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# Review of the Latest Therapeutic Approaches in the Management of Irritable Bowel Syndrome

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## ABSTRACT

Irritable bowel syndrome (IBS) is a common and chronic bowel disease which, although it does not lead to severe and permanent complications, significantly deteriorates patients' quality of life. It constitutes a considerable psychological burden for them and also represents a significant socio-economic problem for the healthcare system.

Although the cause of the disease is complex and still not fully understood, the update of the Rome criteria has led to significant progress in understanding the pathophysiology of the disease and researching alternative treatment methods. As a result, modern therapeutic approaches can be better tailored to the predominant symptoms and individual needs of the patient.

This review compiles the latest research findings on the etiopathogenesis of the disease and discusses available therapeutic strategies, including options unavailable in Poland. This enables a better selection of effective therapy and achievement of satisfactory treatment outcomes through a more individualized approach, tailored to the patient's specific clinical profile.

**Keywords:** ibs, irritable bowel syndrome, gut microbiota, abdominal pain, constipation, diarrhea, rifaximin, neuromodulators

## INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic bowel disease classified as a disorder of the gut-brain axis interaction. Although the prognosis for this condition is good, its troublesome symptoms significantly affect the quality of life and work of those affected. Patients complain of recurrent abdominal pain associated with defecation, a variable bowel movement rhythm, and stool consistency. IBS occurs worldwide, although its prevalence varies depending on

countries and continents. It is estimated to affect 11% of the general population, occurring twice as often in women, with half of the patients reporting symptoms before the age of 35 [1]. So far, no definitive cause of the disease has been established. It is believed that its development may result from various factors. The primary symptom of IBS, present in all patients, is abdominal pain. It can be constant or recurrent, appearing in any area, though most commonly located in the lower abdomen and the lower left side. Patients describe the pain as severe, cramping, and distressing, yet it never wakes them up at night. Abdominal bloating and a sensation of gurgling dominate.

According to the Rome IV criteria, in effect since 2016, to diagnose irritable bowel syndrome, abdominal pain must occur on average at least 1 day per week for the last 3 months (with symptoms appearing at least 6 months earlier) and must meet 2 out of the following 3 criteria: be related to defecation, a change in stool frequency, or a change in stool consistency.

IBS occurs in four forms: with predominant constipation (IBS-C), with predominant diarrhea (IBS-D), with mixed bowel habits (IBS-M), and in an unclassified form (IBS-U). To determine the predominant stool form in patients, who often misidentify their stool consistency, the Bristol Stool Scale can be helpful. Diarrhea in IBS is often preceded by sudden urgency - especially after meals, stress, or in the morning hours. In contrast, with constipation, bowel movements become less frequent, passing stool requires effort, and stools are hard, lumpy, and resemble nuts. Mucus in the stool is also frequently observed.

Additionally, patients report frequent urination, menstrual irregularities, and often experience headaches and fatigue. Constant worry about bowel movement patterns and related issues generate anxiety, social withdrawal, and - in severe cases - may even lead to depressive states. The disease itself has a psychosomatic basis, which means these symptoms can also intensify through a vicious cycle mechanism.

Before diagnosing IBS, for which there is currently no ideal treatment, other conditions that may cause similar symptoms should be ruled out, especially in cases of nonspecific complaints such as fever, blood in the stool, anemia, or weight loss. Comprehensive diagnostics are crucial for an accurate diagnosis and appropriate treatment selection.

The number of people suffering from IBS is systematically increasing, highlighting the need for the development of new therapeutic methods that are more effective and better adapted to the individual mechanisms of the disease, whose primary cause has still not been precisely identified [2].

## ETIOPATHOGENESIS

With the update of the Rome criteria in 2016 and the progress of research, there has been a shift in understanding the pathophysiological mechanisms of this disorder, moving attention from functional causes to complex disorders of the brain-gut axis regulation. The brain-gut axis is a bidirectional system connecting the central nervous system with the gastrointestinal tract, regulated by neurogenic, endocrine, and immune mechanisms, additionally modified by the gut microbiota [3].

