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SYSTEMATIC REVIEWS AND META-ANALYSES

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Systematic Review and Meta-analysis: Efficacy of Mesalamine in Irritable Bowel Syndrome

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BACKGROUND & AIMS: **Some patients with irritable bowel syndrome (IBS) demonstrate low-grade inflammation in the intestine. Mesalamine, which has anti-inflammatory effects, may be an efficacious treatment for IBS, but studies are conflicting. We conducted a systematic review and meta-analysis to assess efficacy and safety of mesalamine in IBS.**

METHODS: **We searched the medical literature up to September 14, 2022, to identify randomized controlled trials (RCTs) of mesalamine in IBS. We judged efficacy and safety using dichotomous assessments of effect on global IBS symptoms, abdominal pain, bowel habit or stool frequency, and occurrence of any adverse event. We pooled data using a random effects model, with efficacy and safety reported as pooled relative risks (RRs) with 95% confidence intervals (CIs).**

RESULTS: **We identified 8 eligible RCTs (820 patients). Mesalamine was more efficacious than placebo for global IBS symptoms (RR of global symptoms not improving, 0.86; 95% CI, 0.79–0.95; number needed to treat = 10; 95% CI, 6-27), but not for abdominal pain or bowel habit or stool frequency. Subgroup analyses demonstrated efficacy of mesalamine in IBS with diarrhea for global IBS symptoms (RR, 0.88; 95% CI, 0.79–0.99), but not patients with other predominant bowel habits or those with post-infection IBS. Adverse event rates were no higher with mesalamine (RR, 1.20; 95% CI, 0.89–1.63) but were reported in only 5 trials.**

CONCLUSIONS: **Mesalamine may be modestly efficacious for global symptoms in IBS, particularly IBS with diarrhea, but quality of evidence was low. Adequately powered high quality RCTs of mesalamine in IBS are needed.**

Keywords: Efficacy; Irritable Bowel Syndrome; Mesalamine; RCT Comparison.

Irritable bowel syndrome (IBS) is a chronic relapsing and remitting functional bowel disorder affecting between 4% and 10% of the general population,[1,2] and characterized by recurrent abdominal pain in association with abnormal bowel frequency and/or consistency.[3] Due to its high prevalence, IBS confers a substantial economic burden on the health care system and society,[4] estimated at between £1.3 and £2 billion per year in a recent United Kingdom study.[5] There are also considerable indirect costs associated with the condition, relating to its negative effects on work productivity and social functioning,[6] with an estimated 180 million hours of work lost per year due to IBS in the United Kingdom.[7] The impact on quality of life of IBS is similar to organic gastrointestinal diseases, such as Crohn's disease.[8]

Although in most people the cause of IBS is unknown,[9] approximately 1 in 10 people will identify an antecedent episode of acute gastroenteritis as the trigger,[10] termed post-infection IBS. Some studies have revealed that, among people with post-infection IBS, there is evidence of prolonged immune activation.[11–13] However, other investigators have demonstrated such abnormalities even among patients with IBS without a post-infection etiology.[14] These include increased levels of pro-inflammatory cytokines,[15] and higher numbers of

Abbreviations used in this paper: **CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; NNH, number needed to harm; NNT, number needed to treat; RCT, randomized controlled trial; RR, relative risk; SD, standard deviation.**

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lymphocytes and mast cells,[16–19] the latter in close proximity to enteric nerve fibers in the gastrointestinal mucosa of these individuals.

Taken together, these findings have led others to investigate the efficacy of anti-inflammatory drugs in IBS. A prior randomized controlled trial (RCT) of prednisolone versus placebo in post-infection IBS demonstrated no effect of active drug on individual or total symptom scores, or any clear effects on markers of immune activation.[20] There have also been RCTs of mesalamine, a 5-aminosalicylate, which is efficacious in ulcerative colitis,[21,22] in unselected patients with IBS, as well as only patients with both post-infection IBS, or only patients with IBS with diarrhea (IBS-D). These have demonstrated conflicting results.[23–27] A meta-analysis of some of these trials, conducted as part of the publication of a recent trial of mesalamine, reported that there was no benefit of the drug in IBS.[28] However, the meta-analysis only pooled mean symptom scores, rather than the proportion of patients in each trial experiencing an improvement in symptoms, and did not appear to include data from all available RCTs. In addition, no analyses were conducted according to IBS subtype or post-infection status. We, therefore, conducted a contemporaneous meta-analysis to examine the efficacy and safety of mesalamine in IBS addressing these deficits in knowledge.

What You Need To Know

Background

Some patients with irritable bowel syndrome (IBS) demonstrate low-grade inflammation in the intestine. Mesalamine, which has anti-inflammatory effects, may be an efficacious treatment, but studies are conflicting.

Findings

Meta-analysis suggests mesalamine may be modestly efficacious for global symptoms in IBS, particularly IBS with diarrhea. The relative risk of global symptoms persisting with mesalamine vs placebo was 0.86 (95% confidence interval, 0.79–0.95).

Implications for patient care

Mesalamine may be efficacious in IBS. Larger trials recruiting only patients with IBS with diarrhea are warranted. Estimates provided by this meta-analysis could inform power calculations for these trials.

Methods

Search Strategy and Selection Criteria

We searched MEDLINE (1946 to September 14, 2022), EMBASE and EMBASE Classic (1947 to September 14, 2022), and the Cochrane central register of controlled trials, as well as clinicaltrials.gov for unpublished trials or supplementary data for potentially eligible RCTs. To identify trials published only as abstracts, we searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week). Finally, we performed a recursive search using the bibliographies of all obtained articles.

RCTs examining the effect of mesalamine versus placebo in adults (≥18 years) with IBS of any subtype were eligible (Supplementary Table 1). The first period of cross-over RCTs were also eligible if efficacy data were provided prior to cross-over. We considered definitions of IBS including either a clinician's opinion or specific symptom-based criteria, for example the Rome criteria. We required a 4-week minimum treatment duration.

