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Therapeutic strategies in irritable bowel syndrome: current standards, emerging options and future challenges

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Abstract: The development of safe and efficient therapeutic interventions in irritable bowel syndrome (IBS) is challenged by the complexity of its pathophysiology and a wide range of symptoms. On the other hand, with the progress in design of diagnostic and analytical tools (including software and artificial intelligence), we understand more about the disease what brings us closer to its successful treatment.
In this review we discuss currently available and potential future pharmacological and non-pharmacological treatments, focusing mainly on clinical proof of their efficiency. Moreover, we aim at identifying risk and challenges that need to be overcome to obtain a marketed drug.

Keywords: irritable bowel syndrome, antispasmodic drugs, neuromodulators, laxatives, opioids, diet, peppermint oil, fecal microbiota transplantation.

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Introduction

Irritable bowel syndrome (IBS) is a chronic, recurrent idiopathic disease of the digestive system [1]. Common symptoms include abdominal pain, changes in stool consistency and bowel movement frequency, excessive gas, mucus in stools, and sensation of incomplete bowel evacuation [2]. Several factors may contribute to the onset or exacerbation of IBS, including psychological stress, hormonal fluctuations, intestinal infections, Western diet, gut dysbiosis, and impaired serotonin (5-HT) regulation, which affect gut motility and visceral hypersensitivity (VH) [1].

Since 2016, IBS has been diagnosed based on the Rome IV Criteria, which focus on symptom-based assessment rather than structural abnormalities [1, 3]. To differentiate IBS from conditions with similar symptoms, such as celiac disease, inflammatory bowel disease, colon cancer, or microscopic colitis, laboratory tests (e.g., serologic tests for celiac disease, fecal calprotectin test) and endoscopic procedures (e.g., colonoscopy) are performed [1].

According to the Rome IV Criteria, diagnosis of IBS requires recurrent abdominal pain occurring at least once a week over the past three months, with the first symptoms appearing at least six months prior. Additionally, at least two of the following criteria must be met: pain relief or worsening after defecation, changes in stool consistency, and changes in bowel movement frequency [3].

Based on the proportion of stool types classified by the Bristol Stool Form Scale (BSFS), IBS is classified into four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), mixed IBS (IBS-M), and unclassified IBS (IBS-U) (as shown in Table 1) [3]. Stool form serves as a clinical indicator of gut transit time and helps guide treatment strategies.

Table 1. Guidelines for IBS subtype classification according to Rome IV Criteria.

IBS Subtypes	Guidelines for IBS Subtype Classification	Percentage share [%]	Additional information	References
IBS-C	Stools of type 1 or 2 according to the Bristol Stool Formation Scale (BSS) account for more than 25% of all bowel movements. Stools of type 6 or 7 according to BSFS account for less than 25% of all bowel movements.	29.3	The most common type of IBS occurring in women. Sensation of incomplete bowel movements.	[3, 4, 90]
IBS-D	Stools of type 1 or 2 according to BSFS constitute less than 25% of all bowel movements. Stools of type 6 or 7 according to BSFS account for more than 25% of all bowel movements.	31.5	Resolving pain after bowel movements. Manifested mostly in the morning by a strong urge to defecate.	[3, 4]
IBS-M	Stools of type 1 or 2 according to BSFS account for more than 25% of all bowel movements. Stools of type 6 or 7 according to BSFS account for more than 25% of all bowel movements.	26.4	There may be a change in stool consistency throughout the day, usually manifested as diarrhea in the morning and constipation in the evening.	[3, 4]
IBS-U	Stools of type 1 or 2 according to BSFS constitute less than 25% of all bowel movements. Stools of type 6 or 7 according to BSFS account for less than 25% of all bowel movements.	11.9	IBS cases that cannot be clearly classified into one of the subgroups: IBS-C, IBS-D, IBS-M.	[3, 4]

BSS — Bristol Stool Formation Scale, IBS — irritable bowel syndrome, IBS-C — irritable bowel syndrome with predominance of constipation, IBS-D — irritable bowel syndrome with predominance of diarrhea, IBS-M — irritable bowel syndrome with a mixed pattern of bowel movements, IBS-U — irritable bowel syndrome unclassified

The estimated global prevalence of IBS, based on the Rome IV criteria is 3.8% [4]. While the number of newly diagnosed cases is rising, changes in diagnostic criteria since 2016 make it difficult to directly compare epidemiological trends with previous years [5]. IBS is more common among younger individuals, women (who account for approximately 70% of cases) [6], individuals with higher education and socioeconomic status, and those with mental health disorders [5].

Several hypotheses attempt to explain the higher prevalence of IBS in women. One theory suggests that hormonal differences may play a role, as elevated estrogen and progesterone levels in women inhibit smooth muscle contractions, potentially contributing to constipation [6]. Another hypothesis points to heightened limbic system activity in response to visceral stimuli, which may be associated with lower pain tolerance. Additionally, social and psychological factors, such as increased exposure to stress — a key IBS risk factor — may contribute to the higher reported incidence in women [6].

Pathophysiology of IBS

Like in the case of other diseases, understanding the pathophysiology of IBS is important for design of successful treatment options. However, the etiopathology of IBS is particularly complex.

VH plays a key role in the pathogenesis of IBS [7]. It is characterized by a lowered pain threshold, leading to an exaggerated pain response to stimuli that usually would not cause discomfort, such as the stretching of intestinal walls by gas or food [8, 9]. VH may be triggered by elevated levels of corticotropin-releasing hormone (CRH), which activates CRH1 receptors and induces hypersensitivity [9]. Increased plasma CRH levels can result from stress, inflammation, or anxiety disorders [10].

Inflammation and acute gastrointestinal infections may be significant predisposing factors for the development of IBS [11]. The pathophysiology of this phenomenon is associated with an increased presence of leukocytes, mainly T lymphocytes and mast cells, in the intestinal mucosa [11, 12]. Mediators released from mast cells, such as histamine, serotonin, and tryptase, contribute to the degradation of tight junctions (TJ) and increased intestinal barrier permeability [11, 12]. In addition, inflammatory mediators sensitize nociceptors and affect smooth muscle cells, leading to the development of VH [9, 13].

