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TITLE PAGE

Title: Efficacy of Soluble Fibre, Antispasmodics, and Gut-brain Neuromodulators in Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis.

Short running head: Network Meta-analysis of Fibre, Antispasmodics, and Gut-brain Neuromodulators Therapies for IBS.

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Abbreviations:

5-HT	5-hydroxytryptamine
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-D	irritable bowel syndrome with diarrhoea
IBS-M	irritable bowel syndrome with mixed stool pattern
MeSH	medical subject heading
o.d.	once daily
q.i.d.	four times daily
RCT	randomised controlled trial
RR	relative risk
SSRI	selective serotonin reuptake inhibitor
t.i.d.	three times daily
TCA	tricyclic antidepressant

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SUMMARY

Background: Although novel therapies for irritable bowel syndrome (IBS) continue to be developed, many doctors rely on more established, "traditional" therapies as first or second-line treatment. These include ispaghula husk, antispasmodic drugs, peppermint oil, and gut-brain neuromodulators (including tricyclic antidepressants, selective serotonin reuptake inhibitors, or alpha-2-delta ligand agents). However, their relative efficacy is unclear because there have been few head-to-head randomised controlled trials (RCTs). The majority of trials compare active therapy with placebo. We conducted a network meta-analysis to compare their efficacy in patients with IBS.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials from inception through to week 2 of August 2019 to identify RCTs assessing the efficacy of all of these therapies in adults with IBS. Trials included in the analysis reported a dichotomous assessment of overall response to therapy, in terms of either improvement in global symptoms, or improvement in abdominal pain. Data were pooled using a random effects model. Efficacy and safety of all treatments were reported as a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise the effect of each comparison tested, and treatments were ranked according to their P-score.

Findings: We identified 51 eligible RCTs, containing 4644 patients. Only 13 trials were at low risk of bias. Based on an endpoint of failure to achieve an improvement in global symptoms, peppermint oil capsules were ranked first at 4 to 12 weeks (RR 0.63; 95% CI 0.48 to 0.83, P-score = 0.84), with tricyclic antidepressants ranked second (RR 0.66; 95% CI 0.53 to 0.83, P-score = 0.77). For failure to achieve an improvement in global symptoms, there were no significant differences between treatments after direct or indirect comparison. When failure to achieve an improvement in abdominal pain was used, tricyclic antidepressants were ranked first (RR 0.53; 95% CI 0.34 to 0.84, P-score = 0.87), although based on only four

trials recruiting 92 patients. For failure to achieve an improvement in abdominal pain, none of the treatments were superior to each other on indirect comparison. Tricyclic antidepressants were more likely than placebo to lead to adverse events.

Interpretation: In a network analysis of RCTs of soluble fibre, antispasmodics, including peppermint oil, and gut-brain neuromodulators for IBS, few of which were judged as being at low risk of bias, peppermint oil appeared to be ranked first for efficacy when global symptoms were used as the outcome measure, and tricyclic antidepressants when abdominal pain was used. However, methodological quality of the included trials means that there is likely to be considerable uncertainty around these estimates and, because treatment duration in most trials was 4 to 12 weeks, the long term relative efficacy of these drugs is unknown.

Funding: None.

RESEARCH IN CONTEXT

Evidence before this study

Irritable bowel syndrome (IBS) is one of the most common functional bowel disorders. Over the last 20 years numerous novel drugs have been developed targeted at receptors and/or putative mechanisms considered relevant to IBS pathophysiology. However, these can be expensive, and some have been withdrawn, or are prescribed rarely, due to safety concerns. Prior meta-analyses, based on randomised controlled trials (RCTs), demonstrated that more traditional treatments including ispaghula husk, antispasmodic drugs, peppermint oil, and gut-brain neuromodulators, were more efficacious than placebo in IBS. However, a comprehensive search of the medical literature using MEDLINE, EMBASE, and EMBASE Classic revealed only three head-to-head RCTs; most trials compared active drug with placebo. The relative efficacy of these treatments is therefore unclear.

Added value of this study

Network meta-analysis is a technique that allows head-to-head comparison of individual treatments across a single disease, even where no trials making direct comparison of one treatment versus another exist. We performed a network meta-analysis of RCTs reporting the effect of ispaghula husk, antispasmodic drugs, peppermint oil, and gut-brain neuromodulators in IBS. The results of the study should allow clinicians to select treatments in IBS based on their relative efficacy, in terms of both improvement in global IBS symptoms, and improvement in abdominal pain, as well as to consider safety.

