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Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease (Review)

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[Intervention Review]

Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Teuta Gjuladin-Hellon[1], Morris Gordon[1,2], Zipporah Iheozor-Ejiofor[1], Anthony K Akobeng[3]

[1]School of Medicine, University of Central Lancashire, Preston, UK. [2]Families Division, Blackpool Victoria Hospital, Blackpool, UK. [3]Sidra Medicine, Doha, Qatar

Contact address: Anthony K Akobeng, Sidra Medicine, PO Box 26999, Doha, Qatar. aakobeng@sidra.org, akobeng@aol.com.

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ABSTRACT

Background

Crohn's disease (CD) is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract. 5-Aminosalicylates (5-ASAs) are locally acting, anti-inflammatory compounds that reduce inflammation of the colonic mucosa with release profiles that vary among various commercially available formulations. This updated Cochrane review summarizes current evidence on the use of 5-ASA formulations for maintenance of surgically-induced remission in CD.

Objectives

To assess the efficacy and safety of 5-ASA agents for the maintenance of surgically-induced remission in CD.

Search methods

We searched MEDLINE, Embase, CENTRAL, the Cochrane IBD Group Specialized Register from inception to 16 July 2018. We also searched references, conference abstracts, and trials registers.

Selection criteria

Randomised controlled trials (RCTs) that included participants with CD in remission following surgery and compared 5-ASAs to no treatment, placebo or any other active intervention with duration of at least three months were considered for inclusion.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The primary outcome was clinical relapse. Secondary outcomes included endoscopic recurrence, radiologic and surgical relapse, adverse events, serious adverse events and withdrawal due to adverse events.

Main results

Fourteen RCTs (1867 participants) were included in the review. Participants (15 to 70 years) were recruited from gastroenterology hospitals and medical clinics in Europe and North America and followed up between 3 and 72 months. The risk of bias was assessed as 'low' in one study, 'unclear' in seven and as 'high' in six.

At 12 months, 36% (20/55) of participants in the 5-ASA group experienced clinical relapse compared to 51% (28/55) in the no treatment control group (RR 0.71, 95% CI 0.46 to 1.10; low certainty evidence). Moderate certainty evidence suggests that 5-ASAs

are more effective for preventing clinical relapse than placebo. During a follow-up period of 12 to 72 months, 36% (131/361) of 5-ASA participants relapsed compared to 43% (160/369) of placebo participants (RR 0.83, 95% CI 0.72 to 0.96; I^2 = 0%; moderate certainty evidence). At 12 months, 17% (17/101) of the 4 g/day mesalamine group relapsed compared to 26% (27/105) of the 2.4 g/day group (RR 0.65, 95% CI 0.38 to 1.13; moderate certainty evidence). There was no evidence of a difference in clinical relapse rates when 5-ASA compounds were compared to purine antimetabolites. At 24 months, 61% (103/170) of mesalamine participants relapsed compared to 67% (119/177) of azathioprine participants (RR 0.90, 95% CI 0.76 to 1.07; I^2 = 28%; low certainty evidence). During 24 months, 50% (9/18) of 5-ASA participants had clinical relapse compared to 13% (2/16) of adalimumab participants (RR 4.0, 95% CI 1.01 to 15.84; low certainty evidence). The effects of sulphasalazine compared to placebo on clinical relapse rate is uncertain. After 18 to 36 months, 66% (95/143) of participants treated with sulphasalazine relapsed compared to 71% (110/155) in the placebo group (RR 0.88, 95% CI 0.56 to 1.38; I^2 = 38%; low certainty evidence).

The effect of 5-ASA drugs on safety was uncertain. During 24 months follow-up, 4% (2/55) of 5-ASA participants experienced adverse events compared to none (0/55) in the no treatment control group (RR 5.00, 95% CI 0.25 to 101.81; very low certainty evidence). An equal proportion of 5-ASA participants (10%; 23/241) and placebo (9%; 20/225) groups experienced an adverse event during a follow-up of 3 to 72 months (RR 1.07, 95% CI 0.60 to 1.91; I^2 = 0%; low certainty evidence). Adverse event rates were similar in the 5-ASA and purine analogues groups. However, serious adverse events and withdrawals due to adverse events were more common in participants who received purine analogues than 5-ASA. At 52 weeks to 24 months, 52% (107/207) of 5-ASA participants had an adverse event compared to 47% (102/218) of purine analogue participants (RR 1.11, 95% CI 0.97 to 1.27, I^2 = 0%; low certainty evidence). Four per cent (6/152) of 5-ASA participants had a serious adverse event compared to 17% (27/159) of purine analogue participants (RR 0.30, 95% CI 0.11 to 0.80; very low certainty evidence). Eight per cent (17/207) of 5-ASA participants withdrew due to an adverse event compared to 19% (42/218) of purine analogue participants (RR 0.48, 95% CI 0.28 to 0.83; low certainty evidence). Adverse event rates were similar in high and low dose mesalamine participants. After 12 months, 2% (2/101) of 4 g/day mesalamine participants had an adverse event compared to 2% (2/105) of 2.4 g/day participants (RR 1.04, 95% CI 0.15 to 7.24; low certainty evidence). The proportion of participants who experienced adverse events over a 24 month follow-up in the mesalamine group was 78% (14/18) compared to 69% (11/16) of adalimumab participants (RR 1.13, 95% CI 0.75 to 1.71; very low certainty evidence). None (0/32) of the sulphasalazine participants had an adverse event at 18 months follow-up compared to 3% (1/34) of the placebo group (RR 0.35, 95% CI 0.01 to 8.38; very low certainty evidence). Commonly reported adverse events in the included studies were diarrhoea, nausea, increased liver function tests, pancreatitis, and abdominal pain.

