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THE ROLE OF RIFAXIMIN IN IRRITABLE BOWEL SYNDROME DERIVED FROM A NETWORK META-ANALYSIS OF RANDOMIZED CONTROL TRIALS

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Abstract – *Objective:* Recent randomized control trials (RCTs), have demonstrated the beneficial therapeutic effects of rifaximin for the treatment of the irritable bowel syndrome (IBS). However, in these studies different drug doses have been used and still the optimal therapeutic dose is missing. We aimed to determine rifaximin therapeutic benefit and optimal dose for IBS as evidenced by the results of a network meta-analysis (NWM) of published randomized controlled trials (RCTs).

Materials and Methods: PubMed/MEDLINE, EMBASE, and Cochrane Library databases were searched for RCTs investigating the therapeutic effects of rifaximin on IBS through December 2019. Data from each selected RCT were evaluated individually based on an intention-to-treat analysis. A Bayesian NWM was performed to investigate the efficacy rank order of rifaximin therapeutic interventions in IBS.

Results: Four eligible studies, including 5 sets of data, were included in this NWM. They included 1,803 IBS patients, randomized to placebo (908 patients), and rifaximin (895 patients). In patients who received rifaximin, four regimens were examined, i.e., (A) = 400 mg tds for 10 days, (B) = 400 mg bid for 10 days, (C) = 550 mg bid for 2 weeks and (D) = 550 mg tds for 2 weeks. The results showed that in IBS rifaximin 400 mg tid for 10 days showed the highest efficacy [SUCRA (surface under cumulative ranking) value 89.5%], in comparison to other rifaximin regimens used and placebo.

Conclusions: This NWM showed that the therapeutic efficacy of rifaximin 400 mg tid in IBS patients was greater than that of placebo and the other rifaximin doses studied.

Keywords: Irritable bowel syndrome, Rifaximin, Dose, Network meta-analysis.

Abbreviations: NWM = network meta-analysis, IBS = irritable bowel syndrome, RCT = randomized controlled trial, OR = odds ratio, CI = confidence interval.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is characterized by chronic intermittent abdominal discomfort with concomitant diarrhea and/or constipation in patients for whom there are no imaging, biochemical, and morphological abnormalities of the digestive tract[1]. Patients with IBS suffer from frequent relapses, which impairs their quality of life. In recent decades, the incidence of IBS has gradually increased to nearly 20% in Europe and America and to 10% in China[2]. It is more common in women and in subjects less than 50 years old[3,4]. Studies have related IBS to altered intestinal microbiota, visceral hypersensitivity, dysfunctional gastrointestinal motility, stress-induced inflammation, brain-gut neuronal axis defects, and psychological factors[5-10]. However, the physiological mechanism underlying the pathogenesis of IBS remains unclear.

Rifaximin is useful for treating intestinal bacterial infections and has been approved by the United States Food and Drug Administration for the treatment of traveler's diarrhea in certain patients[11]. Recently, the therapeutic role of rifaximin in IBS has been examined in RCTs[12-15] and in a pair-wise meta-analysis[16]. The maximal effect was obtained in a subset of patients with IBS-D (diarrhea type). However, in these studies different rifaximin dosing regimens have been used. Therefore, the optimal rifaximin regimen is unclear, meaning that a re-examination of the current evidence concerning rifaximin therapeutic efficacy in IBS and the optimal dose is warranted.

Network meta-analysis (NWM) has been established as a particularly useful evidence synthesis tool for comparing RCTs with several treatment regimens[17-19]. NWM incorporates both direct and indirect evidence in a collection of RCTs, thus providing information concerning the relative effects of three or more therapeutic interventions competing for a similar result. No NWM exists concerning optimal rifaximin dose in IBS and therefore the aim of the present study was to examine the therapeutic efficacy and optimal rifaximin dose in IBS evaluated in relevant RCTs.

MATERIALS AND METHODS

Identification of Studies and Data Extraction.

