Efficacy of Rifaximin in Patients With Abdominal Bloating or Distension

A Systematic Review and Meta-analysis

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Background: Abdominal bloating is a common complaint in patients with functional and organic bowel disease. Rifaximin, a nonabsorbable antibiotic, has been tried for the treatment of this disease. We performed a systematic review and meta-analysis to study the efficacy of rifaximin in abdominal bloating and distension in patients with functional gastrointestinal disorders (FGID).

Methods: We accessed 4 databases (MEDLINE, Embase, SCOPUS, and Web of Science) to identify randomized placebo-controlled trials that utilized rifaximin in FGID. We excluded observational studies, those including patients with organic bowel disorders such as inflammatory bowel diseases, or those in which rifaximin was given for other indications, such as hepatic encephalopathy.

Results: A total of 1426 articles were available, of which 813 articles were screened after removing duplicates and 34 articles were selected for full-text review. Finally, 10 trials (3326 patients) were included. Rifaximin was administered in doses ranging from 400 to 1650 mg per day for 1 to 2 weeks. Rifaximin therapy led to a higher likelihood of improvement in symptoms of bloating (44.6% vs. 34.6%, RR 1.22, 95% CI 1.11, 1.35; n = 2401 patients) without significant heterogeneity. However, daily doses less than 1200 mg/day were similar to placebo ($P = 0.09$). Bloating was quantified subjectively in 7 studies, and rifaximin led to a greater reduction in bloating scores compared with placebo (standardized mean difference −0.3, 95% CI −0.51, −0.1, $P = 0.04$) but carried significant heterogeneity ($I^2 = 61.6\%$, $P = 0.01$).

Conclusions: Rifaximin therapy is associated with an increased likelihood of improvement in bloating and distension, as well as reduces the subjective severity of these symptoms in patients with FGID.

Key Words: Rifaximin, Bloating, IBS, functional gastrointestinal disorders, meta-analysis

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Abdominal bloating is a functional gastrointestinal complaint with high prevalence and a significant impact on quality of life.[1] It may be variably described by patients as a sensation of fullness or gaseous distension of the abdomen and is often associated with other complaints, including dyspepsia, constipation, diarrhea, and cramping abdominal pain. Functional abdominal bloating (FAB)/distension (FAD) is a part of functional GI disorder, and FAB/FAD (or FABD) is defined as recurrent abdominal bloating or distention occurring at least 1 day per week as the predominant symptom; there are insufficient criteria for the diagnosis of other functional gastrointestinal disorders (FGIDs), particularly IBS.[2] The criteria should be fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis. Bloating is often underestimated because it co-exists with other functional GI disorders, especially in IBS, where it affects 66% to 90% of the patients.[3]

Rifaximin is a semi-synthetic oral antibacterial drug belonging to the rifamycin class, which possesses activity against the bacterial RNA polymerase. It has negligible oral absorption, achieving a high drug concentration in the small intestine and the colon, resulting in a bactericidal effect on the pathogenic microbiota of the gut (gram-negative or gram-positive aerobes and anaerobes). The FDA has approved it for use in travellers' diarrhea, hepatic encephalopathy, and IBS. The approval for IBS was restricted to diarrhea-predominant IBS (IBS-D) at a dose of 550 mg thrice daily.[4] The prescription labelling carries no emphasis on which symptoms would be targeted by rifaximin therapy since IBS is well known for being heterogenous in clinical presentation and rarely remits completely.

The treatment protocols for abdominal bloating and distension usually involve dietary modification with a low FODMAP diet to reduce intestinal gas production. Subsequent therapy is directed at associated constipation (eg, linaclotide, lubiprostone, tegaserod, and alosetron) or diarrhea with antispasmodic agents (eg, peppermint oil), while avoiding therapies that can worsen bloating (eg, bile acid

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sequestrants).[5] Two antibiotics have been attempted for short courses to induce symptomatic relief in IBS: neomycin and rifaximin. However, the role of rifaximin specifically in the treatment of bloating or distension has not been defined in most guidelines. Therefore, we aimed to perform a systematic review and meta-analysis of the available literature on the effects of rifaximin on abdominal bloating and distension.

METHODS

Search Strategy

Literature search was performed on MEDLINE, EMBASE, Web of Sciences, and SCOPUS databases from inception up to January 8, 2020. References of the articles selected for full-text review were manually searched for relevant articles. The search was limited to human studies, adults or adolescents aged 14 years or above, in any language. Both abstracts and full research articles were reviewed for eligibility, and authors were contacted in case full-text articles were not available. Randomized clinical trials examining the role of rifaximin in patients with FGIDs were assessed. Studies were required to have subjects with FGIDs such as irritable bowel syndrome, functional dyspepsia, postprandial fullness syndromes, or small intestinal bacterial overgrowth. Since the ROME IV definition of FABD is recent and may not have been followed in older studies, studies following the ROME I–III criteria for abdominal bloating and distension or equivalents were also considered. Studies focusing on treating this condition in the background of IBD and diverticular disease of the colon were excluded, as the pathogenesis of bloating in these patients is more likely to be related to the inflammatory process and stricture formation. Intervention in the trials included an active arm with oral rifaximin therapy while the control arm was administered a placebo. The terms used for the search included: 'bloating,' 'distension,' 'irritable bowel syndrome,' 'functional dyspepsia,' 'postprandial distress syndrome,' 'functional constipation,' and 'functional diarrhea.' These were combined using AND with the term 'rifaximin'.

Selection of Studies

We extracted all the studies resulting from the search strategies, and duplicates were removed by a validated online deduplication software.[6] References were exported to an online resource that allowed a blinded review of titles and abstracts.[7] Two reviewers independently assessed all eligible articles, and any conflicts were solved by a third author. The selected studies were obtained in full, and authors were contacted for studies that were unavailable online. A single author then assessed the full-text articles with regard to the inclusion and exclusion criteria of the systematic review. If studies with overlapping data sets were found, such as a meeting abstract preceding the final publication of a study, the article with the most inclusive data set was included. Also, the reference list of the final included articles was evaluated for similar studies that electronic search may have missed.

