

Rifaximin: Recent Advances in Gastroenterology and Hepatology

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Abstract: Rifaximin was initially developed for the treatment of bacteria-related diarrhea, but appreciation of its potentially broader use has increased as understanding of the importance of enteric bacteria in many organic and functional gastrointestinal diseases has advanced. This article reviews data that have been presented at medical meetings or published in medical journals since the publication of a 2006 rifaximin review in this journal. The data presented expand previous research, suggesting that rifaximin may be considered as monotherapy or combination therapy for a variety of enteric conditions, including *Clostridium difficile*-associated diarrhea, cryptosporidial diarrhea, *Helicobacter pylori*-associated gastritis, inflammatory bowel disease, pouchitis, diverticular disease, hepatic encephalopathy, small intestinal bacterial overgrowth, and irritable bowel syndrome. Although most of the new data come from small, uncontrolled studies, results are encouraging. Together, these studies suggest the efficacy of rifaximin and provide a foundation for further research that will help to better define the potential benefits of rifaximin in gastroenterology and hepatology.

Rifaximin (Xifaxan, Salix Pharmaceuticals) is a minimally absorbed (<0.4%), intestinally targeted, oral antibiotic first introduced 20 years ago in Italy and now available in 22 countries.¹ In the United States, rifaximin was approved in 2004 for use in the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*.¹ The profile of rifaximin has been defined by research and clinical experience spanning two decades and has been described in several reviews.¹⁻⁴ Rifaximin has broad-spectrum in vitro antibacterial activity against gram-positive and gram-negative aerobes and anaerobes, has a favorable tolerability profile, and has not been associated with clinically relevant drug interactions or bacterial resistance.^{4,5} The introduction of rifaximin in the United States appears to have initiated an increase in new research to help further define the clinical utility of this antibiotic and elucidate its potential roles in gastroenterology and hepatology.

Several interesting new studies have been described since the publication of a 2006 rifaximin review in this journal.³ The following article highlights key outcomes from studies published since the previous review and includes data on travelers' diarrhea,

Keywords

rifaximin, travelers' diarrhea, hepatic encephalopathy, Crohn's disease, pouchitis, irritable bowel syndrome

Table 1. Efficacy of Rifaximin, Ciprofloxacin, and Placebo in Treatment of Travelers' Diarrhea

Efficacy measure	Placebo (n=101)	Rifaximin, 600 mg daily (n=197)	Ciprofloxacin, 1 g daily (n=101)	P value	
				Rifaximin vs placebo	Rifaximin vs ciprofloxacin
TLUS, median, h	65.5	32.0	28.8	.0014	.35
Diarrheal symptoms	NR	NR	NR	<.05	>.05
Unformed stools after therapy initiation, n	NR	8.8	6.2	.0002	<.0004*
Patients who achieved wellness, %	61.4	76.6	78.2	.0039	.74
Incidence of treatment failure, %	26.7	14.7	6.9	.0115	.05*

NR=not reported; TLUS=time to last unformed stool.

*Favored ciprofloxacin.

Data from Taylor DN et al.⁹

other enteric and gastric syndromes (eg, *Clostridium difficile*-associated diarrhea [CDAD], cryptosporidiosis, and *Helicobacter pylori*-associated gastritis), inflammatory bowel disease (IBD), pouchitis, diverticular disease, hepatic encephalopathy (HE), small intestinal bacterial overgrowth (SIBO), and irritable bowel syndrome (IBS).

Travelers' Diarrhea

Treatment

In addition to prior studies illustrating that rifaximin 600–1,200 mg daily is safe and effective for the treatment of travelers' diarrhea,^{6,7} a 2001 randomized, double-blind study (N=187) demonstrated comparable efficacy of rifaximin versus ciprofloxacin for the treatment of travelers' diarrhea.⁸ A randomized, double-blind study published in 2006 extended these findings by comparing the efficacy of rifaximin 600 mg daily versus ciprofloxacin 1 g daily or placebo in a larger population of patients (N=399) who developed acute diarrheal disease while traveling in Mexico, Guatemala, India, or Peru.⁹ As in previous reports,^{6,7} rifaximin significantly reduced the duration of illness compared with placebo, determined by the time to last unformed stool (TLUS), and was significantly more effective in improving secondary endpoints compared with placebo (Table 1).⁹