Authors' conclusions

5-ASA preparations are superior to placebo for the maintenance of surgically-induced clinical remission in patients with CD (moderate certainty). The number needed to treat to prevent one relapse was 13 patients. The evidence for endoscopic remission is uncertain. The sulphasalazine class of 5-ASA agents failed to demonstrate superiority against placebo, 5-ASAs failed to demonstrate superiority compared to no treatment (very low and low certainty). The efficacy of two different doses of the same 5-ASA and the efficacy of 5-ASA compared to purine antimetabolites (azathioprine or 6-mercaptopurine) in maintaining surgically-induced remission of CD remains unclear. However, purine analogues lead to more serious adverse events and discontinuation due to adverse events. There is a

low certainty that 5-ASA is inferior for maintaining surgically-induced remission of CD compared to biologics (anti TNF-α). 5-ASA formulations appear to be safe with no difference in the occurrence of adverse events or withdrawal when compared with placebo, no treatment or biologics.

PLAIN LANGUAGE SUMMARY

Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

What is the aim of this review?

The aim of this review was to understand the effectiveness and safety of 5-ASA drugs for maintaining remission following surgery in people with Crohn disease. This review is an update of a previously published Cochrane review.

What is Crohn's disease?

Crohn's is a chronic disease of the gut. Crohn's changes from periods when sufferers have symptoms (relapse) to periods when the symptoms disappear (remission). Symptoms include abdominal pain, diarrhoea and weight loss. People with Crohn's disease may undergo surgery to remove diseased parts of their gut. However, their symptoms may return after a short time. Different drugs can

be given to maintain remission, however, there are concerns about possible side effects. 5-ASA drugs reduce inflammation (pain and swelling) in the gut. We researched whether 5-ASA can maintain remission in people with Crohn's after the diseased part of their gut has been removed.

How up-to-date is this review?

The review authors searched for studies that had been published up to 16 July 2018.

What are the main results of the review?

We found 14 studies (1867 participants). One study was judged to be of high quality, six studies were of low quality and seven were judged to be unclear as authors reported insufficient information to allow a judgement. People who took 5-ASA had fewer relapses than people who had no maintenance treatment. At 12 months, 36% (20/55) of participants in the 5-ASA group relapsed compared to 51% (28/55) in the no treatment control group (1 study, low certainty evidence). Moderate quality evidence from five studies showed that 5-ASA drugs are superior to placebo (e.g. a sugar pill) for maintaining surgically-induced remission of Crohn's disease. During a follow-up period of 12 to 72 months, 36% (131/361) of 5-ASA participants relapsed compared to 43% (160/369) of placebo participants. The analysis of four studies that compared 5-ASA medications to purine antimetabolites (i.e. azathioprine or 6-mercaptopurine - both immunosuppressive drugs) found no difference in the proportion of participants that remained in remission, although the overall quality of evidence was low. At 24 months, 61% (103/170) of 5-ASA participants relapsed compared to 67% (119/177) of purine antimetabolite participants. People who took high dose 5-ASA had fewer relapses than those who took lower dose 5-ASA. At 12 months, 17% (17/101) of the 4 g/day 5-ASA group relapsed compared to 26% (27/105) of the 2.4 g/day group (1 study, moderate certainty evidence). The analysis of the single small study that compared 5-ASA and adalimumab (a biologic drug) showed that 5-ASA was inferior to adalimumab for maintaining surgically-induced remission of Crohn's disease. At 24 months, 50% (9/18) of 5-ASA participants relapsed compared to 13% (2/16) in the adalimumab group (very low certainty evidence). The analysis of two studies that compared sulphasalazine to placebo found no difference in relapse rates. After 18 to 36 months, 66% (95/143) of sulphasalazine participants relapsed compared to 71% (110/155) of placebo participants (low certainty evidence). There was no difference in rates of side effects, serious side effects and withdrawal due to side effects when 5-ASA was compared to placebo. 5-ASA was safer than purine analogues resulting in less serious side effects and discontinuation of treatment due to side effects. Commonly reported side effects included diarrhoea, nausea, increased liver function tests, pancreatitis and abdominal pain.

Conclusions

5-ASA drugs are superior to placebo for maintaining surgically-induced remission of Crohn's disease (moderate certainty evidence). Sulphasalazine failed to demonstrate superiority against placebo (very low certainty evidence), and similarly 5-ASAs failed to demonstrate superiority to no treatment (low certainty evidence). The effectiveness of two different doses of the same 5-ASA and the effectiveness of 5-ASA compared to purine antimetabolites (azathioprine or 6-mercaptopurine) for maintaining surgically-induced remission of Crohn's disease remains unclear. However, purine analogues lead to more serious side effects and discontinuation due to side effects than 5-ASA. There is a low certainty that 5-ASA is inferior to adalimumab for maintaining surgically-induced remission of CD. There was no evidence of a difference in the occurrence of side effects or withdrawal due to side effects with 5-ASA formulations when compared with placebo, no treatment or biologics.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

5-ASA compared to no treatment for maintenance of surgically-induced remission in Crohn's disease

Patient or population: people with surgically-induced remission in Crohn's disease
Setting: outpatient
Intervention: 5-ASA (2.4 g/day)
Comparison: no Treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with 5-ASA				
Clinical relapse Follow-up: 12 months	509 per 1,000	361 per 1,000 (234 to 560)	RR 0.71 (0.46 to 1.10)	110 (1 Study)	⊕⊕◯◯ LOW [12]	Patients in whom CDAI was > 150, and who presented 100 points over their previous value, were considered to be relapsed (Caprilli 1994)
Endoscopic recurrence	Outcome not reported					Not reported
Radiologic relapse	Outcome not reported					Not reported
Adverse events Follow-up: 12 months	0 per 1,000	0 per 1,000 (0 to 0)	RR 5.00 (0.25 to 101.81)	110 (1 Study)	⊕◯◯◯ VERY LOW [13]	We were unable to calculate absolute effects. Adverse events occurred in 4% (2/55) of participants in the 5-ASA group compared to 0% (3/55) in the no treatment control group Reported adverse events included skin rash, epigastric pain, vomiting and nausea

