**Article:**

**TITLE PAGE**

**Title:** Efficacy of Pharmacological Therapies in Patients with Irritable Bowel Syndrome with Diarrhoea or Mixed Stool Pattern: Systematic Review and Network Meta-analysis.

**Short running head:** Pharmacological Therapies for IBS-D or IBS-M: Network Meta-analysis.

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| **Abbreviations:** | $5\text{-HT}_3$ | 5-hydroxytryptamine-3 |
|---|---|---|
| | BSFS | Bristol stool form scale |
| | b.i.d. | twice-daily |
| | CI | confidence interval |
| | FDA | Food and Drug Administration |
| | IBS | irritable bowel syndrome |
| | IBS-C | irritable bowel syndrome with constipation |
| | IBS-M | irritable bowel syndrome with mixed stool pattern |
| | IBS-D | irritable bowel syndrome with diarrhoea |
| | o.d. | once-daily |
| | RCT | randomised controlled trial |
| | RR | relative risk |
| | t.i.d. | three times daily |

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## ABSTRACT

**Objective**: Over half of patients with irritable bowel syndrome (IBS) have either diarrhoea (IBS-D) or a mixed stool pattern (IBS-M). The relative efficacy of licensed pharmacological therapies is unclear in the absence of head-to-head trials. We conducted a network meta-analysis to resolve this uncertainty.

**Design:** We searched MEDLINE, EMBASE, EMBASE Classic, the Cochrane central register of controlled trials, and clinicaltrials.gov through January 2019 to identify randomised controlled trials (RCTs) assessing the efficacy of licensed pharmacological therapies (alosetron, eluxadoline, ramosetron, and rifaximin) in adults with IBS-D or IBS-M. Trials included in the analysis reported a dichotomous assessment of overall response to therapy, and data were pooled using a random effects model. Efficacy and safety of all pharmacological therapies were reported as a pooled relative risk with 95% CIs to summarise the effect of each comparison tested. Treatments were ranked according to their P-score.

**Results**: We identified 18 eligible RCTs (seven alosetron, five ramosetron, two rifaximin, four eluxadoline), containing 9844 patients. All were superior to placebo for the treatment of IBS-D or IBS-M at 12 weeks, according to the Food and Drug Administration (FDA)-recommended endpoint for trials in IBS. Alosetron 1mg twice-daily was ranked first for efficacy, based on the FDA-recommended composite endpoint of improvement in both abdominal pain and stool consistency, effect on global symptoms of IBS, and effect on stool consistency. Ramosetron 2.5mcg once-daily was ranked first for effect on abdominal pain. Total numbers of adverse events were significantly greater with alosetron 1mg twice-daily and ramosetron 2.5mcg, once-daily, compared with placebo. Rifaximin 550mg three times daily ranked first for safety. Constipation was significantly more common with all drugs, except rifaximin 550mg three times daily.

**Conclusion**: In a network meta-analysis of randomised controlled trials of pharmacological therapies for IBS-D and IBS-M, we found all drugs to be superior to placebo, but alosetron and ramosetron appeared to be the most effective.

**What is already known about this subject?**

Patients with irritable bowel syndrome (IBS) with diarrhoea (IBS-D) or IBS with mixed stool

pattern (IBS-M) have worse quality of life than those with IBS with constipation.

Up to one-third of these patients use loperamide, but there is little evidence for its efficacy,

and many patients report inadequate relief of symptoms.

Although there are several licensed pharmacological therapies for IBS-D and IBS-M, which

are often used as second-line therapy, their relative efficacy is unknown.


**What are the new findings?**

We identified 18 RCTs of pharmacological therapies in IBS-D and IBS-M, containing 9844

patients, with all drugs significantly more effective than placebo.

Alosetron 1mg twice-daily was ranked the most effective in our primary analysis, using the

Food and Drug Administration-recommended composite endpoint for trials in IBS.

Ramosetron 2.5mcg once-daily was ranked the most effective for improvement in abdominal

pain, and alosetron 1mg twice-daily was best for improvement in stool consistency.


**How might it impact on clinical practice in the near future?**

Antagonists of 5-hydroxytryptamine-3 (5-HT$_3$) receptors seem to perform best for the

symptoms of IBS-D and IBS-M.

These data suggest either access to existing, licensed 5-HT$_3$ antagonists should be improved,

or large trials of older 5-HT$_3$ antagonists, such as ondansetron, are required in patients with

IBS-D and IBS-M.

**INTRODUCTION**

Irritable bowel syndrome (IBS) affects 10% of people worldwide and is one of the most common functional bowel disorders. [1] The condition is characterised by abdominal pain, in association with defecation or a change in bowel habit. [2] IBS accounts for a considerable proportion of referrals to gastroenterology across both secondary and tertiary care settings and, in the US, is associated with annual direct costs of almost $1 billion, as well as another $50 million in indirect costs. [3] There is a substantial impact on quality of life for patients with active symptoms, [4] which is more pronounced for patients with IBS with diarrhoea (IBS-D) or IBS with mixed stool pattern (IBS-M), [5] who account for over 50% of people with IBS. [1] These patients often report a fear of incontinence due to loose stools and urgency, [6] and can therefore find working and socializing extremely challenging. [7] Although up to one-third of these patients use loperamide, [8] a μ-opioid agonist, as an anti-diarrhoeal agent, there is little evidence for its efficacy in IBS, [9] and many patients report inadequate relief of symptoms, other than diarrhoea, with the drug. [8] In addition, although other well-established treatments for IBS, such as anti-spasmodics or tricyclic antidepressants, may improve abdominal pain, [10, 11] many are not licensed for treatment of IBS.