Two investigators (VCG and ACF) conducted the literature search, independently from each other. We identified studies on IBS with the terms: *irritable bowel syndrome* or *functional diseases, colon* (both as medical subject heading and free text terms), or *IBS*, *spastic colon*, *irritable colon*, or *functional* adj5 *bowel* (as free text terms). We combined these using the set operator AND with studies identified with the terms: *mesalamine* or *aminosalicylic acid* (both as MeSH terms and free text terms), or the following free text terms: *mesalazine*, *pentasa*, *octasa*, *ipocol*, *asacol*, *salofalk*, *MMX*, *5-ASA*, *5ASA*, *5-aminosalicylic$*, *5-aminosalicylate$*, *5aminosalicylic$*, or *5aminosalicylate$*. We did not apply language restrictions. Two investigators (VCG and ACF) evaluated all identified abstracts for eligibility, again independently from each other. We obtained all potentially relevant papers and evaluated them in more detail against our eligibility criteria, using pre-designed forms. We translated foreign language papers, where required. We resolved any disagreements by discussion.

Outcome Assessment

We assessed efficacy of mesalamine in IBS, compared with placebo, in terms of failure to respond to therapy, according to the proportion of patients failing to achieve an improvement in global IBS symptoms, abdominal pain, or bowel habit or stool frequency at trial completion as our primary outcomes. Total number of people experiencing any adverse event was a secondary outcome.

Data Extraction

Two investigators (VCG and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA) as dichotomous outcomes (global IBS symptoms improved or not improved, abdominal pain improved or not

improved, bowel habit or stool frequency improved or not improved). Where studies reported a dichotomous assessment of response to therapy according to these endpoints, for example satisfactory relief of global IBS symptoms or a ≥30% improvement in abdominal pain severity (approximating United States Food and Drug Administration-recommended endpoints in drug trials in IBS), we extracted these data from the article. For studies reporting mean symptom scores at baseline together with follow-up mean symptom scores and standard deviation (SD) for this endpoint for each intervention arm, we imputed dichotomous responder and non-responder data using methodology previously described by Furukawa et al.[29,30] A ≥30% improvement in symptoms is derived from the formula: number of participants in each treatment arm at final follow-up × normal standard distribution, the latter corresponding to (70% of the baseline mean score – follow-up mean score) / follow-up SD. We contacted first and senior authors of studies to provide additional data for individual trials, where required.

Finally, we extracted the following data for each trial, where available: country of origin, number of centers, setting (primary, secondary, or tertiary care), criteria used to define IBS, subtype of IBS, proportion with post-infection IBS, and proportion of female patients. We recorded the duration of treatment, dose, and dosing schedule of mesalamine or placebo. We extracted data as intention-to-treat analyses, assuming all dropouts to be treatment failures (ie, no response to mesalamine or placebo), wherever trial reporting allowed. If this was not clear in the original article, we performed our analyses on all patients with reported evaluable data.

Risk of Bias and Quality of Evidence Assessment

We assessed risk of bias at the study level using the Cochrane risk of bias tool.[31] This was performed by 2 investigators (VCG and ACF) independently; we resolved disagreements by discussion. We recorded the method used to generate the randomization schedule, the method used to conceal treatment allocation, 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. Finally, we summarized quality of the evidence for efficacy of mesalamine in IBS according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[32]

Data Synthesis and Statistical Analysis

We used a random effects model to pool data,[33] which gives a more conservative estimate of the efficacy of mesalamine in IBS. We expressed the impact of mesalamine vs placebo as a relative risk (RR) of global IBS symptoms, abdominal pain, or bowel habit or stool frequency not improving separately, along with 95% confidence intervals (CIs). If the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of mesalamine over placebo. This approach is the most stable, compared with a RR of cure or improvement, or using the odds ratio, for some meta-analyses.[34] We also summarized adverse events data with RRs and 95% CIs. We calculated the number needed to treat (NNT) and the number needed to harm (NNH) with a 95% CI, using the formula NNT or NNH = 1 / (assumed control risk × (1 – RR)).

We assessed heterogeneity between studies using both the χ^2 test, with a P value $< .10$ defining a significant degree of heterogeneity, and the I^2 statistic. The I^2 ranges between 0% and 100%, with values of 25% to 49% considered low, 50% to 74% moderate, and ≥75% high heterogeneity.[35] We used Review Manager version 5.4.1 (The Cochrane Collaboration 2020) to generate forest plots of pooled RRs for all primary and secondary outcomes with 95% CIs. We planned to assess funnel plots for evidence of asymmetry and, therefore, possible publication bias or other small study effects, using the Egger test,[36] where there were sufficient studies (≥10).[37] Where possible, we performed subgroup analyses of trials according to IBS subtype or post-infection status.

Results

The literature search generated 669 citations, 11 of which appeared relevant, which we retrieved for further assessment (Supplementary Figure 1). Of these, we excluded 3 that did not fulfil eligibility criteria, leaving 8 eligible trials including 820 patients,[23–28,38,39] 432 of whom were allocated to mesalamine. Agreement between investigators for trial eligibility was excellent (kappa statistic = 0.81). Detailed characteristics of individual RCTs, including endpoints used, or imputed, are provided in Table 1. Two trials were published as abstracts,[23,26] although further details for both were available on clinicaltrials.gov. We also obtained extra data from investigators of three RCTs.[25–27] Risk of bias for all included trials is reported in Supplementary Table 2. Only one RCT was low risk of bias across all domains,[28] mainly due to the fact that 5 trials did not report an intention-to-treat analysis. We could not assess for presence or absence of publication bias in any of our analyses as there were too few studies.

