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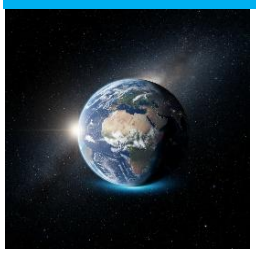

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The Role and Efficacy of Rifaximin in the Treatment of Irritable Bowel Syndrome - Based on current research in 2026

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Abstract

Introduction

In 2026, irritable bowel syndrome (IBS) was recognized as a complex disorder of the gut-brain axis involving microinflammation, increased intestinal permeability and dysbiosis. Modern

therapy is moving away from symptom relief to modulation of the microflora. Rifaximin, due to its minimal absorption and solubility in bile salts, is the first-line treatment for IBS-D. As a eubiotic, it reduces pathogens, supports beneficial microflora and strengthens the intestinal barrier thanks to tight junction proteins. Clinical data shows that it is safe for high-risk groups, such as cardiac patients taking anticoagulants and antiplatelet drugs, due to the absence of systemic interactions.

Aim of the study

Summary of the status of rifaximin alfa in IBS in 2026, focusing on its molecular mechanisms, impact on the gut-brain axis, and safety in patient populations with comorbidities.

Materials and methods

A systematic review of PubMed (last 10 years) was conducted using the keywords: „IBS", „RIFAXIMIN", „TREATMENT". Pediatric studies were excluded.

Conclusions

Rifaximin is the first choice for treating IBS-D, surpassing both traditional methods and low-FODMAP diets. Its advantages include regeneration of the intestinal barrier, physiological modulation of bile acids and reduction of gastrointestinal-specific anxiety (GSA). With a safety profile comparable to placebo and no significant drug interactions (especially with antiplatelet/anticoagulants), it provides stable disease control and improved quality of life.

Keywords: IBS; Rifaximin; Eubiotic; Dysbiosis; Gut-brain axis.

INTRODUCTION:

Irritable Bowel Syndrome (IBS) currently represents one of the most significant and fascinating clinical challenges in both gastroenterology and modern medicine.

It is a frequent and significant psychosocial and economic burden on the adult population [51]. In 2026, the definition of IBS no longer involves mere classification as a gastrointestinal motility disorder; instead, it is recognized as a complex pathophysiological process within the gut-brain axis. Low-grade inflammation, visceral hypersensitivity, and intestinal dysbiosis, which are considered qualitative and quantitative disturbances in microbiota homeostasis, are the main factors that underlie the clinical symptoms of IBS [22, 41].

Epidemiological data indicate that IBS affects a significant percentage of the world's population, and any differences in the prevalence of this condition are due to geographical conditions [3, 48]. In the differential diagnosis of IBS, we will pay particular attention to the exclusion of microscopic colitis and celiac disease [16, 17, 46]. Modern pathophysiological models, on the

other hand, draw attention to the role of serotonin and mast cells in the development of the disease [3, 44].

Rifaximin alfa is an oral chemotherapeutic agent with unique pharmacokinetic properties.

It is characterized by systemic bioavailability close to zero and a broad spectrum of antimicrobial activity in the gastrointestinal tract [3, 44, 51]. Due to the specific structure of the molecule, the activity of rifaximin is restricted only to the intestinal lumen, which allows avoiding systemic side effects and drug interactions. Rifaximin alfa, unlike classical antibiotic therapies, is considered a eubiotic, which means that it is an advanced modulator of the microbiome. This stimulates the restoration of physiological bacterial homeostasis, rather than completely sterilizing the gastrointestinal tract [31]. This property is due to the mechanism of action of the drug, which ensures that it can be dissolved in bile salts [11, 3, 51]. Including rifaximin in treatment protocols is intended not only to temporarily relieve the symptoms of IBS but also to directly intervene in the pathogenetic mechanisms.

This therapy is intended to reduce excessive bacterial fermentation in the gastrointestinal tract, which will translate into a direct reduction in gas production and the elimination of bothersome abdominal bloating [49,51]. In parallel, the drug affects the integrity of the epithelial barrier, limiting the possibility of bacterial endotoxins entering the portal circulation and suppressing the local inflammatory response [10]. An additional, yet important, element of action is also the modulation of the bile acid profile, which is expected to play a key role in normalizing the bowel rhythm and limiting water secretion in patients with the diarrheal form of IBS-D [1, 28]. Studies also show an effect on electrolyte transport in colonocytes [19, 20]. Currently, auxiliary diagnostics also highlight new findings, such as the use of specific biochemical parameters. It has been shown, for example, that total bilirubin levels may negatively correlate with the presence of SIBO in the diarrhea subtype IBS.

