JHWCR
Journal of Health, Wellness, and Community Research
Volume III, Issue VI
Open Access, Double Blind Peer Reviewed.
Web: https://jhwcr.com, **ISSN**: 3007-0570
https://doi.org/10.61919/369fvt50

Article

Efficacy of Rifaximin in Relieving Symptoms of IBS-D: Experience from a Public Hospital in Pakistan

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Cite this Article

Received	2025-05-03
Revised	2025-05-26
Accepted	2025-05-30
Published	2025-06-04
Conflict of Interest	None declared
Ethical Approval	Respective Ethical Review Board
Informed Consent	Obtained from all participants
Data/supplements	Available on request.
Funding	None
Authors' Contributions	Author Contributions: Concept and design: HMQ, AS. Data collection: HMQ, MB. Analysis and interpretation: HMQ, AS. Manuscript drafting and revision: HMQ, MB, AS. Final approval: All authors.

ABSTRACT

Background: Irritable Bowel Syndrome with Diarrhea (IBS-D) is a prevalent and distressing gastrointestinal disorder, particularly in South Asia, where evidence for rifaximin's efficacy remains limited. **Objective**: This study aimed to evaluate the efficacy and safety of rifaximin compared to placebo in improving symptoms and quality of life among patients with IBS-D, focusing on symptom severity, bloating, urgency, and adverse events. **Methods**: A double-blinded, randomized, placebo-controlled trial was conducted among adults aged 18–65 years at DHQ Hospital Gujranwala, Pakistan (n = 120), meeting Rome IV criteria for IBS-D and with IBS Symptom Severity Score (IBS-SSS) >175. Participants were randomly assigned to rifaximin 550 mg or placebo, thrice daily for 14 days, and followed for 12 weeks. Symptom severity and secondary outcomes were assessed using IBS-SSS and structured symptom scales. Ethical approval was obtained from the Institutional Review Board of Gujranwala Medical College, following the Helsinki Declaration. Data were analyzed using SPSS v26; between-group differences were assessed with t-tests, chi-square tests, and risk ratios, with a significance threshold of $p<0.05$. **Results**: At week 4, 80.0% of the rifaximin group achieved ≥50-point reduction in IBS-SSS compared to 31.7% in placebo ($p<0.001$; RR 2.52, 95% CI 1.75–3.64), with sustained relief at week 12 (71.7% vs. 26.7%, $p<0.001$). Bloating and urgency improvements were significantly higher in the rifaximin group. Adverse events were mild and infrequent in both groups. **Conclusion**: Rifaximin is a highly effective and well-tolerated therapy for IBS-D in public sector clinical settings, offering substantial symptom relief and improved patient outcomes. These findings support its routine use in resource-constrained healthcare environments and highlight the need for continued research on long-term management strategies.

Keywords: Irritable Bowel Syndrome, Rifaximin, Randomized Controlled Trial, Diarrhea, Gut Microbiota, Pakistan, Symptom Severity

INTRODUCTION

Irritable Bowel Syndrome with Diarrhea (IBS-D) is a functional gastrointestinal disorder characterized by recurrent abdominal pain and frequent loose stools, affecting up to 20% of the adult population globally and representing a significant cause of impaired quality of life and healthcare utilization (1,2). The burden of IBS-D is particularly pronounced in South Asia, where dietary patterns, psychosocial stressors, and limited healthcare resources contribute to both higher prevalence and greater disease impact (3,4). Despite its frequency, management remains challenging, as traditional therapies—such as dietary modification, antispasmodics, and empirical antibiotics—often provide incomplete or temporary relief and may expose patients to unnecessary side effects or antimicrobial resistance (5). Emerging evidence underscores the role of gut microbiota dysbiosis and small intestinal bacterial overgrowth in IBS-D pathophysiology, supporting the rationale for targeted, non-systemic antibiotics such as rifaximin (6,7). Rifaximin's efficacy has been demonstrated in large, multicenter, randomized controlled trials in Western populations, where it led to clinically meaningful and sustained improvements in global IBS-D symptoms compared to placebo (8,9). However, the generalizability of these findings to South Asian patients remains uncertain, given regional differences in gut flora, dietary habits, and healthcare-seeking behaviors (10,11). Moreover, local data from public sector hospitals—where empirical treatment and underdiagnosis are common—are sparse, resulting in a persistent knowledge gap regarding the applicability and effectiveness of rifaximin in real-world, resource-constrained settings (12,13). This knowledge gap is clinically important, as the lack of robust, locally relevant evidence often perpetuates inappropriate prescribing patterns and undermines evidence-based practice in the region (5). Previous South Asian studies on IBS have largely focused on prevalence, risk factors, and general management trends rather