Another key mechanism in IBS development involves 5-HT dysregulation. It is a major neurotransmitter responsible for gut function regulation, with 95% produced by enterochromaffin cells [14]. Serotonin transporters (SERT) regulate 5-HT availability by reabsorbing it from the synaptic space into enterochromaffin cells [14]. Excessive SERT activity reduces 5-HT levels in the intercellular space, leading to insufficient activation of 5-HT4 receptors, which stimulate gut motility [14]. This can result in constipation and potentially IBS-C. Excessive SERT expression may be linked to genetic variations, such as SLC6A4 variants, or increased hormone levels like glucagon-like peptide 1 [14]. Conversely, SERT deficiency leads to elevated 5-HT levels in the intercellular space, causing overactivation of 5-HT3 receptors, which regulate secretion and gut motility. This may lead to diarrhea and IBS-D [14]. SERT deficiency may result from chronic inflammation, intestinal infections, or gut dysbiosis [14]. Gut dysbiosis also plays a crucial role in the pathogenesis of IBS [7]. Dysbiosis refers to an imbalance in the gut microbiome, characterized by a decrease in symbiotic bacteria and an increase in potentially pathogenic species [15]. Chronic dysbiosis can compromise the intestinal barrier integrity, potentially due to reduced production of tight junction proteins or the breakdown of the mucus layer covering enterocytes [16]. This leads to increased intestinal permeability, allowing bacterial endotoxins (e.g., lipopolysaccharides) or undigested food particles to enter the bloodstream, which can trigger inflammation. This inflammation may contribute to VH and alter SERT expression [16]. Additionally, gut dysbiosis may lead to excessive gas production and bloating, which combined with VH, exacerbates pain [15].

Gut bacteria also produce neurotransmitters, e.g. dopamine and γ-aminobutyric acid (GABA) in the intestinal lumen. Dysbiosis can reduce production of these neurotransmitters, impairing the vagus nerve function, which is part of the gut-brain axis. This dysfunction can lead to disturbances in gut motility, increased anxiety and stress levels, and worsen IBS symptoms [17].

Other phenomena predisposing to the development of IBS, associated with intestinal microbiota dysbiosis, include small intestinal bacterial overgrowth (SIBO) and intestinal methanogen overgrowth (IMO) [18, 19]. In the case of SIBO, intense fermentation processes lead to increased production of gases such as hydrogen and methane, which is the basis for distinguishing its subtypes [18, 19]. SIBO with a predominance of hydrogen-producing bacteria is more commonly observed in patients with IBS-D, while SIBO with a dominant methanogenic flora is more common in patients with IBS-C [18, 19]. IMO, resulting from excessive growth of methanogens, especially representatives of the genus *Methanobrevibacter smithii*, is also more commonly diagnosed in patients with IBS-C [18, 19]. Currently, there is no clear evidence confirming a direct link between hydrogen overproduction and the occurrence of diarrhea. However, it has been shown that increased methane production, by modulating intestinal neuronal activity, promotes the development of constipation [19].

Aim of the work

The diverse pathophysiology underlying IBS pose a significant challenge in selecting appropriate therapeutic interventions to alleviate patients' symptoms. This literature review aims to synthesize existing data on the safety and efficacy of therapeutic modalities and pharmaceutical agents used in IBS management.

Current treatments in IBS

The efficiency of currently available and future treatment options in IBS has been summarized in Table 2.

Antispasmodic drugs in IBS

NICARDIPINE

In the 1980s, calcium channel antagonists, commonly used for cardiovascular diseases, were investigated for their potential role in IBS symptom relief. Nicardipine, a calcium channel blocker that induces vasodilation in blood vessels, was considered for IBS due to its smooth muscle-relaxing effects on the colon. Since abnormal intestinal contractions contribute to IBS symptoms, researchers hypothesized that nicardipine could help alleviate these disturbances [20, 21]. However, the adverse cardiovascular effects limited the use of nicardipine in IBS treatment. This prompted further research into alternative compounds that could selectively target the digestive tract without affecting the cardiovascular system [21].

Table 2. Collected effects of currently available and future treatment options in IBS.

Drug	Research group	Dose/ administration schedule	Effect	Reference
NICARDIPINE	—	—	Relaxing effect on smooth muscle with the adverse cardiovascular effects limited the use of nicardipine in IBS treatment	[20, 21]
ALVERINE CITRATE	—	360 mg/day (120 mg three times)	Reduced symptoms of abdominal pain, bloating, nausea, fullness, as well as an improvement in general well-being, the differences from the placebo group were only moderate (approximately 10%) and not statistically significant	[24]
MEBEVERINE	40	200 mg of mebeverine taken twice daily for 8 weeks	The results of the study suggest a moderate effect of mebeverine in patients with IBS-D	[26]
OTILIUM BROMIDE	—	Doses of 40 to 80 mg over a 4-week period	Alleviate clinical symptoms of IBS	[27–30]
PINAVERIUM BROMIDE	40	50 mg	Significantly reduced the duration of abdominal pain, decreasing it from several hours to just a few minutes	[32]
DROTAVERINE	—	80 mg	Significantly reduces pain intensity and frequency, while also improving stool frequency in patients with all subtypes of IBS	[33]
HYOSCINE BUTYLOBROMIDE	712	30 mg/day	The study demonstrated the potential use of N-butylbromide hyoscine and its combination with paracetamol in the treatment of IBS	[36]
POLYETHYLENE GLYCOL	139	1 to 3 sachets of the drug daily in a divided dose in the morning and evening. The aim was to obtain a 3, 4 or 5 according to the Bristol Stool Chart	PEG significantly outperformed the placebo in reducing constipation symptoms	[38]
LOPERAMIDE	—	2 mg up to twice a day before the onset of diarrhea	In patients with IBS-D, loperamide improves stool consistency and reduces the frequency of defecation.	[39]
ELUXADOLINE	346	100 mg twice daily	Significant improvements in stool consistency, reduced abdominal pain, and a decrease in major IBS symptoms compared to the placebo group	[40]

Table 2. Cont.

