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Review

2025 Seoul Consensus on Clinical Practice Guidelines for Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is a chronic, disabling, and functional bowel disorder that significantly affects social functioning and reduces quality of life and increases social costs. The Korean Society of Neurogastroenterology and Motility published clinical practice guidelines on the management of IBS based on a systematic review of the literature in 2017, and planned to revise these guidelines in light of new evidence on the pathophysiology, diagnosis, and management of IBS. The current revised version of the guidelines is consistent with the previous version and targets adults diagnosed with or suspected of having IBS. These guidelines were developed using a combination of de novo and adaptation methods, with analyses of existing guidelines and discussions within the committee, leading to the identification of key clinical questions. Finally, the guidelines consisted of 22 recommendations, including 3 concerning the definition and risk factors of IBS, 4 regarding diagnostic modalities and strategies, 2 regarding general management, and 13 regarding medical treatment. For each statement, the advantages, disadvantages, and precautions were thoroughly detailed. The modified Delphi method was used to achieve expert consensus to adopt the core recommendations of the guidelines. These guidelines serve as a reference for clinicians (including primary care physicians, general healthcare providers, medical students, residents, and other healthcare professionals) and patients, helping them to make informed decisions regarding IBS management.
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Key Words
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Introduction

Irritable bowel syndrome (IBS) is a chronic and sometimes disabling functional bowel disorder[1,2] characterized by recurrent abdominal pain associated with abnormal stool form or frequency.[3] According to the Rome IV criteria,[4] derived from a consensus process by a multinational group of experts in functional gastrointestinal (GI) disorders, IBS is diagnosed on the basis of recurrent abdominal pain related to defecation or in association with a change in stool frequency or form. It is a common functional GI disorder that has a substantial impact on quality of life and social functioning,[1,2] affecting approximately 10% of the general population worldwide,[5] and is reported to reduce quality of life and increase social costs.[6] The pathophysiology of IBS is only partially understood,[2] so various treatments including lifestyle modification, medication, and psychological therapies have been attempted to improve patients' symptoms and quality of life. However, therapies often focus on targeting only the most troublesome symptoms and are often unsatisfactory.[6] Under these circumstances, the need for evidence-based and systematic guidelines has emerged to reduce patient discomfort and alleviate the socioeconomic burden.

The Korean Society of Neurogastroenterology and Motility (KSNM) published the first version of the medical guidelines for IBS in 2005, named the "Evidence-based guidelines for diagnosis and treatment: diagnostic/therapeutic guidelines for irritable bowel syndrome,"[7,8] and the guidelines were revised twice in 2011[9] and 2017,[10] taking the form of an organized guideline and incorporating knowledge on novel therapeutics. Eight years after the previous guidelines, the KSNM planned to update the organized clinical practice guidelines to support physicians in providing qualified medical services and reducing the socioeconomic burden of IBS, since there have been significant advances in the definition, pathophysiology, and non-pharmacological and pharmacological management of IBS.

The revised version of the guidelines is consistent with the previous versions, and the literature search query used considered continuity with the previous guidelines. The primary target population was adult patients diagnosed with or suspected of having IBS. We focused on patients aged ≥ 18 with IBS, excluding children and individuals with specific conditions (such as bile acid-induced diarrhea). The guidelines cover the definition, epidemiology, and risk factors of IBS; the necessity and limitations of existing diagnostic modalities; and available treatment options, including lifestyle modifications, medications, and psychotherapy, along with their pros and cons. We included both the treatment methods currently available in Korea and those not yet applicable, considering their potential for future introduction. The aim was to facilitate the establishment of Korean guidelines based on an adaptation process. The present guidelines provide practical, evidence-based guidance to clinicians (gastroenterologists, surgeons, and general physicians), medical staff (nurses, paramedical teams, medical students, and healthcare providers), patients, and the public.

Methods

The working group for this effort consisted of 16 gastroenterologists from the Clinical Practice Guideline Committee and IBS research study group of the KSNM. Additionally, 2 psychologists recommended by the Korean Psychosomatic Society joined the working group to provide a multidisciplinary perspective on IBS treatment. These clinical practice guidelines were developed using evidence-based medicine methodology, and 2 ethodological experts (S.H.Y. and S.Y.L.) joined the working team. The development of these guidelines began in May 2023. These guidelines were developed using a combination of de novo and adaptation methods, in consideration of the current developments in IBS diagnosis and management. The adaptation method was used in the absence of differences in scientific evidence or in the presence of systematic reviews and meta-analyses. To educate and review the methodology

of guideline development, a methodology expert (M.C.) conducted 4 workshops on literature search, quality assessment, meta-analysis, recommendation grading, and levels of evidence. Twenty online meetings related to guideline development were conducted. The main processes related to the development of recommendations in these guidelines were as follows: (1) derivation of key questions tailored to the "population, intervention, comparator, and outcome" (PICO) format; (2) selection of appropriate search keywords; (3) systematic review (Preferred Reporting Items for Systematic Reviews and Meta-analyses plot); (4) quality assessment of the selected literature; (5) meta-analysis; (6) summarizing of evidence profiles based on the "grading of recommendations, assessment, development and evaluation" (GRADE) criteria; (7) determination of the quality of evidence and the strength of recommendation; and (8) expert consensus using e-mails and open discussion. To derive the key questions, the working team searched for existing guidelines from Korea and abroad, and selected topics for the diagnosis and management of IBS through discussions during guideline development meetings. The key questions were categorized according to the following aspects: definition and epidemiology, diagnosis, general management, and medical treatment. The team conducted a literature search and a meta-analysis. Two experts were assigned each key question. The key questions were selected using the nominal group technique in accordance with the PICO format.[11] Overall, 22 key questions were derived, and the possibility and necessity of guideline development was discussed and confirmed (Supplementary Table).

A literature search was conducted in the Ovid-MEDLINE, EMBASE, Cochrane Library, and KoreaMed databases using keywords for each key question, without limiting the search year. The search results were complemented by a manual search. The search was completed in September 2023. The process of selecting the final literature was performed by each guideline-working team, in which 2 members independently reviewed the first and second selections and exclusions to increase objectivity. The titles and abstracts of the articles were reviewed during the first selection, the original texts of the first selected articles were reviewed during the second selection, and the reasons for exclusion were recorded in cases of exclusion. Differences in opinions among the reviewers were resolved through consensus throughout the selection process. The common inclusion criteria were as follows: (1) studies on adult human participants or patients; (2) articles in English or Korean; (3) systematic reviews and meta-analyses, randomized controlled or non-randomized trials, and observational studies; (4) published until September 2023; and (5) studies with proper reporting of results. The common exclusion criteria were as follows: (1) studies that were not suitable for the target population, such as those involving children; (2) studies that did not report appropriate results; (3) studies for which the full text, other than the abstract, could not be accessed; and (4) case series and reports, expert opinions, narrative reviews, and guidelines. Meta-analysis was performed by Cochrane review manager (RevMan) version 5.4, and the quality assessment tools were selected based on the study design. Accordingly, systematic literature reviews were assessed using "A MeaSurement Tool to Assess Systematic Reviews", while randomized comparative clinical trials were assessed using the Cochrane's risk of bias 2.0 tool. Non-randomized studies were assessed using the "Risk Of Bias In Non-randomized Studies of Interventions" tool.[12] The quality assessment tools were selected based on the study design. Accordingly, systematic literature reviews were assessed using "A MeaSurement Tool to Assess Systematic Reviews", while randomized comparative clinical trials were assessed using the Cochrane's risk of bias tool. Non-randomized studies were assessed using the "Risk Of Bias In Non-randomized Studies of Interventions" tool.[12] For each key question, 2 or more working group members independently conducted a quality assessment of the final selected literature, and in case of a disagreement, a consensus was reached through discussions. To summarize the evidence, a meta-analysis was performed when quantitative synthesis was deemed possible, and qualitative synthesis was applied when heterogeneity was large or when meta-analysis was not deemed appropriate. The level of evidence was categorized into 4 levels (high, moderate, low, and very low) by assessing the study design and quality of evidence and considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence profiles were created based on the GRADE criteria. The recommendations were classified as "strong" or "weak" according to the level of evidence, clinical usefulness, and benefits and cautions (Table 1).[13] The modified Delphi method was used for expert consensus on draft recommendations based on the key questions. In the first round, a 72-expert panel agreed to participate and provided their responses via email. Each statement was rated on a scale of 1 to 5 (1 = strongly disagree, 2 = disagree, 3 = undecided, 4 = agree with reservation, and 5 = strongly agree). A score of 4-5 was considered an agreement, and a consensus was considered to have been reached if more than 80% of all responses agreed with a recommendation. In the first consensus, 16 of 22 recommendations were agreed upon; 6 recommendations did not reach an agreement of more than 80%. After the first email vote, the working group revised their recommendations for the 6 key questions. The second

Table 1. Definition of Levels of Evidence and Strength of Recommendation (Adapted From Andrews et al[13])

Level of evidence	
High	At least one RCT or SR/meta-analysis with no concerns regarding study quality
Moderate	At least one RCT or SR/meta-analysis with minor concerns regarding study quality or, at least one cohort/case-control/diagnostic test design study with no concerns regarding study quality
Low	Low At least one cohort/case-control/diagnostic test study with minor concerns regarding study quality, or at least one single arm before-after study or cross-sectional study with no concerns regarding study quality
Very low	At least one cohort/case-control/diagnostic test design study with serious concerns regarding study quality, or at least one single arm before-after study or cross-sectional study with minor/severe concerns regarding study quality
Grade of recommendation	
Strong for	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects
Weak for	Weak recommendations are offered when trade-offs are less certain, either because of low-quality evidence or because

RCT, randomized controlled trial; SR, systematic review.

round of voting by face-to-face agreement was held on October 25, 2024, for the revised recommendation. The recommendations for a positive diagnostic strategy, physical activity (PA), bulking agents, rifaximin, probiotics, and guanylate cyclase-C (GC-C) agonists were accepted with 100%, 94%, 100%, 93%, 87%, and 93% agreement, respectively. Finally, 22 recommendations were adopted (Table 2). Guideline development received budget support from the KSNM, but no separate financial support was received. Furthermore, financial support from the KSNM did not influence the decisions made during guideline development. All members of the working team who participated in guideline development declared any competing interests in writing. These guidelines will be uploaded to the KSNM websites and will also be published in Korean. Finally, these guidelines will be updated every 3-5 years to account for the accumulation of new evidence.

To help primary care physicians understand the standard management of IBS, the Guideline Development Committee suggested a clinical algorithm for IBS diagnosis (Fig. 1) and treatment (Fig. 2). In summary, IBS-focused history taking should be conducted first, followed by a physical examination and basic laboratory tests for patients with suspected IBS symptoms. Appropriate tests and treatments should be performed for patients with suspected organic diseases. Colonoscopy is recommended for patients presenting with alarming symptoms such as hematochezia, nocturnal diarrhea, unexplained weight loss, or iron deficiency anemia, as well as for those with a family history of GI malignancies, including colorectal cancer, those who have not received appropriate colorectal cancer screening, and for those with new-onset IBS symptoms who have never undergone a colonoscopy. For patients who do not fall into these categories or those with normal colonoscopy results, IBS would be positively diagnosed, and the initiation of treatment is recommended. The treatment of IBS initially recommends general management such as lifestyle and dietary modifications. Subsequently, pharmacological treatments targeting the main symptoms, such as abdominal pain, diarrhea, and constipation, can be attempted. If symptoms do not improve with conventional drug therapy or if the patient has accompanying psychiatric symptoms, the addition of psychotropic drugs, gut-directed psychotherapy, and a work-up including colonoscopy is recommended. Notably, this algorithm is only a general proposal, and there is no legal or medical basis for following it.

Definition and Risk Factors

Definition

Statement 1. Irritable bowel syndrome is defined as a chronic condition characterized by recurrent abdominal pain or discomfort associated with changes in bowel habits.

- Level of evidence: not applicable
- Strength of recommendation: not applicable
- Expert opinion: strongly agree, 80.6%; agree with reservation, 19.4%; undecided, 0.0%; disagree, 0.0%; and strongly disagree, 0.0%.

Table 2. Summary of the Seoul Consensus on Irritable Bowel Syndrome

Statements	Considerations	Level of evidence	Strength of recommendation
Definition and risk factors			
1. IBS is defined as a chronic condition characterized by recurrent abdominal pain or discomfort associated with changes in bowel habits.	• IBS is diagnosed based on a history of chronic recurrent abdominal pain associated with defecation and changes in stool form or frequency. • If alarm signs are present, it is crucial to proceed with further evaluations, including colonoscopy, to rule out organic diseases. • IBS subtypes are classified as IBS-C, IBS-D, IBS-M, or IBS-U based on the dominant form of the Bristol Stool Form Scale.	N/A	N/A
2. Refractory IBS is defined as a case in which the patient's symptoms are not relieved by conventional interventions, necessitating a more specialized, multidisciplinary approach.	• There is a lack of universally accepted and clear definitions for refractory IBS. • Patients with refractory IBS require a multidisciplinary approach. • Some studies define refractory IBS as symptoms persisting for 6 to 12 months without significant improvement.	N/A	N/A
3. The onset and severity of IBS is influenced by genetic, environmental, psychological, and lifestyle factors.	• A comprehensive patient history should be obtained to identify potential risk factors such as previous GI infections, psychological stress, and a family history of IBS. • Psychological health assessments including screening for depression and anxiety, which can exacerbate IBS symptoms, are important.	Moderate	Weak
Diagnosis			
4. Colonoscopy is recommended for patients with IBS who exhibit alarming features or those who have not undergone appropriate colon cancer screening.	• Routine colonoscopy is not recommended for all patients with IBS. • Patients with new-onset IBS symptoms who have not undergone appropriate colon cancer screening are advised to undergo the procedure. • Colonoscopy should be considered for patients with alarming symptoms such as hematochezia, nocturnal diarrhea, unexplained weight loss, iron deficiency anemia, or a family history of colorectal cancer or other gastrointestinal malignancies. • Colonoscopy is indicated in patients who do not respond to conventional IBS treatments.	Moderate	Strong
5. Laboratory tests are useful for differentiating IBS from organic diseases in patients with alarming features.	• Erythrocyte sedimentation rate, C-reactive protein levels, and fecal calprotectin levels can be used to differentiate IBS-D from IBD. • Routine testing for enteric pathogens and fecal occult blood is not recommended.	Moderate	Strong
6. Anorectal manometry can be considered for patients with IBS who are expected to have concurrent defecatory disorders.	• Anorectal manometry can be considered for patients with abnormal rectal examinations suggestive of anorectal dysfunction, to identify those who might benefit from biofeedback therapy. • Intestinal motility tests are not routinely recommended in patients with IBS. However, they may be considered for patients suspected of having chronic intestinal pseudo-obstruction.	Very low	Weak
7. In patients with typical IBS symptoms, a positive diagnostic strategy and empirical treatment are a viable option in terms of cost-effectiveness compared to an exclusion strategy.	• In an RCT comparing positive and exclusion diagnoses, there were negligible numbers of patients diagnosed with organic bowel disease in both the groups. • Nevertheless, according to a survey, most community providers believe that IBS is a diagnosis of exclusion. • An RCT comparing positive and exclusion strategies showed that the positive diagnosis group had nearly 40% lower overall healthcare costs. • A positive diagnostic strategy compared to an exclusive diagnostic strategy can initiate empiric treatment as soon as possible and reduce unnecessary diagnostic tests.	Moderate	Strong