Also consistent with previously reported data,⁸ there were no significant differences between rifaximin and ciprofloxacin for TLUS, the percentage of patients with improvement of diarrheal symptoms, or the percentage of patients who achieved wellness (Table 1).⁹ However, previous data from the 2001 study indicated no significant differences between rifaximin and ciprofloxacin in reducing the number of unformed stools or in the incidence

of treatment failure,⁸ whereas ciprofloxacin was more effective than rifaximin on these measures in the 2006 study (Table 1).⁹ It is possible that this inconsistency may be due to the administration of a lower dose of rifaximin (600 mg daily) in the 2006 study than in the 2001 study (800 mg daily)⁸ or to the inclusion of patients in the 2006 study who had signs of infection with invasive pathogens that may have been less responsive to rifaximin.⁹

Similar to the 2001 study,⁸ rifaximin was well tolerated in the 2006 study.⁹ The incidence of adverse events (AEs) was comparable for rifaximin, ciprofloxacin, and placebo.⁹ No patient discontinued therapy with rifaximin due to drug-related AEs, but 2 patients who received ciprofloxacin discontinued therapy. The authors of this study concluded that rifaximin is an important alternative therapy to systemic antibiotics for the treatment of travelers' diarrhea caused by noninvasive pathogens and is appropriate for patients for whom quinolones are not recommended.⁹

In addition, a randomized, double-blind study compared the efficacy and safety of rifaximin 600 mg daily with loperamide alone (4 mg initial dose followed by 2 mg administered after each unformed stool, up to 8 mg daily for 2 days) or loperamide plus rifaximin in 311 patients with travelers' diarrhea.¹⁰ The mean TLUS was shorter for patients who received treatment regimens containing rifaximin (33 hours ± 4 hours for rifaximin alone and 27 hours ± 4 hours for rifaximin plus loperamide) compared with loperamide alone (69 hours ± 4 hours; $P=.0019$ for treatments containing rifaximin vs loperamide alone). A higher percentage of patients who received rifaximin alone (77%) or rifaximin plus loperamide (75%) achieved clinical cure compared with loperamide alone (58%; odds ratio, 1.76; 95% confidence interval [CI], 1.26–4.7).

Although the mean number of unformed stools was lower during the first 24 hours after the initiation of treatment for patients who received regimens containing loperamide compared with rifaximin alone, this measure was lower on Days 2 and 3 for patients who received rifaximin or rifaximin plus loperamide compared with loperamide alone ($P=.0076$ for Day 2 and $P=.001$ for Day 3 for regimens containing rifaximin vs loperamide alone). All treatments were well tolerated, but the incidence of nausea and vomiting were reported more frequently with regimens containing loperamide compared with rifaximin alone. These data suggest that combination therapy with rifaximin and loperamide provided safe and rapid symptom relief for patients with travelers' diarrhea.¹⁰

Pathogen-negative Travelers' Diarrhea

The most commonly identified cause of travelers' diarrhea is *E. coli*, followed by other pathogens such as *Campylobacter* and *Salmonella*.¹¹ However, a causative pathogen was not identified in pretreatment stool samples in up to 50% of patients with travelers' diarrhea in clinical studies.^{8,9} A post-hoc analysis of data from 2 randomized, double-blind, placebo-controlled clinical trials^{7,9} evaluated the efficacy of rifaximin for treatment of pathogen-negative travelers' diarrhea.¹² In this analysis, pathogens could not be identified in the pretreatment stool sample in 38% of 322 patients who received rifaximin and 46% of 230 patients who received placebo.¹² Rifaximin was significantly more effective than placebo for several efficacy measures, including median TLUS ($P<.005$), mean number of unformed stools passed during the 5 days after enrollment ($P<.0001$), and incidence of clinical wellness ($P=.01$).¹² These results suggest that rifaximin may be effective for the treatment of travelers' diarrhea in which the causative pathogen cannot be identified.

Prevention

In a previously reported randomized, double-blind, placebo-controlled trial,¹³ rifaximin effectively prevented diarrheal illness when administered prophylactically to individuals traveling to Mexico. Further support for the efficacy of rifaximin for prevention of travelers' diarrhea was reported in an abstract describing a randomized, placebo-controlled, phase III trial in which rifaximin 600 mg daily or placebo was administered to 210 individuals for 14 days within 72 hours of their arrival in Mexico.¹⁴ In this study, 48% of the 102 individuals who received placebo developed travelers' diarrhea during the treatment period, compared with 20% of the 99 individuals who received rifaximin ($P<.001$). The incidence of AEs was similar among individuals who received rifaximin and those who received placebo. These findings were consistent with previous data¹³ and suggest that rifaximin may be beneficial as prophylactic therapy for travelers' diarrhea.