Outcome Assessment

The primary outcomes were the proportion of patients with improvement in symptoms of abdominal bloating or distension at the end of follow-up between rifaximin versus the control arm. Secondary outcomes included a comparison of reduction in objectively measured patient-reported outcomes (PROs) between rifaximin versus control arm as the posttreatment difference in bloating/distension scores. We also performed preplanned subgroup analysis in patients with IBS versus other FGIDs. A dose-response relationship was also assessed for the different dosing regimens for rifaximin, as well as the duration of rifaximin therapy in weeks.

The risk of bias in randomized trials was assessed using the Cochrane Collaboration tool by 2 authors and graphically depicted using Review Manager version 5.3.[8] Bias was assessed as a judgment (high, low, or unclear) for individual elements from 5 domains (selection, performance, attrition, reporting, and other).

Statistical Analysis

Binomial variables were depicted as percentages, and continuous variables as mean ± SD. Data were pooled using the random-effects inverse-variance model with the DerSimonian-Laird estimate of tau^2. Pooled information from binomial variables was presented as a risk ratio along with 95% confidence intervals. The standardized mean difference (SMD) was used to assess the continuous measure between different PRO measures used and calculated using Hedge's g equation. The 'metan' command in Stata v. 14.1 (StataCorp LLC, TX) was employed to obtain pooled statistics and Forest plots. Ethical approval was obtained from the ethical committee of the institute, and the systematic review was registered on PROSPERO (record 201071).

RESULTS

Characteristics of Studies Included for Synthesis

The study flow is shown in the PRISMA chart (Fig. 1). A total of 1426 articles (1422 from database search and 4 obtained from manual bibliography screening) were available, and 613 duplicate articles were removed. In all, 813 article abstracts were screened for eligibility, upon which both reviewers selected 34 articles. After a full-text review, 25 articles were excluded, and nine articles (including 8 full-texts and 1 abstract-only publication) reporting 10 studies were included in the final qualitative and quantitative synthesis.

Nine available articles include studied 3326 patients with FGID randomized to receive either rifaximin (n = 1672) or placebo (n = 1654) in clinical trials (Table 1). A single article was in a language other than English.[9] The mean age of the study populations ranged from 37.7 to 52.2 years. All studies predominantly included females, with the proportion of males ranging from 17.6 to 45.2%, except for the study by Tuteja et al, which included only the male veteran population.[10] Two studies included patients with various FGIDs,[11,12] 1 included patients with functional dyspepsia,[13] and the rest (n = 7) included only patients with IBS. Two studies with IBS included patients with small intestinal bacterial overgrowth within their population.[9,10] Intervention in the rifaximin arm included a daily dose of rifaximin of 800 mg for 1 week in 2 studies,[12,14] a 10-day course of 400 mg[11] in 1 study, 2 weeks of 800 mg[9] or 1200 mg[13] in one study each, and 2 weeks of 1100 mg[10,15] and 1650 mg[16,17] per day in 2 studies each.

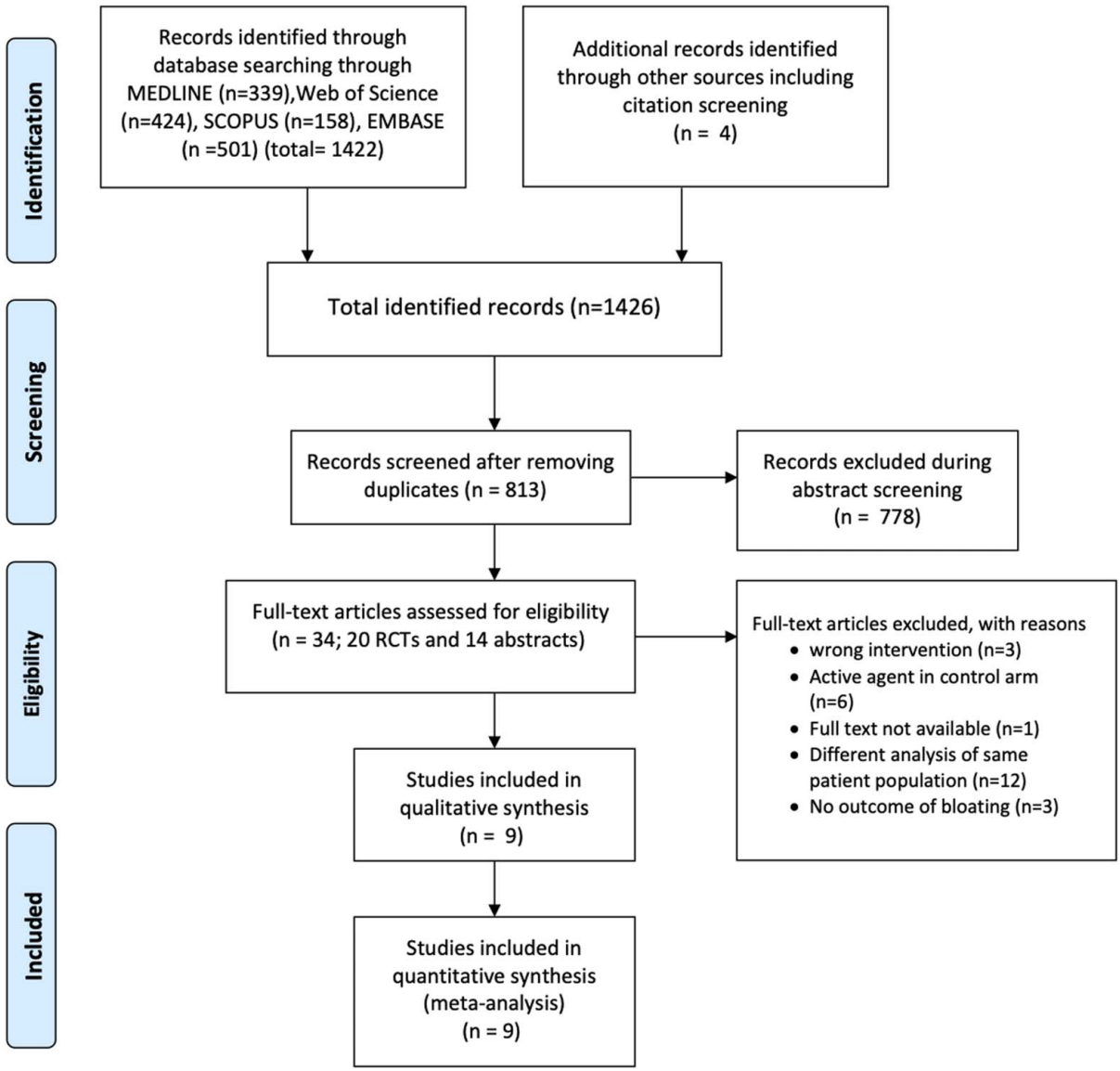

FIGURE 1. PRISMA flow chart for selection of studies included in the quantitative and qualitative synthesis.