Table 2. Continued 1

Statements	Considerations	Level of evidence	Strength of recommendation
General management			
8. A low FODMAP diet is effective in improving the overall symptoms of IBS.	• A low FODMAP diet improves global IBS symptoms, bloating, and bowel habits. Additionally, it can improve patients' quality of life. • The low FODMAP diet comprises 3 phases. The initial "elimination" phase is followed by a "reintroduction" phase and a subsequent long-term "personalization" phase. • Since most studies have involved dieticians, their participation is encouraged. If dietitians are unavailable, high-quality teaching materials should be used. • A restrictive diet based on Immunoglobulin G antibodies or one that contains starch, sucrose, and gluten, can alleviate symptoms of IBS. However, owing to insufficient evidence, it is not recommended as first-line therapy.	Low	Weak
9. Appropriate exercise can help improve the overall symptoms of patients with IBS.	• Although there is limited evidence, appropriate instructions are needed for the type and intensity of exercise, and slow, low intensity exercise such as walking, yoga, and cycling is recommended over hard, strenuous exercise.	Low	Weak
Medical Treatment			
10. Soluble fibers may help improve overall symptoms in patients with IBS.	• There is no evidence that insoluble fiber improves IBS symptoms.	Moderate	Weak
11. PEG laxatives can improve stool frequency and consistency in patients with IBS-C.	• The effectiveness of PEG laxatives in treating abdominal pain in patients with IBS-C remains unclear. • Among osmotic laxatives, lactulose is inadequate for treating IBS-C because its fermentation in the gut can worsen bloating and gas distension.	Low	Weak
12. Antispasmodics can be effective in alleviating global symptoms and abdominal pain in patients with IBS.	• Dry mouth, dizziness, and blurred vision are the most common side effects.	Low	Weak
13. Loperamide may be effective in improving stool frequency and consistency in patients with IBS-D.	• Loperamide should be used with careful titration of the dosage and duration owing to possible side effects, such as severe constipation, abdominal pain, bloating, and nausea.	Very low	Weak
14. Serotonin subtype 3 receptor antagonists are effective in alleviating global IBS symptoms, relieving abdominal pain/discomfort, and improving abnormal bowel habit/stool consistency in patients with IBS-D.	• In a meta-analysis of IBS-D, serotonin subtype 3 receptor antagonists were effective in alleviating global IBS symptoms, relieving abdominal pain/discomfort, and improving abnormal bowel habits/consistency compared to a placebo. • Ramosetron is approved for use in Korea and Japan. Alosetron has only been approved in the United States and is proposed by the American College of Gastroenterology as a second-line drug for women with severe IBS-D symptoms. Ondansetron has not yet been approved for treating IBS.	High	Weak
15. Serotonin subtype 4 receptor agonists may improve stool consistency, abdominal pain/bloating, and the health-related quality of life in patients with IBS-C, whose bowel symptoms are refractory to simple laxatives.	• Tegaserod is the only United States FDA-approved serotonin subtype 4 receptor agonist for the treatment of adult women younger than 65 years with IBS-C. However, it is unavailable in Asian countries. • Prucalopride may improve stool consistency in patients with constipation-dominant IBS whose bowel symptoms are refractory to simple laxatives, although no RCTs on IBS-C are available.	Low	Weak
16. The non-absorbable antibiotic, rifaximin, is effective in improving global symptoms and stool consistency in patients with IBS-D.	• Rifaximin effectively improved the FDA recommended composite endpoint of abdominal pain and stool consistency in patients with IBS-D. • In patients with IBS-D with an initial response to rifaximin who developed recurrent symptoms, retreatment with rifaximin with the same dosage regimen was associated with a greater durable response and prevention of symptom recurrence. • The drug is licensed for IBS-D in the USA; however, it is unavailable for this indication in many other countries.	Moderate	Weak

Table 2. Continued 2

Statements	Considerations	Level of evidence	Strength of recommendation
17. Probiotics may help improve overall IBS symptoms, including abdominal pain and bloating, in patients with IBS.	• Probiotics may alleviate IBS symptoms by modulating the gut microbiota and improving gut barrier integrity. • Owing to the variability in study designs and probiotic strains, specific recommendations for strains or species cannot be made.	Very low	Weak
18. TCAs effectively treat global symptoms and abdominal pain in patients with IBS.	• TCAs modulate pain perception and may influence gut function, typically at doses lower than those used to treat depression to reduce side effects. • TCAs are particularly beneficial for patients with IBS with predominant abdominal pain and are generally preferred for IBS-D cases due to their potential side effect of constipation.	Low	Weak
19. SSRIs may help alleviate IBS symptoms.	• There is insufficient evidence regarding the effectiveness of SSRIs in patients with IBS. • SSRIs may be useful for patients with concurrent mood disorders or for those who are unresponsive to other treatments. • SSRIs can be considered for both IBS-C and IBS-D; however, they are generally preferred for treating IBS-C because of the potential side effect of diarrhea.	Very low	Weak
20. Lubiprostone is effective for abdominal pain and abdominal bloating in patients with IBS-C.	• In a meta-analysis of IBS-C, lubiprostone reduced abdominal pain and bloating compared to placebo. • It is recommended that lubiprostone should be consumed along with meals to prevent nausea, which is its most common side effect.	Moderate	Weak
21. GC-C agonists are effective in improving abdominal pain and bowel movement in patients with IBS-C.	• Linaclotide and plecanatide are GC-C agonists with proven efficacy compared to placebo in patients with IBS-C. • The most common adverse event observed was diarrhea, but no serious adverse events were reported in previous trials. • To date, GC-C agonists, both linaclotide and plecanatide, are not available in Korea.	High	Strong
22. GDH may be effective for treating global symptoms in patients with IBS who are unresponsive to conventional medical therapy.	• Referral can be made in patients with refractory IBS who have moderate to severe symptoms, for whom conventional treatment is not effective, or whose symptoms persist for over 12 months.	Low	Weak

IBS, irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; IBS-U, IBS-unclassified; NA, not applicable; GI, gastrointestinal; RCT, randomized controlled trial; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; PEG, polyethylene glycol; FDA, Food and Drug Administration; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; GC-C, guanylate cyclase C; GDH, gut-directed psychotherapies.

Considerations

- IBS is diagnosed based on a history of chronic recurrent abdominal pain associated with defecation and changes in stool form or frequency.
- If alarm signs are present, it is crucial to proceed with further evaluations, including colonoscopy, to rule out organic diseases.
- IBS subtypes are classified as IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), or IBS-unclassified (IBS-U) based on the dominant form of the Bristol stool form scale.

IBS is a common gut-brain interaction disorder with no evidence of organic GI disease. IBS can negatively affect patients' quality of life and productivity. The prevalence of IBS is reportedly 11.2%, and the incidence of IBS is estimated to be between 1.35% and 1.5%.[1] Women and younger people are more likely to be affected than men and older people.[14] IBS can have a negative impact on quality of life, increase economic burden, decrease social productivity, and increase the risk of psychosocial disorders.[15] To confirm the diagnosis of IBS, organic lesions must be ruled out from relevant studies; thus, alarming features (eg, blood in stools, unintended weight loss, awakened by GI symptoms, family history of colon cancer, symptom onset after age 50, and antibiotic use) suggest further evaluation including colonoscopy.[10,16,17]

The diagnosis of IBS begins with careful history-taking. The diagnostic criteria of IBS are as follows (revised from the Rome IV

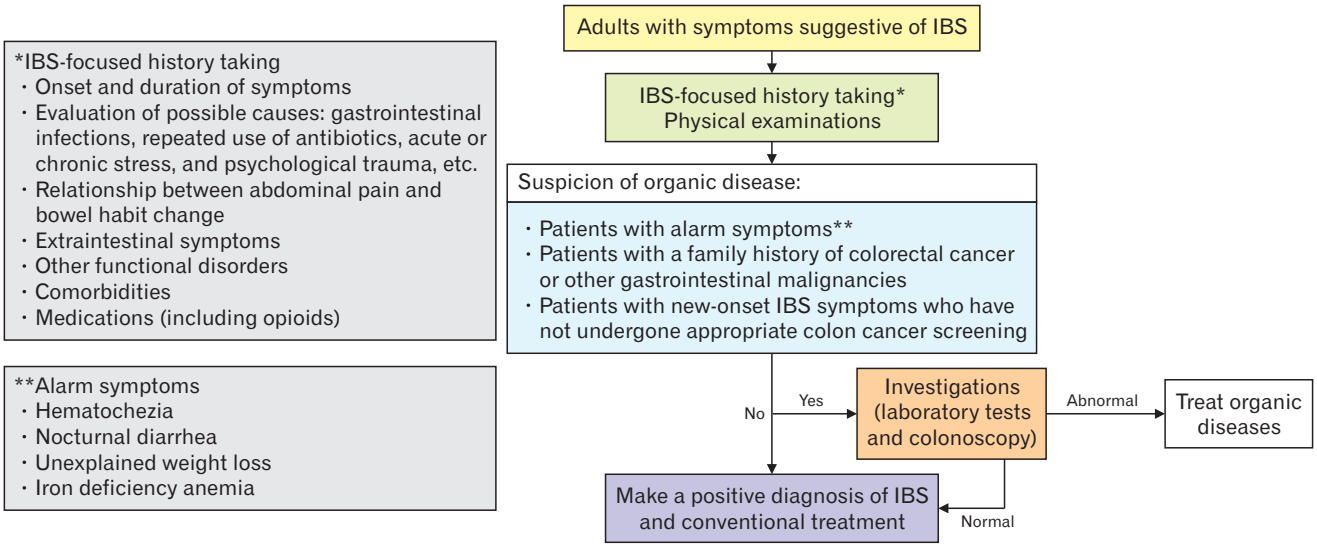


Figure 1. Suggested diagnostic algorithm for irritable bowel syndrome (IBS).

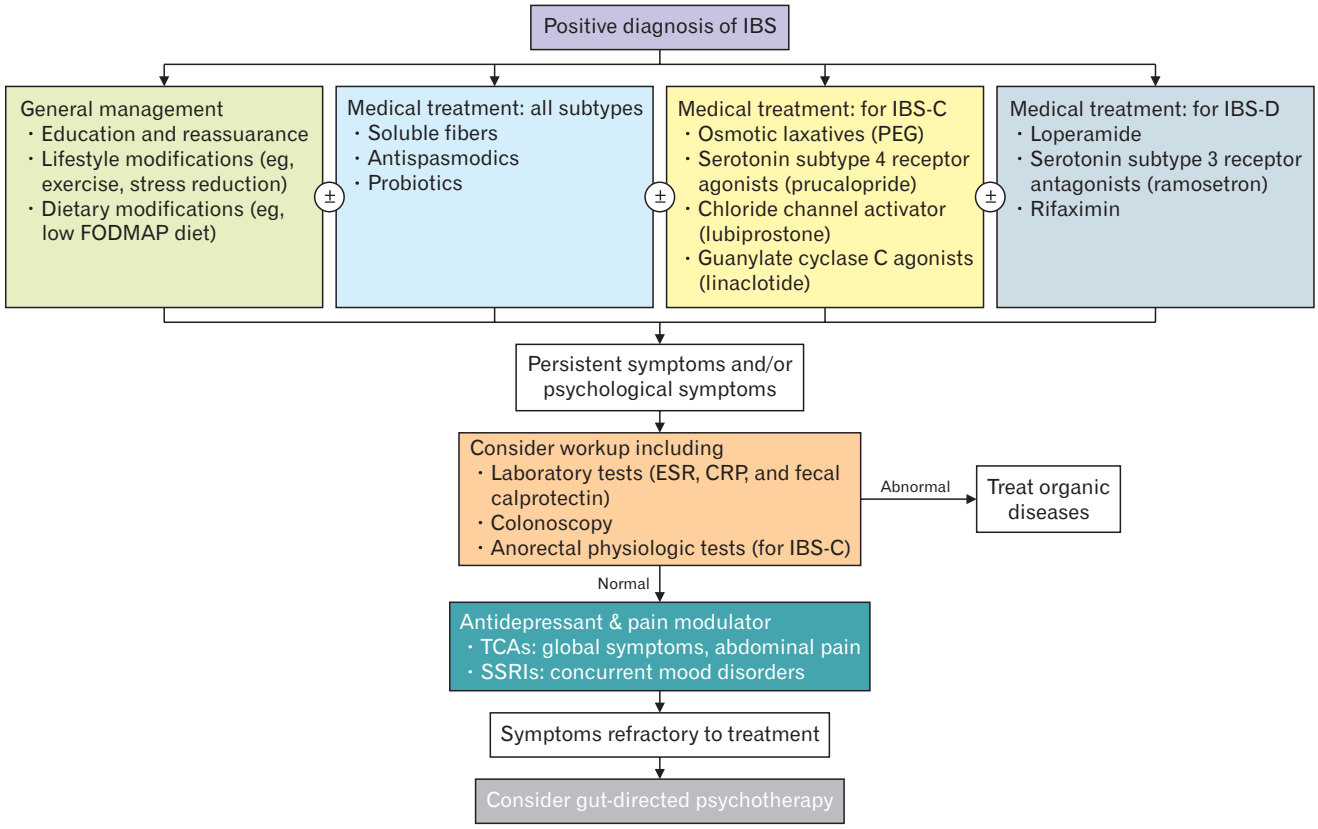


Figure 2. Suggested therapeutic algorithm for irritable bowel syndrome (IBS). FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-C, IBS with predominant constipation; PEG, polyethylene glycol; IBS-D, IBS with predominant diarrhea; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TCAs, tricyclic antidepressants.

criteria for practical application in clinical practice):[1]

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, with symptom onset at least 6 months before diagnosis, associated with 2 or more of the following criteria: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool

Abdominal pain is an essential symptom in the diagnosis of IBS. IBS subtypes are classified according to predominant bowel habit patterns. The Bristol stool form is used to classify the subtypes of IBS.[1] IBS with predominant constipation (IBS-C) refers to > 25% bowel movement with Bristol stool form type 1 or 2 and < 25% bowel movement with Bristol stool form type 6 or 7. IBS with predominant diarrhea (IBS-D) refers to > 25% bowel movement with Bristol stool form type 6 or 7 and < 25% bowel movement with Bristol stool form type 1 or 2. IBS with mixed bowel habits (IBS-M) refers to both Bristol stool forms: type 1 or 2 and type 6 or 7. IBS-unclassified (IBS-U) refers to a subtype which is unsuitable for IBS-C, IBS-D, or IBS-M. Among these, IBS-D is the most common subtype possessing 30-40% of all inflammatory bowel disease (IBD) cases.[15]

Statement 2. Refractory irritable bowel syndrome is defined as a case in which the patient's symptoms are not relieved by conventional interventions, necessitating a more specialized, multidisciplinary approach.