Implications of all the available evidence

Methodological quality of the included trials means that there is likely to be considerable uncertainty around our estimates. In addition, most trials recruited patients with IBS, regardless of predominant stool form, and all data were extracted at 4 to 12 weeks of therapy, so the longer term efficacy of these treatments is unknown. Finally, safety data were not reported in detail. Our study demonstrates that more RCTs of these treatments are required. Future trials should administer treatment over a longer duration (12 weeks), ideally head-to-head against one or more of the other therapies studied in this network meta-analysis, determine efficacy according to IBS subtype, based on predominant stool form, and report adverse events data more thoroughly.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional bowel disorders, with a global prevalence that averaged 11% in a meta-analysis of community-based studies from around the world; (1) it should be noted that the prevalence is lower using the latest iteration of the Rome criteria, at around 6%. (2) The condition is chronic and fluctuating, running a relapsing and remitting course. (3) The cardinal symptoms are recurrent abdominal pain, related to defaecation, in association with a change in either stool form or frequency. IBS accounts for approximately 10% of a gastroenterologist's time in the outpatient clinic, (4) and represents a substantial financial burden to society, (5) due to direct costs of consultations, investigations, and prescribed drugs, as well as indirect costs arising from sickness-related absence from employment and reduced productivity in the workplace. (6)

The aetiology of IBS is complex and incompletely understood, (7) meaning that current treatment is symptom-directed, rather than based on underlying pathophysiological mechanisms. To this end, the current classification system for IBS, the Rome IV criteria, (8) sub-divides patients according to the predominant reported stool pattern; constipation (IBS-C), diarrhoea (IBS-D), mixed stool pattern (IBS-M), or unclassified. Over the last 20 years, the majority of novel drugs have been directed against specific stool patterns, and we have summarised the relative efficacy of these drugs in previous network meta-analyses. (9-11) However, these newer drugs tend to be expensive, and some have either been withdrawn or their use restricted, due to safety concerns, or their availability in the USA and Europe is limited.

The secretagogue lubiprostone was withdrawn from the UK for marketing reasons, due to poor sales. Drugs acting on 5-hydroxytryptamine (5-HT) receptors, such as tegaserod and alosetron were initially withdrawn due to safety concerns, including cardiovascular and

cerebrovascular ischaemic events with the former, and ischaemic colitis with the latter, although they can now be prescribed on a restricted basis in the USA. Ramosetron, another 5-HT receptor antagonist, is only available for the treatment of IBS-D in Japan. There have been cases of acute pancreatitis and sphincter of Oddi dysfunction with eluxadoline, which is a mixed opioid receptor drug available for the treatment of IBS-D in the USA. Finally, the minimally absorbed antibiotic rifaximin, which is licensed for the treatment of IBS-D in the USA, has not received European Medicines Agency approval.

In usual clinical practice, physicians may therefore have to rely on treatments that are viewed as being more "traditional" as first or second-line therapy for IBS. Such treatments include soluble fibre, such as ispaghula husk, antispasmodic drugs, including peppermint oil, and centrally acting gut-brain neuromodulators. There have been numerous randomised controlled trials (RCTs) of these treatments published, but the majority of these trials pre-date the move towards subdividing patients with IBS according to predominant stool pattern. As a result, we did not include any of these treatments in our two recent network meta-analyses in patients with IBS-C, (10) or IBS-D and IBS-M. (9) Although their efficacy has been summarised in several previous meta-analyses, (12-18) their relative efficacy is unknown, as there have been few head-to-head trials. Head-to-head trials would be expensive to conduct, because they need extremely large numbers of patients in order to demonstrate superiority of one drug over another, given the relatively small size of their therapeutic gain over placebo in some RCTs. It is therefore unlikely that any such trials will be performed in the future. We conducted a network meta-analysis to allow comparisons to be made between all of these treatments, as well as to enable their ranking, in order to inform clinical decisions.

METHODS

Search Strategy and Selection Criteria

We searched MEDLINE (1946 to week 2 August 2019), EMBASE and EMBASE Classic (1947 to August 2019), and the Cochrane central register of controlled trials 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, we hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2019. Finally, we performed a recursive search, using the bibliographies of all obtained articles.