Because *Shigella* species have been implicated in travelers' diarrhea,¹¹ a randomized, double-blind study investigated the efficacy of rifaximin in preventing diarrheal illness following exposure to *Shigella flexneri*.¹⁵ None of the 15 individuals who received rifaximin 600 mg daily for 3 days prior to the *S. flexneri* challenge developed diarrhea compared with 60% of the 10 individuals who received placebo ($P=.001$). Similarly, none of the individuals in the rifaximin group showed microbiologic evidence of *S. flexneri* colonization compared with 50% of those in the placebo group ($P<.005$).¹⁵ These findings suggest that rifaximin may also be a beneficial prophylactic therapy for travelers' diarrhea caused by *Shigella* species.

Other Diarrheal and Gastric Syndromes

Clostridium difficile-associated Diarrhea

Previous research has demonstrated robust in vitro activity of rifaximin against *C. difficile*,¹⁶ which has frequently been implicated in antibiotic-associated colitis. An abstract presented by Gerding and associates reported that the geometric mean minimal inhibitory concentration of rifaximin activity against 110 strains of toxigenic *C. difficile* isolates that caused CDAD from 1983–2004 was 0.009 $\mu\text{g/mL}$, compared with 0.15 $\mu\text{g/mL}$ for metronidazole and 0.9 $\mu\text{g/mL}$ for vancomycin.¹⁷ Kokkotou and colleagues reported that rifaximin also prevented or effectively treated *C. difficile* colitis in a hamster model.¹⁸ Although the efficacy of rifaximin for preventing and treating *C. difficile* colitis was similar to that of vancomycin, fewer of the animals that received rifaximin relapsed within 21 days posttreatment ($P=.01$).¹⁸

A 1990 randomized, open-label clinical study suggested that rifaximin was effective for the treatment of *C. difficile* colitis.¹⁹ Given reports of the potential causative role of systemic antibiotics in CDAD, a retrospective chart review²⁰ and two open-label studies^{21,22} investigated the efficacy of rifaximin for treatment of this condition. These studies indicated that rifaximin 800–1,200 mg daily effectively improved symptoms in patients with newly diagnosed CDAD,^{20,21} as well as those with recurrent CDAD (Table 2).^{20,22} Rifaximin 400–800 mg daily also prevented CDAD recurrence after successful treatment with vancomycin; during follow-up ranging from 51–431 days, 7 of 8 patients had no further CDAD episodes.²² These clinical findings suggest that rifaximin may not only be effective for first-line CDAD therapy, but may also effectively prevent CDAD recurrence.

Cryptosporidiosis in Patients with AIDS

The protozoan *Cryptosporidium* is a common cause of diarrhea in patients with AIDS.²³ Previous research reported that open-label treatment with rifaximin (1,800 mg daily for 14 days) improved enteritis symptoms among

Table 2. Summary of Studies Investigating Efficacy of Rifaximin for Initial Treatment of CDAD or Prevention of CDAD Recurrence

	Rubin et al ²¹	Berenbaum ²⁰	Johnson et al ²²
Study type	Prospective, open-label	Retrospective chart review	Prospective, open-label
Patients, n	8	19	8
CDAD diagnosis	Newly diagnosed	New or recurrent	Recurrent*
Rifaximin dose	1,200 mg daily	800 mg daily (n=1) 1,200 mg daily (n=18)	400 mg daily (n=1) 600 mg daily (n=1) 800 mg daily (n=6)
Patients with symptom resolution, n (%)	8 (100)	17 (89)	7(88)
Recurrence during post-treatment follow-up, n	None of 5 reporting within 2 weeks	2 within 15 days	1 within 10 days [†]

*Patients were asymptomatic at the beginning of rifaximin treatment; [†]Failed patient responded to a second course of rifaximin therapy.

CDAD=*Clostridium difficile*-associated diarrhea.