This can serve as a simple indicator to facilitate the decision for treatment qualification [21]. Evidence-based medicine (EBM) is the main factor in determining the choice of rifaximin alfa in 2026. Clinical data confirm that a standard 14-day treatment has a higher safety profile than long-term and chronic use of antispasmodic drugs. It is also much better tolerated by patients than the strict, restrictive Low FODMAP diet [52]. Rifaximin alfa effectively stops the growth of pathogenic and flatworm-inducing groups, including Proteobacteria, which results in a decrease in fermentation processes and hydrogen production within the lumen of the digestive system [22, 49]. What is worth emphasizing and paying special attention to in the perspective of long-term patient care, this therapy results in much more lasting remission of symptoms after

the end of the treatment cycle, which translates into a significant improvement in the quality of life [12, 29, 51].

MECHANISM OF ACTION:

The most significant factor in the therapeutic success of rifaximin alfa in IBS is its unique pharmacodynamics. In light of current knowledge, rifaximin goes beyond the classical mechanisms and features of systemic antibiotic therapy, because the medication does not possess an effect based on the complete eradication of bacterial flora, but modulates the microenvironment of the intestine. A key aspect of the drug's action is its eubiotic effect, which involves selectively supporting the physiological microbiota, which is manifested
by an increase in the population of bacteria of the genera Lactobacillus, Bifidobacterium Faecalibacterium prausnitzii after the end of therapy [31, 37]. At the same time, rifaximin alfa effectively inhibits the multiplication of pathogenic and bloating-leading groups, such as Proteobacteria, which has a direct impact on the reduction of fermentation processes and hydrogen production in the lumen of the gastrointestinal tract [22, 49, 51].
A major achievement of the last decade is the confirmation of the drug’s impact on the regeneration and repair of the intestinal barrier's integrity. This directly implies intervening with the pathophysiological phenomenon of increased epithelial permeability, which is also known as 'leaking intestine'. Rifaximin alfa promotes the expression of strategic tight junction proteins, including occludin and zonulin-1, leading to structural and functional sealing of the epithelial barrier. The low-grade inflammatory response within the mucosal lamina propria and intestinal sensory nerves are calmed and less hypersensitive due to a reduced translocation of Pathogen-Associated Molecular Patterns (PAMPs) and endotoxins into the portal circulation [10].
Concurrently, rifaximin alfa positively alters bile acid metabolism by activating the Pregnane X Receptor (PXR),which serves as the main sensor of toxins and xenobiotics in the intestine. Agonistic action against PXR allows for the inhibition of proinflammatory pathways such as NF-κB and modification of the composition and reabsorption of bile acids. This is crucial in patients with the diarrheal form of IBS-D, in whom excess bile acids in the large intestine enhance peristalsis and create an osmotic effect. Pharmacological therapy in this area allows for normalization of stool consistency and equalization of bowel habits [1, 28].
Additionally, the drug reduces short-chain fatty acids (SCFA) in individuals with an excess [3, 32] and may modify the level of vitamins produced by intestinal flora bacteria [33]. Complementing the versatile effect of the drug is its effect on virulence and adhesion of bacteria

without the need for their eradication. Rifaximin alfa induces changes in the phenotypes of pathogens, which significantly limits their ability to adhere to the mucosa and inhibits the secretion of virulence factors. Thus, it minimizes the potential for inducing inflammation and irritating the intestinal wall, even if some microorganisms survive the therapy [9, 4]. It is also worth noting the extremely important metabolic effect of rifaximin alfa, which is its proven effect on brush border enzymes. Clinical trials have confirmed that following rifaximin therapy, there is a significant increase in lactase activity, resulting in better tolerance of dairy products and symptom reduction in patients with secondary hypolactasia [13].

CLINICAL EFFICACY:

According to current medical knowledge, we have extensive evidence confirming that rifaximin alfa is one of the most thoroughly researched drugs for the treatment of diarrhea-predominant Irritable Bowel Syndrome (IBS-D). The effectiveness of treatment is based not only on the patient's subjective perception but also on complex endpoints (composite ends), which include a simultaneous reduction in abdominal pain intensity and improvement in stool consistency. Recent pooled analyses of studies, including more than 20 clinical trials, place rifaximin among the drugs with the highest reliability and certainty of action, confirming its well-established position in gastroenterology guidelines [22]. Numerous meta-analyses, including Cochrane, confirm the homogeneity of these results
[24, 26, 45, 50]. A significant indicator is the NNT (Number Needed to Treat), which for rifaximin averages 9. This is a better result than when using soluble fiber (NNT≈12) or many popular probiotic preparations of unconfirmed composition [12, 52]. Compared to placebo, patients using rifaximin are significantly more likely to achieve a so-called „sustained response", defined as stable clinical improvement lasting for at least 12 weeks after the end of the standard 14-day treatment cycle [1, 7, 22]. Significant clinical improvement is also maintained in a subgroup of patients with severe symptom intensity [2, 40].
The 2026 data also provides breakthrough findings in a direct comparison of rifaximin use with the Low FODMAP diet. It has been shown that a full, sufficiently long-lasting course of pharmacological treatment is not inferior to the use of a restrictive diet in terms of reducing and calming general symptoms, and additionally achieves an advantage due to significantly higher convenience of use and better patient compliance [7]. Modern medicine recognizes rifaximin alfa as the gold standard for reducing abdominal distension (bloating), which patients report as the most bothersome and treatment-resistant symptom of irritable bowel syndrome. Advanced