Proportion of Patients With Improvement in Bloating or Distension

Five studies reported outcomes on improvement in bloating or distension as binary outcomes using different definitions, and for 1 study[10] the required outcome was provided by the authors through email. We pooled the 6 available studies (Fig. 2), and the risk ratio of improvement in bloating was significantly in favor of rifaximin (RR 1.22, 95% CI 1.11, 1.35). The studies were homogenous for this outcome (I^2 statistic = 0%, p for heterogeneity = 0.697). All studies in whom the outcome was available prescribed rifaximin for a duration of 2 weeks at a dose ranging from 1100 mg to 1650 mg/day. The proportion of patients in the control arm (n/N = 437/1199, 36.4%) and rifaximin arm (n/N = 536/1202, 44.6%) whose bloating or distension improved at follow-up implies a number needed to treat of 12.2.

Effect of Dose and Duration of Rifaximin on Proportion of Patients Showing Improvement

Performing a subgroup analysis for the available daily doses of rifaximin in the study (Fig. 3), we found that doses $\leq$1200 mg/day did not achieve statistical significance (pooled RR 1.16, 95% CI 0.98, 1.38, $P = 0.09$), unlike higher doses of $>$1200 mg/day (that was equivalent to1650 mg/day in all 3 studies) (pooled RR 1.25, 95% CI 1.11, 1.4, $P < 0.001$). We performed a meta-regression on the available data on improvement in bloating from 6 studies and found no effect of male sex ($P = 0.54$), duration of follow-up ($P = 0.28$), or the dose of rifaximin per tablet ($P = 0.56$). All trials that reported the outcome concerning the proportion of patients with significant improvement in abdominal bloating provided therapy for 2 weeks, and thus subgroup analysis was not performed for the duration of therapy.

TABLE 1. Study Characteristics of 10 Clinical Trials From 9 Articles Identified During the Systematic Review

Study References/Country/ language	Number of patients	Study population	Intervention vs. control/ follow-up duration	Proportion of patients with improvement in bloating	Change in bloating score from baseline
Tuteja et al[10] USA, English	N = 35, males Rifaximin = 19 (mean age: 53 y) Control = 16 (mean age: 49 y)	IBS- D or M [Rome III]	Rifaximin 1100 mg/day × 2 weeks vs. placebo	If posttreatment bloating or distension score was lower than the baseline score: 31.6% vs 37.5%	Bowel Disease Questionnaire: −0.2 vs. −0.2
Liu et al China[9] Chinese	N = 78 Rifaximin = 39 (mean age: 37.7 y, males = 46%) Control = 39 (mean age: 38 y, males = 41%)	IBS-D [Rome III] with SIBO	Rifaximin 800 mg/day x 2 weeks vs. Placebo Follow-up duration: 14 d		Hours per day: 0 = none, 1 = 1−3, 2 = 4−6, 3 = ≥7: −0.6 vs −0.1
Tan et al[13] China/Hong Kong English	N = 84 Rifaximin = 40 (mean age: 52.2 y, males = 28%) Control = 44 (mean age: 52.5 y, males = 23%)	Functional dyspepsia [Rome III]	Rifaximin 1200 mg/day × 2 weeks vs. placebo Follow-up duration: 42 d	Adequate response = score of 0 or 4; 4-point Likert scale from 0 to 3: 75% vs. 65.9%	
Lembo et al6 (phase 1)[17] USA English	N = 636 Rifaximin = 328 (mean age: 47.9 y, males = 32%) Control = 308 (mean age: 45.6 y, males = 29%)	IBS-D [Rome III]	Rifaximin 1650 mg/day ×2 weeks vs. placebo Follow-up duration: 28 d	Percentage of patients with a ≥1-point decrease from baseline in the weekly average bloating score for ≥2 weeks during the 4-week primary evaluation period.: 46.6% vs. 41.2%	Likert scale 0 to 6 for IBS-related bloating in the last 24 h: postintervention values not available
Di Stefano et al[14] Italy, English	N = 24*	IBS-C [Rome III]	Rifaximin 800 mg/day × 1 week vs. placebo Follow-up duration: 28 d		Likert scale from 0 to 3: −0.7 vs. 0.2
Pimentel et al (Target 1)[16] USA, English	N = 623 Rifaximin = 309 (mean age: 46.2 y, males = 24%) Control = 314 (mean age: 45.5 y, males = 29%)	IBS [Rome II]	Rifaximin 1650 mg/day × 2 weeks vs. Placebo Follow-up duration: 84 d	Weekly IBS-related bloating: 39.5% vs. 28.7%	Likert scale 0 to 6: −0.9 vs. −0.6
Pimentel et al (Target 2)[16] USA, English	N = 635 Rifaximin = 315 (mean age: 45.9 y, males = 28%) Control = 320 (mean age: 46.3 y, males = 30%)	IBS [Rome II]	Rifaximin 1650 mg/day × 2 weeks vs. Placebo Follow-up duration: 84 d	Weekly IBS-related bloating: 41% vs. 31.9%	Likert scale 0 to 6: −0.8 vs. −0.8
Lembo et al[15] USA, English	N = 388 Rifaximin = 191 (mean age: years, males = 0%) Control = 197 (mean age: y, males = 0%)	IBS-D	Rifaximin 1100 mg/day × 2 weeks vs. placebo Follow-up duration: 98 d	Weekly yes/no responses to questions: 50.3% vs. 42.1%	

