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Aminosalicylates for induction of remission or response in Crohn's disease (Review)

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[Intervention Review]

Aminosalicylates for induction of remission or response in Crohn's disease

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ABSTRACT

Background

Randomized trials investigating the efficacy of aminosalicylates for the treatment of mildly to moderately active Crohn's disease have yielded conflicting results. A systematic review was conducted to critically examine current available data on the efficacy of sulfasalazine and mesalamine for inducing remission or clinical response in these patients.

Objectives

To evaluate the efficacy of aminosalicylates compared to placebo, corticosteroids, and other aminosalicylates (alone or in combination with corticosteroids) for the treatment of mildly to moderately active Crohn's disease.

Search methods

We searched PubMed, EMBASE, MEDLINE and the Cochrane Central Library from inception to June 2015 to identify relevant studies. There were no language restrictions. We also searched reference lists from potentially relevant papers and review articles, as well as proceedings from annual meetings (1991-2015) of the American Gastroenterological Association and American College of Gastroenterology.

Selection criteria

Randomized controlled trials that evaluated the efficacy of sulfasalazine or mesalamine in the treatment of mildly to moderately active Crohn's disease compared to placebo, corticosteroids, and other aminosalicylates (alone or in combination with corticosteroids) were included.

Data collection and analysis

Data extraction and assessment of methodological quality was independently performed by the investigators and any disagreement was resolved by discussion and consensus. We assessed methodological quality using the Cochrane risk of bias tool. The overall quality of the evidence supporting the outcomes was evaluated using the GRADE criteria. The primary outcome measure was a well defined clinical endpoint of induction of remission or response to treatment. Secondary outcomes included mean Crohn's disease activity index (CDAI) scores, adverse events, serious adverse events and withdrawal due to adverse events. For dichotomous outcomes we calculated the pooled risk ratio (RR) and corresponding 95% confidence interval (CI) using a random-effects model. For continuous outcomes we calculated the mean difference (MD) and 95% CI using a random-effects model. Sensitivity analyses based on a fixed-effect model and duration of therapy were conducted where appropriate.

Main results

Twenty studies (2367 patients) were included. Two studies were judged to be at high risk of bias due to lack of blinding. Eight studies were judged to be at high risk of bias due to incomplete outcomes data (high drop-out rates) and potential selective reporting. The other 10 studies were judged to be at low risk of bias. A non-significant trend in favour of sulfasalazine over placebo for inducing remission was observed, with benefit confined mainly to patients with Crohn's colitis. Forty-five per cent (63/141) of sulfasalazine patients entered remission at 17-18 weeks compared to 29% (43/148) of placebo patients (RR 1.38, 95% CI 1.00 to 1.89, 2 studies). A GRADE analysis rated the overall quality of the evidence supporting this outcome as moderate due to sparse data (106 events). There was no difference between sulfasalazine and placebo in adverse event outcomes. Sulfasalazine was significantly less effective than corticosteroids and inferior to combination therapy with corticosteroids (RR 0.64, 95% CI 0.47 to 0.86, 1 study, 110 patients). Forty-three per cent (55/128) of sulfasalazine patients entered remission at 17 to 18 weeks compared to 60% (79/132) of corticosteroid patients (RR 0.68, 95% CI 0.51 to 0.91; 2 studies, 260 patients). A GRADE analysis rated the overall quality of the evidence supporting this outcome as moderate due to sparse data (134 events). Sulfasalazine patients experienced significantly fewer adverse events than corticosteroid patients (RR 0.43, 95% CI 0.22 to 0.82; 1 study, 159 patients). There was no difference between sulfasalazine and corticosteroids in serious adverse events or withdrawal due to adverse events. Olsalazine was less effective than placebo in a single trial (RR 0.36, 95% CI 0.18 to 0.71; 91 patients). Low dose mesalamine (1 to 2 g/day) was not superior to placebo for induction of remission. Twenty-three per cent (43/185) of low dose mesalamine patients entered remission at week 6 compared to 15% (18/117) of placebo patients (RR = 1.46, 95% CI 0.89 to 2.40; n = 302). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to risk of bias (incomplete outcome data) and sparse data (61 events). There was no difference between low dose mesalamine and placebo in the proportion of patients who had adverse events (RR 1.33, 95% CI 0.91 to 1.96; 3 studies, 342 patients) or withdrew due to adverse events (RR 1.21, 95% CI 0.75 to 1.95; 3 studies, 342 patients). High dose controlled-release mesalamine (4 g/day) was not superior to placebo, inducing a clinically non significant reduction in CDAI (MD -19.8 points, 95% CI -46.2 to 6.7; 3 studies, 615 patients), and was also inferior to budesonide (RR 0.56, 95% CI 0.40 to 0.78; 1 study, 182 patients, GRADE = low). While high dose delayed-release mesalamine (3 to 4.5 g/day) was not superior to placebo for induction of remission (RR 2.02, 95% CI 0.75 to 5.45; 1 study, 38 patients, GRADE = very low), no significant difference in efficacy was found when compared to conventional corticosteroids (RR 1.04, 95% CI 0.79 to 1.36; 3 studies, 178 patients, GRADE = moderate) or budesonide (RR 0.89, 95% CI 0.76 to 1.05; 1 study, 307 patients, GRADE = moderate). However, these trials were limited by risk of bias (incomplete outcome data) and sparse data (small numbers of events). There was a lack of good quality clinical trials comparing sulfasalazine with other mesalamine formulations. Adverse events that were commonly reported included headache, nausea, vomiting, abdominal pain and diarrhea.

Authors' conclusions

Sulfasalazine is only modestly effective with a trend towards benefit over placebo and is inferior to corticosteroids for the treatment of mildly to moderately active Crohn's disease. Olsalazine and low dose mesalamine (1 to 2 g/day) are not superior to placebo. High dose mesalamine (3.2 to 4 g/day) is not more effective than placebo for inducing response or remission. However, trials assessing the efficacy of high dose mesalamine (4 to 4.5 g/day) compared to budesonide yielded conflicting results and firm conclusions cannot be made. Future large randomized controlled trials are needed to provide definitive evidence on the efficacy of aminosalicylates in active Crohn's disease.

PLAIN LANGUAGE SUMMARY

Aminosalicylates for treatment of active Crohn's disease

What is Crohn's disease?

Crohn's disease is a chronic inflammatory disease of the intestines. Although Crohn's disease is often found in the ileum (the lower part of the small intestine), it can occur in any part of the digestive tract, from the mouth to the anus. The most common symptoms of Crohn's disease are diarrhea and abdominal pain which often occurs in the lower right region of the abdomen.

What are aminosalicylates?

Aminosalicylates are a family of medications with various formulations that deliver the active ingredient, mesalamine, to target sites. Aminosalicylates are thought to treat Crohn's disease by reducing the inflammation of the intestines caused by the disease.

What did the researchers investigate?

The researchers investigated whether aminosalicylates produce remission or alleviate disease severity in individuals with mildly to moderately active Crohn's disease, and whether they cause any harms (side effects). The researchers searched the medical literature extensively up to June 10, 2015.

What did the researchers find?

The researchers identified twenty studies including a total of 2367 participants. Ten studies were judged to be of moderate to high quality, while the other ten studies were judged to be of low quality. The studies compared aminosalicylates (sulfasalazine, mesalazine and mesalamine) with placebo (inactive pills or tablets), corticosteroids or budesonide (a steroid that is rapidly metabolized by the body and has less side-effects than traditional corticosteroids).

The researchers found that, comparing to placebo, sulfasalazine provides only a modest benefit for the treatment of mild to moderately active Crohn's disease and is inferior to corticosteroids for treatment of active Crohn's disease. Sulphasalazine differs from other aminosalicylates in that it contains a sulpha portion that has been eliminated in the other preparations.

Mesalazine and mesalamine formulations are not effective for inducing remission in active Crohn's disease. Budesonide was compared to high dose mesalamine (4 to 4.5 g/day) but results were conflicting. One study found mesalamine to be inferior to budesonide and the other study found no difference in effectiveness between mesalamine and budesonide.

Side effects are generally mild in nature and typically include headache, nausea, vomiting, abdominal pain and diarrhea.

In conclusion, sulfasalazine is only modestly effective for the treatment of active Crohn's disease. However, the existing data show little benefit for mesalamine.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Sulfasalazine compared to placebo for induction of remission or response in Crohn's disease

Sulfasalazine compared to placebo for induction of remission or response in Crohn's disease

Patient or population: patients with induction of remission or response in Crohn's disease

Settings: Inpatient/Outpatient

Intervention: Sulfasalazine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Sulfasalazine				
Induction of remission (CDAI <150), therapeutic response (VHI decrease >=25%) or clinical improvement Follow-up: 17-26 weeks	291 per 1000 ¹	442 per 1000 (276 to 706)	RR 1.52 (0.95 to 2.43)	289 (3 studies)	⊕⊕⊕⊖ low 2,3	
Induction of remission (CDAI <150) (Random Effects Model) Follow-up: 17-18 weeks	311 per 1000 ¹	429 per 1000 (311 to 588)	RR 1.38 (1 to 1.89)	263 (2 studies)	⊕⊕⊕⊖ moderate 4	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk comes from control arm of meta-analysis, based on included trials.

² Downgraded one level due to sparse data (106 events).

³ Downgraded one level due heterogeneity ($I^2 = 41\%$).

⁴ Downgraded one level due to sparse data (97 events).

Summary of findings 2. Sulfasalazine compared to Corticosteroids for induction of remission or response in Crohn's disease

Sulfasalazine compared to Corticosteroids for induction of remission or response in Crohn's disease

Patient or population: patients with induction of remission or response in Crohn's disease

Settings: Inpatient/Outpatient

Intervention: Sulfasalazine

Comparison: Corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Corticosteroids	Sulfasalazine				
Induction of remission (CDAI <150) Follow-up: 17-18 weeks	598 per 1000 ¹	407 per 1000 (305 to 545)	RR 0.68 (0.51 to 0.91)	260 (2 studies)	⊕⊕⊕⊖ moderate ²	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk comes from control arm of meta-analysis, based on included trials.

² Downgraded one level due to sparse data (134 events).

Summary of findings 3. Sulfasalazine compared to Sulfasalazine and corticosteroids for induction of remission or response in Crohn's disease

Sulfasalazine compared to Sulfasalazine and corticosteroids for induction of remission or response in Crohn's disease

Patient or population: patients with induction of remission or response in Crohn's disease

Settings: Inpatient/Outpatient

Intervention: Sulfasalazine

Comparison: Sulfasalazine and corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants	Quality of the evidence	Comments
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	Assumed risk	Corresponding risk	(studies)		(GRADE)
	Sulfasalazine and corticosteroids	Sulfasalazine			
Induction of remission Follow-up: 18 weeks	786 per 1000 ¹	503 per 1000 (369 to 676)	RR 0.64 (0.47 to 0.86)	110 (1 study)	⊕⊕⊕⊖ moderate ²

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk comes from control arm of the included study

² Downgraded one level due to sparse data (71 events)

Summary of findings 4. Controlled-release mesalamine (1 - 2 g/day) compared to Placebo for induction of remission or response in Crohn's disease

Controlled-release mesalamine (1 - 2 g/day) compared to Placebo for induction of remission or response in Crohn's disease

Patient or population: patients with induction of remission or response in Crohn's disease

Settings: Outpatient

Intervention: Controlled-release mesalamine (1 - 2 g/day)

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Controlled-release mesalamine (1 - 2 g/day)				
Decrease in CDAI >=50, HBI >=2 or improvement/remission (as defined by Tvede et al) Follow-up: 6-16 weeks	350 per 1000 ¹	375 per 1000 (280 to 498)	RR 1.07 (0.8 to 1.42)	342 (3 studies)	⊕⊕⊖⊖ low ^{2,3}	

Induction of remission (CDAI ≤150 + decrease of ≥50 or as defined by Tvede et al) Follow-up: 16 weeks	444 per 1000 ¹	649 per 1000 (396 to 1000)	RR 1.46 (0.89 to 2.4)	302 (2 studies)	⊕⊕○○ low 2,4
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Control group risk comes from control arm of meta-analysis, based on included trials.

2 Downgraded one level because two studies in the pooled analysis were rated as high risk of bias for incomplete outcome data.

3 Downgraded one level; due to sparse data (127 events).

4 Downgraded one level due to sparse data (61 events).

Summary of findings 5. Controlled-release mesalamine (4 g/day) compared to Placebo for Induction of remission or response in Crohn's disease

Controlled-release mesalamine (4 g/day) compared to Placebo for Induction of remission or response in Crohn's disease

Patient or population: patients with Induction of remission or response in Crohn's disease

Settings: Outpatient

Intervention: Controlled-release mesalamine (4 g/day)

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Controlled-release mesalamine (4 g/day)				
Mean change in baseline CDAI (Random effects model) Follow-up: 16 weeks		The mean mean change in baseline cdai (random effects model) in the intervention groups was 19.76 lower (46.22 lower to 6.7 higher)		615 (3 studies)	⊕⊕○○ low 1,2	
Mean change in baseline CDAI (Fixed effects model)		The mean mean change in baseline cdai (fixed effects model) in the intervention groups was 17.54 lower		615 (3 studies)	⊕⊕○○ low 1,2	

Follow-up: 16 weeks (35 to 0.08 lower)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level due to moderate heterogeneity ($I^2 = 54\%$).

² Downgraded one level because all three studies in the pooled analysis were rated as high risk of bias for incomplete outcome data.

Summary of findings 6. Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) compared to Placebo for Induction of remission or response in Crohn's disease

Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) compared to Placebo for Induction of remission or response in Crohn's disease

Patient or population: patients with Induction of remission or response in Crohn's disease

Settings: Outpatient

Intervention: Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day)

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day)				
Induction of remission or clinical improvement - Olsalazine (2 g/day) Follow-up: 16 weeks	489 per 1000 ¹	176 per 1000 (88 to 347)	RR 0.36 (0.18 to 0.71)	91 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	
Induction of remission or clinical improvement - Asacol (3.2 g/day) Follow-up: 16 weeks	222 per 1000 ¹	600 per 1000 (236 to 1000)	RR 2.7 (1.06 to 6.88)	38 (1 study)	⊕⊕⊕⊕ very low ^{2,4}	
Induction of remission (CDAI < 150 + decrease ≥70) - Asacol (3.2 g/day)	222 per 1000 ¹	451 per 1000 (167 to 1000)	RR 2.03 (0.75 to 5.45)	38 (1 study)	⊕⊕⊕⊕ very low ^{2,5}	

Follow-up: 16 weeks

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- 1 Control group risk comes from control arm of the included study.
- 2 Downgraded one level because the study was rated as high risk of bias for incomplete outcome data.
- 3 Downgraded two levels due to very sparse data (30 events).
- 4 Downgraded two levels due to very sparse data (16 events).
- 5 Downgraded two levels due to very sparse data (13 events).

Summary of findings 7. Delayed-release mesalamine (3 - 4.5 g/day) compared to Corticosteroids for Induction of remission or response in Crohn's disease

Delayed-release mesalamine (3 - 4.5 g/day) compared to Corticosteroids for Induction of remission or response in Crohn's disease

Patient or population: patients with Induction of remission or response in Crohn's disease

Settings: Outpatient

Intervention: Delayed-release mesalamine (3 - 4.5 g/day)

Comparison: Corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Corticosteroids	Delayed-release mesalamine (3 - 4.5 g/day)				
Induction of remission (CDAI < or =150 with or without decrease of at least 60 points) Follow-up: 8-12 weeks	526 per 1000 ¹	547 per 1000 (416 to 716)	RR 1.04 (0.79 to 1.36)	178 (3 studies)	⊕⊕⊕⊖ moderate ²	
Induction of remission (CDAI < or =150 with or without decrease of at least 60 points) - 3 g/day	429 per 1000 ³	407 per 1000 (210 to 793)	RR 0.95 (0.49 to 1.85)	50 (1 study)	⊕⊕⊖⊖ low ⁴	

Follow-up: 12 weeks					
Induction of remission (CDAI < or =150 with or without decrease of at least 60 points) - 2.4 g/day Follow-up: 12 weeks	600 per 1000 ³	600 per 1000 (366 to 984)	RR 1 (0.61 to 1.64)	50 (1 study)	⊕⊕⊕○ moderate ⁵
Induction of remission (CDAI < or =150 with or without decrease of at least 60 points) - 4 g/day microgranules Follow-up: 12 weeks	625 per 1000 ³	788 per 1000 (512 to 1000)	RR 1.26 (0.82 to 1.92)	44 (1 study)	⊕⊕⊕○ moderate ⁶
Induction of remission (CDAI < or =150 with or without decrease of at least 60 points) - 4.5 g/day Follow-up: 8 weeks	529 per 1000 ³	355 per 1000 (159 to 773)	RR 0.67 (0.3 to 1.46)	34 (1 study)	⊕⊕○○ low ⁷

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk comes from control arm of meta-analysis, based on included trials.

² Downgraded one level due to sparse data (98 events).

³ Control group risk comes from control arm of the included study.

⁴ Downgraded two levels due to very sparse data (21 events).

⁵ Downgraded one level due to sparse data (40 events).

⁶ Downgraded one level due to sparse data (41 events).

⁷ Downgraded two levels due to very sparse data (15 events).

Summary of findings 8. Mesalamine (4 - 4.5 g/day) compared to Budesonide for Induction of remission or response in Crohn's disease

Mesalamine (4 - 4.5 g/day) compared to Budesonide for Induction of remission or response in Crohn's disease

Patient or population: patients with Induction of remission or response in Crohn's disease

Settings: Outpatient

Intervention: Mesalamine (4 - 4.5 g/day)

Comparison: Budesonide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Budesonide	Mesalamine (4 - 4.5 g/day)				
Induction of remission (CDAI < or = 150) - Pentasa (4 g/day) Follow-up: 16 weeks	602 per 1000 ¹	337 per 1000 (241 to 470)	RR 0.56 (0.4 to 0.78)	182 (1 study)	⊕⊕○○ low ^{2,3}	
Induction of remission (CDAI < or = 150) - Salofalk (4.5 g/day) Follow-up: 8 weeks	695 per 1000 ¹	618 per 1000 (528 to 730)	RR 0.89 (0.76 to 1.05)	307 (1 study)	⊕⊕⊕○ moderate	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk comes from control arm of the included study.

² Downgraded one level because the study was rated as high risk of bias for incomplete outcome data.

³ Downgraded one level due to sparse data (86 events).

⁴ Downgraded one level due to sparse data (202 events).

Summary of findings 9. Mesalamine compared to Sulfasalazine (alone or in combination with corticosteroids) for Induction of remission or response in Crohn's disease

Mesalamine compared to Sulfasalazine (alone or in combination with corticosteroids) for Induction of remission or response in Crohn's disease

Patient or population: patients with Induction of remission or response in Crohn's disease

Settings: Outpatient

Intervention: Mesalamine

Comparison: Sulfasalazine (alone or in combination with corticosteroids)

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
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	Assumed risk	Corresponding risk			
	Sulfasalazine (alone or in combination with corticosteroids)	Mesalamine			
Induction of remission (CDAI < 150) or clinical improvement - Salofalk (1.5 g/ day) Follow-up: 8 weeks	733 per 1000 ¹	865 per 1000 (601 to 1000)	RR 1.18 (0.82 to 1.7)	30 (1 study)	⊕⊕⊕⊕ very low ^{2,3}
Induction of remission (CDAI < 150) or clinical improvement - Salofalk (3.0 g/ day) Follow-up: 12 weeks	885 per 1000 ¹	832 per 1000 (663 to 1000)	RR 0.94 (0.75 to 1.18)	50 (1 study)	⊕⊕⊕⊕ low ^{2,4}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk comes from control arm of the included study.

² Downgraded one level because the study was rated as high risk for blinding.

³ Downgraded two levels due to very sparse data (24 events).

⁴ Downgraded one level due to sparse data (43 events).

BACKGROUND

Crohn's disease is a chronic inflammatory disease characterized by focal, asymmetric, transmural and granulomatous inflammation of the gastrointestinal tract. Although Crohn's disease can affect any part of the gut, it primarily involves the ileum and colon. The majority of patients suffer from chronic relapsing symptoms that are associated with decreased quality of life. In North America, Crohn's disease has a prevalence ranging 26 to 199 cases per 100,000 and an incidence of 3.1 to 14.6 cases per 100,000 person-years. Approximately 630,000 North Americans are affected (Loftus 2004). Pharmacotherapy remains the cornerstone of treatment, with most patients requiring lifelong therapy due to the chronicity of the disease and its typical onset before 30 years of age. Surgery is reserved for medical refractory disease and specific complications (Hanauer 2003).

Aminosalicylates may be used in the treatment of active mild to moderate Crohn's disease. The exact mechanism of action of aminosalicylates remains unknown, but is thought to be related to a topical effect on the gastrointestinal mucosa rather than a systemic one. Aminosalicylates have a wide range of anti-inflammatory and immunomodulatory actions. Aminosalicylates block production of interleukin (IL)-1 and tumor necrosis factor (TNF)- α , and prevent TNF- α binding to its receptor. Aminosalicylates are potent inhibitors of cyclooxygenase and 5-lipoxygenase, and they block production and the proinflammatory activity and chemotactic action of prostaglandin E2 and leukotrienes respectively. Aminosalicylates possess potent antioxidant and free-radical-scavenger properties, and also inhibit antigen presentation, T-cell proliferation, antibody production by B-cells, cytotoxic T-cells, natural killer cells and the activation and expression of adhesion molecules on endothelial cells. The inhibitory effects of aminosalicylates on multiple inflammatory pathways may be explained by the inhibition of nuclear factor kappa B (NF κ B) activation, a pivotal transcription factor that regulates gene expression for many pro-inflammatory cytokines, chemokines, adhesion molecules and inflammatory mediators (MacDermott 2000). Most recently mesalamine has been demonstrated to induce activation of PPAR γ in epithelial cells and lamina propria lymphocytes, resulting in inhibition of NF κ B signalling pathway (Dubuquoy 2006; Rousseaux 2005).

Sulfasalazine in daily doses of 3-6 g is recommended for the treatment of ileocolonic or colonic disease (Hanauer 2001; Sandborn 2003). However, as many as 30-40% of patients, particularly slow acetylators, are intolerant of high doses of sulfasalazine due to systemic absorption of the sulfapyridine carrier molecule. The discovery of the therapeutically active moiety, 5-aminosalicylic acid (5-ASA), in sulfasalazine (Azad 1977) has led to the development of newer sulfa-free 5-ASA formulations, that deliver higher concentrations of 5-ASA without the dose-limiting side effects of sulfasalazine. pH dependent release formulations include a Eudragit-S coated mesalamine formulation (Asacol[®]) that releases 5-ASA in the terminal ileum and cecum at pH 7, while Eudragit-L coated mesalamine formulations (Salofalk[®], Mesasal[®] and Claversal[®]) releases in the mid-ileum at pH 6. A formulation of mesalamine microgranules enclosed within a semi-permeable membrane of ethylcellulose (Pentasa[®]) is designed for time-dependent release throughout the small and large intestine, beginning in the duodenum. Newer azo-bonded formulations designed for release in the colon include 5-ASA dimer, olsalazine

(Dipentum[®]), and balsalazide (Colazal[®]), composed of 5-ASA linked to 4-aminobenzoyl-b alanine.

Aminosalicylates (mesalamine 3.2 to 4 g or sulfasalazine 3 to 6 g daily in divided doses) have been recommended by some experts as first-line therapy for mildly to moderately active Crohn's disease (Hanauer 2001). However, the efficacy of mesalamine has been called into question and first line therapy with sulfasalazine or budesonide was proposed as alternative first line strategies (Sandborn 2003). Early studies demonstrated the efficacy of sulfasalazine in inducing remission in mildly to moderately active Crohn's disease (Summers 1979; Malchow 1984). Much enthusiasm has surrounded the newer 5-ASA formulations as they were expected to be as efficacious as sulfasalazine. A meta-analysis of three large trials of Pentasa in active Crohn's disease demonstrated a statistically significant benefit over placebo in reducing the Crohn's disease activity index (CDAI; (Weighted Mean Difference, WMD, -18 points; 95% CD -35 to -1) (Hanauer 2004). Although this benefit was statistically significant, it is of questionable clinical significance because the minimum detectable difference in CDAI that a physician or patient can detect is approximately 50 points (Brant 1999; Feagan 2004). This systematic review critically examines the current available data regarding the efficacy of sulfasalazine and mesalamine for induction of remission or clinical response in patients with mildly to moderately active Crohn's disease and is an update of a previously published Cochrane review (Lim 2010). Where possible, data from comparable trials were pooled together in meta-analyses to obtain a more precise estimate of the treatment effect.

OBJECTIVES

To evaluate the efficacy of aminosalicylates compared to placebo, corticosteroids, and other aminosalicylates (alone or in combination with corticosteroids) for the treatment of mildly to moderately active Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials that evaluated the efficacy sulfasalazine or mesalamine for the treatment of active Crohn's disease.

Types of participants

Adults with mildly to moderately active Crohn's disease.

Types of interventions

Comparison of oral sulfasalazine or mesalamine alone to placebo, corticosteroids, and other aminosalicylates (alone or in combination with corticosteroids).

Types of outcome measures

The primary outcome measure was a well defined clinical endpoint of induction of remission or response to treatment. Secondary outcomes included mean Crohn's disease activity index (CDAI) scores, adverse events, serious adverse events and withdrawal due to adverse events.

Search methods for identification of studies

We searched PubMed, EMBASE, MEDLINE and Cochrane Central Library from inception to June 10, 2015 to identify relevant studies. There were no language restrictions. The search strategy is reported in [Appendix 1](#). In addition, manual searches of the reference list from potentially relevant papers and review articles, as well as proceedings from annual meetings of the American Gastroenterological Association and American College of Gastroenterology from 1991 to 2015 were performed.

Data collection and analysis

Data Collection

Using the above search strategy, two investigators (W.C.L and S.B.H) independently reviewed the titles and abstracts of all identified citations. Manuscripts of potentially relevant studies that evaluated the efficacy of sulfasalazine or 5-ASA for the treatment of Crohn's disease were retrieved and reviewed and only studies that fulfilled the *a priori* defined inclusion criteria were selected. The following exclusion criteria were applied: (1) Non-randomized, uncontrolled, open-label trials, (2) studies involving pediatric population, (3) patients with severely active Crohn's disease, (4) Crohn's disease in remission (medically- or surgically- induced), (5) ulcerative colitis, (6) rectal, or intestinal lavage drug delivery, (7) studies evaluating efficacy of aminosalicylates in combination with other treatments, (8) studies with no comparators, (9) studies that compared 5-ASA to antibiotics, immunosuppressants, nutritional therapy, herbs, yeast, or surgery, (10) studies assessing effect on fecal flora, and (11) crossover studies that do not provide data prior to the first crossover. The results of each study were independently extracted using a form that was developed by the investigators. Disagreement was resolved by consensus. A recent literature search and citation review were performed by Y.W and J.K.M to modernize a previous update by W.C.L and S.B.H.

Statistical Methods

Results using intention-to-treat (ITT) analysis were reported according to the *a priori* definition of the primary endpoint described in each study. Dropouts from studies were regarded as treatment failures regardless of treatment group. When an ITT analysis was not possible, per-protocol-analysis results were reported instead. Where appropriate, results of comparable studies with similar doses of medication and outcomes were pooled and analyzed. The random effects model of DerSimonian and Laird ([DerSimonian 1986](#)) was used to calculate pooled effects estimates. Sensitivity analyses based on the fixed effect model and duration of therapy were also conducted. Heterogeneity between trials was assessed by calculating the chi square test of heterogeneity and a P value of < 0.10 was used to indicate statistically significant heterogeneity between trials; the I^2 statistic was also used to

quantify heterogeneity: a value of > 30% was considered moderate heterogeneity. The risk ratio (RR), 95% confidence intervals (CI), absolute benefit increase (ABI) and numbers needed to treat (NNT) were calculated for each statistically significant outcome. The Cochrane Collaboration Review Manager (RevMan) software (Version 5.3.5) was used for data analysis.

