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REVIEW

Rifaximin Therapy of Irritable Bowel Syndrome

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Abstract: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by abdominal pain and altered bowel habits in the absence of specific organic pathology. Although the underlying pathogenesis of IBS is not well-understood, small intestinal bacterial overgrowth (SIBO) or other abnormalities in the gut flora is believed to contribute to the development of a subset of IBS cases. Rifaximin is a poorly absorbed antimicrobial with activity against enteric pathogens. A number of studies have shown a significant improvement in IBS symptoms with antibiotic therapy including rifaximin. In this review, we discuss the pharmacokinetics, in vitro susceptibility profile, and efficacy and safety data from clinical trials of rifaximin treatment of IBS.

Keywords: rifaximin, irritable bowel syndrome, small intestinal bacterial overgrowth

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Background

Irritable bowel syndrome (IBS) was first described by William Osler in 1892 as "mucous colitis," a disorder of abdominal colic and intestinal excretion of excess mucus, often recognized in patients with underlying psychopathology.[1] Today, this gastrointestinal illness is one of the most common medical conditions that health care providers encounter and the leading medical diagnosis for gastroenterology visits, affecting up to 20% of the US population[2] and 10% of the global population.[3] Approximately 200 new IBS cases per 100,000 persons are diagnosed each year in the United States.[4] These estimates may underrepresent the true burden of IBS globally, as medical care is sought by relatively few IBS patients.

Irritable bowel syndrome is defined as a functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits in the absence of other gastrointestinal diseases.[3] Clinical manifestations of IBS include chronic gastrointestinal discomfort associated with bloating, fatigue, psychological disorders including depression or anxiety, and non-intestinal pain.[5] This constellation of signs and symptoms has a significant negative impact on the patients' quality of life.[6] Younger women are more likely to present with this disease.[7,8]

The current lack of understanding of the underlying pathophysiology of irritable bowel syndrome presents a significant challenge in accurately diagnosing this disorder, developing appropriate therapies, and evaluating whether these treatments are effective. Psychological factors, such as maladaptive coping[9] and somatization,[10] abnormal neurological responses to visceral pain,[11] autonomic dysfunction,[12] and abnormalities in intestinal physiology, including reduced gut motility,[13] enhanced immune reactivity,[14] permeability,[15] and alteration of gut flora[16] have been associated with development of IBS. Acute gastroenteritis may also serve as a precipitant of IBS, which is known as post-infectious IBS (PI-IBS).[17] Definitive diagnostic tests or imaging studies for IBS are not available, and this gastrointestinal disease is often considered as a diagnosis of exclusion. IBS must be distinguished from organic pathologies including colon cancer, inflammatory bowel disease, lactose intolerance, celiac disease, and infectious diarrhea. Currently, the diagnosis is established by the Rome II or III criteria (Table 1).[18] IBS is subgrouped according

Table 1. Rome III diagnostic criteria* for irritable bowel syndrome.

Recurrent abdominal pain or discomfort** at least 3 days per month associated with at least two of the following criteria:
1. Improvement with defecation
2. Change in stool frequency
3. Change in stool form or appearance

Notes: *Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis; **Discomfort refers to an uncomfortable sensation other than pain.
Adapted from Longstreth et al.[19]

to the predominant gastrointestinal manifestations: IBS with constipation, IBS with diarrhea, and mixed IBS where constipation and diarrhea are both prominent.[19]

Small intestinal bacterial overgrowth (SIBO) has been proposed as an important underlying cause in the pathogenesis of a subset of IBS cases. Up to 84% of IBS patients have been shown to have abnormal hydrogen (H_2) breath tests following ingestion of lactulose or glucose, which may be indicative of SIBO or rapid small bowel transit.[20] Successful eradication of SIBO with antibiotics such as neomycin, confirmed by normalization of positive breath tests, has been correlated with improvement of IBS symptoms.[20,21] However, these findings have been demonstrated in small subgroups of IBS study cohorts, and evidence supporting the role of SIBO in IBS is conflicting, as other studies have demonstrated inconsistent SIBO prevalence in IBS patients. Differences in methods used for diagnosing SIBO and problems with their interpretation likely contribute to the inconsistency.[22] Nevertheless, the hypothesis that SIBO contributes to IBS was the basis for initial antibiotic treatment studies of IBS. Early clinical studies with antimicrobials including neomycin[20,21] and metronidazole[23] demonstrated significant improvement in IBS symptoms. In this review, we discuss the pharmacokinetics, in vitro susceptibility, and efficacy and safety data from clinical trials for the treatment of IBS with rifaximin.