Sharara et al[11] Lebanon, English	N = 124 Rifaximin = 63 (mean age: 42.6 y, males = 48%) Control = 61 (mean age: 39.6 y, males = 43%)	Symptomatic bloating and abdominal distension [Rome II]	Rifaximin 400 mg/day × 10 days vs. Placebo Follow-up duration: 10 d	Likert scale 0 to 4 summed over 10 days: −2.9 vs. −0.7
Di Stefano et al[12] Italy, English	N = 34 Rifaximin = 18 (mean age: 39.3 y, males = 17%) Control = 16 (mean age: 48.2 y, males = 19%)	FGID [ROME II] suffering from excessive flatus, bloating, abdominal discomfort or pain	Rifaximin 800 mg/day× 1 week vs. activated charcoal 400 mg BD × 7 d Follow-up duration: 17 days	Sum of 12 one-hour periods following lactulose ingestion, each being a Likert scale from 0 to 3: −5.8 vs. −4.9

*Number of individuals randomized to each arm was not available.

Improvement in Bloating or Distension Scores

Eight studies had measured bloating or distension on a scale, the measurement of which differed between studies. Four studies employed a Likert scale from 0 to an upper bound between 3 and 6,[11,14,16,17] 2 studies estimated the hours per day patients suffered from bloating or distension,[9,12] and 1 employed the bowel disease questionnaire.[10] However, postintervention scores were unavailable for Lembo et al,[17] which was excluded from this analysis. The number of individuals in each arm was not specified in Di Stefano et al[14] and was assumed to be equal (n = 12 each) due to the randomized design for this analysis. For Pimentel et al[16] the postintervention mean scores were available after communication with the authors, while the postintervention SDs were substituted from the baseline SD since it was reasonable to assume that the interventions did not alter the variability of this outcome measure for the study.[18] There was a significant reduction in a standardized mean difference of postintervention scores between rifaximin and placebo, in favor of rifaximin (pooled SMD −0.30, 95% CI −0.51, −0.10, $P = 0.04$) and is shown in Fig. 4. These results carry significant heterogeneity ($I^2 = 61.6\%$, p for heterogeneity = 0.01). Since the continuous outcomes measured different characteristics (severity of bloating in those with Likert scale or BDQ versus duration in the 2 studies quantifying duration), we performed a sensitivity analysis limited to the studies using the Likert scale, which drew similar conclusions with less heterogeneity. (Supplementary Fig 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A973) Sensitivity analysis was performed by excluding the 2 studies for which missing data were assumed, and the pooled SMD remained significant (−0.33, 95% CI −0.57, −0.09, $I^2 = 71\%$, p for heterogeneity = 0.01).

Subgroup Analysis for Dose and Duration of Rifaximin Therapy (Bloating Severity Scores)

We performed subgroup analysis for the outcome of improvement in bloating severity in terms of scores for both dose and duration of rifaximin therapy. Similarly to the subgroup findings of binomial outcome above, there was a significant benefit in the 2 studies (by the same research group) that utilized doses of 1650 mg/day (pooled SMD −0.27, 95% CI −0.51, −0.1, $P = 0.002$). However, those utilizing lower doses (≤ 1200 mg/day) failed to demonstrate significant benefit (pooled SMD −0.31, 95% CI −0.75, 0.13, $P = 0.17$) and showed significant heterogeneity ($I^2 = 68.4\%$, p for heterogeneity = 0.013) (Fig. 5).

All studies that reported bloating severity in terms of scores treated with rifaximin for a duration varying between 7 and 14 days. We performed a subgroup analysis to assess the effect of the duration of rifaximin therapy, comparing those who were prescribed rifaximin for 2 weeks versus those prescribed shorter courses (7 or 10 d). The shorter courses did not yield a significant reduction in bloating/distension scores ($P = 0.39$), although the data was available for only three studies with significant heterogeneity ($I^2 = 78.8\%$, p for heterogeneity = 0.009). Two weeks of therapy were associated with improved bloating scores in 3 of the 4 studies with a pooled reduction in SMD of −0.28 (95% CI −0.45, −0.11, $P = 0.002$) with moderate heterogeneity present (Supplementary Fig. 2, Supplemental Digital Content 2, http://links.lww.com/JCG/A974).

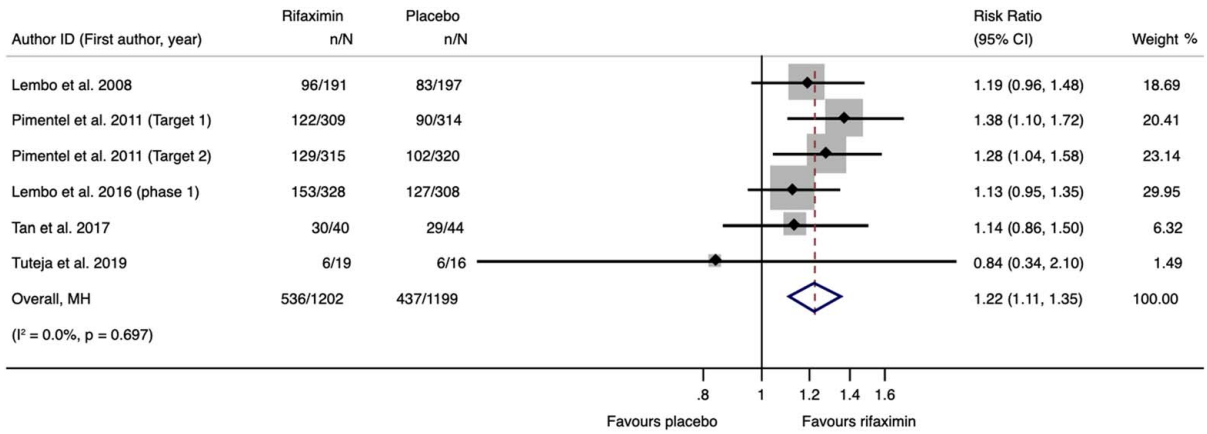

FIGURE 2. Forest plot depicting the proportion of patients demonstrating improvement in abdominal bloating or distension in each study. The pooled risk ratio (1.22, 95% CI 1.11, 1.35) favors intervention (rifaximin).

