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Irritable Bowel Syndrome - current state of knowledge

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ABSTRACT

Introduction and objective: Irritable bowel syndrome (IBS) is a common gastroenterological disorder affecting 9% to 23% of the population worldwide. The disease causes recurrent abdominal pain and abnormal bowel movements without visible anatomical or biochemical changes and diagnosis is often difficult. The purpose of this paper is to analyze the current knowledge of the pathophysiology, risk factors, diagnosis and treatment of IBS.

Review methods: The literature available in the PubMed database was reviewed using the following key words: "irritable bowel syndrome," "constipation," "diarrhea", "abdominal pain", "diagnostics", "treatment". 49 articles were included in the review and 80% were from 2016-2024.

Current state of knowledge: The pathophysiology of IBS is not fully understood, but it is recognized that the disease is a disorder of the gut-brain axis. It can lead to abnormal secretion of serotonin and dopamine, which affects symptoms. The diagnosis of IBS is based on the Rome IV Criteria, defining the characteristics and severity of symptoms.

Summary: IBS is a disorder that significantly affects quality of life. Diagnosis is based on the exclusion of organic diseases and meeting certain criteria. Treatment includes both dietary modification and pharmacotherapy aimed at relieving symptoms. Despite advances in

research, the pathophysiology of IBS is still not fully understood, making it difficult to develop effective treatments.

Key words: irritable bowel syndrome; constipation; diarrhea; abdominal pain; diagnostics; treatment

INTRODUCTION AND PURPOSE OF THE WORK

Irritable bowel syndrome (IBS) is a condition affecting 9-23% of the world's population, significantly impairing their quality of life. [1] It can negatively affect one's ability to study or work, and furthermore promotes comorbidities such as depression, anxiety disorders and chronic fatigue syndrome. [2] It is considered the most commonly diagnosed gastroenterological disorder. [3] IBS is defined as recurrent abdominal pain accompanied by abnormal bowel movements that are not caused by anatomical or biochemical changes. [4] In most individuals, it is characterized by a course with periods of exacerbation and remission. [5] Due to the overlap between the symptoms of IBS and those of many organic diseases of the gastrointestinal tract, general practitioners often run into diagnostic difficulties. [6] This paper aims to collect and analyze the current state of knowledge regarding the pathophysiology, risk factors, diagnosis and treatment of irritable bowel syndrome (IBS).

REVIEW METHODS

The literature review was conducted through a comprehensive analysis of meta-analyses, original research papers, and review articles available in the PubMed database. The keywords used were carefully selected to identify abstracts of relevant articles, which were then evaluated for their applicability: "irritable bowel syndrome", "constipation", "diarrhea", "abdominal pain", "diagnostics", "treatment". To ensure a thorough understanding of IBS, additional sources were incorporated, particularly those that provided the most up-to-date insights into the pathophysiology, diagnostics, and treatment of the condition. In total, 49 articles were included in the review, with 22 published between 2020 and 2024, and 80% of the articles were published after 2016.

STATE OF KNOWLEDGE

IBS pathophysiology

The exact pathophysiology of IBS is not fully understood. The disease is classified as one of the disorders of the gut-brain axis. [7] This axis consists of numerous connections between the central nervous system and the Auerbach plexus. Through them, emotions can affect the regulation of intestinal motility, mucus secretion, and protective functions. The situation is similar in the other direction; gastrointestinal stimuli affect the mental state and emotions. It has been proven that IBS patients experience impaired serotonin and dopamine secretion, which can translate into the disease picture. [8] IBS is often accompanied by depression and anxiety disorders. [9]

Some patients with IBS, especially those who are predominantly constipated, experience increased permeability of the junctions between the cells of the intestinal wall, as well as hypersensitivity to visceral and thermal stimuli, which can result in an impaired sensation of pain and discomfort. [10]

Another factor influencing the development of IBS is the gut microbiota, which interacts with nervous, hormonal and immune processes in the gut. Bacterial imbalance in the gut can negatively affect the barrier function of the intestines and lead to mucosal inflammation. [11]

An important component of IBS is impaired intestinal contractility, which is associated with abnormalities in the serotonin pathway. Levels of 5-hydroxytryptamine (5-HT; serotonin) are elevated in IBS patients with predominant diarrhea and decreased when constipation predominates. [12]

Risk factors of IBS

Lovell et al [13] compiled 14 research studies that showed that the prevalence of IBS is significantly more common in female subjects, and furthermore, significantly more people under 50 years of age suffer from the condition than older patients.