Rifaximin Drug Class and Mechanism of Action

As a poorly absorbed rifamycin derivative, the mechanism of action of this antibiotic is inhibition of bacterial ribonucleic acid (RNA) synthesis by inhibition of

the beta-subunit of the bacterial DNA-dependent RNA polymerase.[24] In the United States, rifaximin is approved (200 mg tablets three times a day for three days) for the treatment of patients 12 years of age or older with travelers' diarrhea caused by non-invasive strains of *Escherichia coli*. More recently, rifaximin 550 mg tablets twice a day has been approved in the United States for secondary prevention of hepatic encephalopathy in patients 18 years of age or older.[25,26]

Rifaximin pharmacokinetics

Rifaximin is virtually unabsorbed (<0.4%) in the human gastrointestinal tract after oral administration. This unique property augments its ability to inhibit replication of enteric pathogens while limiting the amount of systemic absorption. Rifaximin is primarily excreted unchanged in the feces.[26,27] In a pharmacokinetic study of healthy males (n = 14) who received a single dose of 400 mg of rifaximin, the maximum drug concentration (C_{max}) was 4.3 ± 2.8 ng/mL, and the AUC was 19.5 ± 16.5 ng·h/mL, with a median half-life of 1.25 hours.[26]

Despite high detectable fecal concentrations due to its poor absorption, the bioavailability of rifaximin varies throughout the gastrointestinal tract in relation to its solubilization. The hydrophobic nature of rifaximin renders rifaximin largely insoluble in water but approximately 100 fold more soluble in the presence of bile salts.[28] With bile salt concentrations relatively high in the small intestine compared to the colon, rifaximin use may be ideal for small intestinal diseases including SIBO and IBS.

With its lack of systemic absorption, drug interactions with rifaximin are relatively uncommon. Although rifaximin has been shown to induce cytochrome P450 isoenzymes in an in vitro hepatocyte model and in mice,[26,29] clinical studies with midazolam or oral contraceptives containing ethinyl estradiol and norgestimate in healthy volunteers have not shown any similar upregulation of CYP3A enzymes.[30,31] However, it should be noted that in these studies, rifaximin 200 mg three times daily was evaluated rather than 550 mg three times daily which is the dosing regimen used in recent IBS clinical trials. Paracellular absorption of rifaximin, due to disruption of intercellular tight junctions with SIBO, leading to CYP3A4 induction and drug interaction with warfarin has been suggested.[32]

Rifaximin in vitro susceptibility and antimicrobial activity

Rifaximin has broad antimicrobial activity including gram-positive, gram-negative, aerobic, and anaerobic bacteria. In studies of enteric pathogens acquired by travelers to India, Jamaica, Mexico, and Kenya, the minimum inhibitory concentration that inhibited 90% of microorganisms growth (MIC_{90}) ranged from 4–64 μg/mL for enterotoxigenic (ETEC) and entero-aggregative *E. coli* (EAEC), *Salmonella, Shigella, Campylobacter, Plesiomonas*, and *Aeromonas* species.[33] Other studies have confirmed these susceptibility patterns.[34,35] Concern for development of rifaximin resistance exists given well-documented resistance with rifampin. Rifaximin resistance is not common, but has been reported for enteropathogens including *Clostridium difficile*[36,37] and *Campylobacter* species.[38]

Nontraditional antimicrobial activities important for enteric infections have also been attributed to rifaximin including suppression of expression of bacterial virulence factors and transfer of antibiotic resistance plasmids.[39,40] Immunomodulating properties of rifaximin have been described with decreased production of IL-8 and matrix metalloproteinase-9[39] and activation of the pregnane X receptor leading to decreased inflammation.[29] In addition, stabilization of the intestinal epithelia with rifaximin appears to enhance resistance against bacterial enteropathogens.[41]

Clinical Efficacy of Rifaximin for the Treatment of SIBO and Irritable Bowel Syndrome

Rifaximin has been shown to be effective in eradicating bacterial overgrowth in up to 70%–80% of SIBO patients (Table 2).[42,43] In one study of SIBO patients diagnosed by glucose hydrogen breath test (GHBT), significantly more subjects experienced normalization of the H_2 breath test with rifaximin compared to chlortetracycline.[42] In two rifaximin dose finding studies, rifaximin 1600 mg/day was shown to be the most effective dose in treating SIBO, based on GHBT measurements.[43,44]

A small observational study examined treatment of patients of all IBS subtypes and with an abnormal lactulose hydrogen breath test (LHBT) with a one week course of rifaximin (Table 3).[45]

Table 2. Randomized, prospective clinical trials of rifaximin for SIBO or IBS.

