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REVIEW ARTICLE

# Advances in Therapy for Irritable Bowel Syndrome with Diarrhea: Role of Rifaximin in Combination with Metronidazole

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Irritable bowel syndrome (IBS) with diarrhea predominance is a subtype of IBS characterized by recurrent abdominal pain or discomfort along with frequent loose or watery stools. A significant number of individuals are impacted and are physically, socially, and emotionally impacted. Managing diarrhea-predominant IBS (IBS-D) involves a multidimensional approach due to unpredictable nature of the condition involving lifestyle modifications, dietary changes, stress management techniques, and medications. Altered gut microbiota and small intestinal bacterial overgrowth (SIBO) often precede IBS leading to dysbiosis. Systemic antibiotics and other treatment options have been reported with varied outcomes, yielding inconsistent results. Rifaximin, with its broad anti-bacterial action, along with eubiotic activity, limited systemic exposure, gut-specific action, and limited potential for drug interactions along with metronidazole is proposed as a novel treatment option for IBS-D. Rifaximin and metronidazole fixed-dose combination will not only address infectious diarrhea associated with IBS but also SIBO and postinfectious IBS with excellent efficacy and tolerability. For patients with IBS-D, rifaximin along with metronidazole can be a new treatment avenue as increasing evidence supports the hypothesis that bacterial overgrowth may be involved in the pathogenesis of IBS and parasitic infections can be a triggering factor for the exacerbation of IBS. PubMed and Google Scholar were searched through May 2023. Randomized controlled trials and reviews published in English were selected that evaluated rifaximin and/or metronidazole in patients with IBS.

Key words: Irritable bowel syndrome, diarrhea, rifaximin, metronidazole

## INTRODUCTION

Irritable bowel syndrome (IBS) is defined as abdominal discomfort or pain associated with altered bowel habits for at least 3 days per month in the previous 3 months, with the absence of organic disease. Altered bowel habits include diarrhea-predominant, constipation-predominant, and mixed presentation with alternating diarrhea and constipation. IBS is a chronic condition often referred to as a functional disorder, as it does not cause any structural abnormalities in the digestive system.[1]

Diarrhea-predominant IBS (IBS-D) is a subtype of IBS characterized by recurrent abdominal pain or discomfort along with frequent loose or watery stools. It is estimated that IBS-D affects a significant portion of individuals with IBS, making it a common and burdensome condition. The impact of IBS-D on patients is multi-faceted. Physical symptoms, such as frequent bowel movements and abdominal pain, can be distressing and disruptive to daily life. The urgency to find a restroom and the fear of not being able to control bowel movements can cause significant anxiety and embarrassment. IBS-D can also lead to emotional and psychological effects, including increased stress, anxiety, and depression. The unpredictable nature of the condition and its impact on social activities and relationships can further contribute to reduced quality of life and emotional well-being.[2] Managing IBS-D involves a multidimensional approach that may include lifestyle modifications, dietary changes, stress management techniques, and medications.[3]

Rifaximin is a nonsystemic antibiotic used to treat IBS-D, administered as short-course therapy. It has been shown to significantly improve global IBS symptoms including

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bloating and loose or watery stools with good tolerability and a favorable safety profile.[4] Metronidazole is frequently used in community practice in India to treat episodes of diarrhea in patients with IBS and as an anti-protozoal and broad-spectrum anti-bacterial.[5,6] In light of the above literature, this review article proposes fixed-dose combination (FDC) of rifaximin and metronidazole as a useful treatment option in the management of acute diarrhea associated with IBS. PubMed and Google Scholar were searched through May 2023. Randomized controlled trials (RCTs) and reviews published in English were selected that evaluated rifaximin and/or metronidazole in patients with IBS.

## PATHOPHYSIOLOGY OF DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME

The exact cause of IBS is not fully understood, as it involves multiple factors. IBS is often described as a brain-gut disorder, indicating that a complex interaction between the gastrointestinal (GI) system and the central nervous system leads to the manifestation of symptoms. It has been observed that psychosocial stressors frequently precede the onset of symptoms, and therapies targeting the central nervous system have shown improvements in these cases.

Factors that can trigger disruptions in GI motor and sensory functions include irritation from digestion by-products, previous episodes of gastroenteritis, internal irritants, change in gut microbiome, activation of the mucosal immune system, food intolerances, and increased permeability of gut lining. These underlying disruptions give rise to symptoms such as discomfort, altered gut motility, and changes in bowel habits. In addition, there may be a genetic component contributing to the development of this condition. Recent studies have introduced new and innovative hypotheses regarding the underlying mechanisms of IBS. These hypotheses have contributed to the development of various treatment options.[7]