Table 3. Summary of Studies Investigating Efficacy of Rifaximin-containing Regimens for Eradication of *Helicobacter pylori*

	Patients, n	Treatment regimen(s)	Eradication rate, %
Hilal and Hilal ²⁸	5	Rifaximin 1,200 mg daily plus doxycycline 200 mg daily plus lansoprazole 60 mg daily for 14 days	40*
Basu et al ²⁹	20	Rifaximin 800 mg daily plus omeprazole 40 mg daily plus levofloxacin 500 mg daily for 10 days	50 [†]
Gasbarrini et al ³⁰	24	Rifaximin 1,200 mg daily plus clarithromycin 1 g daily plus esomeprazole 40 mg daily for 7 days	58*
	24	or Rifaximin 1,200 mg daily plus levofloxacin 500 mg daily plus esomeprazole 40 mg daily for 7 days	42*

*Determined by urea breath testing; [†]Determined by stool antigen testing.

patients infected with HIV-1 who had confirmed infection with *Cryptosporidium* and were not severely immunocompromised (CD4 counts $\geq 200/\text{mm}^3$).²⁴ Data from an abstract presentation extended these observations to include 5 patients with AIDS who were severely immunocompromised (CD4 counts $< 50/\text{mm}^3$), 4 of whom had *Cryptosporidium* enteritis refractory to other antibiotics.²⁵ In this prospective, open-label study, rifaximin 800 mg daily completely resolved diarrheal symptoms within 2–5 days for all patients and eradicated *Cryptosporidium* within 2–8 weeks among 4 patients who provided follow-up stool specimens. No recurrence of diarrhea was reported during follow-up from 3–15 months. These findings in severely immunocompromised

patients with AIDS support further evaluation of the efficacy and tolerability of rifaximin in the treatment of cryptosporidial diarrhea in controlled clinical trials.

Helicobacter pylori-associated Gastritis

Rifaximin has in vitro activity against *H. pylori*, which has been implicated in peptic ulcer disease and non-ulcer dyspepsia.^{26,27} Three pilot studies that investigated the efficacy of triple therapies containing rifaximin for eliminating *H. pylori* reported eradication rates ranging from 40–58% (Table 3).^{28–30} The relatively low eradication rates reported in these studies could be attributed to numerous factors, including a suboptimal dosing regi-

men or a lack of therapeutic synergy among components of the regimens. Additional research with other antibiotic combinations and other dosage regimens is being undertaken to further assess the effects of rifaximin in *H. pylori*-associated conditions.

Inflammatory Bowel Disease

The chronic inflammation associated with IBD has been hypothesized to result from the disruption of immunoregulatory responses involving intestinal bacteria, which suggests a potential benefit of antibiotic therapy in the management of IBD.³¹ Previously described results from several open-label studies suggested the therapeutic benefit of rifaximin 600–800 mg daily for treatment of Crohn's disease (CD)^{32–34} and ulcerative colitis.^{34,35}

Seven abstracts that focused on the efficacy of rifaximin in CD corroborated these findings.^{36–42} Three reports indicated that rifaximin 400–800 mg daily resolved symptoms and prevented disease flares for up to 14 months in flaring ($n=3$),³⁸ steroid-dependent ($n=1$),³⁶ or refractory ($n=2$)³⁷ CD, and reduced reliance on corticosteroids ($n=1$).³⁶ In retrospective chart reviews of patients with active CD, adjunctive rifaximin therapy 600 mg daily ($n=68$)³⁹ or rifaximin monotherapy ($n=18$)⁴⁰ induced remission (defined as Crohn's disease activity index [CDAI] score <150) in 65% and 67% of patients, respectively.^{39,40} Similar benefit was reported in an open-label, prospective study in which rifaximin 800 mg daily induced complete remission in 67% of 12 patients with mild-to-moderate active CD⁴² and in a retrospective chart review in which 55% of 60 patients with refractory CD responded to rifaximin 600–1,200 mg daily.⁴¹ Several of these studies also suggested that the efficacy of rifaximin may depend on disease location (ie, colonic vs ileal involvement).^{39,41,42} Although the small patient populations and lack of placebo controls in these studies make it difficult to draw firm conclusions, these findings provide support for the potential benefit of rifaximin in the treatment of IBD.