Serious adverse events	Outcome not reported					Not reported
Withdrawal due to adverse events Follow-up: 12 months	0 per 1,000	0 per 1,000 (0 to 0)	RR 5.00 (0.25 to 101.81)	110 (1 study)	⊕◯◯◯ VERY LOW [13]	We were unable to calculate absolute effects. Adverse events occurred in 4% (2/55) of participants in the 5-ASA group compared to 0% (3/55) in the no treatment control group Withdrawals due to adverse events included skin rash, epigastric pain, vomiting and nausea
Health related quality of life	Outcome not reported					Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to high risk of performance bias and unclear risk of selection of bias
[2] Downgraded one level due to serious imprecision (48 events)
[3] Downgraded two levels due to very serious imprecision (2 events)

BACKGROUND

Description of the condition

Crohn's disease is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract. There is no cure for the disease, so management strategies are instead focused on induction and maintenance of remission, as well as supporting the many other symptoms that impact patients affected by the condition.

Approximately 75% of patients with Crohn's disease will eventually undergo surgical resection and this can induce remission (Bernell 2000). Recent studies suggest a rate of 3.8 operations per 100 person years (Ma 2017). However, endoscopic recurrence of disease has been reported to be as high as 73% at one year post surgery (Rutgeerts 1990), and clinical relapse rates have been reported to range from 20% to 86% at five years post surgery Rutgeerts 2002; Gklavas 2017).

Given these high relapse rates, there have been many studies to identify potential methods of prolonging postoperative remission, but there is no standard therapy for the prevention of postoperative recurrence in Crohn's disease (NICE 2012). A number of agents have been studied, but considerable uncertainty remains as to the efficacy of such treatments. 5-aminosalicylates are currently not recommended for maintenance of surgically-induced endoscopic remission (Nguyen 2017; NICE 2019).

Description of the intervention

5-aminosalicylates are a group of compounds that have long been used in inflammatory bowel disease. The first 5-aminosalicylate agent used in clinical practice was sulphasalazine. Sulphasalazine is composed of sulphapyridine linked by an azo bond to 5-aminosalicylic acid (5-ASA). Sulphasalazine was first used in the 1940s as a treatment for arthritis (Svartz 1942). Improvement in gastrointestinal symptoms was noted in patients who had concurrent ulcerative colitis leading to further use of this agent in inflammatory bowel disease.

When the oral dose of sulphasalazine reaches the colon, an azoreductase synthesised by colonic bacteria splits the azo-bond yielding 5-ASA and sulphapyridine. Literally all the sulphapyridine compound is being absorbed from the colon, while most of 5-ASA remains in the colon and is excreted in the faeces. The role of sulphapyridine as a carrier molecule is to deliver 5-ASA, the active therapeutic moiety of sulphasalazine, to the colon (Azad Khan 1977; Klotz 1980; van Hees 1980). However, the most severe adverse effects of sulphasalazine are caused by sulphapyridine (Schroder 1972). Sulphapyridine undergoes acetylation in the liver with subsequent excretion in the urine. Slow acetylator show more of the adverse effects of this component secondary to accumulation of sulphapyridine in the blood prior to excretion in the kidneys (Das 1973). A number of investigations of the use of 5-ASA as a single agent for the treatment of inflammatory bowel disease have recognised that 5-ASA is indeed the active ingredient of sulphasalazine and that sulphapyridine is responsible for most of the side effects. 5-ASA in its unprotected form is, however, readily absorbed in the proximal small intestine (Myers 1987), and does not reach the distal bowel in therapeutic concentrations. Several 5-ASA formulations have been designed in order to inhibit proximal absorption and enable delivery to distal sites of inflammation. The protection of 5-ASA compound can be achieved either by linking it to itself or to another carrier or by using slow release preparations of 5-ASA. Different 5-ASA preparations may allow delivery of 5-ASA to different locations in the gastrointestinal tract.

How the intervention might work

5-aminosalicylic acid agents are locally acting, anti-inflammatory compounds that reduce inflammation of the colonic mucosa with release profiles that vary among various commercially available formulations (Abinusawa 2015). However, in order to express an antiinflammatory effect seen through a negative regulation of cyclooxygenase and lipoxygenase pathways and prevention of prostaglandin and leukotrienes formation (Ligumsky 1981), and increased peroxisome proliferator-activated receptors expression (Rousseaux 2005), 5-ASA agents must be able to directly target the terminal ileum and colon. The commonly used oral 5-ASA formulations include azo compounds, mesalazine delayed-release agents and mesalazine slow-release formulations. For azo compounds, a carrier molecule is linked to 5-ASA by an azo bond using the same principle as sulphasalazine. Olsalazine consists of two molecules of 5-ASA joined together, whilst balsalazide is a prodrug in which a 5-ASA molecule is linked to 4-aminobenzoyl-B-alanine, an inert and biologically inactive carrier molecule. Like sulphasalazine, the azo bond of these drugs is split in the colon by bacterial azo reductases, releasing 5-ASA to exert local therapeutic activity. The 5-ASA compound of immediate-release oral mesalamine formulations is quickly absorbed in the upper gastrointestinal tract resulting in a negligible clinical effect (Rasmussen 1982; Shafil 1982). Therefore, in order to provide stable delivery of the active 5-ASA compound to the colon, controlled-release and pH dependent oral mesalamine agents have been developed (Rasmussen 1982). Mesalazine delayed-release agents (Eudragit-coated) are coated with a resin designed to dissolve at a certain pH which gradually increases from the stomach (approximate pH = 2) via the small intestine (pH = 6) to the colon (pH = 7 to 8) (Nugent 2001). Asacol is coated with Eudragit S which dissolves above pH 7.0 to release 5-ASA in the terminal ileum and colon. Eudragit-L coated mesalazine (Salofalk) dissolves above pH 6.0 to release 5-ASA in the terminal ileum and colon. Mesalazine slow-release formulations include drugs such as Pentasa. Pentasa contains microgranules of 5-ASA that are individually coated with ethylcellulose. The microgranules are dispersed in the gut providing a slow,steady release of 5-ASA along the length of the intestine from the upper

small bowel to the colon. These 5-ASA preparations were intended to avoid the adverse side effects of sulphasalazine whilst maintaining its therapeutic benefits.