To identify studies and extract data in this NWM we have followed the steps described in our previous publications[20]. Thus, PubMed/MEDLINE and EMBASE databases were searched until December 2019 to identify human studies, written in English, using the following search text and/or Medical Topic Heading (MeSH) terms: *"irritable bowel syndrome" OR "ibs" [All Fields] AND ("rifaximin" [MeSH Terms] OR "rifaximin" [All Fields]).* In addition, a manual search of all review articles, published editorials and retrieved original studies, was made. Two authors (T.R. and Y.N.) independently extracted data from each study. Any disagreement was settled with further discussion until consensus was reached. The NWM was performed according to the PRISMA extension statement for interventions[21]. The rating of the quality of RCTs was achieved by using the GRADE (i.e., Grading of Recommendations Assessment, Development and Evaluation) working group modality[22]. Furthermore, we appraised the confidence in estimates derived from NWM, as described in our previous publication[23]. In this process, the construction of a matrix depicting the contribution of direct evidence to NWM results and the construction of a bar graph depicting the risk of bias (RoB) for each network estimate and for the entire network, helped in assessing the quality of evidence in NWM.

Selection Criteria - Primary End Points

We defined the inclusion and exclusion criteria before starting the study investigation. Thus, appropriate studies were included in the meta-analysis if the following criteria were met: a) published as complete articles or abstracts with data that could be extracted; b) written in English, and c) were RCTs comparing rifaximin therapeutic interventions in IBS. Studies that did not meet these criteria were excluded. The resolution of global IBS symptoms at the end of the primary evaluation period was defined as the primary end point.

Statistical Analysis

The coefficient k was used to evaluate the study selection process of the reviewers. For pair-based meta-analyses and heterogeneity estimation we followed the methodology as previously described[20]. In addition to heterogeneity, we assessed inconsistency, as this is critical when conducting a NWM[17-19]. We constructed comparison-adjusted funnel plots and checked their symmetry to assess whether small-scale trials influenced the efficacy of the results.

SUCRA (surfaces under cumulative ranking) values were used in intervention network charts to examine the cumulative ranking probability for each intervention. In this process the efficacy achieved by each intervention is compared to an ideal intervention showing the best efficacy without doubt, i.e., SUCRA = 1 or 100% when expressed as a percentage[17-19]. Data were processed using software suitable for Bayesian network meta-analysis, namely Stata 13.2 (StataCorp, College Station, TX, USA)[17,18] and NetMetaXL[19]. A *p*-value of <0.05 was used to reflect significance for all measurements except for heterogeneity where the corresponding value was 0.1.

RESULTS

Characteristics of Studies

A flowchart showing the study selection is illustrated in Figure 1. Out of 616 titles yielded by the initial search, four RCTs[12-15] were ultimately deemed eligible for meta-analysis. Reviewers' agreement concerning the selection of studies was high [k = 0.97; 95% confidence interval (CI) 0.94-1]. The characteristics of the four involved RCTs are shown in Table 1.