Effect on Global IBS Symptoms

Six RCTs,[23–28] containing 726 patients, provided extractable dichotomous data. Overall, 246 of 385 patients (63.9%) assigned to mesalamine reported unimproved global IBS symptoms following therapy, compared with

Table 1. Characteristics of RCTs of Mesalamine in IBS

Study	Country and setting	Diagnostic criteria used for IBS and proportion with each subtype (% with post-infection IBS)	Endpoint(s) used[a]	Sample size (% female)	Active therapy (number of patients)	Duration of therapy
Corinaldesi 2009[38]	Italy, single center, tertiary care	Rome II, 35% IBS-C, 40% IBS-D, 25% IBS-M (% with post-infection IBS not reported)	≥30% improvement in abdominal pain (imputed) ≥30% improvement in stool frequency (imputed)	20 (65)	Mesalamine 800 mg t.i.d. (10)	8 weeks
Aron 2012[23]	US, multicenter, setting unclear	Rome III, 100% IBS-D (% with post-infection IBS not reported)	≥30% improvement in abdominal pain and a ≥50% reduction in the number of days per week with a Bristol stool scale consistency of 6 or 7	148 (63)	Mesalamine 750 mg (47) or 1.5 g o.d. (51)	12 weeks
Tuteja 2012 [27a]	USA, single center, tertiary care	Rome II, 100% IBS-D (100% with post-infection IBS)	≥30% improvement in global symptoms ≥30% improvement in abdominal pain (imputed) ≥30% improvement in stool frequency (imputed)	20 (35)	Mesalamine 1.6g b.i.d. (10)	12 weeks
Barbara 2016[25]	Italy, 21 centers, tertiary care	Rome III, 20% IBS-C, 38.5% IBS-D, 41% IBS-M (% with post-infection IBS not reported)	Satisfactory relief of IBS symptoms Satisfactory relief of abdominal pain ≥30% improvement in stool frequency (imputed)	180 (59)	Mesalamine 800 mg t.i.d. (92)	12 weeks
Lam 2016[24]	UK, multicenter, primary, secondary, and tertiary care	Rome III, 100% IBS-D (10% with post-infection IBS)	Satisfactory relief of overall IBS symptoms ≥30% improvement in abdominal pain (imputed) ≥30% improvement in stool frequency (imputed)	136 (60)	Mesalamine 2g b.i.d. (68)	12 weeks
Ghadir 2017[39]	Iran, single center, tertiary care	Rome III, 100% IBS-D (% with post-infection IBS not reported)	Improvement in abdominal pain ≥30% improvement in stool frequency (imputed)	74 (31)	Mesalamine 800 mg t.i.d. (37)	8 weeks
Tuteja 2020[26a]	US, single center, tertiary care	Rome III, 100% IBS-D (100% with post-infection IBS)	≥30% improvement in global symptoms ≥30% improvement in abdominal pain (imputed) ≥30% improvement in stool frequency (imputed)	61 (10)	Mesalamine 2.4 g o.d. (31)	8 weeks
Castro Tejera 2022[28]	Norway and Sweden, five centers, tertiary care	Rome III, 15% IBS-C, 40% IBS-D, 45% IBS-M (26.5% with post-infection IBS)	Satisfactory relief of overall IBS symptoms ≥30% improvement in abdominal pain (imputed) ≥30% improvement in bowel habit (imputed)	181 (70)	Mesalamine 2.4 g o.d. (90)	8 weeks

IBS, Irritable bowel syndrome; IBS-C; IBS with constipation, IBS-D; IBS with diarrhea, IBS-M; IBS with mixed bowel habits; o.d., once daily; RCT, randomized controlled trial; t.i.d, 3 times a day.
[a]Full information not reported in published article but obtained after correspondence with the authors.

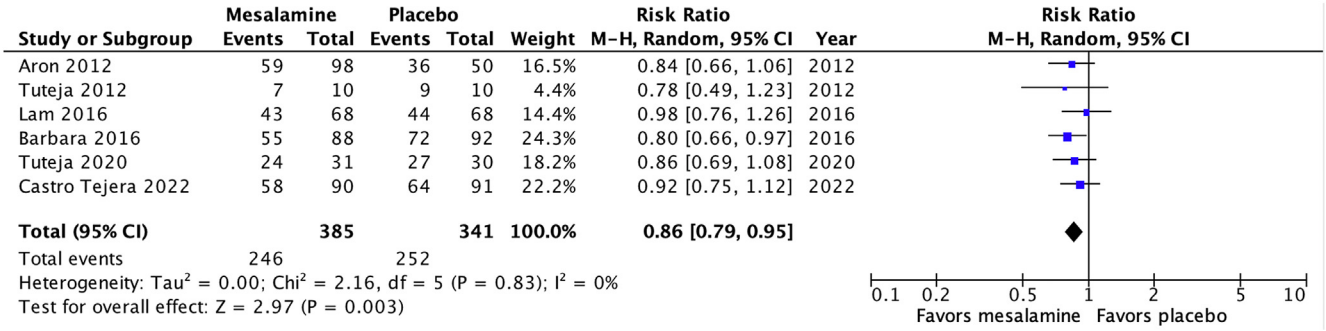

Figure 1. Forest plot of RCTs of mesalamine in IBS: effect on global IBS symptoms.

252 of 341 patients (73.9%) randomized to placebo. The RR of global IBS symptoms persisting with mesalamine vs placebo was 0.86 (95% CI, 0.79–0.95) (Figure 1), with no heterogeneity between studies ($I^2 = 0\%$; $P = .83$). The NNT with mesalamine was 10 (95% CI, 6–27). One study used 2 different mesalamine doses,[23] one of which was only 750 mg per day. Excluding this lower-dose arm from the meta-analysis, the RR of global IBS symptoms persisting was similar (0.86; 95% CI, 0.77–0.94) (Supplementary Figure 2). Four of the trials were conducted only in patients with IBS-D,[23,24,26,27] and 2 trials reported efficacy according to predominant stool pattern.[25,28] Mesalamine was again superior to placebo for global IBS symptoms in this analysis, containing 506 patients (RR, 0.88; 95% CI, 0.79–0.99; NNT = 11; 95% CI, 6.5–136) (Supplementary Figure 3). Two trials reported global IBS symptom data in patients with IBS with constipation or mixed bowel habits.[25,28] In this analysis, mesalamine was of no benefit (RR, 0.83; 95% CI, 0.67–1.03) (Supplementary Figure 4). When data for the 2 trials conducted only in 81 patients with post-infection IBS were included,[26,27] along with 2 trials that reported data for 61 post-infection patients with IBS,[24,28] mesalamine was no longer superior to placebo (RR, 0.87; 95% CI, 0.73–1.04) (Supplementary Figure 5).