Several randomised controlled trials have been published, comparing various 5-ASA agents to placebo, with contradicting results (De Franchis 1997; Gendre 1993; Mahmud 2001). Three previous meta-analyses have suggested that 5-ASA may be beneficial for the maintenance of medically-induced remission in Crohn's disease (Camma 1997; Messori 1994; Steinhart 1994), but in one report the only bibliographic database searched was MEDLINE (Camma 1997), and another meta-analysis did not report how the quality of included studies was assessed (Messori 1994). A Cochrane review on the use of 5-ASA agents for the maintenance of medically-induced remission in Crohn's disease completed in 2005 concluded that there was no evidence to suggest that 5-ASA preparations were superior to placebo for the maintenance of medically-induced remission in Crohn's disease (Akobeng 2005). This review was recently updated and again there was no evidence to suggest that 5-ASA was efficacious in this setting, although these agents had a good safety profile (Akobeng 2016).

Why it is important to do this review

5-ASA agents have been studied extensively in the post-operative setting, and a previous meta-analysis published in 1997 suggested that 5-ASA agents may be beneficial for the prevention of post-operative recurrence in Crohn's disease (Camma 1997). However, at least one subsequent multicentre randomised controlled trial failed to show an overall benefit compared with placebo (Lochs 2000). A previous review by this team in 2011 found evidence that 5-ASA may be efficacious and safe in the post-surgical setting (Gordon 2011). However, an updated systematic review using the Cochrane Collaboration format is indicated to summarise the current evidence on the use of 5-ASA agents for the maintenance of surgically-induced remission in Crohn's disease.

OBJECTIVES

The primary objective was to evaluate the efficacy of 5-ASA agents for the maintenance of surgically-induced remission in Crohn's disease. The secondary objective was to determine the frequency of adverse events associated with the use of 5-ASA agents for the maintenance of remission in Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials which compared sulphasalazine and 5-ASA agents to either placebo or another intervention, with treatment durations of at least three months were considered for inclusion.

Types of participants

Participants of any age and sex with a diagnosis of Crohn's disease confirmed by any established method who were in remission following surgery, defined by a recognized Crohn's disease activity index or endoscopy, or patients who have undergone a curative surgical resection, as defined by the authors of the primary studies were considered for inclusion. Trials conducted in any setting (e.g. single-centre or multicentre) with no language restrictions were considered for inclusion.

Types of interventions

The controlled interventions of interest included any randomised controlled trial which compared any oral 5-ASA agents to a no treatment control, placebo or another active intervention for maintenance of surgically-induced remission in Crohn's disease. For this review, studies employing sulphasalazine preparations have been analysed separately, given that these agents have a unique biochemical structure to other 5-ASA preparations. For the main analysis, all other 5-ASA preparations were considered together and for the purposes of the nomenclature of this review, were termed '5-ASA'. Studies that compared sulphasalazine or 5-ASA agents to an intervention that focuses on enteral nutrition, oral nutrient supplementation, herbal medicines, medical foods, probiotics or parental nutrition, as well as dose optimisation studies were excluded.

Types of outcome measures

Primary outcomes

The primary outcome measure was clinical relapse as defined by the primary studies. We accepted the authors' definitions of what constitutes a clinical relapse.

Secondary outcomes

Secondary outcome measures included:

1) Endoscopic recurrence, as defined by the original studies;
2) Radiologic relapse, as defined by the original studies;
3) Adverse events;
4) Serious adverse events;
5) Withdrawal due to adverse events; and
6) Health related quality of life (HRQoL).

We reported outcome measures at the last time point available (assumed to be at the end of follow-up if not specified) and the time

point specified in the methods as being of primary interest (if this was different from the latest time point available). However, we also indicated when studies report outcomes at other time points.

Search methods for identification of studies

Electronic searching

We searched the following databases from inception to 16 July 2018:
1. MEDLINE (National Library of Medicine, Bethesda, USA);
2. Embase (Elsevier Science, New York, USA);
3. CENTRAL; and
4. Cochrane IBD Group Specialized Register.
No restrictions were placed on publication dates or language. Note that the searches were designed to include RCTs conducted in adults and children, but exclude trials that compare 5-ASA to oral nutrition supplements (enteral nutrition drinks, tube feeds), medical foods, probiotics, parenteral nutrition or a combination of these modalities. The search strategies are reported in Appendix 1.

Searching other resources

Reference searching

We searched reference lists from included articles and any existing relevant reviews.

Abstracts of major gastroenterology meetings

A manual search of abstracts submitted to major gastroenterology meetings (2015 to 2018) was performed for the following journals to identify more trials that may have not been published in full at the time of the review:
1. Gastroenterology (American Gastroenterological Association);
2. Gut (British Society of Gastroenterology);
3. American Journal of Gastroenterology (American College of Gastroenterology);
4. Canadian Journal of Gastroenterology (Canadian Association of Gastroenterology);
5. Journal of Pediatric Gastroenterology and Nutrition (European Society of Paediatric Gastroenterology, Hepatology and Nutrition); and
6. Journal of Pediatric Gastroenterology and Nutrition (North American Society of Paediatric Gastroenterology, Hepatology and Nutrition).
When a relevant abstract was identified, details of the full study methodology and results were requested from the authors in order to allow a thorough assessment of the quality of identified studies. Abstracts for which this information could not be obtained were excluded.

