Current Diagnosis and Treatment of Irritable Bowel Syndrome

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ABSTRACT

Irritable Bowel Syndrome (IBS) is a common functional gastrointestinal disorder characterized by a combination of symptoms, including abdominal pain, bloating, and altered bowel habits, often without any identifiable organic cause. The diagnosis of IBS typically involves a thorough clinical evaluation, including a detailed patient history and symptom assessment, usually the Rome IV criteria. Laboratory tests and imaging studies are generally employed to rule out other conditions. Current treatment strategies for IBS are multifaceted, aiming to alleviate symptoms and improve quality of life. They include dietary modifications, pharmacological treatment for symptoms management, and psychological interventions. Emerging therapies, such as microbiome modulation and novel pharmacologic agents, are under investigation and hold promise for future management of IBS. Overall, an individualized approach to treatment, considering both physiological and psychological factors, is essential for optimal patient outcomes.

Keywords: *Irritable bowel syndrome, diagnosis, treatment*

ABSTRAK

Irritable Bowel Syndrome (IBS) merupakan penyakit gastrointestinal berupa kombinasi dari gejala seperti nyeri perut, kembung, gangguan pola defekasi yang sering tidak disertai oleh penyebab organik lainnya. Diagnosis IBS ditegakkan melalui anamnesis dan penilaian gejala berdasarkan kriteria Rome IV. Pemeriksaan laboratorium dan radiologi digunakan untuk eksklusi penyebab lain. Strategi tatalaksana terkini untuk IBS memerlukan pendekatan multidisiplin untuk meringankan gejala dan meningkatkan kualitas hidup. Tatalaksana berupa modifikasi diet, farmakologi, dan psikologi. Terapi yang sedang berkembang seperti modulasi microbiota usus dan terapi farmakologi lain sedang diteliti dan menjanjikan untuk tatalaksana IBS di masa depan. Secara umum, dibutuhkan pendekatan tatalaksana khusus secara individual dengan mempertimbangkan faktor fisiologis dan psikologis untuk meringankan kondisi pasien.

Kata kunci*: Irritable Bowel Syndrome, diagnosis, tatalaksana*

INTRODUCTION

IBS is a common functional gastrointestinal disorder that impacts a large portion of the global population.[1] It stems from disturbances in the gut-brain axis and was previously categorized as functional gastrointestinal disorders (FGDs).[2] IBS presents significant challenges not only for individuals experiencing it but also for healthcare professionals.[1] There have been significant developments in the diagnosis, pathogenesis, and management of IBS. This review offers a detailed overview of the current diagnostic criteria and treatment methods for IBS, stressing the importance of a tailored approach to effectively manage this disorder.

EPIDEMIOLOGY

The global prevalence of IBS is 3.8% (95% CI 3.1-4.5), while in Indonesia the estimation is about 3.5% (95% CI 2.5- 4.5).[3] The Rome Foundation Global Survey indicates that the prevalence of IBS is 4.1% according to the Rome IV Criteria and 10.1% based on the Rome III Criteria.[4] Women are 1.6 to 2 times more likely to experience IBS than men.[2] The general prevalence of IBS is linked to various aspects including genetics, age, sex, case reporting, economic status, and geographic settings (both urban and rural). IBS is commonly seen in the general population. However, In developing countries, many patients choose not to seek treatment because they believe their condition will resolve on its own, leading to an underestimation of IBS prevalence.