Effect on Abdominal Pain

Two trials reported data on effect on abdominal pain,[25,39] and data were imputed for a further 5 studies.[24,26–28,38] In total, these 7 trials recruited 672 patients, 334 of whom received mesalamine. Overall, 199 patients (59.6%) receiving mesalamine had no improvement in abdominal pain following therapy, compared with 218 of 338 patients (64.5%) allocated to placebo. The RR of abdominal pain persisting with mesalamine vs placebo was 0.92 (95% CI 0.82–1.04) (Figure 2), with no heterogeneity detected between studies ($I^2 = 0\%$; $P = .52$). Four trials were conducted only in patients with IBS-D,[24,26,27,39] and the authors of one trial provided us with data according to IBS subtype.[25] When only patients with IBS-D from these 5 RCTs, containing 360 patients, were included, there was still no significant benefit of mesalamine for abdominal pain in IBS (RR, 0.92; 95% CI, 0.78–1.09) (Supplementary Figure 6). Subgroup analysis in patients with IBS with constipation or mixed bowel habits was not possible. When data for only the 2 trials conducted solely in 81 patients with post-infection IBS were included,[26,27] again, mesalamine was not superior to placebo (RR, 0.90; 95% CI, 0.63–1.29) (Supplementary Figure 7).

Effect on Bowel Habit or Stool Frequency

We imputed data for 7 trials concerning efficacy of mesalamine in terms of improvement in bowel habit or stool frequency.[24–28,38,39] There were 222 of 334 patients (66.5%) randomized to mesalamine with no improvement in bowel habit or stool frequency, compared with 240 of 338 patients (71.0%) allocated to placebo (RR, 0.91; 95% CI, 0.78–1.07) (Figure 3), with moderate heterogeneity between studies ($I^2 = 50\%$; $P =$

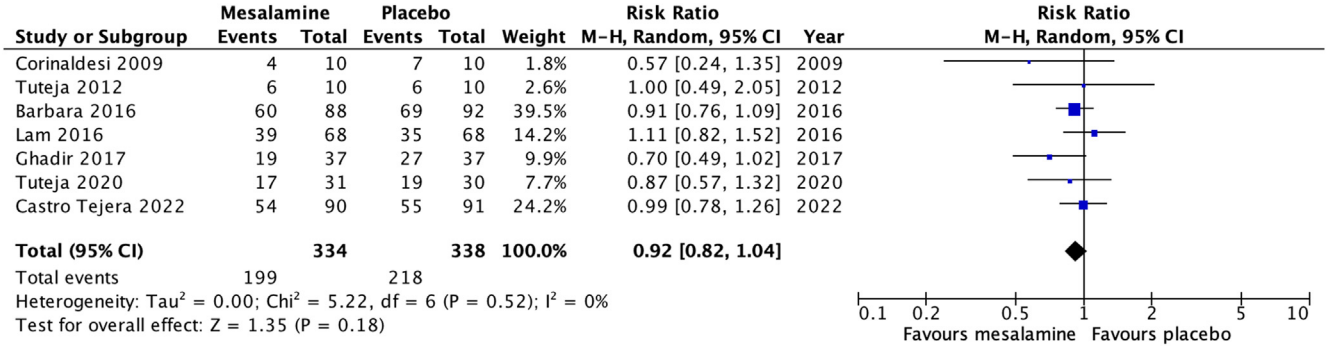

Figure 2. Forest plot of RCTs of mesalamine in IBS: effect on abdominal pain.

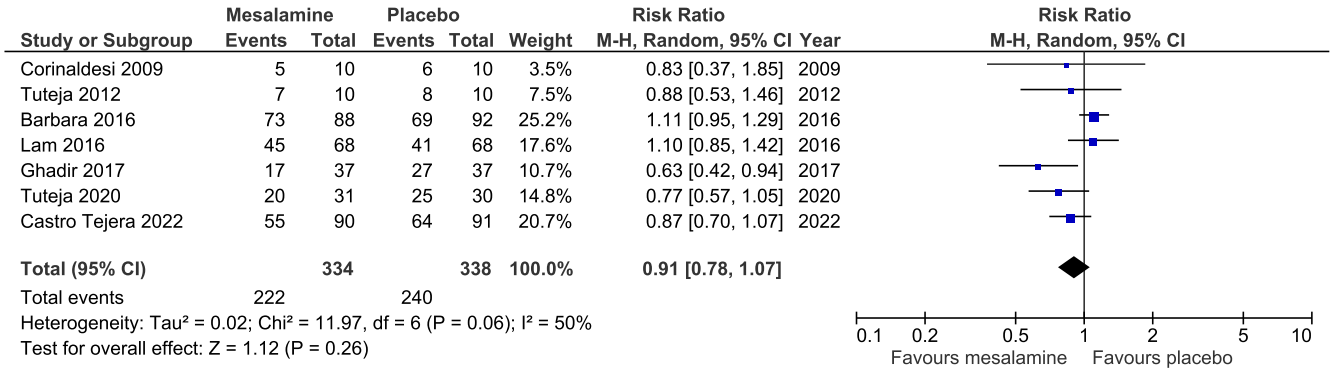

Figure 3. Forest plot of RCTs of mesalamine in IBS: effect on bowel habit or stool frequency.