Drug	Research group	Dose/ administration schedule	Effect	Reference
TCAs (amitriptyline, imipramine and nortriptyline)	—	Not exceeding 75 mg per day	TCAs are used in the treatment of IBS-D due to their capacity to regulate intestinal motility and provide pain relief.	[41, 42]
CITALOPRAM	23	20 mg for 3 weeks, then 40 mg for 3 weeks	Treatment with both doses resulted in reduced abdominal pain, bloating, and improved quality of life compared to the placebo group	[44]
SERTRALINE	55	50 mg	Patients with IBS-C showed symptoms after bowel movements, while those with IBS-D showed symptoms after bowel movements	[45]
ESCITALOPRAM	29	Therapy starts for 5 mg once daily. After one week, the dose was increased to 10 mg once daily, gradually increasing to 20 mg once daily	The study results suggest that the effectiveness of escitalopram varies over time, depending on daily symptom variability and on the presence of anxiety, which mitigates the treatment effect	[47]
VENLAFAXINE	30	37.5 mg/day for two weeks, then 75 mg/day for the next two weeks, and 150 mg/day for the remainder of the three-month study	The study results suggest the effectiveness of venlafaxine in improving IBS symptoms and patients' quality of life	[48]
DULOXETINE	8	60 mg/day	Improvements in abdominal pain, quality of life, and loose stools. No relief was noted for hard stools. Constipation was reported as an adverse effect.	[50]
RAMOSTERON	1623	2.5 µg/day for women and 5 µg/day for men	Reduction of abdominal pain, normalization of bowel movement frequency, and improvement in stool consistency.	[51, 52]
TEGASEROD	9000	0.5-12 mg twice daily	Relief of irritable bowel syndrome symptoms in women, such as abnormal stool consistency and bowel movement frequency disorders	[51, 53]
ALOSETRON	192	2 mg twice daily	Improvement of symptoms such as abdominal pain and abnormal stool consistency.	[51, 54, 55]
RIFAXIMIN	2579	550 mg three times a day	Reduce the occurrence of IBS symptoms. Rifaximin can help reduce flatulence in patients with IBS-D	[57]

Table 2. Cont.

Drug	Research group	Dose/ administration schedule	Effect	Reference
LINACLOTIDE	599	290 μg for 26-week	Significantly reduced abdominal pain associated with IBS-C	[58]
LUBIPROSTONE	—	24 μg twice daily	Improves stool consistency, increases bowel movement frequency, and reduces the sensation of incomplete evacuation and the urge to evacuate	[59, 91]
LOW FODMAP DIET	65	Reduce content of the fermentable oligosaccharides, disaccharides, monosaccharides, and polyols that are widespread in fruits, vegetables, legumes, dairy products, and nuts	Reduction in symptoms	[61]
	15	Patients received increasing amounts of glucose, fructose and fructans in their diet	Patients receiving fructose and fructans reported more severe symptoms compared to the group receiving glucose	[62]
	30	Low-FODMAP (9 g/day), high-FODMAP (50 g/day) for two days	However, the study did not demonstrate a clear and consistent effect of high FODMAP on the severity of IBS symptoms	[63]
FIBER	275	The first group received 10 g of soluble fiber (psyllium), the second group received 10 g of insoluble fiber (bran), and the placebo group received rice flour. Treatment was administrated twice a day for 12 weeks	The greatest benefit was observed in patients taking psyllium	[66]
MODIFICATION OF MICROBIOTA	48 (14 patients in the IBS-C group and 18 patients in the IBS-M)	Proton pump inhibitors, laxatives, nootropics, antispasmodics or antidepressants	Changes in some bacterial species were characteristic of only one of the IBS subtypes, whereas there were no statistically significant differences in microbiome composition between IBS-C and IBS-M.	[67]
FECAL MICROBIOTA TRANSPLANTATION	165	The microbiota was collected from a single, screened, healthy donor and frozen	The results of the study showed a significant improvement in symptoms in the transplanted group	[70]

Table 2. Cont.

Drug	Research group	Dose/ administration schedule	Effect	Reference
NON-VIABLE PROBIOTICS	389	Suspension containing a bacterial lysate of 1.5–4.5 107 E. coli (DSM 17252) and 1.5–4.5 107 E. faecalis (DSM 16440) in 1 ml. 10 drops 3 times a day for a week, 20 drops 3 times a day in the second week, and 30 drops a week three times a day. This dose was maintained from week 3 to week 26.	The results of the study suggest a higher efficacy of non-viable probiotics in IBS-D compared to the placebo group, but it needs further verification.	[72]
MEDITERRANEAN DIET	—	Mediterranean diet	The study found that many components of the Mediterranean diet, such as fruits, vegetables, whole grains, and legumes, exacerbated IBS symptoms.	[73]
	48		The study results suggest an improvement in both gastrointestinal and psychological symptoms with the use of the Mediterranean diet	[74]
GLUTEN-FREE DIET	34	Gluten- free diet for 6 weeks	Noteworthy, gluten was shown to cause gastrointestinal symptoms in individuals with IBS	[76]
	140	Gluten- free diet for 12 weeks	The study did not find significant differences between the two diets. Patients in the gluten-free diet group reported improvements in stool consistency, reduced urgency, and less intestinal gas.	[77]

ALVERINE CITRATE

Research suggested that alverine citrate modulates the sensitivity of intestinal mechanoreceptors, particularly in vagal C-type fibers, inhibiting their response to mechanical distension and spontaneous activity. These findings indicate a potential role of alverine in modulating gut sensory pathways, though its effects appeared transient and selective [22]. Coelho *et al.* [23] reported that alverine citrate functions as a selective 5-HT1A receptor antagonist, inhibiting the action of 5-hydroxytryptophan (5-HTP) and a selective 5-HT1A receptor agonist — 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) [23]. This suggests that alverine may influence 5-HT-mediated signaling in the gut, which is relevant to IBS pathophysiology.

Alverine citrate has been shown to relax the smooth muscles of the gastrointestinal tract and uterus without affecting the cardiovascular system or tracheal muscles at the recommended daily dose of 360 mg/day [24]. However, a double-blind, randomized, controlled trial evaluating the efficacy of a 120 mg capsule given 3 times daily for 12 weeks found that while patients reported reduced symptoms of abdominal pain, bloating, nausea, fullness, as well as an improvement in general well-being, the differences from the placebo group were only moderate (approximately 10%) and not statistically significant [24].

MEBEVERINE

Mebeverine is an antispasmodic drug with mild local anesthetic properties. In the treatment of IBS, it has been shown to significantly reduce abdominal pain and bloating. Additionally, mebeverine has a positive effect on stool frequency, consistency, and overall bowel habits [25].

In the study by Chakraborty *et al.* [26], the effect of 200 mg of mebeverine taken twice daily for 8 weeks was examined. A group of 40 patients, qualified based on Rome IV, were given the drug or placebo. The results of the study suggest a moderate effect of mebeverine in patients with IBS-D [26].

