

Pathogenesis and treatment of irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS), characterized as a functional gastrointestinal disorder, manifests with recurrent abdominal pain and bowel movement issues. The pathogenesis of IBS is a complex process involving factors such as genetics, composition of gut microbiota, previous infections, and environmental factors. Recent studies indicate that gut dysbiosis, caused by chronic inflammation, may damage the intestinal barrier by activating mast cells at the molecular level. The increased quantity of these cells can lead to disrupted communication on the gut-brain axis, consequently induce the development of general pro-inflammatory phenotype and contribute to the development of post-infectious IBS (PI-IBS). Despite progress in understanding the mechanisms, further research is needed to fully comprehend the pathophysiology of IBS. Current therapeutic approaches focus on individualized treatment, encompassing lifestyle changes, cognitive-behavioral therapies, pharmacotherapy, and probiotic therapy.

Introduction

Irritable bowel syndrome (IBS), referred to as a functional gastrointestinal disorder, manifests as recurrent abdominal pain and issues associated with bowel movements to such an extent that it can significantly impact the quality of life for patients. This condition is widely prevalent, affecting 7–21% of individuals across all geographical regions worldwide [1, 2]. The epidemiology of IBS primarily focuses on the populations of South America and Europe, to a lesser extent on Asian countries; however, there are still countries where, unfortunately, data are not available [3]. According to previous studies, women are more likely to suffer from IBS compared to men [4]. The diagnostic criteria for gastrointestinal disorders have been developed by a group of experts and evolve over time due to emerging scientific data [5]. Currently, the diagnosis of the disease is conducted using the so-called Rome IV Criteria, which involve: pain associated with bowel movements, alteration in stool frequency and accompanying pain and changes in stool consistency.

The diagnosis is established based on the presence of symptoms accompanied by recurrent abdominal pain occurring at least 1 day per week for the last 3 months, and meeting a minimum of 2 of the above criteria [6].

IBS can manifest in various forms: constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), mixed-type (IBS-M), or unclassified type, which results from difficulties in determining stool consistency, and therefore does not meet the criteria for IBS-C, D, or M [7].

It is estimated that in the current diagnostic practice using the Rome IV Criteria, patients most frequently report symptoms with a predominance of diarrhea [4]. In comparison to the previously employed Rome III Criteria, the Rome IV Criteria exclusively encompass pain associated with bowel movements, while discomfort has been eliminated due to its unclear definition. Additionally, the Rome IV Criteria consider the occurrence of both IBS-C and IBS-D, allowing for the possibility of both forms coexisting simultaneously. In contrast, the Rome III Criteria only accounted for IBS subtypes as independent entities [5].

The diagnosis of IBS is complicated and largely relies on medical history and symptoms reported by the patient, which are often non-specific. Detailed radiological examinations, such as colonoscopy, are typically conducted when the patient presents with concerning symptoms (known as “red flags”), including issues like bleeding or rapid weight loss [8]. However, the symptoms accompanying IBS are not specific to this medical condition alone. In addition to a detailed medical history, it is recommended to conduct a complete blood count to determine the presence of anemia or leukocytosis, which may suggest other underlying causes requiring further diagnostic evaluation. Testing for C-reactive protein and calprotectin levels may be helpful in excluding non-specific inflammatory bowel disease, while serological tests for celiac disease seem justified in individuals with IBS-D symptoms. Colonoscopy of the large intestine is recommended as a screening test for diagnosing cancer

in individuals experiencing rectal bleeding and those above 50 years of age [9].

The current knowledge regarding the treatment of IBS focuses on alleviating or completely eliminating symptoms. Depending on the predominant subtype, the first-line therapy includes dietary habit modification and the reduction of stressors [10].