- Level of evidence: not applicable
- Strength of recommendation: not applicable
- Expert opinion: strongly agree, 51.4%; agree with reservation, 43.0%; undecided, 4.2%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- There is a lack of universally accepted and clear definitions for refractory IBS.
- Patients with refractory IBS require a multidisciplinary approach.
- Some studies define refractory IBS as symptoms persisting for 6 months to 12 months without significant improvement.

Refractory IBS lacks a universally accepted definition but is commonly characterized as a subgroup of patients whose IBS symptoms persist despite undergoing conventional treatments. Some studies have focused on the duration of symptoms, defining refractory IBS as symptoms lasting for at least 6[18,19] to 12 months or more,[20-22] whereas others have defined it based on the failure of specific treatments. This includes patients who do not experience symptom relief after dietary interventions,[23,24] lifestyle changes,[25] pharmacological treatments,[22,26,27] or psychological therapies.[20,26] Some studies have defined refractory IBS by focusing on the severity of symptoms, specifically moderate-to-severe symptoms.[26,28] The variability in the definition of refractory IBS necessitates a clearer and more consistent definition to enhance the comparability of research findings and improve patient care.[29] Effective management of refractory IBS requires a multidisciplinary approach that integrates dietary, pharmacological, and psychological interventions.

Risk Factors

Statement 3. The onset and severity of irritable bowel syndrome is influenced by genetic, environmental, psychological, and lifestyle factors.

- Level of evidence: moderate
- Strength of recommendation: weak
- Expert opinion: strongly agree, 70.8%; agree with reservation, 25.0%; undecided, 4.2%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- A comprehensive patient history should be obtained to identify potential risk factors such as previous GI infections, psychological stress, and a family history of IBS.
- Psychological health assessments including screening for depression and anxiety

The risk factors for IBS include infection, stress, alterations in the gut microbiota, neurotransmitters, endocrine substances, psychological disorders, and genetic factors. Post-infectious IBS occurs in approximately 10% of patients with infectious enteritis.[30] The prevalence of post-infectious IBS is 6-7 times higher in patients with prior infection than that in those without prior infection.[31] Stress is a major risk factor for IBS, with stress-related psychological disorders (such as depression and anxiety) exacerbating IBS symptoms. IBS patients have a stronger correlation between perceived stress and worsening GI symptoms than healthy controls.[32,33]

Changes in gut microbiota, increased mucosal permeability, and low-grade inflammation also play important roles in IBS.[34] IBS patients tend to have decreased levels of *Bifidobacterium* and *Faecalibacterium* and increased levels of *Lactobacillus*, *Bacteroi-*

des, and Enterobacteriaceae.[35] Additionally, IBS patients exhibit increased mucosal permeability[36] and low-grade inflammation,[31,34,37] which can sensitize neurons that transmit signals from the gut to the central nervous system, thereby worsening IBS symptoms.

Neurotransmitters and endocrine substances are crucial in the pathophysiology of IBS. Serotonin (5-hydroxytryptamine, 5-HT)[38-40] and corticotropin-releasing hormone[41,42] play significant roles in both the gut and brain. Imbalances in the levels of these substances are observed in IBS patients, contributing to their symptoms. Psychological disorders are also closely associated with the development of IBS. Depression, anxiety, and somatization can aggravate IBS symptoms. Research has indicated that initial depressive or anxiety disorders are risk factors for the onset of IBS, whereas IBS and functional dyspepsia are risk factors for the new onset of depressive or anxiety disorders.[43,44] These findings suggest a bidirectional brain–gut and gut–brain connection. In addition, emotional stress is significantly associated with the exacerbation of IBS symptoms, affecting GI motility and increasing symptom severity through altered brain–gut interactions.[45,46] Additionally, childhood abuse, including physical, emotional, and sexual abuse, is strongly linked to the development of IBS in adulthood, likely because of its lasting impact on stress-related physiological pathways and the brain–gut axis.[47,48]

Genetic factors are known risk factors for IBS. Twin studies involving 6060 pairs showed IBS concordance rates of 8.4% in dizygotic twins and 17.2% in monozygotic twins,[49] highlighting the genetic predisposition to IBS. These risk factors can contribute individually or collectively to the development and exacerbation of IBS symptoms.

Diagnosis

Colonoscopy

Statement 4. Colonoscopy is recommended for patients with irritable bowel syndrome who exhibit alarming features or those who have not undergone appropriate colon cancer screening.

- Level of evidence: moderate
- Strength of recommendation: strong
- Expert opinion: strongly agree, 79.2%; agree with reservation, 20.8%; undecided, 0.0%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- Routine colonoscopy is not recommended for all patients with IBS.
- Patients with new-onset IBS symptoms who have not undergone appropriate colon cancer screening are advised to undergo the procedure.
- Colonoscopy should be considered for patients with alarming symptoms such as hematochezia, nocturnal diarrhea, unexplained weight loss, iron deficiency anemia, or a family history of colorectal cancer or other GI malignancies.
- Colonoscopy is indicated in patients who do not respond to conventional IBS treatments.

The diagnosis of IBS should primarily rely on symptom-based criteria, such as the Rome IV criteria, supported by a comprehensive patient history and physical examination.[1] This method emphasizes the significance of clinical symptoms, where a combination of symptoms and negative alarm features provides a high predictive value for diagnosing IBS.[50] Routine colonoscopy is not recommended solely based on typical IBS symptoms like abdominal pain, diarrhea, or constipation, as the overall diagnostic yield in such cases is low.[51,52] Studies have shown that common findings during colonoscopy, such as hemorrhoids and diverticulosis, are not typically responsible for IBS symptoms.[51,53] Therefore, avoiding unnecessary invasive procedures helps to reduce healthcare costs and minimize the health burden on patients, including preparation morbidity, sedation-related effects, and financial costs.

When considering a colonoscopy, it is crucial to assess key patient characteristics known as "alarm features". These include hematochezia, melena, unintentional weight loss, older age at symptom onset, and a family history of IBD, colon cancer, or other significant GI diseases.[51,54-57] The presence of these features raises concerns about potential pathological conditions that might explain the patient's symptoms, and colonoscopy plays a critical role in differentiating IBS from other organic diseases such as colorectal cancer, IBD, and microscopic colitis.[53,54,58] Patients aged ≥ 50 years with new-onset IBS symptoms or significant changes in bowel habits should undergo colonoscopy to screen for colorectal cancer and other organic diseases that are more prevalent in this age group. In addition, colonoscopy is indicated for patients who do not respond to standard IBS treatments, suggesting the possibility of an alternative diagnosis. A recent meta-analysis identified that 2.5% of patients with microscopic colitis met the Rome criteria for IBS-D, whereas others met the Rome criteria for functional diarrhea.[58] For patients experiencing chronic diarrhea, obtaining biopsies from

various segments of the colon may be necessary to exclude the possibility of microscopic colitis.[57]

Western guidelines advise against routine colonoscopy in IBS patients aged < 50 years who do not present with alarming features.[16,17,59] They recommend colonoscopy for IBS patients over 50 years as part of colorectal cancer screening programs and for those with alarming features. In conclusion, a careful approach in deciding whether to conduct colonoscopy in IBS patients ensures accurate diagnosis and appropriate management. This approach aims to distinguish IBS from other GI diseases that may present similarly, thereby facilitating accurate diagnosis and appropriate management.

Laboratory Tests

Statement 5. Laboratory tests are useful for differentiating irritable bowel syndrome from other organic diseases in patients with alarming features.

- Level of evidence: moderate
- Strength of recommendation: strong
- Expert opinion: strongly agree, 40.3%; agree with reservation, 44.4%; undecided, 9.7%; disagree, 2.8%; and strongly disagree, 2.8%.

Considerations

- Erythrocyte sedimentation rate, C-reactive protein levels, and fecal calprotectin levels can be used to differentiate IBS-D from IBD.
- Routine testing for enteric pathogens and fecal occult blood is not recommended.

The diagnosis of IBS is mainly symptom-based, and laboratory tests do not have sufficient diagnostic accuracy to identify it.[60] However, laboratory tests can differentiate IBS from other organic diseases such as celiac disease, IBD, and microscopic colitis.[1] This strategy is particularly useful in patients with alarming features including hematochezia, melena, unintentional weight loss, older age of onset of symptoms, family history of IBD, colon cancer, or other significant GI disease, as mentioned previously.[54] In recent Western guidelines, the significance of laboratory tests for differentiating between IBS and celiac disease has particularly been emphasized.[16,17,59] However, tests for diagnosing celiac disease are underutilized,[61] since the prevalence of celiac disease is known to be much lower in Asia, including Korea, than in Western countries.[62] In the case of IBD, its incidence and prevalence are on the rise,[63] and it is difficult to distinguish IBS-D from IBD based on symptoms alone.[64] The pretest probability of IBD in IBS patients is reported to be approximately 0.5%-1.2%,[55,65] and the probability of IBD in patients with symptoms for more than 5 years is 2.6-5 times higher that of those who do not have the symptoms.[66,67]

Among the blood tests, erythrocyte sedimentation rate and C-reactive protein are commonly used tests.[68,69] C-reactive protein level ≤ 0.5 mg/dL essentially excludes IBD in patients with diarrheal symptoms with a 1% or lower likelihood.[70] Stool tests are superior to serologic tests, with better diagnostic accuracy in discriminating IBD from IBS, although there are some inconveniences.[71-74] Among them, lactoferrin[75,76] and calprotectin[77-79] are available and are useful as markers of intestinal inflammation. Fecal calprotectin is widely used with high sensitivity and specificity for detecting IBD.[76,77] In general, a cutoff value of < 50 mg/g for normal and > 100 mg/g is considered to suggest inflammation. In a recent meta-analysis, a cutoff of < 50 mg/g was found to be optimal, providing the highest sensitivity, specificity, and positive and negative likelihood ratios.[71] The aforementioned study additionally reported that the probability of having IBD was < 1% in subjects with calprotectin level ≤ 40 μg/g.[70] Notably, calprotectin is not a specific marker for IBD and can be elevated in older age groups (age ≥ 45 years) and in those with obesity, infection, malignancy, or by medications, such as proton pump inhibitors or non-steroidal anti-inflammatory drugs.[17]

IBS can arise within months following bacterial, viral, and parasitic GI infections, as the reported risk is 3.5-4.2 times higher in exposed individuals compared to non-exposed individuals,[80-82] although the prevalence of post-infectious IBS varies.[83] Nevertheless, gastroenteritis is generally self-limiting,[84] so testing and treating these infections cannot prevent the development of IBS. Antibiotic exposure is a known risk factor of post-infectious IBS. From this point of view, routine testing for enteric pathogens is not routinely recommended[84] and may be considered for patients with chronic diarrhea who live or have traveled to developing countries.[85] Fecal occult blood or fecal immunochemical testing is not routinely recommended for assessing IBS patients.[86]

Physiologic Tests

Statement 6. Anorectal manometry can be considered for patients with irritable bowel syndrome who are expected to have concurrent defecatory disorder.

- Level of evidence: very low

- Strength of recommendation: weak
- Expert opinion: strongly agree, 27.8%; agree with reservation, 55.5%; undecided, 13.9%; disagree, 2.8%; and strongly disagree, 0.0%.

Considerations

- Anorectal manometry can be considered for patients with abnormal rectal examinations suggestive of anorectal dysfunction to identify those who might benefit from biofeedback therapy.
- Intestinal motility tests are not routinely recommended in patients with IBS. However, they may be considered for patients suspected of having chronic intestinal pseudo-obstruction.

Anorectal dysfunction can accompany all subtypes of IBS (IBS-D, IBS-C, and IBS-M) with estimated prevalence rates as high as 40% in tertiary care practices, since IBS is a multifactorial disorder.[87-90] For instance, dyssynergic defecation (DD) was more frequent in all subgroups (41%) of IBS and both sexes than in healthy controls.[89] As symptoms alone cannot accurately distinguish IBS from DD, accurate diagnosis of DD requires physiological testing such as anorectal manometry, balloon expulsion test, and/or defecography.[91] To date, these studies have not been performed in most patients because of the limited availability and absence of definitive guidelines. However, it may be beneficial to rule out DD in patients with suspected pelvic floor dysfunction by screening subjects for biofeedback and predicting treatment effectiveness.[92-94] The effectiveness of biofeedback treatment in improving both pain and bowel symptoms was proven in a prospective study.[92] In this study, higher rectal sensory thresholds, constipation severity scores, and delayed colonic transit pretreatment were identified as indicators of poor treatment outcomes. Another study reported that biofeedback improved the Patient Assessment of Constipation Symptoms scores by 48%, including abdominal pain and bloating.[94] Although anorectal physiology testing alone may not differentiate DD from IBS, it helps identifying subjects who may be benefit from biofeedback therapy. Anorectal physiology testing, including anorectal manometry, balloon expulsion test, and/or defecography, should be considered in patients with abnormal rectal examinations suggesting dyssynergia or in those who are refractory to medical treatments.