Visceral nociceptors, reacting to contractions, distension, or inflammation of the intestines, transmit impulses via afferent pathways through C-type nerve fibers. These signals are transmitted through sympathetic nerves via neural ganglia to the spinal cord, as well as through dorsal root ganglia to the posterior horn of the spinal cord. There, via ascending pathways, stimuli are transmitted to the thalamus, somatosensory cortex, and other brain regions responsible for pain perception, including the limbic system, insula, and prefrontal cortex. Once the brain registers the pain information, it is modulated through a gate control mechanism via descending fibers from the brainstem, which have the ability to regulate the sensitivity of posterior horn neurons. This enables the modification of visceral sensitivity and central pain perception, which occurs through two neurotransmitters - serotonin (5-HT) and noradrenaline (NA).

In the pathogenesis of IBS, the development of visceral hypersensitivity results from disturbances in the generation, transmission, and processing of pain stimuli. It may also be a consequence of an abnormal response to these stimuli, related to a dysfunctional pain inhibition mechanism [2]. A correlation has been observed between hypersensitivity of sensory nerve endings in the intestines and increased production of certain neurotransmitters, such as serotonin and substance P. Serotonin plays a key role as a neurotransmitter, as nearly 95% of its total amount is found in the gastrointestinal tract. In recent years, the discovery of serotonin receptors (5-HT3 and 5-HT4) has enabled the development of new IBS treatment methods, based on the use of agonists and antagonists of these receptors [2]. In recently published clinical studies, higher expression levels of Takeda 5 protein coupled with G protein in the colonic mucosa of IBS patients compared to the healthy population have also been demonstrated. Increased levels of short-chain fatty acids and bile acids, mainly associated with gastrointestinal absorption disorders, as well as elevated production of tryptophan, hydrogen, and methane, were also observed [4-5]. Higher concentrations of hydrogen and methane in the gastrointestinal tract result from disturbances in digestion and fermentation

processes of the gut microbiome. They influence the slowing down of intestinal transit, which in turn leads to motility disorders of the gastrointestinal tract, causing bloating, constipation, and abdominal pain [5].

Interestingly, a study published in 2021 demonstrated that chronic abdominal pain in IBS patients is associated with structural remodeling of certain brain areas. Increased volume and thickness of the gray matter in the somatosensory cortex and subcortical areas were observed, as well as a reduction in volume, surface area, and thickness of the gray matter in the posterior insula and superior frontal gyrus [6-7]. Moreover, other studies have shown the presence of autonomic nervous system dysfunction in IBS patients, manifested by decreased or increased activity of the vagus nerve or the sympathetic system. Such autonomic dysfunction may also affect visceral perception and play a role in pain perception [7].

Additionally, throughout the entire gastrointestinal tract, there are endocrine cells equipped with sensory microvilli. These microvilli allow for the detection of pressure changes within the intestines in the presence of food, leading to the release of neuroendocrine substances into the lamina propria of the intestinal wall. Studies have shown that substances secreted by these cells, such as histamine, 5-hydroxytryptamine (5-HT), glutamate, and noradrenaline, contribute to the intensification of visceral pain, while gamma-aminobutyric acid (GABA) affects the slowing down of gastrointestinal transit [7].

Beyond visceral hypersensitivity and abnormal gastrointestinal motility, one of the most important etiological factors of irritable bowel syndrome is gut microbiota disturbances. It is estimated that 30-85% of IBS patients have an excessive overgrowth of the gut microbiome (SIBO) [2], which is a manifestation of gastrointestinal dysbiosis. Currently, as a result of the update of the Rome criteria, patients suffering from SIBO have been separated from the group of IBS patients, leading to a decrease in the incidence of irritable bowel syndrome. However, it should be emphasized that this is not due to a reduction in morbidity but rather an effect of changes in the qualification criteria for this disease. Nevertheless, both conditions may coexist simultaneously [3]. Microbiota composition disturbances also affect patients who have previously experienced an acute infectious episode of gastroenteritis. It is believed that in as many as 20% of cases, the disease concerns post-infectious irritable bowel syndrome [2]. The incidence in this group is up to seven times higher than in the group of patients who have not previously had such an infection.

