and low-dose chlordiazepoxide are employed to target both visceral hypersensitivity and anxiety symptoms. This multimodal regimen underscores the bidirectional nature of the gut-brain axis in IBS management.<sup>30</sup> Psychological interventions form an essential component of conventional care. Cognitive Behavioral Therapy (CBT) is a well-established modality that focuses on modifying maladaptive thoughts and behaviors linked to IBS and anxiety. It has demonstrated significant improvements in symptom control, mental health outcomes, and overall quality of life.<sup>18,29,30</sup> Broader brain-gut behavior therapies (BGBT), including gut-directed hypnotherapy, psychodynamic interpersonal therapy, and relaxation techniques, are also utilized to recalibrate gut-brain communication and alter symptom perception.<sup>18</sup>

Complementary and alternative medicine (CAM) approaches like mindfulness-based stress reduction (MBSR), hypnotherapy, yoga, and certain herbal supplements (e.g., ginger) are increasingly used in anxiety-predominant IBS. These methods help reduce symptoms and improve quality of life. Evidence supports combining CAM with conventional treatments for better overall outcomes through personalized, multi-modal care.<sup>18,30</sup>

Recent advances target the gut-brain axis in IBS management. Emerging neuromodulation techniques like vagus nerve stimulation may improve gut function and reduce sensitivity. Digital tools such as app-based CBT and hypnotherapy enhance access to psychological care.<sup>31</sup> Furthermore, preliminary evidence suggests a role for vitamin D supplementation in improving both IBS symptoms and associated anxiety, though further investigation is required to substantiate these findings.<sup>32</sup>

### ADVANTAGES OF ANTICHOLINERGIC ACTION IN ANTISPASMODICS

Antispasmodics play a vital role in IBS management by targeting gastrointestinal motility and visceral pain. They act by blocking muscarinic receptors (especially M3) in the enteric nervous system, inhibiting acetylcholine-mediated smooth muscle contraction. This reduces intestinal spasms, cramping, and bloating. By slowing gut motility, these agents are especially effective in IBS with diarrhea (IBS-D), helping to regulate stool frequency, reduce urgency, and improve stool consistency.<sup>33,34</sup>

Their role in dampening visceral hypersensitivity, which is increasingly recognized as a core pathophysiological feature in IBS. Anticholinergics help reduce the exaggerated pain responses to intestinal stimuli by

decreasing neuromuscular excitability. This contributes to a reduction in the perception of abdominal pain and discomfort, even when objective bowel dysfunction is minimal. Anticholinergics improve quality of life in IBS by easing pain, bloating, and urgency. Their quick relief supports daily functioning and is especially helpful during acute flares.<sup>34</sup> Commonly used anticholinergic antispasmodics include dicyclomine, hyosine butyl bromide, clidinium bromide, and hyoscyamine. Although their efficacy varies depending on patient subtype and symptom severity, multiple clinical trials and meta-analyses have shown favorable outcomes compared to placebo, especially in reducing abdominal pain and bloating.<sup>34,35</sup> Meta-analyses show antispasmodics relieve global IBS symptoms (NNT=5) with few side effects, but evidence certainty is low due to study heterogeneity and small sample sizes.<sup>5</sup>

### Expert's opinion

Spasmolytics remain an effective and preferred first-line option for managing IBS symptoms, with commonly recommended agents such as clidinium, mebeverine, pinaverium, and otilonium offering symptomatic relief in routine practice. Antidepressants, including tricyclic agents, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, help reduce pain, discomfort, and visceral hypersensitivity and may be used alongside antispasmodics in selected patients who exhibit significant pain or psychological comorbidity. A low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet can be considered for a short trial of four to six weeks to assess benefit, although adherence may be challenging in the Indian dietary context. The usual duration of antispasmodic therapy ranges from three to six months, followed by a gradual tapering based on symptom response and clinical judgment.