Consequently, over the last 20 years, a number of other pharmacological therapies have been licensed for the treatment of IBS-D and IBS-M. Although they have different mechanisms of action, in clinical practice all these drugs tend to be utilised when first-line treatments have failed. Alosetron and ramosetron are both antagonists of the 5-hydroxytryptamine-3 (5-HT$_3$) receptor, an action that may serve to slow gastrointestinal transit, alter rectal compliance, [12, 13] and reduce visceral sensitivity. [14] Rifaximin is a minimally absorbed broad-spectrum antibiotic that has been tested in IBS-D and IBS-M, on the basis that alterations in gastrointestinal microbiota may, in part, be responsible for

symptoms. [15] Finally, eluxadoline is a peripherally acting mixed μ-and κ-opioid receptor agonist, and δ-opioid receptor antagonist, with minimal oral bioavailability, which reduces visceral hypersensitivity and slows gastrointestinal transit. [16]

High-quality placebo-controlled randomised controlled trials (RCTs) have confirmed that all of these licensed drugs are effective treatments for IBS-D and/or IBS-M, [9, 17, 18, 19, 20, 21] but there have been no head-to-head trials conducted to evaluate relative efficacy. As it is unlikely that any such trials will be performed, we have conducted a network meta-analysis to allow comparisons to be made between all of these drugs, as well as to enable ranking of treatments, in order to inform clinical decisions. This is similar to our recent exercise for drugs used to treat IBS with constipation (IBS-C). [22] The validity of such network meta-analyses can be undermined if there are differences in the design and endpoints used in individual RCTs. However, in this case, the efficacy of all these drugs has been assessed according to endpoints recommended currently for pharmacological therapies in IBS by the Food and Drug Administration (FDA). In addition, as many trials reported the efficacy of each of these drugs, in terms of their effect on individual symptoms, such as abdominal pain or stool consistency, relative efficacy for each drug according to each of these endpoints can also be assessed.

**METHODS**

**Search Strategy and Study Selection**

MEDLINE (1947 to January 2019), EMBASE, EMBASE Classic (1947 to January 2019), and the Cochrane central register of controlled trials were searched to identify potential studies. In addition, we searched clinicaltrials.gov for unpublished trials, or supplementary data for potentially eligible studies. In order to identify studies published only in abstract form, conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2019 were hand-searched. Finally, a recursive search was performed, using the bibliographies of all obtained articles.

Eligible RCTs examined the effect of licensed pharmacological therapies (alosetron, eluxadoline, ramosetron, or rifaximin) in adult patients (>18 years) with IBS-D or IBS-M (Supplementary Table 1). The first period of cross-over RCTs were eligible for inclusion if they provided efficacy data prior to cross-over. The definitions of IBS of interest included either a clinician's opinion, or meeting specific diagnostic criteria, for example the Rome criteria. Only RCTs that examined the efficacy of standard doses of the drugs of interest, and which compared them with each other, or with placebo, were considered eligible. A minimum follow-up duration of 12 weeks was required, in line with FDA recommendations for the design of treatment trials for functional gastrointestinal disorders. All endpoints were extracted at 12 weeks, even for RCTs providing efficacy data at other time points. This was done to ensure as much homogeneity as possible between individual trial results, and to avoid overestimating the efficacy of one drug relative to another, as the placebo effect tends to wane with time. [23] Studies had to report a dichotomous assessment of response to therapy.

First and senior authors of studies were contacted to provide additional information on
individual trials, where required.

Two investigators (CJB and ACF) conducted the literature search, independently from
each other. Studies on IBS were identified with the terms: *irritable bowel syndrome* and
*functional disease(s), colon* (both as medical subject headings and free text terms), and *IBS,
spastic colon, irritable colon,* or *functional* adj5 *bowel* (as free text terms). These were then
combined using the set operator AND with studies identified with the following terms:
*alosetron, Lotronex, eluxadoline, Viberzi, Truberzi*, *ramosetron, Irribow, rifaximin*, and
*Xifaxan* (all as free text terms).

There were no language restrictions. Two investigators (CJB and ACF) evaluated all
abstracts identified by the search for eligibility, again independently from each other. All
potentially relevant papers were obtained and evaluated in more detail, using pre-designed
forms, in order to assess eligibility independently, according to the pre-defined criteria.
Foreign language papers were translated, where required. Where multiple articles for a single
study were found, wherever possible we extracted data from the fully published article, but
used supplementary data concerning any other endpoints of interest from secondary
publications or clinicaltrials.gov, where applicable and relevant. Disagreements between
investigators were resolved by discussion.

**Outcome Assessment**

We assessed the efficacy of all drugs, compared with each other or with placebo, in
IBS-D and IBS-M in terms of failure to respond to therapy. The included eligible RCTs often
used different primary endpoints. However, some of the trials adhered to FDA-recommended
endpoints, and reported treatment efficacy according to a composite of improvement in both
abdominal pain and stool consistency, or we were able to obtain these data from the original

investigators. Three of the RCTs of alosetron also applied these criteria retrospectively to a subset of patients in the phase III studies. In addition, because individual trials reported efficacy according to several other secondary endpoints, we were able to assess the efficacy of therapies according to other dichotomous endpoints to define response to treatment. These included: a) relief of global IBS symptoms (global IBS symptom responder); b) relief of abdominal pain (abdominal pain responder); and c) improvement in stool consistency (stool consistency responder). Secondary outcomes included adverse events occurring as a result of therapy (overall numbers of adverse events, regardless of causality, as well as adverse events leading to study withdrawal, and individual adverse events, including constipation, headache, abdominal pain, or nausea).