## CURRENT TREATMENT OPTIONS

In patients with IBS-D, therapeutic options include antibiotics, peripheral opioid agonists, mixed opioid agonists/antagonists, bile acid sequestrants, and antagonists of serotonin 5-hydroxytryptamine type 3 (5–$HT_3$) receptors. Loperamide may reduce the frequency of bowel movements and improve stool consistency, but it does not improve global IBS symptoms or abdominal pain and can cause constipation. Eluxadoline is a mixed μ – opioid agonist and δ – opioid antagonist used to slow bowel motility and reduce visceral pain in IBS-D patients. However, it can cause constipation and nausea and is contraindicated in patients with a history of pancreatitis, bile duct obstruction, sphincter of Oddi dysfunction, or alcohol abuse. Bile acid sequestrants, such as cholestyramine, colestipol, and colesevelam, can also be effective in improving stool consistency and decreasing bowel movements, particularly in patients with bile acid malabsorption, but can cause constipation and interfere with drug absorption. Antagonists of serotonin 5-$HT_3$ receptors, such as alosetron, ondansetron, and ramosetron, can be effective in reducing abdominal pain and improving stool frequency and consistency in selected patients with IBS-D, but can cause constipation and ischemic colitis and should be used with caution.[3]

## NEED FOR NEW THERAPY

Current treatment options for IBS often prove ineffective in providing relief, despite attempts at dietary and lifestyle modifications, fiber supplementation, psychological therapy, and pharmacotherapy.[8,9] Since there are no reliable biological or structural markers to assess the effects of pharmacotherapy, patients are typically asked to self-report whether they experienced sufficient relief from their IBS symptoms, with a simple "yes" or "no" response.[10] Considering the shortcomings of the existing therapies, there exists a significant medical requirement for innovative approaches to address the unmet needs of IBS patients.

## ROLE OF RIFAXIMIN

Alterations in the intestinal microbiota have been observed in patients with IBS,[11-13] prompting researchers to explore the potential of targeting the microbiota as a treatment approach for this condition. While neomycin therapy has shown some improvement in certain patients, clinical trials have demonstrated only limited effectiveness, and the use of this drug is hindered by side effects that restrict its usage.[14] The utilization of systemic antibiotics has been reported with varied outcomes, yielding inconsistent results in treating IBS.[15]

Rifaximin administered as short-course therapy (one 550-mg tablet three times daily for 2 weeks with up to two additional rifaximin courses for symptom recurrence) has been shown to significantly improve global IBS symptoms versus placebo (40.7% vs. 31.7%; $P < 0.001$), including bloating and loose or watery stools with good tolerability and a favorable safety profile.[4] Rifaximin is an orally administered, nonsystemic, broad-spectrum antibiotic that specifically targets the GI tract, and it is characterized by a minimal risk of bacterial resistance.[16-18] It has also shown efficacy in clinical studies of IBS.[19,20] A study by Sharara *et al.* showed a

significant difference in global symptom relief with rifaximin versus placebo (41.3% vs. 22.9%, $P = 0.03$) when rifaximin 400 mg was used twice daily.[19] Another study by Pimentel *et al.* also showed that patients receiving 400 mg of rifaximin 3 times daily for 10 days experienced greater improvement in IBS symptoms (36.40% vs. 21.0%; $P = 0.020$).[20]

Data suggest that the gut microbiota may contribute to the development of IBS symptoms, the limited response rate to rifaximin in a study indicates that there are likely other factors involved or that rifaximin may not effectively eliminate the key organisms in most patients.[21] Further evidence supporting the role of specific bacteria in the pathophysiology of IBS could be obtained by targeted modifications of the GI bacterial composition. In a rat model of visceral hypersensitivity, rifaximin was found to have an impact on the microbiome in the ileum, leading to changes in bacterial communities and an increased presence of *Lactobacillus* species. These changes seemed to provide a protective effect against ileal inflammation, impairment in mucosal barrier function, and reduced visceral hypersensitivity when chronic psychological stress was applied to the rats.[22] Neomycin, another antibiotic, did not produce similar effects. These findings highlight that not only antibiotics but also certain probiotics may have modestly beneficial effects on IBS symptoms in patients.[23]

## ROLE OF METRONIDAZOLE

Metronidazole (400 mg three times daily for 10 days) is frequently used in community practice in India to treat episodes of diarrhea in patients with IBS (significant symptom score reduction; $P < 0.001$) and as an anti-protozoal and broad spectrum anti-bacterial. Most patients report relief of symptoms in the short-term treatment with this drug.[5,6] Postinfectious IBS (PIIBS) accounts for 6%–17% of patients with IBS. Metronidazole therapy (400 mg thrice daily for 7 days) results in sustained improvement in pain, stool, and total score in PIIBS and diarrhea-predominant IBS subgroups. From day 7 to day 28 (drug-free period), the stool symptoms continued to improve ($P < 0.05$).[24] As metronidazole is an effective and safe treatment option for IBS-D it should complement rifaximin not only for a greater associated symptoms relief but also for PIIBS.