PATHOGENESIS

IBS is a condition related to the gut- brain axis, arising from the interplay of multiple factors, including biological, psychological, and social influences. Based on the symptoms, IBS can presents with constipation, diarrhea, or both.[5] Some mechanisms underlying the occurrence of IBS are as follows:

Gut-Brain-Axis Disorder

IBS symptoms are linked not only to digestive issues but also to mental health concerns like depression and anxiety.[2] Research indicates that 40% of IBS patients suffer from mood disorders, while about 23% experience anxiety disorders.[1] Other studies suggest that intestinal inflammation, altered cytokine responses, and changes in gut microbiota are associated with mood disorders.[5] Evidence shows that symptomatic treatments can help alleviate psychiatric symptoms.[5] IBS symptoms result from signals originating in the gut and are influenced by memories, emotional stress (such as anxiety and depression), cognitive, or environmental.[2] The gut and brain relationship are connected through the autonomic central nervous system.[5] In IBS, there may be imbalance between overactivity of sympathetic nervous system and hypoactivity of parasympathetic nervous system[6] The decrease in vagal tone due to stress affects gut motility and sensitivity, leading to increased gut permeability and inflammation.[5,6] Factors such as acute or chronic stress, diet, previous gastrointestinal infections, genetic predispositions, and antibiotic use are closely associated with IBS.[7]

Visceral Perception Disorder

About 20% to 60% of patients with IBS report increased sensitivity to various physiological stimuli.[5] Visceral hypersensitivity to mechanical intestinal distension is more common in IBS with diarrhea compared to constipation symptom.[5,8] On the other hand, visceral hyposensitivity is more frequently observed in IBS with constipation compared to diarrhea.[5] The degree of visceral sensitivity is related to the severity of symptoms.[8]

Disturbance of Motility and Transit

Colonic transit irregularities are observed in approximately 10%-20% of individuals with constipation and mixed symptoms. This is more prevalent in IBS with diarrhea, affecting about 20% to 45% of patients.[9] For individuals with IBS-C, there is a reduction in bowel motility, fewer colonic contractions, and slower transit time. Conversely, in those with IBS-D, motility is increased, colonic contractions are more frequent, and transit time is faster.[7,9] Enterochromaffin cells in the gastrointestinal tract store about 90% of the body's serotonin.[5] Serotonin can activate intrinsic and extrinsic primary afferent neurons, influencing gut motility.[5] IBS patients, especially those with diarrhea-predominant symptoms, have a higher number of enterochromaffin cells compared to healthy individual.[5,7] It is thought that 5- HT3 receptors play a key role in sending visceral signals from the gut.[10] Corticotropin-releasing hormone (CRH) may also influence the increased sensitivity to visceral pain associated with IBS.[11] Research involving rats showed that blocking CRH receptor-1 significantly decreased the rise in gut sensitivity.[10,11]

Microbiome

IBS often follows acute gastrointestinal infections.[12] Research involving rats demonstrated that administering probiotics after an infection related to IBS could help modulate visceral hypersensitivity and muscle hypercontractility.[7,12] Dysbiosis has been observed in some IBS cases due to abnormal intestinal fermentation.[5] Furthermore, the colonization of the large intestine by bacteria, similar to what happens in the small intestine, is another mechanism contributing to IBS.[5,12] Studies show that rifaximin improve inflammation and provide protective effects on the intestinal mucosa in cases of visceral hypersensitivity.[13]

Immune system and inflammation

Low-grade inflammation can be found in patients with IBS.[5] In patients with diarrhea, there is proof of immune system stimulation, marked by increased concentrations of pro-inflammatory cytokines in the blood.[14] Particularly, higher cytokine concentrations are observed in patients with anxiety and depression.[5] In IBS patients with food intolerance, significant changes were noted after food exposure, including an increase in intraepithelial lymphocytes, gaps in the epithelium, widening of intervillous spaces, and heightened intestinal permeability.[15] Gastrointestinal infections and food antigens can impair intestinal permeability, triggering a cascade that activates mast cells via the T-helper 2 pathway.[16] These mast cells gather in the lamina propria and release histamine, proteases, and serotonin.[16] The excitation of neurons and contraction of smooth muscles, resulting in abdominal pain and abnormal bowel reflexes.[5] Additionally, the fermentation processes produced by gas-producing bacteria in the intestines cause bloating.[17] All of these factors lead to altered intestinal transit, which can result in diarrhea, constipation, or a combination of both.