Trials Registers

We searched clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing studies.

Data collection and analysis

Selection of studies

Two authors (MG and TGH) independently reviewed each article at each stage of selection including title screening, abstract screening and full-text review. Included and excluded studies were recorded.
Step 1. Title screening using the above search strategy, papers (or abstracts) that appeared to have even a minor possibility of inclusion were selected by two authors (MG and TGH). Adjudication did not occur at the title screening stage and studies that were ambiguous were included by default.
Step 2. Abstract screening: involved selection of articles that report studies with a reasonable possibility of inclusion. Differences in assessment for inclusion were resolved by discussion between the two independent investigators (MG and TGH). Adjudication did not occur at the abstract screening state.
Step 3. Full-text review involved selection of articles based on careful examination of the full report. Differences in assessment for inclusion were resolved by discussion between the two independent investigators. Adjudication was performed as needed by a third author (ZIE).

Data extraction and management

Two authors (ZEI and TGH) independently extracted and recorded the data using a data extraction form developed to extract information on relevant features and results of the included studies. Extracted data included the following items:

- Study design (type of RCT, setting, number of interventions, year, author's contact details);
- Population characteristics: age, sex, disease distribution, disease duration, site of disease, medication, type and time since operation, total number of patients originally assigned to each treatment group;
- Intervention: type and dose of agent;
- Control: no active treatment, placebo, other drugs;
- Concurrent medications; and
- Outcomes: time of assessment, length of follow-up, type of Crohn's disease activity index used, definitions of remission and relapse, site of surgery, relapse rates, adverse events.

Assessment of risk of bias in included studies

Two authors (ZEI and TGH) independently assessed the risk of bias using the Cochrane risk of bias tool (Higgins 2011). Adjudication was performed as needed by a third author (MG). Each domain was assessed as having a low, moderate, high, or unclear risk of bias. Domaines assessed include:

- Sequence generation (i.e. was the allocation sequence adequately generated?);
- Allocation sequence concealment (i.e. was allocation adequately concealed?);
- Blinding of participants and personnel and outcome assessors (i.e. was knowledge of the allocated intervention adequately prevented during the study?);
- Incomplete outcome data (i.e. were incomplete outcome data adequately addressed?);
- Selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?); and
- Other potential sources of bias (i.e. was the study apparently free of other problems that could put it at a high risk of bias?).

Each domain followed standard definitions used for Cochrane systematic reviews (Higgins 2011). Based on the aggregate assessment of these items, study quality was rated as good (low risk of bias), fair, or poor (high or unclear risk of bias). Study authors were contacted for further information when insufficient information was provided to determine the risk of bias.

Summary of findings tables

The overall strength of evidence supporting the primary outcome and selected secondary outcomes was assessed using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) criteria (Guyatt 2008; Schünemann 2011). For the 'Summary of findings' tables, we included the following outcomes: clinical relapse, endoscopic recurrence, radiologic relapse, adverse events, serious adverse events, study withdrawal due to adverse events and health-related quality of life. Though evidence from RCTs starts as high quality, the quality of the evidence can be downgraded due to: risk of bias, indirect evidence, inconsistency (unexplained heterogeneity), imprecision and publication bias. Taking all of these factors into account, we rated the overall quality of evidence as follows:

- High - we are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate - we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- Low - our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; or
- Very low. We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Measures of treatment effect

For binary outcomes, we calculated the risk ratio (RR) estimates and associated two-sided 95% confidence intervals (CI). For nominal or ordinal outcomes, we planned to calculate the RR with corresponding 95% for each category relative to a reference category. For continuous outcomes, we calculated the mean difference (MD) and corresponding 95% CI.

Unit of analysis issues

The unit of analysis was the individual participant. We planned to include cross-over trials if data were available from the first phase of the study (i.e. before cross-over occurred). For outcomes where events recur (e.g. clinical relapses, adverse events), we calculated the proportion of patients who experienced at least one event. Individual events were not counted separately. The studies were otherwise not anticipated to have repeated observations of outcomes or multiple treatment events.

Dealing with missing data

Information on how each trial handled missing data was recorded. When a study appeared to collect and not report on all primary outcomes of interest, the original investigators were contacted to request missing data. If the original investigators did not provide the data, this would be noted in the systematic review. For studies with missing dichotomous data, a separate intention-to-treat analysis was performed where participants with missing data were assumed to have been treatment failures. For the main analysis, the total number of patients was used as a denominator. It was assumed that participants who dropped out of the study, and on whom there was no post withdrawal information, had relapsed during the study period. For missing continuous data, we used an available case analysis.

Assessment of heterogeneity

Heterogeneity and inconsistency was assessed to ensure the validity of the analysis. Initially heterogeneity was assessed through visual inspection of forest plots and the calculation of the Chi^2 and I^2 statistics (Boreinstein 2009). For studies that had qualitative homogeneity, statistical heterogeneity was assessed using the Chi^2 test (P value < 0.10 was considered statistically significant heterogeneity). The degree of heterogeneity across studies was estimated using the I^2 statistic. An I^2 of 25% or less was considered low heterogeneity, 26 to 50% was considered moderate heterogeneity, and 50% and greater was considered substantial heterogeneity. Possible explanations for heterogeneity were examined where sufficient data were available, including factors such as participant characteristics (e.g. age, sex), disease condition severity, treatment type and dose, and healthcare system/country. Where appropriate, these factors were investigated further through sub-group analyses and meta-regression (Boreinstein 2009). Sensitivity analyses were

used to explore possible causes of methodological heterogeneity, where sufficient data were available (Sutton 2000). This included assessing the effects of studies that may be affected by factors such as risk of bias associated with allocation concealment, high loss to follow-up or lack of blinding in assessment of outcomes.