Associated Disease (IBS, SIBO, and Other FGIDs)

We identified 4 studies among the included RCTs that included information on hydrogen breath testing and randomized these patients to rifaximin or placebo.[9,11,14,17] Patients in the trial by Di Stefano et al underwent hydrogen breath testing after oral lactulose to evaluate colonic hydrogen production, which was repeated at the end of treatment (1 week), and 1 month later.[14] They divided the patients into those with normal sensations and those who were hypersensitive according to the presence of visceral hypersensitivity on barostat testing. They found that rifaximin significantly reduced cumulative breath hydrogen production in both groups of patients, but bloating severity improved only in normo-sensitive patients. These patients demonstrated a good correlation between reduced cumulative breath hydrogen excretion and bloating severity ($r = 0.76$, $P < 0.001$). The same group has previously shown a significant reduction in hydrogen breath excretion in patients treated with rifaximin, along with a decrease in overall symptom severity, abdominal girth, and the number of flatus episodes, but not for bloating (11.3 ± 12.3 after treatment vs. 17.1 ± 9.7 before treatment, P value not available) which was possibly underpowered for this outcome.[11] A third study from the group found no effect of rifaximin on bloating severity despite normalization of elevated hydrogen breath excretion in 70% (n/N = 7/10) patients.[19] Sharara et al also found that hydrogen breath excretion decreased significantly among patients who responded to rifaximin with a reduction in bloating scores ($P = 0.01$), not in rifaximin non-responders or placebo groups.[14] Liu et al studied Chinese patients with IBS associated with SIBO and found a significant reduction after receiving rifaximin in the number of hours patients suffered from abdominal distension (1.41 h vs. 1.97 h, $P < 0.05$) as well as inflammatory markers (IL-8, TNF a, NF kappa B), but did not measure hydrogen breath excretion following

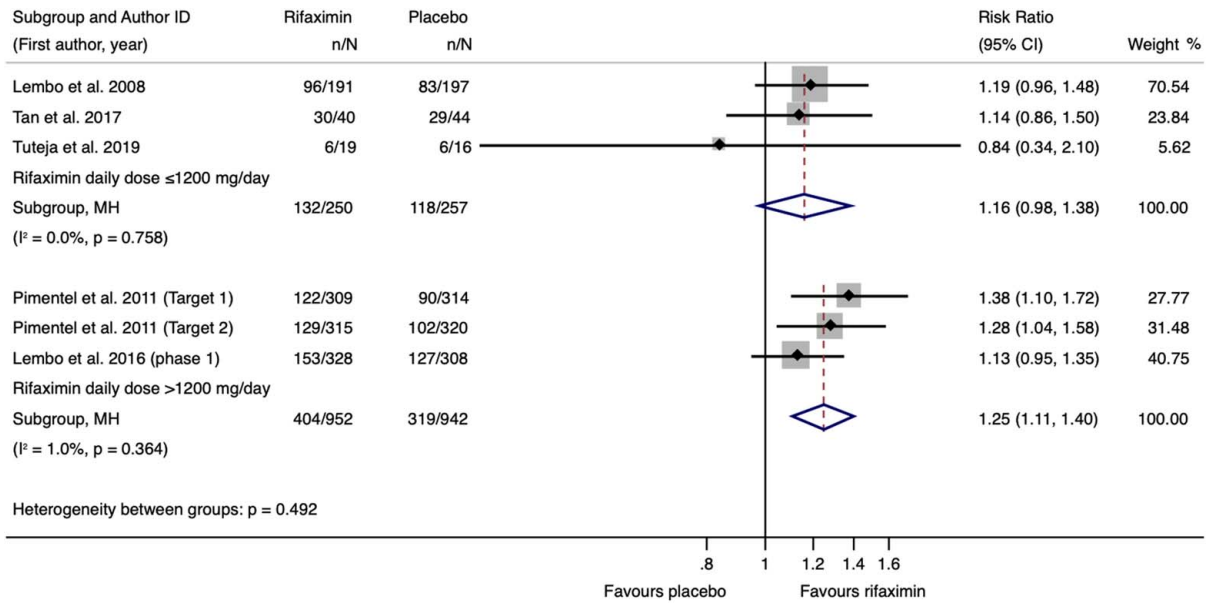

FIGURE 3. Forest plot depicting the proportion of patients with improvement in abdominal bloating or distension with subgroup analysis of different daily doses of rifaximin (≤1200 mg/day and >1200 mg/day). Higher doses (>1200 mg/day) were significantly associated with improvement in bloating or distension, while lower doses demonstrated a trend towards improvement).

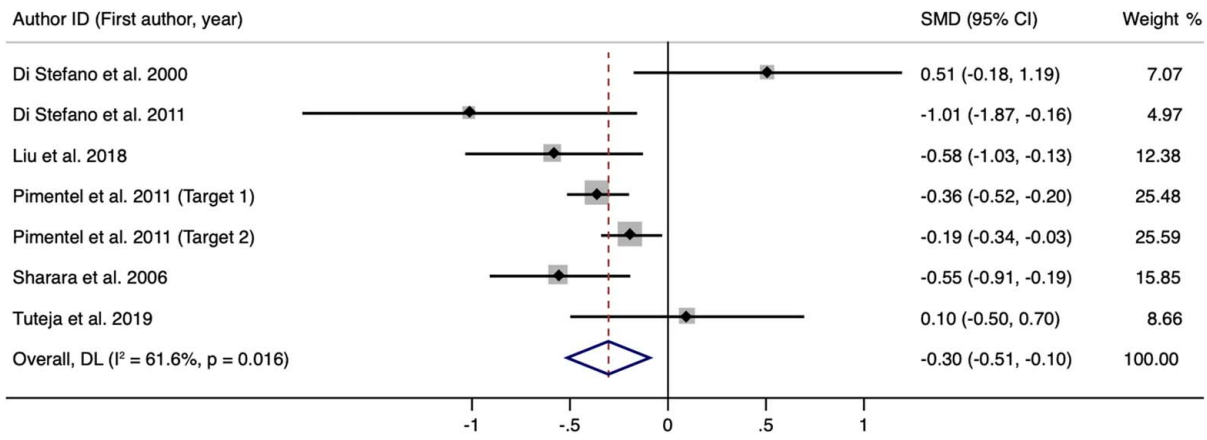

FIGURE 4. Forest plot depicting standardized mean difference of posttreatment bloating scores between rifaximin and placebo. The random-effects pooled SMD favors rifaximin (–0.3, 95% CI –0.51, –0.1), although there was significant heterogeneity between the studies.

treatment.[9] Thus, hydrogen breath excretion may reflect the amount of intestinal dysbiosis, and improvement in intestinal dysbiosis may underlie the improvement in bloating severity seen in patients with IBS, given rifaximin.