Study, reference	Study design	SIBO or IBS subtype studied	No. of subjects	Primary outcome	Results
Di Stefano et al[42]	Randomized, double-blind	SIBO	Rifaximin 400 mg (n = 10) or chlortetracycline 333 mg (n = 11) three times a day for 7 days	Normalization of glucose hydrogen breath test	Rifaximin 70% vs. Chlortetracycline 27% ($P < 0.01$)
Scarpellini et al[43]	Randomized, open label	SIBO	Rifaximin 1,600 mg daily (n = 40) or rifaximin 1,200 mg daily (n = 40) for 7 days	Normalization of glucose hydrogen breath test	Rifaximin higher dose 80% vs. lower dose 58% ($P < 0.05$)
Lauritano et al[44]	Randomized, open label	SIBO	Rifaximin 600 mg daily (n = 30) or 800 mg daily (n = 30) or 1,200 mg daily (n = 30) for 7 days	Normalization of glucose hydrogen breath test	Rifaximin high dose 60% vs. middle dose 27% ($P < 0.01$) vs. low dose 17% ($P < 0.01$)
Pimentel et al[49]	Randomized, double-blind	IBS subtype not specified	Rifaximin 400 mg (n = 43) or placebo (n = 44) three times a day for 10 days	Subjective percentage improvement in overall IBS symptoms	Rifaximin 36% vs. placebo 21% ($P = 0.02$)
Lembo et al[50]	Randomized, double-blind	IBS with diarrhea	Rifaximin 550 mg (n = 191) or placebo (n = 197) two times a day for 14 days	1. Proportion of patients with subjective improvement in overall IBS symptoms 2. Proportion of patients with subjective improvement in bloating	1. Rifaximin 52% vs. placebo 44% ($P = 0.03$) 2. Rifaximin 46% vs. placebo 40% ($P = 0.04$)
Pimentel et al[51] (TARGET 1 and TARGET 2)	Randomized, double-blind	IBS with diarrhea, mixed IBS*	Rifaximin 550 mg (n = 624) or placebo (n = 634) three times a day for 14 days	Proportion of patients with subjective improvement in overall IBS symptoms	Rifaximin 41% vs. placebo 32% ($P < 0.001$)

Note: *Responses were not stratified by IBS subtype.

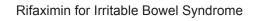**Table 3.** Observational, retrospective, or subanalysis studies of rifaximin for SIBO or IBS.

Study reference	Study design	SIBO or IBS subtype studied	No. of subjects	Primary outcome	Results*
Peralta et al[45]	Observational study, open label	All IBS subtypes**	Rifaximin 1,200 mg daily for 7 days (n = 54)	Normalization of lactulose hydrogen breath test	Normalization 52%
Yang et al[46]	Retrospective chart review	IBS subtype not specified	Rifaximin 400 mg three times a day for 10 days followed by tegaserod daily (n = 84) or other antibiotics (neomycin, doxycycline, amoxicillin/clavulanate, ciprofloxacin) (n = 61)	Subjective improvement in overall IBS symptoms	Rifaximin 69% vs. other antibiotics 44% ($P < 0.01$)
Jolley et al[47]	Retrospective chart review	All IBS subtypes	Rifaximin 1,200 mg daily for initial treatment (n = 162) or 2,400 mg daily for refractory cases (n = 81) for 10 days	1. Complete IBS symptom resolution 2. ≥50% global IBS symptom improvement	1. Initial 12% (diarrhea 11%; constipation 12%; mixed 17%); refractory 11% (diarrhea 13%; constipation 6%; mixed 18%) 2. Initial 49% (diarrhea 56%; constipation 45%) refractory 47% (diarrhea 54%; constipation 38%; mixed 55%)
Sharara et al[48]	Subanalysis of randomized, double-blind trial	All IBS subtypes**	Rifaximin 400 mg (n = 37) or placebo (n = 33) two times a day for 10 days	1. Subjective improvement in overall IBS symptoms 2. Sustained improvement 10 days post-treatment	1. Rifaximin 41% vs. placebo 18% ($P = 0.04$) 2. Rifaximin 27% vs. placebo 9% ($P = 0.05$)

Notes: *( ), response by IBS subtype; **Responses were not stratified by IBS subtype.