In addition to these clinical case reports and small pilot studies, a 2006 randomized, double-blind, placebo-controlled study in 79 patients with mild-to-moderate CD showed that a higher percentage of patients who received rifaximin 800 mg twice daily for 12 weeks achieved clinical remission (CDAI score ≤ 150) or experienced clinical response (≥ 70 -point reduction of CDAI score) compared with placebo (52% and 67%, respectively, with rifaximin vs 33% and 41%, respectively, with placebo; Figure 1).⁴³ Because this study was not powered for significance, neither of the differences between rifaximin and placebo was statistically significant. The proportion of treatment

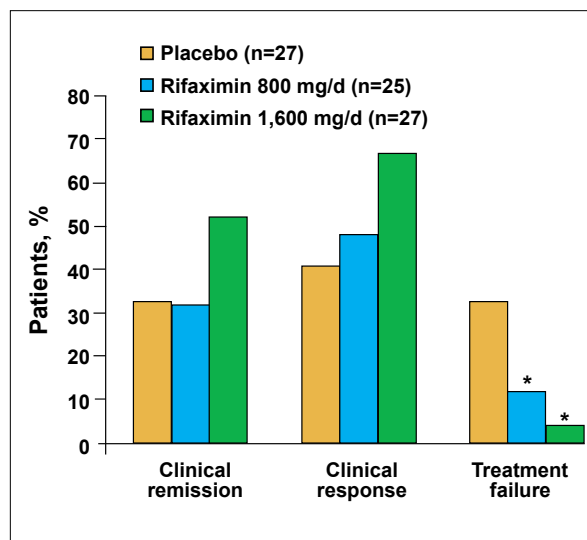


Figure 1. Clinical remission, clinical response, and treatment failure in Crohn's disease patients who received placebo or rifaximin 800 mg daily or 1,600 mg daily for 12 weeks. Clinical remission was defined as Crohn's disease activity index (CDAI) score of 150 points or less, and clinical response was defined as a reduction in CDAI score by 70 points or more.

* $P=.01$ versus placebo.

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failures was significantly higher for patients who received placebo compared with rifaximin 800 mg daily or 1,600 mg daily (Figure 1).⁴³ In a subanalysis of patients with elevated levels of C-reactive protein (CRP) at baseline, a significantly higher percentage of patients who received rifaximin 1,600 mg daily achieved remission (63%) or experienced clinical response (75%) compared with placebo (21%; $P=.032$ and 21%; $P=.013$, respectively), and a significantly lower percentage experienced treatment failure compared with placebo (0% vs 50%; $P=.004$).⁴³ Interestingly, the rifaximin dose (1,600 mg daily) administered in the 2006 study that induced remission was higher than the effective doses (600–1,200 mg daily) administered in newer studies^{32,39–42}; it is unclear if this difference in outcomes is due to differences in the proportion of patients with colonic or ileal disease. The authors proposed that twice-daily dosing of higher doses of rifaximin than those commonly administered for the treatment of travelers' diarrhea may be required for therapeutic efficacy in CD.⁴³ These new data suggest a therapeutic benefit of rifaximin in IBD and warrant further investigation with prospective, controlled clinical studies.

Table 4. Summary of Studies Comparing the Cost-effectiveness of Rifaximin with Lactulose for Treatment of Hepatic Encephalopathy

Outcome parameter	Leevy and Phillips ⁵⁷ (N=145)		Neff et al ⁵⁸ (N=39)	
	Rifaximin 1,200 mg daily	Lactulose 60 mL daily	Rifaximin 1,200 mg daily	Lactulose 60 g daily
Hospitalizations				
Hospitalizations, n	NA	NA	3	19
Hospitalizations, n, mean	0.5*	1.6	NA	NA
Duration per hospitalization, d, mean	2.5*	7.3	3.5 [†]	5.0
Hospital charges/costs				
Hospital charges per patient, \$ [‡]	14,222	56,635	NA	NA
Total monthly drug cost, \$	NA	NA	620	50
Annual treatment cost per patient, \$ [§] , mean	NA	NA	7,958	13,285
Disease severity				
HE stage 3 or 4 post-treatment, n (%)	9 (6)*	36 (25)	NA	NA
Asterixis post-treatment, n (%)	91 (63)*	135 (93)	NA	NA

HE=hepatic encephalopathy; NA=not assessed.

* $P < .001$ versus lactulose; [†] $P < .0001$ versus lactulose; [‡]Calculated in 2005 dollars based on 2003 data from the Healthcare Cost and Utilization Project for the average hospital charge per day for the principal diagnosis of HE (diagnosis code 572.2); [§]Calculation took into account the annual costs of hospitalization, emergency room visits, and drugs.