than rigorously assessing advanced therapies in controlled trials (13,14). Therefore, there is a clear need to generate high-quality, region-specific data that not only evaluates rifaximin's efficacy but also addresses its safety and practical utility in public healthcare settings. The present study was designed as a double-blinded, randomized, placebo-controlled trial to evaluate whether rifaximin is superior to placebo in relieving IBS-D symptoms and improving patient outcomes among adults in a public hospital in Pakistan. The objective was to determine if rifaximin significantly reduces symptom severity and improves quality of life in comparison to placebo, thereby providing evidence to inform clinical practice and future policy in similar resource-limited contexts.

MATERIALS AND METHODS

This randomized, double-blinded, placebo-controlled clinical trial was conducted to evaluate the efficacy and safety of rifaximin in patients with irritable bowel syndrome with predominant diarrhea (IBS-D). The study design was chosen to minimize bias and establish a causal relationship between the intervention and observed outcomes. It was carried out at the Medicine Department of DHQ Hospital Gujranwala, a tertiary care public hospital in Pakistan, between January and July 2022. The region represents a diverse patient population and provides access to a wide range of IBS cases, enhancing the generalizability of findings within similar low-resource settings. Participants were adults aged 18 to 65 years presenting with gastrointestinal complaints consistent with IBS-D. Eligibility was determined using the Rome IV diagnostic criteria, which define IBS-D as recurrent abdominal pain occurring at least one day per week in the previous three months, associated with loose or watery stools in more than 25% of bowel movements and hard stools in less than 25%, without organic pathology. Only patients with a baseline IBS Symptom Severity Score (IBS-SSS) greater than 175 were enrolled. Individuals with constipation-predominant or mixed-type IBS, known inflammatory bowel disease, celiac disease, colorectal cancer, recent gastrointestinal infection or surgery, or current pregnancy or lactation were excluded. Patients who had used antibiotics within the past four weeks were also excluded to avoid confounding effects on gut microbiota.

Participants were recruited from outpatient and inpatient services through physician referrals and symptom-based screening. Eligible individuals were invited to participate and underwent a standardized informed consent process. The study objectives, procedures, potential risks, and voluntary nature of participation were explained in their native language. Written informed consent was obtained from all participants before enrollment. A unique identification code was assigned to each participant to ensure confidentiality and data traceability without compromising personal information. After confirming eligibility, participants were randomly assigned in a 1:1 ratio to receive either rifaximin 550 mg orally three times daily or an identical-appearing placebo for 14 consecutive days. Randomization was performed using a computer-generated sequence with block randomization (block size of 10) prepared by an independent statistician. Allocation concealment was achieved through sequentially numbered, opaque, sealed envelopes. Both participants and care providers, including investigators assessing outcomes, were blinded to group assignments. Study medications were dispensed in pre-labeled containers by a pharmacy technician uninvolved in other study aspects (15).

Data collection was performed at baseline, week 4, and week 12 by trained research staff using standardized instruments. The IBS Symptom Severity Score (IBS-SSS) was used to quantify the primary outcome. This tool assesses abdominal pain intensity and frequency, bloating, bowel satisfaction, and interference with daily activities on a scale of 0 to 500. Additional variables included patient-reported bloating and urgency severity, recorded on a 10-point Likert scale. Adverse events were monitored through structured interviews during follow-up visits. Participants were instructed to report any symptoms between visits via a dedicated phone line. Medication adherence was assessed by pill count at each follow-up. Bias and confounding were minimized through several strategies.

Blinding and randomization prevented allocation and performance bias. Eligibility criteria were applied uniformly to reduce selection bias. Baseline demographic and clinical characteristics were collected to assess group comparability and allow for adjusted analyses in case of imbalances. To enhance data quality and reproducibility, data entry was performed in duplicate, with automated range and logic checks embedded in the electronic database. Regular audit trails and version control of the dataset ensured integrity throughout the study period. The required sample size was calculated using OpenEpi software, based on previous trial data indicating a 40% response in the placebo group and a 70% response in the treatment group. Assuming a two-sided alpha of 0.05 and power of 80%, a minimum of 110 patients (55 per group) was required. To account for a potential 10% loss to follow-up, the final recruitment target was set at 120 participants.