Quality assessment

The methodological quality of the included studies was evaluated using the Cochrane risk of bias tool ([Higgins 2011](#)). Each trial was rated as high, low, or unclear risk for each of the following criteria:

1. Randomization sequence generation;
2. Allocation concealment;
3. Blinding;
4. Missing data and attrition;
5. Outcome reporting; and
6. Other sources of bias.

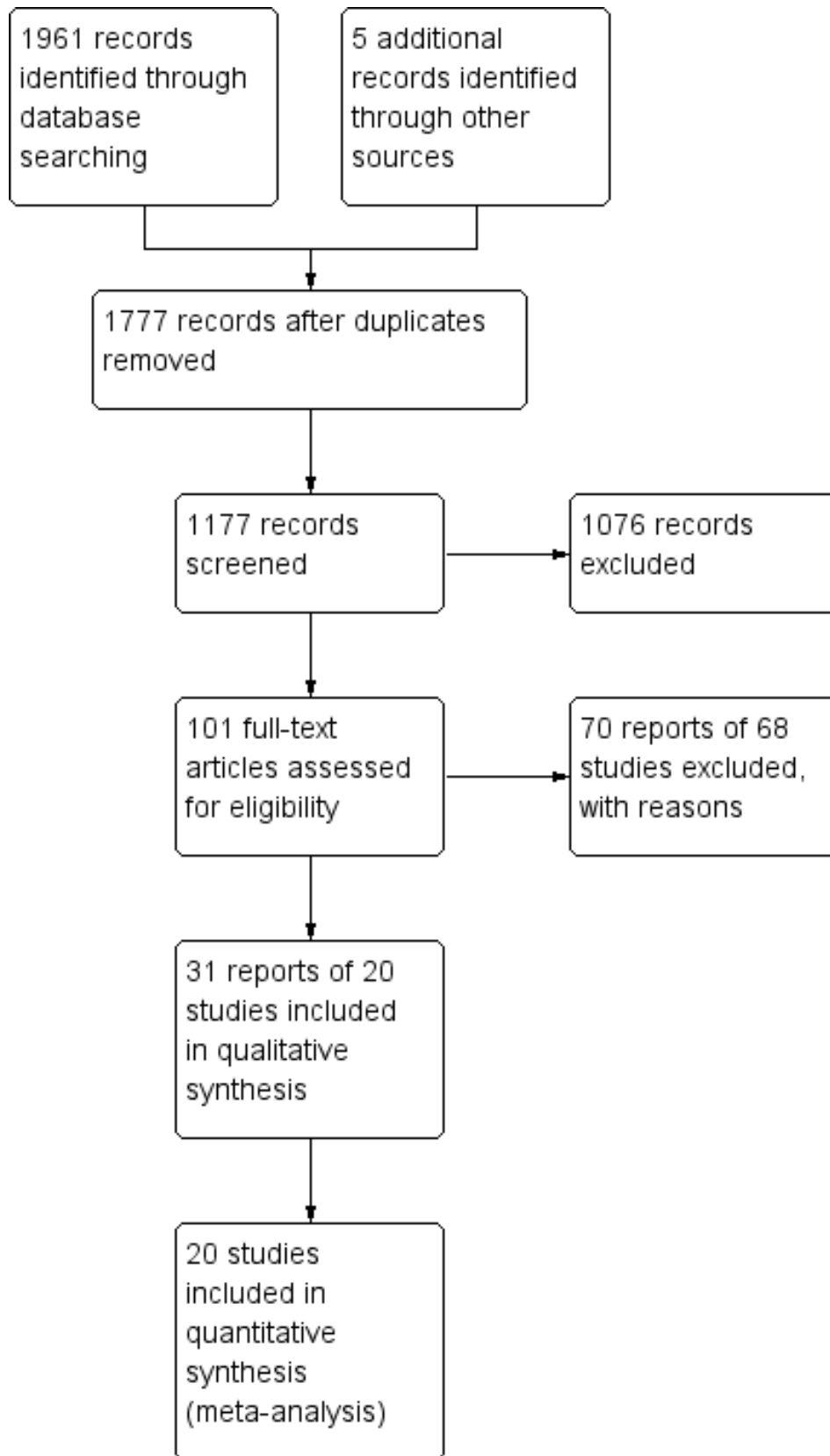
The overall quality of the evidence supporting the primary outcomes was evaluated using the GRADE approach ([Guyatt 2008](#); [Schünemann 2011](#)). Randomized trials are considered to provide high quality evidence, but may be downgraded due to: (1) risk of bias, (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias). The different quality ratings are interpreted as the likelihood that future research would change the effect estimate. Further research is unlikely to change the effect estimate if the evidence is high quality. If the overall evidence is of moderate quality further research may have an impact on our confidence in the effect estimate and may change the estimate. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate when the evidence is rated as low quality. Very low quality research means that we are very uncertain about the finding ([Guyatt 2008](#); [Schünemann 2011](#)).

RESULTS

Description of studies

A literature search conducted on 10 June 2015 identified 1961 studies. Five additional studies were identified through searching of references. After duplicates were removed a total of 1177 reports remained for review of titles and abstracts. Two authors independently reviewed the titles and abstracts of these studies and 101 reports were selected for full text review (See [Figure 1](#)). Seventy reports of 68 studies were excluded (See [Characteristics of excluded studies](#) and additional [Table 1](#)). Thirty-one reports of 20 studies involving a total of 2367 patients, were selected for inclusion (See [Characteristics of included studies](#)).

Figure 1. Study flow diagram.



Two studies included more than two treatments arms ([Malchow 1984](#); [Summers 1979](#)). Comparisons are described below.

- a. Three studies compared the efficacy of sulfasalazine with placebo ([Summers 1979](#); [Van Hees 1981](#); [Malchow 1984](#)).
- b. Two studies compared the efficacy of sulfasalazine with corticosteroids ([Summers 1979](#); [Malchow 1984](#)).
- c. Two studies examined the efficacy of sulfasalazine either alone or in combination with corticosteroids ([Malchow 1984](#); [Rijk 1991](#)).
- d. Eight studies compared the efficacy of mesalamine with placebo ([Saverymuttu 1986](#); [Rasmussen 1987](#); [Mahida 1990](#); [Singleton 1993](#); [Singleton 1994](#); [Crohn's III 1997](#); [Tremaine 1994](#); [Wright 1995](#)).
- e. Four studies compared the efficacy of mesalamine with conventional corticosteroids ([Martin 1990](#); [Scholmerich 1990](#); [Gross 1995](#); [Prantera 1999](#)).
- f. Two studies compared the efficacy of mesalamine with budesonide ([Thomsen 1998](#), [Tromm 2011](#)).
- g. Two studies compared the efficacy of mesalamine with sulfasalazine (either alone or in combination with corticosteroids) ([Maier 1985](#); [Maier 1990](#)).

One German article was translated with the assistance of an interpreter ([Maier 1985](#)).

Risk of bias in included studies

The risk of bias results were summarized in [Figure 2](#). Four of the 20 included studies were rated as low risk of bias for all six items ([Malchow 1984](#); [Prantera 1999](#); [Summers 1979](#); [Tromm 2011](#)). The authors were unable to assess the risk of bias for 2 studies, because they were not fully published ([Crohn's III 1997](#); [Singleton 1994](#)). The risk of bias was high for 2 studies that did not use blinding ([Maier 1985](#); [Maier 1990](#)) or unclear for some quality items in 11 studies (due to inadequate descriptions of methods used for sequence generation and/or allocation concealment; [Gross 1995](#); [Mahida 1990](#); [Martin 1990](#); [Rasmussen 1987](#); [Rijk 1991](#); [Saverymuttu 1986](#); [Scholmerich 1990](#); [Singleton 1993](#); [Tremaine 1994](#); [Van Hees 1981](#); [Wright 1995](#)). Two studies ([Rijk 1991](#); [Wright 1995](#)) scored high risk of bias for incomplete outcome data and selective reporting. In addition, six other studies were rated as high risk for attrition bias ([Crohn's III 1997](#); [Rasmussen 1987](#); [Singleton 1993](#); [Singleton 1994](#); [Thomsen 1998](#); [Tremaine 1994](#)).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Crohn's III 1997	?	?	?	-	?	?
Gross 1995	?	?	+	+	+	+
Mahida 1990	?	+	+	+	+	+
Maier 1985	?	?	-	+	+	+
Maier 1990	?	?	-	+	+	+
Malchow 1984	+	+	+	+	+	+
Martin 1990	?	?	?	+	+	+
Prantera 1999	+	+	+	+	+	+
Rasmussen 1987	?	+	+	-	+	+
Rijk 1991	+	?	+	-	-	+
Saverymuttu 1986	?	?	+	+	+	+
Scholmerich 1990	?	?	+	?	?	+
Singleton 1993	?	?	+	-	+	?
Singleton 1994	?	?	?	-	?	?
Summers 1979	+	+	+	+	+	+
Thomsen 1998	+	+	+	-	+	+
Tremaine 1994	?	?	+	-	+	+
Tromm 2011	+	+	+	+	+	+
Van Hees 1981	?	?	+	+	+	+
Wright 1995	+	?	+	-	-	+

Effects of interventions

See: [Summary of findings for the main comparison](#) Sulfasalazine compared to placebo for induction of remission or response in Crohn's disease; [Summary of findings 2](#) Sulfasalazine compared to Corticosteroids for induction of remission or response in Crohn's disease; [Summary of findings 3](#) Sulfasalazine compared to Sulfasalazine and corticosteroids for induction of remission or response in Crohn's disease; [Summary of findings 4](#) Controlled-release mesalamine (1 - 2 g/day) compared to Placebo for induction of remission or response in Crohn's disease; [Summary of findings 5](#) Controlled-release mesalamine (4 g/day) compared to Placebo for Induction of remission or response in Crohn's disease; [Summary of findings 6](#) Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) compared to Placebo for Induction of remission or response in Crohn's disease; [Summary of findings 7](#) Delayed-release mesalamine (3 - 4.5 g/day) compared to Corticosteroids for Induction of remission or response in Crohn's disease; [Summary of findings 8](#) Mesalamine (4 - 4.5 g/day) compared to Budesonide for Induction of remission or response in Crohn's disease; [Summary of findings 9](#) Mesalamine compared to Sulfasalazine (alone or in combination with corticosteroids) for Induction of remission or response in Crohn's disease

Sulfasalazine

a. Sulfasalazine versus placebo

Three trials compared the efficacy of sulfasalazine with placebo ([Van Hees 1981](#); [Summers 1979](#); [Malchow 1984](#)). Due to a lack of available data in these trials, only per protocol results were reported in this review.

[Van Hees 1981](#)

[Van Hees 1981](#) randomly assigned 27 patients with active Crohn's disease to receive sulfasalazine 4 to 6 g/day (n = 13) or placebo (n = 13) for 26 weeks. More sulfasalazine-treated patients responded ($\geq 25\%$ decrease in baseline Van Hees Activity Index [VHAI]) than those assigned to placebo (61.5% [8/13] versus 7.7% [1/13], $P = 0.03$; RR 8; 95% CI 1.16 to 55.2), ABI = 53.8%, NNT = 2). Firm conclusions cannot be made due to the small sample size of this study.

[Summers 1979](#)

The National Cooperative Crohn's Disease Study (NCCDS) compared the efficacy of sulfasalazine, prednisone and azathioprine to placebo in a two-part, multicenter trial ([Summers 1979](#)). Six hundred and four patients with Crohn's disease were randomized into Part I or Part II of the study. Thirty-five randomized patients were excluded from the final analysis due to an erroneous diagnosis (20), inappropriate entry (12) or administrative error during the conduct of the trial (3). In part I of the study, data from 295 patients with active Crohn's disease, randomized to 1 g/15kg sulfasalazine (n = 74), 0.25 to 0.75 mg/kg prednisone (dose adjusted according to disease activity, n = 85), 2.5 mg/kg azathioprine (n = 59) or placebo (n = 77) for 17 weeks were analyzed. The dose of sulfasalazine ranged from 2 to 5 g/day (mean 4 g/day). Remission (CDAI < 150) was achieved in 38% (28/74) of sulfasalazine-treated patients versus 26% (20/77) in the placebo group ($P = 0.12$). Patients with Crohn's colitis (with [$P = 0.027$] or without [$P = 0.006$] small bowel disease) or those who were treatment-naïve at entry ($P = 0.01$) were more likely to respond. These data suggest that patients who continued to have active disease despite prior treatment with steroids or sulfasalazine were

unlikely to respond to further sulfasalazine therapy. There was no statistically significant difference in the proportion of patients who experienced an adverse event or serious adverse event. Fourteen per cent of patients sulfasalazine experienced at least one adverse event during the induction study compared to 6% of placebo patients (RR 2.08, 95% CI 0.75 to 5.80). There were no serious adverse events in the sulfasalazine group compared to one event in the placebo group (RR 0.35, 95% CI 0.01 to 8.38). Adverse events reported in the sulfasalazine group included skin rash, nausea and vomiting, headache and leukopenia. Adverse events reported in the placebo group included depression, abscess, candidiasis of mouth and duo ulcer (serious adverse event).

[Malchow 1984](#)

In the European Cooperative Crohn's Disease Study (ECCDS) ([Malchow 1984](#)) randomized 455 patients with Crohn's disease to receive sulfasalazine, 6-methylprednisolone, combination therapy (sulfasalazine with 6-methylprednisolone) or placebo. Three patients were excluded after randomization due to an incorrect diagnosis. Of 452 patients, 215 had active disease (CDAI ≥ 150) were treated with sulfasalazine 3 g/day (n = 54), 6-methylprednisolone (48 mg/day tapered weekly to 12 mg/day, n = 47), combination therapy (n = 56) or placebo (n = 58) for 6 weeks. Patients could be re-treated with the same drug regimen once or twice if induction therapy was not successful. Although there were significantly fewer "treatment failures and relapses" in the sulfasalazine group compared to placebo ($P < .05$), particularly in patients with colonic disease ($P < .01$), the difference in proportions of patients in remission (CDAI < 150) before the end of 18 weeks was not significant (sulfasalazine: 27/54, 50%; placebo: 22/58, 38%; $P = 0.20$). Common adverse events reported in the sulfasalazine group included nausea, headache, infection, hypertension, anorexia, back pain, and skin rash. Common adverse events reported in the placebo group included nausea, headache, infection, hypertension, anorexia, back pain, skin rash and acne.

[Pooled analysis](#)

In a combined analysis of three trials (n = 289), sulfasalazine was not superior to placebo for inducing remission or response at 17 to 26 weeks of follow-up (See [Analysis 1.1](#)) Forty-five per cent (63/141) of sulfasalazine patients entered remission or responded compared to 29% (43/148) of placebo patients (RR 1.52; 95% CI 0.95 to 2.43; $P = 0.08$). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to sparse data and heterogeneity (See [Summary of findings for the main comparison](#)). However, moderate heterogeneity was observed (test of heterogeneity $\chi^2 = 3.38$, $P = 0.18$, $I^2 = 41\%$) for this comparison. A visual inspection of the forest plot indicated that the [Van Hees 1981](#) study was the likely source of this heterogeneity and this study employed different measures of treatment response and duration of therapy than the larger trials ([Summers 1979](#); [Malchow 1984](#)). A sensitivity analysis combining data from only the NCCDS and ECCDS (n = 263) that employed similar efficacy measures, therapeutic endpoints and duration of therapy (See [Analysis 1.2](#); [Analysis 1.3](#)) reduced the I^2 value to zero. A trend in favour of sulfasalazine over placebo for inducing remission was observed at 17-18 weeks follow-up (random-effects model: RR 1.38; 95% CI 1.00 to 1.89, $P = 0.05$; fixed-effect model: RR 1.38; 95% CI 1.01-1.90; $P = 0.05$, ABI = 12%, NNT = 8). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (See [Summary of findings for the main comparison](#)). A pooled analysis of three studies (n = 289 patients)

found no difference in the proportion of patients who withdrew due to adverse events. Seven per cent (10/141) of sulfasalazine patients withdrew due to an adverse event compared to 6% (9/148) of placebo patients (RR 1.00, 95% CI 0.26 to 3.83).

b. Sulfasalazine versus corticosteroids

Two trials, the NCCDS (Summers 1979) and ECCDS (Malchow 1984), compared the efficacy of sulfasalazine with corticosteroids. Per-protocol results were reported due to lack of data.

Summers 1979

In the NCCDS, 38% (28/74) of sulfasalazine-treated patients achieved remission compared to 47% (40/85) in the prednisone group ($P = 0.25$). Common adverse events reported in the prednisone group included acne, ecchymosis, moon face, psychic disturbances, peptic symptoms and hypertension.

Malchow 1984

In the ECCDS, less sulfasalazine-treated patients achieved remission compared to 6-methylprednisolone (50% [27/54] versus 83% [39/47], $P = 0.001$). Common adverse events reported in the 6-methylprednisolone group included acne, moon face, headache, hypertension and infection.

Pooled analysis

Combining results from these two trials ($n = 260$), sulfasalazine was clearly inferior to corticosteroids at 17 to 18 weeks of follow-up (See [Analysis 2.1](#)). Forty-three per cent (55/128) of sulfasalazine patients entered remission compared to 60% (79/132) corticosteroid patients (RR 0.68; 95% CI 0.51 to 0.91, $P = 0.009$). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (See [Summary of findings 2](#)). A sensitivity analysis using a fixed-effect model had minimal impact: RR 0.70; 95% CI 0.55 to 0.88. A sensitivity analysis based on duration of therapy was not carried out, as the two trials had a similar duration of treatment.

c. Sulfasalazine versus combination therapy with sulfasalazine and corticosteroids

Two trials examined the efficacy of sulfasalazine either alone or in combination with corticosteroids. Per-protocol results were reported due to the lack of data.

Malchow 1984

In the ECCDS (Malchow 1984), 50% (27/54) of sulfasalazine-treated patients achieved remission at 18 weeks compared with 79% (44/56) in the combination therapy group (RR 0.64; 95% CI 0.47 to 0.86; $P = 0.003$). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (See [Summary of findings 3](#)). In those that achieved remission, the CDAI score decreased to approximately 32% (sulfasalazine group) and 29% (combination group) of its initial value at the end of 18 weeks (See [Comparison 3](#), Outcome 01; [Analysis 3.1](#)). The overall final CDAI in each treatment group was not reported. Common adverse events reported in the combination therapy group included acne, moon face, headache, back pain, hypertension and infection.

Rijk 1991

Rijk 1991 randomly assigned 71 patients (11 dropouts) with active CD to receive higher doses of sulfasalazine at 4 to 6 g/day alone

($n = 30$) or in combination with lower doses of corticosteroids, prednisone 30 mg/day, equivalent to methylprednisolone 24 mg/day ($n = 30$, tapered 5 mg/2-weeks and maintained at 10 mg/day) for 16 weeks. Therapeutic response in the initial 6 weeks (initial response) and the last 4 weeks (final response) were assessed using the Van Hees Activity Index (VHAI) and CDAI. Based on VHAI scores, a significantly greater and more rapid initial response was observed with combination therapy (median 30% decrease versus 13%, $P = 0.001$). This advantage remained statistically significant only in the a priori subgroup analysis of patients with severe disease at entry (VHAI ≥ 175) in the final response (median decrease 58% versus 30%, $P = 0.02$). A greater but insignificant decline in CDAI scores was seen with combination therapy (initial response: decrease of 35% versus 25%, $P > 0.2$; final response: decrease of 35% versus 24%, $P = 0.19$). The proportion of patients in remission was not reported in this trial. Although three of 11 drop-outs withdrew due sulfasalazine-related adverse events, adverse events were not reported on as an outcome.

Although results from these 2 trials could not be pooled together as they employed differing dosages, treatment regimens and endpoints, the results are consistent: sulfasalazine monotherapy was inferior to combination therapy with corticosteroids, particularly in patients with severe disease.

Mesalamine

a. Mesalamine versus placebo

Eight placebo-controlled trials evaluated the efficacy of different dosages of controlled-release mesalamine (Pentasa), delayed-release mesalamine (Asacol) and olsalazine (Dipentum) for the treatment of mildly to moderately active Crohn's disease.

Controlled-release Mesalamine 1 to 2 g/day

Saverymuttu 1986

Saverymuttu 1986 provided some evidence that controlled-release mesalamine reduced gut inflammation in mildly-moderately active Crohn's colitis. Twelve patients were randomized to receive 1.5 g/day of Pentasa ($n = 6$) or placebo ($n = 6$) for 10 days. The primary outcome of the study was assessment of disease activity at the end of the study period with fecal granulocyte excretion, CDAI and erythrocyte sedimentation rate (ESR). Fecal granulocyte excretion was significantly reduced in all Pentasa-treated patients (5% decrease, $P < 0.01$) but not in the placebo group (2.1% decrease, $P = \text{NS}$). No significant changes in CDAI or ESR were observed in this small study. One placebo patient withdrew due to an adverse event (nausea). No other adverse events were reported.

Three subsequent published studies (Rasmussen 1987; Mahida 1990; Singleton 1993) and one unpublished studies (Singleton 1994) examined the therapeutic efficacy of controlled-release mesalamine at 1 to 2 g/day. Results based on ITT analysis are reported in this review.

Rasmussen 1987

Sixty-seven patients with active Crohn's disease were randomized to Pentasa 1.5 g/day ($n = 30$) or placebo ($n = 37$) for 16 weeks (Rasmussen 1987). There was no significant difference between the treatment groups in the proportion of patients who achieved remission (as defined by Tvede 1983) or improvement (Pentasa 13/30, 43.3% versus placebo 9/37, 24.3%; RR 1.78; 95% CI 0.88 to

3.59). In addition, the cumulative proportion of patients achieving a > 33% reduction in CDAI did not differ between the 2 groups: 26% (Pentasa) versus 24% (placebo), $P > 0.5$. Common adverse events included headache, nausea and vomiting and itching. No serious adverse events were reported.

Mahida 1990

Similarly, Mahida and colleagues (Mahida 1990) did not find any therapeutic benefit of Pentasa 1.5 g/day in a pilot trial in which 40 patients with active Crohn's disease were randomly assigned to Pentasa 1.5 g/day ($n = 20$) or placebo ($n = 20$) for 6 weeks; 40% (8/20) and 35% (7/20) in the Pentasa and placebo group achieved "improvement" respectively, defined as a reduction of Harvey Bradshaw Index (HBI) by = 2 points ($P = 0.74$). Seven patients in the Pentasa group withdrew due to adverse events including deteriorating Crohn's disease (4 patients), abdominal distension and pain (1 patient) and malaise (2 patients). Four patients in the placebo group withdrew due to adverse events including deteriorating Crohn's disease (3 patients) and nausea (1 patient).

Singleton 1993

In the third trial, Singleton and colleagues (Singleton 1993) compared three daily doses of Pentasa at 1 g ($n = 80$), 2 g ($n = 75$) and 4 g ($n = 75$) with placebo ($n = 80$) in 310 patients with active CD for 16 weeks. Mean CDAI reductions (baseline to final study visit) in patients taking the 1 g/day (-8) and 2 g/day (-29) doses did not differ significantly from placebo-treated patients (-21). Remission (defined as CDAI ≤ 150 with > 50-points reduction) and therapeutic benefit (defined as ≥ 50 -points reduction) was achieved in 22.5% (18/80) and 36.3% (29/80) in the 1-g group, 24% (18/75) and 38.7% (29/75) in the 2-g group, 17.5% (14/80) and 40% (32/80) in the placebo group respectively ($P > 0.05$). Results for the higher 4 g/day dose will be discussed in the next section. Common adverse events included nausea or vomiting, headache, abdominal pain, diarrhea and rash.

Singleton 1994

In a second trial by the same investigator (Singleton 1994, not fully published), 232 patients with active Crohn's disease were randomized to receive Pentasa 2 g/day ($n = 82$), 4 g/day ($n = 75$), or placebo ($n = 75$) for 16 weeks. Remission rates were not reported. There were no significant differences in CDAI scores between the Pentasa 2 g, 4 g and placebo groups ($P > 0.05$). The actual CDAI values were not available for the 2 g group; results on the 4 g group are discussed in the next section.

Pooled analysis

Result from these three studies (Rasmussen 1987; Mahida 1990; Singleton 1993), were combined and analyzed ($n = 342$). Pentasa at 1 to 2 g/day was not superior to placebo for inducing a therapeutic benefit defined by improvement in disease activity. Thirty-eight per cent (79/205) of Pentasa patients improved compared to 35% (48/137) of placebo patients (RR 1.07; 95% CI 0.80 to 1.42; $P = 0.65$; See Analysis 4.1). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to sparse data and risk of bias (See Summary of findings 4). For the endpoint of induction of remission, results from Rasmussen 1987 and Singleton 1993 were pooled ($n = 302$). Similarly, Pentasa 1 to 2 g/day was not superior to placebo at 16 weeks follow-up (See Analysis 4.2). Twenty-three per cent (43/185) of Pentasa patients entered remission compared to 15% (18/117) of placebo patients (RR 1.46; 95% CI 0.89 to 2.40; $P = 0.14$). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome

was low due to sparse data and risk of bias (See Summary of findings 4). Sensitivity analyses using a fixed-effect model had minimal impact on point estimates with with a pooled RR of 1.08 for clinical improvement (95% CI 0.81 to 1.43) and 1.46 for clinical remission (95% CI 0.89 to 2.40) respectively. Sensitivity analysis based on duration of therapy, performed by excluding Mahida 1990, yielded similar RR of 1.08 (95% CI 0.75 to 1.54) and 1.46 (95% CI 0.89 to 2.40) respectively. A pooled analysis of two studies (342 patients) showed no statistically significant difference in the proportion of patients who had an adverse event or withdrew due to adverse events. Twenty-eight per cent (58/205) of Pentasa patients had an adverse event compared to 23% (31/137) of placebo patients (RR 1.33, 95% CI 0.91 to 1.96). Twenty per cent (41/205) of Pentasa patients withdrew due to an adverse event compared to 15% (21/137) of placebo patients (RR 1.21, 95% CI 0.75 to 1.95).

Controlled-release Mesalamine 4 g/day

The efficacy of higher doses of Pentasa at 4 g/day was evaluated in three similarly designed, randomized, double-blind, placebo-controlled trials (Singleton 1993, Singleton 1994, Crohn's III 1997). Results based on ITT analysis are reported here. The proportion of patients in remission was only available for Singleton 1993. An attempt to provide additional information regarding the efficacy of high dose controlled release 5-ASA in a meta-analysis was performed by Hanauer 2004 using individual patient data from the three trials. This analysis revealed a small difference in reduction of CDAI between Pentasa and placebo treated patients of only 18 points ($P = 0.04$).