A promising approach in treating symptoms appears to be the application of specific dietary restrictions involving the group of fermentable oligo-, di- and monosaccharides (FODMAPs, Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols). The effectiveness of this modification is considered to have a positive impact on the content of endocrine cells in the intestines, which are responsible for producing hormones involved in digestive and nutrient absorption processes [11, 12]. However, not all patients respond to a single treatment regimen, therefore, an individualized approach to the patient is crucial. In cases where non-pharmacological therapy does not yield the desired results, temporary pharmaceutical interventions are introduced [13].

The aim of this review is to gather and summarize the current knowledge regarding the complex pathomechanisms responsible for the occurrence of IBS.

Review methodology

The aim of this review is to present and summarize the current state of knowledge on the complex pathomechanisms responsible for the involvement of stress in visceral hypersensitivity and bacterial dysbiosis, potentially leading to the development of IBS. Within this review, current therapeutic strategies, including dietary and pharmacological approaches, employed in the treatment of IBS, are also outlined. In order to obtain the latest information regarding the pathogenesis and treatment of IBS, a search was conducted in reputable academic databases such as PubMed, Scopus, and Google Scholar. The searched terms included, among others, IBS pathophysiology, IBS pathophysiological diagnosis, etiological factors of IBS, interactions between the brain and the intestines (gut-brain axis), stress and IBS, intestinal motility dysfunction, the significance of diet in IBS, inflammatory state in the intestines, cognitive-behavioral therapy (CBT therapy) in IBS, and pharmacological treatment in IBS. The search for articles has been narrowed down to current data, mostly up to a maximum of 10 years ago. Articles have been excluded due to their old publication dates. Review articles, meta-analyses, interventional studies, randomized or non-randomized comparative studies were included. Inclusion criteria for studies encompassed diagnosis based on Rome III and IV Criteria, the studied population and demographic data, intervention and control details, as well as study methodology and information enabling systematic error assessment.

Pathogenesis

The pathogenesis of IBS remains not fully understood, however, the current state of knowledge in this field suggests that the development of the disorder is influenced by various factors. Among these are genetic predispositions, the composition of gut microbiota, past infections, and environmental elements. The significant role of stress is underlined as a factor in the body's reaction, underscoring its relevance to the development of IBS [14].

The impact of stress on the brain-gut-microbiome axis

One of the mechanisms leading to disorders of motility and visceral hypersensitivity, as well as central nervous system (CNS) disorders, involves alterations within the brain-gut-microbiome axis (BGM). The gastrointestinal tract connects through neuronal networks present in the enteric nervous system (ENS) with spinal cord and brain. The communication between the brain and the intestines occurs bidirectionally, transmitting signals from the brain to the intestines and from the intestines to the CNS, and occurs through the use of mediators, which include cytokines, hormones, neurotransmitters, as well as short-chain fatty acids. The occurrence of symptoms related to the gastrointestinal system is increasingly associated with disruptions in the central nervous system [15–17]. Research indicates that chronic stress can influence molecular-level changes and potentially lead to alterations in gene expression, consequently resulting in a change in the phenotype without a simultaneous change in the underlying gene sequence [18].

The stressor activates the hypothalamic-pituitary-adrenal (HPA) axis, releasing corticotropin-releasing hormone (CRH), followed by adrenocorticotrophic hormone (ACTH), and cortisol. In a properly functioning stress response, the body, through gluconeogenesis, elevates blood sugar levels, enhances protein and fat metabolism, and suppresses immune functions. Glucocorticoid receptors (GR) interpret signals and lower glucocorticoid levels, including cortisol, by regulating the HPA axis through a mechanism of negative feedback. Furthermore, the central nucleus of the amygdala (CeA), located in the brain, participates in the perception of visceral pain by linking visceral sensory signals with the expression of GR receptors and corticotropin-releasing hormones in the stress response. An increasing body of research confirms the hypothesis that individuals with IBS exhibit reduced expression of GR receptors due to chronic stress. Stressors may lead to dysregulation of the HPA axis through its excessive stimulation, ultimately resulting in a diminished negative feedback response and decreased expression of GR receptors. Impairment of these mechanisms contributes to altered brain function, thereby

contributing to stress-induced pain and visceral hypersensitivity [17–21].