OTILONIUM BROMIDE

Otilonium bromide works by reducing intestinal motility and altering visceral sensation, in addition to exerting a spasmolytic effect on the colon. Its efficacy has been confirmed in three randomized controlled trials, which collectively suggest that doses of 40 to 80 mg over a 4-week period can alleviate clinical symptoms of IBS [27–30].

PINAVERIUM BROMIDE

Pinaverium bromide is a selective G1 calcium channel antagonist with a strong antispasmodic effect in the gastrointestinal tract. It works by inhibiting calcium influx into smooth muscle cells in the intestine through the blockade of L-type calcium channels. Additionally, pinaverium bromide inhibits the action of cholecystokinin, gastrin, and substance P [31]. In a randomized, double-blind, placebo-controlled study by Awad *et al.* [32], 40 patients were given either 50 mg of pinaverium bromide or a placebo. The results showed that pinaverium bromide significantly reduced the duration of abdominal pain, decreasing it from several hours to just a few minutes [32].

DROTAVERINE

Drotaverine has a strong spasmolytic effect: it binds to the surface of smooth muscle and changes its permeability and membrane potential. It directly inhibits smooth muscle contraction and indirectly the phosphodiesterase (PDE) enzyme system. Currently, drotaverine is used to relieve pain associated with IBS, as well as intestinal, biliary, and ureteral colic. Studies have shown that drotaverine in 80 mg dose significantly reduces pain intensity and frequency, while also improving stool frequency in patients with all subtypes of IBS [33].

HYOSCINE BUTYLOBROMIDE

Hyoscine butylbromide (HBB), originally derived from the leaves of the Duboisia tree is an anticholinergic drug indicated for the treatment of abdominal pain associated with gastrointestinal spasms. It acts on muscarinic and nicotinic receptors and has a potent relaxant effect on smooth muscle cells [34].

Hyoscine butylbromide can also be used in the treatment of IBS [35]. In the study by Schäfer *et al.* [36], the effect of HBB in combination with paracetamol was tested. The study group included 712 patients suffering from IBS, divided into four groups. For four weeks, one group received oral HBB at a dose of 30 mg/day; the second group — HBB at the same dose combined with paracetamol 1500 mg/day, also orally; the third group received paracetamol 1500 mg/day alone. The fourth group received three placebo tablets daily. The study groups showed a 76%, 81%, 72%, and 64% response rate, respectively for abdominal pain and the differences between the groups were statistically significant. Thirty-eight people experienced adverse events that did not require treatment. The study demonstrated the potential use of HBB and its combination with paracetamol in the treatment of IBS [36].

Laxatives

POLYETHYLENE GLYCOL

Polyethylene glycol (PEG) is a high molecular weight iso-osmotic laxative commonly used to treat constipation. Clinical studies have shown that PEG increases water content in stool in a dose-dependent manner, which helps to soften the stool and improve intestinal motility and the defecation mechanism [37]. In a study on chronic constipation conducted by Nakajima *et al.* [37], treatment with PEG with electrolytes (PEG3350+E) provided short-term relief from constipation and led to lasting improvement of intestinal function [37]. Building on these findings, researchers explored the efficacy of PEG3350+E in treating IBS-C. Patients took 1 to 3 sachets of the drug daily in a divided dose in the morning and evening; the amount depending on the stool consistency. The aim was to obtain a 3, 4 or 5 according to the Bristol Stool Chart. If after 24 hours the patient had stools of 6 or 7 according to the scale, the treatment was discontinued for 24 hours; the patient then took 1 sachet in the morning. In the case of constipation lasting 3 days, patients could take 1–2 tablets of 5 mg bisacodyl at night. Patients were not allowed to use laxatives. After a preparatory period, 139 participants were enrolled in the study, with 71 in the placebo group and 68 in the PEG3350+E group. The results demonstrated that PEG significantly outperformed the placebo in reducing constipation symptoms [38].

Opioids

LOPERAMIDE

Loperamide works by binding to the μ-opioid receptor which reduces smooth muscle contractility in the intestinal wall and affects the passage of water and electrolytes. More recent studies have revealed that loperamide acts as an antagonist of both acetylcholine and prostaglandin [39].

In patients with IBS-D, loperamide improves stool consistency and reduces the frequency of defecation. It is recommended for use preventively in IBS-D patients, taken at a dose of 2 mg up to twice a day before the onset of diarrhea. However, long-term use of loperamide has been associated with adverse effects, including abdominal pain, flatulence, nausea, vomiting and prolonged QT interval [39].

ELUXADOLINE

Eluxadoline is a peripherally acting agonist of the μ- and κ-opioid receptors, and an antagonist of the δ-opioid receptor. It works by reducing intestinal motility and the risk of drug-induced constipation, with clinical studies demonstrating its ability to relieve abdominal pain [40]. The therapeutic efficacy of eluxadoline has been confirmed in clinical trials, including a relatively recent study involving patients aged 18 to 80 who met the Rome III criteria for IBS-D. This 12-week trial included 346 participants, with 174 in the placebo group and 172 in the eluxadoline group (100 mg twice daily); of these, 295 patients completed the study. Follow-up assessments were conducted at weeks 4, 8, and 12. The results showed that patients receiving eluxadoline experienced significant improvements in stool consistency, reduced abdominal pain, and a decrease in major IBS symptoms compared to the placebo group [40].

Neuromodulators

TCAs

TCAs act by inhibiting the reuptake of 5-HT and norepinephrine at the presynaptic membrane, which increases the concentration of these neurotransmitters in the synaptic cleft. In addition, TCAs interact with various receptors, including 5-HT2A, 5-HT2C, 5-HT3, muscarinic (M1), histamine (H1), adrenergic (α1), and presynaptic α2 receptors. TCAs are used in the treatment of IBS-D due to their capacity to regulate intestinal motility and provide pain relief. Oh *et al.* [41] demonstrated a reduction in the discomfort in up to 57.3% of IBS patients treated with TCAs; however, the full therapeutic effect is observable after a minimum of four weeks of drug administration [42]. The most used drugs in this group include amitriptyline, imipramine and nortriptyline; their typical dosage is low, not exceeding 75 mg per day [42]. The potential adverse effects of TCAs include dry mouth (occurring in approximately 30% of treated individuals), drowsiness (in approximately 20% of cases) and fatigue (in approximately 10% of cases) [41, 42].