Randomised controlled trials examining the effect of ispaghula husk, antispasmodic drugs, peppermint oil, or gut-brain neuromodulators in adult patients (>18 years) with IBS of any subtype were eligible (Supplementary Table 1, appendix page 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 considered within this network meta-analysis included either a clinician's opinion, or those that met specific symptom-based criteria, for example the Rome criteria. Trials that examined the efficacy of any dose of the drugs of interest, and which compared them with each other, or with placebo, were considered eligible. A minimum treatment duration of 4 weeks, and a maximum duration of 12 weeks, was required. The Food and Drug Administration (FDA) recommend a minimum treatment duration of 12 weeks in treatment trials conducted in functional gastrointestinal disorders. However, many of the RCTs of the therapies of interest were conducted before this guidance, so we extracted data at the point of completion of therapy in all included trials. Studies had to report a dichotomous

assessment of response to therapy. We contacted first and senior authors of studies 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 diseases, colon (both as medical subject heading (MeSH) and free text terms), and IBS, spastic colon, irritable colon, and functional adj5 bowel (as free text terms). For RCTs of ispaghula, antispasmodics, and peppermint oil, these were combined using the set operator AND with studies identified with the terms: dietary fibre, psyllium, parasympatholytics, scopolamine derivatives, scopolamine hydrobromide, trimebutine, muscarinic antagonists, butylscopolammonium bromide, Menthol, Menthol or piperita (both as MeSH and free text terms), or the following free text terms: bulking agent, psyllium fibre, fibre, fiber, husk, ispaghula, metamucil, fybogel, spasmolytics, spasmolytic agents, antispasmodics, antispasmodic agents, mebeverine, alverine, pinaverium, otilonium, octilonium, cimetropium, hyoscine, hyoscine butyl bromide, butylscopolamine, drotaverine, dicyclomine, dicycloverine, propinox, rociverine, pirenzepine, prifinium, peppermint oil, peppermint, mintec, or colpermin. For RCTs of gut-brain neuromodulators these were combined using the set operator AND with studies identified with the terms: psychotropic drugs, antidepressive agents, antidepressive agents (tricyclic), desipramine, imipramine, trimipramine, doxepin, dothiepin, nortriptyline, amitriptyline, serotonin uptake inhibitors, paroxetine, sertraline, fluoxetine, citalopram, pregabalin, gabapentin, or duloxetine (both as MeSH terms and free text terms), or the following free text terms: antidepressants, selective serotonin re-uptake inhibitors, selective serotonin reuptake inhibitors, serotonin re-uptake inhibitors, serotonin reuptake inhibitors, desimipramine, venlafaxine, efexor, prozac, or seroxat.

There were no language restrictions. Two investigators (CJB and ACF) evaluated all abstracts identified by the search for eligibility, again independently from each other. We

obtained all potentially relevant papers and evaluated them in more detail, using pre-designed forms, in order to assess eligibility independently, according to the pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators (CJB and ACF) by discussion.

We assessed the efficacy of all therapies in IBS, compared with each other or with placebo, in terms of failure to respond to therapy, with the endpoints of interest used to define response reported below. We sub-grouped gut-brain neuromodulators into RCTs of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or alpha-2-delta ligand agents. Secondary outcomes included adverse events occurring as a result of therapy (total numbers of adverse events, as well as adverse events leading to study withdrawal, and individual adverse events, including diarrhoea, constipation, drowsiness, headache, abdominal pain, or nausea, if reported).

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). We assessed efficacy according to the following: a) the proportion of patients failing to achieve an improvement in global symptoms of IBS; and b) the proportion failing to achieve an improvement in abdominal pain. We also extracted the following data for each trial, where available: country of origin, setting (primary, secondary, or tertiary care), diagnostic criteria used to define IBS, proportion of patients with IBS of each subtype, proportion of female patients, and dose and duration of therapy. We extracted data as intention-to-treat analyses, with dropouts assumed to be treatment failures (i.e. no response to therapy), wherever trial reporting allowed. If this was not clear from the original article, we performed an analysis on all patients with reported evaluable data.