Singleton 1993

In the first Singleton trial (described in the previous section), Pentasa 4 g/day significantly reduced baseline CDAI (-72 versus -21, $P = 0.005$). A greater proportion of patients in the Pentasa 4 g/day group achieved remission (42.7% [32/75] versus 17.5% [14/80], $P = 0.001$; RR 2.44 [95% CI 1.42 to 4.20], ABI = 25% and NNT = 4) and therapeutic benefit (64% [48/75] versus 40% [32/80], $P = 0.004$; RR 1.6 [95% CI 1.16 to 2.20], ABI = 24% and NNT = 4) when compared to placebo. The largest CDAI reduction was observed in those with isolated ileal disease (Singleton 1993). There was no statistically significant difference in the proportion of patients who experienced an adverse event or withdrew due to an adverse event. Twenty-seven per cent (20/75) of Pentasa 4 g/day patients had an adverse event compared to 19% (15/80) of placebo patients (RR 1.42, 95% CI 0.79 to 2.57). Twelve per cent (9/75) of Pentasa 4 g/day patients withdrew due to an adverse event compared to 19% (15/80) of placebo patients (RR 0.64, 95% CI 0.30 to 1.37). Common adverse events included nausea or vomiting, headache, abdominal pain, diarrhea and rash.

Singleton 1994

In the second Singleton trial (described in the previous section), there were no significant differences in reduction of CDAI scores between the Pentasa 4 g/day and placebo groups (Pentasa 4 g/day -41 versus placebo -35; WMD -6; 95% CI -39 to -27) (Singleton 1994). Remission rates were not reported.

Crohn III 1997

In this third, unpublished, trial, Hanauer and colleagues (Crohn's III 1997), randomly assigned 310 patients to receive Pentasa 4 g/day ($n = 154$) or placebo ($n = 156$) for 16 weeks. There were no statistically significant differences in CDAI scores between the Pentasa 4 g/day and placebo groups (Pentasa 4 g/day -72 versus placebo -64; WMD

-8; 95% CI -33 to -17). The proportions of patients that achieved remission or therapeutic benefit were not reported.

Pooled analysis

Data from these three studies were combined using an ITT approach (n = 615). A non-significant mean difference (Pentasa - placebo) in CDAI reduction of -19.8 (95% CI -46.2 to 6.7, P = 0.14) points was obtained (See [Analysis 5.1](#)). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to heterogeneity and risk of bias (See [Summary of findings 5](#)). However, a sensitivity analysis based on a fixed-effect model yielded a mean difference in CDAI reduction of -17.5 (95% CI -35 to -0.1, P = 0.05; See [Analysis 5.2](#)). This difference is of questionable clinical significance because the minimum detectable difference in CDAI that a patient can detect is approximately 50 points (Brant 1999; Feagan 2004).

Delayed-release mesalamine

Tremaine 1994

Thirty-eight patients with active Crohn's disease were randomly assigned to Asacol 3.2 g/day (n = 20) or placebo (n = 18) for 16 weeks (Tremaine 1994). On ITT analysis, more patients in the Asacol group (12/20, 60%) achieved 'complete success' (CDAI < 150 with ≥ 70-points reduction) or 'partial success' (CDAI ≥ 150 with ≥ 70-points reduction) compared to only 22.2% (4/18) in the placebo group (RR 2.70; 95% CI 1.06 to 6.88; P = 0.04; ABI = 37.8%; NNT = 3). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to high risk of bias due to incomplete outcome data and very sparse data (See [Summary of findings 6](#)). The difference in proportions of patients with 'complete success' (i.e. clinical remission) was not statistically significant (Asacol: 9/20, 45%; placebo: 4/18, 22.2%; RR 2.02, 95% CI 0.75 to 5.45; P = 0.16). Given the small sample size, a type II error has to be considered (See [Analysis 6.1](#); [Analysis 6.2](#)). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to high risk of bias due to incomplete outcome data and very sparse data (See [Summary of findings 6](#)). Common adverse events included arthralgias, headache, abdominal cramps, nausea and dizziness.

Azo-bonded mesalamine: Olsalazine

Wright 1995

Ninety-one patients with active Crohn's disease were randomized to receive olsalazine 2 g/day (n = 46) or placebo (n = 45) for 16 weeks (Wright 1995). A high withdrawal rate was observed: 35 of 46 (76.1%) patients taking olsalazine and 24 of 45 (53.3%) patients taking placebo. Although withdrawal rates for uncontrolled active disease were similar (28.3% versus 33.3% respectively, P = 0.6), a significant proportion of patients in the olsalazine group withdrew because of diarrhea (22% versus 4% respectively, P = 0.015). On ITT analysis, only 17.4% (8/46) olsalazine-treated patients entered remission or had symptomatic improvement compared with 48.8% (22/45) placebo-treated patients (RR 0.36, 95% CI 0.18 to 0.71; P = 0.004). However, this study was limited by high withdrawal rates and the small number of patients that actually completed the study (See [Analysis 6.1](#)). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to high risk of bias due to incomplete outcome data and very sparse data (See [Summary of findings 6](#)). Common adverse events included diarrhea, vomiting, pain, anorexia and itching rash.

b. Mesalamine versus corticosteroids

Delayed-release mesalamine versus conventional corticosteroids

Four published trials compared delayed-release mesalamine with a tapering dose of conventional corticosteroids.

Scholmerich 1990

In the first trial, Schölmerich and colleagues (Scholmerich 1990), randomized 62 patients with active Crohn's disease to Salofalk 2 g/day (n = 30) or 6-methylprednisolone 48 mg/day (n = 32, tapered to 8 mg/day over 5 weeks) for 24 weeks: 73% (22/30) Salofalk-treated patients stopped treatment due to "insufficient efficacy" compared to 34% (11/32) in the 6-methylprednisolone group (P = 0.002), with corresponding lesser reduction in median CDAI scores (-58 versus -151 respectively, P < .001).

Three subsequent trials evaluated the efficacy of higher doses of delayed-release mesalamine (3 to 4.5 g/day) compared to conventional corticosteroids, with a total of 178 patients. Results based on ITT analysis are reported here.

Martin 1990

Martin and colleagues compared the efficacy of Salofalk 3 g/day (n = 22) with prednisone 40 mg (n = 28, 4 mg/week taper from third week) in 50 patients with active Crohn's disease (60% with isolated ileitis) over 12 weeks (Martin 1990). At week 12, remission (CDAI < 150) was achieved in 40.9% (9/22) Salofalk group and 42.9% (12/28) prednisone group (RR 0.95, 95% 0.49 to 1.85; P = 0.89). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to very sparse data (See [Summary of findings 7](#)). Final mean CDAI reductions (-144 versus -147 respectively) were similar, although initial CDAI reduction was more rapid in the prednisone group. Post hoc subgroup analysis revealed that prednisone was significantly better at reducing CDAI at almost all time points in patients with ileocolitis; however, no difference in efficacy was found in patients with ileitis alone. Although a higher proportion of patients in the prednisone group experienced at least one adverse event (16/28) compared to the Salofalk group (6/22), the difference was not statistically significant (P = 0.05). Adverse events reported in the Salofalk group included insomnia, headache, edema and nausea. Adverse events reported in the prednisone group included hyperactivity, insomnia, headache, tiredness, edema, acne, and candidiasis. There was no difference in the proportion of patients who experienced a serious adverse event (P = 0.85). There were two serious adverse events in the Salofalk group (one patient with viral hepatitis and one patient with headaches and continuous vomiting) compared to three in the prednisone group (one patient with severe headache, one patient with severe intercostal herpes zoster and patient with severe cushingoid symptoms).

Gross 1995

In the second trial, 34 patients with active Crohn's disease (majority ileocolitis) were randomized to Salofalk 4.5 g/day (n = 17) or 6-methylprednisolone 48 mg/day (n = 17, 8 mg weekly taper) for 8 weeks (Gross 1995). At 8 weeks, 35.3% (6/17) and 52.9% (9/17) patients achieved remission (CDAI < 150 with ≥ 60-points decrease) respectively (RR 0.67, 95% CI 0.30 to 1.46; P = 0.3). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to very sparse data (See [Summary of findings 7](#)). Median change in CDAI: -85 (Salofalk) versus -122 (6-methylprednisolone), P = 0.74. Although a trend towards higher

efficacy with 6-methylprednisolone was observed, a true difference may have been missed given the small size of this study. There was no statistically significant difference in the proportion of patients who had an adverse event. Sixty-five per cent (11/17) of patients in the Salofalk group had an adverse event compared to 58% (10/17) of 6-methylprednisolone patients ($P = 0.72$).

Prantera 1999

In the third and largest trial, 94 patients with active Crohn's disease (distal ileum or ileocecal region) were randomly assigned to treatment with Asacol tablets ($n = 35$) or Asacol microgranules ($n = 28$) at 4 g/day (tapered to 2.4 g/day), or 6-methylprednisolone 40 mg/day ($n = 31$, 4mg weekly taper from third week) for 12 weeks (Prantera 1999). Stringent entry criteria led to recruitment of only 43% of the original planned sample size. At 12 weeks, remission ($CDAI \leq 150$) was achieved in 60% (21/35), 78.6% (22/28) and 61.3% (19/31), with median CDAI reduction of 113.5, 123 and 154 in the Asacol tablets, Asacol microgranules and 6-methylprednisolone groups respectively ($P = 0.27$ and $P = 0.07$). The RR for the comparison of Asacol tablets to corticosteroids was 1.00 (95% CI 1.00, 95% CI 0.61 to 1.64). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (See [Summary of findings 7](#)). The RR for the comparison of Asacol granules to corticosteroids was 1.26 (95% CI 0.82 to 1.92). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (See [Summary of findings 7](#)). A significantly higher proportion of adverse events was reported in the 6-methylprednisolone group (14/31) compared to the Asacol tablets (5/35) and Asacol microgranules (3/28) groups. Adverse events thought to be related to steroids included acne, moon faces, hypertension, insomnia and excitability. Adverse events thought to be related to mesalamine included acute pancreatitis. A higher proportion of serious adverse events was reported in the 6-methylprednisolone group (5/31) compared to the Asacol tablets (0/35) and Asacol microgranules (1/28) groups.

Pooled analysis

The results of these three trials examining higher doses of delayed-release mesalamine were combined and analyzed ($n = 178$). No significant difference in efficacy between delayed-release mesalamine and conventional steroids was found. Fifty-seven per cent (58/102) of mesalamine patients achieved remission compared to 53% of corticosteroid patients (RR 1.04, 95% CI 0.79 to 1.36; See [Analysis 7.1](#)). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (See [Summary of findings 7](#)). Sensitivity analysis based on the fixed effect model and duration of therapy (by excluding Gross et al) had minimal effects on the results: RR 1.00 (95% CI 0.75 to 1.31) and 1.10 (95% CI 0.82 to 1.47) respectively. When the three studies were pooled to assess adverse events there was no statistically significant difference in the proportion of patients who experienced at least one adverse event, a serious adverse event, or withdrawal due to adverse events. Twenty-four per cent (25/102) of mesalamine patients had at least one adverse event compared to 53% (40/76) of corticosteroid patients (RR 0.49, 95% CI 0.23 to 1.05; $P = 0.07$). Three per cent (3/102) of mesalamine patients had a serious adverse event compared to 10% (8/76) of corticosteroid patients (RR 0.35, 95% 0.10 to 1.27; $P = 0.11$). Four per cent (4/102) of mesalamine patients withdrew due to an adverse event compared to 13% (10/76) of corticosteroid patients (RR 0.39, 95% 0.13 to 1.15; $P = 0.09$).

Mesalamine versus budesonide

Two studies evaluated the efficacy of controlled-release (Pentasa) and delayed-release (Salofalk) mesalamine compared with budesonide in patients with mildly to moderately active Crohn's disease.

Thomsen 1998

The first trial compared Pentasa with budesonide (Entocort®) (Thomsen 1998). One hundred and eighty-two patients with active Crohn's disease (disease limited to distal ileum and ascending colon) were randomly assigned to receive Pentasa 4 g/day ($n = 89$) or budesonide 9 mg/day ($n = 93$) for 16 weeks. Pentasa was significantly less effective than budesonide for inducing remission ($CDAI \leq 150$): 33.7% (30/89) Pentasa group versus 60.2% (56/93) budesonide group at 16 weeks (RR 0.56, 95% CI 0.40 to 0.78; $P = 0.0007$; See [Analysis 8.1](#)). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to high risk of bias due to incomplete outcome data and sparse data (See [Summary of findings 8](#)). For budesonide, the calculated RR was 1.79 (95% CI 1.28-2.50), ABI = 26.5% and a NNT = 4. Lower remission rates were observed for patients with more severe disease at entry ($CDAI > 300$, 11% Pentasa versus 41% budesonide, $P = 0.01$, RR 0.26 [95% CI 0.08 to 0.84]) and in those with colonic involvement (23% versus 56% respectively, $P = 0.03$, RR 0.41 [95% CI 0.21 to 0.77]) although budesonide was still more effective than Pentasa. The median time to remission was numerically but not significantly longer with mesalamine treatment (28 versus 58 days, $P = 0.12$) (Thomsen 2001). There was no statistically significant difference in the proportion of patients who had an adverse event or serious adverse event. Seventy-two per cent (64/89) of Pentasa patients experienced at least one adverse event compared to 63% (59/93) of budesonide patients (RR 1.13, 95% CI 0.93 to 1.39; $P = 0.22$). Nineteen per cent (17/89) of Pentasa patients had a serious adverse event compared to 12% (11/93) of budesonide patients (RR 1.61, 95% CI 0.80 to 3.25; $P = 0.18$). Significantly more Pentasa patients withdrew due to an adverse event compared to budesonide patients. Thirty-nine per cent (35/89) of Pentasa patients withdrew due to an adverse event compared to 14% (13/93) of budesonide patients (RR 2.81, 95% CI 1.60 to 4.96; $P = 0.0003$). Common adverse events included headache, abdominal pain, enteritis, nausea, back pain, dizziness, vomiting, anemia, depression and flatulence.

Tromm 2011

Tromm 2011 compared Salofalk to budesonide (Budenofalk) in a study that was originally designed to assess the superiority of budesonide over mesalamine, but was converted to a non-inferiority study due to a higher than expected response in the mesalamine arm. Three hundred and nine patients with mildly to moderately active Crohn's disease confined to the terminal ileum and/or ascending colon (84%) or distal colon (16%) were randomly assigned to receive Salofalk 4.5 g/day ($n = 153$) or budesonide 9 mg/day (taken 9 mg once daily [$n = 76$] or 3 mg three times daily [$n = 78$]; 2 patients were excluded from the analysis as baseline CDAI was less than 150) for 8 weeks. Remission ($CDAI \leq 150$) was achieved in 62.1% (95/153) in those who received Salofalk compared to 69.5% (107/154) in the budesonide group (RR 0.89; 95% CI 0.76 to 1.05; $P = 0.17$; See [Analysis 8.1](#)). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (See [Summary of findings 8](#)). The median time to

remission (mesalamine 16 days; budesonide 14 days) and mean change in CDAI scores from baseline (mesalamine -130; budesonide -149) also did not differ significantly between the two treatment groups. However, budesonide was more efficacious at inducing remission in patients with high baseline erythrocyte sedimentation rate (> 20 mm/hr) while a trend in favour of budesonide was also observed in patients with high baseline CRP (> 10 mg/L) and CDAI scores (> 300), suggesting that budesonide was more effective than delayed-release mesalamine in patients with more severe inflammation. Clinical remission and response rates did not differ significantly between the two budesonide groups. There was no statistically significant difference in the proportion of patients who had an adverse event or withdrew due to adverse events. Forty-seven per cent (72/153) of Salofalk patients experienced at least one adverse event compared to 43% (66/154) of budesonide patients (RR 1.10, 95% CI 0.86 to 1.41; $P = 0.46$). Five per cent (8/153) of Salofalk patients withdrew due to an adverse event compared to 3% (4/154) of budesonide patients (RR 2.01, 95% CI 0.62 to 6.55; $P = 0.24$). Common adverse events included abdominal pain, worsening Crohn's disease, vomiting, pyrexia, viral infection, decreased blood cortisol (in budesonide patients), back pain and headache.

As the two studies evaluated different formulations of mesalamine, results were not pooled for analysis.

c. Mesalamine versus sulfasalazine alone or in combination with corticosteroids

Two trials evaluated the efficacy of delayed-release mesalamine compared to sulfasalazine (alone or in combination with corticosteroids).

Maier 1985

In an early small trial, Maier and colleagues (Maier 1985), randomly assigned 30 patients with active Crohn's disease to receive either Salofalk 1.5 g/day ($n = 15$) or sulfasalazine 3 g/day ($n = 15$) for 8 weeks. Compared to baseline values, mean CDAI decreased significantly in both groups (Salofalk: -189, $P < .0001$, Sulfasalazine: -148, $P = 0.0001$). There was no difference in clinical improvement rates. Eighty-seven per cent of (13/15) Salofalk patients improved clinically compared to 73.3% (11/15) of sulfasalazine patients (RR 1.18, 95% CI 0.82 to 1.70; $P = -0.37$; See Analysis 9.1). The addition of corticosteroid therapy (Salofalk: 6; Sulfasalazine: 7) to patients who were still symptomatic after 5 days of aminosalicylates therapy, probably led to these impressive results. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to risk of bias due to blinding and very sparse data (See Summary of findings 9). The authors reported no adverse events in the Salofalk group and four adverse events in the sulfasalazine group (RR 0.11, 95% CI 0.01 to 1.90; $P = 0.13$). Sulfasalazine had to be withdrawn in four patients due to intolerance.

Maier 1990

In a subsequent trial, the same authors randomized 54 patients (4 dropouts) with active Crohn's disease to Salofalk 3 g/day ($n = 24$) or combination therapy with sulfasalazine 3 g/day and 6-methylprednisolone 40 mg/day ($n = 26$, reductions of 4 mg/week) for 12 weeks (Maier 1990). At week 12, 83.3% (20/24) Salofalk-treated patients and 88.5% (23/26) in the combination group achieved remission (CDAI < 150) (RR 0.94, 95% CI 0.75 to 1.18; $P = 0.61$, See Analysis 9.1). A GRADE analysis indicated that the overall

quality of the evidence supporting this outcome was low due to risk of bias due to blinding and very sparse data (See Summary of findings 9). There was a mean change in CDAI of -148 and -146 respectively ($P = 0.90$). There was no difference in the proportion of patients who experienced an adverse event. Twelve per cent (3/24) of Salofalk patients experienced an adverse event compared to 23% (6/26) of sulfasalazine patients (RR 0.54, 95% CI 0.15 to 1.93). It should be noted that Maier 1985 and Maier 1990 were not designed as formal equivalence or non-inferiority trials. Future trials would require the randomization of large numbers of patients.

DISCUSSION

The focus of this review was broad, and all information pertaining to the efficacy of sulfasalazine or 5-ASA alone for the treatment of mildly to moderately active Crohn's disease when compared to placebo, corticosteroids, and other aminosalicylates (alone or in combination with corticosteroids) was sought. To ensure that effect estimates were interpretable and clinically meaningful in this review where trials were anticipated to be diverse with different aminosalicylate formulations, dosages, comparators and outcome, each combination was considered separately and only results from similar trials were synthesized. A random-effects model was used for pooling data as it allowed between-trial variability to be accounted for in the overall effect estimate, producing more conservative results with wider 95% confidence intervals. Results based on a fixed-effect model and duration of therapy were also presented in sensitivity analyses planned *a priori* and these did not significantly alter the results obtained with the random-effects model or when trials with different duration of treatment were included.

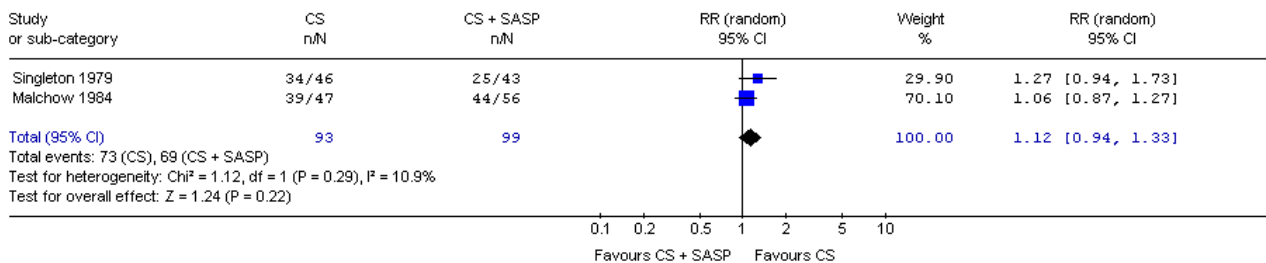
The results showed that sulfasalazine at 3 to 6 g/day had only modest efficacy for inducing remission, and a trend towards benefit of sulfasalazine over placebo was observed (pooled RR 1.38, random-effects model 95% CI 1.00 - 1.89, fixed-effect model 95% CI 1.01-1.90). This benefit was limited to patients with Crohn's colitis. Patients with small bowel disease or those who continued to have active disease despite previous corticosteroid and sulfasalazine treatment were not likely to benefit. Sulfasalazine was less effective than corticosteroids with a pooled RR of 0.68, that is, sulfasalazine-treated patients had 32% less chance of achieving remission than corticosteroid-treated patients. In addition, sulfasalazine monotherapy was less effective than combination therapy with corticosteroids. The question of whether sulfasalazine is a useful adjunct to corticosteroid therapy, while not the primary focus of this review, was addressed in the TAS (Trial of adjunctive sulfasalazine in Crohn's disease) study (Singleton 1979) and ECCDS: 74% (34/56) and 83% (39/47) in the corticosteroid group versus 58% (25/43) and 79% (44/56) in the combination group achieved remission (CDAI < 150) at the end of 8 weeks and 18 weeks respectively ($P = 0.12$ and 0.57 respectively) with a pooled RR of 1.12 (95% CI 0.94 to 1.33) (See Figure 3), demonstrating that sulfasalazine was not a useful adjunct to corticosteroid therapy. These data suggest that sulfasalazine may be considered for patients with mildly to moderately active Crohn's colitis, reserving the more potent corticosteroids for patients failing sulfasalazine therapy. This is consistent with the pharmacology of sulfasalazine, an azo-bonded prodrug that requires colonic bacteria azo-reductases for the release and targeted delivery of active 5-ASA moiety to the colon. In contrast, olsalazine, a new azo-bonded 5-ASA dimer, was shown to lack therapeutic effect, with

a significant proportion developing worsening diarrhoea (Wright 1995). This is a common and unique dose-related complication of olsalazine therapy, a consequence of increased ileal secretion

and gastrointestinal transit (Rao 1987; Wadworth 1991; Sandborn 2002a).

Figure 3.

Review: The efficacy of sulfasalazine and 5-ASA in the treatment of mildly to moderately active Crohn's disease
Comparison: 06 Corticosteroids (CS) versus combination therapy of corticosteroids (CS) with sulfasalazine (SASP)
Outcome: 01 Induction of remission (CDAI <150)



While mesalamine has similar efficacy to sulfasalazine when equimolar doses are used in ulcerative colitis (3 to 6 g of sulfasalazine is equivalent to 1.2 to 2.4 g of mesalamine), low dose controlled-release mesalamine (Pentasa at 1 to 2 g/day) was not more effective than placebo for inducing remission in active Crohn's disease (Analysis 4.2). Predictably, delayed-release mesalamine (Salofalk at 2 g/day) was less efficacious than corticosteroids (Scholmerich 1990).

Trials assessing higher doses of mesalamine produced conflicting results. Controlled-release mesalamine (Pentasa) at 4 g/day produced a clinically insignificant reduction in CDAI compared to placebo (Singleton 1993; Singleton 1994; Crohn's III 1997, Comparison 05, Outcome 01 and 02; Analysis 5.1; Analysis 5.2), and was inferior to budesonide for inducing remission in active Crohn's disease (Thomsen 1998; Analysis 8.1). The positive effect of Pentasa at 4 g/day in one study (Singleton 1993), was in contrast to the lack of effect in similarly designed trials (Singleton 1994; Crohn's III 1997). Moderate heterogeneity and rather large placebo effects could have reduced the power to detect a statistically significant difference between placebo and mesalamine, should one exist. However, placebo remission and response rates were not reported for the Singleton 1994 and Crohn's III 1997 studies and only changes in CDAI scores were available. Based on a mean difference in CDAI scores of approximately 10 points these studies would have needed to randomize a very large number of patients to have the statistical power to detect a significant difference between placebo and controlled-release mesalamine. The Singleton 1994 and Crohn's III 1997 studies were therefore too small and lacked the statistical power to detect any significant difference between placebo and controlled-release mesalamine. A meta-analysis of clinical trials in active Crohn's disease has estimated placebo remission and response rates at 18% (95% CI 14 to 24%) and 19% (95% CI 13 to 28%) respectively (Su 2004). High placebo response rates may reduce the power to detect a small but statistically significant difference between placebo and active treatment. Randomized, placebo-controlled trials assessing biologic therapy in active Crohn's disease exhibited placebo response rates of 23.5% and 35.6% respectively (Sandborn 2004; Schreiber 2005). In *post hoc* subgroup analyses of patients with elevated C-reactive protein (CRP) at baseline the placebo remission rates were 15.5% and 17.9% respectively (Sandborn 2004; Schreiber 2005), improving the apparent efficacy of active study drug. High CRP, an indicator of

active inflammation, appeared to improve the 'efficiency' of clinical trials by separating placebo from drug responders. Therein lies the limitations of using CDAI as a measure of disease activity and efficacy endpoint in clinical trials: it is an indicator of 'illness' rather than inflammation. The CDAI may not correlate with pathology and laboratory markers (Cellier 1994), and is heavily weighted to 'intensity of abdominal pain' and 'general well being', subjective items that rely substantially on patients' perception of their disease (Sandborn 2002b). High placebo response rates may result from the inclusion of patients with mild disease or predominantly functional symptoms, frequent study visits and intense contact with health care providers during the trial period (Su 2004).

While delayed-release mesalamine was not superior to placebo (Tremaine 1994), no difference in efficacy was found when compared to corticosteroids (Gross 1995; Martin 1990; Prantera 1999), or budesonide (Tromm 2011), for inducing remission in patients with mildly to moderately active Crohn's disease. While no difference for induction of remission relative to placebo was demonstrated for delayed-release mesalamine (Asacol) at a dosage of 3.2 g/day (Analysis 6.2), no significant difference was found between corticosteroids and delayed-release mesalamine (Asacol, Salofalk) at doses ranging 3 to 4.5 g/day (Analysis 7.1). Subgroup analyses found that systemic corticosteroids appeared to be more effective than delayed-release mesalamine in patients with more extensive ileocolonic disease (Martin 1990, Gross 1995). There was no difference in efficacy when the disease was confined to the ileum or ileocecal region (Martin 1990, Prantera 1999). However, these results must be interpreted with caution as: (a) these trials were limited by the relatively small number of patients (4 studies ranging from 34 to 94 patients) and were thus underpowered, increasing the probability of a type II error, (b) a fixed dose of mesalamine was compared with a tapering dose of corticosteroids, which may have obscured any differences between the two agents. If higher doses of corticosteroids had been used a difference may have been found, (c) studies comparing delayed-release mesalamine versus corticosteroids were small in size and were not designed as formal equivalence or non-inferiority trials, (d) subgroup analyses involved small numbers of patients and results should be interpreted with care, and (e) the heterogeneous spectrum of clinical patterns in Crohn's disease could also account for the difference in response to therapy in these trials, and focusing on a more homogenous group of patients should be

considered in future trials of active Crohn's disease. Furthermore, budesonide has been shown to be superior to controlled-release mesalamine (Thomsen 1998), and conventional corticosteroids have been shown in other studies to be somewhat superior to budesonide (Rutgeerts 1994; Gross 1996; Campieri 1997; Bar-Meir 1998). In contrast to Thomsen 1998, delayed-release mesalamine (Salofalk) at 4.5 g/day was at least as effective as budesonide in patients with mildly to moderately active ileocolonic Crohn's disease (Tromm 2011), although budesonide still appeared to be more effective in those with more severe disease, characterized by high ESR, CRP and CDAI >300. It was postulated that this unexpected result may be accounted for by the inclusion of patients with less previous resections, shorter duration of disease and a slightly higher dose of mesalamine using a formulation designed to release mesalamine in the terminal ileum with greater mesalamine absorption (compared to Thomsen 1998). However, the relatively small size of this non-inferiority study and the inclusion of 50-60% of patients with normal inflammatory markers (CRP < 5 mg/L, ESR < 20 mm/hr) does not allow any firm conclusions to be made on the efficacy of delayed-release mesalamine in active Crohn's disease (Levesque 2012).