The gut microbiota is a kind of "superorganism" consisting of various microorganisms such as bacteria, viruses, and other eukaryotes inhabiting the human body, with the gastrointestinal

tract being its primary habitat. Maintaining a proper microbiota balance, both quantitatively and qualitatively, is crucial for maintaining health. Dysbiosis - the disruption of this homeostasis, plays a significant role in the pathogenesis of irritable bowel syndrome. As a result, there is a decrease in the number of beneficial bacteria in favor of pathogenic microflora, leading to gastrointestinal dysfunction, including increased intestinal permeability and associated with it unpleasant symptoms [2].

In the gut microbiota of IBS patients, a reduction in the number of beneficial bacteria from the Lactobacillus and Bifidobacterium genera has been found, with a simultaneous increase in the numbers of Escherichia coli, Streptococcus, and bacteria from the Clostridium spp. genus. Additionally, an imbalance between Bacteroidetes and Firmicutes strains has been observed [8]. The most numerous group of bacteria in the gut microbiota consists of Lactobacillus species, which have the ability to produce lactic acid. Their species diversity contributes to the specificity of the intestinal ecosystem and can influence the activation of different signaling pathways in the immune system. It has been proven that Lactobacillus plantarum, a probiotic bacterium that has been present in plant products for thousands of years, protects against the increase in intestinal permeability caused by E. coli, which is present in greater quantities in the gut microbiota of IBS patients. Unfortunately, the development of the food industry and modern food preservation methods contribute to the reduction of L. plantarum consumption, reinforcing the view that taking probiotics, especially those containing the mentioned bacterium, has a beneficial effect on gut microbiota in these patients [9].

Besides, increased intestinal permeability due to dysbiosis predisposes to the release of neurotransmitters and inflammatory cytokines, creating ideal conditions for the development of a state called neuroinflammation. The composition of the gut microbiota exerts such a strong influence on brain function, behavior, and cognitive abilities that some authors, including Dinan et al. [10], have proposed expanding the concept of brain-gut axis interaction to a brain-gut-microbiota axis. Moreover, it is estimated that as many as 70-90% of patients suffer from personality disorders, depression, or increased anxiety [11]. The number of studies indicating a link between dysbiosis and the risk of psychiatric disorders, especially in the context of depression and anxiety disorders, continues to grow. Research findings indicate that the gut microbiota composition in the healthy population differs significantly from that observed in patients with depression [12]. Furthermore, a recently conducted meta-analysis found that the use of antidepressants is associated with changes in the composition of gut microbiota. Among the most significant in this regard is Escitalopram, which shows the

greatest ability to inhibit bacterial overgrowth. However, its action also affects the inhibition of beneficial bacteria growth, such as L. rhamnosus and B. bifidum [13-14].

## NON-PHARMACOLOGICAL TREATMENT

Although many factors contributing to the occurrence of irritable bowel syndrome have been identified, its etiology has not yet been clearly determined. As a result, at this moment, we do not have a causal treatment and are continuously searching for the most appropriate symptomatic therapy. In IBS patients, in addition to pharmacological treatment, non-pharmacological management is equally important. Attention is drawn to the role of moderate physical activity, weight reduction until BMI normalization, sleep hygiene, and stress management skills. As previously mentioned, psychological factors play a significant role in the pathophysiology of the disease, including increased anxiety, personality disorders, depression, and difficulties in coping with stress [15]. It is therefore not surprising that this issue has attracted considerable research interest. The largest number of analyses has been dedicated to the effectiveness of cognitive-behavioral therapy in the treatment of irritable bowel syndrome (IBS). Other forms of psychotherapy have also been considered in studies. Particularly effective have been cognitive-behavioral therapy, hypnosis, and complex psychotherapy. It is also worth noting the effectiveness of acupuncture due to its long-term effects [1].