A study conducted by Videlock *et al.* demonstrated that individuals with IBS exhibited a disrupted HPA axis response to stress compared to the control group. Furthermore, the expression of GR receptors in peripheral tissues was reduced in individuals with IBS compared to the control group, correlating with an increased HPA axis response and, consequently, increased symptom severity. The study also highlighted the significance of gender in the overall stress response in patients with IBS. Gender differences may arise from the opposing influence of ovarian hormones and androgens on the expression of CRH and GR (ovarian hormones increase CRH and decrease GR expression). Furthermore, it has been demonstrated that women may exhibit increased brain activation in response to negative emotions in several areas, including the corpus amygdala [22]. Schaper and Stengel found that the impact of psychological stress alters gastrointestinal motility, thereby exacerbating symptoms in individuals with IBS. Furthermore, a portion of IBS patients exhibited increased activation of neurons of the sympathetic nervous system [23]. Guleria *et al.* observed significantly greater activation in certain brain regions (supplementary motor area (SMA), middle temporal gyrus (MTG), supra-marginal gyrus (SMG), and cerebellum) in response to colonic stimulation in patients with IBS. There is no definitive answer, and more studies are needed to better understand the mechanisms of these changes and how they may impact the development of IBS [24].

Changes in intestinal microflora

The gut microflora consists of millions of microorganisms inhabiting the intestines. The main types of bacteria include *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Fusobacteria*. Their composition is variable and depends on various factors, including lifestyle, dietary habits, age, and medication intake [25, 26]. Under normal conditions, the intestinal barrier is integrated and enables the maintenance of organism homeostasis. It serves as protection against pathogens and other mediators of inflammation that can trigger increased immunologic reactions. Compromising the tightness and integrity of the intestines may contribute to dysbiosis of microorganisms, thereby contributing to the development of IBS [27, 28]. There has been a growing body of evidence suggesting that intestinal dysbiosis is significantly involved in the pathogenesis of IBS [29]. It has been proven that bacteria living in the intestine and their metabolites are involved in many processes underlying the development of IBS [30]. Many studies focused on the condition of the microflora following antibiotic therapies or a past stomach inflammation caused by pathogens [31, 32]. Chronic inflammation

can contribute to damage to the intestinal barrier at the molecular level, leading to the activation of mast cells. These cells play a significant role in inflammatory reactions within the body. It has been observed that an increased number of mast cells may indicate a low-grade inflammatory state that has been experienced. Furthermore, alongside mucosal inflammation, excessive production of mast cells can disrupt communication on the gut-brain axis, leading to alterations in the neuroendocrine system and GR receptor genes, which consequently lead to the development of a general pro-inflammatory phenotype, thereby leading to the occurrence of IBS symptoms [33, 34]. It is estimated that the incidence of developing post-infectious irritable bowel syndrome (PI-IBS) is approximately 4–36%. Furthermore, available data indicate a higher occurrence of PI-IBS after bacterial infections compared to viral infections [35]. According to various studies, individuals who have experienced an infection with the *Campylobacter* bacteria are more likely to develop PI-IBS [36]. In the study by Sundin *et al.*, the composition of the microbiota was compared using 16S rRNA sequencing from mucosal biopsies and stool samples of patients with IBS, PI-IBS, and healthy individuals. Obtained results revealed significant differences in the microbiota composition among the studied groups. Patients with PI-IBS exhibit a significant number of symptoms and clinical features common to general IBS. Research indicates that they differ in terms of the composition of gut microbiota. In patients with PI-IBS, both gut microbiota and mucosa tend to align with a phenotype characterized by a higher abundance of *Bacteroidetes*, whereas in patients with general IBS without a preceding infectious episode, there is a higher abundance towards of *Clostridium* cluster XIVa and IV phenotypes. Consequently, the gut microbiota of PI-IBS patients appears to be more similar to that of healthy individuals than to IBS patients without an infectious episode. Moreover, earlier studies have shown that patients with PI-IBS have a higher likelihood of returning to health compared to those with general IBS [37]. Pityayanon *et al.* studied differences in the composition of the microbiota in individuals with IBS compared to healthy individuals. In affected patients, a decreased quantity of bacteria belonging to *Clostridiales I*, the genus *Faecalibacterium*, including *Faecalibacterium prausnitzii*, and the genus *Bifidobacterium* were observed [38]. On the other hand, Vich Vila *et al.* demonstrated a moderate decrease in *Faecalibacterium prausnitzii* and the family of sulfate-reducing bacteria *Desulfovibrionaceae*, accompanied by an increase in the abundance of the genera *Streptococcus*, *Actinomyces* and *Blautia* in individuals with IBS participating in the study [39]. Mujagic *et al.* demonstrated that certain features of the metabolome of the microbiota isolated from the feces of individuals suffering from IBS were associated with abnormal serotonin metabolism and an