Diet

The symptoms of IBS can be triggered by a high "FODMAP" diet (fermentable oligo-saccharides, disaccharides, mono- saccharides, and polyols).[5] The fermentation of FODMAP generates byproducts that trigger clonogenic activity and atypical differentiation of intestinal stem cells.[17] This results in dysmotility, increased visceral sensitivity, and irregular intestinal secretion.[17] Less than 5% patients with celiac disease misdiagnosed as having IBS, but some studies reports that the incidence might be higher.[1] However, celiac disease is more common in Western countries than Asian countries. A gluten-free diet is more beneficial in countries with a high prevalence of celiac disease, although non-celiac gluten hypersensitivity is also frequently encountered in IBS cases.[17]

Genetic

There is evidence indicating that the occurrence of IBS is more prevalent in identical twins.[5] A pilot study found that among 49 IBS patients with abdominal pain, mutations in the SCN5A gene were present. This genetic mutation was observed in about 2% of patients with IBS, with a higher prevalence among those exhibiting constipation rather than diarrhea as their clinical manifestation.[5] Other genes linked to IBS include tumor necrosis factor, interleukin 6, toll-like receptor, e-cadherin-1, and G298S.[18]

DIAGNOSIS OF IRRITABLE BOWEL SYNDROME

The Rome IV criteria define IBS as a condition marked by repeated abdominal pain, along with alteration in bowel habits, such as variations in the periodicity of bowel movements and/or different stool consistency, happening at least once a week for the past three months, with symptoms starting at least six months prior **(table 1).**[7] Patients with IBS are then categorized into four groups based on their predominant bowel habits: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed bowel habits (IBS-M), and unclassified IBS (IBS-U).[7]

Currently, there are no biomarker tests available for diagnosing IBS. The diagnosis of IBS is determined by evaluating symptoms and signs, along with supporting tests such as a complete blood count, stool analysis, erythrocyte sedimentation rate (ESR), and serological tests for celiac disease.[1,7]

Biomarkers, such as fecal calprotectin, can assist in ruling out cases of Inflammatory Bowel Disease (IBD).[1] However, an increase in calprotectin is not exclusive to IBD in individuals with chronic diarrhea.

Elevated calprotectin levels can also occur in other conditions such as older age (over 50), obesity, infections, malignancies, and the use of medications like Proton-pump inhibitors (PPI) and Non-steroidal anti-inflammatory drugs (NSAIDs).[1] If fecal calprotectin levels remain high (above 250 µg/g), IBD exclusion tests is recommended.[1] Routine fecal occult blood tests or fecal immunochemical tests are not typically performed to diagnose IBS.[7]

Table 1. Diagnostic criteria and classification of IBS[7]

The Rome IV Criteria for IBS
1. Recurrent abdominal pain occurring, on average, at least once a week over the past three months, accompanied by two or more of the following: a. Related to defaecation b. Related to change in frequency of stool; c. Related to change in shape of stool AND
2. Criteria met for the past three months, with symptoms beginning at least six months before diagnosis.
Classification
IBS-C ≥ 25% of bowel movements of Bristol stool form types 1 or 2, and <25% of Bristol stool form types 6 or 7
IBS-D ≥ 25% of bowel movements of Bristol stool form types 6 or 7, and <25% of Bristol stool form types 1 or 2
IBS-M ≥ 25% of bowel movements of Bristol stool form types 1 or 2, and ≥ 25% of Bristol stool form types 6 or 7
IBS-U Patients who meet criteria for IBS, but who do not fall into one of the other three subgroups according Bristol stool form typ

Some guidelines suggest screening for colorectal and ovarian cancer in patients suspected of having IBS. In general, colonoscopy is not indicated for patients with IBS, except for those with alarm symptoms or for patients with IBS-D who are at risk for colitis.[3,7] These risk factors include being female, over 50 years old, having an autoimmune disease, experiencing nocturnal diarrhea, having diarrhea lasting less than 12 months, significant weight loss, and the use of medications such as NSAIDs and PPIs.[3,7]