Assessment of reporting biases

If there were an appropriate number of studies in a pooled analysis (i.e. > 10 studies), we planed to investigate potential publication bias using funnel plots (trial effects versus trial size). However, the number of studies in each comparison group was smaller than 10.

Data synthesis

The Cochrane Collaboration review manager (RevMan) software (version 5.3.5) was used for data analyses. Data were analysed according to the intention-to-treat principle. Patients with final missing outcomes were assumed to have relapsed.

Analyses were grouped by type of intervention treatment (e.g. 5-ASA versus purine analogues, 5-ASA versus placebo). Studies were synthesised through a narrative review with tabulation of results of included studies. Where possible, treatment effects for all comparisons and outcomes were synthesized through meta-analyses, with the approach taken dependant on the outcome assessed and the data available (Boreinstein 2009). Although the primary outcome assessed focused on the dichotomous outcomes of clinical relapse and endoscopic recurrence, secondary outcomes involved other data types.

Subgroup analysis and investigation of heterogeneity

We planned to assess the impact of potential effect modifiers such as age of patients (paediatric versus adult studies) and length of follow-up (12 months or less versus greater than 12 months). However, there were insufficient data for these analyses.

Sensitivity analysis

Methodological heterogeneity was to be examined through sensitivity analysis, including components of risk of bias and dose of 5-ASA, however, this was not possible due to insufficient data.

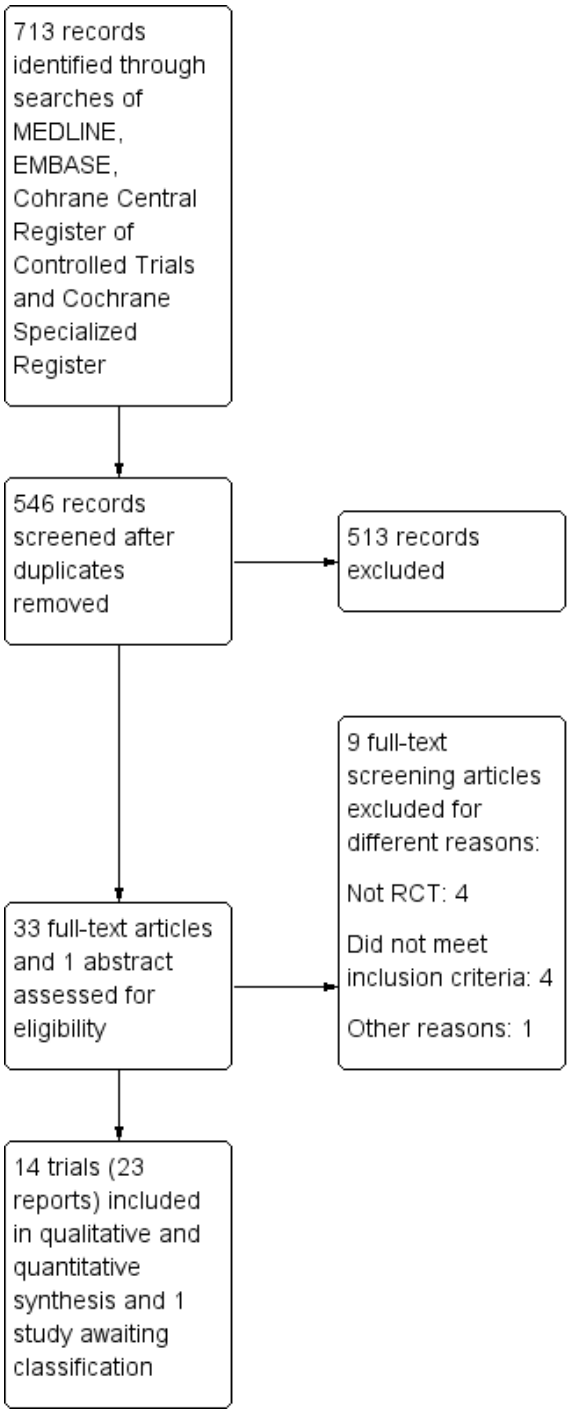
RESULTS

Description of studies

Results of the search

The results of the updated search conducted on 16 July 2018 are reported in the PRISMA flow diagram (See Figure 1). We identified 713 records of which 546 citations remained after duplicates were removed. Following title and abstract screening, 33 potentially relevant reports were identified and subjected to further scrutiny. Fourteen RCTs (1867 participants) reported in 23 articles satisfied the inclusion criteria and were included in this review (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Ewe 1989; Florent 1996; Hanauer 2004; Herfarth 2006; Lochs 2000; McLeod 1995; Reinisch 2010; Savarino 2013; Sutherland 1997; Wenckert 1978). One study was awaiting classification (NCT00976690). The rest of the studies were excluded. Detailed information about these studies are presented in the Characteristics of included studies, Characteristics of excluded studies, and additional Table 1 and Table 2, and are summarised below.