Pouchitis

Although antibiotics such as metronidazole and ciprofloxacin have been shown to be effective for treating pouchitis, the potential for adverse effects during prolonged administration may limit their benefits.⁴⁴ Given the favorable safety profile of rifaximin, the efficacy and safety of this agent for the treatment of pouchitis are being investigated. A previous open-label pilot study in 10 patients with pouchitis showed that rifaximin monotherapy induced remission in the majority of patients.⁴⁵ Data from two open-label studies reported as abstracts supported previous findings.^{46,47} In a study of 16 patients with refractory pouchitis, the addition of rifaximin 600–800 mg daily to current therapy provided clinical improvement in 81% of patients within 3 weeks of the initiation of treatment.⁴⁶ This clinical improvement was sustained for a mean follow-up period of 16 weeks with rifaximin maintenance therapy, with no AEs reported.⁴⁶ The efficacy of rifaximin for maintaining pouchitis remission was also shown in a study of 51 patients with antibiotic-dependent pouchitis who received rifaximin 200 mg daily (escalating to 1,800 mg daily, as needed) to maintain remission.⁴⁷ A total of 33 patients (65%) maintained remission for 3 months with rifaximin maintenance therapy, and 16 patients maintained remission for 12 months.⁴⁷ These pilot studies suggest that rifaximin may be safe and effective for inducing and maintaining pouchitis remission and that randomized, double-blind, controlled trials are warranted.

Colonic Diverticular Disease

Although the precise mechanism underlying colonic diverticular disease is unknown, bacterial overgrowth has been hypothesized to play a potential role.⁴⁸ Two previous studies in 217–968 patients with symptomatic, uncomplicated diverticular disease demonstrated that rifaximin 800 mg daily for 7 consecutive days every month added to daily therapy with glucomannan 2–4 g daily was more effective in reducing symptoms than monotherapy with glucomannan alone.^{49,50} A 2007 prospective, randomized, open-label study (N=307) corroborated these findings and reported that rifaximin 800 mg daily for 7 consecutive days every month added to daily fiber supplementation for 24 months significantly reduced the frequency of lower abdominal pain ($P=.05$), bloating ($P<.002$), tenesmus ($P=.05$), and abdominal tenderness ($P<.001$) compared with fiber supplementation alone.⁵¹ This rifaximin therapy regimen was also associated with a significantly lower frequency of symptom recurrence ($P<.03$) compared with fiber supplementation alone.⁵¹ Similar benefits of rifaximin were also reported in a 2007 randomized, double-blind, crossover study in 64 patients with symptomatic, uncomplicated diverticular disease who received rifaximin 1,200 mg daily or placebo in addition to fiber supplementation for 14 days.⁵² These findings suggest that rifaximin may increase the beneficial effects of fiber supplementation in patients with uncomplicated diverticular disease and that further investigation is warranted.

Hepatic Encephalopathy

Rifaximin is indicated for the treatment of HE in several countries⁵³ and has been granted orphan drug status for HE in the United States by the Food and Drug Administration.⁵⁴ The efficacy of rifaximin in the treatment of HE has been reported in more than 20 clinical studies. A prospective, randomized study in Asian patients with cirrhosis and grades 1–3 HE extended these findings.⁵⁵ In this study, rifaximin 1,200 mg daily (n=32) and lactulose 90 mL daily (n=22) exhibited statistically similar improvements in neuropsychiatric outcomes of mental status grade, number connection test grade, and HE index score, as well as blood ammonia concentrations.⁵⁵ Similarly, a meta-analysis of 11 randomized, controlled studies that compared the efficacy and tolerability of rifaximin with nonabsorbable disaccharides (lactulose or lactitol) or other antibiotics (neomycin or paromomycin) reported a nonsignificant increase in the risk of no improvement with lactulose or lactitol versus rifaximin (relative risk, 1.48; 95% CI, 0.96–2.26; $P=.075$) and with other antibiotics versus rifaximin (relative risk, 1.57; 95% CI, 0.93–2.66; $P=.09$).⁵⁶ Although rifaximin was significantly better than nonabsorbable disaccharides at lowering blood ammonia concentrations ($P<.0001$), it did not differ from other antibiotics on this measure. Rifaximin was generally better tolerated than nonabsorbable disaccharides and other antibiotics.⁵⁶ Given the similar efficacy and more favorable tolerability of rifaximin compared with nonabsorbable disaccharides and systemic antibiotics, rifaximin may be a valuable therapeutic option for treatment of HE.