Several methodological weaknesses may limit the generalizability and precision of effect estimates in this review. First, two trials rated as being of poor quality were included and the results of these studies should be interpreted with caution (Maier 1985; Maier 1990). Second, the use of different scoring systems and definitions of endpoints have added to the difficulty of comparing and pooling results. In this review, pooled risk ratios of trials comparing controlled-release mesalamine (1 to 2 g/day) with placebo and delayed-release mesalamine with corticosteroids were calculated despite these deficiencies and should be interpreted with a degree of caution. Recent recommendations to adopt common definitions of endpoints in clinical trials for Crohn's disease will aid in the comparison and synthesis of results in future conducted trials (Sandborn 2002b). Third, the number of patients whose results were pooled in each analysis was relatively small and the precision of effect estimate was thus less than ideal. Lastly, the possibility of publication bias could not be excluded as visual interpretation of funnel plots have limited power to detect bias in this review due to the small number of studies in each analysis (Munafa 2004). In addition, we did not contact other inflammatory bowel disease investigators or manufacturers of sulfasalazine and other 5-ASA formulations for unpublished papers. These limitations are reflected in the GRADE analyses which rate the overall quality of the evidence supporting the outcomes assessed in this review as very low (See Summary of findings 6; Summary of findings 9), low (See Summary of findings for the main comparison; Summary of findings 4; Summary of findings 5; Summary of findings 7; Summary of findings 8; Summary of findings 9), or moderate quality (See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 7; Summary of findings 8).

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, current available data suggests that for the treatment of mildly to moderately active Crohn's disease:

1. Sulfasalazine at 3 to 6 g/day was only modestly effective (trend towards benefit over placebo), with benefit confined to those with colitis.
2. Sulfasalazine was inferior and not a useful adjunct to corticosteroid therapy.
3. Olsalazine and mesalamine at 1 to 2 g/day were ineffective and not superior to placebo.
4. Higher doses of controlled-release mesalamine at 4 g/day:
 - a. Have resulted in statistically significant but clinically non significant changes in CDAI scores but have not been consistently shown to be effective for induction of remission in mild to moderately active Crohn's disease.
 - b. Are inferior to budesonide.
5. Higher doses of delayed-release mesalamine at 3-4.5 g/day may be as effective as budesonide in those with mildly to moderately active ileocolonic disease. Although the superiority of conventional steroids has not been consistently demonstrated, in the absence of a sufficiently powered formal equivalence or non-inferiority study, it is likely that delayed-release mesalamine would be inferior to conventional steroids.
6. There was a lack of good quality clinical trials comparing sulfasalazine with other mesalamine formulations.

Implications for research

There has been an evolution of clinical trials over the past 30 plus years, during which aminosalicylates have been evaluated for the treatment of mild-moderate Crohn's disease. The heterogeneity in clinical trials with respect to patients enrolled, entry and exclusion criteria, end-points, duration, dose, delivery system and placebo responses contribute to the inconsistent trial outcomes and interpretations of a large body of evidence pertaining to aminosalicylates in mild-moderate Crohn's disease. To date, while a body of evidence suggests a small modest benefit for aminosalicylates on clinical indices used to assess Crohn's disease activity, there is insufficient evidence to indicate that they are effective for induction of remission or mucosal healing. Future large randomized controlled trials are needed to provide definitive evidence on the efficacy of aminosalicylates in active Crohn's disease. As mesalamine is likely to be most effective in the terminal ileum and proximal colon, future trials should examine its efficacy in patients with this disease distribution.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Crohn's III 1997

Methods	Multicenter study. Randomized. Double blind. Parallel design. Methods of randomization/ blinding, concealment of allocation, adequate follow up could not be assessed as study has not been fully published
Participants	Male and female patients, adults with mildly to moderately active Crohn's disease, entry CDAI 200 to 400. Disease location: ileum and/or colon. Pentasa 4 g/day: mean age 42 years, mean CDAI 265; placebo: mean age 39, mean CDAI 265
Interventions	Pentasa 4 g/day versus placebo for 16 weeks. n = 310; allocation: 154 to Pentasa 4 g/day, 156 to placebo
Outcomes	Primary endpoint: change in CDAI from baseline to final study visit
Notes	Study has not been fully published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	50/154 patients in the Pentasa group and 60/156 patients in the placebo group did not complete the study/
Selective reporting (reporting bias)	Unclear risk	Unable to assess
Other bias	Unclear risk	Unable to assess

Gross 1995

Methods	Multicenter study. Randomized, method of randomization not described. Double-blind with use of double-dummy. Parallel design. Follow up described: yes
Participants	Male and female patients, entry CDAI 150 to 350. Disease location: ileum and/or colon. Mean age 26.4 years, 31.9 years and mean entry CDAI 251.5, 236.2 for Salofalk and 6-Methylprednisolone respectively
Interventions	Salofalk 4.5 g/day versus 6-methylprednisolone 48mg (tapering doses) for 8 weeks. n = 34; allocation: 17 to Salofalk, 17 to 6-methylprednisolone
Outcomes	Remission rates after 8 weeks of treatment. Remission defined as CDAI < 150 and decrease \geq 60 points
Notes	

Risk of bias

Gross 1995 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/17 in the 5-ASA group and 7/17 in the 6-methylprednisone group discontinued the study for various reasons; intent-to-treat and per-protocol analyses were performed.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in the published study
Other bias	Low risk	No other sources of bias were identified

Mahida 1990

Methods	Single center study. Randomized using block randomization methods. Double blind with use of identical placebo. Parallel design. Follow ups described: yes
Participants	Male and female patients, age ≥ 18 years, with active Crohn's disease not requiring steroids. Disease location: ileum and/or colon. Pentasa group: mean age 32.7 (18 to 50) years, HBI 5.2 +/-1.8; placebo group: mean age 35 (19 to 74) years, HBI 5.0 +/- 1.3
Interventions	Pentasa 1.5g/day versus placebo for 6 weeks. n = 40; allocation: 20 to Pentasa group, 20 to placebo group. 11 dropouts: 7 (Pentasa group), 4 (placebo group)
Outcomes	Improvement, defined as a reduction of HBI by ≥ 2 points
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised to receive Pentasa or dummy tablets according to a pre-arranged schedule in blocks of 6 patients
Allocation concealment (selection bias)	Low risk	Centralized randomization, where a pre-arranged schedule was held by the hospital pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind with use of identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/20 patients in the Pentasa group and 4/20 patients in the placebo group failed to complete the 6-week study; intent-to-treat analyses were performed

Mahida 1990 (Continued)

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in the published report
Other bias	Low risk	No other sources of bias were identified

Maier 1985

Methods	Randomized, method of randomization not clearly stated. Not double-blind. Parallel design. Follow ups described: no
Participants	Male and female patients. Median age and CDAI: 29.5 years, 308 (Salofalk); 26.9 years, 310 (SASP)
Interventions	Salofalk 1.5 g/day versus SASP 3 g/day for 8 weeks. n = 30, allocation: 15 to Salofalk, 15 to SASP. 6-methylprednisolone added if clinical symptoms persisted after 5 days at 40 mg/day followed by 5 mg weekly reductions
Outcomes	Improvement in CDAI at 8 weeks
Notes	Additional corticosteroid therapy was necessary in 13 patients: 6 (Salofalk group), 7 (SASP group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Patients, investigators and assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for at the end of the study
Selective reporting (reporting bias)	Low risk	All expected outcomes are reported in the published report
Other bias	Low risk	No other sources of bias were identified

Maier 1990

Methods	Single center. Randomized, method of randomization not described. Not blinded. Parallel design. Follow ups not adequately described
Participants	Male and female patients. Mean age and entry CDAI: 32 years, 264 (Salofalk group) and 30 years, 281 (SASP + 6-methylprednisolone group). Disease location: small bowel and/or colon
Interventions	Salofalk 3 g/day versus Sulfasalazine 3 g/d + 6-methylprednisolone 40 mg (4 mg weekly taper) for 12 weeks. n = 54, 4 dropouts; allocation: 24 to Salofalk group, 26 to combination therapy group

Maier 1990 (Continued)

Outcomes Remission defined as CDAI < 150

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Patients, investigators and assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/54 enrolled patients discontinued the study and were not included the data analyses
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in the published report.
Other bias	Low risk	No other sources of bias were identified

Malchow 1984

Methods Multicenter study. Randomized, method of randomization described. Double-blind with use of identical placebo. Parallel design. Follow ups described: yes

 Participants 452 male and female patients with Crohn's disease randomized to receive SASP and 6-methylprednisolone alone or in combination, and placebo. of these, 215 patients had active Crohn's disease (CDAI \geq 150), and received acute phase treatment. Disease location: small bowel and/or colon. Mean CDAI 265 (SASP), 243 (6-methylprednisolone), 241 (combination) and 241 (placebo)

Interventions Active phase treatment: SASP 3 g/day versus 6-Methylprednisolone 48 mg/d versus SASP + 6-Methylprednisolone versus placebo for 6 weeks. 6-methylprednisolone tapered weekly over 6 weeks to 12 mg/day. Patients were retreated with the same regimen at most twice if CDAI fails to fall below 150 (maximum 18 weeks treatment). Allocation: 54 to SASP, 47 to 6-Methylprednisolone, 56 to combination therapy, 58 to placebo

Outcomes Remission as defined by CDAI < 150 within 18 weeks

Notes Maintenance drug regime (for those with entry CDAI < 150 or achieved remission after active phase treatment): SASP 3 g/day, 6-methylprednisolone 8 mg/day, SASP + 6-methylprednisolone or placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomization described

Malchow 1984 (Continued)

Allocation concealment (selection bias)	Low risk	Centralized randomization: tablets were packaged centrally and labelled with a code number to keep both physician and patient unaware of what treatment was actually given
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with use of identical placebo: the placebo looked like the corresponding active drug
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients were accounted for in the study. Only 3 patients excluded from the analysis due to unconfirmed diagnosis.
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Martin 1990

Methods	Multicenter study. Randomized, randomization method not described. Described as double-blind. Method of blinding not described. Parallel group design. Follow up described: yes
Participants	Male and female patients, age >18 years, entry CDAI 200 to 450. Disease location: ileum or ileocolon. Mean age 29.2 years, 30.6 years and mean CDAI 295, 291 in the Salofalk and prednisolone group respectively
Interventions	Salofalk 3 g/day versus Prednisone 40 mg (4 mg weekly taper from 3rd week) for 12 weeks. n = 50, allocation: 22 to Salofalk, 28 to prednisone
Outcomes	Remission defined as CDAI < 150
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/22 patients in the Salofalk group and 2/28 the prednisone group were excluded from efficacy and safety analysis.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in the published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Prantera 1999

Methods	Multicenter study. Randomized, using computerized randomization in balanced blocks performed centrally for each center. Double-blind, double-dummy. Parallel design. Follow up described: yes
Participants	Male and female, age \geq 18 years, mild to moderately active Crohn's disease (CDAI 180 to 350) limited to distal ileum or distal ileum plus cecum. Mean age 36.8 years, 32.4 years, 38.3 years and median entry CDAI 220, 222 and 233 for Asacol tablets, Asacol microgranules and 6-Methylprednisolone respectively
Interventions	Asacol tablets 4 g/day versus Asacol microgranules 4 g/day versus 6-methylprednisolone 40 mg/day for 12 weeks. Mesalamine doses were tapered to 3.2 g/day after 7 weeks and 2.4 g/day after 10 weeks. Steroid doses tapered at 4 mg weekly from the 3rd week reaching 4 mg/day after 11 weeks. n = 94, allocation: 35 to Asacol tablets, 28 to Asacol microgranules, 31 to 6-methylprednisolone
Outcomes	Remission rates at 12 weeks, defined as CDAI \leq 150
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/35 patients in the mesalamine tablets group, 4/28 patients in the mesalamine microgranular group, and 12/31 patients in the 6-methylprednisolone group withdrew, Intent-to-treat analyses were performed.
Selective reporting (reporting bias)	Low risk	All expected outcomes were presented in the published report
Other bias	Low risk	The study appears to be free of other sources of biases

Rasmussen 1987

Methods	Multicenter study. Randomized but method of randomization not described. Double blind with use of identical placebo. Parallel design. Follow ups described: Yes
Participants	Male and female patients, mildly to moderately active Crohn's disease as defined by Binder 1982 Disease location: small bowel +/- colon. Age ranged 14-79 years. Median CDAI at entry 153 (Pentasa), 177 (placebo)
Interventions	Pentasa 1.5 g/day versus placebo for 16 weeks. n = 67; allocation: 30 to Pentasa, 37 to placebo. Dropouts: 7 from Pentasa group, 10 from placebo
Outcomes	Improvement or remission according to Tvede 1983 at 16 weeks

Rasmussen 1987 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with identical placebo. The control group received the same number of tablets without 5-ASA but identical in appearance, weight, and taste. Efficacy variables were evaluated before breaking the code.
Incomplete outcome data (attrition bias) All outcomes	High risk	5/30 patients in the 5-ASA group and 12/37 patients in the placebo group left the study prematurely and they were excluded from the analysis.
Selective reporting (reporting bias)	Low risk	The published study reported all expected outcomes.
Other bias	Low risk	The study appeared to be free of other sources of bias

Rijk 1991

Methods	Multicenter study. Randomized, randomization using Begg and Iglewicz method. Double-blind with use of identical placebo. Parallel design. Follow ups described: Not adequately
Participants	Male and female patients, active Crohn's disease with Van Hees activity index ≥ 140 . Disease location: small bowel and/or colon. SASP + prednisone group: mean age 29.4 years, mean VHAI 178.4/ CDAI 304.9; SASP alone: mean age 27.9 years, VHAI 173.2 / CDAI 254.8
Interventions	SASP 4 to 6 g/day versus SASP 4 to 6 g/day + prednisone 30 mg for 16 weeks. Prednisone tapered in steps of 5 mg/ 2 weeks to 10 mg/day after 8 weeks at maintained until end of study. 71 patients randomized with 11 dropouts (not stated from which arm). 60 patients were analyzed (30 in each treatment group)
Outcomes	Therapeutic response as measured by the change in VHAI and CDAI in the initial 6 weeks and last 4 weeks

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization using Begg and Iglewicz method
Allocation concealment (selection bias)	Unclear risk	Not described

Rijk 1991 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with use of identical placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	11/71 patients dropped out of the study and were not included in the analyses.
Selective reporting (reporting bias)	High risk	Baseline characteristics excluded individuals who dropped out of the study. Four patients with premature treatment failure (1 from SASP + prednisone and 3 from SASP + placebo) were excluded from the trial.
Other bias	Low risk	The study appeared to be free of other sources of bias

Saverymuttu 1986

Methods	Single center study. Randomized, method of randomization not described. Double-blind, placebo identical in size and shape. Parallel design. Follow ups described: yes	
Participants	Male and female, mild to moderately active Crohn's colitis, age 23 to 64 years. Mean CDAI 116 (Pentasa), 155 (Placebo)	
Interventions	Pentasa 1.5 g/day versus placebo for 10 days. n = 12; allocation: 6 to Pentasa group, 6 to placebo group. 1 withdrawal from placebo group from nausea	
Outcomes	Change in Fecal 111In granulocyte excretion, CDAI and ESR after 10 days of treatment	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo identical in size and shape
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/6 patient from the placebo group and 0/6 patient from the 5-ASA group withdrew from the study.
Selective reporting (reporting bias)	Low risk	All expected outcomes were presented in the published report.
Other bias	Low risk	No other sources of bias were identified.

Scholmerich 1990

Methods	Multicenter study. Randomized, method of randomization not described. Double-blind with use of double-dummy. Parallel design. Follow ups described: yes
Participants	Male and female patients, entry CDAI 150 to 350 or VHAI > 200 + CDAI < 350, disease location: small bowel and/or colon. Mean age, CDAI and VHAI: 32 years, 241 and 177 (Salofalk); 30 years, 241 and 184 (6-methylprednisolone)
Interventions	Salofalk 2 g/day versus 6-methylprednisolone 48 mg/day (taper to 8mg/day) for 24 weeks. n = 62; allocation: 30 to Salofalk group, 32 to 6-methylprednisolone group
Outcomes	Cessation of treatment due to "insufficient efficacy"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described in detail
Selective reporting (reporting bias)	Unclear risk	Unable to confirm the reporting of all outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Singleton 1993

Methods	Multicenter study. Randomized, method of randomization not well described. Double blind with use of identical placebo and blister card packaging. Parallel design. Follow ups described: yes
Participants	Male and female patients, age \geq 18 years old, mildly to moderately active Crohn's disease with CDAI between 151 and 400. Disease location: ileum and/or colon. Pentasa 1 g/day: mean age 36 years, mean CDAI 271; Pentasa 2 g/day: mean age 36 years, mean CDAI 265; Pentasa 4 g/day: mean age 37 years, mean CDAI 260; Placebo: mean age 37 years, mean CDAI 277
Interventions	Pentasa 1 g/day versus 2 g/day versus 4 g/day versus placebo for 16 weeks. n = 310. Allocation: 80 to 1 g/day, 75 to 2 g/day, 75 to 4 g/day and 80 to placebo. Early termination in 154 patients for various reasons
Outcomes	Primary endpoint: change in CDAI from baseline to final study visit. Remission defined as CDAI < 151 and > 50 points decrease; therapeutic benefit defined as \geq 50 points decrease in CDAI
Notes	

Singleton 1993 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind with use of identical placebo and blister card packaging
Incomplete outcome data (attrition bias) All outcomes	High risk	41/80 patients in the placebo group, 48/80 in the 1 g/day group, 39/75 in the 2 g/day group, and 26/75 in the 4 g/day group did not complete the study. All randomized patients were analysed on the intent-to-treat basis.
Selective reporting (reporting bias)	Low risk	All expected outcomes are presented in the published report,
Other bias	Unclear risk	The study appeared to be free of other sources of bias

Singleton 1994

Methods	Multicenter study. Randomized. Double blind. Parallel design. Methods of randomization/ blinding, concealment of allocation, adequate follow up could not be assessed as study has not been fully published
Participants	Male and female patients, adults with mildly to moderately active Crohn's disease, entry CDAI 200 to 400. Disease location: ileum and/or colon. Pentasa 4 g/day: mean age 37 years, mean CDAI 248; placebo: mean age 38 years, mean CDAI 255
Interventions	Pentasa 2 g/day versus 4 g/day versus placebo for 16 weeks. n = 232: allocation: 82 to Pentasa 2 g/day, 75 to Pentasa 4 g/day, 75 to placebo
Outcomes	Primary endpoint: change in CDAI from baseline to final study visit. Remission defined as CDAI < 151 and > 50 points decrease; therapeutic benefit defined as ≥ 50 points decrease in CDAI
Notes	Study has not been fully published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Singleton 1994 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	35/75 patients in the Pentasa group and 34/75 patients in the placebo group terminated the study early
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

Summers 1979

Methods	Multicenter study. Described as randomized, method of randomization described. Double-blind with use of identical placebo. Parallel design. Follow ups not adequately described
Participants	Two part study: part I (active Crohn's disease), part II (quiescent Crohn's disease). 604 patients randomized; 35 excluded from final analysis due to erroneous diagnosis (20), inappropriate entry (12) or administrative error during the conduct of the trial (3); 295 patients in part I and 274 patients in part II. Part I entry criteria 150 < CDAI < 450. Male and female patients, mean age 33.7 years (placebo), 29.6 years (SASP), 31.8 years (prednisone). Disease location: small bowel and/or colon, mean CDAI at randomization, 256 (SASP), 243 (prednisone), 241 (azathioprine), 242 (placebo)
Interventions	SASP 1 g/15kg (max dose 5 g/day) versus prednisone 0.25 to 0.75 mg/kg (according to disease activity, max dose 60 mg/day) versus azathioprine 2.5 mg/kg versus placebo for 17 weeks. Allocation: 74 to SASP, 85 to prednisone, 59 to azathioprine, 77 to placebo
Outcomes	Remission as defined by CDAI < 150 and maintained through rest of study period
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomization described
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with use of identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for in the study
Selective reporting (reporting bias)	Low risk	Outcomes were incorporated into the ranking scheme using the Wilcoxon Rank Sum method.
Other bias	Low risk	The study appeared to be free of other sources of biases.

Thomsen 1998

Methods	Multicenter study. Randomized, in permuted blocks of four performed at each center with sealed, opaque treatment-code envelopes. Double-blind, double-dummy. Parallel design. Follow ups described: yes
Participants	Male and female, mild to moderately active Crohn's disease confined to distal ileum, ileocecal and ascending colon, entry CDAI 200 to 400. Pentasa group: median age 31 years, median CDAI 278; budesonide group: median age 34 years, median CDAI 266
Interventions	Pentasa 4 g/day versus budesonide 9 mg/day for 16 weeks. n = 182, allocation: 89 to Pentasa, 93 to budesonide
Outcomes	Remission rates at 16 weeks. Remission defined as CDAI \leq 150
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sealed, opaque treatment-code envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	High risk	16/93 patients in the budesonide group and 49/89 patients in the mesalamine group withdrew from the study. Intention-to-treat analyses were performed.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in the published study.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Tremaine 1994

Methods	Single center study. Randomized. Patients stratification by disease location, baseline CDAI and use of steroids and randomized within strata. Double blind with use of identical placebo. Parallel design. Follow up described: yes
Participants	Male and female adult, mildly to moderately active Crohn's disease, CDAI 150 to 450. Disease location: colon or ileocolon. Asacol: median age 31 years, mean CDAI 231.7; Placebo: median age 38 years, mean CDAI 204.8
Interventions	Asacol 3.2 g/day versus placebo for 16 weeks. n = 38; allocation: 20 to Asacol, 18 to placebo. 2 dropouts, 1 from each arm
Outcomes	"Complete success" (remission) defined as CDAI $<$ 150 and \geq 70 points decrease. "Partial success" (response) defined as CDAI $>$ 150 and \geq 70 points decrease
Notes	

Tremaine 1994 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, identical appearing placebo tablets
Incomplete outcome data (attrition bias) All outcomes	High risk	8/20 patients in the Asacol group and 10/18 patient in the placebo group did not complete the study protocol. Intent-to-treat analyses were performed.
Selective reporting (reporting bias)	Low risk	All expected outcomes were included in the published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Tromm 2011

Methods	Multicentre study. Randomized: randomization list generated by computer in blocks of 4 (RANDCODE 3.6; IDV, Gauting, Germany); study drug was then dispensed to investigating centre according to each patient's unique randomization number. Double-blind, double-dummy. Parallel design. Follow ups described: yes.
Participants	Male and female patients with mildly to moderately active Crohn's disease confined to the terminal ileum and/or ascending colon or distal colon. Entry CDAI 200 to 400. Salofalk group: mean age 37.8 years, mean CDAI 267, 49.7% with CRP \leq 5mg/L; budesonide group: mean age 36.8 years, mean CDAI 266, 48.7% with CRP \leq 5mg/L.
Interventions	Salofalk 4.5 g/day (n = 153) versus budesonide 9mg/ day (given 9mg once daily [n = 76] or 3mg tid [n = 78])
Outcomes	Remission as defined by CDAI \leq 150 at 8 weeks.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy

Tromm 2011 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	51/154 patients in the budesonide group and 34/153 patients in the mesalazine group did not complete the study, Both intent-to-treat and per-protocol analyses were performed.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in the published study.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Van Hees 1981

Methods	2 center study. Described as randomized, allocation via minimization method. Described as double-blind, with use of identical placebo. Parallel design. Follow-up not adequately described	
Participants	Male and female patients, active Crohn's disease with Van Hees activity index ≥ 140 . Disease location: small bowel and/or colon. SASP group: mean age 34.3 years, VHAI 185 +/- 30; placebo group: mean age 32.9 years, VHAI 165 +/- 22	
Interventions	SASP 6 g/day (reduction to 4 g/day allowed if side effects occurred) versus placebo for 26 weeks. n = 27, 13 allocated to SASP, 13 allocated to placebo, 1 dropout	
Outcomes	Favorable response at 26 weeks defined as a decrease in Van Hees activity index $\geq 25\%$	
Notes	8 patients had dose reduced to 4 g/d because of adverse effects	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, identical placebo: Sulphasalazine and placebo tablets were identical in internal and external appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/13 patients in the sulphasalazine group and 4/13 patients in the placebo group withdrew early from the study due to uncontrolled disease.
Selective reporting (reporting bias)	Low risk	All expected outcomes were presented in the published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Wright 1995

Methods	Multicenter study. Randomized using computer-generated series of random numbers. Double blind with use of identical placebo. Parallel design. Follow ups described: yes	
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Wright 1995 (Continued)

Participants	Male and female adult patients, age ≥ 18 years, mildly to moderately active Crohn's disease as defined by De Dombal 1974 Disease location: ileum and/or colon. Olsalazine: median age 33 years, HBI 7; placebo: median age 32, HBI 7
Interventions	Olsalazine 2 g/day versus placebo for 16 weeks. n = 91; allocation: 46 to Olsalazine, 45 to placebo
Outcomes	Remission or improved symptoms by physician assessment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, identical placebo: Those taking placebo received the same number of tablets with an identical appearance containing dicalcium phosphate and riboflavin as a colouring agent
Incomplete outcome data (attrition bias) All outcomes	High risk	35/46 patients in olsalazine group and 24/45 patients in placebo group withdrew from the study.
Selective reporting (reporting bias)	High risk	Only HBI was reported in the published manuscript
Other bias	Low risk	The study appeared to be free of other sources of bias

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anonymous 1985	Uncontrolled trial with no comparator group
Anonymous 1990	Crohn's disease in remission. The primary outcome was clinical relapse
Anthonisen 1974	Crossover study, only overall results are provided. No data before the first crossover are available
Arber 1995	Crohn's disease in remission. Primary outcome was clinical relapse
Ardizzone 2004	Crohn's disease in remission. The comparator was azathioprine. The primary outcomes were clinical and surgical relapse
Beck 1988	Uncontrolled study
Bergman 1976	Crohn's disease in surgical remission. Combination therapy (Sulfasalazine + corticosteroids). The primary outcome was clinical relapse