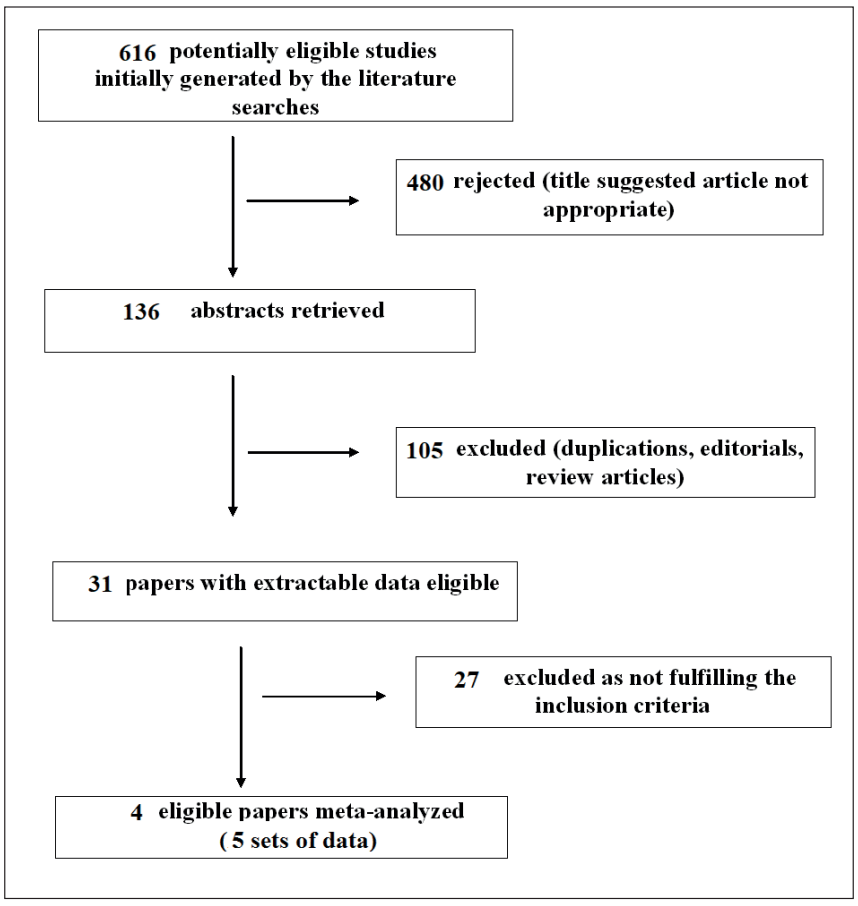


Figure 1. Flow chart of studies included in the network meta-analysis.

TABLE 1. THE MAIN CHARACTERISTICS OF THE STUDIES INCLUDED IN THE NETWORK META-ANALYSIS.

Study (ref.)	Year/country	Study type/ total No. of included patients	IBS type	Diagnostic criteria	Rifaximin dose/ No. of patients included	Comparator/ No. of patients included	Definition of efficacy	Treatment duration
Pimentel[12]	2006/USA	RCT/n=87	Not defined	Rome I	400 mg tds/n=43	Placebo/n=44	IBS symptom resolution at the end of treatment period	10 days
Sharara[13]	2008/ Lebanon	RCT/n=70	Diarrhea, constipation, mixed types	Rome II	400 mg bid/n=37	Placebo/n=33	IBS symptom resolution at the end of treatment period	10 days
Lembo[14]	2008/USA	RCT/n=388	Mainly diarrhea	Rome II	550 mg bid/n=191	Placebo/n=197	IBS symptom resolution at the end of treatment period	2 weeks
Pimentel[15]	2011/USA	RCT/n=1258 (TARGET 1 and TARGET 2 studies)	Bloating, abdominal pain, and loose or watery stools No constipation	Rome II	550 mg tds/n=624	Placebo/n=634	IBS symptom resolution at the end of treatment period	2 weeks

They included 895 rifaximin allocated patients and 908 placebo allocated patients. One of these studies[15] included two separate RCTs (TARGET 1 and TARGET 2) with identical methodology, and therefore, in these 4 RCTs there were a total of 5 data sets. In patients who received rifaximin, four regimens were studied, i.e., rifaximin (A) = 400 mg tds for 10 days, rifaximin (B) = 400 mg bid for 10 days, rifaximin (C) = 550 mg bid for 2 weeks and rifaximin (D) = 550 mg tds for 2 weeks. Study quality, double-blinding and randomization methods were adequately described in all of the included RCTs, whereas allocation concealment was described adequately in only 2 of these studies[13,15]. Concerning tolerability, in three of the included RCTs[12,13,15], minor side effects, such as abdominal pain, nausea, vomiting, and headache were reported.

Network Meta-Analysis

Network map

The network map of the rifaximin therapeutic interventions included in the RCT studies is depicted in Figure 2. In this map the node size reflects the number of patients allocated to each treatment, i.e., placebo, rifaximin 400 mg tds, rifaximin 400 mg bid, rifaximin 550 mg bid, rifaximin 550 mg tds. The edge thickness is in proportion to the precision, i.e., the inverse of variance of each direct comparison[17].