Colonic transit is abnormal in 10-20% of patients with IBS-C and IBS-M and 25-45% of patients with IBS-D.[95,96] However, patients with normal transit can still have abnormal fasting and postprandial motility.[97] Patients with IBS-C display reduced motility, whereas those with IBS-D show increased motility and accelerated transit.[98] In previous studies of IBS patients evaluating total and segmental colonic transit time, stool form and frequency as assessed by the Bristol stool scale correlated well with total colonic transit time,[96] but symptoms such as abdominal pain, bloating, and flatulence did not correlate well with colonic transit.[96,99] Summarizing those results, intestinal motility tests are not routinely recommended and would be considered in selected patients with chronic intestinal pseudoobstruction or with the suspicion of intestinal motility disorders as the cause of diarrhea.

Diagnostic Strategy

Statement 7. In patients with typical irritable bowel syndrome symptoms, a positive diagnostic strategy and empirical treatment are a viable option in terms of cost-effectiveness compared to an exclusion strategy.

- Level of evidence: moderate
- Strength of recommendation: strong
- Expert opinion: strongly agree, 42.9%; agree with reservation, 57.1%; undecided, 0.0%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- In an randomized controlled trial (RCT) comparing positive and exclusion diagnoses, there were negligible numbers of patients diagnosed with organic bowel disease in both the groups.
- Nevertheless, according to a survey, most community providers believe that IBS is a diagnosis of exclusion.
- An RCT comparing positive and exclusion strategies showed that the positive diagnosis group had nearly 40% lower overall healthcare costs.
- A positive diagnostic strategy compared to an exclusive diagnostic strategy can initiate empiric treatment as soon as possible and reduce unnecessary diagnostic tests.

Since the diagnosis of IBS relies on symptom-based criteria, many clinicians are concerned about overlooking organic diseases. In a RCT of positive diagnosis versus exclusion diagnosis, there were negligible and comparable numbers of patients diagnosed with organic bowel disease in the 2 groups.[100] Nevertheless, according to a survey, most community providers believe that IBS is a diagnosis of exclusion; this belief is associated with increased resource use.[101]

The American Gastroenterology College (recommends initiation of empirical treatment as soon as possible to reduce unnecessary diagnostic tests. This aligns with the positive diagnostic strategy, which improves cost-effectiveness, rather than extensive exclusionary testing.[17] Additionally, British guidelines strongly recommend

that clinicians should make a positive diagnosis of IBS based on symptoms, in the absence of alarm symptoms or signs, and abnormalities on simple blood and stool tests.[16] In the European Society of Neurogastroenterology and Motility (ESNM) guidelines on functional bowel disorders with diarrhea, the ESNM recommends a symptom-based approach compared to a diagnostic strategy of exclusion; however, minimal diagnostic assessment is mandatory due to the multitude of conditions causing chronic diarrhoea.[102]

A positive diagnostic strategy for IBS is more cost-effective than an exclusive one. In a head-to-head randomized study comparing a positive diagnosis strategy to an exclusion strategy in a primary care setting, the positive diagnosis group had nearly 40% lower overall healthcare costs ($3160 per year vs $5075 per year). This significant cost difference demonstrates the economic advantage of the positive diagnostic approach.[103] This strategy not only reduces costs but also maintains the quality of care. There were no differences in GI symptoms, patient satisfaction, or health-related quality of life between the 2 groups. This indicates that cost savings do not occur at the expense of patient outcomes.

Physicians who view IBS as an exclusionary diagnosis are likely to order 1.6 more tests and spend $364 more than those who do not. This additional testing and cost associated with the exclusionary approach further supports the cost-effectiveness of the positive diagnostic strategy.[101] In low- and middle-income countries, a positive diagnostic approach with proven cost-effectiveness is the best option for diagnosing IBS patients.[104] The positive diagnostic strategy is based on symptom-based criteria; therefore, this approach allows for quicker diagnosis and treatment initiation, potentially reducing the overall cost of care.

In conclusion, evidence strongly suggests that a positive diagnostic strategy is more cost-effective than an exclusive diagnostic strategy for IBS. It reduces overall healthcare costs, maintains quality of care, allows for earlier treatment initiation, and decreases the number of unnecessary tests and procedures.

Management

Lifestyle Modification

Statement 8. A low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet is effective in improving the overall symptoms of irritable bowel syndrome.

- Level of evidence: low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 22.2%; agree with reservation, 61.1%; undecided, 16.7%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- A low FODMAP diet improves global IBS symptoms, bloating, and bowel habits. Additionally, it can improve patients' quality of life.
- The low FODMAP diet comprises 3 phases. The initial "elimination" phase is followed by a "reintroduction" phase and a subsequent long-term "personalization" phase.
- Since most studies have involved dieticians, their participation is encouraged. If dietitians are unavailable, high-quality teaching materials should be used.
- A restrictive diet based on IgG antibodies or one that contains starch, sucrose, and gluten can alleviate IBS symptoms. However, owing to insufficient evidence, it is not recommended as first-line therapy.

Over 80% of IBS patients report food-related symptoms, and in one survey, more than 60% of patients made dietary changes to manage IBS.[105,106] Consequently, there has been renewed interest in dietary therapy as a treatment option. One of the most widely accepted approaches is a diet that is low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) (Table 3). FODMAPs include short-chain carbohydrates that can be fermented by intestinal bacteria, and they can increase the osmotic pressure in the intestinal tract, changing the pattern of bowel movements or producing gas, which can worsen the symptoms of patients with IBS.[107] We identified 14 RCTs comparing a low FODMAP diet with various dietary control interventions, including habitual diet, high FODMAP diet, traditional dietary advice as recommended by the National Institute for Health and Care Excellence guidelines (NICE) and British dietetic association, or a sham diet.[108-121] The low FODMAP diet was associated with a significant higher symptom improvement than all the control interventions (risk ratio [RR] 1.51; 95% confidence interval [CI], 1.26-1.80) (Fig. 3A). The low FODMAP diet was associated with a significant reduction in IBS-SSS compared with the different comparators (mean difference −66.2; 95% CI, −81.62-−50.77) (Fig. 3B). The low FODMAP diet was also associated with decreased bloating, decreased stool frequency, and improved stool consistency. No serious adverse events were reported in the low FODMAP diet group in 14 RCTs. A decrease in some micronutrients such as calcium, iron, and magnesium was reported in 2 studies.[110,121]

Table 3. Foods With High Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols Contents

Food	Oligosaccharides	Disaccharides	Monosaccharides	Polyols
Sauce	Chicory drinks, Ketchup, Cream pasta source, Tomato-based pasta sauce, Energy bar, Strawberry jam, Kimchi, Doenjang, Gochujang, Ssamjang, Dumpling, Dimsum, Tom-yum soup, Thai curry paste		Honey, High-fructose corn syrup	
Food additives	Inulin, Wasabi powder, FOS			Sorbitol, Mannitol, Maltitiol, Xylitol, Isomalt
Fruits	Peach, Persimmon, Watermelon		Apple, Cherry, Mango, Pear, Watermelon	Apple, Pear, Prune, Cherry, Blackberries, Apricot, Avocado, Nectarine, Plum
Vegetables	Garlic, Leek, Onion, Peas, Beetroot, Brussels Sprout, Chicory, Fennel, Artichokes		Asparagus, Artichokes, Sugar snap peas, Pickled onion	Mushroom, White cabbage, Cauliflower, Snow peas
Milk and milk products		Milk, Yogurt, Ice cream, Custard, Soft cheeses		
Grains and cereals	Wheat, Rye, Barley			
Nuts and seeds	Almonds, Pistachios			
Legumes	Legumes, Chickpeas, Lentils			

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FOS, fructooligosaccharides.

The low FODMAP diet can have unintended effects on the gut microbiota. A meta-analysis on the effect of the low FODMAP diet on colonic microbiota reported that the low FODMAP diet led to a lower abundance of Bifidobacteria.[122] The aforementioned 14 RCTs focused solely on the initial "elimination" phase of the low FODMAP diet, which lasts between 3 and 6 weeks, and not the subsequent reintroduction and long-term "personalization" phase. The effects of FODMAP reintroduction on IBS symptoms and long-term effects of a low FODMAP diet have not been sufficiently reported. The low FODMAP diet requires the service of a properly trained GI dietician to provide proper counseling during the 3 phases of the plan. If a trained GI dietician is not available, it is important for physicians to distribute high-quality teaching materials that can allow IBS patients to implement their diet in a medically responsible manner.

Exercise

Statement 9. Appropriate exercise can help improve the overall symptoms of patients with irritable bowel syndrome.

- Level of evidence: low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 35.3%; agree with reservation, 58.8%; undecided, 0.0%; disagree, 5.9%; and strongly disagree, 0.0%.

Considerations

- Although there is limited evidence, appropriate instructions are needed for the type and intensity of exercise, and slow, low-intensity exercise such as walking, yoga, and cycling is recommended over hard, strenuous exercise.

PA is defined as any body movement produced by the skeletal muscles that results in energy expenditure.[123] Some studies have reported that inactive PA worsens symptoms and reduces the quality of life in IBS patients.[124] Therefore, exercise that promotes PA may provide many benefits to IBS patients. Mild exercise enhances intestinal gas clearance and reduces symptoms in patients complaining of abdominal bloating.[125] Additionally, the effect of exercise in IBS patients is associated with modulation of the brain–gut axis and increased gut microbial diversity.[126]

A recent Cochrane review published the results of a systematic review and meta-analysis of the effects of PA in 622 adult IBS patients.[127] In this review, yoga, qigong, treadmill, and exercise counseling were compared to usual care. This review showed

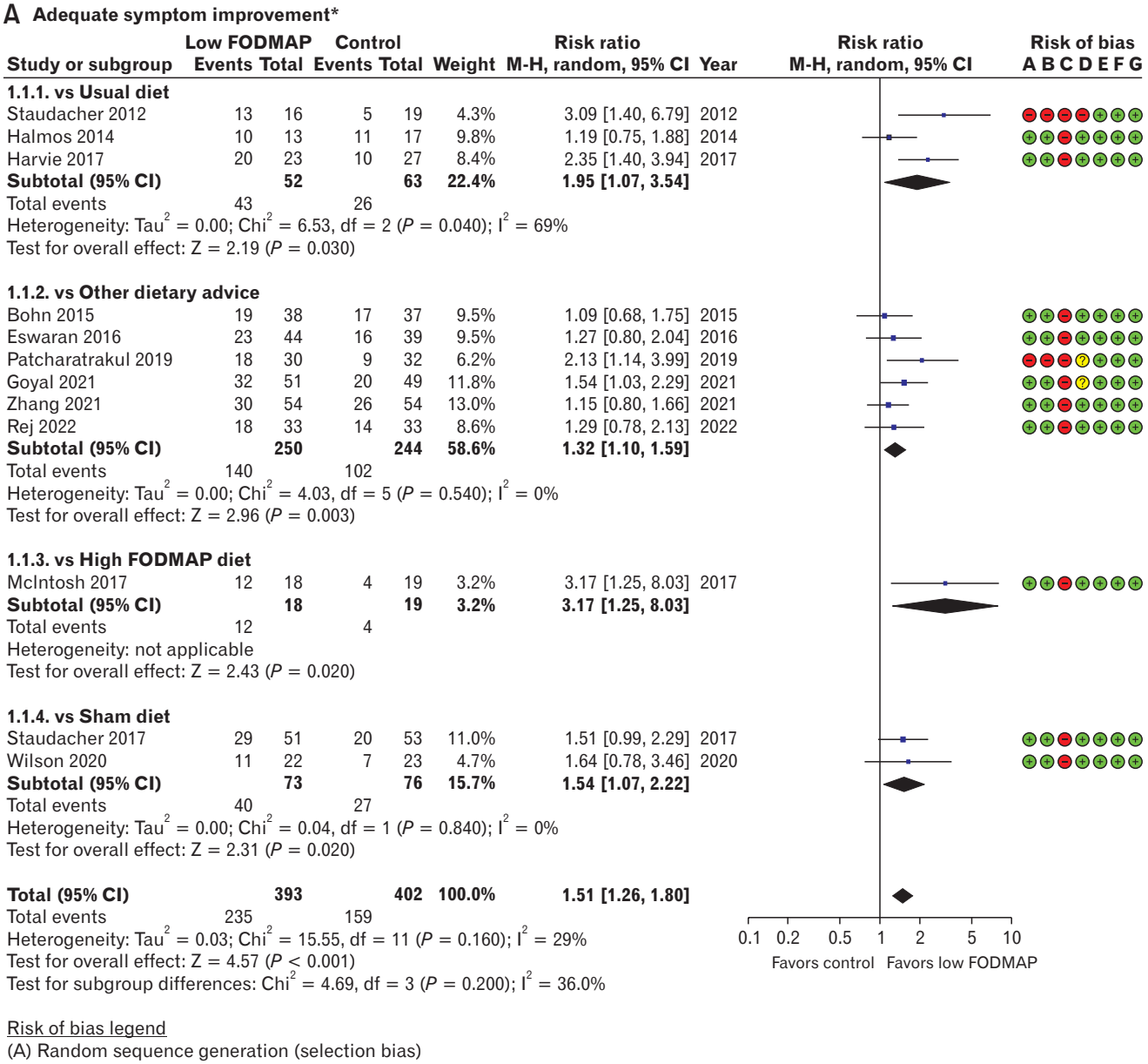


Figure 3. The effectiveness of low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diet for improving irritable bowel syndrome (IBS) symptoms: (A) adequate symptom improvement and (B) change of IBS severity scoring system (IBS-SSS). LFD, low FODMAP diet; M-H, Mantel-Haenszel. *Criteria for symptom improvement: reduction of IBS-SSS ≥ 50 (Bohn 2015, McIntosh 2017, Goyal 2021, Rej 2022), IBS-SSS < 175 (Harvie 2017), 30% decrease of symptom score (Eswaran 2016, Wilson 2020, Staudacher 2012 and 2017, Patcharatrakul 2019, Zhang 2021).

that PA may improve global IBS symptoms (standardized mean difference [SMD], −0.93; 95% CI, −1.44-−0.42; 185 participants). It is uncertain if it improves the quality of life (SMD, 1.17; 95% CI; −0.30-2.64; 134 participants) and abdominal pain (SMD, 0.01; 95% CI, −0.48-0.50; 64 participants) compared to usual care. However, the authors stated that confidence in their