We used the Cochrane risk of bias tool (19) to assess this at the study level. Two

investigators (CJB and ACF) performed this independently; we resolved disagreements by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, 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 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, (20) in order to explore direct and 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, (21, 22) and can rank treatments to inform clinical decisions. (23)

We examined the symmetry and geometry of the evidence by producing a network plot with node size corresponding to the number of study subjects, and connection size corresponding to the number of studies. 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. (24) 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 one treatment over another, or over placebo. As there were direct comparisons between some of the treatments for some of the endpoints of interest, we were able to perform consistency modelling to check the correlation between direct and indirect evidence. (25)

We assessed global statistical heterogeneity across all comparisons 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 considered low, moderate, and high levels of heterogeneity, respectively. (26) We assessed inconsistency in the network analysis by comparing direct and indirect evidence, where available, by producing a network heat plot. (25, 27) These plots have grey squares, which represent the size of the contribution of the direct estimate in columns, compared with the network estimate in rows. (27) The coloured squares, around these, represent the degree of inconsistency, with red squares indicating "hotspots" of inconsistency. In order to investigate sources of potential inconsistency, we planned to remove studies that introduced any red "hotspots", and repeat the analyses.

We ranked treatments according to their P-score, which is a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates, and measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. (28) Higher scores indicate a greater probability of the treatment being ranked as best, (28) 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. We performed two sensitivity analyses. First, given the multiple proposed mechanisms of action of the various antispasmodic drugs under study, we performed an analysis with these subcategorised into those drugs acting purely as antimuscarinic agents (including cimetropium, hyoscine,

pirenzipine, rociverine, and trimebutine), and those acting in other ways (including alverine, drotaverine, mebeverine, otilonium, pinaverium, and propinox). Second, due to previous concerns in the literature about non-Western IBS trials, including their methodology and placebo response rates, (29) we conducted an analysis with only Western RCTs included.

Role of the funding source

No funding was received. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Trial Assessment and Risk of Bias

The search strategy generated 5863 citations, 81 of which appeared to be relevant to the systematic review and were retrieved for further assessment (Figure 1). Of these, we excluded 30 for various reasons, leaving 51 eligible articles, which contained 4644 patients, allocated to active therapy or placebo as described in Supplementary Table 2, appendix page 2. (30-80) Agreement between investigators for trial eligibility was excellent (kappa statistic = 0.84). Detailed characteristics of individual RCTs are provided in Table 1. All trials, except one, (48) were published in full.

Risk of bias for all included trials is reported in Supplementary Table 3, appendix pages 3 to 6; only 13 were at low risk of bias. (30, 35, 57, 59-61, 66, 70, 73-75, 77, 80) There were five trials of ispaghula husk versus placebo; (30-34) only one was at low risk of bias. (30) There were 18 RCTs of antispasmodic drugs, (35-52) with only one trial judged as low risk of bias. (35) There were eight trials of peppermint oil; (53-60) three were low risk of bias. (57, 59, 60) There were 10 RCTs of TCAs, (61-70) and three were low risk of bias. (61, 66, 70) There were six trials of SSRIs; (71-76) three were low risk of bias. (73-75) There was one trial of alpha-2-delta ligand agents, (77) which was judged as low risk of bias. There were another three trials making head-to-head comparisons of one therapy versus another; one of ispaghula husk or an antispasmodic drug versus placebo, (78) one of ispaghula husk, an antispasmodic drug, or a TCA versus placebo, (79) and one of a TCA or a SSRI versus placebo. (80) Only one of these trials was at low risk of bias. (80) We were therefore able to compare some therapies using both direct and indirect evidence meta-analysis. Of the 18 trials of TCAs and SSRIs, (61-76, 79, 80) five screened for, and excluded, patients with depression. (61, 66, 74-76)