abnormal response to stress, in correlation with gastrointestinal symptoms [40].

Diet

Another potential factor influencing the pathogenesis of IBS is the adopted dietary pattern. Nutritional components from food affect intestinal motility, barrier functions, and the diversity of the gut microbiome. Dietary habits can modify the state of gut microflora and its metabolism, thus playing a significant role in visceral hypersensitivity. Numerous studies have demonstrated differences in the composition of the microbiota in patients with IBS compared to healthy individuals depending on the applied dietary models. However, microbial diversity can vary, both by excluding products that exacerbate symptoms in affected patients and by adhering to monotonous diets with low nutritional content. Additionally, consuming foods that trigger visceral hypersensitivity can lead to increased intestinal epithelial permeability and the development of mild inflammation, which may contribute to the symptoms of IBS [6, 41–43].

Treatment

Diet therapy in IBS

Among patients suffering from IBS, there is a belief that dietary habits play a significant role in alleviating gastrointestinal symptoms. In interviews, they often point to specific food groups or individual food items that, when consumed, result in intestinal discomfort. As a result, there is a growing interest in the scientific community regarding the role of diet in the treatment of IBS [44–46].

The Polish recommendations developed by the Task Force organized by the Board of the Polish Society of Gastroenterology (BPSG) include recommendations for patients with IBS. The recommendations for non-pharmacological management of the disease include: motor and psychological therapies and implementation of a transitional diet (6 weeks) containing poorly absorbable, easily fermentable oligo-, di-, monosaccharides and polyols (low-FODMAP diet). Given the lack of scientific evidence, BPSG does not recommend implementing this dietary model. Additionally, they do not recommend following a gluten-free diet or an elimination diet based on the concentration of antibodies against specific nutrients. According to BPSG, patients who follow elimination diets should have an individually tailored dietary model that takes into account the patient's nutritional experiences. BPSG also recommends consuming soluble fiber in the amount of 10–25 g/day, as well as supplementation with peppermint oil at a dose of 180–225 mg twice a day [47].

The latest guidelines from the UK National Institute for Health and Care Excellence (NICE) published in 2017 advocate the implementation of di-

etary strategies as the first-line treatment for patients with IBS. In cases where the introduced changes do not achieve the intended effects in terms of alleviating gastrointestinal symptoms, the implementation of the so-called Low FODMAP diet (LFD) protocol is recommended [48]. The British Dietetic Association (BDA) supports that the patient should first be advised to make simpler dietary changes, in accordance with the NICE guidelines [49]. These modifications include: eating small, regular meals, limiting the consumption of coffee and tea and drinking more water, minimizing alcohol consumption, and reducing the consumption of fruit, sorbitol and resistant starch (Table 1). The NICE guidelines are general in nature, focusing not only on restricting specific products that may be a source of FODMAPs but also on changing dietary behaviors. In practice, this means that they are simpler to maintain and do not expose the patient to the risk of deficiencies, as is in the case with the implementation of the LFD [12, 48]. General recommendations of the NICE protocol are summarized in Table 1.