## RATIONALE OF NOVEL RIFAXIMIN AND METRONIDAZOLE COMBINATION

Rifaximin is a nonabsorbable rifamycin that has been shown to be effective in reducing IBS symptoms, bloating, and loose or watery stools after 2 weeks of 550 mg three times daily treatment, and is well-tolerated in two identically designed, phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2) with no significant adverse events.[25] Rifaximin (550 mg three times daily for 2 weeks) has also been found to be safe and effective in repeated treatments in a phase 3 study of patients with relapsing symptoms of IBS-D. The percentage of responders for abdominal pain (50.6% vs. 42.2%; $P = 0.018$) was significantly greater with rifaximin than placebo. Significant improvements were also noted for the prevention of recurrence, durable response, and bowel movement urgency.[26] Moreover, rifaximin eradicates small intestinal bacterial overgrowth (SIBO) in up to 84% of patients with IBS, with results sustained up to 10 weeks posttreatment. Rifaximin demonstrated a more favorable adverse event profile than systemic antibiotics, without clinically relevant antibiotic resistance.[27] Metronidazole is an antimicrobial agent that has been used in clinical medicine for more than 45 years.[5] Metronidazole in a dose of 400 mg three times daily for 10 days has shown to provide symptom relief in IBS, without affecting rectosigmoid motility[6] in addition to anti-protozoal and broad-spectrum anti-bacterial activity.[5] Metronidazole therapy also resulted in sustained improvement in pain, stool, and total score in PIIBS and diarrhea-predominant IBS subgroups who had no preceding gastroenteritis.[24] Furthermore, a large majority of patients with symptomatic giardiasis and diarrhea have preexisting IBS, (indicated by a clinical history of at least 2 years) and are not cured by metronidazole alone treatment.[28] Rifaximin with metronidazole combination can be useful in these patients for complete amelioration of symptoms.

## DISCUSSION

There has been an increasing recognition of the significance of GI flora in both maintaining good health and contributing to diseases. The quantity of GI bacteria surpasses the number of human cells in the body by a factor of 10, indicating their importance in our evolutionary development. However, certain conditions, such as IBS, demonstrate that these bacteria can have a detrimental impact. For instance, individuals with IBS may exhibit abnormal lactulose breath tests, indicating an overgrowth of bacteria in the small intestine. Treating normal flora that causes disease presents two major challenges. First, normal flora encompasses a vast and diverse group of organisms, with over 500 bacterial species in the GI tract, many of which remain poorly characterized. Due to this diversity, broad-spectrum antibiotics are often required for treatment. However, the use of broad-range antibiotics poses a significant problem as it may lead to the development of opportunistic infections, such as *Clostridioides difficile* colitis, within the GI tract. Second, these disorders potentially

affect a large number of patients; it could contribute to the emergence of highly virulent and antibiotic-resistant bacterial strains, thereby perpetuating GI infections. Furthermore, IBS-D is associated with SIBO, PIIBS, and infectious diarrhea involving parasites.

Rifaximin exhibits minimal absorption from the GI tract, <0.4%, indicating that its effects primarily target the GI flora. This characteristic minimizes the potential for systemic adverse effects, allergic reactions, and the development of drug resistance by bacteria outside of the intestinal tract. Furthermore, rifaximin has a broad spectrum of activity and is often twice as effective in eradicating bacterial overgrowth compared to systemic antibiotics. This broad range of activity implies that rifaximin may be effective in treating various GI disorders associated with imbalances in intestinal flora, such as hepatic encephalopathy, *C. difficile colitis*, travelers' diarrhea, and functional bowel disorders. Furthermore, the mechanisms of action of rifaximin are not limited to direct bactericidal activity; it can positively modulate the gut microbial composition. Therefore, rifaximin could potentially be redefined as a gut environment modulator. Rifaximin is recommended as a treatment for global IBS-D symptoms by ACG guidelines for managing IBS.[29] Rifaximin was also found to be effective and safe in eradicating SIBO, in a systematic review and meta-analysis that analyzed a total of 21 observational studies and 5 RCTs involving 874 patients.[30] Rifaximin was also approved by the US Food and Drug Administration in 2015 to treat adult patients with moderate to severe IBS with diarrhea.

Metronidazole may be suitable for SIBO treatment since it is effective against Gram-negative and Gram-positive anaerobic bacteria such as *Bacteroides*, *Fusobacterium,* and *Peptostreptococci*.[31] Other antibiotics neomycin,[14] clarithromycin, and metronidazole[6] have been well evaluated for the management of IBS.

For patients with IBS-D, rifaximin along with metronidazole can be a new treatment avenue as increasing evidence supports the hypothesis that bacterial overgrowth may be involved in the pathogenesis of IBS and parasitic infections can be a triggering factor for the exacerbation of IBS. Furthermore, rifaximin and metronidazole combination can be useful not only in controlling diarrheal episodes associated with IBS but also for SIBO and PIIBS with excellent efficacy and tolerability.

## CONCLUSION

IBS is a complex disorder with multifactorial etiology, involving alterations in gut microbiota, GI motility, microscopic inflammation, bile acid malabsorption, and alterations in the enteric nervous system. Rifaximin, with its broad anti-bacterial action, along with eubiotic activity, limited systemic exposure, gut-specific action, limited potential for drug interactions along with metronidazole is proposed as a novel treatment option for IBS-D. Rifaximin and metronidazole FDC will not only address infectious diarrhea associated with IBS but also SIBO and postinfectious IBS with excellent efficacy and tolerability.

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### Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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### Conflicts of interest

There are no conflicts of interest.

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