In some IBS patients, especially those with coexisting SIBO symptoms, adherence to a low-FODMAP diet brings relief from ailments along with an improvement in quality of life. This diet is characterized by a low content of fermentable oligo-, di-, and monosaccharides as well as polyols. Studies show that easily fermentable, poorly absorbed carbohydrates with high osmotic pressure, such as fructose, lactose, fructans, and polyhydroxy alcohols (sorbitol, mannitol, and xylitol), can contribute to the exacerbation of irritable bowel syndrome symptoms. Although the low-FODMAP diet yields satisfactory results, it is an elimination diet that is both gluten-free and lactose-free, which can lead to significant changes in gut microbiota composition, metabolism of intestinal epithelial cells, and contribute to the development of vitamin and mineral deficiencies, which may have serious consequences with prolonged use. For this reason, it is recommended to follow the diet for about six weeks and then gradually reintroduce products to expand the diet. A gluten-free diet or any elimination diet is not recommended for long-term use in these patients [16]. Furthermore, patients with all forms of IBS are advised to regularly supplement with soluble fiber at a dose of 10–25g

per day (e.g., psyllium husk, oat bran), rather than insoluble fiber, which was previously recommended. Studies have shown that insoluble fiber, found in wheat bran or flaxseed, exacerbates pain, bloating, and constipation [1].

In alleviating disease symptoms, especially bloating, a feeling of fullness, and abdominal pain, the herbal preparation STW 5, containing extracts from nine plants, has been found to be effective. This product exhibits anti-inflammatory properties, prevents excessive intestinal epithelial permeability in the colon, restores gut microbiota balance, and regulates the contractile activity of intestinal smooth muscle, providing the so-called eukinetic effect [17].

To mitigate symptom severity, regular consumption of peppermint oil is also recommended. This substance, through calcium channel blockade and direct interaction with the enteric nervous system, leads to smooth muscle relaxation. Additionally, it has visceral sensory-modulating, antibacterial, and anti-inflammatory properties. However, it is worth noting that, according to a study conducted by Alam et al. [18], intestinal symptoms tend to recur after discontinuation of peppermint oil. Therefore, due to the lack of long-term safety and efficacy studies, its use is recommended for no longer than 12 weeks [1].

In addition to a well-balanced diet, special attention should be given to the use of appropriately selected probiotics in restoring gut microbiota balance. It is recommended to carefully choose strains that have been studied for efficacy and safety and to select a single probiotic for a minimum period of four weeks to properly assess its effects on the patient. As previously mentioned, the Lactobacillus plantarum species is particularly recommended for IBS patients due to its well-documented efficacy in alleviating troublesome symptoms such as bloating and abdominal pain [19]. Other studies also suggest the use of probiotics containing Saccharomyces boulardii or Bifidobacterium infantis [1].

## PHARMACOLOGICAL TREATMENT

In combating pain and bloating, in the absence of expected effects after implementing non-pharmacological management, the use of antispasmodic drugs is suggested as the first-line treatment in all forms of IBS. Antispasmodic medicines constitute a large, heterogeneous group of relatively safe medicinal substances, characterized by various mechanisms of action and levels of effectiveness. Therefore, it is recommended to take those antispasmodic medications whose efficacy in alleviating IBS symptoms has been confirmed in randomized, placebo-controlled trials. Among those available in Poland, drotaverine and hyoscine are distinguished [1, 20-21].

In all non-constipated forms of IBS (IBS-D, IBS-M, IBS-U), in cases of persistent pain, bloating, and diarrhea, a 14-day therapy with rifaximin α at a dose of 4 x 400 mg or 3 x 400 mg per day is recommended, with the caveat that the latter is expected to be less effective. The key studies confirming the effectiveness of rifaximin α in treating IBS symptoms turned out to be the TARGET 1 and TARGET 2 studies. In contrast, in the case of recurrence therapy in patients, the TARGET 3 study was of significant importance, as it demonstrated treatment efficacy even in two subsequent relapses in patients who responded positively to initial therapy [22-23]. Rifaximin α is the only known eubiotic that helps restore the proper composition of the intestinal microbiota. It selectively acts on harmful bacteria such as Clostridium, Peptostreptococcaceae, and Escherichia, while after 14 days of therapy, it also increases the number of beneficial bacteria, such as Bifidobacterium, Lactobacillus, and Faecalibacterium prausnitzii. Moreover, it exhibits anti-inflammatory, immunomodulatory effects and restores intestinal barrier integrity - each of these mechanisms plays an important role in treating IBS symptoms [1].