### ROLE AND SCOPE OF CLIDINIUM CHLORDIAZEPOXIDE COMBINATION IN ANXIETY MANIFESTATIONS OF IBS

#### *Dual mechanism approach: targeting gastrointestinal and psychological symptoms in IBS*

The combination of clidinium, an anticholinergic agent, and chlordiazepoxide, a benzodiazepine, offers a strategic dual-action therapeutic approach for the management of IBS, particularly in patients where anxiety significantly worsens gastrointestinal symptoms. By targeting both physiological and psychological aspects of IBS, this combination aligns with the modern understanding of the gut-brain axis and its role in symptom generation.<sup>35</sup> Clidinium primarily acts on peripheral muscarinic receptors in the gastrointestinal tract. Its anticholinergic action reduces smooth muscle contractions, leading to decreased motility and relief from abdominal pain, cramping, bloating, and other distressing gastrointestinal symptoms commonly observed in IBS. This mechanism is

particularly effective in controlling the somatic manifestations of IBS, especially in cases with predominant diarrhea and urgency.<sup>36,37</sup> On the other hand, chlordiazepoxide exerts its effect centrally by modulating gamma-aminobutyric acid (GABA) neurotransmission in the brain. As an anxiolytic, it reduces excessive neural activity associated with anxiety and stress factors that are closely linked to symptom exacerbation in IBS patients. By calming the central nervous system and dampening the stress response, chlordiazepoxide contributes to the normalization of the gut-brain communication pathway.<sup>37,38</sup> This combination provides synergistic benefits by targeting both the physical and psychological aspects of IBS.

Clidinium relaxes gut muscles to reduce spasms and pain, while chlordiazepoxide alleviates anxiety linked to symptoms. Together, they improve overall symptom control and quality of life in IBS patients.<sup>36</sup>

#### ***Clinical evidences and efficacy of clidinium/chlordiazepoxide in anxiety-prominent IBS***

The clidinium/chlordiazepoxide combination is indicated to control emotional and somatic factors in gastrointestinal disorders. This may also be used as adjunctive therapy in the treatment of peptic ulcer and in the treatment of IBS (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.<sup>37</sup> Several clinical and observational studies have explored the utility of this combination in managing functional gastrointestinal disorders (FGIDs), including IBS, especially when associated with anxiety manifestations.<sup>36,38,39</sup> These outcomes are supported by various clinical studies and are summarized in Table 1.<sup>36,39-41</sup> Importantly, real-world clinician insights reveal that over 91.4% of physicians consider this combination effective in anxiety-dominant IBS. The anxiolytic effect of chlordiazepoxide complements the gut-directed antispasmodic action of clidinium, creating a harmonized therapeutic approach particularly useful in patients with stress-induced symptom flares.<sup>31,36</sup>

Although the triple combination (Clidinium + Chlordiazepoxide + Dicyclomine) is used by a slightly higher percentage (15.2%) of physicians than the dual combo (11.7%), its use is limited due to higher anticholinergic burden and side effect concerns such as dry mouth, constipation, and urinary retention, especially in the elderly. Experts advise against polypharmacy when symptom control is achievable with fewer agents, positioning the dual combination as safer and equally effective for most patients.<sup>30</sup> A comparative overview of these agents in terms of mechanism, efficacy, safety, and clinical preference is summarized in Table 2.<sup>33,38,40,43</sup>

#### ***Expert's opinion***

Combination therapy of antispasmodics like clidinium-chlordiazepoxide with probiotics or antibiotics can be considered tailored to IBS subtypes. Clidinium-

chlordiazepoxide combination is effective in managing post-infectious IBS by reducing bowel movements and anxiety symptoms. Chlordiazepoxide offers anxiolytic effects by maintaining serotonin turnover; it should be used cautiously in patients with severe psychiatric illnesses or those already on benzodiazepines after psychiatric evaluation. Combining clidinium with tricyclic antidepressants (e.g., amitriptyline) or SSRIs (e.g., escitalopram) may provide synergistic symptom control in anxiety-induced IBS. Clidinium, chlordiazepoxide, and mebeverine together show synergistic effects in symptom relief; clinical use over two decades supports this combination.

#### ***Limitations, monitoring, and safety considerations***

The clidinium- chlordiazepoxide combination, while effective in managing gastrointestinal symptoms associated with IBS and functional dyspepsia, must be used with caution due to the addiction potential of chlordiazepoxide, a benzodiazepine.<sup>37</sup> Prolonged use can lead to dependency; hence, it is recommended for short-term therapy and should be tapered off gradually under medical supervision.<sup>39</sup> Common side effects include drowsiness, dry mouth, constipation, blurred vision, and dizziness, primarily due to clidinium's anticholinergic action and chlordiazepoxide's CNS depressant effects.<sup>36,38</sup> This combination is contraindicated in patients with glaucoma, prostatic hypertrophy, bladder neck obstruction, or hypersensitivity.