Rifaximin led to a negative LHBT in approximately half of the subjects. Subjects who experienced normalization of their LHBT also reported a significant reduction of IBS symptoms. In a retrospective chart review, the efficacy of antibiotic therapy followed by daily tegaserod for SIBO in IBS patients was evaluated.[46] Clinical improvement of abdominal symptoms was observed more commonly in patients treated with rifaximin compared to patients who received other antibiotics including neomycin, doxycycline, amoxicillin/clavulanate, and ciprofloxacin. Among 20 treatment failures with antibiotics other than rifaximin, 75% experienced symptomatic improvement with subsequent rifaximin therapy. Rifaximin was also successful in treating symptom recurrence in a small number of patients. Among a subset of these patients who had followup LHBT (n = 50), 56% of patients had normalization of the LHBT with rifaximin. A significant association was noted between normalization of LHBT and clinical response.

A retrospective review of treatment of IBS patients of all types with a positive LHBT with 10 days of rifaximin 1,200 mg per day for initial treatment or 2,400 mg per day for refractory cases was performed.[47] Although complete resolution of symptoms for subjects receiving one and repeated treatments was experienced in only 12% and 11% of IBS subjects, respectively, approximately 50% of subjects in both groups described 50% or greater improvement in global IBS symptoms after treatment. Only 2% of IBS subjects normalized their LHBT with initial therapy, while 11% of subjects had negative LHBT with higher dosage therapy. Rifaximin therapy for IBS was also evaluated in a subanalysis of a small double-blind trial of rifaximin given to subjects with chronic abdominal bloating and flatulence.[48] IBS of all subtypes were included. Subjective symptomatic improvement upon completion of 10 days of treatment was endorsed significantly more frequently in IBS subjects randomized to rifaximin than subjects who received placebo. A trend for maintenance of the clinical improvement was observed with rifaximin compared to placebo at the end of 10 days of followup post-treatment. Interestingly, none of the IBS patients had an abnormal LHBT at baseline.

Several well-designed randomized, double-blind trials have evaluated the efficacy of rifaximin as treatment of irritable bowel syndrome (Table 2). Pimentel and colleagues conducted a clinical trial comparing the efficacy of 10 days of rifaximin 400 mg three times daily to placebo in reducing global IBS symptoms in patients diagnosed with any IBS subtype.[49] Hydrogen and methane breath testing was performed but not reported. Rifaximin subjects described significantly greater improvement in overall IBS symptom scores averaged over 10 weeks of followup than placebo subjects. Similarly, severity of bloating symptoms improved significantly more with rifaximin than with placebo.

A second randomized, double-blind trial compared rifaximin to placebo for the treatment of diarrhea-associated IBS.[50] Significantly more subjects who received rifaximin 550 mg twice daily for 14 days compared to placebo reported adequate relief of global IBS symptoms and bloating symptoms. Improvement of IBS symptoms was sustained over 12 weeks after discontinuation of the study medication.

Two randomized, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2) for diarrhea predominant and mixed IBS patients were recently conducted, enrolling a total of 1,260 subjects.[51] Patients were randomized to receive either rifaximin 550 mg or placebo three times a day for 2 weeks, then followed for 10 weeks. Improvement of IBS symptoms was assessed by a simple "yes" or "no" response to a question regarding adequate relief with the study medication. Evaluation for SIBO or hydrogen production was not conducted. A significantly greater proportion of subjects who received rifaximin compared to subjects given placebo experienced improvement in overall IBS symptoms and bloating for at least two of the initial four weeks after treatment. The significant relief in global IBS symptoms with rifaximin compared to placebo continued over the 10 weeks of followup. However, a decline in the rifaximin treatment response over time was observed. Although the decrease in bloating was not sustained over 10 weeks in the TARGET 1 trial, significantly more rifaximin subjects in the second trial and in the two collective studies reported relief of IBS-related bloating during this time period.