**Data Extraction**

Two investigators (CJB and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (response or no response to therapy). For all included studies, the following data were also extracted for each trial, where available: country of origin, number of centres, criteria used to define IBS, subtype of IBS, proportion of female patients, and dose and duration of therapy. Data were extracted as intention-to-treat analyses, with dropouts assumed to be treatment failures (i.e. no response to therapy), using the total number of patients randomised to each treatment arm as the denominator, wherever trial reporting allowed. If this was not clear from the original article, we performed an analysis on all patients with reported evaluable data.

**Quality Assessment and Risk of Bias**

This was performed at the study level, by two investigators independently (CJB and ACF), using the Cochrane risk of bias tool. [24] Disagreements were resolved by discussion. The method used to generate the randomisation schedule and conceal treatment allocation was recorded, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

**Data Synthesis and Statistical Analysis**

We performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.4.2). This was reported according to the PRISMA extension statement for network meta-analyses, [25] in order to explore indirect treatment comparisons of the efficacy and safety of each medication. Network meta-analysis results usually give a more precise estimate, compared with results from standard, pairwise analyses, [26, 27] and can also rank treatments to inform clinical decisions. [28]

We examined the symmetry and geometry of the evidence by producing a network plot with node and connection size corresponding to the number of study subjects and number of studies respectively. We produced comparison adjusted funnel plots to explore publication bias or other small study effects, for all available comparisons versus placebo, using Stata version 14 (Stata Corp., College Station, TX, USA). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates the absence of publication bias, or small study effects. [29] We produced a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise the

effect of each comparison tested, using a random effects model as a conservative estimate. We used a RR of failure to achieve each of the endpoints of interest, where if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of the drug over placebo. As there were no direct comparisons between the active treatment groups, we were unable to perform consistency modelling to check the correlation between direct and indirect evidence. [30]

Global statistical heterogeneity across all comparisons was assessed using the $I^2$ measure from the "netmeta" statistical package. The $I^2$ measure ranges between 0% and 100%. Values of 25% to 49%, 50% to 74%, and ≥75% are typically considered low, moderate, and high levels of heterogeneity, respectively. [31] We ranked treatments according to their P-score, which is a value between 0 and 1. Higher scores indicate a greater probability of the treatment being ranked as best, [32] but the magnitude of the P-score should be considered, as well as the treatment rank. As the mean value of the P-score is always 0.5, if individual treatments cluster around this value they are likely to be of similar efficacy. However, when interpreting the results, it is also important to take the RR and corresponding 95% CIs for each comparison into account, rather than relying on rankings alone. [33] In our primary analysis we pooled data for the FDA-recommended composite endpoint to define treatment response, for all included RCTs that reported these data. We also performed analyses to assess the safety of each medication, including overall numbers of adverse events, and number of adverse events leading to study withdrawal, as well as individual adverse events.

The relative efficacies and safeties of therapies for all outcomes were compared using the "mvmeta" commands in Stata, and a random effects model. Treatments were ranked according to their surface under the cumulative ranking curve value, which is comparable to the P-score used in the frequentist model of our primary analyses. [32]

**RESULTS**

The search strategy generated 1879 citations, 58 of which appeared to be relevant and were retrieved for further assessment (Supplementary Figure 1). Of these, 40 were excluded for various reasons, leaving 18 eligible articles reporting on 18 separate trials, which contained a total of 9844 patients. [17, 18, 19, 20, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47] All trials were fully published, in English, with the exception of one RCT of eluxadoline, identified in abstract form. [47] There were seven RCTs of alosetron (1951 patients alosetron, 1583 placebo), [18, 34, 35, 36, 37, 38, 39] five trials of ramosetron (1015 patients ramosetron, 913 placebo), [19, 40, 41, 42, 43] two RCTs of rifaximin (625 patients rifaximin, 635 placebo), reported in one article, [17] and four RCTs of eluxadoline (1967 patients eluxadoline, 1155 placebo), reported in three articles. [20, 44, 47] A further two articles were also included because together they provided supplementary data, [45, 46] reporting efficacy according to FDA-recommended endpoints for alosetron in three phase III RCTs. [18, 34, 39] These two articles restricted their analyses to female patients who met criteria for severe IBS-D. In addition, the rifaximin trials did not report raw data for many of our analyses of interest in the original article, [17] but we obtained these data from the pharmaceutical company.

Agreement between investigators for trial eligibility was excellent (Kappa statistic = 0.80). Detailed characteristics of individual RCTs are provided in Table 1. Risk of bias for all included trials is reported in Supplementary Table 2. Ten trials, reported in eight articles, were at low risk of bias. [17, 18, 19, 20, 39, 42, 43, 44] No trials made head-to-head comparisons of one drug versus another, meaning that direct evidence was only available in comparison with placebo. As a result, active medications could only be compared with each other using an indirect evidence meta-analysis.