Concurrent use with opioids, alcohol, or CNS depressants may cause severe sedation and respiratory depression, requiring patient counseling. Elderly patients are at higher risk of sedation and cognitive decline, so cautious dosing and close monitoring are essential. Regular monitoring for dependency, sedation, liver function, and blood abnormalities is essential during treatment. Psychiatric evaluation before starting therapy helps avoid masking underlying mood disorders. Due to risks of tolerance and dependence, this combination should be used only for acute symptom flares or short-term bridging, with careful patient selection and ongoing risk-benefit assessment to guide discontinuation or switch to safer long-term options.<sup>37</sup>

#### **IBS WITH COMORBIDITIES- PATIENT PROFILES FOR CLIDINIUM-CHLORDIAZEPOXIDE IN IBS MANAGEMENT**

IBS is frequently accompanied by diverse comorbidities that compound its clinical complexity and symptom severity. A meta-analysis, a significant association between IBS and metabolic syndrome, with increased prevalence of obesity, elevated BMI, waist circumference, hypertension, dyslipidemia (raised LDL, triglycerides, total cholesterol; decreased HDL), and greater insulin resistance (HOMA-IR), though not necessarily with diabetes or elevated fasting glucose.<sup>40</sup> IBS also commonly coexists with hypothyroidism, where overlapping

symptoms like bloating, altered bowel habits, and fatigue may stem from thyroid-related changes in gut motility. While hypothyroidism does not cause IBS, it can worsen its manifestations and is identified as a frequent comorbidity in hypothyroid patients.<sup>41</sup> Another key contributor is gut dysbiosis, an imbalance in intestinal microbiota marked by reduced diversity and altered microbial composition. Dysbiosis affects gut barrier integrity, immune signaling, and neurotransmitter balance

(e.g., serotonin), thereby playing a central role in IBS pathophysiology. It is particularly linked to bloating, diarrhea, and anxiety in IBS subtypes.<sup>42</sup> IBS comorbidities highlight the need for a comprehensive, multidisciplinary approach. Functional dyspepsia presents as postprandial distress syndrome or epigastric pain syndrome. In severe, refractory cases unresponsive to PPIs, clidinium-chlordiazepoxide can improve symptoms and quality of life.<sup>43</sup>

**Table 1: Clinical evidence on Clidinium-Chlordiazepoxide in functional gastrointestinal disorders.**

Study	Study design/population	Functional GI disorders targeted	Key outcomes/findings	Noted adverse effects
<b>McHardy et al<sup>39</sup></b>	Double-blind, placebo-controlled crossover; 34 adults	Functional GI disorders including, Gastric ulcer, duodenal ulcer, duodenitis, regional enteritis, ulcerative colitis, esophageal hiatal hernia, diverticulosis of the colon.	Chlordiazepoxide-clidinium bromide significantly superior to placebo in alleviating abdominal pain, nausea, heartburn, diarrhea, and flatulence.	Drowsiness, xerostomia, blurring of vision, and constipation.
<b>Hock<sup>40</sup></b>	Clinical trial of clidinium bromide 2.5 mg + chlordiazepoxide 5 mg) in 100 patients with various GI disorders and prominent anxiety/tension, ages 13-72 years	Functional GI disorders, including functional bowel distress, peptic ulcers, gastritis, and others with a improve phrasing.	Excellent or good symptom improvement in 76% of patients; significant relief in both psychic symptoms (anxiety, tension, insomnia, depression) and GI symptoms (epigastric burning, gas, abdominal pain); adjunctive to antacids and dietary therapy; treatment duration 4-16 weeks	Constipation most frequent (21%); mild side effects such as dry mouth, drowsiness, blurred vision.
<b>Wayne<sup>41</sup></b>	Double-blind, placebo-controlled crossover; 42 patients with functional GI disorders.	Functional GI disorders with physiological and psychic symptoms.	67.5% overall excellent-to-good response with clidinium/chlordiazepoxide versus 37.5% with placebo; significant improvement in 4 of 8 target symptoms; improvement in physiological and psychological symptoms; better outcomes when active drug administered first.	Mild side effects typical of anticholinergic and sedative drugs, such as drowsiness and dry mouth; no major adverse events reported.
<b>McHardy et al<sup>39</sup></b>	Open-label clinical experience, 106 patients	Upper GI diseases (e.g., dyspepsia)	85% of patients had marked symptom improvement without major adverse events.	Not specified
<b>Puasripun et al<sup>38</sup></b>	Prospective, Randomized, double-blind, placebo-controlled trial; 78 adults with functional dyspepsia (refractory to PPI)	Functional Dyspepsia (Rome IV) – postprandial distress syndrome (PDS) and mixed subtypes of FD, with modest results in epigastric pain syndrome (EPS)	Clidinium/chlordiazepoxide add-on to PPI group showed responder rate 41.03% vs 5.13% for placebo at 4 weeks, with significant improvement in global dyspepsia score and quality of life. Improvements in symptoms such as bloating, fullness, belching, and abdominal discomfort, especially effective in PDS and mixed subtype.	Drowsiness, generally mild, no major events
<b>Ramesh et al<sup>35</sup></b>	Indian Perspective Review (2024)	IBS, functional GI disorders	Combination therapy approved in India for IBS; cited as having dual benefit (anxiety reduction + GI symptom relief); high rate of patient-reported improvement	No major issues reported