Figure 1. Study flow diagram



Included studies

Study design and setting

The 14 RCTs (23 reports) included in this review were single or multi-centre studies with a duration ranging from 12 weeks (Florent 1996) to a maximum of 72 months (McLeod 1995). The included studies were published between 1978 and 2017. There were two single-centre studies, both conducted in Italy (Ardizzone 2004; Savarino 2013). The multi-centre studies were conducted in Germany (Ewe 1989; Herfarth 2006), Canada (McLeod 1995; Sutherland 1997), and Italy (Caprilli 1994; Caprilli 2003), or as a multinational collaboration of several countries across Europe (Lochs 2000; Reinisch 2010, Wenckert 1978) and Europe and the USA (Hanauer 2004). Regarding the trial setting, studies were conducted either in gastroenterology hospitals and medical clinics/centres (Ewe 1989; Florent 1996; Lochs 2000; Reinisch 2010; Sutherland 1997; Wenckert 1978, or as a collaboration of university clinics and hospitals and medical centres (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Hanauer 2004; McLeod 1995; Savarino 2013). Herfarth 2006 did not report the trial setting.

Participants

The total number of randomised participants included in all 14 trials studies was 1867, with sample sizes ranging between 51 (Savarino 2013) and 324 (Lochs 2000). The participants of the included studies ranged in age from 15 to 70 years.

The age of participants was reported in most studies and ranged between an average of 33.6 (Lochs 2000) to 38.4 years (Ardizzone 2004) in 11 trials, while two trials reported age as median (Ewe 1989; Wenckert 1978). Herfarth 2006 did not report on participant age. All studies appear to have been be conducted on adult population of both genders, except Wenckert 1978 that included male and female patients aged $\geq$ 15 years. None of the studies was conducted in paediatric patients only.

Maintenance therapy was started less than three months postoperatively in all but two studies. One study randomised patients between 6 to 24 months after surgery (Reinisch 2010), while the time from, surgery until the start of the intervention remained unclear in Sutherland 1997.

Interventions were conducted postsurgically in patients with quiescent Crohn's disease established by generally accepted endoscopic, histological or radiological criteria, except in Wenckert 1978 where diagnosis of clinical remission and relapse was not based on index calculation, but on information collected from special control charts including the presence or absence of symptoms such as fever, diarrhoea, rectal bleeding, abdominal pain, extra-intestinal manifestations, palpable abdominal masses, fistulae, abscesses and loss of working days. It is important to note that Reinisch 2010 included participants with subsequent postoperative clinical remission (Crohn's disease activity index CDAI < 200), but with signs of moderate to severe endoscopic recurrence.

The use of concurrent treatment was specifically reported in all but three studies (Brignola 1995; Ewe 1989; McLeod 1995). In most of the studies previous treatment with aminosalicylates, metronidazole and any other Crohn's disease specific treatment had to be discontinued before surgery, while concomitant treatment for Crohn's disease during the trial was prohibited. However, corticosteroids were allowed to be tapered by standardized stepwise dose reductions in Ardizzone 2004, Hanauer 2004, and Lochs 2000. Symptomatic treatment with antacids, antidiarrhoeal or spasmolytic medication on demand was permitted in three studies (Ardizzone 2004; Caprilli 2003; Lochs 2000), but had to be scrupulously recorded. Continous use of nonsteroidal anti-inflammatory drugs was prohibited and only occasional use of paracetamol and tramadol was allowed in Savarino 2013.

Interventions

Twelve of the included studies were parallel two arm trials with the exception of Hanauer 2004 and Savarino 2013, both of which included three intervention arms. The studies compared the efficacy of sulphasalazine and other oral 5-aminosalicylic acid treatments to no treatment, placebo or another active treatment. Given its unique biochemical structure, interventions utilising sulphasalazine were analysed separately from the rest of the oral 5-ASA preparations. Detailed information on study interventions are reported in additional Table 1 and Table 2 and are summarised as follows:

- Studies comparing sulfasalazine versus placebo (Ewe 1989; Wenckert 1978);
- Studies comparing 5-ASAs to a no treatment control (Caprilli 1994);
- Studies comparing 5-ASAs to placebo (Brignola 1995; Florent 1996; Hanauer 2004; Lochs 2000; McLeod 1995; Sutherland 1997);
- Studies comparing 5-ASAs to purine antimetabolites (Ardizzone 2004; Hanauer 2004; Herfarth 2006; Reinisch 2010; Savarino 2013);
- Studies comparing 5-ASAs to anti-tumour necrosis factor-alpha antagonists (TNF-α) (Savarino 2013); and
- Studies comparing high dose (4 g/day) 5-ASA to low dose (2.4 g/day) 5-ASA (Caprilli 2003).

Outcomes

Outcome data where reported at multiple time points in six studies (Ewe 1989; Florent 1996; Herfarth 2006; Lochs 2000; McLeod 1995; Wenckert 1978), and at a single time point in eight studies (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Hanauer 2004; Reinisch 2010; Savarino 2013; Sutherland 1997). We disregarded follow-up data in studies which continued to monitor participants beyond the end of treatment.
Studies reported the following outcomes:

Primary outcome

Thirteen studies included clinical relapse as the primary outcome (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Ewe 1989; Hanauer 2004; Herfarth 2006; Lochs 2000; McLeod 1995; Reinisch 2010; Savarino 2013; Sutherland 1997; Wenckert 1978).

Secondary outcomes

Secondary outcomes reported in the primary studies include the following:
1) Endoscopic recurrence (Brignola 1995; Hanauer 2004; Lochs 2000);
2) Endoscopic and/or radiological recurrence combined (McLeod 1995);
3) Radiological relapse (Hanauer 2004; Savarino 2013);
4) Surgical relapse (Ardizzone 2004);
5) Adverse events (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Florent 1996; Hanauer 2004; Herfarth 2006; McLeod 1995; Reinisch 2010; Savarino 2013; Wenckert 1978);
6) Serious adverse events (Ardizzone 2004; Hanauer 2004; Lochs 2000; McLeod 1995; Reinisch 2010);
7) Withdrawal due to adverse events (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Florent 1996; Hanauer 2004; Herfarth 2006; McLeod 1995; Reinisch 2010; Savarino 2013; Wenckert 1978); and
8) HRQoL (Reinisch 2010; Savarino 2013; Sutherland 1997).