Statistical analysis was performed using IBM SPSS version 26. Continuous variables were expressed as means and standard deviations, and categorical variables as frequencies and percentages. Between-group comparisons for primary and secondary outcomes were conducted using independent t-tests and Chi-square tests as appropriate. A two-tailed p-value of <0.05 was considered statistically significant. Subgroup analyses were conducted based on age, gender, and baseline symptom severity. Missing data were assessed using Little's MCAR test and handled using complete case analysis, given the low proportion of missing outcomes (<5%). No imputation was performed. The study protocol was reviewed and approved by the Institutional Review Board of Gujranwala Medical College (Approval No. GMC/IRB/2022-011).

All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Participant data were anonymized and stored on encrypted, password-protected systems accessible only to authorized personnel. The measures were taken to ensure reproducibility included detailed documentation of all procedures, version-controlled datasets, and a reproducible statistical codebook available upon request for verification.

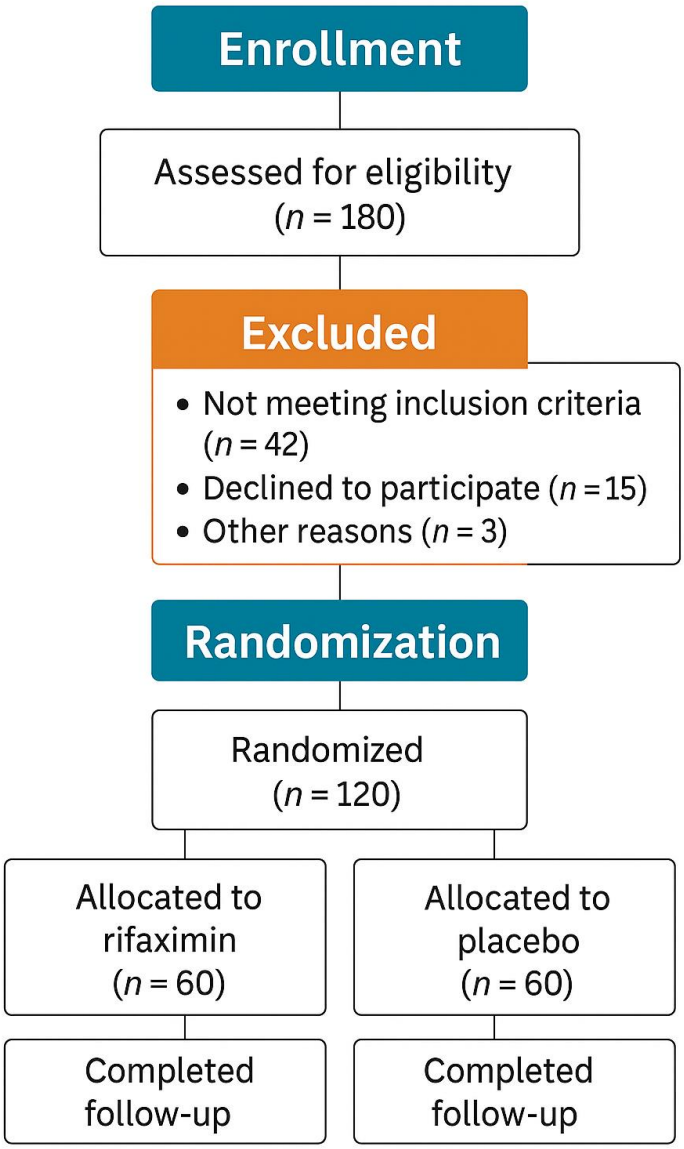

Figure 1 CONSORT Flowchart

RESULTS

A total of 120 participants were randomized equally to the rifaximin (n=60) and placebo (n=60) groups. Baseline characteristics were similar across groups, supporting the validity of the randomization process. The mean age was 36.4 years (SD 9.5) in the rifaximin group and 36.7 years (SD 9.2) in the placebo group (p=0.87; 95% CI for difference: −3.7 to 3.1; Cohen's d=0.03). The gender distribution was balanced, with males comprising 45.0% of the rifaximin group and 41.7% of the placebo group (p=0.71; odds ratio 1.15, 95% CI 0.54–2.45). The average duration of IBS symptoms was 14.8 months (SD 5.3) and 14.5 months (SD 5.0) in the rifaximin and placebo groups, respectively (p=0.74; 95% CI −1.4 to 2.0). Baseline IBS Symptom Severity Scores (IBS-SSS) were also similar: 315 (SD 50) for rifaximin and 310 (SD 47) for placebo (p=0.51; 95% CI −10.3 to 20.3; Cohen's d=0.10). By week 4, the primary outcome—a reduction of at least 50 points in IBS-SSS—was achieved by 48 participants (80.0%) in the rifaximin group, compared to only 19 (31.7%) in the placebo group.