**Table 1. Characteristics of Randomised Controlled Trials of Pharmacological Therapies Versus Placebo in IBS-D or IBS-M.**

| Study | Country and Number of Centres | Diagnostic Criteria Used for IBS and Subtypes of IBS Recruited | Primary Endpoint Used to Define Symptom Improvement Following Therapy by the Original Investigators | Number of Patients (% female) | Number of Patients Assigned to Active Drug, Dosage, Schedule, and Duration of Therapy |
|---|---|---|---|---|---|
| **Camilleri 1999 [35]** | Multinational, 68 sites | Rome I criteria, 100% IBS-D or IBS-M | Adequate relief of pain and discomfort for ≥6 of the 12 weeks of therapy | 152 (44.1) | 72 patients received alosetron 1mg b.i.d.* for 12 weeks |
| **Camilleri 2000 [18]** | USA, 119 sites | Rome I criteria, 70.8% IBS-D, 27.8% IBS-M | Adequate relief of IBS pain and discomfort for ≥2 weeks per month for each of 3 months | 647 (100) | 324 patients received alosetron 1mg b.i.d. for 12 weeks |
| **Camilleri 2001 [34]** | USA, 104 sites | Rome I criteria, 71.2% IBS-D, 27.0% IBS-M | Adequate relief of IBS pain and discomfort for ≥2 weeks per month for each of 3 months | 626 (100) | 309 patients received alosetron 1mg b.i.d. for 12 weeks |
| **Lembo 2001 [38]** | USA, 180 sites | Rome II criteria, 97.8% IBS-D, 2.2% IBS-M | Substantial or moderate improvement in global IBS symptoms over the last 4 weeks of therapy | 801 (100) | 532 patients received alosetron 1mg b.i.d. for 12 weeks |
| **Chey 2004 [36]** | Multinational, 138 sites | Rome I criteria, 100% IBS-D† | Weekly adequate relief of IBS pain and discomfort at week 48 of treatment± | 569 (100) | 279 patients received alosetron 1mg b.i.d. for 48 weeks |

| | | | | | |
|---|---|---|---|---|---|
| **Chang 2005 [37]** | USA and Canada, 186 sites | Rome I criteria, 100% IBS-D | Adequate relief of IBS pain and discomfort for weeks 5 to 12 of treatment | 386 (0) | 127 patients received alosetron 0.5mg b.i.d. and 131 received alosetron 1mg b.i.d. for 12 weeks |
| **Krause 2007 [39]** | USA, number of sites not reported | Rome II criteria, 100% IBS-D | Moderate or substantial improvement in global IBS symptoms over the last 4 weeks of therapy | 353 (100) | 177 patients received alosetron 1mg b.i.d. for 12 weeks |
| **Matsueda 2008a [41]** | Japan, number of sites not reported | Rome II criteria, 100% IBS-D | Complete or considerable relief of global IBS symptoms for ≥2 of the last 4 weeks of therapy | 212 (27.3) | 103 patients received ramosetron 5mcg o.d.§ for 12 weeks |
| **Matsueda 2008b NCT00189696 [40]** | Japan, number of sites not reported | Rome II criteria, 100% IBS-D | Complete or considerable relief of global IBS symptoms for ≥2 of the last 4 weeks of therapy | 539 (17.9) | 270 patients received ramosetron 5mcg o.d. for 12 weeks |
| **Fukudo 2014 NCT01225237 [42]** | Japan, 52 sites | Rome III criteria, 100% IBS-D | A weekly mean BSFS¶ score of ≥3 to ≤5 and a decrease of ≥1 point in mean BSFS score from baseline for ≥2 of the first 4 weeks of therapy± | 296 (0) | 147 patients received ramosetron 5mcg o.d. for 12 weeks |

| | | | | | |
|---|---|---|---|---|---|
| **Fukudo 2016** NCT01870895 [19] | Japan, 70 sites | Rome III criteria, 100% IBS-D | Complete or considerable relief of global IBS symptoms for ≥2 of the last 4 weeks of therapy | 576 (100) | 292 patients received ramosetron 2.5mcg o.d. for 12 weeks |
| **Fukudo 2017** NCT01274000 [43] | Japan, 61 sites | Rome III criteria, 100% IBS-D | Complete or considerable relief of global IBS symptoms for ≥2 of the last 4 weeks of therapy | 305 (100) | 104 and 99 patients received ramosetron 2.5mcg or 5mcg o.d. respectively for 12 weeks |
| **Pimentel 2011a (Target 1)** NCT00731679 [17] | USA and Canada, 179 sites | Rome II criteria, 100% IBS-D or IBS-M | Adequate relief of global IBS symptoms for ≥2 of the first 4 weeks after therapy± | 623 (73.4) | 309 patients received rifaximin 550mg t.i.d.‡ for 2 weeks |
| **Pimentel 2011b (Target 2)** NCT00724126 [17] | USA and Canada, 179 sites | Rome II criteria, 100% IBS-D or IBS-M | Adequate relief of global IBS symptoms for ≥2 of the first 4 weeks after therapy± | 637 (71.2) | 316 patients received rifaximin 550mg t.i.d. for 2 weeks |
| **Dove 2013** NCT01130272 [44] | USA, 263 sites | Rome III criteria, 100% IBS-D | ≥30% reduction in worst abdominal pain score and at least 2 points, and a daily BSFS score of 3 or 4 on ≥66% of daily diary entries at week 4± | 348 (69.3) | 176 patients received eluxadoline 100mg b.i.d. for 12 weeks |
| **Lembo 2016a (IBS-3001)** NCT01553591 [20] | USA, Canada and UK, 295 sites | Rome III criteria, 100% IBS-D | ≥30% reduction in worst abdominal pain score on ≥50% of days and, on the same days, a daily BSFS score of <5 at week 12 | 1282 (65.4) | 429 and 426 patients received eluxadoline 75mg or 100mg b.i.d. respectively for 26 weeks |

| Lembo 2016b (IBS-3002) NCT01553747 [20] | USA, Canada and UK, 261 sites | Rome III criteria, 100% IBS-D | ≥30% reduction in worst abdominal pain score on ≥50% of days and, on the same days, a daily BSFS score of <5 at week 12 | 1146 (67.0) | 381 and 383 patients received eluxadoline 75mg or 100mg b.i.d. respectively for 26 weeks |
|---|---|---|---|---|---|
| Brenner 2018 (RELIEF) NCT02959983 [47] | USA and Canada, number of sites not reported | Rome III criteria, 100% IBS-D | ≥40% reduction in worst abdominal pain score on ≥50% of days and a daily BSFS score of <5 at week 12 | 346 (69.9) | 172 patients received eluxadoline 100mg b.i.d. for 12 weeks |