Study	Reason for exclusion
Blichfeldt 1978	Double-blind cross-study of metronidazole or placebo in active CD patients on treatment with SASP or prednisolone. Combination therapy included SASP + metronidazole versus prednisolone. Inappropriate comparator included SASP versus prednisolone + metronidazole.
Bresci 1994	Crohn's disease in remission. The primary outcome was clinical relapse
Brignola 1992	Crohn's disease in remission. The primary outcome was clinical relapse
Brignola 1995	Crohn's disease in surgical remission. The primary outcome was endoscopic relapse
Caprilli 1994	Crohn's disease in surgical remission. The primary outcome was endoscopic relapse
Caprilli 2003	Crohn's disease in surgical remission. The primary outcome was endoscopic relapse
Cezard 2009	Pediatric Crohn's disease in surgical remission. The primary outcome was clinical relapse
Cohen 2000	Crohn's disease in surgical remission. The primary outcome was endoscopic recurrence.
Colombel 1999	The comparator was ciprofloxacin
de Franchis 1997	Crohn's disease in remission. The primary outcome was clinical relapse
Del Corso 1995	Crohn's disease in remission. The primary outcome was clinical relapse
Dirks 1989	Uncontrolled trial of patients with Crohn's disease in remission. Combination therapy included 5-ASA + corticosteroids versus surgery. The primary outcome was clinical relapse
Ewe 1976	Crohn's disease in remission. The primary outcome was relapse
Ewe 1984	Crohn's disease in surgical remission. The primary outcome was clinical relapse
Ewe 1986	Crohn's disease in surgical remission. The primary outcome was clinical relapse
Ewe 1989	Crohn's disease in surgical remission. The primary outcome was clinical relapse
Fiasse 1990	Crohn's disease in surgical remission. The primary outcome was relapse
Florent 1996	Crohn's disease in surgical remission. The primary outcome was endoscopic relapse
Gendre 1993	Crohn's disease in remission. The primary outcome was clinical relapse
Gerhardt 2001	The comparator was <i>Bowsellia serrata</i> extract H15
Goldstein 1987	Retrospective study design. No comparator group.
Griffiths 1993	Pediatric study population
Guslandi 2000	Crohn's disease in remission. The comparator was <i>Saccharomyces boulardii</i> . The primary outcome was clinical relapse
Hanauer 1993	Uncontrolled trial with no comparator or placebo group
Hanauer 2004b	Crohn's disease in surgical remission. The primary outcomes were clinical, endoscopic and radiographic relapse

Study	Reason for exclusion
Howaldt 1993	Crohn's disease in remission. The primary outcome was clinical relapse
Klein 1995	Crohn's disease in surgical remission. The primary outcome was endoscopic relapse
Klotz 1980	Sulfasalazine was compared to sulfapyridine or rectal 5-ASA
Lennard-Jones 1977	Crohn's disease in remission. The primary outcome was clinical relapse
Lichtenstein 2009a	Crohn's disease in remission. Prospective, uncontrolled study. No comparator or placebo group. Primary endpoint was clinical relapse.
Lichtenstein 2009b	Prospective, uncontrolled study. No comparator or placebo group.
Lochs 1991	Combination therapy included sulfasalazine + corticosteroids versus enteral nutrition
Lochs 2000	Crohn's disease in surgical remission. The primary outcome was clinical relapse
Mahmud 2001	Crohn's disease in remission. The primary outcome was clinical relapse
Malchow 1990	Combination therapy included sulfasalazine + corticosteroids versus enteral nutrition
Mantzaris 2003	Crohn's disease in remission. Primary outcomes were clinical relapse and quality of life
Mate-Jimenez 2000	Study population included steroid dependent Crohn's disease and ulcerative colitis. Comparator groups included methotrexate or 6-mercaptopurine. The primary outcomes were clinical remission and relapse
McLeod 1995	Crohn's disease in surgical remission. The primary outcome was clinical relapse
Modigliani 1996	Crohn's disease in steroid-induced remission. The primary outcomes were clinical relapse and steroid weaning
Orlando 2012	Crohn's disease in remission (surgical). Prospective uncontrolled study with no comparator group. The primary outcome was endoscopic recurrence.
Papi 2009	Crohn's disease in surgical remission. Retrospective study design. The primary outcome was clinical/ surgical relapse.
Prantera 1992	Crohn's disease in remission. The primary outcome was clinical relapse
Rasmussen 1983	Uncontrolled trial with no comparator or placebo group
Reinisch 2010	Crohn's disease in remission. The primary outcome was therapeutic failure. 5-ASA was compared to azathioprine.
Romano 2005	Crohn's disease in remission. Paediatric population. Combination therapy of 5-ASA + omega-3 fatty acids vs 5-ASA alone. The primary outcome was clinical relapse.
Rosen, Ursing 1982	Comparator group was metronidazole
Savarino 2013	Crohn's disease in surgical remission. The primary outcome was endoscopic and clinical relapse. 5-ASA was compared to azathioprine and adalimumab.
Schneider 1985	Combination therapy included sulfasalazine + corticosteroids +/- metronidazole versus metronidazole

Study	Reason for exclusion
Schreiber 1994	Crohn's disease in remission. The primary outcome was clinical relapse
Singleton 1979	Combination therapy included sulfasalazine + corticosteroids versus corticosteroids alone
Stober 1983	Pediatric study population. Combination therapy included sulfasalazine + corticosteroids versus sulfasalazine + elemental diet +/- corticosteroids. The primary outcomes included laboratory parameters and body weight
Sutherland 1997	Crohn's disease in remission. The primary outcome was clinical relapse
Tao 2009	Crohn's disease in surgical remission. The primary outcome was clinical relapse. 5-ASA was compared to Tripterygium wilfordii.
Terranova 2001	Combination therapy included 5-ASA + enteral nutrition versus 5-ASA + corticosteroids
Terrin 2002	Combination therapy included 5-ASA + corticosteroids versus semi-elemental diet.
Thomson 1995	Crohn's disease in remission. The primary outcome was clinical relapse
Triantafyllidis 2010	Crohn's disease in remission. The primary outcome was clinical relapse. 5-ASA was compared to Modulen®IBD.
Wellmann 1986	Combination therapy included total parenteral nutrition + corticosteroids +/- 5-ASA lavage
Wellmann 1988	Crohn's disease in remission. The primary outcome was clinical relapse
Wenckert 1978	Crohn's disease in surgical remission. The primary outcome was clinical relapse
Yamamoto 2009	Crohn's disease in surgical remission. Prospective, non-randomized. The primary outcome was clinical relapse. 5-ASA was compared to azathioprine and infliximab.

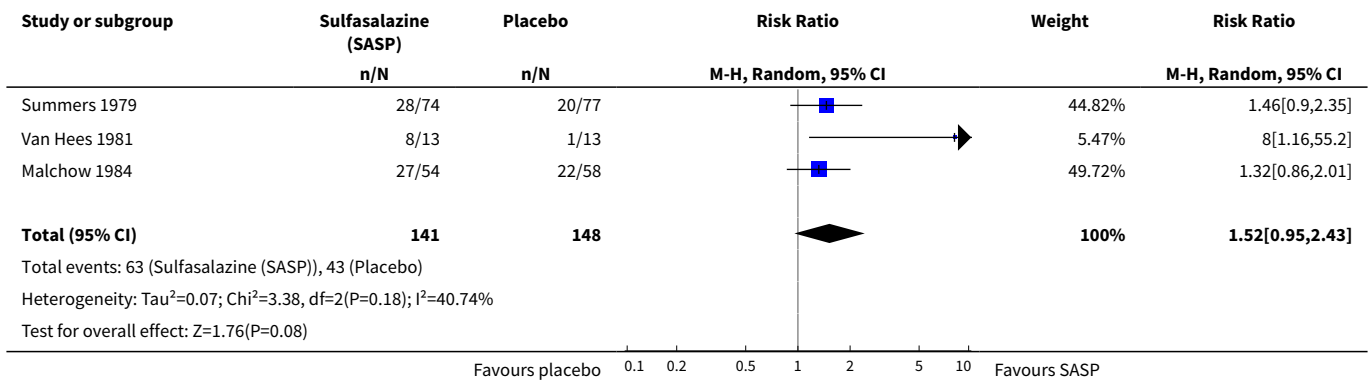
DATA AND ANALYSES

Comparison 1. Sulfasalazine versus placebo

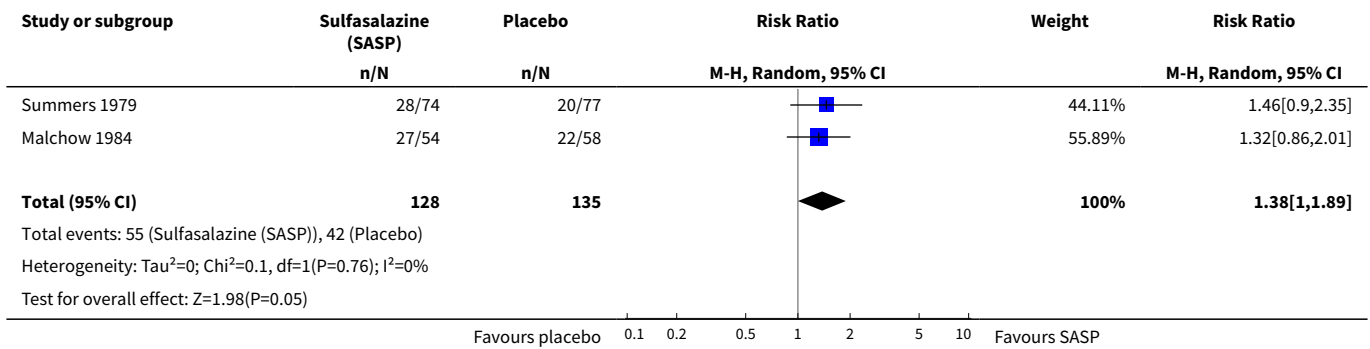
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of remission (CDAI <150), therapeutic response (VHI decrease >=25%) or clinical improvement	3	289	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.95, 2.43]
2 Induction of remission (CDAI <150) (Random Effects Model)	2	263	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.00, 1.89]
3 Induction of remission (CDAI <150) (Fixed Effect Model)	2	263	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.01, 1.90]
4 Adverse events	1	151	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.75, 5.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Serious adverse events	1	151	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.38]
6 Withdrawal due to adverse events	3	289	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.26, 3.83]

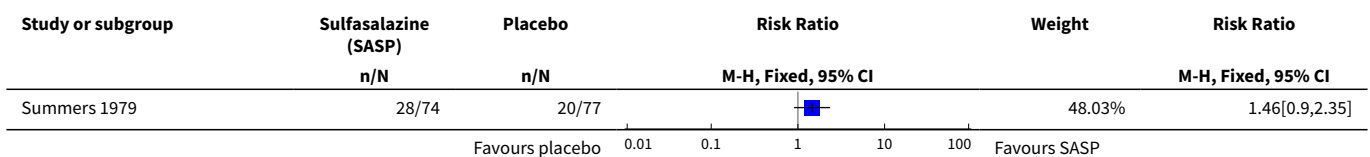
Analysis 1.1. Comparison 1 Sulfasalazine versus placebo, Outcome 1 Induction of remission (CDAI <150), therapeutic response (VHI decrease >=25%) or clinical improvement.

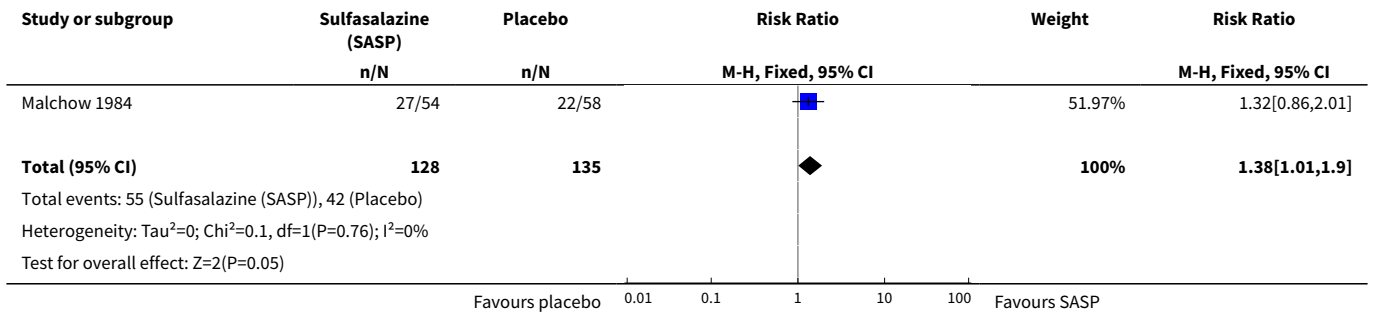


Analysis 1.2. Comparison 1 Sulfasalazine versus placebo, Outcome 2 Induction of remission (CDAI <150) (Random Effects Model).

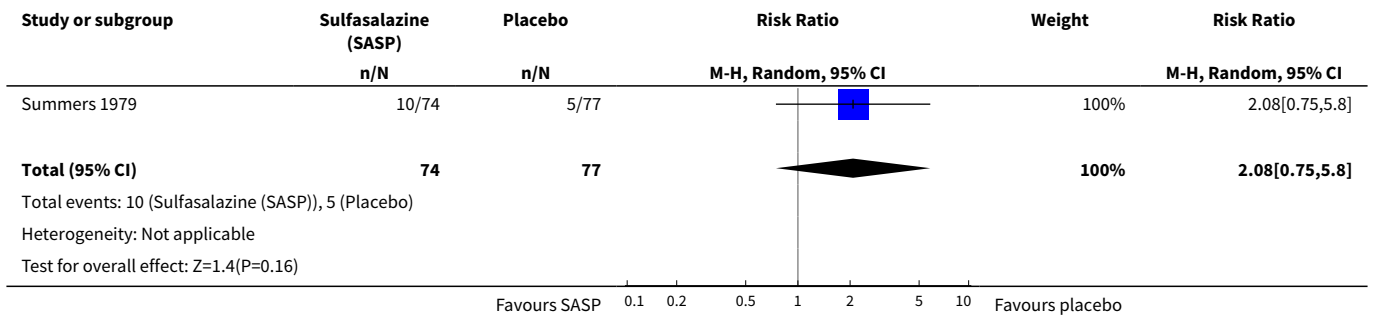


Analysis 1.3. Comparison 1 Sulfasalazine versus placebo, Outcome 3 Induction of remission (CDAI <150) (Fixed Effect Model).

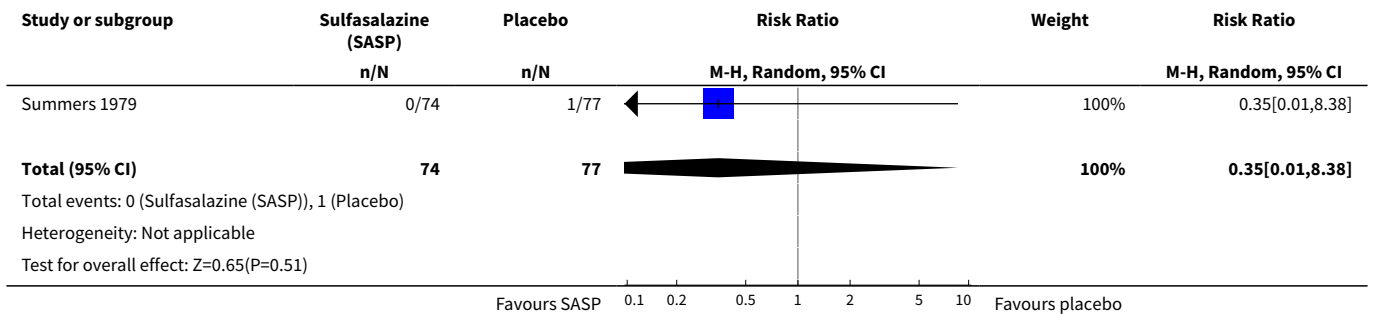




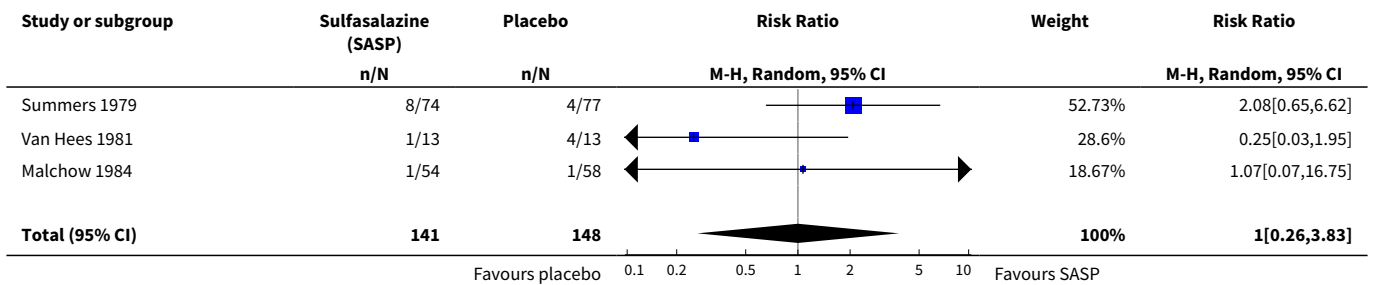
Analysis 1.4. Comparison 1 Sulfasalazine versus placebo, Outcome 4 Adverse events.

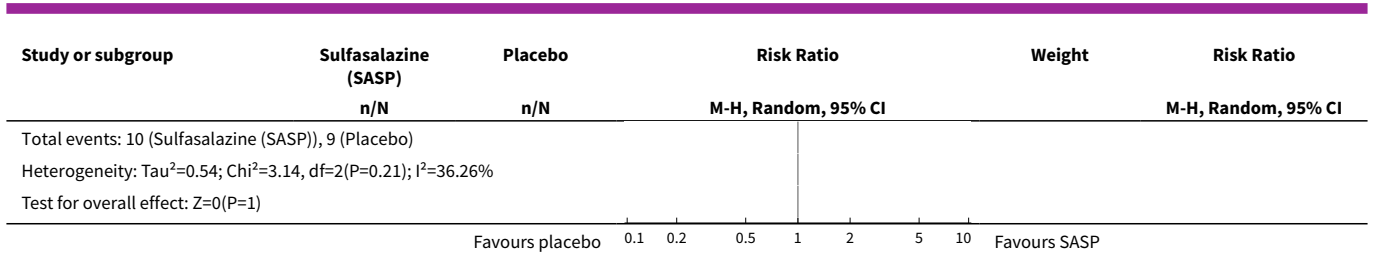


Analysis 1.5. Comparison 1 Sulfasalazine versus placebo, Outcome 5 Serious adverse events.



Analysis 1.6. Comparison 1 Sulfasalazine versus placebo, Outcome 6 Withdrawal due to adverse events.

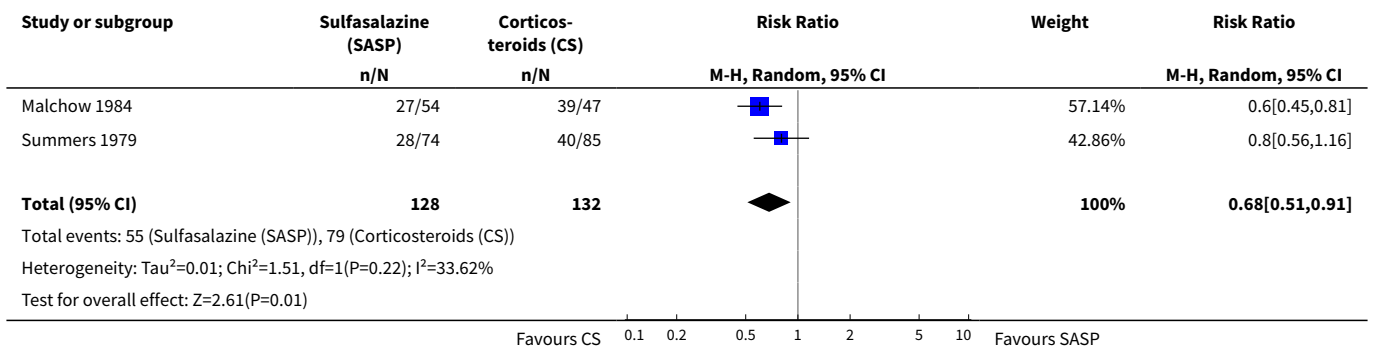




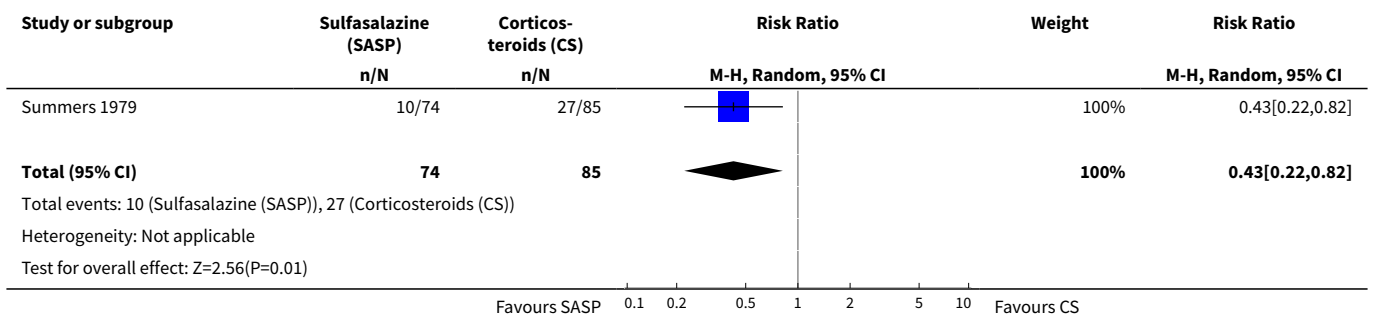
Comparison 2. Sulfasalazine versus corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of remission (CDAI <150)	2	260	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.91]
2 Adverse events	1	159	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.22, 0.82]
3 Serious adverse events	1	159	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 3.12]
4 Withdrawal adverse events	2	260	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.59]

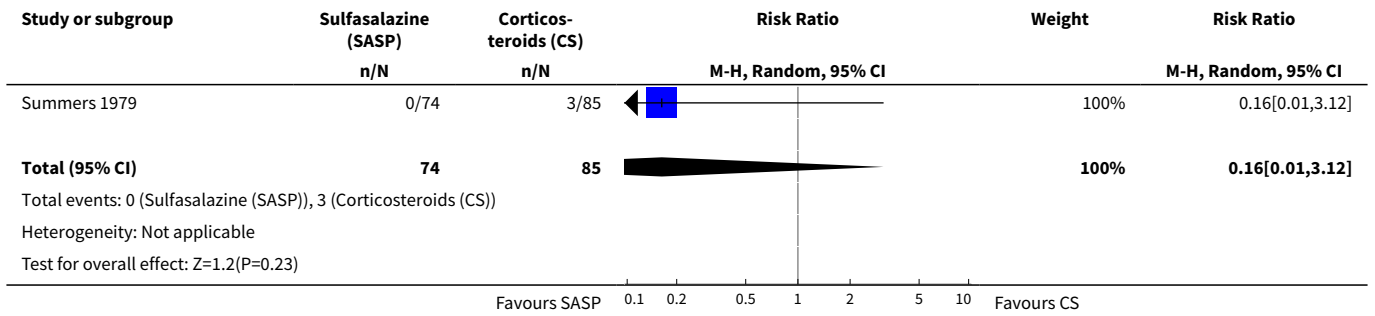
Analysis 2.1. Comparison 2 Sulfasalazine versus corticosteroids, Outcome 1 Induction of remission (CDAI <150).



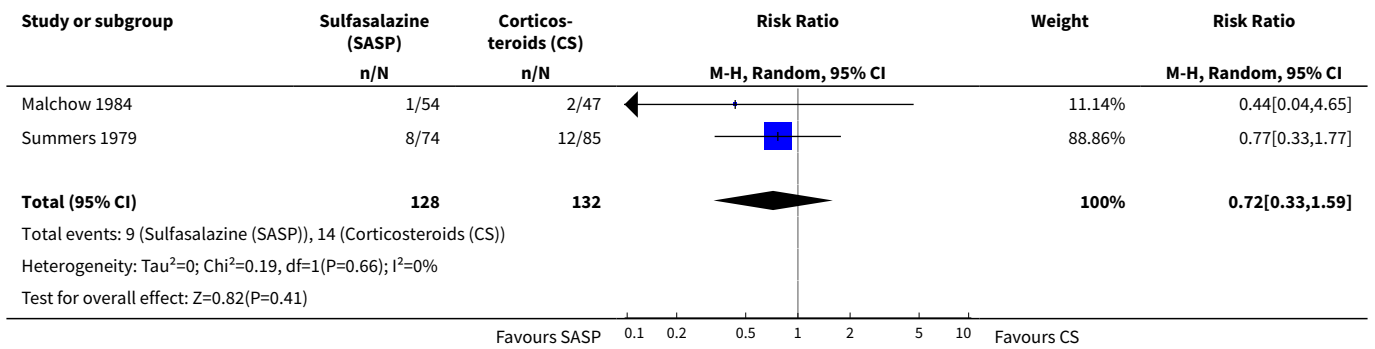
Analysis 2.2. Comparison 2 Sulfasalazine versus corticosteroids, Outcome 2 Adverse events.



Analysis 2.3. Comparison 2 Sulfasalazine versus corticosteroids, Outcome 3 Serious adverse events.



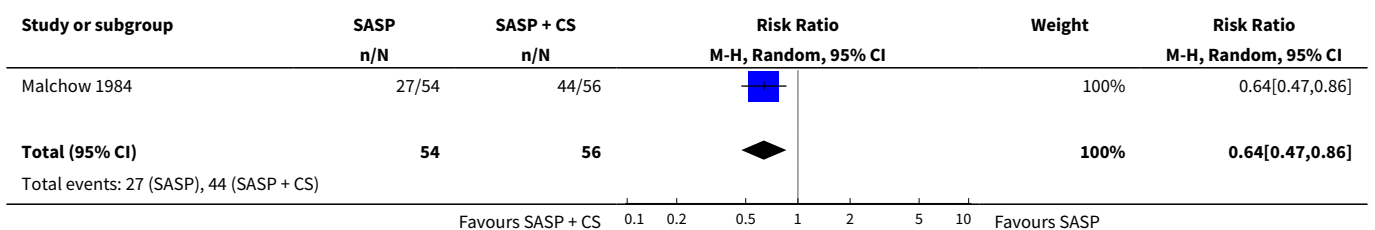
Analysis 2.4. Comparison 2 Sulfasalazine versus corticosteroids, Outcome 4 Withdrawal adverse events.

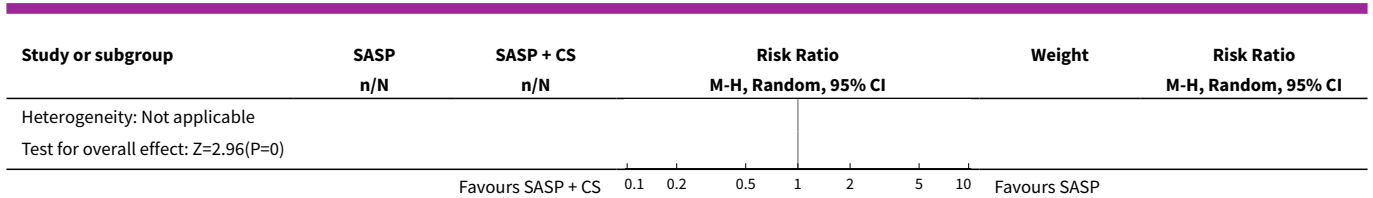


Comparison 3. Sulfasalazine versus sulfasalazine and corticosteroids

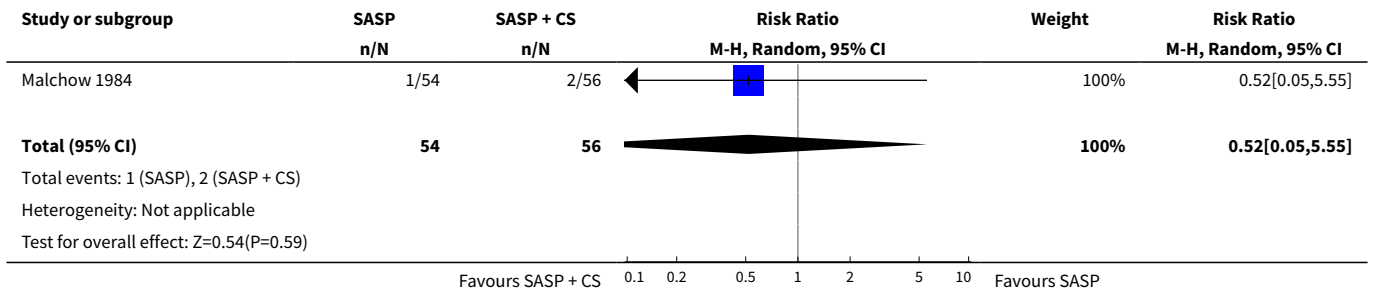
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of remission	1	110	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.47, 0.86]
2 Withdrawal due to adverse events	1	110	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.55]

Analysis 3.1. Comparison 3 Sulfasalazine versus sulfasalazine and corticosteroids, Outcome 1 Induction of remission.