SSRIs

CITALOPRAM

Citalopram is a serotonin reversible inhibitor used to treat depression [43]. In the study by Tack *et al.* [44], 23 individuals with IBS but without depression were recruited. A crossover study was performed in which a group of patients were treated with citalopram (20 mg for 3 weeks, then 40 mg for 3 weeks) for 6 weeks. The second group received a placebo. Treatment with both doses resulted in reduced abdominal pain, bloating, and improved quality of life compared to the placebo group [44].

SERTRALINE

Sertraline acts as a serotonin reversal inhibitor. It is used to treat anxiety and depression. It is believed to have a pain-regulating mechanism, which is why it is used for psychosomatic pain. A randomized, single-blind study by Saleh *et al.* [45] included 55 patients. The study group had been diagnosed with IBS based on the ROME III. Thirty patients received 50 mg of sertraline and 25 received a placebo for 4 weeks. About 67% of patients taking sertraline experienced alleviation of symptoms compared to 32% of patients taking placebo; the greatest improvement was observed in IBS-C patients, and the least in IBS-D. In addition, sertraline users showed a greater reduction in anxiety and depression [45].

ESCITALOPRAM

Escitalopram is a serotonin reuptake inhibitor used in advanced depression and anxiety disorders [46]. A study by Vork *et al.* [47] included a group consisting of 29 individuals suffering from IBS (IBS-C, IBS-D, and IBS-M) and panic disorders, of which 15 received escitalopram and 14 — placebo. The experiment lasted six months; the therapy began with a dose of 5 mg once daily and after one week, the dose was increased to 10 mg once daily, further increasing to 20 mg once daily. The study results suggest that the effectiveness of escitalopram varies over time, depending on daily symptom variability and on the presence of anxiety, which mitigates the treatment effect [47].

SNRIs

VENLAFAXINE

Venlafaxine is a drug used for anxiety and depressive disorders. It inhibits serotonin, norepinephrine, and dopamine reabsorption and does not affect the monoamine oxidase enzyme or muscarinic, nicotinic, histaminergic, or adrenergic receptors [48]. A double-blind, randomized study by Sharbafchi *et al.* [48] examined 30 individuals aged 18–65 with documented IBS based on the ROME III and referred by a gastrointestinal specialist to a psychosomatic clinic. Patients were randomly divided into two groups: one group received venlafaxine at a dose of 37.5 mg/day for two weeks, then 75 mg/day for the next two weeks, and 150 mg/day for the remainder of the three-month study while the other group received placebo. The study results suggest the effectiveness of venlafaxine in improving IBS symptoms and patients' quality of life [48].

DULOXETINE

Duloxetine is a drug used to treat major depression or anxiety disorders; it is also used for chronic musculoskeletal pain. It inhibits serotonin and norepinephrine reuptake [49]. Brennan *et al.* [50] investigated the efficacy of duloxetine in IBS. The 12-week study included 15 patients with IBS without major depressive disorder. Eight patients completed the study, seven withdrew due to adverse drug reactions, and 14 completed a single assessment. Patients took 60 mg/day. The study demonstrated improvements in abdominal pain, quality of life, and loose stools (no relief was noted for hard stools). Constipation was reported as an adverse effect. The study results suggest the usefulness of duloxetine in the treatment of IBS and suggest further placebo-controlled studies [50].

SEROTONIN RECEPTOR LIGANDS

RAMOSTERON

Ramosteron belongs to the group of drugs that act as antagonists of the 5-HT3 serotonin receptor [51, 52]. It is used in the treatment of patients with IBS-D. A meta-analysis including 1623 patients demonstrated the effectiveness of ramosteron in reducing abdominal pain, normalizing bowel movement frequency, and improving stool consistency [51, 52]. This treatment proved effective in both women and men, with improvement observed in approximately 50% of patients [51, 52].

The incidence of adverse events in patients receiving ramosteron was comparable to that in the placebo group (54.9% vs. 49.0%, respectively) [51, 52]. However, a higher incidence of mild constipation (7% vs. 2%) and harder stools (14% vs. 3%) was recorded among those treated with ramosteron [51, 52].

TEGASEROD

Tegaserod is a non-selective agonist of the 5-HT_4 receptor and an antagonist of the 5-HT_2B receptor [51, 53]. It is used in the treatment of IBS-C. Clinical trials including more than 9,000 patients have confirmed its efficacy in alleviating IBS symptoms in women, such as abnormal stool consistency and disturbed defecation frequency [51, 53]. The estimated effectiveness of tegaserod therapy ranges from 33.7% to 44.9%, compared to 24.2% to 28.7% observed in placebo groups [51, 53].

The most common adverse effects include mild diarrhea (8.8% vs. 3.8% for placebo), abdominal pain (with no significant difference compared to placebo), headache, and dizziness (15% vs. 12.3% for placebo) [51, 53]. No association has been demonstrated between tegaserod use and increased cardiovascular risk [51, 53]. Currently, the drug is recommended exclusively for women under 65 years of age [51, 53].

ALOSETRON

Alosetron is a selective 5-HT3 receptor antagonist used in the treatment of IBS-D. Similar to tegaserod, alosetron is indicated exclusively for use in women [51, 54, 55]. In a study involving 192 female patients, 45% reported concurrent improvement in symptoms — such as abdominal pain and abnormal stool consistency — lasting for at least half of the treatment period, compared to 25% in the placebo group [51, 54, 55].

Despite its documented clinical efficacy, the use of alosetron is associated with a considerable risk of adverse effects [51, 54, 55]. The most commonly observed ones include constipation (in approximately 25% of patients), abdominal pain (~5%), and nausea (~5%). Among more serious adverse events, cases of ischemic colitis (0.1%), hypertension (2% of patients), and tachyarrhythmia (0.1%) have been reported [51, 54, 55]. The overall incidence of adverse effects is estimated to be 1.7 times higher than in the placebo group [51, 54, 55].

Other treatments

RIFAXIMIN

Rifaximin is an orally administered antibiotic that has shown promise in treating IBS. A 2014 study by Xu *et al.* [56], conducted on a rat model, demonstrated its positive effect on reducing intestinal permeability, visceral hyperalgesia, and mild inflammation induced by stress. In addition, Lembo *et al.* [57] performed randomized controlled trials, which revealed that administering rifaximin three times a day at a dose of 550 mg modestly reduced the occurrence of IBS symptoms. However, rifaximin did not affect stool consistency, as constipation occurred in both the treatment and control groups. Moreover, the treated group reported additional side effects, such as nausea. Despite this, studies indicate that rifaximin can help reduce flatulence in patients with IBS-D. Overall, rifaximin is considered an effective first- or second-line treatment for patients with IBS-D [56, 57].