Re-treatment With Rifaximin

Only 2 available RCTs attempted to study the Efficacy of re-treatment with rifaximin. Lembo et al[14] performed an RCT in two phases, and in the first phase they found that 64.4% of patients who had initially responded to rifxaimin suffered a relapse of symptoms. In the second phase of the RCT, these patients were randomized to 2-week course of either rixaimin or placebo in a double-blind manner. They found a statistically nonsignificant difference in abdominal bloating (46.6% vs. 41.2%, $P = 0.14$) between the 2 groups. They demonstrated an improvement in abdominal pain and stool consistency (38.1% vs. 31.5%, $P = 0.03$) and increased durable response from these 2 IBS symptoms (17.1% vs. 11.7%, $P = 0.04$) following re-treatment with rifaximin, compared with placebo. Another study from the same study

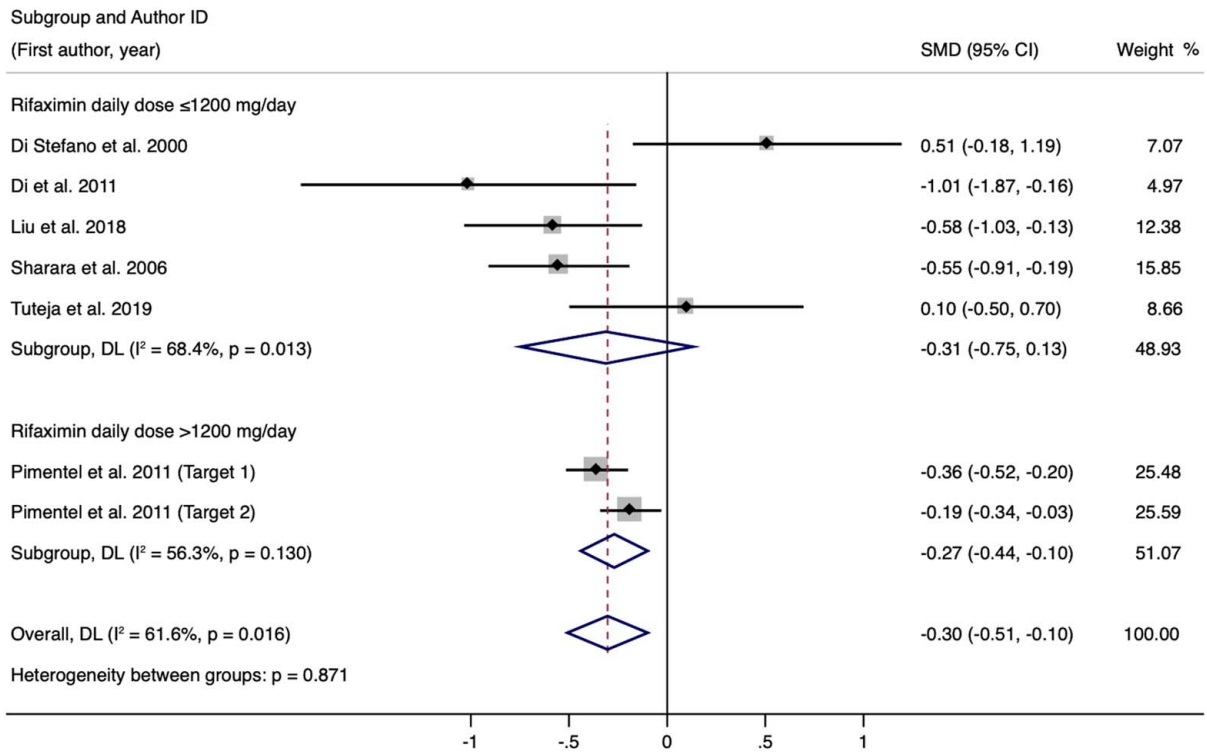

FIGURE 5. Forest plot depicting standardized mean difference of posttreatment bloating scores with the subgroup analysis of different doses of rifaximin therapy (>1200 mg/day vs. ≤1200 mg/day). Higher doses were significantly associated with improvement in bloating or distension severity ($P = 0.002$), while lower doses carried significant heterogeneity and did not achieve statistically significant benefit ($P = 0.17$).

population found that IBS-related quality of life (QOL) improved by 54.9% in the first open-label rifaximin treatment.[20] Those who responded to rifaximin in the first phase with a significant reduction in weekly response in pain and stool consistency also demonstrated better IBS-related QOL. In the second phase randomizing patients who had responded to rifaximin initially to rifaximin or placebo, a larger proportion of patients in the rifaximin arm versus placebo (38.6% vs. 29.6%, $P = 0.009$) had a clinically relevant improvement in their IBS-related QOL scores. Thus, it is unclear if repeat prescriptions of rifaximin among patients who responded initially will improve symptoms of abdominal bloating. Still, it may improve other symptoms of IBS, such as abdominal pain and stool consistency, and consequently, QOL.