One of the commonly used drugs in the IBS-D form is loperamide. Although it does not reduce overall IBS symptoms, it effectively decreases the severity of diarrhea.

On the other hand, polyethylene glycol (PEG) preparations - macrogols - may prove to be a valuable option for patients with IBS-C, as they exhibit a laxative effect. Similar to loperamide, these drugs do not alleviate overall IBS symptoms, and therefore, they are intended solely for use as supportive therapy [1].

**NEUROMODULATORS**

In cases of unsatisfactory effects after the application of the above-mentioned treatment methods, the use of neuromodulators - also referred to as antidepressants and anxiolytics - proves helpful in alleviating symptoms. The term “neuromodulators” is increasingly used instead of “antidepressants” in the context of IBS treatment because it emphasizes their impact on the enteric nervous system rather than the patient’s mental state. This term better reflects the medication’s mechanism of action in the context of the disease while also avoiding the stigmatization of patients for whom depression is not the primary issue. However, it is worth remembering that depression may coexist due to the significant role of psychological factors in the mechanisms of disease development. Given that IBS is caused by a disruption in the gut-brain axis interaction, neuromodulators are intended to normalize its function. In addition to treating coexisting mental disorders, they regulate intestinal motility,

improve the central modulation of visceral signals, and enhance neurogenesis [24]. When selecting an appropriate neuromodulator for a patient, both its pharmacological properties and the dominant clinical symptoms should be taken into account. The most commonly used neuromodulators in IBS treatment include TCA - tricyclic antidepressants, SSRI - selective serotonin reuptake inhibitors, and SNRI - serotonin-norepinephrine reuptake inhibitors. Polish guidelines suggest using these medicines at the lowest possible doses for a period of four to twelve weeks, with no clearly defined maximum duration of therapy. Therefore, if the treatment is effective and well tolerated by the patient, it may be continued for a longer period [1].

**TCA**

Tricyclic antidepressants (TCA) are central neuromodulators whose mechanism of action is based on varying degrees of inhibition of serotonin (5-HT) and norepinephrine (NA) reuptake. Moreover, individual TCAs exhibit additional effects due to their affinity for serotonergic, histaminergic, or muscarinic receptors and may inhibit dopamine (DA) reuptake. For this reason, TCAs have a stronger analgesic effect compared to other antidepressants that selectively act on only one monoaminergic system, such as selective serotonin reuptake inhibitors (SSRI). This group modulate pain at the central level by influencing the ascending afferent pathways of visceral receptors and central pain processing mechanisms. Peripherally, they act by altering histaminergic and/or cholinergic transmission within the intestines, resulting in slowed intestinal transit. Furthermore, they stimulate interneurons that secrete substances with an inhibitory effect on intestinal motility, such as gamma-aminobutyric acid (GABA) and endogenous opioids, and by blocking the NMDA receptor, they contribute to a reduction in abdominal pain perception. Therefore, they are particularly recommended for patients with the diarrheal form of irritable bowel syndrome (IBS-D) [25].

However, their complex mechanism of action also leads to an increased risk of side effects. Most of them result from the anticholinergic effect, causing, among others, blurred vision, dry mouth, constipation, and difficulty urinating. Frequently occurring dizziness or orthostatic hypotension are due to antagonism towards α1-adrenergic receptors. QT interval prolongation, headaches, drowsiness, and sexual dysfunctions are additional adverse effects characteristic of TCAs, which is why, before initiating therapy, the condition of the cardiovascular system should be checked, at least by performing a basic electrocardiographic examination [24].

**SSRI**

Selective serotonin reuptake inhibitors (SSRI) act by blocking the presynaptic serotonin transporter (SERT), thereby inhibiting serotonin reuptake into the neuron. As a result, more serotonin remains in the synaptic cleft, leading to increased activation of postsynaptic receptors.