Efficacy

Failure to Achieve an Improvement in Global IBS Symptoms

Forty RCTs, including 3793 patients, reported these data at 4 to 12 weeks. (31-35, 37-39, 41-47, 49-51, 53, 55, 56, 58-66, 68, 70, 72, 74-80) There were 2016 (53%) patients randomised to active treatment. The network plot is provided in Figure 2. When data were pooled there were moderate levels of statistical heterogeneity (I^2 = 60.5%). On visual inspection, there was evidence of funnel plot asymmetry, suggesting publication bias, or other small study effects (Supplementary Figure 1, appendix page 7). However, this was due to a dearth of small studies showing positive results, rather than small studies showing no effect of the interventions studied. The network heat plot had no red "hotspots" of inconsistency (Supplementary Figure 2, appendix page 8). Peppermint oil, TCAs, and antispasmodic drugs were all significantly more efficacious than placebo after 4 weeks to 12 weeks of treatment, but peppermint oil was ranked as the most efficacious, relative to placebo (P-score 0.84), in six RCTs (RR = 0.63; 95% CI 0.48 to 0.83) (Figure 3a). This means that the probability of peppermint oil being the most efficacious when all treatments, including placebo, were compared with each other was 84%. However, TCAs were ranked second and performed similarly (P-score 0.77, RR = 0.66; 95% CI 0.53 to 0.83). Two of the six trials of peppermint oil were at low risk of bias, (59, 60) compared with four of the nine RCTs of TCAs. (61, 66, 70, 80) After direct or indirect comparison of active treatments, there were no significant differences seen between individual treatments (Figure 4a).

After sensitivity analysis according to type of antispasmodic drug, moderate heterogeneity between studies remained (I^2 = 60.9%), and peppermint oil was still ranked first (P-score 0.83), TCAs second, and antimuscarinic-type antispasmodic drugs third (Supplementary Figure 3, appendix page 9), with no significant differences seen between

individual treatments on direct or indirect comparison. Similarly, in a sensitivity analysis restricted to Western RCTs, there was moderate heterogeneity (I^2 = 65.6%), and peppermint oil was still ranked first (P-score 0.84), but TCAs were second with an almost identical RR and P-score, and antispasmodic drugs third (Supplementary Figure 4, appendix page 10), with no significant differences between individual treatments seen on direct or indirect comparisons.

Failure to Achieve an Improvement in Abdominal Pain

Twenty-five trials reported these data at 4 to 12 weeks. (30, 32, 35, 36, 38-40, 43, 46, 48, 49, 52, 54, 57, 59, 60, 62, 67-69, 71-73, 75, 76) There were 2247 patients, 1157 (51.5%) of whom were randomised to active treatment. The network plot is provided in Figure 5. When data were pooled there were moderate levels of statistical heterogeneity (I^2 = 69.7%), but no evidence of publication bias, or other small study effects (Supplementary Figure 5, appendix page 11). As there were no head-to-head trials using abdominal pain as an endpoint we could not assess for evidence of inconsistency between direct and indirect results. TCAs, peppermint oil, and antispasmodic drugs were significantly more efficacious than placebo at 4 to 12 weeks. TCAs were ranked as the most efficacious (P-score 0.87) in four RCTs (RR = 0.53; 95% CI 0.34 to 0.83) (Figure 3b), but containing only 92 patients, with antispasmodic drugs ranked second, and peppermint oil third. None of the trials of TCAs were at low risk of bias, but three of the RCTs of peppermint oil were. (57, 59, 60) After indirect comparison of active treatments, there were no significant differences seen between any of the active treatments (Figure 4b).

Sensitivity analysis according to type of antispasmodic drug revealed moderate heterogeneity between studies (I^2 = 59.3%), with “other” antispasmodic drugs ranked first (P-score 0.93), and TCAs second (Supplementary Figure 6, appendix page 12). Antimuscarinic-

type antispasmodic drugs were no longer more efficacious than placebo, and were ranked last. However, this was driven mainly by two RCTs of drotaverine conducted in India, which demonstrated a 35% to 45% therapeutic gain over placebo. (48, 52) "Other" antispasmodic drugs were superior to all treatments except TCAs and peppermint oil, and TCAs were superior to antimuscarinic-type antispasmodic drugs on indirect comparison. When the analysis was restricted to Western RCTs, there was borderline moderate heterogeneity (I^2 = 51.7%), with peppermint oil ranked first (P-score 0.77), TCAs second, and antispasmodic drugs third (Supplementary Figure 7, appendix page 13). However, none of the treatments was superior to placebo in this analysis, and there were no significant differences between individual treatments on indirect comparison.