Results from two pharmacoeconomic studies suggest that the therapeutic benefits of rifaximin in HE may affect healthcare utilization and financial costs (Table 4).^{57,58} In a retrospective chart review of 145 patients diagnosed with HE and treated with lactulose 60 mL daily for 6 or more months followed by rifaximin 1,200 mg daily for 6 or more months, rifaximin therapy, compared with lactulose therapy, was associated with fewer hospitalizations (0.5 vs 1.6; $P<.001$), fewer days per hospitalization (2.5 days vs 7.3 days; $P<.001$), less total time of hospitalization (0.4 weeks vs 1.8 weeks; $P<.001$), and lower hospital charges per patient (\$14,222 vs \$56,635), respectively.⁵⁷ These beneficial outcomes may be attributed to less severe illness with rifaximin than with lactulose, as indicated by fewer patients with grade 3 or 4 HE (6% vs 25%; $P<.001$) and asterixis (63% vs 93%; $P<.001$) at the end of rifaximin therapy compared with lactulose therapy, respectively.⁵⁷ Similarly, another retrospective chart review of 39 patients with grade 2 HE reported fewer hospitalizations (3 vs 19) and shorter duration of average hospital stay (3.5 days vs 5.0 days; $P<.0001$) with rifaximin 1,200 mg daily compared with

lactulose 60 g daily, respectively.⁵⁸ Although the monthly drug cost was higher for rifaximin than lactulose (\$620 vs \$50, respectively), the overall annual cost of therapy per patient, including the costs of hospitalization, emergency room visits, and drugs, was \$5,327 lower with rifaximin than with lactulose (\$7,958 vs \$13,285, respectively), suggesting that the short-term cost of rifaximin was outweighed when long-term outcomes were taken into consideration.⁵⁸

In addition to these comparisons of rifaximin with other HE therapies, the efficacy of rifaximin 1,200 mg daily (n=25) for preventing HE following transjugular intrahepatic portosystemic shunt (TIPS) placement was compared with lactitol 60 mL daily (n=25) or no treatment (n=25).⁵⁹ After 1 month of treatment, the cumulative incidence of HE was statistically similar among treatment groups, as was the number of episodes of grade 3 or 4 HE.⁵⁹ Further investigation is warranted to determine if longer treatment duration and follow-up may improve the efficacy of rifaximin in preventing HE following TIPS placement.

Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome

SIBO has been reported in many patients with IBS, and the conditions share many signs and symptoms.⁶⁰ It has been hypothesized that SIBO may contribute to the manifestations of IBS through bacterial fermentation and stimulation of a gastrointestinal (GI) immune response characterized by the release of proinflammatory mediators.⁶⁰ Previously published research suggests a potential therapeutic benefit of rifaximin in the treatment of SIBO and intestinal symptoms such as flatulence and bloating.^{3,61-63}

Eight studies in patients with SIBO extended previous findings and included two retrospective chart reviews,^{64,65} three open-label investigations,⁶⁶⁻⁶⁸ and three randomized dose-comparison studies (Table 5).⁶⁹⁻⁷¹ In these studies, rifaximin 600–1,600 mg daily eradicated SIBO, as determined by the normalization of breath tests, in 17–83% of patients^{64-66,69-71} and improved symptoms associated with SIBO, including diarrhea,^{64,66,68} bloating,⁶⁶⁻⁶⁸ gas,⁶⁶ abdominal pain,^{64,68} and constipation⁶⁶⁻⁶⁸ in 43–86% of patients. A series of randomized dose-finding studies indicated that the incidence of AEs was similar among patients who received rifaximin 600–1,200 mg daily (n=90),⁶⁹ but the AE incidence increased with rifaximin 1,600 mg daily (n=60) without a further increase in efficacy.⁷⁰ However, in a randomized study of 80 patients, the incidence of AEs was similar for patients who received rifaximin 1,200 mg daily and those who received rifaximin 1,600 mg daily.⁷¹

Table 5. Summary of Studies Investigating Efficacy of Rifaximin for Treatment of Small Intestinal Bacterial Overgrowth