.06). Four studies only recruited patients with IBS-D,[24,26,27,39] but there was no significant benefit of mesalamine when only these studies were pooled (RR, 0.85; 95% CI, 0.66–1.09) (Supplementary Figure 8). Subgroup analysis in patients with IBS with constipation or mixed bowel habits was not possible. Again, when only the 2 trials conducted in patients with post-infection IBS were included,[26,27] mesalamine was not superior to placebo (RR, 0.80; 95% CI 0.61–1.04) (Supplementary Figure 9).

Adverse Events

There were 5 studies reporting adverse events data,[23,26–28,38] including 430 patients. In total, 104 of 239 patients (43.5%) allocated to mesalamine experienced any adverse event, compared with 79 of 191 patients (41.4%) assigned to placebo. The RR of experiencing any adverse event among those taking mesalamine was 1.20 (95% CI, 0.89–1.63) (Figure 4), with minimal heterogeneity detected between studies ($I^2 = 17\%$; $P = .30$).

Discussion

This meta-analysis has evaluated the efficacy and safety of mesalamine in the treatment of IBS, identifying 8 RCTs containing 820 patients and performing subgroup analyses according to predominant stool pattern and post-infection status. Mesalamine was more efficacious than placebo in terms of effect on global symptoms, although this effect was modest with a NNT of 10, but not for abdominal pain or bowel habit or stool frequency. There appeared to be a beneficial effect on global symptoms in patients with IBS-D, with a NNT of 11 in this patient group, but again no benefit on abdominal pain or bowel habit or stool frequency. Analyses by post-infection status did not show any beneficial effects in this subset of patients, although numbers were small. Adverse events were no more likely with mesalamine than with placebo, although 3 RCTs did not report total adverse events data.[24,25,39] There was no evidence of heterogeneity between studies in most of our analyses, but only one trial was at low risk of bias across all domains,[28] and there were insufficient studies to assess for funnel plot asymmetry. Based on these limitations of the evidence, by GRADE criteria,[32] our confidence in the results of the meta-analysis would be low, and further large trials at low risk of bias would be informative. It is likely that a future large study, if negative, would demonstrate that mesalamine is not efficacious in IBS when pooled with the existing studies.

We used rigorous and reproducible methods to conduct this meta-analysis. Our search strategy was contemporaneous and augmented by searching the "gray" literature and clinicaltrials.gov to identify all eligible RCTs of mesalamine in IBS, as well as to obtain supplementary data for published trials. We contacted investigators of individual trials, and imputed endpoints of interest, to maximize the number of RCTs contributing data to each analysis. We used a random effects model to pool data and an intention-to-treat analysis to minimize

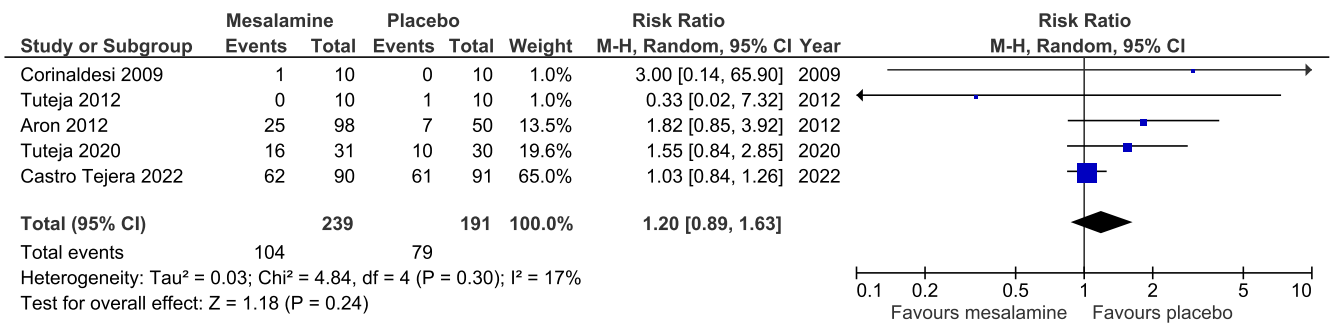

Figure 4. Forest plot of RCTs of mesalamine in IBS: total adverse events.

the likelihood that the efficacy of mesalamine in IBS has been overestimated. We conducted subgroup analyses according to predominant stool pattern and post-infection status to assess whether there was a beneficial effect in a subset of patients with IBS.

Limitations include heterogeneity in 2 of our analyses, insufficient studies to assess for publication bias, or other small study effects, and only one RCT at low risk of bias. This was partly due to incomplete reporting of trial methodology, with respect to methods used to generate the randomization schedule and conceal treatment allocation, and partly due to the fact that few trials reported an intention-to-treat analysis. Trial protocols, which may have contained information addressing randomization and treatment allocation, were not available for many of the studies, and should be a requirement for all RCTs. Two of the RCTs were published as abstracts only.[23,26] The reasons for this are unclear, but the results of these may not be as reliable as those from trials published in full after peer review. A variety of doses were used, including a dose of 4 g in one trial.[24] Mesalamine can cause diarrhea as a side effect, so it may be that in trials using a higher dose, symptoms were exacerbated in some patients. Several trials had small sample sizes, meaning that they are probably underpowered for efficacy. In addition, the total number of patients experiencing adverse events was not available for some trials. Finally, several trials used historical definitions of IBS or failed to judge efficacy according to United States Food and Drug Administration-recommended endpoints for treatment trials in IBS. However, our imputation of data using a 30% or more improvement in global symptoms or abdominal pain approximates these endpoints, although it should be pointed out that the exact criteria for judging abdominal pain response were not reported in one RCT.[39]