Analysis 3.2. Comparison 3 Sulfasalazine versus sulfasalazine and corticosteroids, Outcome 2 Withdrawal due to adverse events.

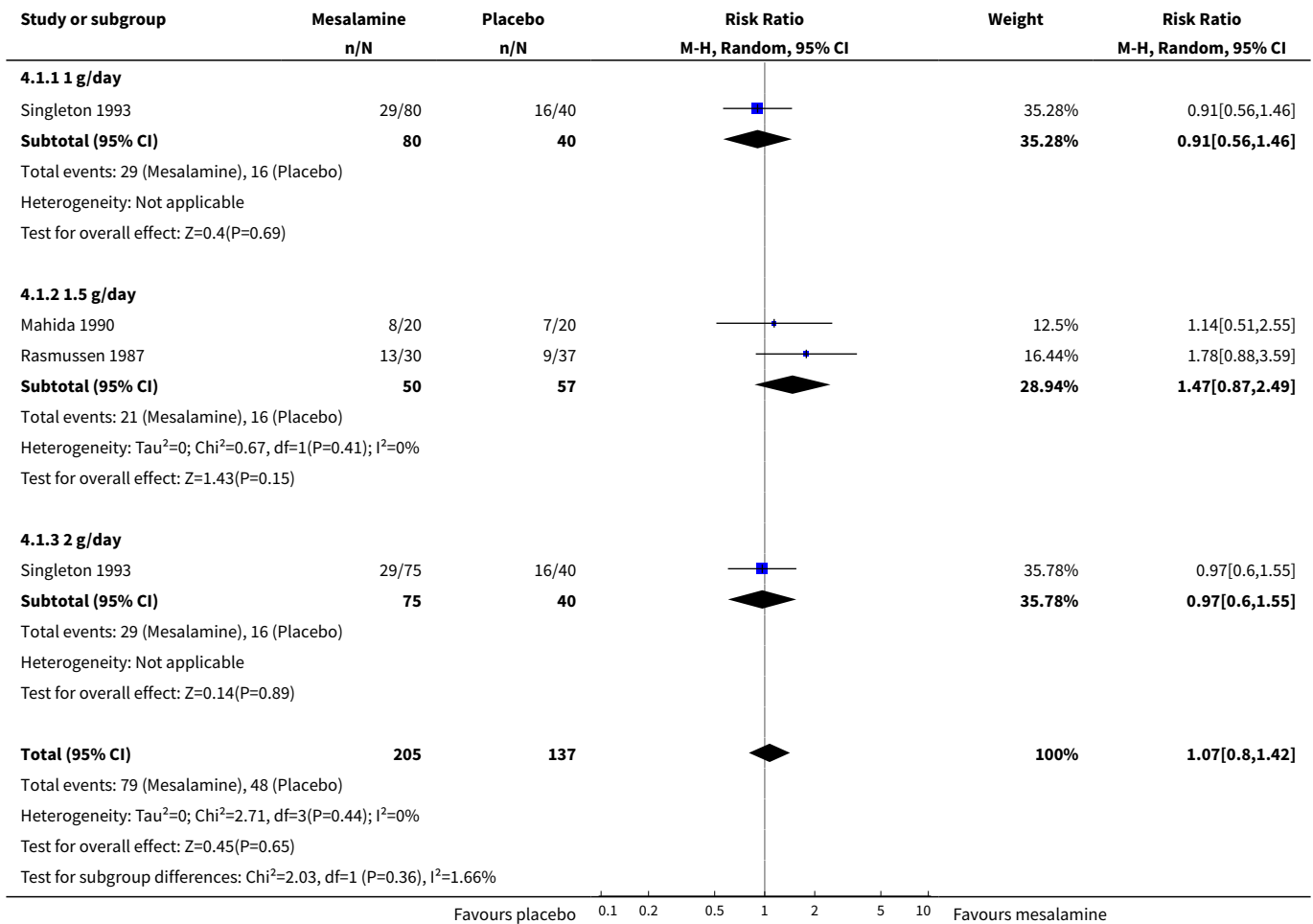


Comparison 4. Controlled-release mesalamine (1 - 2 g/day) versus placebo

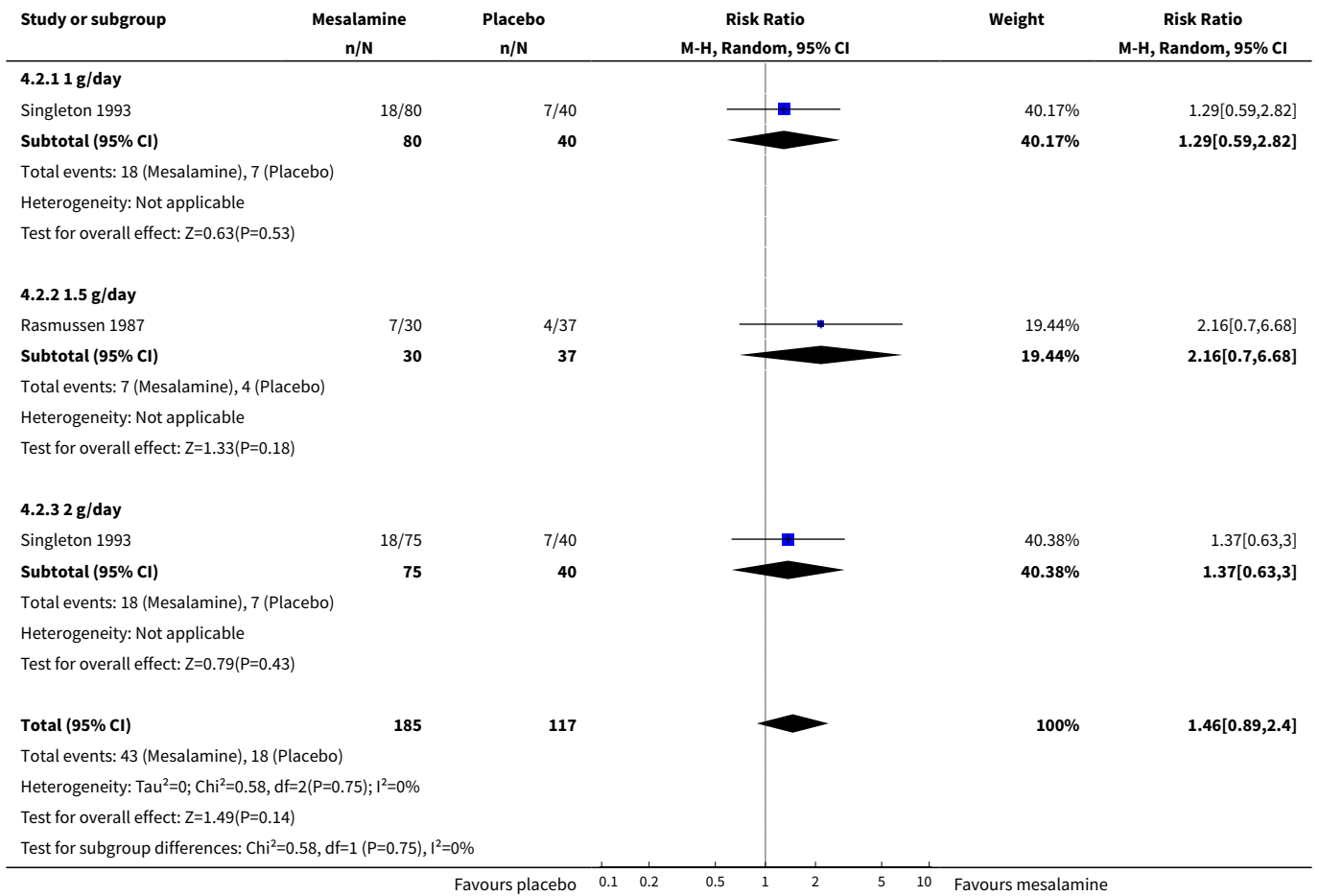
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Decrease in CDAI >=50, HBI >=2 or improvement/remission (as defined by Tvede et al)	3	342	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.80, 1.42]
1.1 1 g/day	1	120	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.56, 1.46]
1.2 1.5 g/day	2	107	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.87, 2.49]
1.3 2 g/day	1	115	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.60, 1.55]
2 Induction of remission (CDAI <=150 + decrease of >=50 or as defined by Tvede et al)	2	302	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.89, 2.40]
2.1 1 g/day	1	120	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.59, 2.82]
2.2 1.5 g/day	1	67	Risk Ratio (M-H, Random, 95% CI)	2.16 [0.70, 6.68]
2.3 2 g/day	1	115	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.63, 3.00]
3 Adverse events	3	342	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.91, 1.96]
3.1 1 g/day	1	120	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.55, 2.69]
3.2 1.5 g/day	2	107	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.73, 2.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 2 g/day	1	115	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.76, 3.11]
4 Withdrawal due to adverse events	3	342	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.75, 1.95]
4.1 1 g/day	1	120	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.48, 2.42]
4.2 1.5 g/day	2	107	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.56, 3.86]
4.3 2 g/day	1	115	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.57, 2.51]

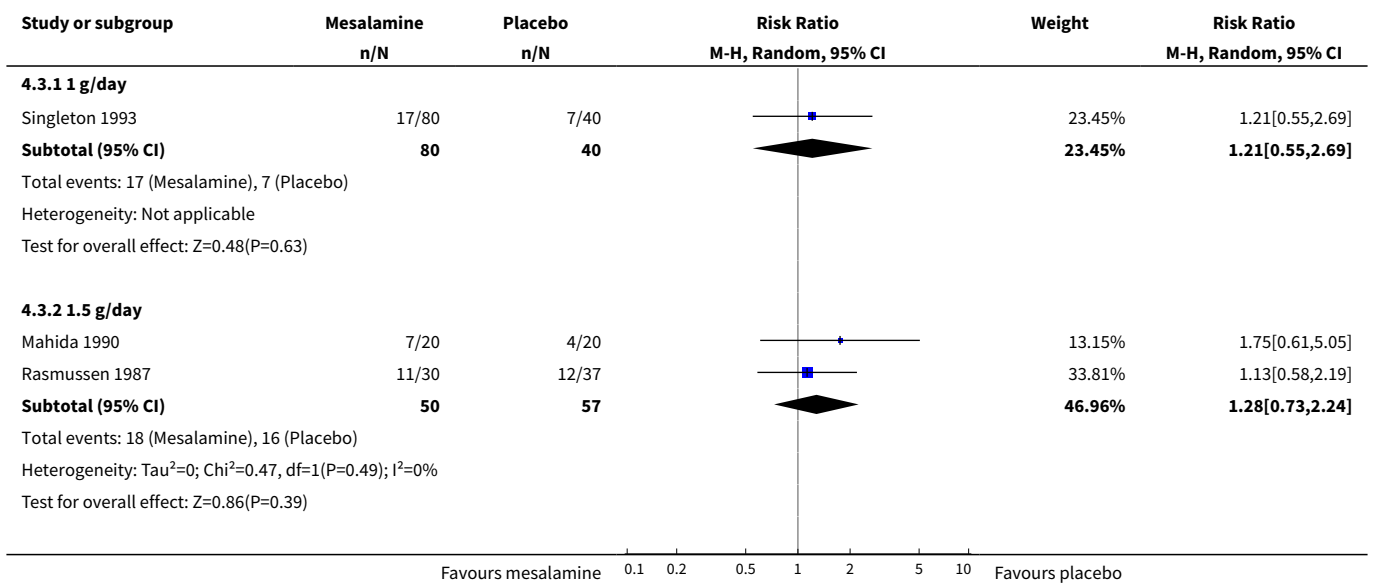
Analysis 4.1. Comparison 4 Controlled-release mesalamine (1 - 2 g/day) versus placebo, Outcome 1 Decrease in CDAI >=50, HBI >=2 or improvement/remission (as defined by Tvede et al).

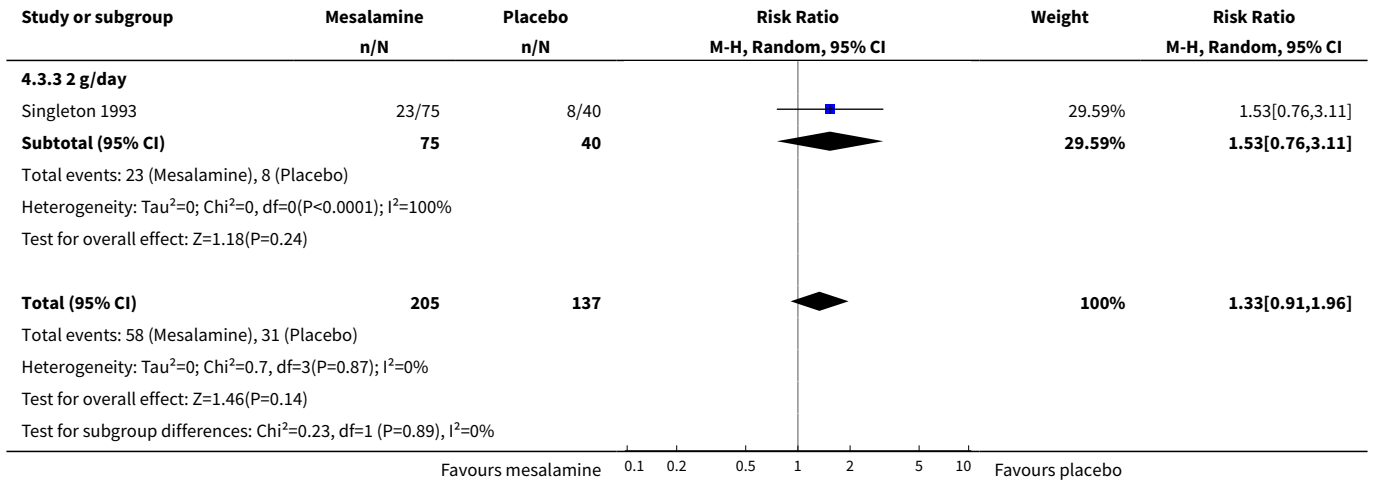


Analysis 4.2. Comparison 4 Controlled-release mesalamine (1 - 2 g/day) versus placebo, Outcome 2 Induction of remission (CDAI <=150 + decrease of >=50 or as defined by Tvede et al).

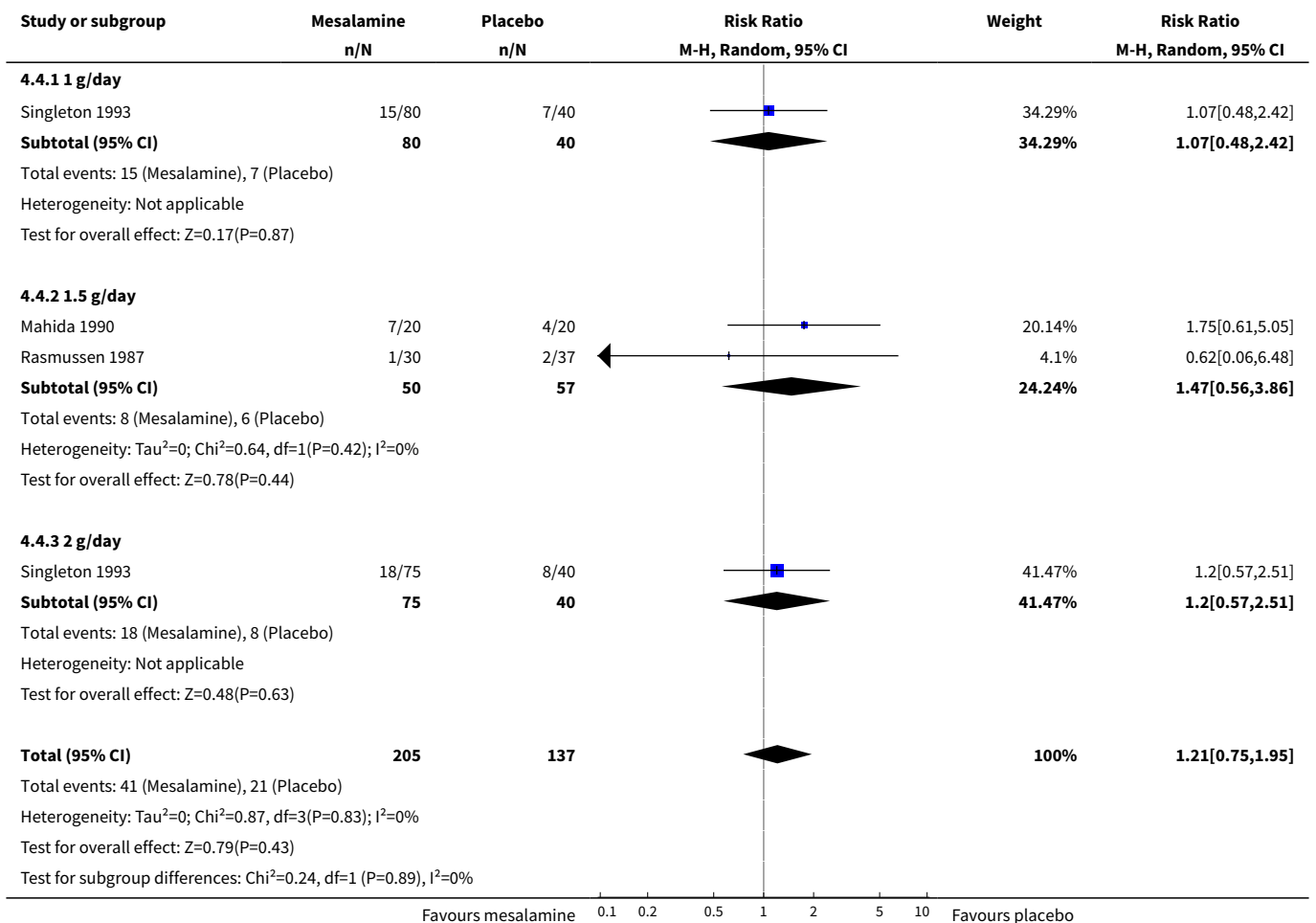


Analysis 4.3. Comparison 4 Controlled-release mesalamine (1 - 2 g/day) versus placebo, Outcome 3 Adverse events.





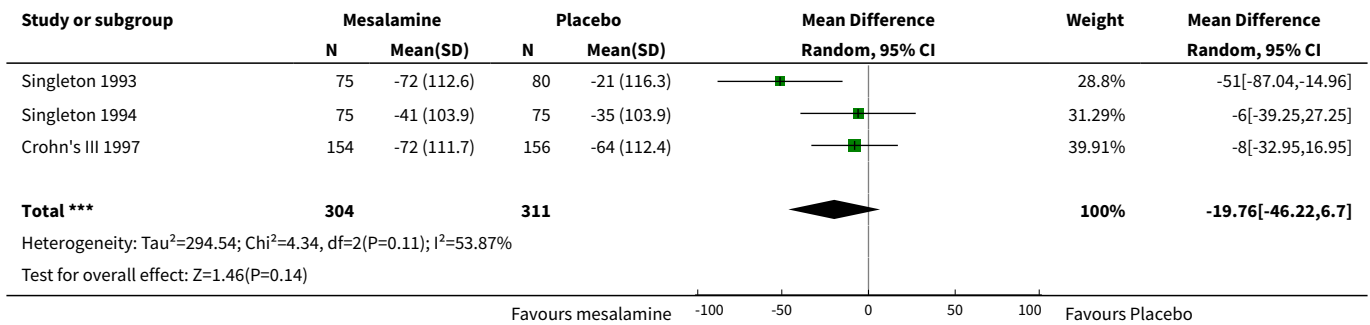
Analysis 4.4. Comparison 4 Controlled-release mesalamine (1 - 2 g/day) versus placebo, Outcome 4 Withdrawal due to adverse events.



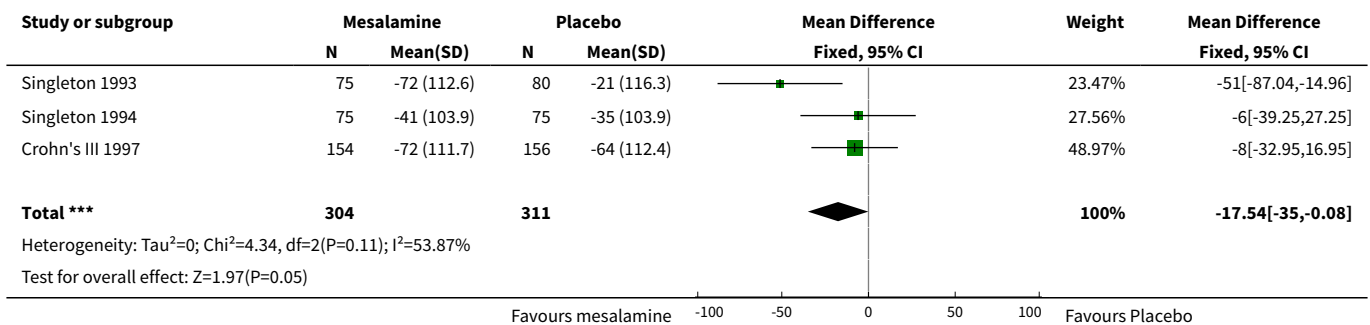
Comparison 5. Controlled-release mesalamine (4 g/day) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in CDAI from baseline (random-effects model)	3	615	Mean Difference (IV, Random, 95% CI)	-19.76 [-46.22, 6.70]
2 Mean change in CDAI from baseline (fixed-effect model)	3	615	Mean Difference (IV, Fixed, 95% CI)	-17.54 [-33.00, -0.08]
3 Adverse events	1	155	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.79, 2.57]
4 Withdrawal due to adverse events	1	155	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.30, 1.37]

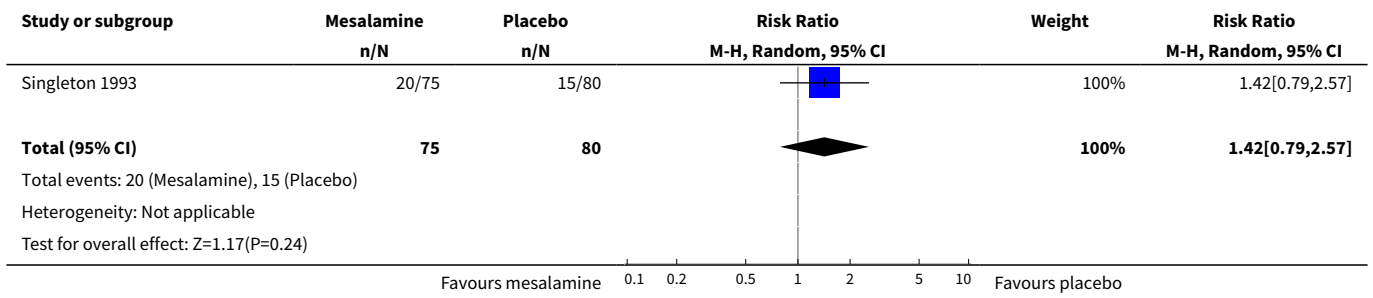
Analysis 5.1. Comparison 5 Controlled-release mesalamine (4 g/day) versus placebo, Outcome 1 Mean change in CDAI from baseline (random-effects model).



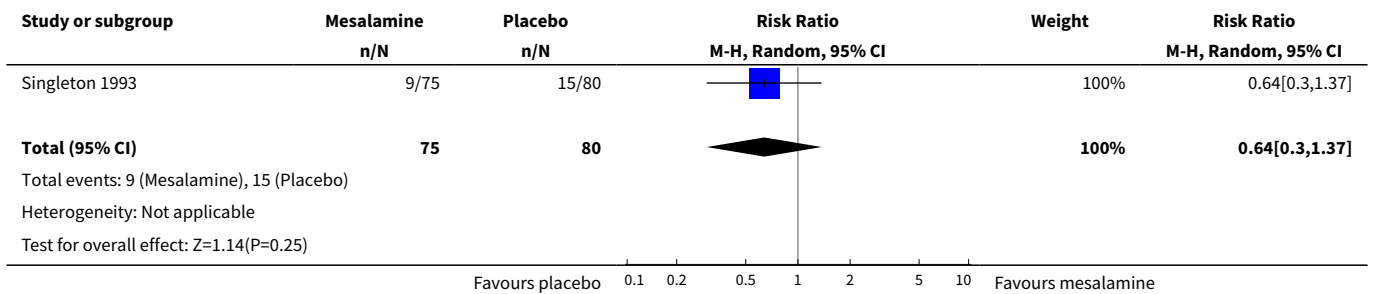
Analysis 5.2. Comparison 5 Controlled-release mesalamine (4 g/day) versus placebo, Outcome 2 Mean change in CDAI from baseline (fixed-effect model).



Analysis 5.3. Comparison 5 Controlled-release mesalamine (4 g/day) versus placebo, Outcome 3 Adverse events.



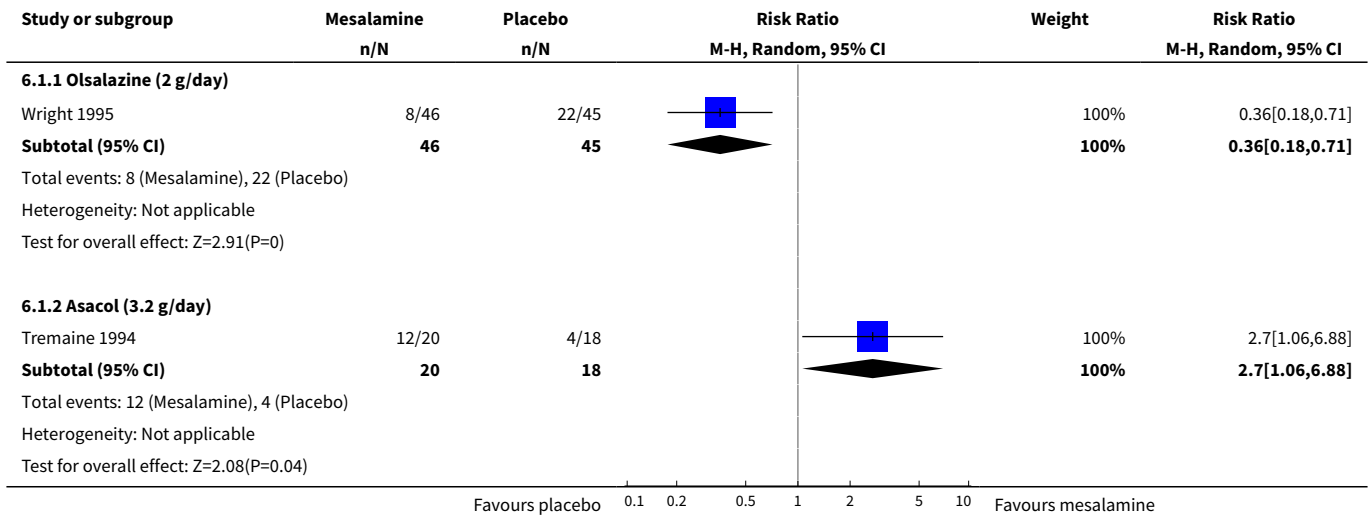
Analysis 5.4. Comparison 5 Controlled-release mesalamine (4 g/day) versus placebo, Outcome 4 Withdrawal due to adverse events.