Risk of Bias Assessment

Two reviewers assessed the studies for risk of bias using the Cochrane risk of bias tool. The findings for individual studies are cross-tabulated in Fig. 6 and summarized in Supplementary Fig. 3, Supplemental Digital Content 3, http://links.lww.com/JCG/A975. Overall, since the binomial outcome of improvement in bloating or the continuous outcome of bloating severity is subjective, the low to unclear risk of performance bias (blinding) was reassuring. However, 3 studies (30%) suffered from a high risk of reporting bias as only select outcomes planned for analysis were reported on available for interpretation. These necessitated contacting the manuscript authors, imputation of data, and exclusion from certain analyses, possibly leading to bias. Except for this domain, most domains had patients at low risk of bias. For the binary outcome of improvement in bloating, the analyzed studies usually had a low risk of bias in all domains except selective reporting, which was at high risk of bias[16,17] in 2 studies and unclear risk[10,15] in 2 studies. Overall, in the review author's judgment, this outcome carries a low risk of bias due to the low risk of selection bias and adequate blinding in the studies that hold more importance in a subjective outcome, such as bloating. For the continuous outcome of quantitative improvement in bloating or distension scores measuring severity and duration of bloating, there was significant heterogeneity in the measured outcome regarding the scale used and its administration. Further, unclear risk[9] and high risk of bias[14] were present in 1 study each analyzed for this outcome for the blinding, which was an important domain for this outcome —consequently, the review authors judge this outcome to be at unclear risk of bias overall.

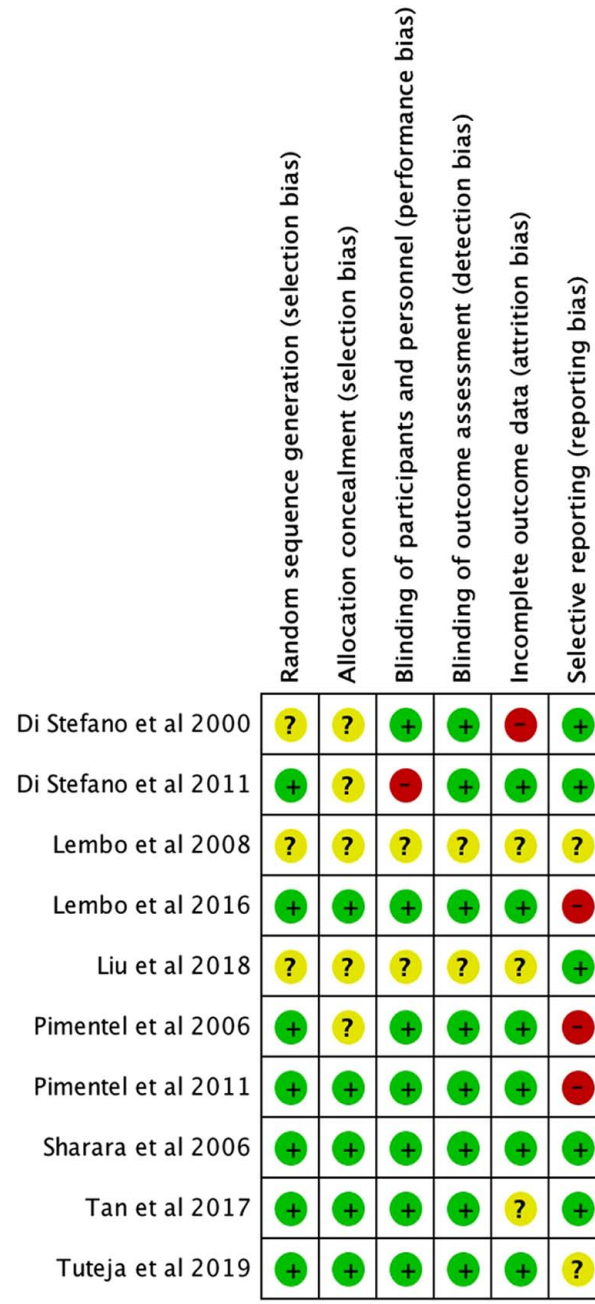

FIGURE 6. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

DISCUSSION

There is a considerable prevalence of bloating or distension in the community, estimated at 15% to 20%, and frequent coexistence with IBS and functional constipation. Potential etio-pathologic factors include visceral hypersensitivity, abnormal intestinal gas transit, impaired evacuation of rectal gas, colonic fermentation, small intestine bacterial overgrowth, and gut microbiota alterations.[21,22] Among these, small intestinal bacterial overgrowth and dysbiosis act as the predominant pathologies and affect the intestinal microbiota, gas production, transit, and visceral sensory function, paving the way for the use of antibiotics in patients with bloating.[23] Rifaximin may act through multiple mechanisms in abdominal bloating and distension.[24] It inhibits bacterial RNA synthesis and reduces the attachment and internalization of bacteria, thus decreasing bacterial overgrowth. Secondly, it favors the growth of nonpathogenic bacteria, reduces the virulence of pathogenic strains, and inhibits plasmid transfer from donor to recipient bacteria by 99%, correcting intestinal dysbiosis. It affects inflammatory cytokine release and upregulates proteins involved in detoxification, thus normalizing gut immune function. We found that rifaximin significantly increases the probability of improvement in bloating symptoms [3201 patients, pooled RR 1.22 (95% CI 1.11, 1.35)] with low heterogeneity (I^2 statistic = 0%, P value = 0.69) and a low

risk of bias across the studies. We also found that rifaximin reduces the bloating or distension severity or duration reported using patient-reported outcomes (1553 patients, pooled SMD = −0.30, 95% CI −0.51, −0.10, $P = 0.04$). However, this outcome carried significant heterogeneity ($I^2 = 61.6\%$, p for heterogeneity = 0.01) and was at an unclear risk of bias.