A recent report of a clinical trial, which also included a meta-analysis, suggested that the evidence for a lack of benefit of mesalamine in IBS was convincing, and that it would be hard to justify future trials on this basis.[28] Mesalamine has been used for the treatment of ulcerative colitis for many years and is effective in inducing and maintaining remission of disease activity.[21,22] Due to its anti-inflammatory effects, it reduces rectal bleeding and stool frequency. It may also be beneficial for the diarrhea experienced by patients with microscopic colitis.[40] It does not appear to influence colonic transit, and it does not act as a secretagogue. It seems, therefore, unlikely that it would be of benefit in mixed populations of patients with IBS, in terms of bowel habit, yet some of the largest studies of mesalamine have recruited such populations, with less than 50% having IBS-D. This may mean that the group of patients most likely to benefit from mesalamine have not been studied. Hence, our subgroup analyses according to IBS subtype are useful. Similarly, due to the reports of low-grade inflammation in some patients with post-infection IBS, the fact that only a small number of such patients have been included in some of these trials may also have underestimated any benefit. Again, we conducted subgroup analyses in this group of patients. Although these did not demonstrate a benefit in post-infection IBS, patient numbers were small. Nevertheless, to date, in attempting to assess whether the drug is efficacious, RCTs may have recruited the wrong group of patients with IBS by including patients with predominant bowel habits other than diarrhea.

Although the current meta-analysis suggests that mesalamine may be an efficacious treatment for IBS, confidence intervals around the estimates of effect were wide, and the NNT of 10 is only modest. However, this is of a similar magnitude to that observed in trials of rifaximin,[41] which is licensed for the treatment of IBS-D, and whose use, similar to mesalamine, is based on a potentially relevant pathophysiological mechanism. In addition, confidence in the evidence, by GRADE criteria, was low. We would, therefore, not suggest guidelines for the management of IBS should recommend the use of mesalamine based on our results.[42,43] However, the drug did not appear to be associated with an excess of adverse events in the RCTs that reported these data. Patients with IBS-D have limited treatment options,[44] and there are safety concerns with licensed drugs such as alosetron or eluxadoline.[45,46] Therefore, mesalamine could be a safe and efficacious treatment option for some patients. Given the heterogeneous nature of IBS, our results suggest that further trials recruiting only patients with IBS-D and reporting efficacy according to post-infection status may be warranted. These need to be powered adequately, and the estimates provided by this meta-analysis could inform those calculations.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.02.014.

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Christopher J. Black (Conceptualization: Equal; Writing – review & editing: Equal)

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Conflicts of interest
This author discloses the following: Alexander C. Ford has received research funding from Tillotts Pharma and DrFalk UK. The remaining authors disclose no conflicts.

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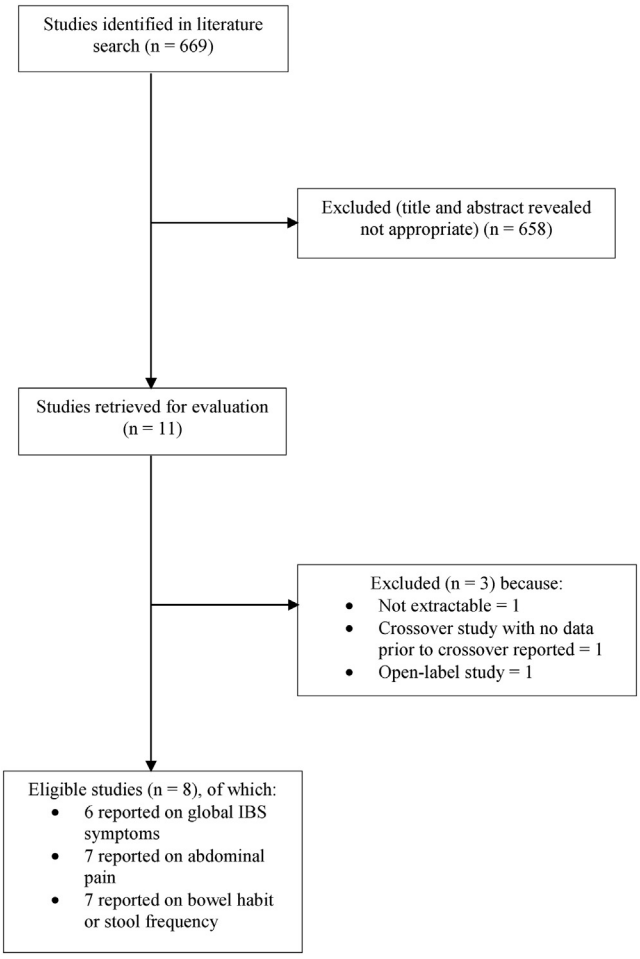
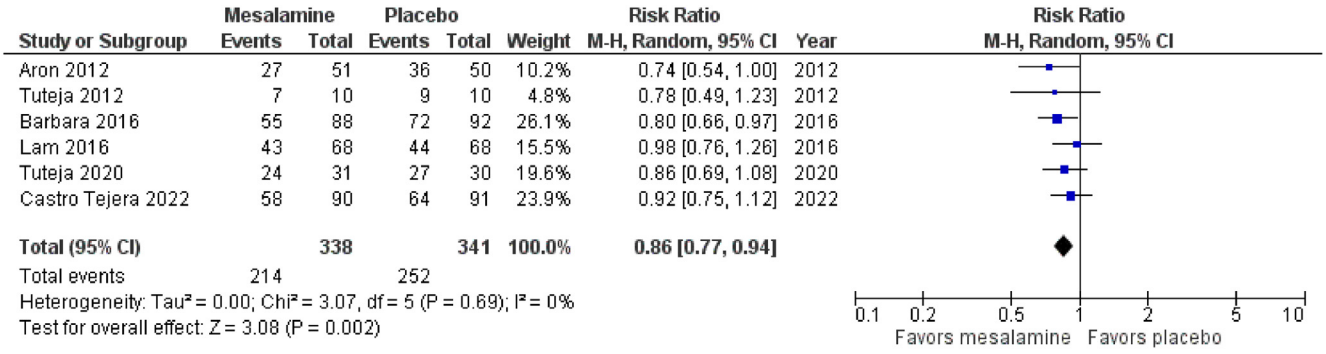
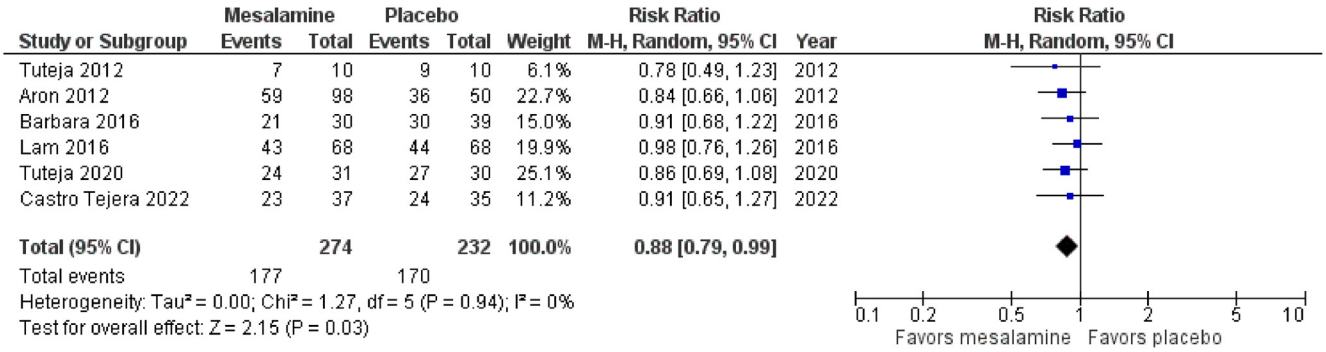