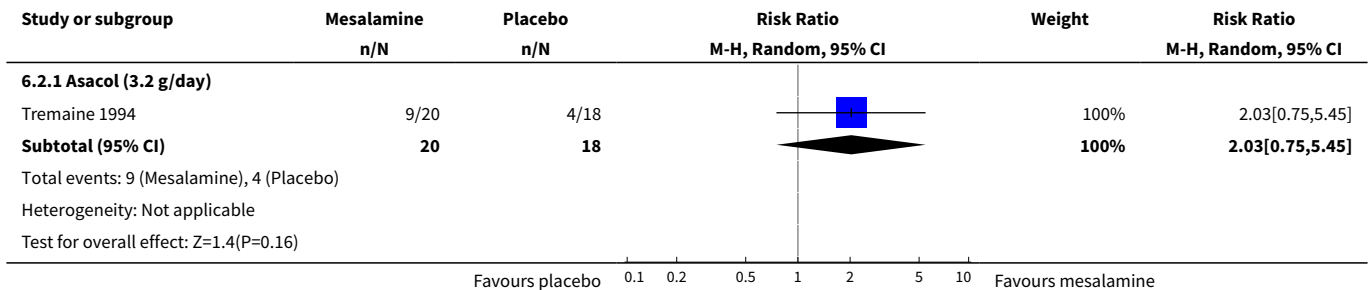
Comparison 6. Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of remission or clinical improvement	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Olsalazine (2 g/day)	1	91	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.18, 0.71]
1.2 Asacol (3.2 g/day)	1	38	Risk Ratio (M-H, Random, 95% CI)	2.70 [1.06, 6.88]
2 Induction of remission (CDAI < 150 + decrease >=70)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Asacol (3.2 g/day)	1	38	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.75, 5.45]
3 Adverse events	1	38	Risk Ratio (M-H, Random, 95% CI)	0.9 [0.68, 1.18]
4 Withdrawal due to adverse events	1	91	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.99, 2.24]

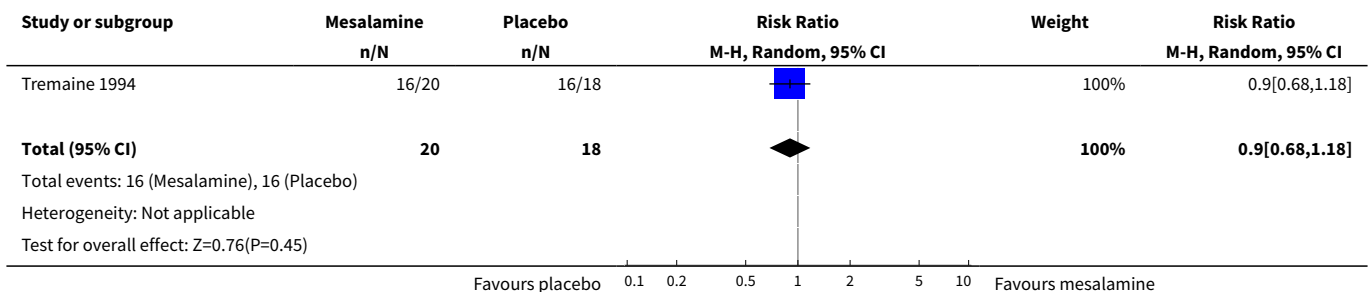
Analysis 6.1. Comparison 6 Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) versus placebo, Outcome 1 Induction of remission or clinical improvement.



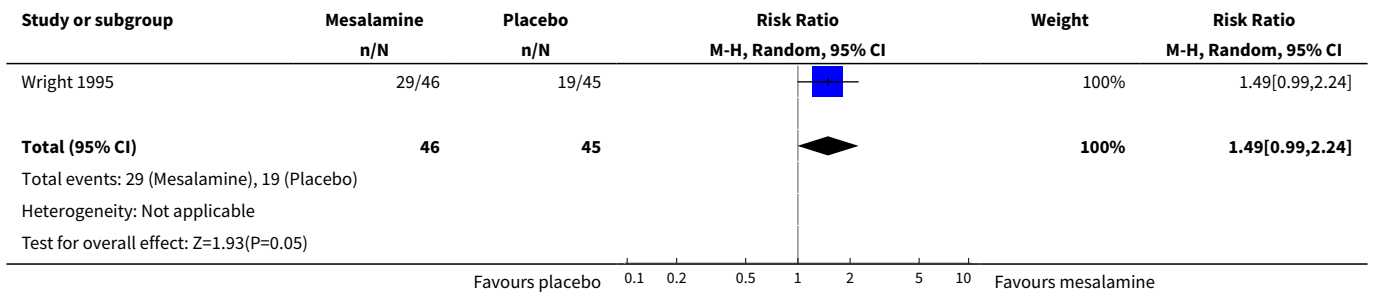
Analysis 6.2. Comparison 6 Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) versus placebo, Outcome 2 Induction of remission (CDAI < 150 + decrease >=70).



Analysis 6.3. Comparison 6 Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) versus placebo, Outcome 3 Adverse events.



Analysis 6.4. Comparison 6 Azo-bonded and delayed-release mesalamine (2 - 3.2 g/day) versus placebo, Outcome 4 Withdrawal due to adverse events.

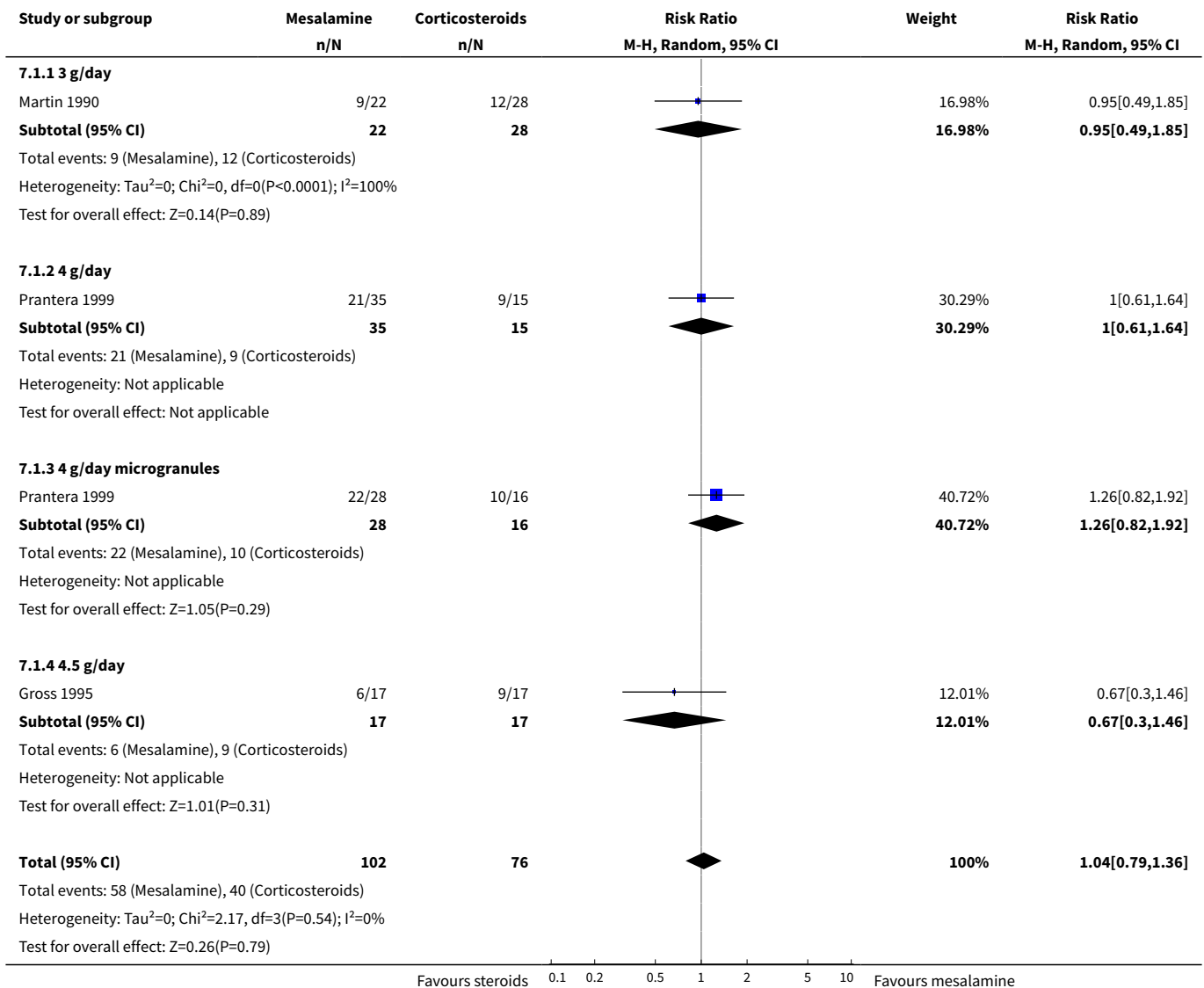


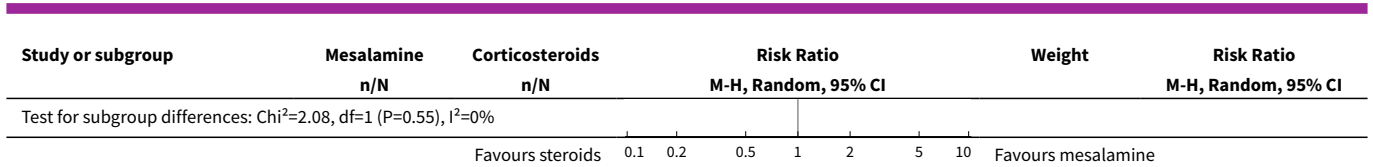
Comparison 7. Delayed-release mesalamine (3 - 4.5 g/day) versus corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of remission (CDAI < or =150 with or without decrease of at least 60 points)	3	178	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.79, 1.36]
1.1 3 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.49, 1.85]
1.2 4 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.61, 1.64]
1.3 4 g/day microgranules	1	44	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.82, 1.92]
1.4 4.5 g/day	1	34	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.30, 1.46]
2 Adverse events	3	178	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.23, 1.05]
2.1 3 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.22, 1.01]
2.2 4 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.12, 0.81]
2.3 4 g/day microgranules	1	44	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.07, 0.82]
2.4 4.5 g/day	1	34	Risk Ratio (M-H, Random, 95% CI)	1.1 [0.65, 1.87]
3 Serious adverse events	3	178	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.10, 1.27]
3.1 3 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.16, 4.64]
3.2 4 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.00, 1.75]
3.3 4 g/day microgranules	1	44	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.68]
3.4 4.5 g/day	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

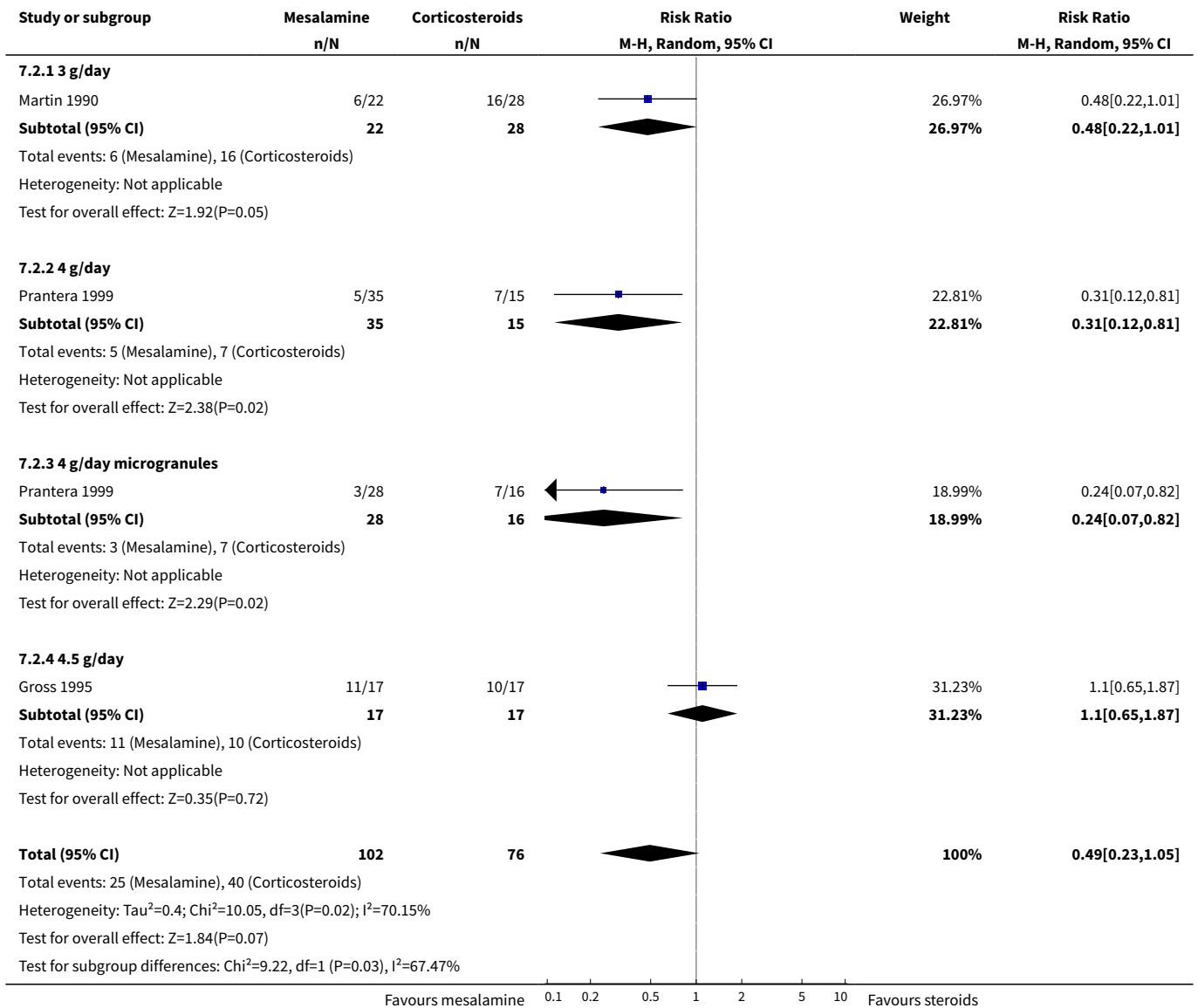
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Withdrawal due to adverse events	3	178	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.13, 1.15]
4.1 3 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.16, 4.64]
4.2 4 g/day	1	50	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.00, 1.75]
4.3 4 g/day microgranules	1	44	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.68]
4.4 4.5 g/day	1	34	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.01]

Analysis 7.1. Comparison 7 Delayed-release mesalamine (3 - 4.5 g/day) versus corticosteroids, Outcome 1 Induction of remission (CDAI <=150 with or without decrease of at least 60 points).

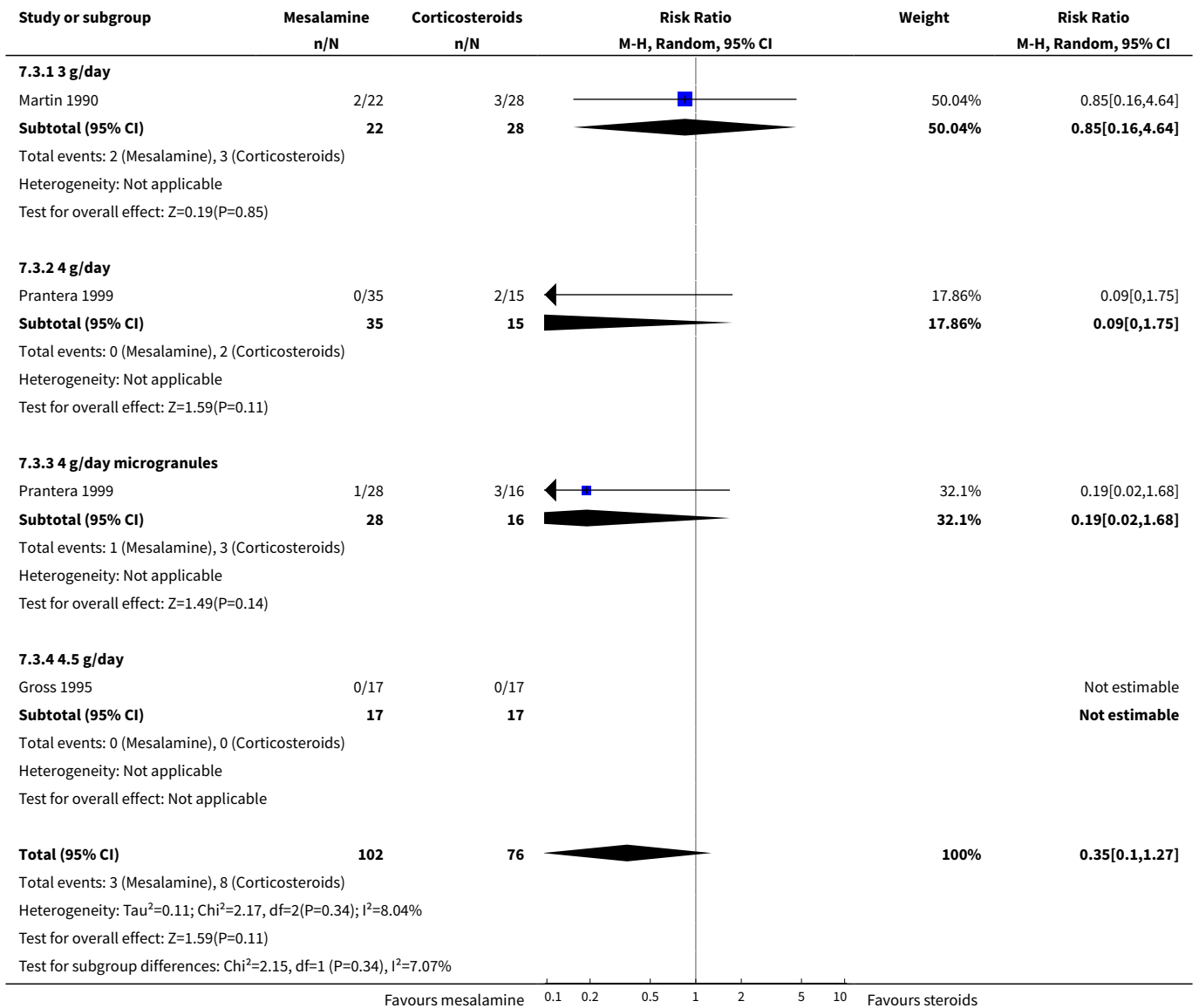




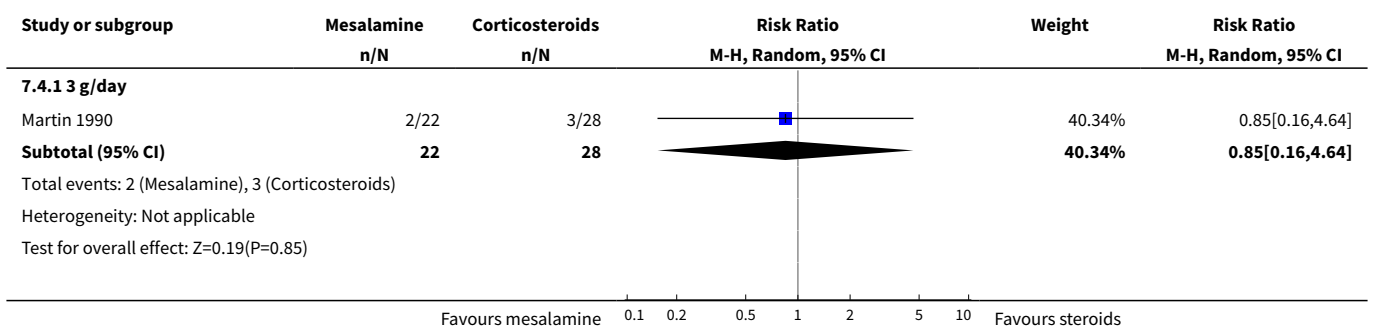
Analysis 7.2. Comparison 7 Delayed-release mesalamine (3 - 4.5 g/day) versus corticosteroids, Outcome 2 Adverse events.

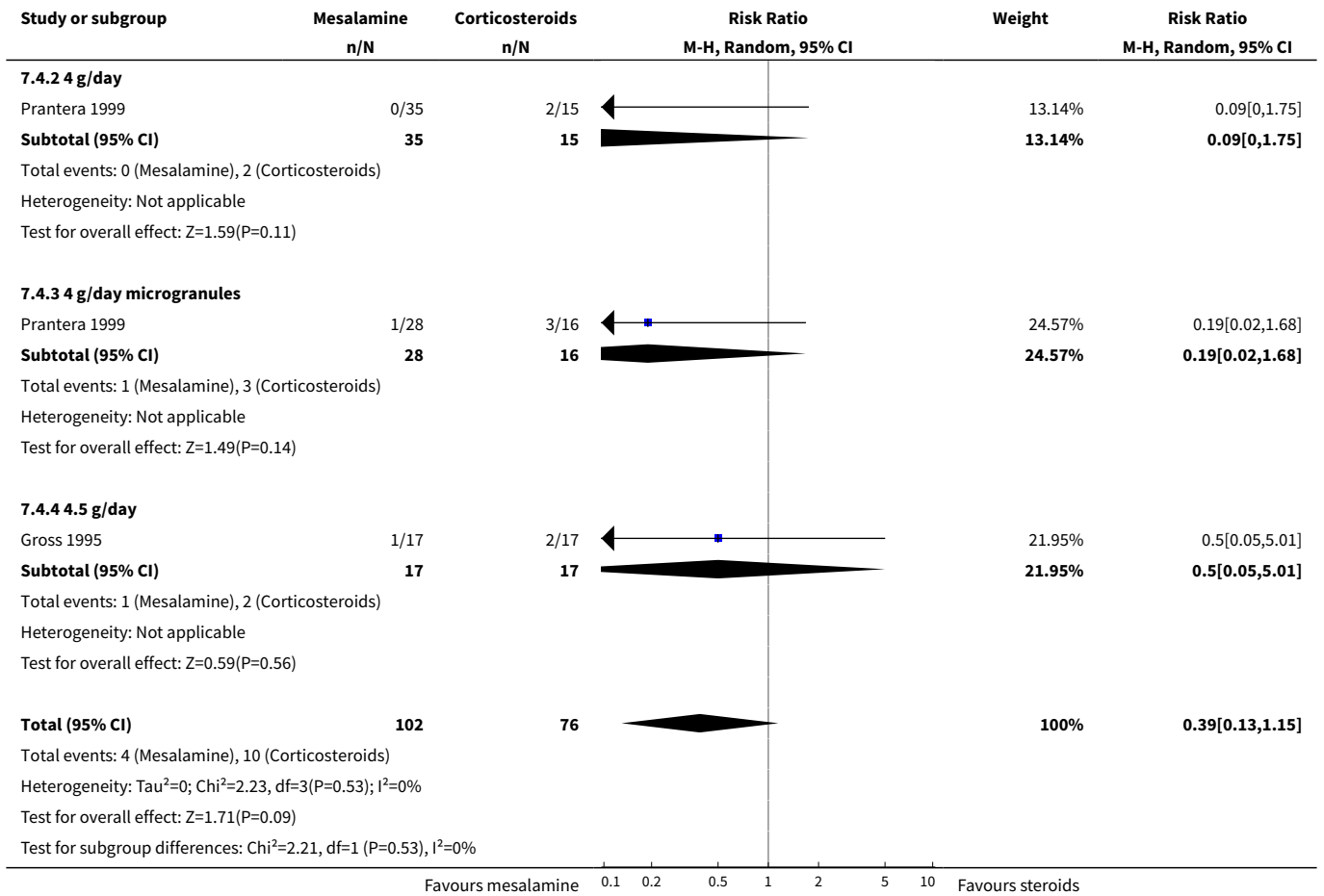


Analysis 7.3. Comparison 7 Delayed-release mesalamine (3 - 4.5 g/day) versus corticosteroids, Outcome 3 Serious adverse events.



Analysis 7.4. Comparison 7 Delayed-release mesalamine (3 - 4.5 g/day) versus corticosteroids, Outcome 4 Withdrawal due to adverse events.