Although well-designed and robust, these two clinical trials were limited by the lack of adjustment for the potential confounding influence of proton pump inhibitors, which may predispose individuals to small intestinal bacterial colonization.[52] In addition, long-term follow-up to establish the value and need for additional rifaximin treatment in IBS was not examined. Given the chronicity of IBS, the duration of rifaximin's effect past 10 weeks, in terms of relapses requiring re-treatment, the effectiveness of successive treatments, and the effects of prolonged or intermittent rifaximin administration on development of antimicrobial resistance remains unanswered.[53] To provide uncontrolled long-term follow-up data with rifaximin therapy, Pimentel and colleagues retrospectively examined IBS patients without constipation, who were treated with rifaximin, for the prevalence of relapse and response to re-treatment.[54] Rifaximin dosing ranged from 400 to 550 mg three times daily for 10–14 days (personal communication with Pimentel). Among 169 IBS subjects initially treated with rifaximin, 71 (42%) required ≥2 rifaximin treatments, 48 (28%) received ≥3 treatments, 22 (13%) received ≥4 treatments, 7 (4%) received ≥5 treatments, and 4 (2%) received 6 courses of rifaximin. For each successive treatment, a response was elicited in approximately 75% of subjects lasting a median of greater than 4 months. No decline in efficacy or reduction in duration of benefit with repeated treatments was observed. However, exclusion of IBS subjects who requested a rifaximin refill without a clinic visit may have falsely lowered the observed relapse rates.

Rifaximin adverse effects
The poor oral bioavailability of rifaximin contributes to its excellent safety profile and low incidence of adverse events. Over 1,200 subjects have been enrolled in clinical trials evaluating rifaximin for irritable bowel syndrome.[51] The frequency of adverse events reported by study participants was similar for those receiving rifaximin versus placebo. Overall, the most common adverse effects (≤6% of all subjects) in these clinical trials were headache, upper respiratory tract infection, nausea, nasopharyngitis, and abdominal pain. Serious adverse events (≤1% of all subjects) included chest pain, breast cancer, and cholecystitis.

No serious adverse events were attributed to the study medication. No *Clostridium difficile* infections were detected. Large clinical trials for travelers' diarrhea and hepatic encephalopathy provide further support for the safety profile of rifaximin.[55–61] The safety and effectiveness of rifaximin in pregnant women has not been evaluated.

Discussion
The underlying assumption that SIBO contributes to the pathogenesis of IBS remains controversial, as reports of SIBO prevalence in IBS patients have been markedly discrepant. The difficulty in establishing the diagnosis of SIBO contributes to the confusion. Aspiration and culture of the jejunum with detection of $\geq 10^5$ colony forming units of bacteria/milliliter (CFU/mL) of bacteria is considered as the gold standard for SIBO diagnosis.[62] However, contamination of cultures with oropharyngeal flora,[63] limitations of sampling to only the proximal small bowel,[20–22] and recent reports of approximately 60% of the intestinal microbiome uncultivatable with conventional methods raise doubt of the value of this diagnostic method for SIBO.[64] In addition, jejunal aspiration is an invasive and costly procedure. As a result, indirect assessments of intestinal bacteria, such as breath tests, are commonly used. Breath tests measure H_2 or methane produced by intestinal bacteria, especially colonic flora, as they ferment carbohydrates such as lactulose and glucose. Unfortunately, interpretation of these breath tests is difficult, as many factors may affect hydrogen excretion in the gastrointestinal tract leading to potential false negative results with the presence of methanogenic bacteria and false positives with decreased intestinal transit time, malabsorption, and certain dietary patterns. In addition, different criteria are used to define a positive breath test in different studies.[62] The heterogeneity of diagnostic methods and their limitations in interpretation have led to significant variation in the reported prevalence of SIBO in IBS patients. SIBO detection in IBS patients has ranged from 4% by jejunal culture to 78% by lactulose breath test measuring hydrogen concentrations within 90 minutes of lactulose ingestion.[21,65] The use of proton pump inhibitors, which may contribute to bacterial colonization of the

intestinal tract and SIBO, is a potential confounder of SIBO in IBS studies.[52]