Network plots

The comparative efficacy of different therapeutic interventions was checked by conducting a total of 10 possible pairwise comparisons (direct and indirect) as shown in the forest plot in Figure 3. There was no significant heterogeneity and also the evaluation of inconsistency yielded insignificant overall results, meaning that the comparative effect sizes that were obtained by direct and indirect comparisons are consistent. In this plot the direct comparisons show the significant superiority of two rifaximin regimens, i.e., regimen A = 400 mg tid for

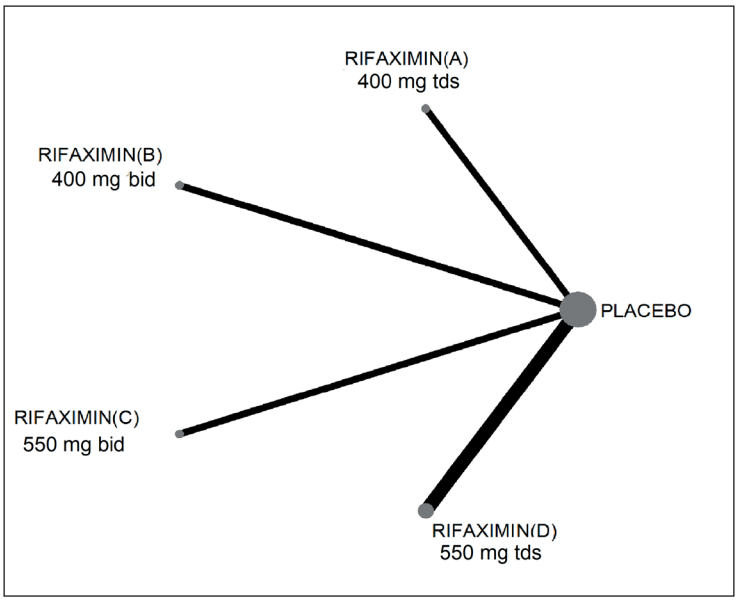


Figure 2. Network map of the rifaximin therapeutic interventions for irritable bowel syndrome (IBS) included in the relevant randomized control trials (RCTs). Node size reflects the number of patients randomly assigned to each treatment. Edge thickness is in proportion to the precision, i.e. the inverse of variance of each direct comparison.
Treatment labels: Rifaximin (**A**) = 400mg tds for 10 days, rifaximin (**B**) = 400mg bid for 10 days, rifaximin (**C**) = 550mg bid for 2 weeks and rifaximin (**D**) = 550mg tds for 2 weeks.