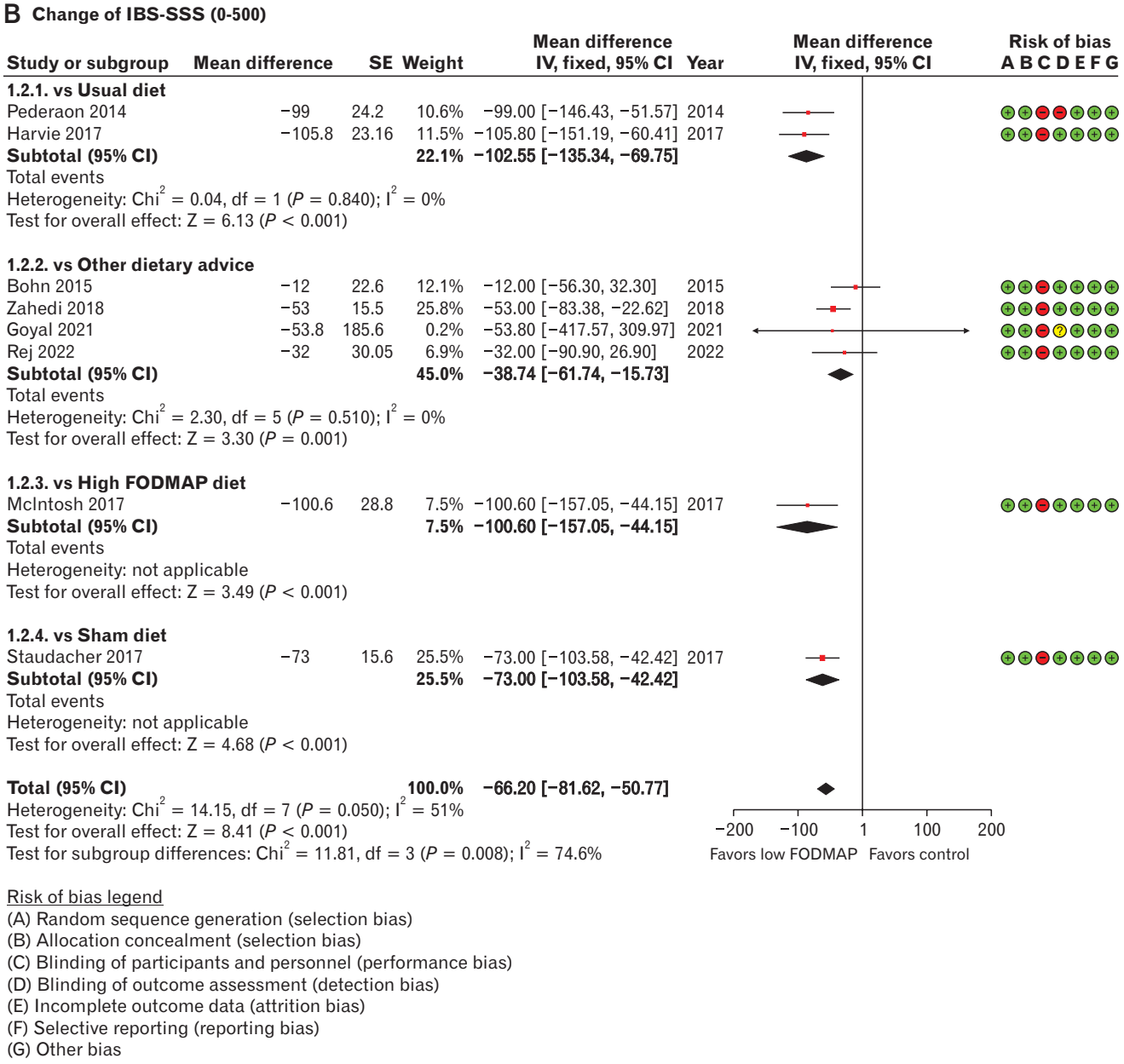


Figure 3. Continued.

conclusions was limited because of the very low certainty of the evidence.

Some studies have reported that exercise is helpful in improving the symptoms of patients with IBS-C.[128] This result is believed to be due to the high prevalence of psychiatric disorders, such as anxiety and depression, in patients with IBS-C.[129] The differences in IBS symptom changes depending on the type of exercise are unclear. A study reported by Shahabi et al[130] found that yoga reduced somatic symptoms, and regular walking tended to relieve GI discomfort and reduce anxiety and negative emotions. Intense PA may increase gut permeability and reduce intestinal mucus thickness, which may contribute to the aggravation of GI symptoms.[131] Therefore, gentle, slow, low-intensity exercises such as walking, yoga, cycling, swimming, and aerobics are recommended for IBS patients.

Medical Treatment

Bulking Agent

Statement 10. Soluble fibers may help improve overall symptoms in patients with irritable bowel syndrome.

- Level of evidence: moderate
- Strength of recommendation: weak
- Expert opinion: strongly agree, 41.2%; agree with reservation, 58.8%; undecided, 0.0%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- There is no evidence that insoluble fiber improves IBS symptoms.

This recommendation remains unchanged from the 2017 Korean guidelines.[10] Bulking agents include soluble (eg, psyllium [ispaghula husk]) and insoluble (eg, wheat bran and some vegetables) fibers and are used in patients with IBS-C. A meta-analysis of 14 RCTs searched up to December 2013 demonstrated that ispaghula, a soluble fiber, was superior to placebo in improving IBS symptoms (RR, 0.83; 95% CI, 0.73-0.94; number needed to treat [NNT] = 7; 95% CI, 4-25), but bran, an insoluble fiber, provided no significant benefit for IBS symptoms (RR, 0.90; 95% CI, 0.79-1.03).[132] Of the 14 RCTs, 6 provided information on IBS subtypes, of which only 2 recruited patients with IBS-C.[132] The mechanism by which soluble fibers help relieve IBS symptoms is not fully understood. Soluble fibers like psyllium undergo fermentation, producing short-chain fatty acids (SCFAs) such as butyrate, which serves as an energy source and anti-inflammatory agent for colonic mucosal cells, while also promoting colonic transit by influencing intestinal nerve cells and motility. These effects may help alleviate symptoms of IBS.[133] Additionally, SCFAs or other fermentation products can serve as substrates for intestinal bacteria; accordingly, psyllium may act as a prebiotic, affecting the composition of the gut microbiome to promote intestinal health and reduce GI symptoms.[133]

Osmotic Laxatives

Statement 11. Polyethylene glycol laxatives can improve stool frequency and consistency in patients with irritable bowel syndrome with predominant constipation.

- Level of evidence: low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 44.4%; agree with reservation, 52.8%; undecided, 1.4%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- The effectiveness of polyethylene glycol (PEG) laxatives in treating abdominal pain in patients with IBS-C remains unclear.
- Among osmotic laxatives, lactulose is inadequate for treating IBS-C because its fermentation in the gut can worsen bloating and gas distension.

This recommendation remains unchanged from the 2017 Korean guidelines.[10] Osmotic laxatives are poorly absorbed by the gut and induce water secretion into the intestinal lumen, which softens and eases the passage of stool. Osmotic agents such as PEG, lactulose, and magnesium hydroxide have been validated in several RCTs for chronic constipation, whereas only PEG has been evaluated in 2 RCTs for IBS-C. These 2 RCTs were published in 2010[134] and 2013,[135] respectively, and no new RCTs have been published since then. In a 4-week RCT comparing the efficacy of PEG (n = 68) versus placebo (n = 71) in patients with IBS-C, PEG was superior to placebo for spontaneous bowel movement number, stool consistency, and severity of straining, but did not show a beneficial effect on abdominal discomfort/pain compared to placebo.[135] Another 30-day RCT involving patients with IBS-C reported that PEG (n = 20) was superior to placebo (n = 22) for stool consistency, but had had no significant effect on abdominal discomfort/pain.[134] Comprehensive and long-term evaluation of the efficacy of PEG in IBS-C is very limited because there are only 2 RCTs with a small number of patients, and both trials were followed for only 1 month. Although PEG improves constipation symptoms, large-scale studies are required to adequately assess its efficacy in patients with IBS-C and abdominal pain. Meanwhile, lactulose is inadequate for the treatment of patients with IBS-C because its fermentation in the gut can worsen bloating and gas distension.[136]

Antispasmodics

Statement 12. Antispasmodics can be effective in alleviating global symptoms and abdominal pain in patients with irritable bowel syndrome.

- Level of evidence: low

- Strength of recommendation: weak
- Expert opinion: strongly agree, 26.4%; agree with reservation, 68.0%; undecided, 4.2%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- Dry mouth, dizziness, and blurred vision are the most common side effects.

Antispasmodics are among the most commonly used medications for treating IBS and are broadly categorized into antimuscarinics (otilonium, hyoscine, cimetropium, and dicyclomine) and smooth muscle relaxants (alverine, mebeverine, pinaverium, drotaverine, trimebutine, and rociverine). These drugs are known to relax intestinal smooth muscles and reduce visceral hypersensitivity, potentially improving IBS symptoms such as abdominal pain.[137]

A previous Cochrane review analyzed 22 RCTs involving 2983 patients, comparing 12 different antispasmodics to placebo.[138] Patients using antispasmodics experienced significantly greater overall improvement in IBS symptoms than those on placebo (RR, 0.67; 95% CI, 0.55-0.80). Specifically, antispasmodics significantly alleviated abdominal pain compared to placebo (RR, 0.74; 95% CI, 0.59-0.93). However, the certainty of this evidence was considered low or very low owing to the risk of bias and publication bias. Additionally, the effects of individual antispasmodics were difficult to analyze because of the insufficient patient numbers in the studies for each drug. A subsequent meta-analysis reported in 2018 included 26 RCTs with 2811 patients, comparing 13 antispasmodics to placebo.[139] Despite high heterogeneity among the studies and publication bias, this meta-analysis similarly concluded that antispasmodics significantly improved IBS symptoms (NNT = 5; RR, 0.65; 95% CI, 0.56-0.76). Specifically, otilonium, pinaverium, hyoscine, cimetropium, drotaverine, and dicyclomine significantly improved IBS symptoms compared to placebo. Conversely, alverine, mebeverine, trimebutine, and rociverine did not show significant improvement over placebo. The certainty of this evidence remains low or very low, owing to the small number of patients in the studies for each drug and high heterogeneity. Adverse events were more frequent in the antispasmodic group than in the placebo group, with the most common adverse effects being dry mouth, dizziness, and blurred vision. However, serious adverse events were not reported.[139] The dosage, side effects, and precautions of the currently available antispasmodics are summarized in Table 4.

Table 4. Antispasmodics Used for Irritable Bowel Syndrome Treatment

Class	Drug	Starting dosage	Maximum dosage	Representative adverse effects	Comments
Calcium channel blocker	Alverine citrate	60-180 mg/day	360 mg/day	Abdominal pain, diarrhea, vomiting, nausea, headache	Only combination with simethicone reduced abdominal pain and discomfort compared to placebo
	Mebeverine	300 mg/day	405 mg/day	Urticaria, angioedema, anaphylaxis	Superior in controlling abdominal pain compared with placebo
	Otilonium bromide	60 mg/day	120 mg/day	Increased intraocular pressure	Reduced abdominal pain frequency and bloating and improved stool frequency and patient global assessment compared with placebo; lower symptom recurrence after treatment
	Pinaverium bromide	150 mg/day	300 mg/day	Abdominal distension, abdominal pain, diarrhea	Superior in improving global symptoms compared with placebo
	Peppermint oil	0.6 mL/day	-	Heartburn	Superior in controlling abdominal pain
Anticholinergic agent	Hyoscine	30 mg/day	60 mg/day	Dry mouth, tachycardia, impaired vision	Superior in controlling abdominal pain
	Cimetropium	100 mg/day	150 mg/day	Dry mouth, nausea, vomiting, constipation	Superior in controlling abdominal pain
Miscellaneous	Trimebutine	300 mg/day	600 mg/day	Dry mouth, constipation, diarrhea	Superior in controlling abdominal pain
	Phloroglucinol	160 mg/day	-	Dry mouth, dizziness, and blurred vision	Significantly improved subjects' global assessment and decreased stool frequency

Loperamide

Statement 13. Loperamide may be effective in improving stool frequency and consistency in patients with irritable bowel syndrome with predominant diarrhea.

- Level of evidence: very low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 40.3%; agree with reservation, 56.9%; undecided, 1.4%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- Loperamide should be used with careful titration of the dosage and duration owing to possible side effects, such as severe constipation, abdominal pain, bloating, and nausea.

This recommendation remains unchanged from the 2017 Korean guidelines.[10] Loperamide is a synthetic μ-opioid agonist that inhibits peristalsis and has antisecretory activity, increasing intestinal transit time. A previous systematic review analyzed 2 RCTs from the late 1980s involving 42 patients with IBS-D and IBS-M.[139] Loperamide improved stool frequency and consistency, but had no effect on abdominal pain or global symptom improvement (RR, 0.44; 95% CI, 0.14-1.42). However, these findings are based on only 2 very small studies from the late 1980s,[140,141] a time when high-quality clinical trial guidelines were lacking, resulting in a very low certainty of evidence. According to these studies, the incidence of adverse events with loperamide was similar to that with placebo. However, loperamide can cause severe constipation, abdominal pain, bloating, and nausea, necessitating caution when administered. It is essential to carefully titrate the dosage and duration of loperamide based on the patient's symptom pattern and underlying condition and to exercise considerable caution with continuous use.

Serotonin Subtype 3 Receptor Antagonists

Statement 14. Serotonin subtype 3 receptor antagonists are effective in alleviating global irritable bowel syndrome symptoms, relieving abdominal pain/discomfort, and improving abnormal bowel habit/stool consistency in patients with irritable bowel syndrome with predominant diarrhea.

- Level of evidence: high
- Strength of recommendation: weak
- Expert opinion: strongly agree, 38.9%; agree with reservation, 52.8%; undecided, 6.9%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- In a meta-analysis of IBS-D, serotonin subtype 3 receptor antagonists were effective in alleviating global IBS symptoms, relieving abdominal pain/discomfort, and improving abnormal bowel habits/consistency compared to placebo.
- Ramosetron is approved for use in Korea and Japan. Alosetron has only been approved in the United States and is proposed by the American College of Gastroenterology as a second-line drug for women with severe IBS-D symptoms. Ondansetron has not yet been approved for treating IBS.