Study	Patients, n	Rifaximin dose	Breath test normalized, %	Symptom improvement, %
Cuoco and Salvagnini ⁶⁴	92	1,200 mg daily for 14 days	83*	52*
George et al ⁶⁷	14	800 mg daily or 1,200 mg daily for 10 days	NR NR	86 43
Lauritano et al ⁶⁹	90	600 mg daily, 800 mg daily, or 1,200 mg daily for 7 days	17 27 60 [†]	NR NR NR
Lauritano et al ⁷⁰	60	1,200 mg daily or 1,600 mg daily for 7 days	60 63	NR NR
Lee et al ⁶⁵	50	NR	56	62
Majewski et al ⁶⁶	20	800 mg daily for 4 weeks	53 [‡]	70
Scarpellini et al ⁷¹	80	1,200 mg daily or 1,600 mg daily for 7 days	58 80 [§]	NR NR
Weinstock et al ⁶⁸	82	1,200 mg daily for 10 days	NR	60 [¶]

NR=not reported.

*Data available for 23 patients; [†] $P<.001$ versus rifaximin 600 mg daily and $P<.01$ versus rifaximin 800 mg daily; [‡]Data calculated for 19 patients; [§] $P<.05$ versus rifaximin 1,200 mg daily; [¶]Data available for 81 patients.

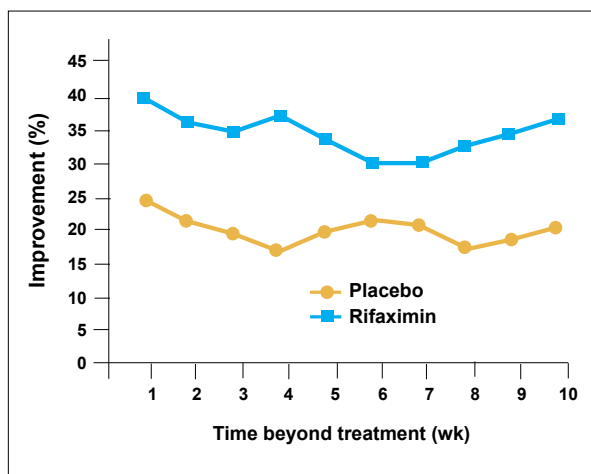


Figure 2. Improvement (based on patient symptom diary) from baseline irritable bowel syndrome symptoms during 10-week posttreatment follow-up among patients who received rifaximin 1,200 mg daily versus placebo for 10 days.

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In addition to these studies investigating the efficacy of rifaximin for SIBO treatment, a study by Pimentel and colleagues evaluated the efficacy of rifaximin for IBS treatment.⁷² In this randomized, double-blind, placebo-controlled study, 87 patients who met Rome I criteria for IBS received rifaximin 1,200 mg daily (n=43) or placebo (n=44) for 10 days and were followed for 10 weeks post-treatment. Mean global improvement of IBS symptoms from baseline was significantly higher for patients who received rifaximin compared with placebo during the 10-week follow-up period (36% vs 21%, respectively; $P=.02$; Figure 2). Assessment of the effects of rifaximin on individual IBS symptoms showed that rifaximin significantly improved bloating compared with placebo ($P=.01$) but did not significantly improve diarrhea or constipation. The incidence of AEs was similar for rifaximin and placebo.⁷² The maintenance of posttreatment clinical improvement shown in this study is consistent with the hypothesis that rifaximin directly impacts a pathogenic mechanism of IBS. The results of these studies in patients with SIBO or IBS underlie the important contribution of interactions

among bacterial flora and intestinal mucosa in functional GI symptoms⁶⁰ and support further investigation of the potential therapeutic benefit of rifaximin in the treatment of SIBO and IBS.

Summary

Rifaximin was initially developed for the treatment of travelers' diarrhea, but appreciation of its broader potential has increased as advances have been made in the understanding of the importance of enteric bacteria in many organic and functional GI diseases. The data reviewed in this paper complement and extend the results of research conducted since the introduction of rifaximin in Italy in 1987 by showing that rifaximin may be beneficial as monotherapy and in combination with other agents for the treatment of multiple enteric conditions. Many of these observations are from small, uncontrolled studies, but they show consistent therapeutic benefits and support the need for large, randomized, controlled clinical trials. In addition, randomized, double-blind, placebo-controlled trials have demonstrated the benefits of rifaximin for functional GI symptoms, including those of IBS. Together, these studies provide a foundation for further research that will help to define the role of rifaximin in gastroenterology and hepatology more clearly.

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