The physiological anorectal examination is recommended for patients with IBS who exhibit pelvic floor disorder symptoms and/or refractory constipation that does not respond to pharmacological therapy. The most commonly found anorectal dysfunction is dyssynergia of defecation, which can be identified through anorectal manometry (ARM), the balloon expulsion test (BET), or the pelvic floor distress inventory questionnaire.[1]

In patients with nocturnal diarrhea symptoms or a history of previous cholecystectomy, a scan for 23-seleno- 25-homotaurocolic acid (SeHCAT) scanning, or measurement of serum 23- seleno-25-homotaurocolic acid levels can be performed.[7] It can help distinguish IBS from bile acid diarrhea.

Generally, the diagnostic algorithm for suspected IBS patients for healthcare professionals working in health facilities is outlined in the **figure 1.**

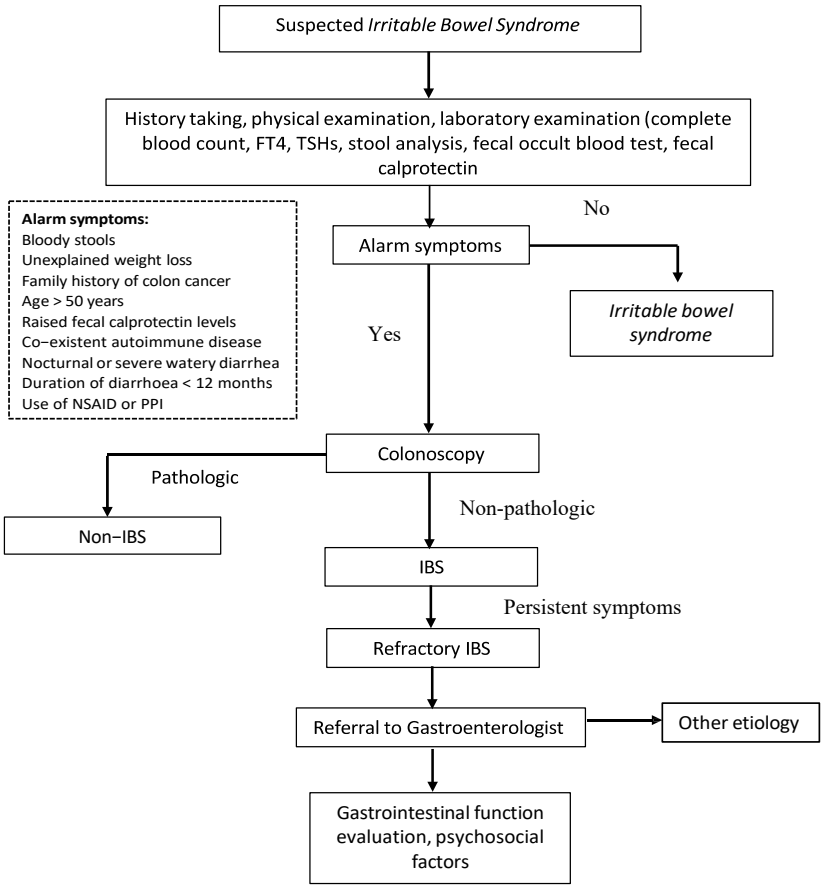

Figure 1. Diagnostic algorithm of IBS[3]

TREATMENT

The management of IBS focuses on alleviating the primary symptoms that patients encounter. This involves lifestyle adjustments, dietary modifications, physical activity, educational support, counseling, and the use of medications. Several randomized controlled trials (RCTs) indicates that regular exercise can be particularly helpful for those with IBS- related constipation.[1,3,7] Patients may also receive dietary interventions and first-line medications. Second-line treatments are designed for patients with persistent symptoms despite of initial treatment. It's important to assess treatment effectiveness every three months, and if there's no improvement, the next available treatment option may be explored.[7] There are several scoring systems used to evaluate IBS symptoms, such as the Gastrointestinal Symptoms Rating Scale-IBS and the Functional Bowel Disorder Severity Index. The IBS severity scoring system is alidated and widely used to assist in determining the degree of severity of IBS.[2]