The LFD is an alternative approach to treat IBS symptoms through the diet. It is recommended by the BDA in cases where following the NICE guidelines proves unsuccessful [50]. The LFD is also used to test patients' tolerance to certain food products by eliminating them [51]. The FODMAP group includes food products containing poorly absorbed carbohydrates in the gastrointestinal tract, such as fructose, lactose, and polyols. Unabsorbed substances increase water content in the small intestine. Additionally, indigestible fructans and galactooligosaccharides undergo fermentation, producing gases, which may contribute to the exacerbation of symptoms [51, 52].

The LFD protocol consists of three phases:

- the first phase involves “FODMAP restriction” lasting 4–8 weeks,
- the second phase is “FODMAP reintroduction” lasting 6–10 weeks,
- the third phase involves individualizing the diet, taking into account FODMAP-containing products that are well-tolerated by the specific patient [53].

In the meta-analysis by Black *et al.*, the effectiveness of various dietary patterns was analyzed, including the LFD, dietary advice from the BDA and NICE, clear dietary advice, usual diet, alternative dietary advice and high FODMAP diet. In the data analysis, the LFD was identified as the most effective dietary model in terms of reducing gastrointestinal symptoms. An essential aspect of the study was the emphasis on the intervention and the supervision of a qualified dietitian in the introduction of the LFD. According to the analysis, patients working with a specialist have a greater chance of achieving a clinically significant effect. Collaboration with a specialist enabled the creation of a well-structured dietary plan, in line with the principles of the LFD diet, as well as patient con-

Table 1. General NICE recommendations on lifestyle and diet for people with IBS [48]

1. Providing information on overall lifestyle improvement, diet, physical activity, and symptom-relieving pharmacotherapy.
2. Encouraging by the healthcare workers to utilize leisure time for relaxation.
3. Assessing the level of physical activity in patients with IBS using the General Practice Physical Activity Questionnaire (GPPAQ) by healthcare workers.
4. Evaluating the dietary habits of IBS patients and providing the following advice: – consuming regular meals – avoiding long gaps between meals – drinking at least eight glasses of fluids per day, mainly water and herbal teas – limiting the intake of strong tea and coffee to three cups per day – restricting consumption of carbonated beverages and alcohol – reducing high-fiber products – decreasing resistant starch intake – limiting fresh fruit consumption to three servings per day (one serving approximately 80 g) – avoiding the addition of sorbitol to food for IBS-D patients – recommending the inclusion of oats and flaxseed for individuals experiencing bloating and excessive gas
5. Assessing dietary fiber intake in individuals with IBS, determining the optimal amount of soluble fiber in the patient's diet.
6. Instructing individuals with IBS who have opted for probiotic therapy to take the product for at least 4 weeks according to the manufacturer's recommendations and monitoring the therapy's effects.
7. Encouraging healthcare workers to advocate the use of aloe in therapy.

Table 2. Types and composition of FODMAPs in various food products [55]

Types of FODMAP	Composition	Rich food products
Oligosaccharides	Fructans and galactooligosaccharides	Agave, artichokes, barley, black beans, cashews, chicory root extract, garlic, inulin, common beans, onion, peaches, white peas, pistachios, plums, rye, shelled peas
Disaccharides	Lactose	Milk products
Monosaccharides	Fructose	Apples, pear, watermelon, mango, cherries, figs, dried fruits, honey
Polyols	Sorbitol and mannitol	Apples, blackberries, peaches, plums

trol over adherence to the guidelines [54]. Types, composition and products rich in various FODMAPs are presented in Table 2.