**Table 2: Comparison of Mebeverine, Clidinium + Chlordiazepoxide, and Dicyclomine for IBS.**

Parameter	Mebeverine	Clidinium + Chlordiazepoxide	Dicyclomine
<b>Class</b>	Musculotropic antispasmodic.	Quaternary anticholinergic + Anxiolytic (Benzodiazepine)	Anticholinergic.
<b>Mechanism of action</b>	Direct smooth muscle relaxant, maintains gut motility, no anticholinergic effect. <sup>33</sup>	Clidinium: blocks muscarinic receptors-reduces GI motility, Chlordiazepoxide: provides sustained anxiolysis via GABAergic mechanisms, reduces visceral pain perception. <sup>43</sup>	Inhibits GI smooth muscle contractions. <sup>38</sup>
<b>Most recommended for</b>	IBS-C, elderly patients, mild-moderate non-secretory IBS. <sup>33</sup>	Stress/anxiety-predominant IBS. <sup>43</sup>	Severe/refractory cases <sup>38</sup>
<b>Onset of action (tmax)</b>	Moderate (1–2 hours). <sup>43</sup>	Moderate (Clidinium: ~1–2 hours, Chlordiazepoxide: 1–2 hours) <sup>43</sup>	Fast (1–1.5 hours) <sup>40</sup>
<b>Duration of action</b>	Short (half-life 2–5 hours)	Long (Clidinium: 20–24 hours, Chlordiazepoxide: 5–30 hours) <sup>43</sup>	Intermediate. <sup>43</sup>
<b>Safety profile</b>	High, especially in the elderly. <sup>33</sup>	Moderate (monitor elderly for anticholinergic load) <sup>38,43</sup>	Lower safety margin due to CNS and systemic effects. <sup>38</sup>

### MAPPING PERCEPTION- EMERGING CONCEPTS ON INTERACTIVE IBS TOOLS

Illness perception significantly impacts IBS management, influencing symptom reporting, care-seeking behavior, and treatment adherence. Patients' views on the emotional and physical consequences of IBS can affect both symptom severity and response to treatment. Since perception and symptoms interact bidirectionally, assessing these beliefs helps in delivering personalized, psychologically informed care.<sup>44,45</sup> IBS care is advancing with digital tools like Bowelle, mySymptoms, Auggi, Dieta, and MyGiHealth. These apps track symptoms, diet, and triggers, offering more accurate insights and better adherence than recall-based methods.<sup>46</sup>

Telemedicine expands access to IBS care with remote CBT, hypnotherapy, and dietary support. AI tools and wearables further aid stool assessment, stress tracking, and personalized management. Recognizing the value of digital interventions, the American College of Gastroenterology (ACG) endorses several patient-centric tools. Notable examples include the IBS Test, a digital symptom questionnaire, and the IBS Treatment Matrix, an evidence-based resource that outlines therapeutic options and their relative effectiveness to guide individualized care plans.<sup>47</sup>

Digital health interventions (DHIs) improve IBS outcomes by reducing symptom severity, enhancing quality of life, and supporting psychological well-being. These self-directed tools offer personalized education, real-time feedback, and social support features like chatbots and peer groups, fostering sustained engagement and proactive self-management. Integrating behavioral support and monitoring reshapes illness perceptions and boosts treatment success.<sup>48,49</sup>

### CONCLUSION

IBS management in India requires a personalized, symptom-based approach that addresses both gastrointestinal discomfort and psychological comorbidities. The clidinium-chlordiazepoxide combination offers a unique advantage in anxiety-predominant IBS by targeting both visceral hypersensitivity and gut-brain axis dysfunction. While mebeverine remains widely prescribed, clidinium-chlordiazepoxide is better suited for patients with stress-exacerbated symptoms. Polypharmacy with agents like dicyclomine should be used cautiously due to increased side effect risk. Embracing individualized therapy, supported by expert insights and evolving diagnostic tools, is key to improving outcomes in Indian IBS patients.

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