Most RCTs for first-line therapies, such as antidepressants and psychological therapies, use efficacy parameters like improvement in abdominal pain symptoms. In RCTs for second-line therapies, parameters approved by the FDA are employed, such as the increase in complete spontaneous bowel movements (CSBM) per week for IBS with constipation and the reduction in the frequency of liquid or watery stools for IBS with diarrhea. The British Society of Gastroenterology (BSG) 2021, American College of Gastroenterologists (ACG) 2021, and Indonesian National Consensus 2021 recommends management options including a low FODMAP diet, gluten-free diet, probiotics, anti-diarrheal medications, antispasmodics (including peppermint oil), laxatives, gut-brain neuromodulators (tricyclic antidepressants and SSRIs),

eluxadoline, 5-HT receptor antagonists, antibiotics, and psychological therapies (including gut-directed hypnotherapy).[1,7]

PHARMACOLOGIC TREATMENT

First-line Pharmacologic Treatment

Antispasmodics are the most commonly used treatment for IBS, categorized into antimuscarinics and smooth muscle relaxants. This medication such as dicycloverine, propantheline, otilonium bromide, and hyoscine butylbromide, decrease intestinal motility, while alverine and mebeverine work by directly relaxing the intestinal smooth muscle. IBS symptoms often stem from gastrointestinal spasms and dysmotility. A meta-analysis of showed that antispasmodics were more effective than placebo in alleviating overall symptoms (RR 0.65; 95% CI 0.56 to 0.76).[19] However, potential side effects like dry mouth, vision issues, and dizziness should be taken into account when using these medications.[3,7]

A systematic review of two RCTs found that loperamide improved diarrhea frequency and stool consistency in patients with IBS-D and IBS-M, but it did not significantly impact overall symptoms like abdominal pain, bloating, nausea, or constipation.[20] Loperamide effectively decreases the activity of the myenteric plexus, leading to a longer intestinal transit time and increased water absorption.[7]

Osmotic laxatives, stimulant laxatives, and chloride channel activators can help increase bowel movements in patients with IBS-C.[7] Osmotic laxatives such as polyethylene glycol (PEG) and lactulose are the most commonly used for managing constipation. In a RCT, PEG was effective in addressing constipation, but not in alleviating global symptoms such as abdominal pain.[3] The use of lactulose in IBS with constipation is not recommended, as it can increase gas production in the stomach and intestines, leading to bloating.[21]

Most of patients with IBS experience anxiety and depression. In a meta-analysis, the use of tricyclic anti-depressants (TCAs) was shown to be effective in improving global symptoms or reducing abdominal pain. (RR 0.65; 95% CI 0.55 to 0.77).[22] Similarly, selective serotonin reuptake inhibitors (SSRIs) also showed effects on improving global symptoms or abdominal pain (RR 0.68; 95% CI 0.51 to 0.91).[22] TCAs can be used as a treatment for IBS, starting with a low dose of 10 mg and titrating up to a maximum dose of 30 to 50 mg per day.[7] However, the use of this medication should consider potential side effects.

Peppermint oil is a commonly used treatment for IBS management abroad. The exact mechanism of action is not fully understood. but it is believed to function as an antispasmodic by blocking calcium channels via L-menthol.[1] Peppermint oil can be used to relieve global symptoms of IBS.[1] In a meta-analysis, The use of peppermint oil was more effective in alleviating abdominal pain and overall symptoms compared to a placebo (RR 0.58; 95% CI 0.34 to 0.98).[23]

Second-line Pharmacologic Treatment

For patients with IBS who experience diarrhea and do not respond to first-line anti-diarrheal therapy, it is recommended to proceed to second-line treatment.