Safety

Thirty-two trials reported total number of adverse events in 3307 patients, 1666 (50%) of whom received active treatment. (30, 32, 35-42, 44-46, 48, 49, 51, 52, 54-59, 61, 64-66, 68, 69, 73, 75, 77) There was no global statistical heterogeneity (I^2 = 0%), and no evidence of publication bias, or other small study effects (Supplementary Figure 8, appendix page 14). When comparing total numbers of adverse events, there was a significant difference, compared with placebo, for TCAs (RR = 1.59; 95% CI 1.23 to 2.06). When ranked using a P-score, ispaghula husk was the best, and TCAs the worst, in terms of total number of adverse events (P-scores 0.65 and 0.16 respectively) (Supplementary Figure 9, appendix page 15). Indirect comparison of active treatments revealed that ispaghula husk (RR =0.71; 95% CI 0.51 to 0.98) was significantly less likely than TCAs to lead to adverse events, but there were no other significant differences.

Data concerning withdrawals due to adverse events were provided by 22 RCTs, containing 2007 patients, 1037 (52%) of whom were assigned to active therapy. (32, 38, 44-

46, 50, 52, 55, 56, 59, 60, 62, 64, 66, 68, 69, 71, 73-77) There was no statistical heterogeneity (I^2 = 0%), and no evidence of publication bias, or other small study effects (Supplementary Figure 10, appendix page 16). None of the therapies were more likely to lead to withdrawal due to adverse events than placebo. When ranked using a P-score, ispaghula husk was the best, and peppermint oil the worst, in terms of adverse events leading to withdrawal (P-scores 0.68 and 0.23 respectively) (Supplementary Figure 11, appendix page 17), although 95% CIs were wide for some of these estimates, and P-scores were similar for many of the lower ranked therapies. There were no significant differences between therapies on indirect comparison. Individual adverse events were reported incompletely by included trials, precluding any meaningful pooling of data.

DISCUSSION

To our knowledge, this is the first systematic review and network meta-analysis of RCTs of these treatments for IBS. When we used improvement in global symptoms as the endpoint of interest, peppermint oil, TCAs, and antispasmodic drugs were all significantly more efficacious than placebo after 4 weeks to 12 weeks of treatment, but peppermint oil was ranked first. However, there were no significant differences seen between treatments. When we used improvement in abdominal pain as the endpoint of interest, TCAs, antispasmodic drugs, and peppermint oil were significantly more efficacious than placebo at 4 to 12 weeks, with TCAs ranked first. Again, there were no significant differences between individual treatments. However, the sensitivity analysis conducted using Western RCTs revealed that TCAs were no longer the most efficacious, in terms of improvement in abdominal pain. Only TCAs were more likely to lead to adverse events than placebo and, among active treatments, only ispaghula husk was significantly less likely than TCAs to lead to adverse events. None of the therapies studied were more likely to lead to withdrawal due to adverse events than placebo. Data for individual adverse events were limited, precluding meaningful analysis.

The literature search, eligibility assessment, and data extraction for this network meta-analysis were undertaken independently by two reviewers, with any discrepancies resolved by consensus. We used an intention-to-treat analysis, with all dropouts assumed to have failed therapy, and pooled data with a random effects model, in order to reduce the likelihood that any beneficial effect of these therapies in IBS has been overestimated. We also contacted authors of individual studies to obtain supplementary data for their studies in order to maximise the number of eligible RCTs in the network.

There are some limitations of this study. Because a substantial proportion of the 51 RCTs were conducted more than 20 years ago, only 13 were at low risk of bias. (30, 35, 57, 59-61, 66, 70, 73-75, 77, 80) This means the results of the network meta-analysis should be

interpreted with caution. It is well known that trials that do not report their methodology in sufficient detail tend to overestimate the efficacy of the intervention studied. (81) For some of the therapies studied in this network meta-analysis there is also the possibility of unblinding, even in trials judged to be at low risk of bias, due to the nature of the active intervention used. Peppermint oil has a distinctive taste, and both TCAs and antispasmodic drugs can lead to dry mouth, drowsiness, and constipation. It also needs to be emphasised that the positive studies on peppermint oil involved very specific preparations and formulations. Given the regulatory category assigned to peppermint oil in many jurisdictions, as a medical food or food supplement, many other preparations are available for direct public sale to the public. The results of the studies reported here are as positive therefore cannot, therefore, be extrapolated to all peppermint oil preparations. In addition, the majority of trials predate recommendations from the Rome committee for the design of treatment trials for the functional gastrointestinal disorders, (82) and most did not use FDA-recommended endpoints to judge treatment efficacy in IBS. The included trials, therefore, used a wide range of measures of treatment efficacy, and reported these at various different time points, rather than at 12 weeks, as is currently recommended. Most trials recruited patients with IBS, regardless of predominant stool form; as a result making recommendations for the selection of treatment in individual patients is difficult. Finally, only six trials were conducted either entirely, or partly, in primary care, (30, 46, 59, 60, 66, 74) meaning that the relative efficacy of these drugs in patients in this setting, which is the group in whom they are most likely to be used, is unclear.