studies using scintigraphy and precise measurements of intestinal gas have confirmed that the drug not only reduces the production of hydrogen and methane, but also improves the movement of gases through the intestines, which provides patients with real-world relief [22, 49]. Significantly, rifaximin also finds use in IBS-C forms where, in combination with neomycin, it reduces methane levels [34, 39]. Reducing bloating has been shown to have a more significant impact on patients' quality of life than simply controlling their bowel movements [7]. When comparing rifaximin with the frequently overused loperamide, it has a significant advantage. Loperamide inhibits diarrhea but is also responsible for the severity of bloating and abdominal pain, while rifaximin treats the cause, which is dysbiosis, and normalizes the consistency of stools without causing constipation
[11, 25, 29]. Consequently, patients less frequently require additional "rescue" medications during long-term follow-up [32].

To evaluate the durability of the therapeutic effect, the Treatment-Free Interval (TFI) has been introduced. The use of real-world data confirms that appropriately and conscientiously followed rifaximin therapy significantly extends symptom-free periods in patients, thereby reducing overall healthcare costs. Additionally, patients are less likely to use other rescue medications [24].

The benefits of use of rifaximin also extend to extra-intestinal manifestations, affecting psychological well-being. As a result of sealing the intestinal barrier and silencing inflammation, patients experience a reduction in anxiety specific to intestinal symptoms (GSA - Gut-Specific Anxiety), which is manifested by a lower sense of anxiety about losing control of bowel movements [12]. Reducing the amount of toxins and ammonia concentration in the body also improves cognitive function and eliminates the feeling of „brain fog” that often accompanies patients with severe IBS, even without overt encephalopathy.

This influence is also visible in clinical imaging studies of the gut-brain axis [17, 28].

Analysis of the effect of rifaximin alfa on the gut-brain axis showed that improving the integrity of the gut barrier results in a significant reduction in GSA anxiety.

The fact of limiting the passage of bacteria and extinguishing microinflammation results in less activation of sensory receptors, which reduces stress levels and improves the overall mental well-being of patients [18]. Additionally, in patients with comorbid functional dyspepsia, the presence of IBS does not impair the response to treatment, making rifaximin the preferred choice in overlap syndromes [43]. For the most optimal and effective treatment, it should be directed primarily to people with diarrheal or mixed forms, in whom flatulence and symptoms suggestive of bacterial overgrowth (SIBO) predominate. An additional indicator for

qualification is slightly elevated fecal calprotectin (50 - 150 µg/g), suggesting low-grade inflammation that rifaximin effectively resolves. Eligibility for treatment may be supported by assessment of inflammatory markers [40, 42].

PRACTICAL DOSAGE AND TREATMENT REGIMEN:

The current rules for the use of rifaximin alfa in the diarrheal form of IBS are not only strictly defined but also based on reliable scientific evidence. They meet the conditions of EBM (evidence based medicine).

An important element of effective and successful therapy is not only the inclusion of the drug itself, but also the strictly observed taking of the recommended dose and determining the duration of the treatment, which is intended to ensure proper modification of the intestinal microflora. The primary recommended rifaximin regimen for adult patients is a daily dose of 1650 mg administered in three divided doses of 550 mg for 14 days. Clinical trials have shown this regimen to be the most effective for alleviating pain and improving stool form while remaining entirely safe [22, 27]. Reducing the treatment time to less than two weeks is considered a therapeutic error, which may consequently lead to the recurrence of dysbiosis and the recurrence of symptoms.

Although rifaximin alfa shows high efficacy when used alone, recent reports indicate synergistic effects in polytherapy using selected bacterial strains. Combining the substance with Bifidobacterium longum W11 or spore-forming Bacillus spp. can improve clinical outcomes and accelerate the restoration of eubiosis [6, 8, 31, 52].

It is now also known that irritable bowel syndrome is a chronic disease with relapses, so current guidelines define a strategy for managing relapses. The breakthrough TARGET 3 study provided clear instructions: in patients who responded positively to the first cycle but experienced a recurrence, a repeat 14-day therapy at the same dose is effective for achieving another remission [27]. Currently, up to two additional therapeutic cycles per year are permitted if justified by recurrence of symptoms, which allows the patient to maintain long-term control of the disease without losing the effectiveness of the drug [1, 27, 34].

This strategy is also safe in post-infectious IBS [15, 24, 35].