SSRI significantly affect gastrointestinal function, especially since approximately about 95% of serotonin is located in the intestines. Increasing its concentration leads to stimulation of 5-HT3 and 5-HT4 receptors, which enhances intestinal peristalsis, resulting in loose stools and diarrhea. This effect is utilized in patients with the constipated form of irritable bowel syndrome (IBS-C). However, due to the lack of noradrenergic action, SSRIs do not relieve pain and, therefore, will not be effective in patients where abdominal pain is the predominant symptom. Their primary serotonergic effect will bring more benefits to patients whose IBS symptoms are associated with anxiety, phobias, or obsessive-compulsive disorders. It is worth noting that although all SSRIs share the same mechanism of action, each of them has unique additional pharmacological properties. Paroxetine, for example, has additional anticholinergic effects, which means that its use - unlike other SSRIs - may result in constipation [14], while citalopram modulates the tone and excitability of the large intestine [25].

**SNRI**

The action of serotonin-norepinephrine reuptake inhibitors is similar to that of SSRI, with the difference that, in addition to serotonergic transmission, they also enhance noradrenergic signaling. As a result, SNRIs exhibit strong analgesic properties while not causing the typical side effects of TCAs related to antihistaminergic and anticholinergic effects. This translates into a better safety profile for this group. SNRI representatives include duloxetine, milnacipran, and venlafaxine. SNRIs are indicated for the treatment of neuropathic pain and fibromyalgia; however, their effectiveness in treating visceral pain has not yet been sufficiently studied. Nevertheless, they are often used off-label for this purpose as an alternative to TCAs, offering a lower risk of adverse effects [14]. Duloxetine may benefit IBS patients in whom chronic abdominal pain predominates, especially if accompanied by depression or anxiety. In rodent studies, milnacipran was found to be effective in alleviating visceral pain in irritable bowel syndrome models, indicating its potential effectiveness in IBS treatment. However, its impact on human symptoms has not yet been thoroughly studied and requires further observation [26]. Venlafaxine, on the other hand, may prove effective in alleviating gastrointestinal symptoms in IBS patients experiencing coexisting stress, anxiety,

and depressive symptoms. However, it should be emphasized that achieving venlafaxine's analgesic effect requires a minimum dose of 175 mg per day to activate its noradrenergic component. Since SNRIs cause less constipation than TCAs, their use should be considered when selecting therapy for patients with the constipated form of irritable bowel syndrome (IBS-C), especially if accompanied by anxiety or depression [25].

## PHARMACEUTICALS NOT AVAILABLE IN POLAND

In cases of severe disease course resistant to previous treatments, symptom relief may be provided by new medications that have been studied for all forms of IBS and registered for use in other countries but are not yet available in Poland. These drugs act on various intestinal receptors and are intended for the treatment of the constipated form IBS-C (linaclotide, plecanatide, lubiprostone) and the diarrheal form IBS-D (alosetron, eluxadoline) [2].

### In the constipated form IBS-C

### LINACLOTIDE

Studies have shown that linaclotide is an effective medicine for alleviating overall IBS symptoms in patients with the constipated form. Linaclotide is an agonist of guanylate cyclase-C (GC-C) receptors located in the intestinal mucosa, on the luminal side. By binding to these receptors, it increases the production of cGMP, activates chloride channels, and subsequently enhances fluid and electrolyte secretion. As a result, intestinal motility increases, which is why linaclotide is used exclusively by patients with the constipated form. Additionally, elevated cGMP levels reduce the sensitivity of afferent nociceptors, contributing to the relief of visceral hypersensitivity and abdominal pain. Consequently, all these mechanisms effectively lead to the reduction of IBS-C symptoms as a whole. The effective drug dose has been established at 290 μg per day. However, due to the lack of long-term safety studies, the recommended treatment duration is six months. The manufacturer also states that if no improvement is observed after four weeks of use, reconsideration of therapy continuation is advised [1, 27].

### PLECANATIDE

Another GC-C receptor agonist recommended for treating the constipated form of IBS is plecanatide. Its action is similar to linaclotide, with the difference that its activation depends on pH levels. Clinical studies have shown that plecanatide significantly increases bowel movement frequency, alleviates the sensation of straining, improves stool consistency, reduces

bloating and abdominal pain compared to placebo. Abdominal pain relief is a clinically significant achievement, as it is a key indicator of IBS severity, reduced health-related quality of life, and increased healthcare utilization. A recommended dosage is 3 mg per day for 12 weeks [1, 28].