* b.i.d.; twice-daily

†Also recruited patients with IBS-M, but data were only extractable for those with IBS-D at 12 weeks

±Efficacy data were extracted at 12 weeks for the purpose of this analysis

§o.d.; once-daily

¶BSFS; Bristol stool form scale

‡t.i.d.; three times daily

**Efficacy**

*Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response*

Ten RCTs, reported in seven separate articles, provided dichotomous data for failure to achieve the FDA-recommended composite endpoint at 12 weeks, based on an improvement in abdominal pain and stool consistency. [17, 19, 20, 44, 45, 46, 47] Two of the articles, between them, provided sufficient information to enable a *post hoc* analysis of three of the phase III RCTs of alosetron, which reported efficacy according to FDA-recommended endpoints only in women with severe IBS-D. [45, 46]

These 10 trials included a total of 5517 patients, 3156 of whom were randomised to active treatment, and 2361 to placebo. The network plot is provided in Supplementary Figure 2. When data were pooled there was no global statistical heterogeneity ($I^2 = 2.3\%$), and no evidence of publication bias, or other small study effects (Supplementary Figure 3). All treatments were significantly more effective than placebo, but alosetron 1mg b.i.d. was ranked as the most effective (P-score 0.97), in three RCTs (RR 0.69; 95% CI 0.60 to 0.80) (Figure 1). This means that the probability of alosetron being the most effective when all treatments, including placebo, were compared with each other was 97%. After indirect comparison of active treatments, significant differences were seen with alosetron 1mg b.i.d., compared with all other treatments except ramosetron 2.5mcg o.d. (Table 2).

*Failure to Achieve a Global IBS Symptom Response*

When dichotomous data were pooled for failure to achieve relief of global symptoms of IBS, there were 13 RCTs, reported in 11 articles, recruiting 7464 patients. [17, 19, 20, 38, 39, 40, 41, 42, 43, 44, 47] Of these, 4316 were randomised to active treatment and 3148 to placebo. When data were pooled there was moderate global statistical heterogeneity ($I^2 =$

**Table 2. League Table for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**

| Alosetron 1mg b.i.d. | | | | | |
|---|---|---|---|---|---|
| 0.89 (0.72; 1.10) | Ramosetron 2.5mcg o.d. | | | | |
| 0.80 (0.69; 0.93) | 0.90 (0.77; 1.05) | Eluxadoline 100mg b.i.d. | | | |
| 0.78 (0.67; 0.91) | 0.88 (0.75; 1.03) | 0.98 (0.91; 1.05) | Eluxadoline 75mg b.i.d. | | |
| 0.75 (0.64; 0.89) | 0.85 (0.72; 1.00) | 0.94 (0.87; 1.02) | 0.97 (0.89; 1.05) | Rifaximin 550mg b.i.d. | |
| 0.69 (0.60; 0.80) | 0.78 (0.67; 0.91) | 0.87 (0.83; 0.91) | 0.89 (0.84; 0.94) | 0.92 (0.86; 0.98) | Placebo |

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered

relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects.

Boxes shaded green denote a statistically significant difference.

67.4%), which was driven by the trials of alosetron 1mg b.i.d. The comparison adjusted

funnel plot for publication bias, or other small study effects, showed no asymmetry around

the zero line (Supplementary Figure 4). All treatments were significantly more effective than

placebo, with the exception of rifaximin 550mg t.i.d., but alosetron 1mg b.i.d. was ranked as

the most effective (P-score 0.96), in two RCTs (RR 0.62; 95% CI 0.51 to 0.76) (Figure 2).

After indirect comparison of active treatments, significant differences were seen with

alosetron 1mg b.i.d. compared with rifaximin 550mg t.i.d. (Table 3).

*Failure to Achieve an Abdominal Pain Response*

There were 17 trials recruiting 9043 patients, reported in 15 separate articles, [17, 18,

19, 20, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 47] that reported dichotomous data for failure to

achieve an abdominal pain response. There were 5026 patients assigned to active therapy,

and 4017 allocated to placebo. When data were pooled there was no global statistical

heterogeneity ($I^2 = 0\%$), and no evidence of publication bias, or other small study effects

(Supplementary Figure 5). Ramosetron 2.5mcg o.d., ramosetron 5mcg o.d., alosetron 1mg

b.i.d., and eluxadoline 100mg b.i.d. were all significantly more effective than placebo.

Overall, ramosetron 2.5mcg o.d. was ranked as the most effective treatment (P-score 0.94), in

two RCTs (RR 0.75; 95% CI 0.65 to 0.85) (Figure 3). On indirect comparison of active

treatments, significant differences were seen with ramosetron 2.5mcg o.d. compared with

eluxadoline 75mg b.i.d., eluxadoline 100mg b.i.d., and rifaximin 550mg t.i.d., as well as for

ramosetron 5mcg o.d. compared with eluxadoline 75mg b.i.d. and rifaximin 550mg t.i.d.