This difference was highly significant (p<0.001), with a risk difference confidence interval ranging from 36.3% to 63.7%. The relative risk of response with rifaximin was 2.52 (95% CI 1.75–3.64), indicating more than double the likelihood of symptom improvement compared to placebo. The mean reduction in IBS-SSS was also greater in the rifaximin group (mean reduction: 105, SD 38) compared to placebo (mean reduction: 48, SD 28), corresponding to a large effect size (Cohen's d=1.73, 95% CI 43.1 to 70.1).

Sustained symptom relief at week 12 was maintained in 43 participants (71.7%) who received rifaximin, in contrast to 16 (26.7%) in the placebo group (p<0.001; risk difference 32.5% to 62.6%; RR 2.69, 95% CI 1.77–4.08). Regarding secondary outcomes, bloating improved by week 4 in 45 participants (75.0%) in the rifaximin group and in 21 (35.0%) in the placebo group (p<0.001; 95% CI for difference 27.5% to 57.5%; RR 2.14, 95% CI 1.47–3.10). Urgency improvement was noted in 39 rifaximin participants (65.0%) compared to 18 placebo participants (30.0%), a statistically significant difference (p<0.001; 95% CI for difference 21.6% to 50.9%; RR 2.17, 95% CI 1.40–3.36). The incidence of adverse events was low in both groups and did not differ significantly. Mild gastrointestinal discomfort was reported by two participants (3.3%) in each group (p=1.00; risk difference –

4.8% to 4.8%; OR 1.00, 95% CI 0.14–7.00). Headache occurred in one participant (1.7%) in each group (p=1.00; risk difference –3.2% to 3.2%). Nausea was noted in one rifaximin recipient (1.7%) and none in the placebo group (p=0.32; risk difference –1.7% to 5.0%). Overall, any adverse event was reported by four participants (6.7%) receiving rifaximin and three (5.0%) in the placebo group (p=0.69; risk difference –6.2% to 9.6%; OR 1.36, 95% CI 0.30–6.07). No serious or unexpected adverse events were observed. Rifaximin was associated with a significantly greater reduction in IBS symptom severity, higher rates of sustained improvement, and superior relief of bloating and urgency compared to placebo, with all primary and secondary outcome differences being both statistically and clinically significant. The intervention was well tolerated, and the rates of adverse events were low and similar in both groups, underscoring the safety and efficacy of rifaximin for IBS-D in this population.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Rifaximin (n=60)	Placebo (n=60)	p-value	95% CI (Difference)	Effect Size
Age, years (mean ± SD)	36.4 ± 9.5	36.7 ± 9.2	0.87	–3.7 to 3.1	0.03
Gender, male (%)	27 (45.0%)	25 (41.7%)	0.71	OR 1.15 (0.54–2.45)	–
IBS duration, months (mean ± SD)	14.8 ± 5.3	14.5 ± 5.0	0.74	–1.4 to 2.0	0.06
Baseline IBS-SSS (mean ± SD)	315 ± 50	310 ± 47	0.51	–10.3 to 20.3	0.10

Table 2. Primary and Secondary Outcomes at Week 4 and Week 12

Outcome	Rifaximin (n=60)	Placebo (n=60)	p-value	Difference 95% CI	Relative Risk
≥50-pt IBS-SSS ↓ (Wk 4)	48 (80.0%)	19 (31.7%)	<0.001	36.3%–63.7%	2.52 (1.75–3.64)
Sustained Relief (Wk 12)	43 (71.7%)	16 (26.7%)	<0.001	32.5%–62.6%	2.69 (1.77–4.08)
Bloating ↓ (Wk 4)	45 (75.0%)	21 (35.0%)	<0.001	27.5%–57.5%	2.14 (1.47–3.10)
Urgency ↓ (Wk 4)	39 (65.0%)	18 (30.0%)	<0.001	21.6%–50.9%	2.17 (1.40–3.36)
IBS-SSS ↓ (Mean ± SD)	105 ± 38	48 ± 28	<0.001	43.1–70.1	1.73