LINACLOTIDE

Linaclotide is a synthetic peptide composed of 14 amino acids and acts as a guanylate cyclase 2C (GC-C) agonist. By activating GC-C receptors located on the intestinal epithelial luminal surface, linaclotide increases cyclic guanosine monophosphate (cGMP) levels, which in turn stimulates the secretion of chloride, bicarbonate, and water into the intestinal lumen. The efficacy of linaclotide has been well-established in clinical settings. For instance, in 2012, a multicenter, randomized, double-blind study was conducted to assess the efficacy and safety of linaclotide at a dose of 290 μg over a 26-week period [58]. Patients were selected based on the Rome II criteria for IBS-C. Out of 805 qualified participants, 599 completed the study. The results indicated that linaclotide, administered at a daily dose of 290 μg, significantly reduced abdominal pain associated with IBS-C [58].

LUBIPROSTONE

Lubiprostone is a bicyclic fatty acid metabolite analog of prostaglandin E1, approved for the treatment of IBS-C in both men and women. Clinical studies have shown that lubiprostone, when administered at a dose of 24 μg twice daily, improves stool consistency, increases bowel movement frequency, and reduces the sensation of incomplete evacuation and the urge to evacuate [59].

LOW FODMAP DIET

The low FODMAP diet is characterized by a reduced content of the fermentable oligosaccharides, disaccharides, monosaccharides, and polyols that are widespread in fruits, vegetables, legumes, dairy products, and nuts. According to a meta-analysis conducted by Bertin *et al.* [60], low FODMAP diet has been shown to be the most effective of all other dietary interventions used.

There are two ways to introduce the low FODMAP diet. The top-down method, considered more effective, involves eliminating products containing FODMAPs. The next step is to gradually reintroduce the restricted products to the diet and, according to patient's own assessment, create a modified diet based on individual tolerance. The bottom-up method is characterized by gradual exclusion of FODMAP products for a specified period of time.

In 2006, Shepherd *et al.* [61] conducted a study that examined the use of the low FODMAP diet by 65 patients with IBS; of those, 74% reported a reduction in symptoms. In 2008, the same research group conducted the first double-blind, randomized trial in which the patients received increasing amounts of glucose, fructose and fructans in their diet [62]. Between trials, patients had a 10-day washout period. Patients receiving fructose and fructans reported more severe symptoms compared to the group receiving glucose [62]. In 2010, Ong *et al.* [63] conducted a single-blind, crossover study in 15 patients with IBS (according to Rome III) and 15 healthy subjects. Participants were exposed to a low-FODMAP (9 g/day) and high-FODMAP (50 g/day) diet for two days. By the end, the high-FODMAP diet produced more hydrogen, which led to increased gastrointestinal symptoms in IBS patients and elevated gas production in healthy subjects, which in turn resulted in increased methane levels [63]. However, the study did not demonstrate a clear and consistent effect of high FODMAP on the severity of IBS symptoms [60, 63]. Concurrently, Böhn *et al.* [64] conducted a multicenter, parallel, single-blind study on low FODMAP diet. Seventy-five patients were enrolled based on the Rome III criteria for IBS and randomly assigned to a group with low FODMAP diet (38 participants) or a diet commonly recommended for patients with IBS (37 participants), which consisted of regular meals, yet limiting the intake of fat, insoluble fiber, caffeine, and selected vegetables (beans, cabbage, and onions). Throughout the study, patients rated their symptoms and filled out a food diary. The study was completed by 67 patients who followed one of the diets for 4 weeks; both groups showed a reduction in IBS symptoms, with no significant differences between the diets [64].

FIBER

Fiber absorbs water into the stool and slows down digestion, and it comes in two types: insoluble fiber, found in wheat bran, whole grains, and seeds, and soluble fiber, found in psyllium, oat bran, and the pulp of fruits and vegetables [65]. In a randomized, placebo-controlled trial by Bijkerk *et al.* [66], involving 275 patients who met the Rome II criteria for IBS, participants were randomly assigned to one of three groups: the first group received 10 g of soluble fiber (psyllium, 85 participants), the second group received 10 g of insoluble fiber (bran, 97 participants), and the placebo group received rice flour (93 participants). Treatment was administered twice daily for 12 weeks; moreover, participants were instructed to maintain their usual diet and drink adequate fluids. Treatment effectiveness was assessed monthly, with improvement defined as reporting symptom relief for at least two of the previous four weeks. Additional outcomes measured included the intensity of abdominal pain and overall quality of life. Results indicated that the greatest benefit was observed in patients taking psyllium [66].

New treatment options

Modification of microbiota

Growing body of evidence strongly suggest that changes in the gut microbiota may significantly contribute to the development of pathologies in the gut, including IBS. Studies have shown a decrease in the number of *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium* and *Clostridium* in patients with IBS, and an increase in *Enterobacteriaceae*, *Veillonella* and *Ruminococus* compared to the healthy group [67, 68]. A study by Gryaznova *et al.* [67] indicated an increase (especially in patients with IBS-D) in *Collinsella aerofaciens* — a strain that metabolizes glucose to hydrogen, ethanol and formate. Hydrogen produced in the intestines reduces intestinal transit and contributes to the development of IBS. Concurrently, the metabolites produced by the Dorea group (anaerobic, gram-positive bacteria) may cause abdominal pain and bloating, and may contribute to intestinal leakage [67, 68]. On the other hand, an increase in the Dialister group of bacteria, which belong to the order *Firmicutes* is believed to affect the severity of IBS [67]; however, in patients with the IBS-D subtype, it did not affect clinical symptoms [67].

An even more important phenomenon is the possible influence of well-known anti-IBS treatments (without an indicated anti-microbial activity) on intestinal microbiota in IBS patients. In a recent attempt to address this issue, Gryaznova *et al.* [67] undertook a study involving 48 subjects: 12 men in the control group, 14 patients in the IBS-C group and 18 patients in the IBS-M group, diagnosed based on symptoms according to the Rome IV criteria and laboratory tests. Patients were treated with proton pump inhibitors, laxatives, nootropics, antispasmodics or antidepressants. As a result, patients' stool samples showed differences in the composition of the microbiome in individual IBS subtypes vs. the healthy group. Differences in the microbiome were characterized at both the phylum and species level. At the phylum level, increased *Firmicutes*/*Bacteroidetes* ratios, increased abundance of *Actinobacteria*, and presence of *Verrucomicbiota* were observed in both IBS subtypes. At the species level, microbiome aberrations were identified that were broadly consistent in both IBS-C and IBS-M and in accordance with previous studies. Changes in some bacterial species were characteristic of only one of the IBS subtypes, whereas there were no statistically significant differences in microbiome composition between IBS-C and IBS-M. This study was also the first to demonstrate the association of *Turicibacter sanguinis*, *Mitsuokella jalaludinii*, *Erysipelotrichaceae* UCG-003, *Senegalimassilia anaerobia*, *Corynebacterium jeikeium*, *Bacteroides faecichinchillae*, *Leuconostoc carnosum*, and *Parabacteroides merdae* with IBS.