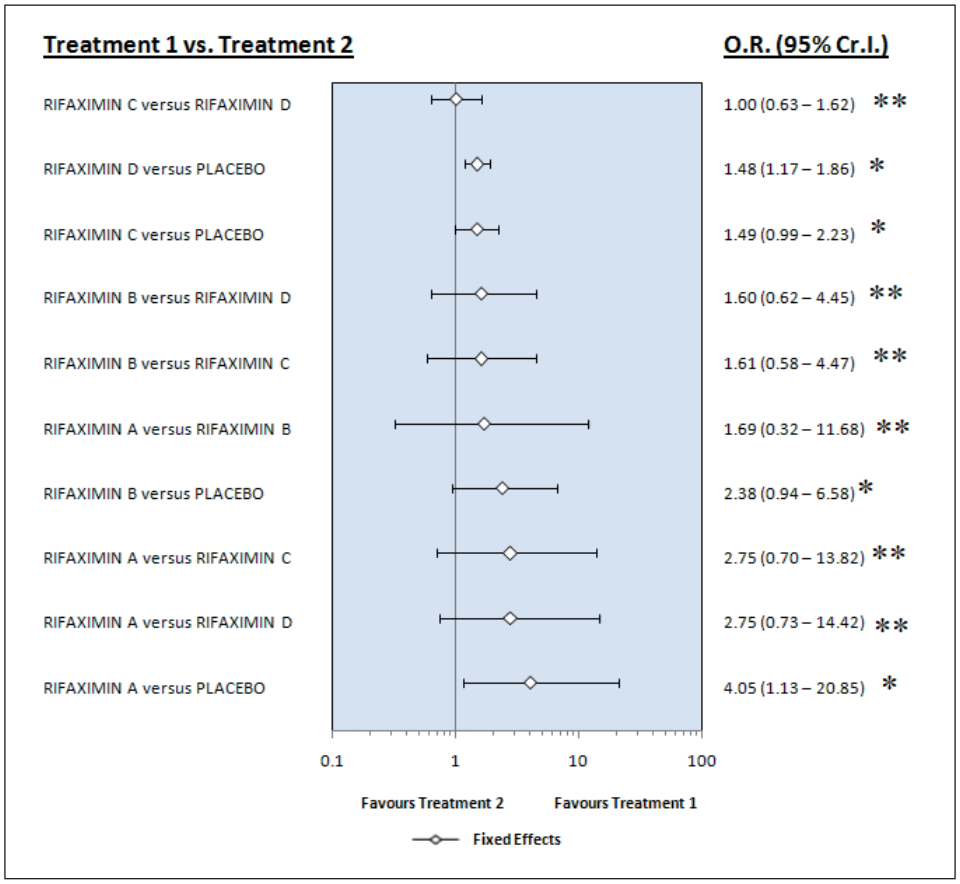


Figure 3. Forest plot illustrating all possible pairwise comparisons of rifaximin therapeutic interventions for irritable bowel syndrome (IBS) included in the randomized control trials (RCTs), according to their efficacies. The horizontal lines represent the credible intervals (CrI). *= direct comparison, **=indirect comparison.
Treatment labels: Rifaximin (**A**) = 400mg tds for 10 days, rifaximin (**B**) = 400mg bid for 10 days, rifaximin (**C**) = 550mg bid for 2 weeks and rifaximin (**D**) = 550mg tds for 2 weeks.

ten days and regimen D = 550 mg tid for two weeks, in comparison to placebo [OR (95% CrI), 4.05 (1.13-20.85) and 1.48 (1.17-1.86) respectively]. The contribution of each comparison in the network is demonstrated in the constructed contribution plot (Figure 4A). The associated bar graph (Figure 4B) depicts the bias risk for each network assessment, demonstrating the volume of information originating from high, unclear and low risk of bias studies. The relevant funnel plot (Figure 4C) appeared symmetric, reflecting the lack of publication bias and no effects from small studies in the network.

League table and rankogram

The superiority of rifaximin A (400 mg tds), in comparison to the other therapeutic interventions studied, i.e., placebo, rifaximin 400 mg bid, rifaximin 550 mg bid, rifaximin 550 mg tds is shown in the league table of the comparative efficacies of IBS therapeutic modalities (Figure 5) and also in the rankogram of Figure 6A (reflecting the areas under the curves) together with SUCRA (surfaces under cumulative ranking) values (Figure 6B). Thus, the SUCRA value for rifaximin regimen A (400 mg tds for 10 days) was 89.5%, rifaximin B (400 mg bid for 10 days) 71.8%, rifaximin C (550 mg bid for 2 weeks) 43.3% and rifaximin D (550 mg tds for 2 weeks) 43.2%. The respective SUCRA value for placebo represented the least efficacious regimen (2.1%).