Whether the benefit of antidepressants arises from the treatment of co-existent depression is controversial. Data from the trials included in this network meta-analysis are conflicting; three studies reported no significant relationship between depression scores and improvement in IBS symptoms, (68, 72, 73) but a fourth demonstrated that treatment effect with the TCA desipramine was greater in those without co-existent depression. (70) Among

the five trials that screened for, and excluded, depressed individuals, (61, 66, 74-76) one RCT of the SSRI citalopram showed no benefit of the drug in IBS. (74) The dose of the various SSRIs used in these trials in IBS were almost identical to those used to treat depression, but any effect on mood would seem less likely for TCA trials, where the doses used were often considerably lower than those used to treat depression. Interestingly, other investigators have shown that the presence of depression seems to modify central pain response in patients with IBS. (83) This suggests that if antidepressants are improving mood in patients with IBS this could have other beneficial effects on gastrointestinal symptoms.

Although peppermint oil and TCAs were ranked highly for efficacy for both endpoints studied in these trials, the number of included participants was small in comparison with RCTs of newer drugs in IBS. Hence, there is need for considerable caution in the assessment of the efficacy of these more "traditional" therapies, in particular the gut-brain neuromodulators, which may be associated with significant adverse effects and appeared to be of lower efficacy than peppermint oil for both global symptoms and abdominal pain when the analysis was restricted to only Western trials. For global symptoms, peppermint oil was ranked first based on data from six trials, allocating 342 patients to active therapy, and TCAs second pooling data from nine trials, randomising 355 patients to active therapy. For abdominal pain, TCAs were ranked first when data were pooled from four RCTs, including only 92 patients randomised to active therapy, and peppermint oil second based on four RCTs, containing 260 patients who received active therapy. The limitations of our current assessment are demonstrated by the comparison with other network meta-analyses in this field. Thus, in contrast, in a recent network meta-analysis of RCTs of secretagogues in IBS-C, almost 5000 patients were assigned to active therapy and contributed data to the analysis for global symptom response, and more than 4000 for abdominal pain. (10) Similarly, in another network meta-analysis of RCTs of drugs for IBS-D and IBS-M, almost 4500 patients

assigned to active therapy contributed data to the analysis for global symptom response, and more than 5000 to the analysis for abdominal pain. (9) This highlights the need for larger RCTs of these commonly used therapies in patients with IBS, in order estimate their efficacy more precisely. Ideally, these should be conducted in primary care settings, where these treatments are most likely to be used, report efficacy according to predominant stool type, and examine safety more systematically than the eligible trials we were able to identify.

The effect sizes seen in this network meta-analysis were much larger than in our network meta-analyses of treatments for IBS-C, IBS-D, and IBS-M, (9, 10) but the 95% CIs were wide. Clearly, direct comparisons of efficacy between the therapies studied here and these, more recently developed, novel drugs based on the results of these three network meta-analyses is inappropriate. However, the larger, and less precise, effect sizes seen in the current study are likely to reflect a combination of the less stringent endpoints used to judge efficacy in these older trials, risk of bias of the included RCTs, and the shorter treatment duration in many of the included trials. Only two trials, one of pinaverium and one of peppermint oil, used an FDA-recommended endpoint to judge treatment efficacy, (35, 60) although another four of the included RCTs used adequate relief of symptoms, (30, 74, 77, 80) which was the previous gold standard to define treatment success in IBS treatment trials. (84) In addition, it is likely that the RCTs considered in this network meta-analysis recruited a spectrum of patients with milder symptoms than those involved in studies of newer pharmacological therapies; patients recruited into trials of the latter agents in the last 15 years are likely to have already failed treatment with one or more of the therapies assessed in this network meta-analysis. However, head-to-head trials of newer drugs compared with these commonly used therapies are scarce. One 12-week trial of alosetron versus mebeverine demonstrated that alosetron was superior in terms of adequate relief of abdominal pain and

discomfort, (85) but another 4-week RCT of ramosetron versus mebeverine suggested no significant difference between the two in terms of adequate relief of global symptoms. (86)