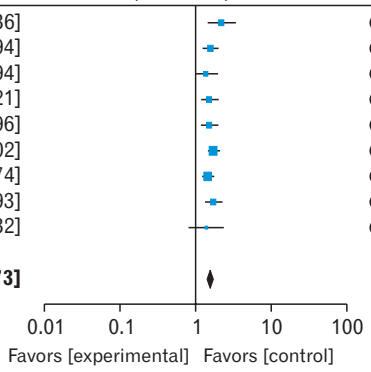
5-HT is a neurotransmitter that modulates secretory, motor, and sensory functions of the GI tract.[142] Serotonin receptors are mainly localized in the enterochromaffin cells of the intestine and the brain.[143,144] In the intestine, 5-HT_3 receptors play an important role in regulating intestinal motility, secretion, and visceral sensitivity.[145] Thus, 5-HT_3 receptor antagonists have been suggested as a therapeutic option for IBS-D through the complex modulation of intestinal 5-HT_3 action.

The effectiveness of 5-HT_3 receptor antagonists in the treatment of IBS-D has been confirmed in a systematic review, meta-analysis, and network meta-analysis of RCTs.[146-150] Ramosetron is approved for use in Korea and Japan. In a meta-analysis examining the efficacy and safety of ramosetron for IBS-D, including 4 RCTs, ramosetron was effective in relieving overall IBS symptoms and abdominal discomfort/pain and improved abnormal bowel habits and stool consistency.[149] Ramosetron can lead to the overall relief of IBS symptoms in both male and female patients. No serious adverse effects have been reported.[149] In a long-term phase 3 study, no serious adverse effects related to ramosetron were noted in patients receiving 2.5 or 5 μg ramosetron. However, constipation occurred in 19.7% of patients receiving 2.5 μg and 10.5% of patients receiving 5 μg ramosetron.[151] Alosetron is only approved in the United States (US) and is only available as a second-line treatment for chronic IBS-D in women. Alosetron was restricted to prescriptions from providers enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program because of post-marketing reports of ischemic colitis and severe complicated constipation; however, in September 2023, the Food and Drug Administration (FDA) determined that the REMS program for alosetron was no longer needed, based on the judgment that the drug's benefits, including the serious complications of isch-

A **Improvement of global IBS symptom**

Study or subgroup	5-HT$_3$ receptor antagonist Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Fukudo 2014	58	147	26	148	3.4%	2.25 [1.50, 3.36]
Fukudo 2016	148	292	91	284	13.2%	1.58 [1.29, 1.94]
Fukudo 2017	121	307	29	102	4.8%	1.39 [0.99, 1.94]
Matsueda 2008	115	238	65	233	9.1%	1.73 [1.36, 2.21]
Krause 2007	250	529	54	176	9.5%	1.54 [1.21, 1.96]
Lembo 2001	388	509	113	258	25.5%	1.74 [1.50, 2.02]
Lembo 2004	167	246	113	246	21.2%	1.48 [1.26, 1.74]
Matsueda 2008	124	263	81	265	11.1%	1.54 [1.24, 1.93]
Ida 2017	21	44	16	47	2.2%	1.40 [0.85, 2.32]
Total (95% CI)		**2575**		**1759**	**100.0%**	**1.61 [1.49, 1.73]**
Total events	1392		588			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.51, df = 8 (P = 0.590); I^2 = 0%
Test for overall effect: Z = 12.57 (P < 0.001)

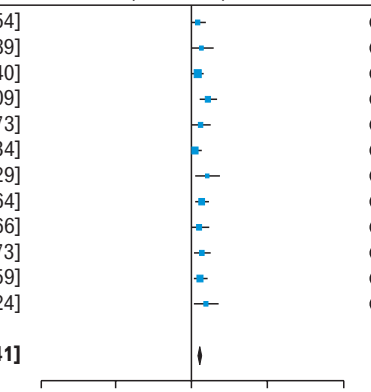


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

B **Relief of abdominal pain and discomfort**

Study or subgroup	5-HT$_3$ receptor antagonist Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Bardhan 2000	72	114	60	117	7.9%	1.23 [0.98, 1.54]
Camilleri 1999	111	213	26	68	3.9%	1.36 [0.98, 1.89]
Camilleri 2000	183	324	151	323	16.0%	1.21 [1.04, 1.40]
Camilleri 2001	133	309	82	317	7.8%	1.66 [1.33, 2.09]
Chang 2005	69	131	51	128	5.7%	1.32 [1.01, 1.73]
Chey 2004	177	351	160	363	15.2%	1.14 [0.98, 1.34]
Fukudo 2014	60	147	37	148	3.6%	1.63 [1.16, 2.29]
Fukudo 2016	150	292	107	284	11.1%	1.36 [1.13, 1.64]
Fukudo 2017	163	307	42	102	6.3%	1.29 [1.00, 1.66]
Matsueda 2008	120	263	87	265	8.4%	1.39 [1.12, 1.73]
Krause 2007	293	529	74	176	10.8%	1.32 [1.09, 1.59]
Matsueda 2008	122	298	27	104	3.4%	1.58 [1.11, 2.24]
Total (95% CI)		**3278**		**2395**	**100.0%**	**1.32 [1.23, 1.41]**
Total events	1653		904			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 11.99, df = 11 (P = 0.360); I^2 = 8%
Test for overall effect: Z = 8.20 (P < 0.001)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4. The effectiveness of 5-hydroxytryptamine 3 (5-HT$_3$) receptor antagonists for improving irritable bowel syndrome (IBS) symptoms: (A) global IBS symptom, (B) abdominal pain and discomfort, and (C) abnormal bowel habits or stool consistency. M-H, Mantel-Haenszel.

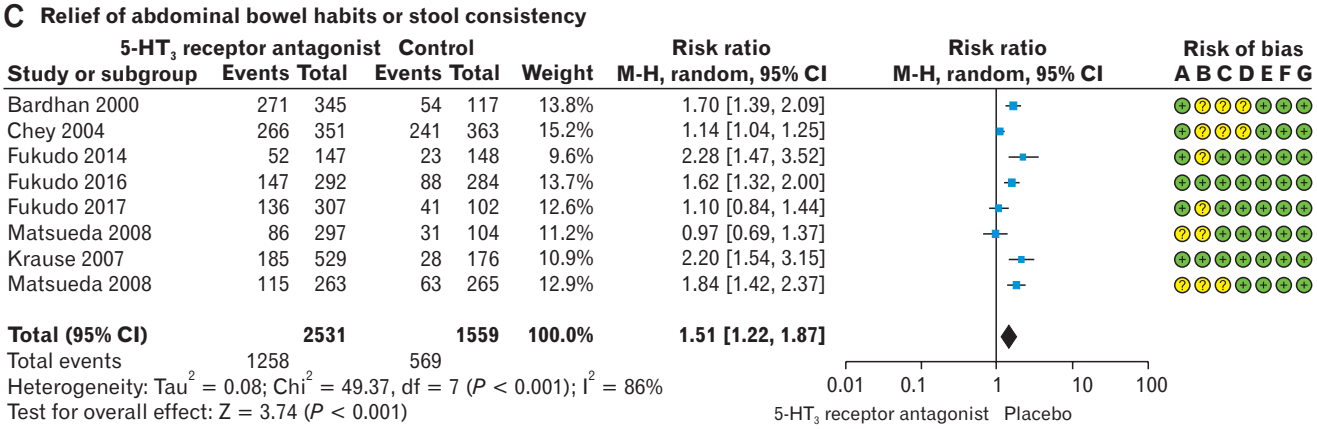


Figure 4. Continued.

emic colitis and constipation, outweighed its risks.[152] Ondansetron is licensed for the treatment of chemotherapy-induced nausea and vomiting, but is not yet approved for use in IBS patients. A recent RCT of a 12 mg once daily (od) bimodal release formulation of ondansetron reported a greater effect than placebo on diarrhea, but not abdominal pain.[153] Similarly, a recent network meta-analysis comparing the therapeutic effects of different 5-HT_3 receptor antagonists in IBS-D showed that ondansetron was the best choice for improving bowel habits/consistency.[148]

We performed a meta-analysis of 15 randomized trials,[38,154-167] and the results of the analysis are presented in Figure 4 (the funnel plot results for assessing publication bias are presented in Supplementary Fig. 1-3). We confirmed that 5-HT_3 receptor antagonists were superior to placebo in improving global IBS symptoms (RR, 1.61; 95% CI, 1.49-1.73), relieving abdominal pain/discomfort (RR, 1.32; 95% CI, 1.23-1.41), and abnormal bowel habit/stool consistency (RR, 1.51; 95% CI, 1.22-1.87) in patients with IBS-D (Fig. 4). In subgroup analyses, both ramosetron and alosetron were effective in improving global IBS symptoms, relieving abdominal pain/discomfort, and improving abnormal bowel habits/stool consistency compared to the placebo (Supplementary Fig. 4 and 5).

Serotonin Subtype 4 Receptor Agonists

Statement 15. Serotonin subtype 4 receptor agonists may improve stool consistency, abdominal pain/bloating, and the health-related quality of life in patients with irritable bowel syndrome with predominant constipation, whose bowel symptoms are refractory to simple laxatives.

- Level of evidence: low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 30.6%; agree with reservation, 58.3%; undecided, 9.7%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- Tegaserod is the only US FDA-approved serotonin subtype 4 receptor agonist for the treatment of adult women younger than 65 years with IBS-C. However, it is unavailable in Asian countries.
- Prucalopride may improve stool consistency in patients with constipation-dominant IBS, whose bowel symptoms are refractory to simple laxatives, although no RCTs on IBS-C are available.

5-HT_4 receptors are distributed throughout the GI tract, and

stimulation of these receptors enhances intestinal secretion, augments the peristaltic reflex, and increases GI transit.[168,169] Tegaserod, a first-generation 5-HT_4 receptor agonist, was approved in 2002 by the FDA for IBS-C. It was withdrawn in 2007 due to an increased risk of cerebrovascular and cardiovascular ischemic events.[170] In 2019, tegaserod was reintroduced in the US for women IBS-C patients younger than 65 years without a history of cardiovascular ischemic events such as myocardial infarction, stroke, transient ischemic attack, or angina.[171] It was withdrawn in 2022 from the US market based on a business decision.[172] Tegaserod is the only US FDA-approved 5-HT_4 receptor agonist for the treatment of adult women aged < 65 years with IBS-C and is effective in symptom relief using the FDA responder endpoint (≥ 30% reduction in average daily worst abdominal pain scores and an increase of ≥ 1 complete spontaneous bowel movements per week for ≥ 6 of 12 weeks) for IBS-C.[171,173,174]

Among 5-HT_4 agonists, prucalopride and mosapride are available for clinical use in South Korea. Prucalopride is a high-affinity and highly selective 5-HT_4 agonist.[175] It was approved in Europe for the symptomatic treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief (2009 for women; 2015 for men) and in the US in 2018 for adults with chronic idiopathic constipation.[172] Prucalopride accelerates GI and colonic transit in patients with constipation.[176] Prucalopride 2 mg od for 12 weeks was more efficacious than a placebo in improving stool frequency and consistency, thereby decreasing the need for rescue medications and reducing symptoms of constipation in Asian and non-Asian women, and was safe and well-tolerated.[177-182] Unlike nonselective 5-HT_4 agonists (cisapride and tegaserod), which are associated with significant interactions with other receptors, leading to adverse cardiovascular events and resulting in withdrawal of these drugs from the market, serious cardiovascular toxicity has not been reported in patients taking prucalopride.[172] Because no data on the efficacy or safety of these agents for the treatment of IBS are available, when bowel symptoms are refractory to simple laxatives, prucalopride can be considered in patients with IBS-C.

Antibiotics

Statement 16. The non-absorbable antibiotic, rifaximin, is effective in improving global symptoms and stool consistency in patients with irritable bowel syndrome with predominant diarrhea.

- Level of evidence: moderate
- Strength of recommendation: weak
- Expert opinion: strongly agree, 33.3%; agree with reservation, 60.0%; undecided, 6.7%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- Rifaximin effectively improved the FDA-recommended composite endpoint of abdominal pain and stool consistency in patients with IBS-D.
- In patients with IBS-D with an initial response to rifaximin who developed recurrent symptoms, retreatment with rifaximin with the same dosage regimen was associated with a greater durable response and prevention of symptom recurrence.
- The drug is licensed for IBS-D in the US; however, it is unavailable for this indication in many other countries.

Rifaximin is a minimally absorbed broad-spectrum antibiotic with activity against both gram-negative and gram-positive anaerobic and aerobic bacteria. It has been tested in IBS-D and IBS-M patients on the basis that alterations in the GI microbiota may, in part, be responsible for the symptoms.[183,184] The poor absorption of rifaximin enables an effective concentration to be maintained in the intestinal lumen. It is approved by the US FDA for the treatment of IBS-D at a dosage of 550 mg 3 times per day for 14 days. Patients who experience symptom recurrence can be retreated up to 2 times with the same dosage regimen.

Several double-blinded, randomized, placebo-controlled trials and systemic literature reviews show that rifaximin is effective in improving various IBS symptoms.[185,186] A recent systematic review and network meta-analysis of pharmacological therapies in patients with IBS-D or IBS-M evaluated rifaximin, and the 2 major RCTs of rifaximin were included (rifaximin n = 624, placebo n = 634).[150] Rifaximin 550 mg 3 times per day for 14 days was more effective than placebo in achieving the FDA-recommended endpoint (≥ 30% reduction in average daily worst abdominal pain scores and ≥ 50% reduction in the number of days per week with at least 1 stool that has a consistency of Bristol Stool Form Scale type 6 or 7) and stool consistency response. The 2 major RCTs on rifaximin were conducted in North American populations; therefore, their findings may not be generalizable to Asian patients with IBS-D or IBS-M. Additionally, the use of rifaximin in IBS patients has not yet been approved by the Korean Health Insurance System.

Therefore, the efficacy of rifaximin may have decreased over time. In a phase 3 retreatment trial with rifaximin,[187] 692 (64.4%) of 1074 patients who responded to open-label rifaximin relapsed

within the 18-week follow-up period. Responders who relapsed were randomized to either 2 14-day repeated treatment courses of rifaximin (550 mg 3 times per day) or a placebo for 2 weeks, separated by 10 weeks. Significantly more patients experienced an improvement in global symptoms with rifaximin after each treatment course, and a more durable response and prevention of symptom recurrence were identified. This study supported the FDA approval for rifaximin treatment, with up to 2 additional treatments for symptom recurrence.