Some studies suggest that a gluten-free diet (GFD) may provide relief in symptoms for some patients, even in the absence of celiac disease. However, these results are conflicting, and not all experts agree on the effectiveness of a gluten-free diet in treating IBS. Correlations have been observed between the use of a GFD in healthy individuals for a month and a reduction in the number of beneficial bacteria, such as *Bifidobacterium* spp. (especially *B. longum*), *Clostridium lituseburense*, and *Faecalibacterium prausnitzii*, while simultaneously noting a significant increase in *Enterobacteriaceae* and *Escherichia coli*. The reduction of *B. longum* after a GFD can be explained by its involvement in the metabolism of carbohydrates and polysaccharides. Additionally, studies have also noted an increase in pathogenic species, such as *Enterococcus*,

Staphylococcus, *Salmonella*, *Shigella*, and *Klebsiella* after a GFD, which may impact the microbial profile and long-term homeostasis of the intestinal mucosa in healthy individuals [55, 56].

The impact of the ketogenic diet (KD) on the level of gut microorganisms has also been investigated. Reduced microbial diversity has been observed with the adoption of this dietary model. This is correlated with a reduction in carbohydrate intake, leading to a decrease in polysaccharide content and a subsequent reduction in the number of bacteria obtaining energy from polysaccharides. Moreover, the KD appears to lower blood glucose levels and body weight while increasing ketone levels in the blood. These effects were associated with an increase in bacteria producing short-chain fatty acids (SCFA), such as *Akkermansia muciniphila* and *Lactobacillus*, and a decrease in taxa with pro-inflammatory effects, such as *Desulfovibrio* and *Turicibacter*. However, further research is needed

to explore the beneficial impact of the KD on the treatment of IBS, especially the IBS-D subtype [56].

Psychological therapies

IBS is often associated with psychological disorders such as depression and anxiety. Therefore, a holistic approach is recommended in the treatment of IBS, considering both physical and psychological aspects. Behavioral therapy and pharmacotherapy may be helpful in reducing psychological symptoms [57].

The most commonly used psychological therapy for patients with IBS is CBT. Its goal is to educate the patient and provide ways to cope with symptoms, challenging situations, and thoughts that may exacerbate IBS symptoms. Additionally, it includes teaching relaxation techniques such as meditation, aimed at calming the nervous system and improving the quality of life [58]. In the meta-analysis performed by Black *et al.*, CBT interventions and gut-directed hypnotherapy showed the highest long-term effectiveness and were characterized by the strongest evidence base [59]. However, in the study by Jacobs *et al.*, it was observed that the level of microbiota and serotonin was associated with the response to CBT therapy through correlations in brain networks and the gut microbiome. Nevertheless, larger studies are needed to characterize the associations and mechanisms of changes in gut microbiota [60]. In a randomized controlled trial involving 436 IBS patients, including 80% of women, a significant and long-term improvement in gastrointestinal symptoms was demonstrated through the use of a home-based version of CBT therapeutic techniques. Patients were trained on IBS, lifestyle, physical activity, diet, and stress management. These results proved the importance of awareness and education for patients with IBS [61].

Pharmacological treatment

Antidepressants

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) can also be used in the treatment of IBS in patients with diagnosed psychiatric disorders. Their action aims to increase the levels of neurotransmitters, which may help reduce IBS symptoms by influencing the ENS. TCAs, through their antagonistic action on histamine H1 receptors, adrenergic receptors, and muscarinic acetylcholine receptors, may directly induce side effects such as drowsiness, orthostatic hypotension, blurred vision, and even constipation. Therefore, in studies, SSRIs are preferred and used as the first-line treatment of IBS with depression symptoms due to their potentially lower incidence of side effects. In the considered studies, the most commonly used medications from the TCAs group were desipramine, trimipramine, amitriptyline, imipramine, and doxepin, while from

the SSRIs group, medications such as fluoxetine, paroxetine, and citalopram were employed [62, 63]. However, there is evidence regarding the use of low-dose amitriptyline, ranging from 10 to 30 mg once daily, as a second-line therapy (when lifestyle modifications and symptomatic medications prove ineffective) in patients with IBS in primary care. Amitriptyline was proved to be more effective than a *placebo* in alleviating IBS symptoms while maintaining safety and good tolerance, especially when adjusted based on individual responses to symptoms and side effects. When the justification for using this tricyclic antidepressant in IBS treatment is clearly presented, many IBS patients consider this drug acceptable and beneficial, which provides adequate support. However, further research is needed to confirm the evidence of the beneficial impact of TCAs in treating IBS [64].