FECAL MICROBIOTA TRANSPLANTATION

One method of replenishing the microbiome, which has a positive impact on the digestive system, is fecal microbiota transplantation [69]. El-Salhy *et al.* [70] conducted a randomized, double-blind, placebo-controlled trial, which included 165 patients randomly assigned to one of the three groups: the first placebo group received a transfer of their own feces, the second group received 30 g of transplanted microbiota, and the third group received 60 g at transplantation. The microbiota was collected from a single, screened, healthy donor and frozen; subsequently, it was administered through a gastroscope. The results of the study showed a significant improvement in symptoms in the transplanted group; the greatest was noted in the group receiving 60 g of transplant [70]. In a study by Holster *et al.* [71], 17 patients were assigned to the placebo group (transplantation of their own feces) or the group transplanted from a healthy donor. The collected material was transplanted to the patients using a colonoscope after prior bowel cleansing. The study did not describe significant differences between the two groups in terms of IBS symptoms. However, the group receiving transplanted material from a healthy donor showed a decrease in symptoms after transplantation [71].

NON-VIABLE PROBIOTICS

The efficiency of a nonviable bacterial lysate of cells and cell fractions from *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) has recently been characterized in a multi-center, randomized, double-blind study which included 389 patients of both sexes, qualified based on the Rome III criteria [72]. Patients in the study group were treated with a suspension containing a bacterial lysate of 1.5–4.5 10^7 *E. coli* (DSM 17252) and 1.5–4.5 10^7 *E. faecalis* (DSM 16440) in 1 ml. The treatment consisted of 10 drops 3 times a day for a week, 20 drops 3 times a day in the second week, and 30 drops a week three times a day. This dose was maintained from week 3 to week 26. The results of the study suggest a higher efficacy of non-viable probiotics in IBS-D compared to the placebo group, but it needs further verification [72].

Dietary interventions

MEDITERRANEAN DIET

The Mediterranean diet primarily consists of whole grains, fruits, vegetables, nuts, seeds, and moderate amounts of white meat and fish. Red meat is consumed occasionally, while olive oil serves as the primary source of fat. This diet is rich in phenols, which have anti-inflammatory effects and help regulate the microbiota responsible for producing short-chain fatty acids [73]. A study by Staudacher *et al.* [74] also suggests that the Mediterranean diet can alleviate symptoms of depression through various mechanisms, potentially influencing brain function and behavior [74].

The applicability of the Mediterranean diet in regulating IBS symptoms was explored by Chen *et al.* [73]. In their study, the group of participants included individuals diagnosed with IBS according to Rome III or IV criteria, along with healthy controls. Throughout the trial, patients completed questionnaires on gastrointestinal and bowel symptoms, as well as the severity of IBS. Fear of gastrointestinal symptoms was also assessed, and the participants' diets were evaluated using the Alternative Healthy Eating Index. The groups were similar in age, race, gender, and weight. Surprisingly, the study found that many components of the Mediterranean diet, such as fruits, vegetables, whole grains, and legumes, exacerbated IBS symptoms. This could be attributed to the presence of FODMAPs in these foods, which are likely to increase the incidence of symptoms [73].

A randomized, parallel-group study conducted by Staudacher *et al.* [74] included patients aged 18 to 65 years with IBS symptoms, identified by the Rome IV classification, who experienced abdominal pain at least twice a week along with mild to moderate symptoms of anxiety or depression. These psychological symptoms were measured using the Anxiety and Depression Scale (HADS). Exclusion criteria included other gastrointestinal conditions, active COVID-19 infection, eating disorders, and severe depressive/anxiety disorders. Participants were randomly assigned to follow either the Mediterranean diet or continue their usual diet. Importantly, the nature of the study was not disclosed to participants before enrollment; however, due to the nature of the control diet, blinding was not feasible.

Control visits were conducted online at baseline and after 6 weeks due to the COVID-19 pandemic. Patients were asked to provide stool samples on or before visit days. During the first visit, demographic, anthropometric, and clinical data were collected. Those in the intervention group received personalized dietary advice, while the control group continued their usual diet. Weekly remote visits assessed changes in medication, therapy, or adverse events. At the 6-week visit, body weight, current medication, and dietary records were re-evaluated. Both groups received the same medical interventions.

A total of 59 participants were enrolled in the study (29 in the Mediterranean diet group, 30 in the control group). Eleven participants were withdrawn (5 from the diet group, 6 from the control group). The study results suggest an improvement in both gastrointestinal and psychological symptoms with the use of the Mediterranean diet [74].

GLUTEN-FREE DIET

A gluten-free diet focuses on the exclusion of gluten, a protein found in the endosperm of cereals such as wheat, barley, and rye. While a gluten-free diet can help alleviate symptoms in some individuals, it may also lead to nutritional deficiencies. Therefore, it is crucial to first identify the specific triggers of IBS symptoms before implementing such a diet [75].

A study by Biesiekierski *et al.* [76] included 34 patients aged 29 to 59 years (4 men), all of whom were excluded from celiac disease diagnoses. Participants followed either a controlled gluten-free diet or a regular diet for 6 weeks. Noteworthy, gluten was shown to cause gastrointestinal symptoms in individuals with IBS.

The effect of a gluten-free diet on IBS patients was also examined by Hajiani *et al.* [77]. In their study, 140 patients diagnosed with IBS based on the Rome III criteria were randomly assigned to either a gluten-free diet or a regular diet for 12 weeks. The study did not find significant differences between the two diets. However, patients in the gluten-free diet group reported improvements in stool consistency, reduced urgency, and less intestinal gas. In contrast, the regular diet group experienced fewer bowel movements and increased abdominal pain. The positive response rate was 67% in the gluten-free group compared to 52% in the regular diet group.