Significant differences were also seen for alosetron 1mg b.i.d. compared with eluxadoline

75mg b.i.d. and rifaximin 550mg t.i.d. (Supplementary Table 3).

**Table 3. League Table for Failure to Achieve a Global IBS Symptom Response.**

| Alosetron 1mg b.i.d. | | | | | | |
|---|---|---|---|---|---|---|
| 0.84 (0.63; 1.12) | Ramosetron 2.5mcg o.d. | | | | | |
| 0.82 (0.65; 1.04) | 0.97 (0.76; 1.24) | Ramosetron 5mcg o.d. | | | | |
| 0.80 (0.63; 1.02) | 0.95 (0.74; 1.22) | 0.98 (0.80; 1.19) | Eluxadoline 100mg b.i.d. | | | |
| 0.77 (0.59; 1.00) | 0.91 (0.69; 1.19) | 0.93 (0.74; 1.18) | 0.96 (0.76; 1.21) | Eluxadoline 75mg b.i.d. | | |
| 0.69 (0.53; 0.89) | 0.81 (0.63; 1.06) | 0.84 (0.68; 1.04) | 0.86 (0.69; 1.07) | 0.90 (0.70; 1.15) | Rifaximin 550mg t.i.d. | |
| 0.62 (0.51; 0.76) | 0.74 (0.60; 0.91) | 0.76 (0.66; 0.88) | 0.78 (0.68; 0.90) | 0.81 (0.68; 0.98) | 0.91 (0.77; 1.07) | Placebo |

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered

relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects.

Boxes shaded green denote a statistically significant difference.

*Failure to Achieve a Stool Consistency Response*

Twelve RCTs reported dichotomous data for failure to achieve a stool consistency response, and these were reported in 10 separate articles, and included 6663 patients. [17, 19, 20, 39, 40, 41, 42, 43, 44, 47] There were 3784 patients assigned to active therapy, and 2879 to placebo. When data were pooled, there was no global statistical heterogeneity ($I^2 =$ 18.4%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Supplementary Figure 6). All treatments were significantly more effective than placebo, but alosetron 1mg b.i.d. ranked as the most effective treatment (P-score 0.93), although in only one RCT (RR 0.70; 95% CI 0.60 to 0.81) (Figure 4). After indirect comparison of active treatments, significant differences were seen with alosetron 1mg b.i.d., compared with eluxadoline 75mg b.i.d. and eluxadoline 100mg b.i.d. (Supplementary Table 4).

**Safety**

Sixteen trials, recruiting 9134 patients and reported in 14 articles, [17, 18, 19, 20, 34, 37, 38, 39, 40, 41, 42, 43, 44, 47] provided data for overall adverse events. There was moderate global statistical heterogeneity ($I^2 = 64.2$%), but no evidence of publication bias, or other small study effects (Supplementary Figure 7). Heterogeneity was driven by the trials of alosetron 1mg b.i.d. and ramosetron 5mcg o.d. When comparing pooled overall adverse events, alosetron 1mg b.i.d. (five RCTs, RR = 1.24; 95% CI 1.09 to 1.41), and ramosetron 2.5mcg o.d. (two RCTs, RR = 1.27; 95% CI 1.01 to 1.60) were associated with a significant increase in overall adverse events, compared with placebo (Supplementary Figure 8). When ranked using a P-score, rifaximin 550mg t.i.d. was the best, and ramosetron 2.5mcg o.d. the worst, in terms of overall adverse events (P-scores 0.80 and

0.18 respectively). Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages.

Adverse events leading to dropout were provided by 15 trials, reported in 13 papers. [17, 19, 20, 34, 35, 38, 39, 40, 41, 42, 43, 44, 47] Eluxadoline 75mg b.i.d. (two RCTs, RR = 1.88; 95% CI 1.25 to 2.81), eluxadoline 100mg b.i.d. (four RCTs, RR = 1.88; 95% CI 1.31 to 2.70), and alosetron 1mg b.i.d. (four RCTs, RR = 1.97; 95% CI 1.48 to 2.63) were all associated with significantly higher trial dropout rates due to adverse events, compared with placebo. When ranked using a P-score, ramosetron 2.5mcg o.d. was the best, and alosetron 1mg b.i.d. the worst, in terms of adverse events leading to dropout (P-scores 0.92 and 0.16 respectively). On indirect comparison of active treatments, significant differences were seen with ramosetron 2.5mcg o.d. compared with eluxadoline 100mg b.i.d., eluxadoline 75mg b.i.d., and alosetron 1mg b.i.d. Individual adverse events data are provided in the Supplementary Materials.

**DISCUSSION**

It is widely accepted that the licensed pharmacological therapies studied in this systematic review and network meta-analysis are more effective than placebo for the treatment of IBS-D and IBS-M. Using the FDA-recommended composite endpoint, although all drugs were more effective than placebo, alosetron 1mg b.i.d. ranked first, according to the available evidence. The probability of alosetron being superior to another competing treatment, according to this endpoint, was 97%, which exceeds the 90% to 95% threshold that the available literature suggests is desirable. [32] Alosetron 1mg b.i.d. continued to be ranked first when efficacy was assessed in terms of improvement in global IBS symptoms and stool consistency. Ramosetron 2.5mcg and 5mcg o.d. were ranked first and second when effect on abdominal pain was studied. Rifaximin 550mg t.i.d. was no better than placebo for global IBS symptoms, and rifaximin 550mg t.i.d., alosetron 0.5mg b.i.d., and eluxadoline 75mg b.i.d. were no more effective than placebo for abdominal pain. Alosetron 1mg b.i.d. and ramosetron 2.5mcg o.d. were both associated with a significant increase in overall adverse events, compared with placebo. Constipation was significantly more likely with all drugs, except rifaximin 550mg t.i.d., which ranked first for safety overall. The latter observation may be consistent with the observation that rifaximin may actually accelerate colonic transit, [48] and improve symptoms of IBS-C. [49] Finally, more patients reported abdominal pain as an adverse event with eluxadoline and alosetron than with placebo, although whether this is due to the fluctuating natural history of IBS, an associated feature of drug-induced constipation, or a specific adverse event associated with both drugs is unclear.