Antispasmodic and spasmolytic drugs

In recent years, several pharmacological therapies have been registered for the treatment of IBS. They are applied when dietary modification therapies do not yield the intended results. One of the active substances used in the treatment of functional gastrointestinal disorders, including IBS, is trimebutine maleate. Trimebutine has prokinetic and antinociceptive effects; it acts as an agonist on delta, mu, and kappa opioid receptors in the smooth muscles of the gastrointestinal tract, modulates the release of peptides, and induces motilin release. It has been demonstrated that this medication accelerates gastric emptying, stimulates intestinal motility, modulates colonic contractions, and may play a role in regulating visceral sensitivity [59, 65, 66]. However, trimebutine therapy alone may prove to be insufficient. In a study by Makarova *et al.*, trimebutine therapy did not achieve the intended clinical effects in patients with IBS. Additionally, anxiety and depression scores remained high according to psychometric scales [67].

Alosetron and ramosetron are compounds that also find application in the treatment of IBS, primarily in its diarrhea-predominant form. They are 5-hydroxytryptamine-3 (5-HT₃) receptor antagonists, and therefore, they can be used to slow down gastrointestinal transit and reduce visceral sensitivity. In a meta-analysis by Black *et al.*, it was demonstrated that the use of 1 mg of alosetron twice daily significantly influenced the overall relief of IBS symptoms and improved stool consistency compared to the placebo group. Additionally, the use of ramosetron at a dose of 2.5 µg once daily showed significant improvement in alleviating abdominal pain in individuals with IBS [68].

Rifaximin is an antibiotic with reduced absorption and a broad spectrum of applications. Although the mechanism of action remains unclear, some studies have shown beneficial effects following antibiotic therapy in individuals with IBS. The durability

Table 3. Pharmacotherapy of IBS (current recommendations)

Substance	Mechanism of action	Research/Recommendation	References
Trimebutine	Acts as a prokinetic and antinociceptive agent Is an agonist of delta, mu, and kappa opioid receptors Modulates the release of peptides and induces the release of motilin	Accelerates gastric emptying Stimulates intestinal motility Modulates colonic contractions May participate in regulating visceral sensitivity	[58, 64, 65]
Alosetron and ramosetron	5-hydroxytryptamine-3 receptor antagonists	recommended for patients with IBS-D Can be used to slow down gastrointestinal transit and reduce visceral sensitivity Improvement in stool consistency	[67]
Rifaximin	Antibiotic with reduced absorption The mechanism of action in individuals with IBS still remains unclear	May contribute to reducing symptoms such as bloating, abdominal pain, and changes in stool consistency Exhibits fewer side effects compared to metronidazole	[68, 69]
Linaclotide	Activates the function of ion channels in the epithelial cells of the intestinal lining	Recommended for individuals suffering from IBS-C Affects stool softening and increased intestinal transit May contribute to reducing the sensation of pain	[67, 70]

of benefits in IBS-D patients has been demonstrated through the alleviation of symptoms such as bloating, abdominal pain, and changes in stool consistency. Additionally, rifaximin exhibited fewer side effects compared to metronidazole and lower antibiotic resistance in patients [69, 70].