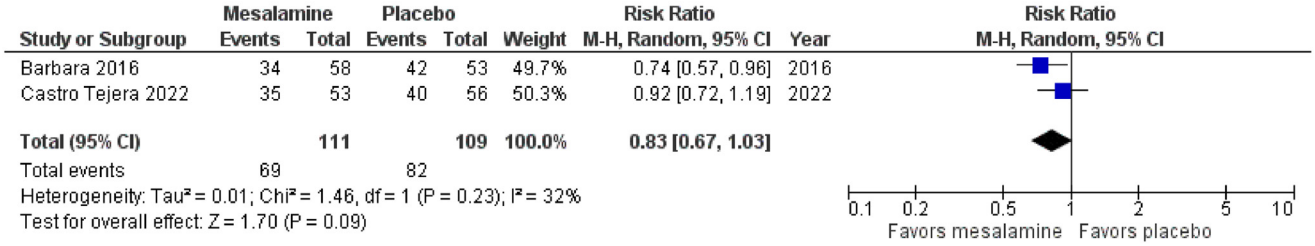
Supplementary Figure 1. Flow diagram of assessment of studies identified in the systematic review.



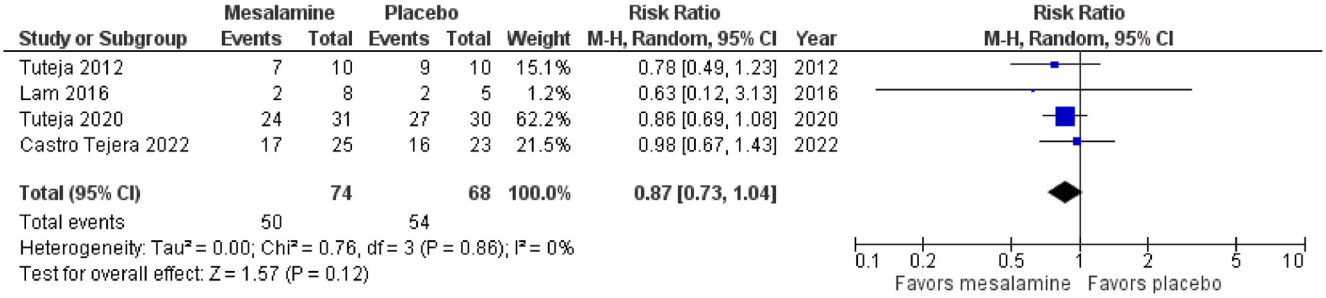
Supplementary Figure 2. Forest plot of RCTs of higher dose mesalamine in IBS: effect on global IBS symptoms.



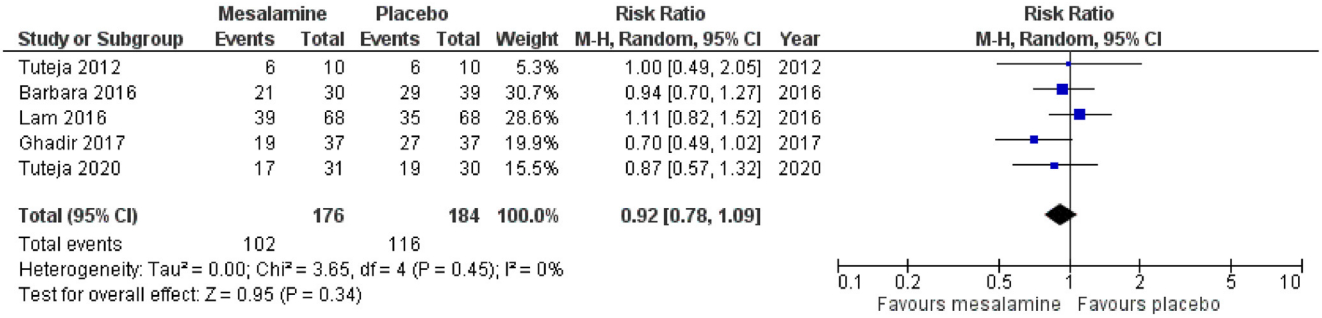
Supplementary Figure 3. Forest plot of RCTs of mesalamine in IBS-D: effect on global IBS symptoms.