Probiotics

Statement 17. Probiotics may help improve overall irritable bowel syndrome symptoms, including abdominal pain and bloating, in patients with irritable bowel syndrome.

- Level of evidence: very low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 0.0%; agree with reservation, 86.7%; undecided, 6.7%; disagree, 6.7%; and strongly disagree, 0.0%.

Considerations

- Probiotics may alleviate IBS symptoms by modulating the gut microbiota and improving gut barrier integrity.
- Owing to the variability in study designs and probiotic strains, specific recommendations for strains or species cannot be made.

The use of probiotics in the treatment of IBS has been supported by several clinical trials and meta-analyses.[16,17,188,189] Probiotics are believed to alleviate IBS symptoms primarily through the modulation of the gut microbiota, making them a promising option for patients with bloating, abdominal pain, and overall symptom burden.[190]

In 2023, a meta-analysis by Goodoory et al[188] reported the effectiveness of probiotics in IBS patients. This meta-analysis included data from 31 RCTs with a total of 1733 patients in the probiotics group and 1636 patients in the control group. The analysis demonstrated a pooled RR for the persistence of global IBS symptoms of 0.78 (95% CI, 0.71-0.87), indicating a significant improvement in symptoms with probiotics compared to placebo. Heterogeneity among the studies was moderate ($I^2 = 71\%$), but the overall effect was statistically significant ($P < 0.001$). Similarly, for abdominal pain relief, data from the same 31 RCTs with a total of 1775 patients in the probiotics group and 1694 patients in the control group showed a pooled RR for the persistence of abdominal pain of 0.72 (95% CI, 0.64-0.82), indicating a significant reduction in abdominal pain with probiotics compared to placebo. Although heterogeneity among the studies was high ($I^2 = 72\%$), the overall effect was still statistically significant ($P < 0.001$). For abdominal bloating relief, data from 26 RCTs with a total of 1153 patients in the probiotics group and 1069 patients in the control group demonstrated a pooled RR for the persistence of abdominal bloating of 0.75 (95% CI, 0.64-0.88), showing a significant reduction in abdominal bloating with probiotics compared to placebo. Heterogeneity among the studies was high ($I^2 = 78\%$), with a statistically significant overall effect ($P < 0.001$). However, when considering individual strains, the effectiveness of probiotics varied significantly. Escherichia strains show moderate certainty in improving global IBS symptoms. *Lactobacillus* strains have low certainty, with specific strains such as *Lactobacillus plantarum* 299V showing some benefits. *Bifidobacterium* strains also have low certainty, with *Bifidobacterium infantis* 35 624 demonstrating efficacy at certain doses. Combinations of probiotics and *Bacillus* strains generally show low certainty, although some combinations have shown promise in limited trials. *Saccharomyces* strains, particularly *Saccharomyces cerevisiae* I-3856, have shown low certainty in reducing abdominal pain. Therefore, owing to variations in the study designs, probiotic strains, and species used, it is not possible to make specific recommendations for particular species or strains.

Probiotics provide symptomatic relief in IBS patients via multiple mechanisms. They modulate the composition and activity of the gut microbiota, increasing beneficial bacteria and reducing harmful bacteria.[191] This helps to suppress pathogenic bacteria that contribute to IBS symptoms. Probiotics also enhance gut barrier function by upregulating tight junction proteins, which maintain intestinal lining integrity and reduce gut permeability associated with IBS.[192] Additionally, probiotics have immunomodulatory effects by interacting with the gut-associated lymphoid tissue to modulate immune responses.[193] They increase anti-inflammatory cytokines (like IL-10) and decrease pro-inflammatory cytokines (like TNF-α and IL-6), thereby reducing gut inflammation. Certain probiotics produce short-chain fatty acids, such as butyrate, which have anti-inflammatory properties and serve as an energy source for colonocytes.[194] This helps maintain immune tolerance and reduce inflammation. Probiotics also influence the enteric nervous system by modulating neurotransmitter levels, such as serotonin, which affects gut motility and sensation.[195] This can alleviate symptoms such as abdominal pain and altered bowel habits in IBS patients. These mechanisms collectively contribute to the relief of IBS symp-

toms including bloating, abdominal pain, and discomfort.

Although probiotics are generally considered safe, they can cause mild side effects such as bloating, gas, and diarrhea in some patients.[196] These side effects are usually transient and less severe than those associated with pharmaceutical treatments. However, probiotics can potentially cause adverse effects in certain populations, including systemic infections, GI issues, skin complications, and immune system stimulation.[197] The most at-risk groups include infants, the elderly, hospitalized patients, and immunocompromised individuals.[198] Despite their potential benefits, careful evaluation of the risk-benefit ratio is recommended before prescribing probiotics, especially in vulnerable populations.[199] It is important for clinicians to monitor patients for any adverse effects and adjust treatment as necessary.

Probiotics are a valuable treatment option for IBS, particularly for patients experiencing significant bloating, abdominal pain, and discomfort. Despite the very low level of evidence owing to the variability among studies, existing data support conditional recommendations for their use. Future studies should aim to identify specific strains and dosing strategies that may provide the greatest benefits to IBS patients.

Tricyclic Antidepressants

Statement 18. Tricyclic antidepressants effectively treat global symptoms and abdominal pain in irritable bowel syndrome patients.

- Level of evidence: low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 34.7%; agree with reservation, 52.8%; undecided, 11.1%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- Tricyclic antidepressants (TCAs) modulate pain perception and may influence gut function, typically at doses lower than those used to treat depression to reduce side effects.
- TCAs are particularly beneficial for patients with IBS with predominant abdominal pain and are generally preferred for IBS-D cases due to their potential side effect of constipation.

The use of TCAs in the treatment of IBS has been supported by several clinical trials and meta-analyses.[200-209] TCAs are believed to alleviate IBS symptoms primarily through pain modulation, making them a promising option for patients suffering from abdominal pain and overall symptom burden. A meta-analysis that included 8 RCTs[202-209] comparing TCAs with placebo in 578 patients treated with TCAs and 509 patients given a placebo demonstrated a RR of 0.66 (95% CI, 0.53-0.81) for not improving, indicating that TCAs are significantly more effective than placebo in improving global IBS symptoms. Heterogeneity among the studies was moderate (I^2 = 56%), suggesting variability in the study results but an overall beneficial effect of TCAs. In the subset analysis focusing on abdominal pain, the pooled data from 4 studies[202,203,206,209] showed an RR of 0.61 (95% CI, 0.39-0.94). This result indicates a significant reduction in abdominal pain compared to placebo, despite the high heterogeneity (I^2 = 73%).

TCAs provide symptomatic relief to IBS patients through multiple mechanisms. They exert central analgesic effects by increasing the synaptic concentration of neurotransmitters, such as serotonin and norepinephrine, which play a role in pain modulation and mood regulation.[210] Additionally, TCAs have anticholinergic properties that help reduce GI spasms and cramps, which can alleviate abdominal pain.[211] Their effects on gut motility are complex and not fully understood, but they may normalize bowel habits by slowing GI transit, which can be particularly helpful for symptoms of diarrhea.

While TCAs can be effective for symptom relief, they have potential side effects, such as dry mouth, drowsiness, constipation, and more serious cardiovascular effects, including arrhythmias.[212,213] These risks necessitate caution during treatment. TCAs are typically prescribed at lower doses for IBS (10 mg/day to 50 mg/day) than for depression (75 mg/day to 150 mg/day), which helps to minimize side effects.[214] However, even at these lower doses, the potential for serious side effects means that regular monitoring and individualized dose adjustments are crucial to safely manage these risks. Owing to these considerations, TCAs are generally considered a second-line therapy for IBS, typically used in patients who do not respond adequately to first-line treatments, such as dietary modifications, antispasmodics, or other medications.

TCAs are a valuable treatment option for IBS, particularly in patients experiencing significant abdominal pain and discomfort. Despite the overall low level of evidence owing to study variability and heterogeneity, the existing data support a conditional recommendation for their use. Future research should aim to optimize dosing strategies and identify specific patient subgroups that may benefit the most from TCAs in IBS management.

Selective Serotonin Reuptake Inhibitors

Statement 19. Selective serotonin reuptake inhibitors may alleviate irritable bowel syndrome symptoms.

- Level of evidence: very low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 13.9%; agree with reservation, 68.0%; undecided, 16.7%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

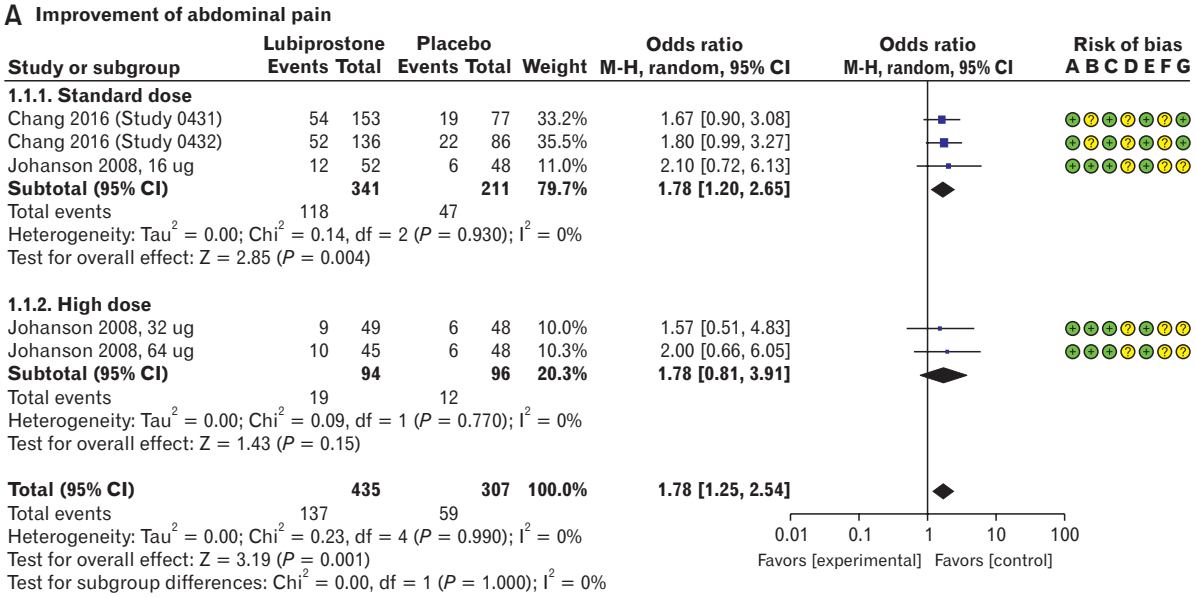
- There is insufficient evidence regarding the effectiveness of Selective serotonin reuptake inhibitors (SSRIs) in patients with IBS.
- SSRIs may be useful for patients with concurrent mood disorders or those who are unresponsive to other treatments.
- SSRIs can be considered for both IBS-C and IBS-D; however, they are generally preferred for treating IBS-C because of the potential side effect of diarrhea.

SSRIs, such as citalopram, fluoxetine, and paroxetine, increase the bioavailability of tissue serotonin by reducing its reuptake by epithelial cells, thus enhancing prokinetic and prosecretory effects of serotonin. A meta-analysis of 7 RCTs involving 356 patients found that SSRIs were superior to placebo for overall IBS symptoms or abdominal pain but not for abdominal pain alone.[200] However, significant heterogeneity existed among the trials. A more recent network meta-analysis, which included 6 trials with some at a low risk of bias, concluded that SSRIs were not significantly more effective than placebo after 4-12 weeks of treatment, and ranked lower in efficacy than antispasmodics and soluble fibers.[215] The primary limitations of these studies were small sample sizes and a lack of detailed reporting on stool patterns and IBS subtypes. SSRIs are beneficial for mood disorders and have shown possible improvements in symptom relief in some IBS studies.[216] Although inconsistencies and imprecision exist, central and peripheral effects of SSRIs offer potential benefits in managing IBS as a gut–brain disorder. A previous study conducted in Korea found that the selective serotonin reuptake enhancer tianeptine showed comparable effectiveness to the TCA amitriptyline in improving the overall relief of IBS symptoms, including abdominal pain/discomfort, stool frequency/consistency, quality of life, and overall treatment satisfaction in patients diagnosed with IBS-D.[217] SSRIs are generally better tolerated with fewer side effects than TCAs, and the likelihood of serious adverse events is minimal. Given their better tolerability and fewer side effects than TCAs, SSRIs may be an option for patients who do not respond to TCAs.

Overall, the mixed evidence indicates that SSRIs are not the first-line treatment for IBS, particularly for patients with IBS-D. Current guidelines generally advise against the use of SSRIs for treating IBS.[59,173,218] However, SSRIs may play a role in specific cases, such as in patients with coexisting mood disorders or those who do not respond to other treatments. Current data suggest that the benefits of SSRIs are limited, but can provide meaningful symptom relief for some patients. Further well-designed RCTs are necessary to better understand the role of SSRIs in IBS management and to identify the subgroups of patients that may benefit from their use. The dosage, side effects, and precautions for currently available antidepressants are summarized in Table 5.