People with somatic disorders, i.e. fibromyalgia, chronic fatigue syndrome [14] or other gastroenterological diseases, i.e. GERD, and dyspepsia, are also at higher risk for IBS.

Factors such as diet, history of abdominal or pelvic surgery, stress, adaptive disorders, or poor social conditions also have an impact. [15]

The best-described risk factor for IBS is a history of acute infectious diarrhea, which is characterized According to Adriani et al, [1] 10% of patients with IBS are affected. It can result from inflammation of the intestinal mucosa, changes in the immune processes of the mucosa and enteric nervous system, as well as disorders of the intestinal microflora. The risk of post-infectious IBS is favored by the aforementioned female gender, antibiotic use and severity of infection. [16]

Diagnosis and clinical picture of IBS

IBS is characterized by a complex and multifactorial pathogenesis, so the diagnosis requires a stepwise approach with the exclusion of organic disease and the fulfillment of the 2016 opulized Rome IV criteria. They represent the latest update of the diagnostic criteria for gut-brain interaction disorders, previously referred to as functional gastrointestinal disorders in the old Rome III Criteria. [17]

According to the latest criteria, IBS can be diagnosed if the patient has had abdominal pain for at least 1 day per week for at least 1 day per week in the past 3 months with the presence of symptoms for a minimum of 6 months prior to diagnosis, accompanied by at least 2 of the following 3 criteria: [18]

- association with defecation (1)
- association with a change in the frequency of bowel movements (2)
- association with a change in the appearance (consistency) of stool (3)

Depending on the predominant clinical picture, the Rome IV criteria distinguish 4 different subtypes of IBS: with predominant diarrhea (IBS-D), with predominant constipation (IBS-C), mixed form (IBS-M), and unclassified form (IBS-U). [19] The division into subtypes is based on stool consistency according to the Bristol Stool Formation Scale assessed at times when it deviates from normal. The Bristol Scale distinguishes 7 types of stool, [20] which are presented in Table 1.

Table 1. Bristol Stool Chart

Stool appearance	Type	Description
	1	Separate, hard lumps resembling nuts (difficulty in expelling them)
	2	Elongated, compact, but still lumpy
	3	Stool elongated but not lumpy, cracks on the surface
	4	Stool elongated, smooth and soft
	5	Soft separate pieces with clearly defined edges, easy to expel
	6	Stool mushy, flocculent, jagged pieces
	7	Liquid stool, without solid fragments, completely watery

Source: table adapted basing on the file licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. Available on: http://cdn.intechopen.com/pdfs-wm/46082.pdf.

The forms of IBS are classified as follows: [21]

- *IBS with predominant constipation (IBS-C):* >25% of stools with types 1 and 2; <25% of stools with types 6 and 7

- *IBS with predominant diarrhea (IBS-D):* >25% of stools with types 6 and 7; <25% of stools with types 1 and 2

- *Mixed form of IBS (IBS-M)*: >25% of stools with types 1 and 2; >25% of stools with types 6 and 7

- *Unclassified form of IBS (IBS-U)*: patients meeting the criteria for IBS who cannot be classified into 1 of the 3 groups above

In clinical practice, however, for IBS-C and IBS-D it is usually sufficient for a patient to report that the majority of stools passed are type 1 and 2 or type 6 and 7, respectively. [17] In a study conducted by Blake et al [20] 169 healthy volunteers provided a stool sample and used the Bristol Stool Form Scale to classify stool form, which was compared with measured stool water content and values obtained from 19 patients with IBS-D. It was estimated that 81% of the subjects rated their stool form correctly, and a significant difference was confirmed between the scale scores in healthy subjects (mean score = 3.7) and those with IBS-D (mean score 5.0). [20] This confirms the reliability of the Bristol Scale in terms of its usefulness in the diagnosis of IBS.