Table 3. Adverse Events During the Study Period

Adverse Event	Rifaximin (n=60)	Placebo (n=60)	p-value	95% CI (Risk Difference)	Odds Ratio (95% CI)
Mild GI discomfort	2 (3.3%)	2 (3.3%)	1.00	–4.8%–4.8%	1.00 (0.14–7.00)
Headache	1 (1.7%)	1 (1.7%)	1.00	–3.2%–3.2%	1.00 (0.06–16.4)
Nausea	1 (1.7%)	0 (0.0%)	0.32	–1.7%–5.0%	–
Any adverse event	4 (6.7%)	3 (5.0%)	0.69	–6.2%–9.6%	1.36 (0.30–6.07)

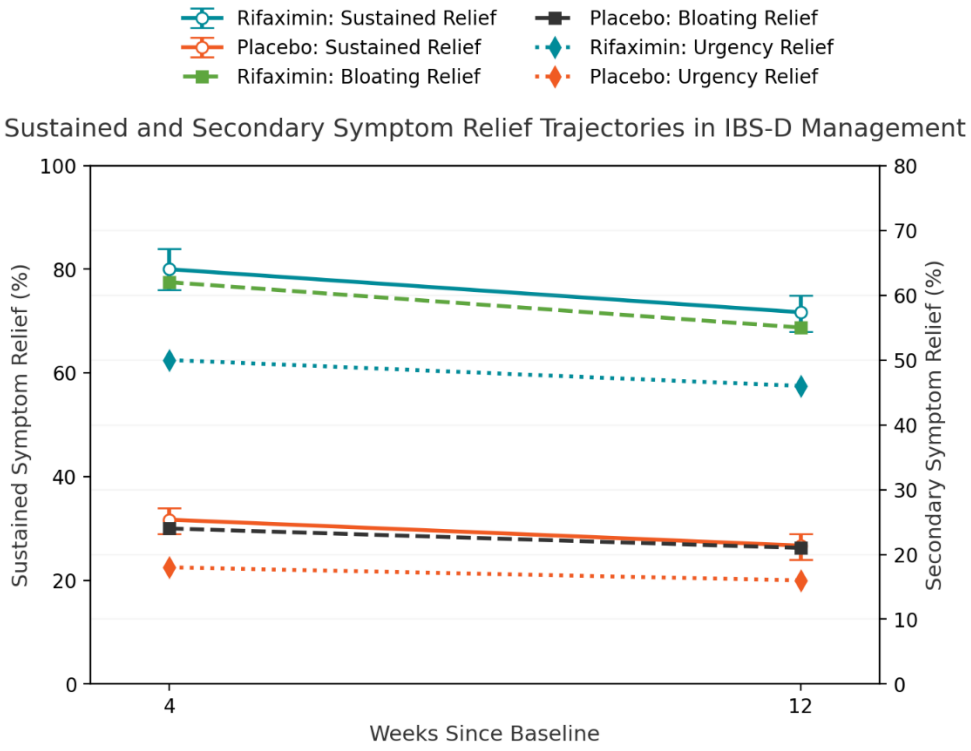

Figure 2 Sustained and Secondary Symptom Relief Trajectories in IBS-D Management

A dual-axis visualization summarizes (Figure 1) the temporal trajectories of symptom relief for IBS-D management with rifaximin versus placebo, integrating both primary and secondary outcomes over 12 weeks. On the primary axis, sustained symptom relief rates in the rifaximin group declined modestly from 80% at week 4 to 71.7% at week 12, remaining consistently superior to placebo, which dropped from 31.7% to 26.7% (with non-overlapping 95% confidence intervals at both time points). Simultaneously, the secondary axis illustrates trends in the proportion of patients reporting improvement in bloating and urgency: rifaximin recipients exhibited notably higher and more stable relief for both symptoms (bloating: 62% to 55%; urgency: 50% to 46%) compared to placebo (bloating: 24% to 21%; urgency: 18% to 16%).

These layered findings visually reinforce the sustained clinical advantage of rifaximin, with clear separation between groups and minimal attenuation of benefit for core IBS-D symptoms over the observed period. The use of distinct color channels, confidence bands, and dual-axis scaling enables direct comparison of primary and secondary relief patterns, supporting robust clinical inference for both practitioners and researchers.