Safety and adverse effects in the pharmacotherapy of Irritable Bowel Syndrome

Pharmacotherapy is one of the main methods of treating IBS. However, due to the high heterogeneity of symptoms and the not fully understood pathophysiological mechanisms, the selection of appropriate interventions is difficult and may be associated with adverse effects (see Table 3) [78–80].

Antispasmodic drugs, which can be used in all forms of the disease, are well tolerated and side effects are rare (most commonly nausea and/or bloating) [81].

Laxatives, especially osmotic ones, are considered safe for short-term therapy. The most commonly reported side effects include bloating, abdominal pain, and general digestive disorders. However, there is a lack of research on their effects with long-term use [82].

Opioids used in the treatment of IBS-D, although proven effective in relieving pain and improving stool consistency, are associated with numerous adverse effects, including nausea, vomiting, bloating, cramping, and prolonged constipation [78–80, 83]. Additionally, they may induce sphincter of Oddi spasm, thereby increasing the risk of acute pancreatitis, particularly in post-cholecystectomy patients [78–80, 83]. Therefore, opioid therapy requires regular monitoring of patient status.

Table 3. Overview of adverse effects and safety profiles of IBS therapies.

Therapy	The most common side effects	Serious side effects	Safety assessment	References
Antispasmodic drugs	Nausea and bloating	Not recorded	Safe for short-term use, but their long-term effects remain poorly studied	[81]
Laxatives	Bloating, abdominal pain and general digestive disorders	Not recorded	Safe for short-term use, but their long-term effects remain poorly studied	[82]
Opioids	Nausea, vomiting, bloating, cramping and prolonged constipation	Pancreatitis, sphincter spasm	Requires regular monitoring	[78–80, 83]
Neuromodulators	Dry mouth, drowsiness, dizziness, sleep disturbances and diarrhea	QT interval prolongation, serotonin syndrome	Requires regular monitoring	[42, 84]
Non-absorbable antibiotics	Abdominal pain, nausea and vomiting	Resistance potential	Safe for short-term use, but their long-term effects remain poorly studied	[85, 86]
Low-FODMAP diet	Nutritional imbalance	Risk of eating disordered	Generally safe	[87]
Probiotics	Bloating and excessive gas	Infections	Generally safe	[88]
Fecal Microbiota Transplantation	Discomfort and bloating	Infections	Generally safe	[89]

Neuromodulators employed in the management of IBS have demonstrated efficacy in alleviating pain and visceral hypersensitivity, although their use in this context is considered off-label [42, 84]. These agents may cause adverse effects such as dry mouth, drowsiness, dizziness, sleep disturbances, diarrhea, QT interval prolongation, and drug–drug interactions [42, 84]. One of the most severe complications is serotonin syndrome, which underscores the necessity of careful patient monitoring during treatment [42, 84].

Non-absorbable antibiotics, such as rifaximin, are used in IBS-D therapy due to their ability to modulate the gut microbiota [85]. The incidence of adverse effects during rifaximin treatment is similar to that observed in placebo groups [85]. The most commonly reported symptoms include abdominal pain, nausea, and vomiting, whereas serious adverse events are rare (<1%) [85]. Nevertheless, concerns remain regarding its long-term use, particularly the potential for bacterial resistance development and prolonged alterations within the gut microbiome [86].

A low-FODMAP diet, characterized by reduced intake of fermentable carbohydrates and polyols, is considered a safe and effective approach for reducing abdominal pain and bloating [87]. However, it is important to ensure proper nutritional balance during dietary implementation to prevent nutrient deficiencies and the development of disordered eating behaviors [87].

Probiotics represent one of the most thoroughly investigated strategies for modulating the composition of the gut microbiota in patients suffering from IBS [88]. A meta-analysis conducted by

Ford *et al.* [88] demonstrated moderate efficacy of selected bacterial strains, such as *Lactobacillus plantarum* and *Bifidobacterium infantis*, with a low incidence of adverse effects, mainly limited to bloating and excessive gas [88]. However, when applying this form of therapy, it is necessary to consider the potential variability of strains and formulations, which may reduce its predictability [88].

Among more invasive approaches to gut microbiota modulation is FMT. Findings from a study by Lo *et al.* [89] suggest that this method may be effective in alleviating abdominal pain in IBS patients. The most frequently reported short-term side effects include discomfort and bloating, while long-term effects have not yet been sufficiently elucidated [89]. It should be noted that FMT appears unsuitable for individuals with immunodeficiencies due to the risk of infection [89].

Conclusion

This review focuses mainly on the clinical evidence of IBS treatment efficacy; in this view, presented future IBS interventions have yet very little proof for being safe. Especially the long-term safety of these therapies, particularly those that alter gut microbiota or involve neuromodulation, is not yet fully understood. On the other hand, the selection made allowed us to present and discuss probably the safest options currently examined.

With that in mind, we strongly underline the need for further efforts in the research on IBS treatments as well as for the re-examination of therapies used currently in other indications. It is very likely that re-purposing of the drugs may be more effective than aiming at the discovery of novel targets and interventions.

Authors' contributions

W.J., G.M.K. and J.F. provided the overall concept and framework of the review; W.M.J., G.M.K., A.T.Z. and J.F. researched and identified appropriate articles, and wrote the manuscript; W.M.J., G.M.K., A.T.Z. and J.F. revised the manuscript. All authors read and approved the final version of the manuscript.

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Abbreviations

5-HT — 5-hydroxytryptamine, serotonin
BSS — Bristol Stool Scale
CCK — cholecystokinin
CRH — corticotropin-releasing hormone
GABA — γ-aminobutyric acid
GC-C — guanylate cyclase 2C

HBB — Hyoscine butylbromide
IBS — irritable bowel syndrome
IBS-C — irritable bowel syndrome with predominance of constipation
IBS-D — irritable bowel syndrome with predominance of diarrhea
IBS-M — irritable bowel syndrome with a mixed pattern of bowel movements
IBS-U — irritable bowel syndrome unclassified
IMO — intestinal methanogen overgrowth
PDG — phenylbiguanide
PEG — polyethylene glycol
SERT — serotonin transporter
SIBO — small intestinal bacterial overgrowth
SNRIs — serotonin-norepinephrine reuptake inhibitors
SSRIs — selective serotonin reuptake inhibitors
TCAs — tricyclic antidepressants
TJ — tight junctions
VH — visceral hypersensitivity

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