In most cases, the course of IBS is wavelike, with periods of hypotension and remission; symptoms can change over time - 2-18% of patients experience worsening, 30-50% maintain stable symptoms, while 12-38% of cases improve. [22]

When making a diagnosis, special attention should be paid to alarm symptoms such as onset of symptoms after age 50 unintentional weight loss, presence of blood in the stool, anemia, subfebrile states and fever, leukocytosis, ascites or a family history of inflammatory bowel disease, colon cancer and celiac disease. [23] These factors require the physician to expand the diagnostic workup, including a basic physical examination, per rectum examination, morphology, CRP, TSH, calprotectin, fecal lactoferrin anti-tTG and IgA antibodies (especially in the IBS-D form) [24] to rule out organic diseases.

IBS treatment

The goal of IBS therapy is to reduce abdominal pain and bowel complaints, often being targeted at the most bothersome symptom. [25] Treatment can be divided into non-pharmacologic and pharmacologic; it begins with lifestyle modification through dietary changes physical activity and consumption of soluble fiber, the next steps include drug therapy and psychological therapy. [25]

1. Diet

The general recommendations of international gastroenterological societies in IBS recommend eating regular meals at consistent times, avoiding oversized portions or skipping them altogether, drinking 2L of fluids a day, with restrictions on carbonated and alcoholic beverages, saturated fats, insoluble fiber and caffeine. [26]

When basic dietary changes do not have a satisfactory effect, it is recommended to introduce a diet low in FODMAPs, i.e. fermentable oligo-, di- and monosaccharides and polyols. These products pass unchanged into the intestine, causing fluid accumulation in its lumen due to osmotic properties. This results in increased intestinal motility. In the large intestine, these substances are fermented by bacteria, which produce excessive amounts of CO2 and H2O. In a further stage, hydrogen sulfide and methane are formed. This leads to abdominal discomfort, diarrhea or constipation and bloating. [27] Examples of high and low FODMAP foods are shown in Table 2.

IBS therapy based on a low FODMAP diet begins with the elimination of all high FODMAP products for 6-8 weeks, replacing them with low FODMAP products (phase 1). Examples of products are shown in Table 2. The patient's diet is then gradually expanded to include products with higher FODMAP content, and finally personalized in terms of limiting only those products with high FODMAP content that cause discomfort.

Table 2. Examples of high and low FODMAP foods

Products	Vegetables	Fruits	Protein sources	Milk and dairy products	Cereal products
High FODMAP content	garlic, onion, cabbage	apple, pear, peach	legume seeds	animal milk, soy milk, mascarpone	wheat bread, rye bread, wheat pasta
Low FODMAP content	cucumber, tomato, carrots, potatoes	banana, berries, strawberries	meat, fish, poultry	parmesan cheese, mozzarella, butter, rice/almond milk	spelt bread, oatmeal, rice

Source: own elaboration based on [27].

A meta-analysis by Black et al, [28] based on 13 randomized clinical trials comparing the degree of symptom distress of IBS patients following a low FODMAP diet and those following a normal diet, or any other type of diet, found that the low FODMAP diet was the most effective (RR of symptoms not improving=0.67; 95% CI 0.48 to 0.91, P-score=0.99). Other diets used for IBS do not have sufficient evidence of efficacy in scientific studies, and moreover may lead to worsening of nutritional status, in many cases eliminating foods of high

nutritional value. [29] Neither a gluten-free diet nor regular testing for food intolerances is recommended. [24] It is noteworthy, however, that FODMAP and other dietary modifications do not help every patient, so further treatment steps are often used, [29] including pharmacological treatment.

2. Physical activity and reduction of psychological discomfort

In order to prevent and treat IBS, it is essential to educate the patient about maintaining an adequate amount of physical activity.

Shababi et al [30] studied the effects of regular walking and yoga on the severity of IBS symptoms and the patient's overall well-being. A 6-month follow-up showed that regular walking helped the study patients reduce gastrointestinal symptoms and also had a positive effect on overall well-being.