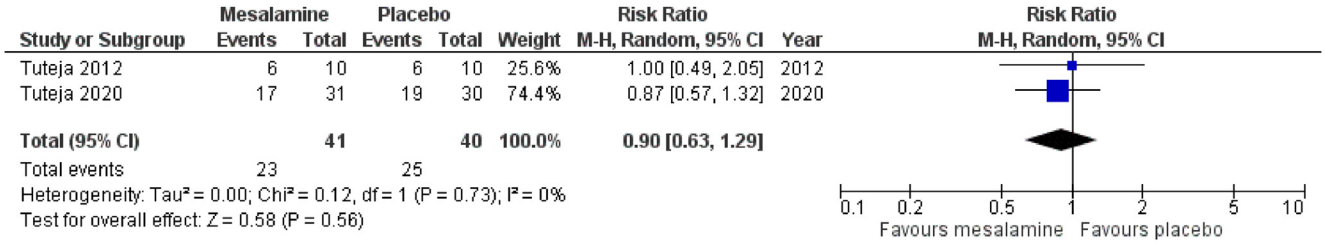
Supplementary Figure 4. Forest plot of RCTs of mesalamine in IBS with constipation or mixed bowel habits: effect on global IBS symptoms.



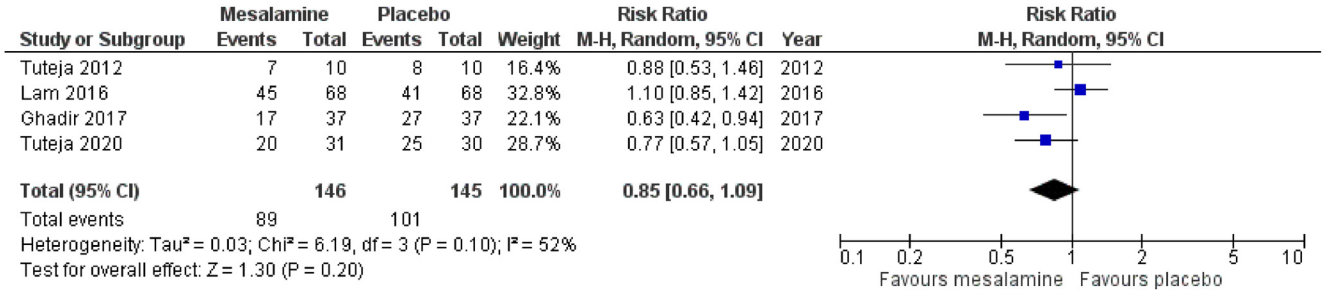
Supplementary Figure 5. Forest plot of RCTs of mesalamine in post-infection IBS: effect on global IBS symptoms.



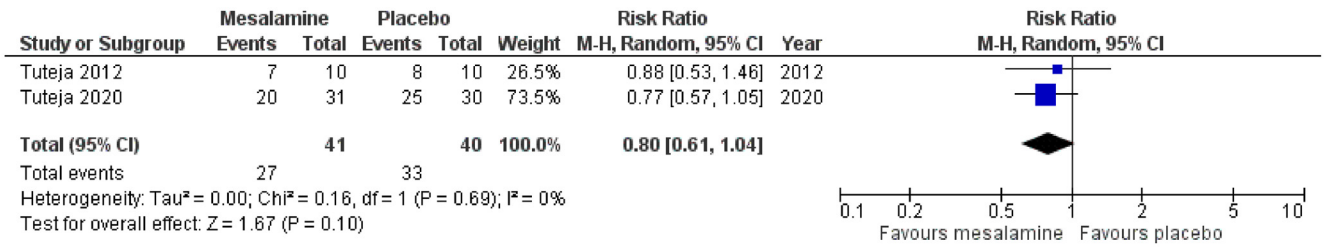
Supplementary Figure 6. Forest plot of RCTs of mesalamine in IBS-D: effect on abdominal pain.



Supplementary Figure 7. Forest plot of RCTs of mesalamine in post-infection IBS: effect on abdominal pain.



Supplementary Figure 8. Forest plot of RCTs of mesalamine in IBS-D: effect on bowel habit or stool frequency.



Supplementary Figure 9. Forest plot of RCTs of mesalamine in post-infection IBS: effect on bowel habit or stool frequency.

Supplementary Table 1. Eligibility Criteria

Randomized controlled trials
Adults (aged ≥18 years)
Diagnosis of IBS based on either a clinician's opinion, or meeting specific diagnostic criteria,[a] supplemented by negative investigations where trials deemed this necessary
Compared mesalamine with placebo
Minimum duration of therapy of 4 weeks
Dichotomous assessment of response to therapy in terms of effect on either global IBS symptoms or abdominal pain following treatment[b]

IBS, Irritable bowel syndrome.
[a]Manning criteria, Kruis score, Rome I, II, III, or IV criteria.
[b]Preferably patient-reported, but if this was not available then as assessed by a physician or questionnaire data.

Supplementary Table 2. Risk of Bias of RCTs of Mesalamine in IBS

Study	Method of generation of randomization schedule stated?	Method of concealment of treatment allocation stated?	Blinding?	No evidence of incomplete outcomes data?	No evidence of selective reporting of outcomes?
Corinaldesi 2009[1]	Low	Unclear	Low	Low	Low
Aron 2012[2]	Unclear	Unclear	Low	Low	Low
Tuteja 2012[3]	Low	Low	Low	High	Low
Barbara 2016[4]	Low	Low	Low	High	Low
Lam 2016[5]	Low	Low	Low	High	Low
Ghadir 2017[6]	Low	Low	Low	High	Low
Tuteja 2020[7,a]	Low	Low	Low	High	Low
Castro Tejera 2022[8]	Low	Low	Low	Low	Low

IBS, Irritable bowel syndrome; RCTs, randomized controlled trials.
[a]Full information not reported in published article but obtained after correspondence with the authors.