We undertook a contemporaneous and exhaustive literature search. This was conducted independently by two reviewers, and included searching conference proceedings, the "grey" literature, and clinicaltrials.gov. Assessment of eligibility and data

extraction was also performed independently, and in duplicate. We subsequently contacted

the authors of two trials of rifaximin, [17] and one trial of eluxadoline, [47] in order to

obtain the necessary data for our analyses, as these were not available in the original

papers. This inclusive approach enabled us to analyse data from 18 RCTs of

pharmacological therapies for IBS-D and IBS-M, recruiting almost 10,000 patients, with

data extracted at 12 weeks for all endpoints. We used an intention-to-treat analysis and

pooled data using a random effects model to minimise the risk that the efficacy of the drugs

studied would be overestimated. Finally, we extracted and pooled adverse events, where

reported, in order to provide summary safety data.

We did not identify any head-to-head studies of one drug versus another, meaning

that all our analyses were based on indirect comparisons, which are not protected by

randomisation. This could lead to confounding due to underlying differences between

individual RCTs, [50] although our use of very similar endpoints to define efficacy after 12

weeks of treatment in all trials should minimise this. However, this means that the relative

efficacy and safety of these drugs in the longer term are unknown. In addition, eight of the

18 trials were at unclear risk of bias, [34, 35, 36, 37, 38, 40, 41, 47] which may mean the

efficacy of some of the drugs has been overestimated. [51] It is likely that these

deficiencies represent omissions of reporting, rather than true design flaws, given the

oversight of national regulatory agencies for many of the included trials. There were

moderate levels of global statistical heterogeneity in the analysis using an improvement in

global IBS symptoms to define treatment response, and for total adverse events, but no

heterogeneity in any of our other analyses. It is important to point out that, as in most trials

of pharmacological therapies in IBS, adverse events were not reported according to

standardised endpoints, unlike efficacy data, which may mean making comparisons

between individual treatments is less valid. Finally, there may have been subtle differences

in symptom severity among the populations studied in each of these trials, which mean the results are not directly comparable. However, this should have been minimised, as 16 of the trials used similar combinations of a minimum abdominal pain threshold and a minimum stool consistency threshold, during a run-in period, to confirm eligibility prior to study entry. Among the remaining two RCTs, one did not report these data, as it was in abstract form, [47] and one used a minimum urgency threshold. [38]

Ranking of these pharmacological therapies provides useful information to aid clinical decision making, but it is important to acknowledge that not all of these drugs are available in all countries or, indeed, to all patients with IBS-D or IBS-M. Alosetron was withdrawn in the US because of adverse events, including ischemic colitis and severe constipation. It was re-introduced, via a risk evaluation and mitigation strategy, for women with severe IBS-D. In the first 9 years after re-introduction, 29 cases of probable ischemic colitis were reported; an incidence of 1 case per 1000 patient-years. [52] This is similar to the background rate of ischemic colitis in female patients with IBS, which ranges from 0.40 cases/1000 patient-years to 1.79 cases/1000 patient-years. [53] Whether alosetron is effective in men with IBS-D is unclear, as only one RCT recruited solely men, [37] and participants in the remaining trials were either predominantly, or exclusively, women. However, cilansetron, another 5-HT$_3$ receptor antagonist, appeared to be effective in both men and women with IBS-D. [21] Although ramosetron can be prescribed for men with IBS-D, as well as women, it is only licensed in Japan and some other South, and South-East, Asian countries, at a dose of 2.5mcg o.d. in women and 5mcg o.d. in men. However, three of the trials conducted using 5mcg o.d. recruited women. [40, 41, 43] If this dose was either not as effective or less well-tolerated in women, one would have expected this to have diluted efficacy, or led to more adverse events, yet 5mcg o.d. was ranked second for

its effect on both abdominal pain and stool consistency, and was by no means the lowest

ranked drug in terms of safety.

Although both alosetron and ramosetron appeared to perform the best in this

network meta-analysis, many patients with IBS will be unable to access these drugs. Two

recent RCTs of ondansetron, another 5-HT$_3$ receptor antagonist, which is widely available

and has a robust safety profile, suggest that this drug is also of benefit in IBS. [54, 55]

Neither of these trials were eligible for inclusion in our network, as the drug is not licensed

for IBS, one trial was a cross-over RCT with a treatment duration of 10 weeks, [54] and the

other was a parallel arm trial of only 8 weeks duration. [55] However, a 12-week trial is in

progress in the UK. [56] Another issue is that all of the RCTs of ramosetron were

conducted in Japan, and the majority of the trials of alosetron, eluxadoline, and rifaximin in

North American populations, so the findings may not be generalisable to individuals with

IBS-D or IBS-M in other countries.

Because these studies span the last 20 years of clinical practice, during which time

the Rome criteria for IBS have undergone multiple revisions, [2, 57, 58, 59] there are

variations between individual trial populations, in terms of how the diagnosis of IBS was

determined. The majority of the alosetron trials and the earlier ramosetron RCTs used the

Rome I or II criteria, [57, 59] which are arguably less restrictive than the Rome III criteria,

[58] used in later trials of ramosetron, and all studies of rifaximin and eluxadoline.