Given the scarcity of head-to-head trials of individual therapies, the conclusions in this network meta-analysis are derived from data based mainly on indirect treatment comparisons of trials that are not as methodologically rigorous as those included in our other recent network meta-analyses. (9, 10) Network meta-analysis allows credible ranking systems of the likely efficacy and safety of different treatments to be developed in order to inform clinical decisions, even in the absence of trials making direct comparisons. (23) Therefore, despite these limitations, the results of our study may still be useful for both patients and policy makers, in order to help inform first and second-line treatment decisions for IBS. The information contained in this network meta-analysis should also allow evidence-based recommendations for the management of IBS to be updated. (87, 88)

In summary, this systematic review and network meta-analysis has demonstrated that peppermint oil, TCAs, and antispasmodic drugs were more efficacious than placebo for both global symptoms and abdominal pain in IBS, with peppermint oil ranked first for global symptoms, and TCAs first for abdominal pain using data from all trials, and second to peppermint oil based on Western RCTs only. Only TCAs were more likely to cause adverse events than placebo, which is in keeping with their known side effect profile. Although this information may assist clinicians and patients with IBS in making therapy-related choices, it is important to point out that the quality of the evidence was low, due to the risk of bias of included trials, and the endpoints used to judge efficacy were less stringent than those used in RCTs of newer drugs. In addition, despite the fact that many of these therapies are likely to be used as first or second-line treatment in primary care, and before referral to a gastroenterologist, the majority of trials were conducted in referral populations, and did not report efficacy according to predominant stool type. More RCTs of these treatments, ideally

head-to-head against one or more of the other therapies studied in these trials, which are powered adequately, conducted in primary care, examine efficacy according to stool type, and report adverse events data more thoroughly are required.

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AUTHORS CONTRIBUTIONS

CJB, YY, CPS, MC, EMMQ, PM, and ACF conceived and drafted the study. CJB, PM, YY, CPS, and ACF collected all data. CJB, PM, and ACF analysed and interpreted the data. CJB and ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

Christopher J. Black: none. Yuhong Yuan: none. Christian P. Selinger: has acted as a consultant for Abbvie, Dr. Falk, Eily Lilly, Fresenius Kabi, Janssen, Pfizer, and Roche and received research funding from Abbvie and Takeda, which are outside the submitted work. Michael Camilleri: has received research funding from Allergan, Novartis, and Takeda, which are outside the submitted work. Eamonn M.M. Quigley: has acted as a consultant for Alimentary Health, Biocodex, Ironwood, Salix, and Vibrant, and received research funding from 4D Pharma, Vibrant and Zealand, which are outside the submitted work. Paul Moayyedi: None. Alexander C. Ford: has acted as a consultant for, and received research funding from, Almirall, which are outside the submitted work.

ETHICS COMMITTEE APPROVAL

Not required.

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FIGURES

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.

Figure 2. Network Plot for Failure to Achieve an Improvement in Global IBS Symptoms at 4 to 12 Weeks.

Node size (size of the circle) corresponds to the number of study subjects for each intervention, and connection size (line thickness) corresponds to the number of studies for each comparison.

Figure 3a. Forest Plot for Failure to Achieve an Improvement in Global IBS Symptoms at 4 to 12 Weeks.

Note: The P-score is the probability of each treatment being ranked as best in the network.

Figure 3b. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain at 4 to 12 Weeks.

Note: The P-score is the probability of each treatment being ranked as best in the network.

Figure 4a. League Ranking for Failure to Achieve an Improvement in Global IBS Symptoms at 4 to 12 Weeks.

Figure 4b. League Ranking for Failure to Achieve an Improvement in Abdominal Pain at 4 to 12 Weeks.

Figure 5. Network Plot for Failure to Achieve an Improvement in Abdominal Pain at 4 to 12 Weeks.

Node size (size of the circle) corresponds to the number of study subjects for each intervention, and connection size (line thickness) corresponds to the number of studies for each comparison.