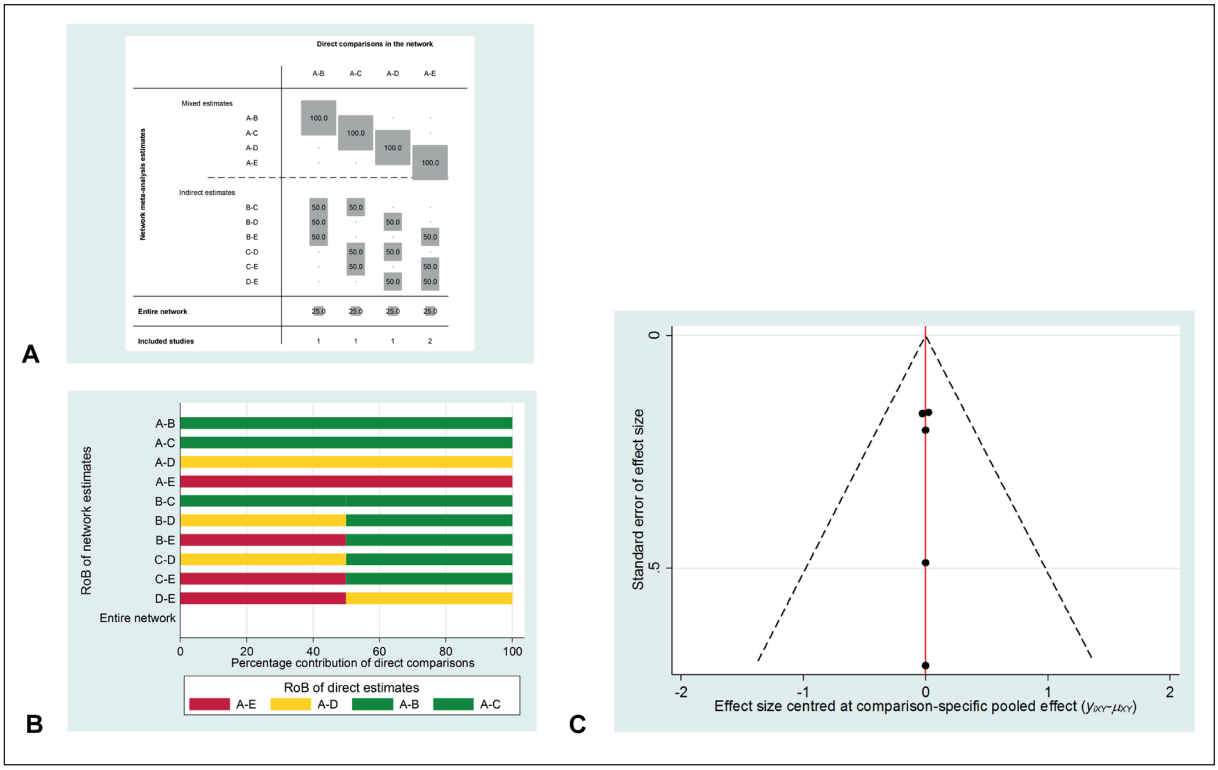
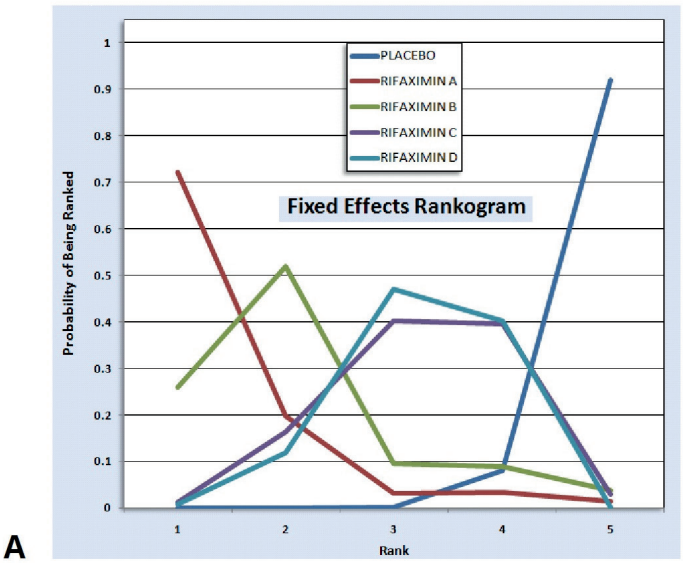


Figure 4. A, Contribution plot for the comparisons network. The numbers represent the percentage contribution of the column showing direct comparisons to the row defining network meta-analysis estimates. **B**, Bar graph depicting the risk of bias (RoB) for each network estimate. Green color = low RoB, Yellow color = unclear RoB, Red color = high RoB. **C**, Comparison-adjusted funnel plot.
Treatment labels: Rifaximin (**A**) = 400mg tds for 10 days, rifaximin (**B**) = 400mg bid for 10 days, rifaximin (**C**) = 550mg bid for 2 weeks and rifaximin (**D**) = 550mg tds for 2 weeks.

League table

RIFAXIMIN A				
1.69 (0.32 – 11.68)	RIFAXIMIN B			
2.75 (0.70 – 13.82)	1.61 (0.58 – 4.47)	RIFAXIMIN C		
2.75 (0.73 – 14.42)	1.60 (0.62 – 4.45)	1.00 (0.63 – 1.62)	RIFAXIMIN D	
4.05 (1.13 – 20.85)	2.38 (0.94 – 6.58)	1.49 (0.99 – 2.23)	1.48 (1.17 – 1.86)	PLACEBO

Figure 5. League table showing the comparative efficacies of rifaximin therapeutic interventions for irritable bowel syndrome (IBS) included in the randomized control trials (RCTs).
Treatment labels: Rifaximin (**A**) = 400mg tds for 10 days, rifaximin (**B**) = 400mg bid for 10 days, rifaximin (**C**) = 550mg bid for 2 weeks and rifaximin (**D**) = 550mg tds for 2 weeks.