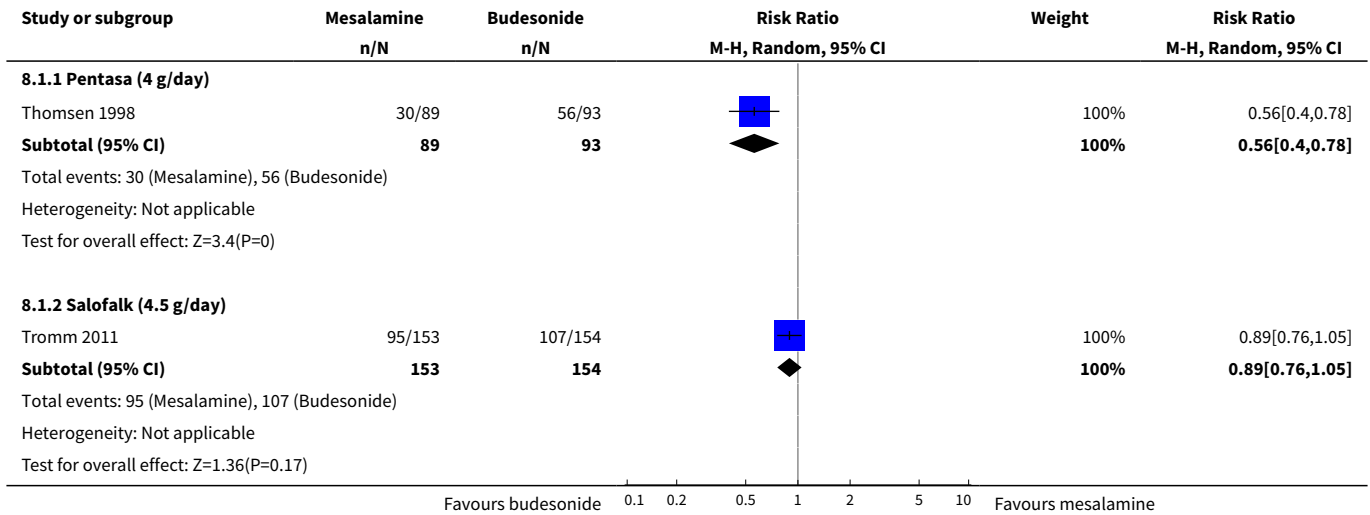


Comparison 8. Mesalamine (4 - 4.5 g/day) versus budesonide

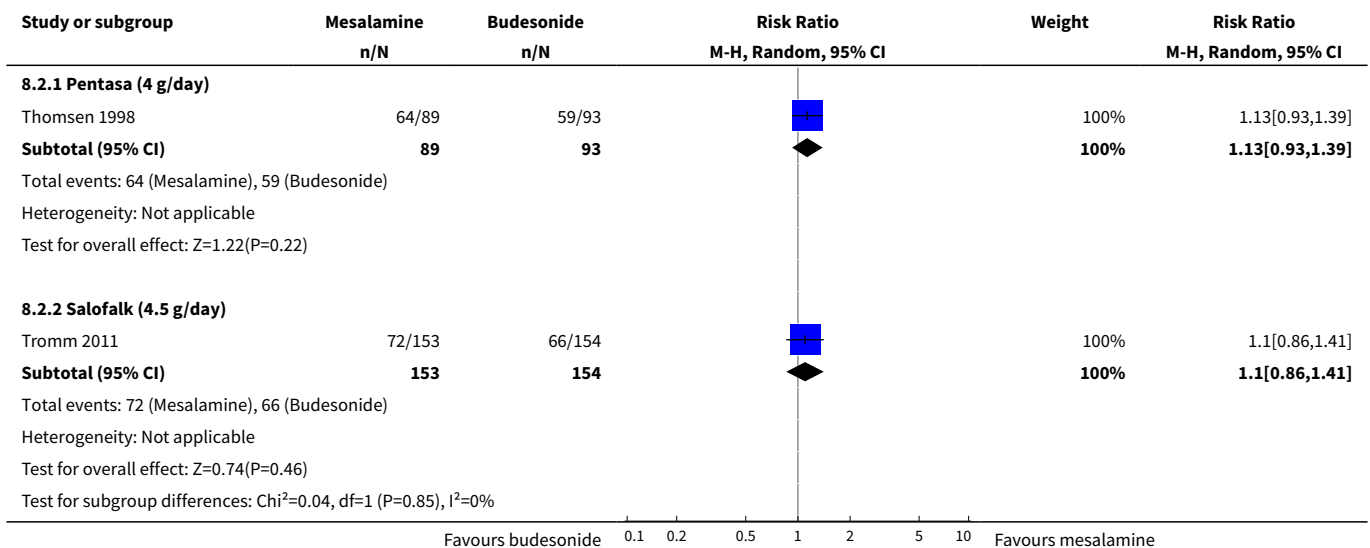
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of remission (CDAI < or = 150)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Pentasa (4 g/day)	1	182	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.40, 0.78]
1.2 Salofalk (4.5 g/day)	1	307	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.76, 1.05]
2 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Pentasa (4 g/day)	1	182	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.93, 1.39]
2.2 Salofalk (4.5 g/day)	1	307	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.86, 1.41]
3 Serious adverse events	1	182	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.80, 3.25]
4 Withdrawal due to adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Pentasa (4 g/day)	1	182	Risk Ratio (M-H, Random, 95% CI)	2.81 [1.60, 4.96]
4.2 Salofalk (4.5 g/day)	1	307	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.62, 6.55]

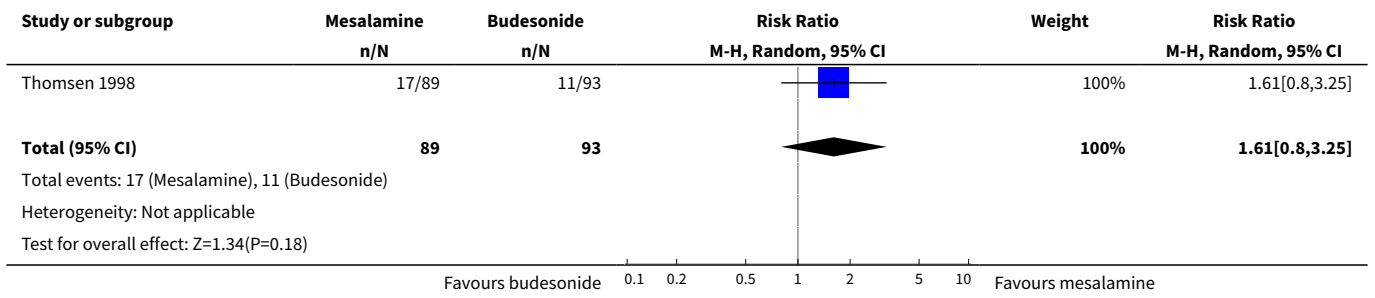
Analysis 8.1. Comparison 8 Mesalamine (4 - 4.5 g/day) versus budesonide, Outcome 1 Induction of remission (CDAI < or = 150).



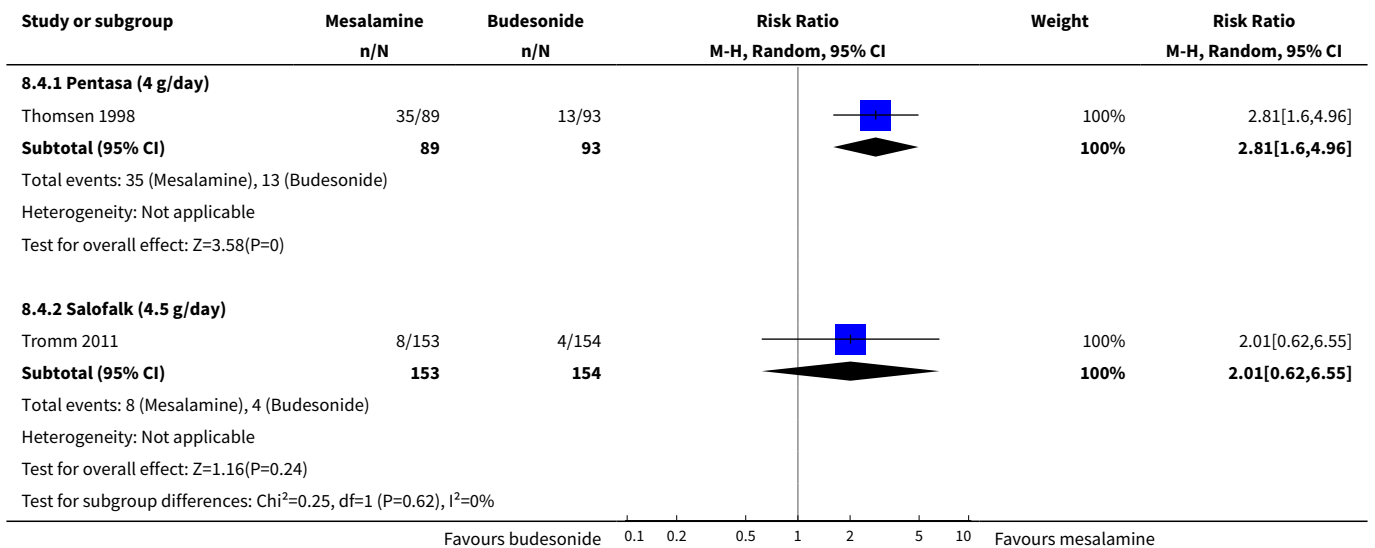
Analysis 8.2. Comparison 8 Mesalamine (4 - 4.5 g/day) versus budesonide, Outcome 2 Adverse events.



Analysis 8.3. Comparison 8 Mesalamine (4 - 4.5 g/day) versus budesonide, Outcome 3 Serious adverse events.



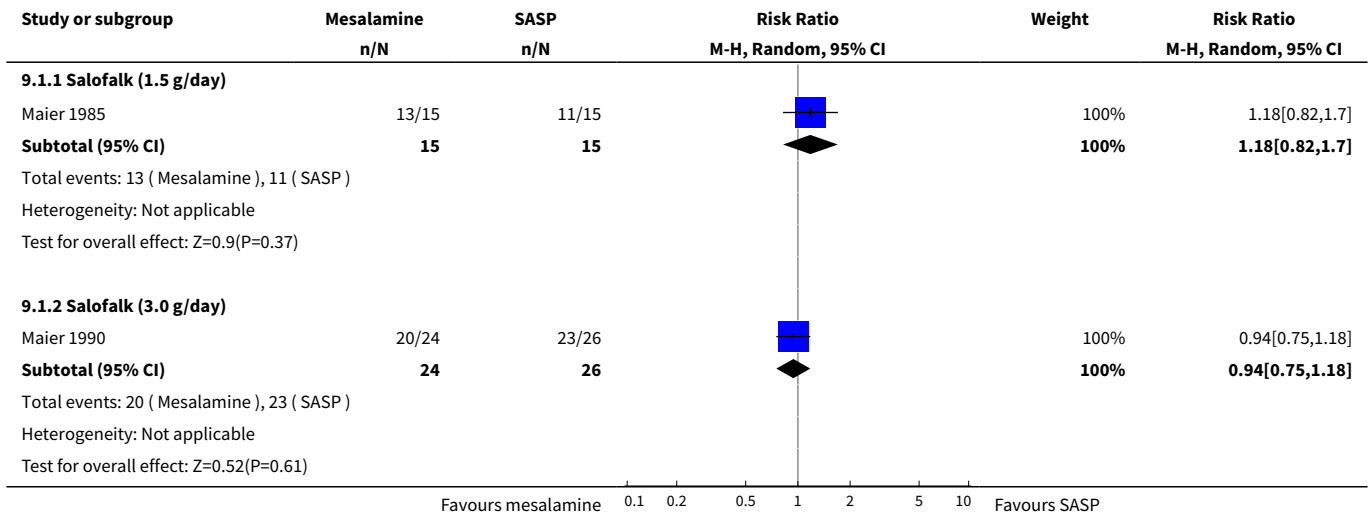
Analysis 8.4. Comparison 8 Mesalamine (4 - 4.5 g/day) versus budesonide, Outcome 4 Withdrawal due to adverse events.



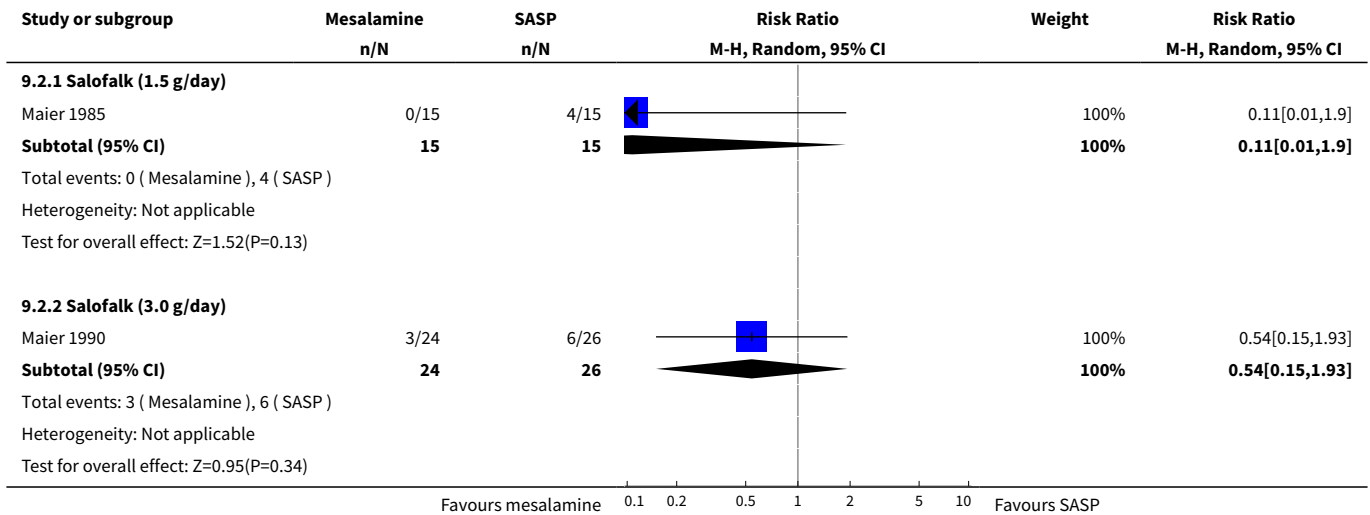
Comparison 9. Mesalamine versus sulfasalazine (alone or in combination with corticosteroids)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of remission (CDAI < 150) or clinical improvement	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Salofalk (1.5 g/day)	1	30	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.82, 1.70]
1.2 Salofalk (3.0 g/day)	1	50	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.18]
2 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Salofalk (1.5 g/day)	1	30	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.90]
2.2 Salofalk (3.0 g/day)	1	50	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.15, 1.93]

Analysis 9.1. Comparison 9 Mesalamine versus sulfasalazine (alone or in combination with corticosteroids), Outcome 1 Induction of remission (CDAI < 150) or clinical improvement.



Analysis 9.2. Comparison 9 Mesalamine versus sulfasalazine (alone or in combination with corticosteroids), Outcome 2 Adverse events.



ADDITIONAL TABLES

Table 1. Characteristics of Excluded Studies

Study ID	Comparators	Endpoint	Study design	Patient Population	Exclusion reasons
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Table 1. Characteristics of Excluded Studies (Continued)

Anonymous 1985	SASP 1 g/15 kg /day alone	Clinical response	Uncontrolled	Active CD	1, 5
Anonymous 1990	5-ASA 1.5 g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission (Medical/Surgical)	2, 6
Anthonisen 1974	SASP (1.5 g for 3 days followed by 3 g/day) versus Placebo	Clinical improvement	Double-blind placebo controlled cross-over	Active CD	7
Arber 1995	5-ASA 1 g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission	2, 6
Ardizzone 2004	5-ASA 3 g/day versus Azathioprine	Clinical and surgical relapse	Open label, randomized	CD in remission (Surgical)	2, 5, 6
Beck 1988	5-ASA versus SASP	Clinical response	Uncontrolled	Active CD	1
Bergman 1976	SASP + CS versus No Treatment	Clinical relapse	Randomized controlled	CD in remission (Surgical)	2, 4, 6
Blichfeldt 1978	SASP versus prednisolone (Metronidazole/ placebo cross-over)	Clinical improvement	Double-blind cross-over	Active CD	4, 5
Bresci 1994	5-ASA 2.4 g/day versus No Specific Therapy	Clinical relapse	Randomized controlled	CD in remission (Medical)	2, 6
Brignola 1992	5-ASA 2 g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission	2, 6
Brignola 1995	5-ASA 3 g/day versus Placebo	Endoscopic relapse	Double-blind placebo controlled	CD in remission (Surgical)	2, 6
Caprilli 1994	5-ASA 2.4 g/day versus No Treatment	Endoscopic relapse	Randomized controlled	CD in remission (Surgical)	2, 6
Caprilli 2003	5-ASA 2.4 g/day versus 5-ASA 4 g/day	Clinical and endoscopic relapse	Randomized controlled	CD in remission (Surgical)	2, 6
Cezard 2009	5-ASA versus Placebo	Clinical relapse	Double-blind placebo-controlled	CD in remission (Paediatric)	2, 6
Cohen 2000	5ASA versus Placebo	Endoscopic recurrence	Randomized, controlled	CD in remission (Surgical)	2, 6
Colombel 1999	5-ASA versus Antibiotic	Remission	Randomized controlled	Active CD	5
de Franchis R 1997	5-ASA 3 g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission (Steroid-induced)	2, 6
Del Corso 1995	5-ASA 2.4 g/day versus No Treatment	Clinical relapse	Controlled trial	CD in remission (Medical/Surgical)	2, 6

Table 1. Characteristics of Excluded Studies (Continued)

Dirks 1989	SASP + CS versus Surgery	Clinical relapse	Uncontrolled	CD in remission	1,2,4,5,6
Ewe 1976	SASP versus Placebo	Relapse	Double-blind	CD in remission	2, 6
Ewe 1984	SASP, radical versus restricted surgery	Clinical relapse	Partially randomized, double-blind	CD in remission (Surgical)	2,6
Ewe 1986	SASP, radicality of surgery	Clinical relapse		CD in remission (Surgical)	2,6
Ewe 1989	SASP versus Placebo	Clinical relapse	Randomized controlled	CD in remission (Surgical)	2, 6
Fiasse 1990	5-ASA versus Placebo	Relapse	Double-blind placebo-controlled	CD in remission (Surgical)	2, 6
Florent 1996	5-ASA 3 g/day versus Placebo	Endoscopic relapse	Double-blind placebo-controlled	CD in remission (Surgical)	2, 6
Genre 1993	5-ASA 2 g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission	2, 6
Gerhardt 2001	5-ASA versus Boswellia serrata extract H15	Change in CDAI	Randomized controlled	Active CD	5
Goldstein 1987	SASP alone	Clinical response	Retrospective	Active small bowel CD	1, 5
Griffiths 1993	5-ASA 50 mg/kg versus Placebo	Change in CDAI, VHI	Randomized controlled	Active small bowel CD (Paediatric)	2
Guslandi 2000	5-ASA 3 g/day versus 5-ASA 2 g/day + <i>Saccharomyces boulardii</i> (yeast)	Clinical relapse	Randomized controlled	CD in remission	2, 5, 6
Hanauer 1993	5-ASA 4g/day alone	Clinical response	Uncontrolled	Active CD and CD in remission	1, 5
Hanauer 2004b	5-ASA 3 g/day versus 6-MP 50 mg/day versus placebo	Clinical, endoscopic and radiographic relapse	Randomized controlled	CD in remission (Surgical)	2, 6
Howaldt 1993	5-ASA 1.5 g/day versus 4-ASA 1.5 g/day	Clinical relapse	Randomized controlled	CD in remission	2, 6
Klein 1995	5-ASA 1.5 g/day versus Placebo	Endoscopic relapse	Controlled trial	CD in remission (Surgical)	2, 6
Klotz 1980	SASP versus Sulfapyridine versus Rectal 5-ASA	Activity index, stool quality, remission rate	Randomized controlled	Active CD and UC	3, 5
Lennard-Jones 1977	SASP versus Placebo	Clinical relapse	Double-blind placebo-controlled	CD in remission (Medical/Surgical)	2, 6

Table 1. Characteristics of Excluded Studies (Continued)

Lichtenstein 2009a	5-ASA alone	Clinical relapse	Prospective, uncontrolled	CD in remission	1, 2, 5, 6
Lichtenstein 2009b	5-ASA alone	Clinical remission	Prospective, uncontrolled	Active CD	1, 5
Lochs 1991	SASP 3 g/day + CS versus Enteral Nutrition	Clinical remission	Randomized controlled	Active CD	4, 5
Lochs 2000	5-ASA 4 g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission (Surgical)	2, 6
Mahmud 2001	5-ASA 2 g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission	2, 6
Malchow 1990	SASP + CS versus Enteral Nutrition	Clinical remission	Randomized controlled	Active CD	4, 5
Mantzaris 2003	5-ASA 3 g/day versus Budesonide 6 mg/day	Clinical relapse and quality of life	Randomized controlled	CD in remission (Steroid-dependent)	2, 6
Mate-Jimenez 2000	5-ASA 3g/day versus MTX 15 mg/week versus 6-MP 1.5 mg/kg/day	Clinical remission and relapse	Randomized controlled	CD and UC (Steroid-dependent)	2, 5, 6
McLeod 1995	5-ASA 3g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission (Surgical)	2, 6
Modigliani 1996	5-ASA 4g/day versus Placebo	Clinical relapse, steroid weaning	Randomized controlled	CD in remission (Steroid-induced)	2, 6
Orlando 2012	5-ASA alone	Endoscopic recurrence	Prospective, uncontrolled	CD in remission (Surgical)	1, 2, 5, 6
Papi 2009	5-ASA alone vs No Treatment	Clinical and surgical relapse	Retrospective	CD in remission (Surgical)	1, 2, 6
Prantera 1992	5-ASA 2.4 g/day versus placebo	Clinical relapse	Randomized controlled	CD in remission	2, 6
Rasmussen 1983	5-ASA 1.5 g/day alone	Clinical response	Uncontrolled	Active CD	1, 5
Reinisch 2010	5-ASA versus Azathioprine	Therapeutic failure	Double-blind, Double-dummy, Randomized controlled	CD in remission, moderate/severe endoscopic recurrence	2, 5, 6
Romano 2005	5-ASA+omega-3 FA versus 5-ASA	Clinical relapse	Randomized controlled, double-blind	CD in remission (Paediatric)	2, 4, 6
Rosen 1982 Ursing1982	SASP 3 g/day versus Metronidazole	Remission	Randomized controlled	Active CD	5

Table 1. Characteristics of Excluded Studies (Continued)

Savarino 2013	5ASA versus Azathioprine versus Adalimumab	Endoscopic and clinical recurrence	Randomized controlled	CD in remission (Surgical)	2, 5, 6
Schneider 1985	Metronidazole versus CS + SASP +/- Metronidazole	Clinical response	Randomized controlled	Active CD or discharging fistulae	4, 5
Schreiber 1994	5-ASA 1.5 g/day versus 4-ASA 1.5 g/day	Clinical relapse	Randomized controlled	CD in remission	2, 6
Singleton 1979	SASP 1 g/15 kg + CS versus CS alone	Clinical remission and response	Randomized controlled	Active CD	4
Stober 1983	SASP+CS versus Elementary Diet + SASP +/- CS	Laboratory parameters, body weight		Active CD (Paediatric)	2, 4, 5, 6
Sutherland 1997	5-ASA 3g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission (Medical or Surgical)	2,6
Tao 2009	5-ASA versus Tripterygium wilfordii	Clinical relapse	Randomized controlled	CD in remission (Surgical)	2, 5, 6
Terranova 2001	5ASA + Enteral Nutrition versus 5-ASA + CS	Clinical improvement, biohumoral markers	Randomized controlled	Active CD and UC	4, 5
Terrin 2002	5-ASA + CS versus Semi-Elemental Diet	Clinical remission	Randomized controlled	Active CD	4, 5
Thomson 1995	5-ASA 3g/day versus Placebo	Clinical relapse	Randomized controlled	CD in remission	2, 6
Triantafyllidis 2010	5-ASA vs Modulen®IBD	Clinical relapse	Randomized controlled	CD in remission	2, 5, 6
Wellman 1986	TPN + steroids with or without 5-ASA lavage	Endotoxemia, clinical response	Randomized controlled	Active CD	3, 4, 5
Wellmann 1988	5-ASA versus Placebo	Clinical relapse	Double-blind placebo-controlled	CD in remission	2, 6
Wenckert 1978	SASP versus Placebo	Clinical relapse	Double-blind placebo-controlled	CD in remission (Surgical)	2, 6
Yamamoto 2009	5-ASA versus Azathioprine versus Infliximab	Clinical relapse	Prospective	CD in remission (Surgical)	1, 2, 5, 6

1=Inappropriate study design (Uncontrolled, open-label), 2= Inappropriate study population (pediatric, CD in remission, severe CD), 3= Inappropriate route of drug delivery (rectal, lavage), 4= combined therapy, 5= inappropriate comparator, 6= inappropriate endpoint, 7=cross-over studies that did not provide data prior to first crossover. Numbers in bold indicate primary reason for exclusion.

APPENDICES

Appendix 1. Search Strategies

MEDLINE on PUBMED was searched using the following search terms:

#1 crohn*

#2 sulphasalazine OR sulfasalazine OR salazosulphapyr* OR salazosulfapyr* OR salicylazosulphapyr* OR salicylazosulfapyr* OR salazopyrin

#3 mesalamine OR mezalamine OR aminosalicylate* OR aminosalicylic acid OR 5-aminosalicylate* OR 5-aminosalicylic acid OR 5-ASA

#4 #2 OR #3

#5 #4 AND #1

#6 singl* OR doubl* OR tripl* OR trebl* OR blind* OR mask* OR placebo* OR single-blind* OR double-blind* OR triple-blind* OR random* OR (controlled clinical)

#7 #5 AND #6

EMBASE database was searched using the following search terms:

#1 random\$.tw.

#2 factorial\$.tw.

#3 (crossover\$ or cross over\$ or cross-over\$).tw.

#4 placebo\$.tw.

#5 single blind.mp.

#6 double blind.mp.

#7 triple blind.mp.

#8 (singl\$ adj blind\$).tw.

#9 (double\$ adj blind\$).tw.

#10 (tripl\$ adj blind\$).tw.

#11 assign\$.tw.

#12 allocat\$.tw.

#13 crossover procedure/

#14 double blind procedure/

#15 single blind procedure/

#16 triple blind procedure/

#17 randomized controlled trial/

#18 or/1-17

#19 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

Aminosalicylates for induction of remission or response in Crohn's disease (Review)

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#20 #18 not #19

#21 exp salazosulfapyridine/

#22 (sulphasalazine or sulfasalazine or salazosulphapyr* or salazosulfapyr* or salicylazosulphapyr* or salicylazosulfapyr* or salazopyrin*).tw.

#23 mesalamine.tw. or exp mesalazine/

#24 exp aminosalicilyc acid/

#25 aminosalicilate*.tw. or exp aminosalicilyc acid derivative/ or exp aminosalicilyc acid/

#26 (mesalazine or aminosalicilyc acid or 5-aminosalicylate* or 5-aminosalicylic acid or 5-ASA or olsalazine).tw.

#27 or/21-26

#28 exp Crohn disease/ or crohn*.tw.

#29 #20 and #27 and #28

OID MEDLINE(R) database was searched using the following search terms:

#1 random\$.tw.

#2 factorial\$.tw.

#3 (crossover\$ or cross over\$ or cross-over\$).tw.

#4 placebo\$.tw.

#5 single blind.mp.

#6 double blind.mp.

#7 triple blind.mp.

#8 (singl\$ adj blind\$).tw.

#9 (double\$ adj blind\$).tw.

#10 (tripl\$ adj blind\$).tw.

#11 assign\$.tw.

#12 allocat\$.tw.

#13 crossover procedure/

#14 double blind procedure/

#15 single blind procedure/

#16 triple blind procedure/

#17 randomized controlled trial/

#18 or/1-17

#19 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

#20 #18 not #19

#21 exp salazosulfapyridine/

#22 (sulphasalazine or sulfasalazine or salazosulphapyr* or salazosulfapyr* or salicylazosulphapyr* or salicylazosulfapyr* or salazopyrin*).tw.

#23 mesalamine.tw. or exp mesalazine/

#24 exp aminosalicilyc acid/

#25 aminosalicylate*.tw. or exp aminosalicilyc acid derivative/ or exp aminosalicilyc acid/

#26 (mesalazine or aminosalicilyc acid or 5-aminosalicylate* or 5-aminosalicylic acid or 5-ASA or olsalazine).tw.

#27 or/21-26

#28 exp Crohn disease/ or crohn*.tw.

#29 #20 and #27 and #28

Cochrance Central Library database was searched using the following search terms:

#1 crohn*

#2 sulphasalazine or sulfasalazine or salazosulphapyr* or salazosulfapyr* or salicylazosulphapyr* or salicylazosulfapyr*

#3 mesalamine or mezalamine or aminosalicylate* or aminosalicilyc acid or 5-aminosalicylate* or 5-aminosalicylic acid or 5-ASA

#4 #2 or #3

#5 #1 and #4

The Cochrane IBD-FBD Specialized Register was searched using the following terms:

#1 (sulpha or sulfa or sala or salicyl or mesala or aminosal or 5-aminosal or 5-ASA or olsal).ti.

#2 Crohn.ti.

#3 1 and 2

WHAT'S NEW

Date	Event	Description
10 June 2015	New search has been performed	New literature search performed on June 10, 2015. One new study was added.

Date	Event	Description
10 June 2015	New citation required and conclusions have changed	Updated review with minor changes to conclusions and new authors

DECLARATIONS OF INTEREST

Wee-Chian Lim: Wee-Chian Lim's institution has received funds from Takeda Pharmaceuticals (Asia Pacific) Pte. Ltd, JANSSEN ASIA PACIFIC, a division of Johnson & Johnson Pte Ltd, and Abbvie Pte Ltd for participant in Advisory Boards. All of these financial activities are outside of the scope of the present review.

Yongjun Wang: None known

John MacDonald: None known

Stephen Hanauer: Stephen Hanauer has received funds from Abbvie, Cellgene, Janssen, Ferring, Takeda, Pfizer, Merk, UCB, Actavis, and Shire for consultancy; and fees from Abbvie, Takeda and Janssen as payment for lectures; and travel expenses from Falk Foundation. All of these financial activities are outside of the scope of the present review.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminosalicylic Acids [therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Budesonide [therapeutic use]; Crohn Disease [*drug therapy]; Delayed-Action Preparations; Gastrointestinal Agents [*therapeutic use]; Induction Chemotherapy [*methods]; Mesalamine [therapeutic use]; Randomized Controlled Trials as Topic; Sulfasalazine [therapeutic use]

MeSH check words

Humans