**LUBIPROSTONE**

Lubiprostone is a derivative of prostaglandin E1 and a type 2 chloride channel activator in the gastrointestinal tract. Its mechanism of action is based on stimulating the secretion of sodium chloride and water by enterocytes and colonocytes, leading to accelerated intestinal transit and relief of constipation symptoms. Additionally, clinical data indicate that lubiprostone therapy resulted in significant improvement in all major IBS-C symptoms, including abdominal pain, bloating, the sensation of straining, and constipation severity. An increase in bowel movement frequency and improved stool consistency were observed. An effective treatment dose was identified as 8 μg administered twice daily, with therapeutic effects lasting for up to three months for most symptoms [1, 29].

**In the diarrheal form IBS-D**

**ALOSETRON**

One of the factors involved in the pathogenesis of IBS is intestinal motility dysfunction, associated with impaired regulation of the 5-hydroxytryptamine (5-HT) pathway. Patients with diarrhea-predominant IBS (IBS-D) have elevated plasma levels of 5-HT, making this pathway a target for pharmacological therapy. In this context, 5-HT3 receptor antagonists, which slow intestinal transit, are utilized. Alosetron, a potent and selective 5-HT3 receptor antagonist, not only modulates colonic motility and improves bowel movement parameters (frequency and stool consistency) but also effectively alleviates abdominal pain through central and peripheral mechanisms that reduce visceral hypersensitivity. Consequently, it enhances the quality of life for patients with IBS-D. However, may cause serious adverse effects, including acute ischemic colitis and constipation, leading to its temporary market withdrawal at one point. After several years, it was reintroduced but with significant restrictions. Currently, alosetron is recommended exclusively for women with severe, disabling diarrhea-predominant IBS, with therapy initiation advised at low doses [1, 30-31].

**ELUXADOLINE**

In 2015, alongside rifaximin, the FDA approved eluxadoline for the treatment of IBS-D in both women and men. Eluxadoline is a poorly absorbable, locally acting mixed agonist of μ-

and ƙ-opioid receptors, as well as an antagonist of δ-opioid receptors. Opioid receptors in the intestines play a key role in regulating essential gastrointestinal functions such as motility, secretion, digestion, and visceral sensation. While μ-opioid receptor activation slows intestinal transit and reduces gastrointestinal secretion, δ-opioid receptor antagonism weakens these effects. Consequently, bowel function is normalized, producing an effect more similar to the natural physiological activity of the colon, unlike the effects of non-antagonized μ-opioid receptor agonists such as loperamide [32]. Eluxadoline alleviates overall IBS-D symptoms, though its therapeutic effect is more pronounced in reducing diarrhea than in alleviating other general complaints. Due to its peripheral mechanism of action, it does not cause the characteristic opioid-related side effects. The medicine is generally well tolerated and can be used chronically. However, it should be emphasized that its use is contraindicated in individuals who have undergone cholecystectomy, suffer from pancreatitis, have severe liver disease, problems with the sphincter of Oddi, or abuse alcohol, due to the risk of acute pancreatitis. This warning should be conveyed to all patients for whom therapy is being considered [1].

## CONCLUSIONS

With the update of the Rome criteria in 2016, the perception of irritable bowel syndrome shifted from a psychosomatic functional disorder to a complex disorder of brain-gut axis regulation, which some view as the brain-gut-microbiota axis. This change has driven further research into the exact etiopathogenesis of the disease. It is now known that IBS-related abdominal symptoms result from visceral hypersensitivity, an increased amount of neuroendocrine substances secreted by gastrointestinal endocrine cells, an abnormal gut microbiota composition leading to increased intestinal permeability, and impaired gastrointestinal motility. Advancements in understanding the causes of the disease have enabled the development of clinical studies aimed at maximizing the effectiveness of currently used treatment methods through a more individualized approach tailored to the patient's dominant symptoms, but also has encouraged the search for new, alternative treatment methods targeting specific receptors.

**Disclosure**

**Authors' contribution:**

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Formal analysis: Igor Zydlewski
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The authors deny any conflict of interest.

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