In the treatment of IBS-C, medications are used that activate ion channels in the epithelial cells of the intestinal lining, thereby increasing the content of electrolytes and fluids in the intestinal lumen, which softens the stool and enhances intestinal transit. According to studies, the most effective substance for treating IBS-C appears to be linaclotide. The recommended dosage of 290 µg/day of linaclotide resulted in a reduction in pain sensation and an increase in bowel movement frequency; however, the use of the drug led to frequent undesirable side effects in the form of diarrhea. Nevertheless, further research is needed to assess the effectiveness of the drug [68, 71] (Table 3).

Probiotic therapy

Considering that most probiotics are registered as dietary supplements, i.e. products from the food category, this therapy can also be included as one of the nutritional therapy strategies. Probiotics are living microorganisms that, when consumed in adequate amounts, can have a beneficial impact on the host's health. Currently, the precise mechanisms of probiotic action in the human body are not fully understood.

The potential effects of probiotics include inhibiting the excessive growth of pathogenic bacteria, improving the functioning of the intestinal barrier and interactions with receptors, as well as the production or secretion of SCFA and neurotransmitters. Various studies confirm the effectiveness of probiotic therapy in treating IBS. However, there is still no clarity on which specific strains or combinations of strains are most effective in alleviating symptoms. In the study by Xie *et al.*, the greatest effectiveness in alleviating IBS symptoms was demonstrated when using the *Lactobacillus* strain (e.g. *L. planetarium*, *L. reuteri*, *L. acidophilus*, *L. beri* or *L. casei Shirota*), indicating a recommendation for its inclusion in dietary plans. On the other hand, Dale *et al.* compared the results of studies involving multi-strain and single-strain preparations, observing a greater tendency to alleviate IBS symptoms in patients using complex preparations [72, 73]. In the meta-analysis, the mechanism of action of probiotics in alleviating IBS symptoms was summarized, but this is still subject to further speculation. Despite studies suggesting the beneficial impact of strains such as *Lactobacillus acidophilus*, which have the ability to modify pain receptor expression in the intestines of mice, and research on the ability of *Bifidobacterium infantis* to normalize interleukin levels in IBS patients, it has not been proven that probiotics are responsible for the positive effect. Further research is needed to clarify the mechanisms behind the achieved effects [62].

Summary

The pathogenesis of IBS involves various factors such as genetic predispositions, gut microbiota composition, past infections, and environmental factors. Increasing attention is being paid to the role of stress in the development of this condition. Chronic stress can lead to dysregulation of the negative feedback mechanism in the stress response and changes in brain function, thereby contributing to stress-induced pain and visceral hypersensitivity. Furthermore, some studies suggest that gut dysbiosis resulting from chronic inflammation may damage the intestinal barrier at the molecular level by activating mast cells to the development of PI-IBS. The treatment of IBS focuses on an individualized approach to alleviate symptoms and improve the patient's quality of life. Therapeutic interventions include lifestyle and dietary modifications, cognitive-behavioral therapies, pharmacological treatments, and probiotic therapy. Nutritional treatment guidelines recommend implementing simpler dietary modifications that may be easier to maintain and do not carry the risk of nutrient deficiencies associated with long-term restrictive diets. In the case of pharmacotherapy, antispasmodic and spasmolytic drugs, such as trimebutine, alosetron, and ramosetron, also constitute a therapeutic aspect in IBS treatment, albeit with certain differences in efficacy and safety profiles. Antidepressant drugs are also noteworthy recommendations. Low-dose TCAs, such as amitriptyline have a positive impact on alleviating IBS symptoms, especially in patients unresponsive to lifestyle modifications and symptomatic drugs. There are also reports confirming the effectiveness of probiotic therapy in alleviating IBS symptoms. However, clear evidence is still lacking on which strains or their combinations are the most effective. In summary, there are many therapeutic strategies for treating IBS; however, none are fully effective and well understood to assess their guaranteed clinical response. This is due to the complex pathophysiology of the disease and its ambiguous accompanying symptoms. Further research is necessary to understand the occurring changes and their mechanisms in the pathophysiology of IBS.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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