Eluxadoline is an agonist for μ-opioid and κ-opioid receptors and an antagonist for δ- opioid receptors.[7] It works by delaying intestinal transit time and reducing visceral hypersensitivity.[7] In several Meta-analysis, eluxadoline reduces abdominal pain and improves stool consistency in IBS-D patients, with relative risks (RR) of 0.89 (95% CI 0.84 to 0.94) and 0.87 (95% CI 0.83 to 0.91), respectively.[24] The treatment group reported side effects like constipation, nausea, and headaches more often than the placebo group. Serious side effects, including pancreatitis and spasms of the sphincter of Oddi, took place in small number of patients in this study.[24] Eluxadoline should not be used by individuals with sphincter of Oddi dysfunction, a history of gallbladder removal, alcohol addiction, pancreatitis, or significant liver dysfunction.[1,7]

5-HT3 receptor antagonists like alosetron and ramosetron can be used to treat IBS.[7] Their mechanism involves slowing down the movement of food through the intestines, decreasing visceral hypersensitivity, and improving rectal function.[7] A meta-analysis found that taking alosetron at 1 mg daily and ramosetron at 2.5 μg daily is effective in alleviating abdominal pain and improving stool consistency with relative risks of 0.69 (95% CI 0.60 to 0.80) and 0.78 (95% CI 0.67 to 0.91), respectively.[24] However, these medications may not be available in all countries. The most common side effect reported is constipation.

Secretagogues and 5-HT4 agonists are second-line medications that can be used to treat IBS with constipation. Secretagogues function by activating ion channels on the inner surface of enterocytes. Examples of this medication include linaclotide, lubiprostone, plecanatide, and tenapanor. This process promotes the movement of ions and water into the interstitial lumen, resulting in softer stools and faster intestinal transit.[1,7] 5-HT4 agonists, like tegaserod, promote intestinal motility and can shorten transit time in the digestive tract.[7]

A meta-analysis has shown that rifaximin helps reduce overall symptoms of IBS-D with favorable safety profile.[25] Rifaximin is an antibiotic absorbed in the intestines, which enables effective levels to be achieved in the intestinal lumen. Research has shown that rifaximin positively impacts gut microbiota by reducing inflammation and offering protective benefits to the intestinal mucosa in cases of visceral hypersensitivity.[1] The recommended starting dose is 550 mg twice daily for two weeks, and this can be repeated up to two times if symptoms persist.[3]

DIET

Approximately 80% of patients with IBS report symptoms triggered by consuming fermented carbohydrates and fats. Person with severe gastrointestinal symptoms due to food hypersensitivity also report other complaints such as muscle pain, chronic fatigue, and decreased quality of life. Almost all patients with IBS want to know which foods to avoid and desire dietary changes. Various mechanisms may underlie how IBS triggers symptoms (through chemical, immunological, mechanical, and neuroendocrine mechanisms) and other secondary effects (byproducts of fermentation, changes in intestinal pH, and effects from gut microbiota). Testing for food-specific IgG antibodies is not recommended for IBS.

In a meta-analysis of 15 RCTs regarding the role of dietary fiber on IBS patient outcomes, soluble fiber, such as Psyllium/ispaghula, shows benefit of improving IBS global symptoms, with an RR of 0.83, 95% CI (0.73 – 0.94).[7] Insoluble fiber, such as wheat, may trigger abdominal discomfort and distention. It is recommended to start fiber intake with a low dose (3-4 grams) and titrate upwards according to tolerance, up to 20-30 grams per day.[3,7] This can increase the amount and volume of water in the large intestine, and eventually resolves the symptoms in patient with IBS-C.[3]

Patients with IBS are not advised to consume foods containing capsaicin.[3] Capsaicin is present in spicy foods. The transient receptor potential vanilloid type-1 (TRPV-1) found in the intestines is believed to contribute to visceral hypersensitivity and abdominal pain associated with IBS. In individuals with IBS, the number of nerve fibers that react to TRPV-1 is markedly increased.[26]