A key factor in ensuring cooperation with the patient is information about minimal absorption of the drug from the gastrointestinal tract, thanks to which its action is focused solely on the target site, i.e. the intestinal lumen. This allows rifaximin alfa to be taken with or without food, and the lack of significant interactions with other systemic medications, including antiplatelet

or anticoagulants, makes it a safe choice for patients with other diseases
[25, 30, 34].

The lack of effect on cytochrome P450 activity means that the drug does not modify the therapeutic concentrations of these drugs (anticoagulants used in AF or embolism, or antiplatelet drugs used in the prevention of infarction), which is crucial in the safe care of cardiac patients [44]. Rifaximin alfa occupies the position of first-line therapy in adults with confirmed IBS-D or a mixed form with a predominance of flatulence, especially when previous therapeutic management, such as lifestyle modification, does not bring improvement or the patient is unable to maintain nutritional restriction in the form of a Low FODMAP diet [22, 32]. The indication for the inclusion of rifaximin is also the suspicion of the presence of SIBO in the form of symptoms such as sudden enlargement of the abdominal circumference after meals or a positive breath test result [34].

EUBIOTIC PROFILE AND SPECIAL POPULATIONS:

In 2026, current standards of treatment and care for patients with IBS-D emphasize both long-term safety and therapeutic efficacy itself. Due to its unique molecular structure and lack of systemic absorption, rifaximin alfa presents a tolerability profile nearly identical to placebo. This makes it one of the safest drugs in gastroenterology, as confirmed by meta-analyses where the incidence of adverse events (e.g., nausea, headache) was comparable to control groups [12, 32]. A very important issue from a clinical point of view is the practically non-existent risk of Clostridioides difficile infection. Unlike systemic antibiotics, rifaximin does not increase the probability of pseudomembranous colitis because it does not disrupt the beneficial anaerobic flora of the colon [2, 5]. Short-term treatment therefore does not lead to “sterilization” of the gastrointestinal tract, but is based on transient modulation of the eubiotic flora followed by its rapid recovery [31]. It is also safe in patients with diabetes and obesity [30, 47]. This has also been demonstrated in studies on microbiome stability in adults [14, 23, 36].

Bacterial resistance remains another important issue, but in the case of rifaximin alfa the evidence gathered is promising and reassuring. It has been confirmed that resistance genes are not easily transferred between different bacterial species due to the mechanism of resistance transfer, as it is chromosomal and not plasmid-based [9].

Long-term observations confirmed the absence of resistance buildup and the absence of loss of drug efficacy even after repeated therapeutic cycles in the same patients [27, 35].

Rifaximin alfa is also a key drug for the aging patient population, for whom IBS-D poses a significant clinical challenge. Given its negligible bioavailability and lack of hepatic metabolism, it does not interact with common cardiac, antidiabetic, or anticoagulant medications [2, 25, 44]. High and good tolerance in people over 65 years of age allows for effective therapy with this drug, especially in terms of controlling diarrhea and avoiding significant geriatric complications, such as dehydration, while maintaining effectiveness that does not differ from that observed in younger adults [24]. However, despite this high safety profile in the qualification process for rifaximin treatment, caution should be exercised in patients with severe hepatic impairment (Child-Pugh class C). It is also important to observe and exclude alarm symptoms, such as unintentional weight loss, the presence of blood in the stool or anemia, which always require additional diagnosis for oncological diseases before considering the symptoms as a manifestation of irritable bowel syndrome [25].

SUMMARY AND CONCLUSIONS:

The current approach to treating IBS, specifically its diarrheal form, is departing from the temporary and sporadic use of medications designed to conceal symptoms and instead focusing on modifying the intestinal microflora. Rifaximin alfa's unique eubiotic profile and broad anti-inflammatory and intestinal barrier-sealing effects make it an essential component of first-line treatment [52]. To achieve therapeutic success, patients must adhere to the full 14-day dosing protocol (1650 mg/d) and use a retreatment strategy in the event of symptom recurrence.

Rifaximin alfa therapy went beyond just bowel control. It also provides patients with other metabolic benefits, such as improved lactose tolerance, and psychosomatic benefits by reducing intestinal anxiety (GSA) and brain fog. The use of the Treatment-Free Interval (TFI) parameter allows for an objective assessment of long-term effectiveness, confirming that the drug brings not only clinical but also economic effects. Due to the lack of significant interactions with other drugs and its high safety, this drug remains a favorable choice for patients at particular risk, including seniors with multimorbidity and cardiac patients taking anticoagulants and antiplatelet drugs. Rifaximin alfa not only improves quality of life by alleviating symptoms but also provides durable disease control based on solid Evidence-Based Medicine (EBM).

Supplementary materials:

Not applicable.

Author's contribution:

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The data presented in this study are available upon request from the correspondent author.

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