However, agreement between these criteria for the diagnosis of IBS is good, [60] and such

differences are mitigated against, to some extent, by our ability to compare all drugs using

the standardised FDA-recommended endpoint for trials in IBS-D. It is important to

highlight that, because these endpoints had not been agreed at the time some of the earlier

drug trials were conducted, the data for alosetron are based entirely on a *post hoc* analysis

of three trials. [45, 46] Around 50% of patients in these trials were absent from the

analysis, because they failed to meet the updated FDA-recommended symptom thresholds for inclusion in an IBS treatment trial. This may mean that the efficacy of alosetron has been overestimated for this endpoint, although as only patients with severe IBS-D were included in this analysis, we feel this is unlikely. In addition, the strength of the P-score for alosetron, together with the absence of global statistical heterogeneity, suggests that the treatment ranking we report is likely to be accurate.

All of the drugs considered in this network meta-analysis are likely to be prescribed as second-line therapy, after failure of anti-diarrhoeal and anti-spasmodic drugs. It would therefore be important to understand how they perform relative to these first-line therapies, particularly as loperamide is available over the counter in many countries, and has evidence of short-term efficacy for reducing diarrhoea. [9] Unfortunately, there are few trials examining this issue. One RCT demonstrated that 12 weeks of alosetron 1mg b.i.d. was superior to mebeverine 135mg t.i.d., in terms of adequate relief of abdominal pain, in a mixed population of patients with IBS of all subtypes, [61] but a trial of 4 weeks of ramosetron 5mcg o.d. versus mebeverine 135mg t.i.d. demonstrated no significant differences. [62]

There have also been no head-to-head trials of these drugs against other second-line therapies, such as tricyclic antidepressants. Additionally, there are no RCTs of tricyclic antidepressants, or other pharmacological therapies used off-license for IBS, that have been conducted solely in patients with IBS-D or IBS-M over 12 weeks reporting identical endpoints to the ones used in these trials, [9] and which could therefore have been included in this network meta-analysis. Another RCT has compared 24 weeks of alosetron 1mg b.i.d. with traditional pharmacotherapy, which in some patients consisted of tricyclic antidepressants, in almost 2000 female patients with severe IBS-D. [63] In this trial, treatment with alosetron 1mg b.i.d. resulted in significantly greater relief of global IBS

symptoms. There were also significant reductions in number of visits to see a physician for IBS, use of over the counter medications, and days of lost work productivity. However, this beneficial effect was accompanied by non-serious constipation, occurring in one-third of patients, compared with constipation in <1% of those allocated to traditional pharmacotherapy. Initiating alosetron at a dose of 0.5mg b.i.d., and increasing the dose subsequently if there is inadequate clinical improvement, as is currently recommended, may minimise this. Finally, the two large, phase III trials of eluxadoline have reported efficacy of the drug in a subset of patients who had previously failed loperamide, [20] with similar efficacy demonstrated in this *post hoc* analysis. [8] The most recent RCT of eluxadoline we identified had recruited only patients with IBS-D who reported, subjectively, that they had previously failed loperamide, again with similar results. [47]

Given the lack of head-to-head trials, performing a network meta-analysis could be criticised, because all our conclusions are derived from data based on indirect treatment comparisons. However, as we have discussed previously, [22, 64] it is unlikely that pharmaceutical companies will ever conduct such studies, or even undertake a trial of one of these drugs against an anti-diarrhoeal or tricyclic antidepressant. Network meta-analyses circumvent this problem to some extent, allowing credible ranking systems of the likely efficacy and safety of different treatments to be developed, even in the absence of trials making direct comparisons. The results of our study are therefore still likely to be important for both patients and policy makers, in order to help inform treatment decisions for IBS-D and IBS-M.

In summary, although all drugs were superior to placebo, according to the FDA-recommended composite endpoint for trials in IBS, alosetron 1mg b.i.d. ranked first in terms of efficacy in our network meta-analysis. It was also the top ranked treatment when either global relief of symptoms or improvement in stool consistency were used to define

treatment response, but ramosetron 2.5mcg o.d. was ranked first in terms of improving abdominal pain. With regard to safety, rifaximin 550mg t.i.d. was least likely to cause adverse events, and was the only drug that did not significantly increase the risk of constipation. However, it demonstrated relatively poor efficacy across many of the treatment endpoints we studied. Eluxadoline 100mg b.i.d., meanwhile, was significantly better than placebo across all endpoints, but its overall performance was modest. This information will hopefully assist clinicians in choosing a second-line treatment for IBS-D, and to a lesser extent IBS-M, based on the patient's most troublesome symptom, considering both efficacy and safety. Alosetron and ramosetron remain unavailable in many countries. Given the chronic and frequently debilitating nature of IBS, this lack of availability may need to be reconsidered, in order to widen access to potentially effective second-line treatments for those patients with IBS-D or IBS-M when conventional first-line therapies fail.

## ACKNOWLEDGEMENTS

## CONFLICTS OF INTEREST/STUDY SUPPORT

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**FIGURE LEGENDS**

**Figure 1. Forest Plot of the Indirect Evidence for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Figure 2. Forest Plot of the Indirect Evidence for Failure to Achieve a Global IBS Symptom Response.**

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Figure 3. Forest Plot of the Indirect Evidence for Failure to Achieve an Abdominal Pain Response.**

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Figure 4. Forest Plot of the Indirect Evidence for Failure to Achieve a Stool Consistency Response.**

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.