Foods that are generally high in FODMAPs should be avoided by patients with IBS, these include apples, pears, watermelon, peaches, plums, asparagus, broccoli, onions, mushrooms, cauliflower, cassava, cow's milk, soy milk, yogurt, wheat, pistachios, green beans, red beans, honey, and coconut milk.[3] Some Asian foods that are rich in FODMAPs include gyoza, kimchi, doenjang, samjang, tom yum, curry, dim sum, wonton, mantou, red bean soup, and green bean soup.[27] Consuming these foods may trigger abdominal symptoms in patient with IBS.[17]

PROBIOTIC

The presence of fermenting bacteria in the small intestine, akin to small intestinal bacterial overgrowth, has been proposed as a possible underlying mechanism of IBS..[5] The dysbiosis observed in certain individuals with IBS is thought to lead to abnormal levels of fermentation in the intestines.[5] Alterations in the bacteria within the gastrointestinal tract could support the idea that specific bacteria contribute to the pathophysiology of IBS. These points emphasize that not just antibiotics, but also some probiotics, may provide limited relief from symptoms in individuals with IBS. A meta-analysis randomized controlled trials revealed that several probiotics can improve abdominal pain symptoms in IBS patients.[25] Specifically, the analysis found effectiveness in combinations of probiotics (RR 0.79; 95% CI 0.7-0.89), Lactobacillus (RR 0.75; 95% CI 0.6-0.94), Bifidobacterium (RR 0.8; 95% CI 0.7-0.91), and Escherichia (RR 0.86; 95% CI 0.79-0.93).[25] There were no significant differences in side effects between the probiotic and placebo groups. Probiotics, while not tied to specific strains, are effective for managing general symptoms and abdominal pain in IBS.[1,7] They are recommended for use in IBS patients for 12 weeks, with discontinuation advised if symptoms do not improve.[7]

PSYCHOTHERAPY SUPPORT

Several meta-analyses have demonstrated the effectiveness of psychological therapies for IBS. The psychological therapies that have proven beneficial for IBS patients include Cognitive Behavioral Therapy (CBT) and Gut-directed Hypnotherapy.[1,7]

CBT is tailored to therapeutic targets; for reducing depression, activities that bring joy and efforts to eliminate negative thoughts can be employed. To alleviate anxiety, one can avoid situations that trigger it. Meta-analyses show the effectiveness of various types of CBT for IBS, including face-to-face CBT (RR 0.62; 95% CI 0.48 to 0.80), self-administered or minimal contact CBT (RR 0.61; 95% CI 0.45 to 0.83), therapist-delivered CBT via phone (RR 0.50; 95% CI 0.29 to 0.84), and group CBT (RR 0.41; 95% CI 0.19 to 0.91).[1,7]

Gut-directed hypnotherapy is a psychological approach for treating IBS that has robust evidence supporting its effectiveness in both the short and long term. This therapy aims to teach patients self-management skills and help them gain control over their gut functions. It follows a specific IBS protocol and incorporates techniques such as imagery, metaphors, tactile methods for pain relief, and diaphragm relaxation to alleviate abdominal distension and bloating. Typically, patients undergo 6 to 12 sessions per week with trained practitioners. Meta-analyses of randomized controlled trials demonstrate the efficacy of this hypnotherapy, comparing it to education and support in reducing IBS symptoms (RR 0.73; 95% CI 0.55 to 0.97) and against a waiting list control (RR 0.67; 95% CI 0.49 to 0.91). It is advisable to recommend psychological therapy for IBS patients whose symptoms persist after 12 months of treatment.

CONCLUSION

In conclusion, this review emphasizes IBS as a complex disease that demands a detailed approach for effective management. Accurate diagnosis is crucial, relying on symptom-based criteria while ruling out other gastrointestinal issues. Treatment should be customized to meet individual needs and may include dietary modifications, medications, and psychological support, emphasizing the importance of a holistic approach to reduce symptoms and enhance quality of life. In progress studies into the underlying mechanisms of IBS and the development of new treatment options is anticipated to enhance understanding and management of this prevalent condition.

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