Xu Gao et al [31] studied the effects of physical activity and amount of sleep on the occurrence of IBS. Among the initial 345,338 participants in the study, 19,885 cases of IBS were reported over a period of 8.45 years. Individual analysis showed that people with sedentary lifestyles, regardless of sleep duration, were at increased risk of IBS, while physical activity reduced the risk of IBS. Among people sleeping a maximum of 7h per day, replacing 1 hour of static activities with 1 hour of light physical activity, intense physical activity and sleep reduced the risk of IBS by 8.1%, 5.8% and 9.2%, respectively. In subjects sleeping more than 7 hours a night, light and intense physical activity reduced the incidence of IBS by 4.8% and 12.0%, respectively. However, a study by Ribichini et al [32] showed that while light to moderate physical activity can reduce IBS symptoms, very intense exercise can induce gastroenterological symptoms such as bloating, abdominal pain and diarrhea. This phenomenon is particularly common in professional athletes. It is worth noting that the topic of physical activity in IBS still has limited scientific evidence placement also requires further research.

Some authors indicate that, alternatively, cognitive-behavioral therapy [33] or psychodynamic therapy [34] and relaxation techniques may also have a positive effect on IBS symptoms, which, through stress reduction, emotion regulation, improved defense mechanisms and quality of life, may reduce the frequency/severity of IBS symptoms.

3. Modifications of the gut microbiota - prebiotics, probiotics, synbiotics

Because of the above-described proven influence of the intestinal microbiota on IBS symptoms, substances that allow modification of the composition of bacteria in the human postnatal tract through the supply of prebiotics, probiotics and synbiotics are used to relieve discomfort in IBS.

Probiotics are orally administered selected live bacterial cultures and yeast that have a positive effect on the gastrointestinal tract. Nobaek et al [35] showed that people with IBS-C have a reduced amount of bacteria from the genus *Bifidobaterium* and *Lactobacilli*. Bacteria from these genera have proven effects in reducing bloating, relieving abdominal pain, reducing stool frequency for diarrhea, and improving overall quality of life. [36] Positive effects on IBS have also been reported for cultures i.e. *Clostridium butyricum, Bacillus coagulans* and *S. salivarius subsp. Thermophilus.* [37] However, despite positive results in some studies, due to conflicting results, there is still no strict guideline on the proposed composition of bacterial culture combinations in formulations. [38]

Prebiotics are substances that are substrates for bacteria that colonize the human gastrointestinal tract, positively influencing intestinal health. They include inulin, oligofructose and galactolysaccharides, among others. [39] Prebiotics have been shown to stimulate the growth of important intestinal bacteria of the genus *Bifidobacterium*, in addition to increasing the amount of short-chain fatty acids in feces and reducing markers of inflammation. [40]

Prebiotics and probiotics are often combined into synbiotics, in which the former serve as a substrate for the latter, resulting in a synergistic effect. Prebiotics have been shown to reduce inflammation, reduce pathogenic bacteria in the gastrointestinal tract through competition, regulate intestinal contractility, modulate bile acid salt metabolism. [41]

4. Pharmacological treatment of IBS-D

Therapy for IBS with predominant diarrhea includes antibiotics (rifaximin), peripherally acting μ opioid receptor antagonists (loperamide), mixed μ and Ƙ opioid receptor agonists and δ receptor antagonists (eluxadoline), ion exchange resins (cholestyramine, colestipol, colesevelam), and 5-HT3 receptor antagonists (ondasetron, ramosetron). [1]

Rifaximin, which is a non-absorbable gastrointestinal antibiotic belonging to the rifamycin group, has shown efficacy in bloating and reducing the frequency of watery stools. In addition, rifaximin reduces methanogenic bacteria, which improves intestinal transit. [24] It

is recommended to use it at a dose of 1600 mg/day (4 times 2 tablets each) for 14 days with the possibility of cyclic therapy. At least one-month intervals should be maintained between cycles. Rifaximin relative to other drugs used in IBS-D shows the best safety profile. [42]