IBS appears to be a multifactorial disease. Only a subset of IBS patients suffer SIBO and presumably, would benefit from antibiotic therapy. In the two large TARGET trials, 41% of rifaximin subjects experienced relief. Since the placebo response was 32%, the therapeutic gain was only 9%.[51,53] The high placebo response in these clinical trials is consistent with other IBS studies with antibiotic treatment. Placebo response has ranged from 21% to 51% in these studies, decreasing the therapeutic gain of antibiotics such as rifaximin.[20,49] In addition, the success of nonpharmacologic agents including education, relaxation training, and cognitive behavioral therapy in alleviating IBS symptoms indicates that a significant proportion of IBS subjects may have important underlying disorders other than SIBO.[3,66] These IBS patients may not benefit from traditional antibiotic therapy. Further studies are needed to evaluate whether rifaximin therapy may provide any benefit to IBS patients who lack SIBO, given its potential for bacterial virulence modification and immunomodulatory effects.

One of the main concerns regarding use of antibiotics such as rifaximin for treatment of IBS is the potential magnitude of patients who would receive antibiotics, fostering development of antibiotic resistance. Although several studies have demonstrated little if any change in bacterial susceptibility with rifaximin,[55,67] there is still concern that widespread, prolonged use of any antimicrobial including rifaximin may induce resistance over time. Rifaximin resistance in *C. difficile* has been reported.[36] IBS is a chronic disorder and persistent or repeated courses of rifaximin may be necessary to control symptoms. If bacterial overgrowth is the underlying cause of IBS symptoms as these clinical investigators suggest,[49,51] then IBS symptoms are likely to recur because SIBO recurs in up to 44% of patients after successful rifaximin treatment, particularly in individuals with predisposing conditions for SIBO, such as chronic proton-pump inhibitor use.[68] A slight decline in the treatment response over the ten weeks was observed in the TARGET trials,[51,53] possibly representing recurrence of IBS symptoms over time. The importance of potential drug-induced complications with recurrent exposure to antibacterial drugs such as rifaximin for IBS needs further study. Whether repeated rifaximin courses for IBS will have little impact on the microbial community similar to chronic antibiotic usage for acne vulgaris or rheumatic fever or may lead to significant complications such as the emergence of the epidemic, hypervirulent *C. diffcile* strains with fluoroquinolone use is unknown.

Greater understanding of the pathogenesis of IBS is needed. Abnormal physiologic changes in IBS patients are increasingly being recognized. As IBS becomes better characterized and underlying alterations in gut physiology are defined, this disease will likely no longer be considered as a functional bowel disorder in the future. Identification of biologic markers in patients with IBS is needed to better diagnose this disorder and to monitor response to treatment with rifaximin and other putative treatment options. Current use of questionnaires such as the Rome criteria is insensitive for measuring changes in severity of disease and is not useful for showing responses to treatment. Qualitative assessment of clinical response of global IBS symptoms with "yes" or "no" questions in clinical trials is inadequate and possibly subject to bias.

Conclusions

Current therapeutic options for management of IBS symptoms are limited. Lupristone is the only approved agent for constipation-predominant IBS,[69] and alosetron is approved for diarrhea-predominant IBS.[70] However, alosetron was previously withdrawn and is approved now only for severe, chronic IBS unresponsive to alternative therapies because of uncommon but serious adverse events including ileus, bowel obstruction, fecal impaction, perforation, and ischemic colitis. Tegaserod, another agent for IBS with constipation, was withdrawn in 2007 due to increased cardiovascular complications.[71] Rifaximin is a well-tolerated, safe, nonabsorbed antibiotic that appears promising as treatment for diarrhea-predominant and mixed IBS. However, the US FDA has recently requested a prospective, controlled clinical trial evaluating the efficacy of rifaximin for re-treatment of recurrent symptoms in IBS patients before considering approval of rifaximin treatment for IBS.[72]

Author Contributions

Analysed the data: SS, HLK, DBH, HLD. Wrote the first draft of the manuscript: SS. Contributed to the writing of the manuscript: SS, HLK, DBH, HLD. Agree with manuscript results and conclusions: SS, HLK, DBH, HLD. Jointly developed the structure and arguments for the paper: SS, HLK. Made critical revisions and approved final version: SS, HLK, DBH, HLD. All authors reviewed and approved of the final manuscript.

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Competing Interests

HLD has consulted with, received honoraria for speaking, and has received research grants administered through his university from Salix Pharmaceutical Company. HLK has received a NIDDK grant. Other authors disclose no conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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