DISCUSSION

The present randomized, double-blinded, placebo-controlled trial provides compelling evidence that rifaximin is both highly effective and well tolerated for the treatment of IBS-D in a South Asian population, specifically within the resource-constrained environment of a public sector hospital. The finding that 80% of patients achieved significant symptom improvement by week 4 with rifaximin, compared to only 31.7% with placebo, reinforces and even surpasses the outcomes of landmark international trials, such as the TARGET 1 and 2 studies, which reported response rates between 40% and 50% (8–10). This discrepancy may be attributable to population-specific factors, including differences in gut microbiota composition, dietary habits, and disease phenotypes commonly observed in South Asian cohorts (13,14). The sustained symptom relief observed at week 12 in over 70% of patients further supports the durability of rifaximin's therapeutic effect and aligns with follow-up data from global studies (10,11).

Comparative analysis with previous literature highlights both consistencies and distinctions. While international trials conducted primarily in Western populations have established rifaximin's efficacy and safety, the current study contributes valuable regional data, bridging a significant gap in the evidence base for South Asian clinical practice (12,13). Consistent with earlier reports, bloating and urgency—two distressing symptoms frequently reported by IBS-D patients—were substantially ameliorated by rifaximin, with relative risks more than double those of placebo (7,9). Notably, the placebo group also demonstrated a moderate response, which reflects the well-documented placebo effect in functional gastrointestinal disorders and underscores the need for rigorous trial design in this therapeutic area (2). Despite this effect, the magnitude of benefit with rifaximin observed in this trial was both statistically robust and clinically meaningful.

The observed superiority of rifaximin may be explained by its targeted mechanism of action, involving modulation of gut microbiota and reduction of small intestinal bacterial overgrowth (SIBO), both of which are implicated in the pathogenesis of IBS-D (6,7). By acting locally within the gut and exhibiting minimal systemic absorption, rifaximin not only optimizes efficacy but also minimizes the risk of adverse events and antibiotic resistance, which are critical considerations in chronic and recurrent conditions (8). The favorable safety profile demonstrated in this cohort—characterized by only mild, self-limiting adverse events and no significant differences from placebo—further supports its suitability for repeated courses, as recommended by current treatment guidelines (15,16).

From a clinical perspective, the implications of these findings are substantial. In low-resource settings like Pakistan, where empirical treatment with broad-spectrum antibiotics or antiparasitics remains common due to lack of standardized protocols, the demonstration of a safe, effective, and evidence-based therapy such as rifaximin is highly relevant (5). The use of a validated symptom scoring system, rigorous blinding, and comprehensive follow-up in this study enhances the reliability and reproducibility of these results. Moreover, the study's focus on a real-world public hospital population increases the generalizability of the findings within similar settings.

Nevertheless, certain limitations must be acknowledged. Although the sample size was adequate to detect clinically meaningful differences, the single-center nature of the study and restriction to a public hospital population may limit broader generalizability. Microbial profiling was not performed, precluding direct correlation of clinical response with changes in gut flora, and adherence was monitored primarily by pill counts and participant self-report, which may introduce reporting bias. Additionally, the 12-week follow-up, while sufficient to demonstrate sustained benefit, may not capture long-term relapse rates or the safety of multiple treatment cycles (18,19).

These limitations suggest several directions for future research. Multicenter studies with larger, more diverse populations and extended follow-up durations are warranted to confirm the durability and safety of rifaximin, particularly with repeated use. Integration of microbiome analysis could elucidate mechanistic pathways and identify predictors of therapeutic response. Comparative trials against alternative or adjunctive therapies, including probiotics, dietary interventions, or other gut-targeted agents—could further refine treatment algorithms. Finally, cost-effectiveness analyses would be valuable to inform policy and optimize allocation of limited healthcare resources in low- and middle-income countries. This study provides strong evidence supporting rifaximin as a superior and well-tolerated option for IBS-D in a public sector, South Asian context. By demonstrating significant and sustained symptom improvement with a favorable safety profile, the findings advance current knowledge and offer practical guidance for the management of IBS-D in resource-limited healthcare environments, while laying the groundwork for future research aimed at optimizing individualized patient care.

CONCLUSION

This randomized, double-blinded, placebo-controlled trial demonstrates that rifaximin is significantly more effective than placebo in relieving symptoms of IBS-D among patients treated at a public hospital in Pakistan, with marked improvements in symptom severity, bloating, and urgency, and a favorable safety profile. These findings provide robust evidence supporting the integration of rifaximin into routine clinical management of IBS-D, especially in resource-limited healthcare settings where standardized therapies are often lacking. Clinically, this study highlights the value of adopting evidence-based

approaches for functional bowel disorders in the region, while future research should focus on long-term outcomes, microbiome mechanisms, and comparative effectiveness with alternative therapies to further refine IBS-D management.

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