The initial treatment regimen for FABD includes dietary modification with a low FODMAP diet (fermentable oligo-, di-, monosaccharides, and polyols), reduced intake of gas-promoting foods (beans, carrots, bananas, caffeine), the trial of lactose-free diet, and sometimes the trial of gluten-free diet in an attempt to reduce the production of intestinal gas and consequent visceral sensation. A low FODMAP diet has been studied in randomized trials and shown to lead to sustained improvement in abdominal symptoms, including bloating, although in only half of the patients.[25] FODMAP avoidance remains the most effective therapy for abdominal bloating (50-82% reduction in symptoms),[5] and prokinetic agents (linaclotide, prucalopride, and lubiprostone) have been used but are associated with a lower likelihood of reduction in symptoms compared with rifaximin (33% of patients treated with linaclotide showed improvement in bloating, versus 44.6% for rifaximin in our review). Antidepressants (tricyclic antidepressants) have been recommended in the management of global symptoms of IBS, but no improvement in bloating has been demonstrated with this therapy and may worsen associated constipation due to its anticholinergic effects. Among those with IBS-D, recently FDA-approved therapies, in addition to rifaximin, include alosetron and ramosetron (5HT3 agonist) and eluxadoline (peripherally acting mixed μ-opioid and κ-opioid receptor agonist, and δ-opioid receptor antagonist) both of which reduce gastrointestinal transit and visceral hypersensitivity. Both classes of drugs were found to be effective for global IBS symptoms in rank order of alosetron, ramosetron, eluxadoline, and finally, rifaximin.[26] However, these therapies have been associated with serious adverse effects such as ischemic colitis (1 per 1000 patients with IBS) in alosetron, for which it was temporarily withdrawn from the market.

Rifaximin has been extensively studied in patients with IBS having a beneficial effect on stool frequency and abdominal pain symptoms. Li et al performed a meta-analysis of RCTs on the therapeutic role and adverse effects of rifaximin in patients with IBS.[27] They included 3 RCTs in their analysis[11,15,16] and found significant improvement in overall IBS symptoms (pooled OR 1.19; 95% CI 1.08, 1.32, $I^2 = 15\%$) at the end of the treatment period. However, it included a single study[15] on the outcome of abdominal distension, which showed a significant benefit of rifaximin in reducing distension at the end of the follow-up period, but not at the end of treatment. Black et al recently published their network meta-analysis in drug therapy for IBS-D or M and included 3 main outcomes: global IBS symptoms, abdominal pain, and stool consistency.[26] They included 18 RCTs recruiting 9844 patients and found Alosetron 1 mg b.i.d. to be the most effective therapy for global symptoms (pooled RR for failure to achieve treatment response 0.69, 95% CI 0.6, 0.8), followed by ramosetron. They found that rifaximin reduced the probability of failure to achieve treatment response compared with placebo but did not significantly improve global IBS symptom response. This result is lower than expected and may be explained as only 2 trials of rifaximin from a single publication were included by the authors, unlike the more extensive inclusion meta-analysis by Li et al[27] They also compared the safety of these therapies and found rifaximin to be safest, while alosetron, ramosetron, and eluxadoline were associated with increased risk of adverse effects compared with placebo. Pimentel et al, in their review, showed that SIBO was frequently present in IBS and that rifaximin effectively eradicated SIBO in 84% of patients on follow-up.[28] Treatment with rifaximin demonstrated improvement in global symptoms, but this was largely limited to symptoms of bloating, while abdominal pain, diarrhea, and constipation did not differ compared with placebo.[29]

In terms of dosage and duration, we found that doses above 1200 mg/day and duration of therapy of 2 weeks were associated with benefits in terms of the proportion of patients with improvement in bloating as well as a reduction in bloating or distension severity in terms of quantitative scores. Rifaximin doses of 1200 mg/day or below and shorter regimens (7 or 10 d) did not show statistically significant differences. Thus, it appears that the currently recommended doses of 550 mg thrice daily should be preferred when rifaximin is prescribed for abdominal bloating in IBS, and probably other FGIDs as well. Subsequent trials should utilize this dosing regimen in assessing the benefit of bloating/distension.

Two other important considerations for rifaximin are the cost of therapy and its safety profile. Worldwide, the cost of therapy with rifaximin has been prohibitive for widespread use, given the high number needed to treat for improvement in IBS symptoms. Estimates of $29.78 per pill in the United States have been used to calculate that rifaximin therapy would not be cost-effective in reducing quality-adjusted life year lost to IBS symptoms when using the results from Pimentel et al as reference.[30] They estimated that a minimum reduction in prices of 12% to 84%, depending on the form of insurance coverage, would be required to achieve cost-effectiveness. However, other countries that market generic rifaximin would likely carry much lower costs of therapy obviating this concern.

Rifaximin has been considered safe due to its negligible gastrointestinal absorption. Schoenfeld et al pooled results from 2 phase-3 studies and a phase-2b trial (for which results are unavailable publicly at the time of writing this article). They found rifaximin to be safe and tolerable with drug-related adverse effects (AEs), serious AEs, AEs necessitating drug discontinuation, GI AEs, and infection-associated AEs to be similar to negligible and comparable to placebo, with zero cases of *Clostridioides difficile* colitis or deaths related to the drug.[31]

The novelty offered by the present review is that it focused on the symptom complex of bloating or distension, incorporated more recent well-conducted trials published after the conclusion of previous meta-analyses, included FGID other than IBS, and assessed the effect on bloating or distension in FGID irrespective of diagnosis. All previous reviews have included fewer than 3 trials for the effect of rifaximin on bloating or distension and thus could not definitively comment on its role.

The present review suffers from the following limitations: firstly, we included patients with functional GI disorders regardless of their classification and the presence or absence of SIBO. Thus, we evaluated if these factors modify the pooled effect by performing sensitivity analysis for studies limited to the diagnosis of IBS as well as those excluding patients with SIBO, respectively. Secondly, our analysis restricted itself to the measurement of bloating or distension.

We did not assess other functional GI symptoms (such as abdominal pain) or the safety profiles, for which prior reviews and meta-analyses have provided clarity.[26,27,31] Thirdly, for the measurement of bloating severity as a continuous measure, there were wide differences between the tools used among studies and, consequently, heterogeneity in the pooled result.

We conclude that rifaximin effectively improves the symptoms of bloating or distension in patients with functional GI disorders, including IBS. It increases the likelihood of symptomatic relief compared with placebo and reduces the severity of these symptoms. Therapy utilizing a dose of 1650 mg/day (as 550 mg thrice daily) and a duration of 2 weeks was consistently associated with improvement compared to placebo, lower doses, and a shorter duration of therapy. In light of established safety, it may be offered to patients with FGIDs symptomatic with bloating or distension who fail to improve on diet modification alone.

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