Loperamide is a synthetic opioid drug, devoid of analgesic effects, which, acting on opioid μ receptors in the intestinal wall, causes a decrease in the secretion of prostaglandins and acetylcholine, increases water and electrolyte resorption by enterocytes. This results in inhibition of peristaltic movements and an increase in rectal sphincter tone, in addition, it decreases water and electrolyte loss, thus reducing the frequency and volume of bowel movements. [3] Loperamide does not cross the blood-brain barrier, so it does not act centrally. [3] It is often the drug of first choice in IBS-D, and can be used permanently in chronic diarrhea, as well as only when symptoms are present. However, it should be remembered that loperamide should be used with caution, especially in cases of mixed symptoms, as it can lead to severe constipation, and can also cause abdominal pain in a few cases. [4] The daily dose ranges from 2 mg/d to 16 mg/d). [1]

Eluxadoline is a relatively new drug, approved for the European market in 2016. Its effects partially overlap with loperamide - through agonism to opioid μ receptors, it reduces the severity of peristalsis, while its antagonistic action on δ receptors results in a reduction of visceral pain. In a study by Lembo et al, [43] 2427 patients with IBS-D received eluxadoline 75 mg or 100 mg or placebo twice daily. The endpoint was a reduction in the severity of abdominal pain and the achievement of optimal stool consistency on the same day for at least half of the days during the observation period from week 1 to week 12. Over the study period, the endpoint was achieved by 28.9% of subjects taking eluxadoline 75 mg and 29.6% taking 100 mg compared to 16.2% receiving placebo, demonstrating the significant efficacy of eluxadoline in the treatment of IBS-D symptoms. However, its intake may be associated with side effects, i.e. nausea, constipation, abdominal pain and, in a few extreme cases, acute pancreatitis, hence the drug is contraindicated in patients with a history of IBS, gallstones or alcohol abuse. [19]

Approximately one-third of IBS-D patients have biliary diarrhea, [44] and ion exchange resins are used in therapy, which have a proven effect in improving stool consistency and reducing increased intestinal peristalsis. Because of the risk of constipation, therapy should begin with a low dose, [1] which can then be gradually increased.

The last group of drugs in IBS-D are 5-HT3 receptor antagonists. These drugs through central and peripheral mechanisms not only provide relief from nausea and vomiting, for

which they are best known, but also reduce peristalsis, stool pushing and abdominal pain, hence they are among the most effective drugs in the diarrheal form of IBS. Introducing them into therapy requires prior evaluation of the risk of ischemic colitis and constipation. [45]

5. Pharmacological treatment of IBS-C

Pharmacological therapy for IBS with predominant constipation is usually started with fiber supplementation and bulking agents (laxatives). [1] It is important that this be soluble fiber (e.g., psyllium, ispaghula), as sources of insoluble fiber can exacerbate symptoms such as abdominal pain and bloating. In addition, to avoid them, it is recommended to consume 3-4 g of fiber per day initially, and then gradually increase the amount up to 30 g. [46]

Laxatives, including polyethylene glycol (PEG), also known as macrogol, are used relatively frequently in IBS-C. Some studies have shown its peristalsis-stimulating properties, but since it has no abdominal pain-reducing effect, it should not be used as monotherapy. [47]

An alternative treatment is prucalopride , a 5-HT4 receptor agonist and prokinetic, which in studies has shown significantly better effects than placebo in reducing chronic constipation .[5] Other drugs in this group, i.e. cisapride or tegaserod, are not as often used, due to their cardiotoxic effects; however, prucalopride, which has a much higher affinity for 5-HT4 receptors, has no negative cardiovascular effects. [19] It should be noted, however, that it is an expensive drug.

For IBS-C symptoms, one of 4 intestinal secretagogues is often recommended: lubiprostone, linaclotide, plecanatide and tenapanor. These drugs interact with the ion channels of intestinal cells to cause water secretion, softening the consistency of stool in constipation. [47] Lubiprostone interacts with type 2 chloride channels, linaclotide and plecanatide with the guanylate cyclase receptor and CFT4 channel, while tenapanor is a sodium reuptake inhibitor via sodium-hydrogen exchanger-3. In a meta-analysis involving 15 randomized control trials, [48] all of the above drugs showed greater efficacy in treating IBS-C than placebo. Linaclotide showed the greatest efficacy in terms of abdominal pain and peristalsis, while tenapanor had the best effect in terms of reducing bloating. Plecanatide showed the greatest safety profile, and lubiprostone was the least likely to cause diarrhea. [48]