Table 5. Antidepressants Used for Treatment of Irritable Bowel Syndrome

Class	Drug	Starting dosage	Maximal dosage	Adverse effects	Comments
TCAs	Amitriptyline	10-25 mg/day	30 mg/day	Dry mouth, constipation, difficulty sleeping, difficulty urinating, sexual difficulties, headache, nausea, dizziness and/or drowsiness	Begin with low dose (at bedtime) and titrate by response
	Imipramine	25 mg/day	50 mg/day		
	Desipramine	50 mg/day	150 mg/day		
	Trimipramine	50 mg/day			
SSRIs	Paroxetine	10-20 mg/day	50 mg/day	Agitation, dizziness, nausea, headache, vivid dreams, sleep disturbances, sexual difficulties, and/or diarrhea	Begin with low dose and titrate by response
	Citalopram	20 mg/day	40 mg/day		
	Fluoxetine	20 mg/day	-		



Risk of bias legend
(A) Random sequence generation (selection bias)
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(C) Blinding of participants and personnel (performance bias)
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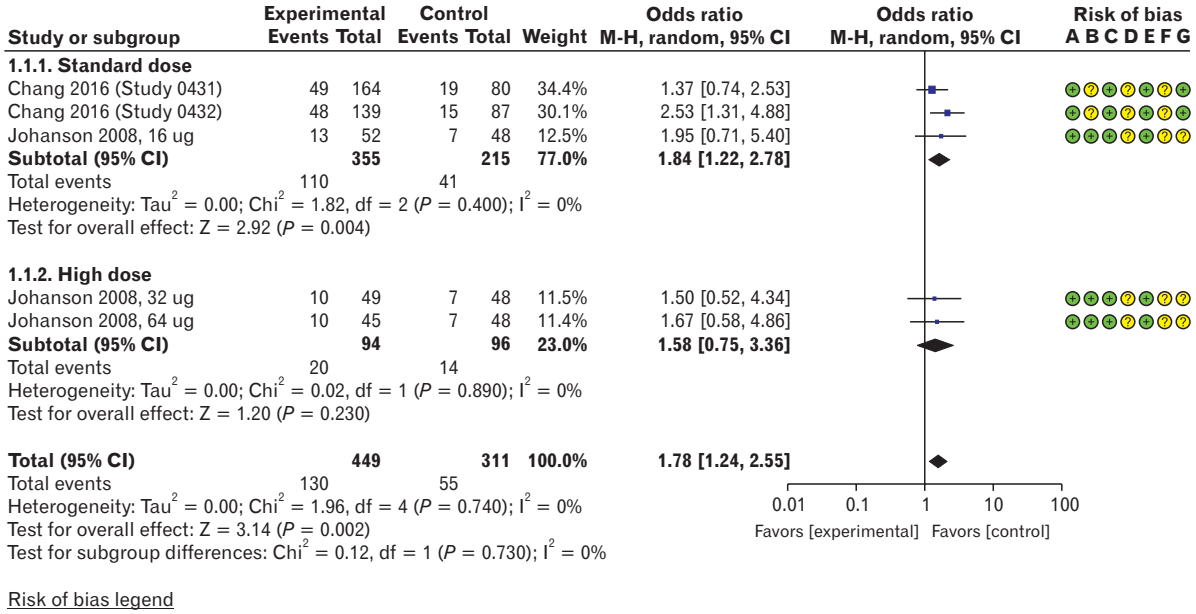
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 5. The effectiveness of lubiprostone, a chloride channel activator, for improving irritable bowel syndrome symptoms: (A) abdominal pain and (B) bloating. M-H, Mantel-Haenszel.

Chloride Channel Activator

Statement 20. Lubiprostone is effective for abdominal pain and bloating in patients with irritable bowel syndrome with predominant constipation.

- Level of evidence: moderate
- Strength of recommendation: weak
- Expert opinion: strongly agree, 25.0%; agree with reservation, 61.1%; undecided, 12.5%; disagree, 1.4%; and strongly disagree, 0.0%.

Considerations

- In a meta-analysis of IBS-C, lubiprostone reduced abdominal pain and bloating compared to placebo.
- It is recommended that lubiprostone should be consumed along with meals to prevent nausea, which is its most common side effect.

Lubiprostone acts as a type 2 chloride channel activator, promoting chloride influx into the GI lumen, which accelerates intestinal transit.[219] Johanson et al[220] analyzed the clinical improvement of IBS-C patients treated with placebo and daily doses of 16, 32, and 64 μg lubiprostone over a 12-week period. This study demonstrated that the lubiprostone groups showed significant improvements in abdominal pain/discomfort, abdominal bloating, degree of straining, and severity of constipation compared to the placebo group. In Drossman's study,[221] which analyzed 2 RCTs (Study 0431 and Study 0432), a significant response rate was observed compared to placebo. This response was associated with improvements in abdominal discomfort/pain, bloating, constipation severity, stool consistency, and straining. In a subsequent study by Chang et al,[222] which separately analyzed changes in abdominal pain and bloating symptoms from Drossman's previous research, the use of 16 μg of lubiprostone demonstrated significant reductions in both abdominal pain and bloating at 12 weeks compared to placebo. In an extended 12-month follow-up of previous study results, it was reported that the effectiveness of lubiprostone was sustained over long-term use. The most common adverse events were diarrhea and nausea, although these were generally mild.[223] To evaluate the effectiveness of lubiprostone, we analyzed data from RCTs, specifically those conducted by Johanson et al[220] and Chang et al.[222] These studies examined the daily doses of 16, 32, and 64 μg of lubiprostone and compared their effects on abdominal pain and bloating improvement against placebo.[220,222] The meta-analysis results confirmed that the lubiprostone groups demonstrated a statistically significant improvement in abdominal pain at both the standard (RR, 1.78; 95% CI, 1.20-2.65) and total (RR, 1.78; 95% CI, 1.25-2.54) doses (Fig. 5A). Similarly, a significant reduction in abdominal bloating was observed in the lubiprostone groups at both the standard (RR, 1.84; 95% CI, 1.22-2.78) and total (RR, 1.78; 95% CI, 1.24-2.55) doses compared to the placebo group (Fig. 5B).

Guanylate Cyclase-C Agonist

Statement 21. Guanylate cyclase-C agonists are effective in improving abdominal pain and bowel movement in patients with irritable bowel syndrome with predominant constipation.

- Level of evidence: high
- Strength of recommendation: strong
- Expert opinion: strongly agree, 40.0%; agree with reservation, 53.3%; undecided, 6.7%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- Linaclotide and plecanatide are GC-C agonists with proven efficacy compared to placebo in patients with IBS-C.
- The most common adverse event observed was diarrhea, but no serious adverse events were reported in previous trials.
- To date, GC-C agonists, both linaclotide and plecanatide, are not available in Korea.

GC-C agonists activate GC-C receptors located on the apical membranes of intestinal epithelial cells and increase intestinal fluid secretion and peristalsis, with reduced activation of visceral nociceptive neurons.[17] Linaclotide and plecanatide are 2 FDA-approved GC-C agonists for the treatment of IBS-C, but they are not yet widely available in most Asian countries.[14]

Linaclotide (290 μg od) is an FDA-approved agent for the treatment of IBS-C and has been recommended in the recent AGA and BSG guidelines.[16,173] Shah et al conducted a systematic review and meta-analysis in 2018, including 3 RCTs regarding the efficacy of linaclotide in patients with IBS-C.[224-227] This study showed significantly better efficacy in meeting the FDA responder endpoint in the linaclotide group than in the placebo group (OR, 2.43; 95% CI, 1.48-3.98), although there was substantial heterogeneity within the studies (F = 77.1).[227] In the AGA clinical practice guideline for IBS-C published in 2022, four RCTs, including a new multinational study with 3 previous studies, were included.[173,228] Accord-

ing to this guideline, linaclotide showed improvement compared to placebo with respect to IBS-C symptoms based on the FDA responder endpoint (RR, 0.81; 95% CI, 0.77-0.85), global assessment measure of adequate relief of IBS-C symptoms over the first 12 weeks (RR, 0.71; 95% CI, 0.67-0.76), abdominal pain (RR, 0.83; CI, 0.78-0.88), and complete spontaneous bowel movements (CSBMs) response (RR, 0.86; 95% CI, 0.83-0.89). Based on this evidence, linaclotide is strongly recommended for patients with IBS-C.[173] In the BSG guidelines for IBS published in 2021, another new study was included, along with 4 previous phase III studies,[229] and it was suggested that linaclotide was likely to be the most efficacious secretagogue for patients with IBS-C (RR, 0.82; 95% CI, 0.78-0.87) compared to other secretagogues, such as tenapanor, plecanatide, and lubiprostone.[16,230] In a previous network meta-analysis on the efficacy of secretagogues in patients with IBS-C, linaclotide ranked first in efficacy based on the FDA endpoint for IBS-C, abdominal pain, and CSBM.[230] Diarrhea was the most common adverse event related to the use of linaclotide and the leading cause of discontinuation, but there were no serious adverse events in all previous trials.

Plecanatide (3 mg or 6 mg od) is another GC-C agonist that binds in a pH-dependent manner compared to linaclotide and has shown efficacy in IBS-C, although it is not yet available for the treatment of IBS-C outside the US. According to the AGA clinical practice guideline, plecanatide showed improvement compared to placebo with respect to IBS-C symptoms based on the FDA responder endpoint (RR, 0.87; 95% CI, 0.83-0.92), abdominal pain (RR, 0.86; CI, 0.81-0.92), and CSBMs response (RR, 0.84; 95% CI, 0.79-0.91), and was recommended in patients with IBS-C.[173] In the BSG guideline, plecanatide 3 mg (RR, 0.88; 95% CI, 0.82-0.94) and 6 mg od (RR, 0.87; 95% CI, 0.81-0.93) were suggested as effective agents for the treatment of IBS-C.[16] In a previous network meta-analysis on the efficacy of secretagogues in patients with IBS-C, plecanatide 6 mg od ranked first for safety.[230] Diarrhea was the most common adverse event, but there was no SAEs in all previous trials, like linaclotide.

Gut-directed Psychotherapies

Statement 22. Gut-directed psychotherapies may be effective for treating global symptoms in irritable bowel syndrome patients who are unresponsive to conventional medical therapy.

- Level of evidence: low
- Strength of recommendation: weak
- Expert opinion: strongly agree, 20.8%; agree with reservation, 61.1%; undecided, 18.1%; disagree, 0.0%; and strongly disagree, 0.0%.

Considerations

- Referral can be made in patients with refractory IBS who have moderate to severe symptoms, for whom conventional treatment is not effective, or whose symptoms persist for over 12 months.

The pathophysiology of IBS is multifactorial, as previously mentioned, and the role of brain–gut–microbiome axis has recently been in the spotlight.[18] Psychological alterations are considered common and important in IBS patients; fear of symptoms, pain catastrophizing, attentional bias/hypervigilance, somatization, and stress sensitivity would play a major role.[59] Multiple psychological alterations are associated with more severe GI symptoms[231] and a worse prognosis.[232] From this perspective, gut-directed psychological therapies, including IBS-specific cognitive behavioral therapy (CBT), relaxation, gut-directed hypnotherapy, mindfulness-based stress reduction, stress management, and psychodynamic therapy, are believed to be effective in the treatment of depression, anxiety, and chronic pain to manage symptoms of IBS.[28,200,233,234]

To date, gut-directed psychotherapies (GDH) have been tested as adjuncts to medical therapies in moderate-to-severe IBS,[235] but there is still controversy regarding which specific treatment is most effective, and the level of evidence is not high. The largest RCTs are of CBT,[27,234,236-239] and RCTs for GDH trials are fewer but show similar outcomes to CBT.[240-242] Recently, there were a couple of network meta-analyses conducted to analyze the effect of gut-directed psychotherapy.[200,243] Psychological therapies appeared to be effective treatments for IBS with an NNT of 4 in both analyses,[200,243] with CBT-based interventions and GDH having the largest evidence base.[243] However, the risk of bias was high, as most of the included studies were small with significant heterogeneity between the studies; the efficacy of psychological therapies is therefore likely to have been overestimated. In addition, adverse events were not well reported in most of the trials.

As mentioned previously, the diagnostic criteria for refractory IBS are not clearly defined, and refractory IBS is defined in various ways such as duration of symptoms lasting (for at least 12 months), refractoriness to dietary intervention, lifestyle modification, conventional treatments, or severity of symptoms (moderate-to-severe symptoms in most studies).[29] In a recent systematic review, CBT and GDH were shown to improve symptom scores and quality of life in patients with refractory IBS, although the criteria for enrollment were inconsistent between the studies (symptom severity or

Table 6. Summary of the Efficacy and Cautions of Lifestyle Modification and Medical Treatment

Management	Level of evidence	Strength	Cautions
Low FODMAP diet	+	↓	
Exercises	+	↓	
Bulking agents	++	↓	Insoluble bulking agents (abdominal distention and flatulence)
Osmotic laxatives	+	↓	PEG (diarrhea, abdominal pain, and nausea) Lactulose (bloating and gas distension)
Antispasmodics	+	↓	Dry mouth, dizziness, and blurred vision
Loperamide	-	↓	Constipation, abdominal pain, bloating, and nausea
Serotonin subtype 3 receptor antagonists	+++	↓	Headache, constipation, weakness, tiredness, chills, and drowsiness
Serotonin subtype 4 receptor agonists	+	↓	In patients with renal and hepatic impairment and elderly
Rifaximin	++	↓	Peripheral edema, hypersensitivity, and diarrhea
Probiotics	-	↓	In immunocompromised patients
Tricyclic antidepressants	+	↓	Dry mouth, constipation, difficulty sleeping, difficulty urinating, sexual difficulties, headache, nausea, dizziness and/or drowsiness
Selective serotonin reuptake inhibitors	-	↓	Agitation, dizziness, nausea, headache, vivid dreams, sleep disturbances, sexual difficulties, and/or diarrhea
Chloride channel activator	++	↓	Nausea In patients with hepatic impairment and pregnancy
GC-C agonists	+	↑	Diarrhea
GDH	+	↓	

-, very low; +, low; ++, moderate; +++, high; ↑, strong; ↓, weak.
FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; PEG, polyethylene glycol; GC-C, guanylate cyclase C; GDH, gut-directed psychotherapies.

refractoriness to conventional treatments).[244] In this context, some existing guidelines recommend considering the application of gut-directed psychotherapy in patients with refractory IBS. For instance, the NICE[245] and British guidelines[16] recommend gut-directed psychotherapy when symptoms do not improve after 12 months of drug treatment. In summary, psychological therapies can be recommended in refractory IBS patients who have moderate-to-severe symptoms, for whom conventional treatment is not effective, or whose symptoms persist for over 12 months.

Conclusion

The 2025 Seoul Consensus on Clinical Practice Guidelines for IBS provides evidence-based information derived from recent systematic reviews and meta-analyses. During the development of these guidelines, reliability and expertise were increased through participation in a multidisciplinary approach. These guidelines highlight the necessity and limitations of diagnostic methods for IBS, such as laboratory tests, colonoscopy, and anorectal manometry. Additionally, the guidelines present treatment options for IBS, including their effectiveness, advantages, disadvantages, and availability (Table 6). The current guidelines will be periodically updated in response to new evidence.

Supplementary Materials

Note: To access the supplementary table and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm25007.

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