Treatment	SUCRA
RIFAXIMIN A	0.8944
RIFAXIMIN B	0.7184
RIFAXIMIN C	0.4335
RIFAXIMIN D	0.4327
PLACEBO	0.021

B

Figure 6. A, Rankogram network for the rifaximin therapeutic interventions for irritable bowel syndrome (IBS) included in the randomized control trials (RCTs), showing the cumulative rank order for each intervention. **B**, SUCRA (surface under the cumulative ranking) values for the 5 therapeutic interventions.
Treatment labels: Rifaximin (**A**) = 400mg tds for 10 days, rifaximin (**B**) = 400mg bid for 10 days, rifaximin (**C**) = 550mg bid for 2 weeks and rifaximin (**D**) = 550mg tds for 2 weeks.

DISCUSSION

Rifaximin is a broad-spectrum antibiotic inhibiting the beta subunit of bacterial DNA-dependent RNA polymerase and therefore suppressing bacterial gene expression. This antibiotic is routinely used for the treatment of traveler's diarrhea and hepatic encephalopathy[24-26] and previous studies have reported significant improvement in IBS patient symptoms[27-28]. The significance of the gut microbiota in human inflammation and disease has attracted considerable international interest in recent decades[29,30]. There is evidence[31] that rifaximin can exert important eubiotic effects, producing a favorable gut microbiota perturbation without changing its overall composition and diversity.

Although the efficacy of rifaximin treatment for IBS has been demonstrated in various non-RCT studies, inconsistencies between studies have been noted concerning patient selection, clinical endpoints, and statistical analyses[32,33]. Therefore, RCTs in this field were necessary and indeed recently studies[13-15] examining the role of rifaximin in IBS have been published. However, in these studies different rifaximin regimens have been used and therefore the question of which is the optimal regimen needs an answer. One pair wise meta-analysis[16], showed the superiority of rifaximin in comparison to placebo, but did not address the above question.

In the present NWM we included all RCTs, investigating the therapeutic role of rifaximin for IBS. We examined IBS clinical outcomes at the end of the treatment and we showed that the overall symptom resolution was significantly greater in the rifaximin than in the placebo patients. In addition, the results showed that, among the various therapeutic doses used, rifaximin 400 mg tds for ten days was the most efficacious, in comparison to other rifaximin doses used, i.e., rifaximin 400 mg bid for ten days, rifaximin 550 mg bid for two weeks and rifaximin 555 mg tds for two weeks. We also examined whether rifaximin treatment was associated with a greater risk of adverse effects. In this regards, we found no significant difference in the risk of abdominal pain, nausea, vomiting, and headache between the rifaximin and placebo groups at the treatment endpoint demonstrating that rifaximin was well-tolerated.

The lack of significant inconsistency in this NWM strengthens our results. However, despite the messages which emerge concerning the effectiveness of rifaximin *vs.* placebo and optimal rifaximin dose in IBS, some limitations should be noted. The main limitation is related to the fact that the studies involved in this NWM were assessed as being of moderate quality when considering factors such as blindness and power. These might reflect some risk of bias through the overall appraisal of confidence in estimates. Other limitations are related to different protocols used in the included RCTs. All the above data highlight the need for well-designed RCTs to better define the efficacy and optimal dose of rifaximin in IBS patients. In addition, future RCTs are needed to study the effectiveness of long term and cyclical rifaximin administration in IBS.

CONCLUSIONS

The results of this NWM show that rifaximin plays a role in the therapeutic armamentarium for IBS and the optimal regimen is 400 mg tds for 10 days. This finding is expected to be taken into account when considering therapeutic options for IBS. However, since there are a number of questions still to be answered, well-designed RCTs are needed to ensure the efficacy, safety profile and optimal dose of rifaximin in IBS patients.

Conflicts of Interest:

The authors have declared no conflicts of interest.

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