6. Pharmacological treatment of IBS-M and IBS-U

Mixed and unidentified forms of IBS present a therapeutic challenge, as it is difficult to standardize the clinical profile of a given patient. Each case must be treated individually, so a detailed history is an essential part of diagnosis. Depending on whether a given patient is

more bothered by diarrhea or constipation at a given time, he or she is selected for a drug regimen from those described above for IBS-D and IBS-C therapy. One should start with small doses of medication, carefully observing whether stool consistency changes too much. [19]

7. Treatment for abdominal pain

The drugs described above such as laxatives, anti-diarrheal drugs and prokinetics have a significant effect on peristalsis and stool consistency, but sometimes they do not have a sufficient analgesic effect. Spasmolytics, which by relaxing the intestinal musculature, bring pain relief to the patient, cope with this dora.

In all types of IBS drugs are used, i.e. dicyclomine, otilonium and mebeverine. Their mechanism involves anticholinergic properties (dicyclomine) or calcium channel inhibition (otilonium, mebeverine). Studies have shown their significant advantage over placebo. Peppermint oil also has similar properties. [1] Another therapeutic is trimebutine, which not only has a spasmolytic effect, but also has agonist properties toward μ, κ and δ intestinal opioid receptors, thereby modifying pain sensitivity by acting on smooth muscle, visceral nerves and intersitial cells of Cajal that play a key role in regulating intestinal motility. [49]

Antidepressants, which reduce pain sensation and regulate the brain-gut axis, can also be used to reduce pain. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are used in IBS, while there is little information for serotonin-norepinephrine reuptake inhibitors (SNRIs). [1] Since TCAs can cause constipation as a side effect, they are better used in IBS-D. TCAs may also better benefit patients suffering from anorexia, weight loss or eating problems. In IBS-C, SSRIs seem to be a better choice, as one of their side effects is potential diarrhea. It is important to start with low doses of antidepressants and increase them gradually until a satisfactory effect is achieved. [1]
A summary of IBS therapy is shown in Table 3.

Table 3. Summary of therapies for IBS

IBS SYMPTOM	TREATMENT
Diarrhea	Rifaximin (1600 mg/day [4 times 2 tablets] for 14 days) Loperamide (2-4 mg/d, up to 16 mg/d) Eluxadoline (100 mg b.i.d.). Ion exchange resins: • cholestyramine (9g b.i.d.-t.i.d.) • colestipol (2 g q.d.-b.i.d.) • celesevelam (625 mg q.d.-b.i.d.) 5-HT3 receptor antagonists: • ondasetron (4-8 mg t.i.d.) • ramosetron (5 mg q.d.)
Constipation	Soluble fiber: psyllium (up to 30 g/d in divided doses) Laxatives: polyethylene glycol (17-34 g/d) Type 2 chloride-channel activator: lubiprostone (8 µg b.i.d.) Guanylate cyclase-C agonist: linaclotide (290 µg q.d.)
Pain	Antispasmodics: • dicyclomine (10-20 mg q.i.d.). • otilonium (40-80 mg b.i.d.-t.i.d.).

	• mebeverine (135 mg t.i.d.) Peppermint oil: 250-750 mg, b.i.d.-t.i.d. Tricyclic antidepressants: • amitriptyline (10-50 mg/d) Selective serotonin reuptake inhibitors: • paroxetine (10-40 mg/d) • sertraline (25-100 mg/d)
Other	Diet (FODMAP), physical activity, hypnotherapy, psychotherapy, relaxation training, probiotics, prebiotics, synbiotics

Source: own elaboration based on: [1]

Summary

Irritable bowel syndrome (IBS) is a common condition that significantly reduces patients' quality of life. IBS symptoms can be linked to a variety of factors, including stress and diet, suggesting that treatment should be multifaceted. Studies have found that an approach that includes lifestyle modifications, pharmacotherapy and psychological support can improve patients' health. At the same time, more research is needed to better understand the pathophysiological mechanisms of IBS and develop more effective treatments. IBS remains a challenge for medicine, requiring an individualized approach to the patient.

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