Funding and declaration of interest

Seven studies reported support from pharmaceutical companies (Caprilli 1994; Caprilli 2003; Florent 1996; Hanauer 2004; Herfarth 2006; Reinisch 2010; Sutherland 1997), but only one study included a declaration of conflicts of interest (Reinisch 2010). The study authors were contacted to clarify the role of these pharmaceutical companies: the authors of two studies confirmed that the companies had no role in the study design, data analysis or writing of the paper (Hanauer 2004; Sutherland 1997), whereas the remaining authors did not respond. Funding and conflict of interest was not reported in four studies (Ardizzone 2004,Brignola 1995; Ewe 1989; Lochs 2000), but our attempts to clarify this by contacting the authors were unsuccessful.

Excluded studies

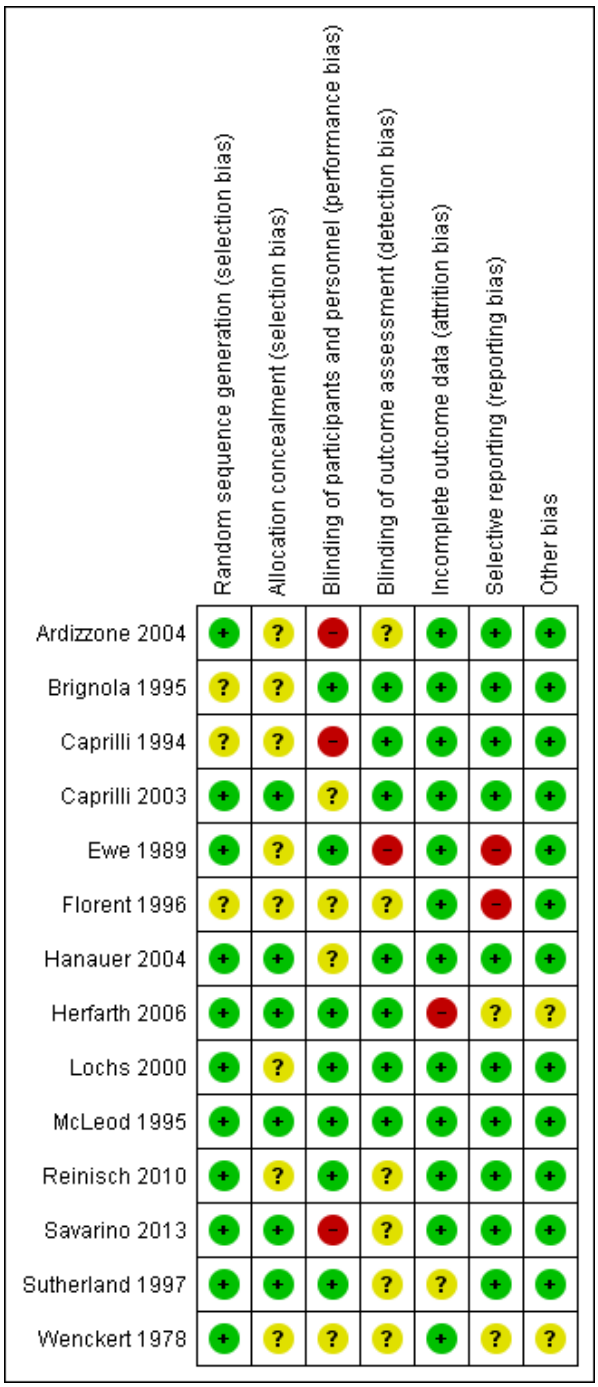
Nine studies were excluded for various reasons. These studies are listed in Characteristics of excluded studies table and summarised as follows:

- Four were classified as non-randomised controlled trials (Dumois 2001; Ewe 1981; McLeod 1997; Orlando 2012);
- Four trials did not meet intervention inclusion criteria (ISRCTN84003996; NCT00225810; NCT00245505; NCT00300118); and
- One clinical trial was terminated due to the lack of accrual (NCT01696942).

Risk of bias in included studies

Risk of bias was assessed using the Cochrane risk of bias tool (Higgins 2011). The risk of bias was assessed as 'low' in one study (McLeod 1995), 'unclear' in seven (Brignola 1995; Caprilli 2003; Hanauer 2004; Lochs 2000; Reinisch 2010; Sutherland 1997; Wenckert 1978), and as 'high' in rest of the studies (Ardizzone 2004; Caprilli 1994; Ewe 1989; Florent 1996; Herfarth 2006; Savarino 2013). Details of the risk of bias assessment for each study are presented in the Characteristics of included studies and Figure 2, and are summarised below.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item of included study.



Allocation

Random sequence generation

In all the included studies allocation of participants to an active treatment, no treatment or placebo was reported as random. Eleven studies reported sufficient information regarding random sequence generation and were judged as being at low risk of bias for this item (Ardizzone 2004; Caprilli 1994; Ewe 1989; Hanauer 2004; Herfarth 2006; Lochs 2000; McLeod 1995; Reinisch 2010; Savarino 2013; Sutherland 1997; Wenckert 1978). The method of randomisation was not adequately described in three studies (Brignola 1995; Caprilli 1994; Florent 1996) and were judged as being at an unclear risk of bias. None of the studies was judged as having a high risk of bias for random sequence generation.

Allocation concealment

Allocation concealment was initially graded adequate and of low risk of bias in five studies (Caprilli 2003; Hanauer 2004; Herfarth 2006; Savarino 2013; Sutherland 1997), and unclear in the rest. The authors of these studies were contacted to clarify allocation concealment, but only one response was received. The response was from Dr. McLeod, who gave further information to confirm her study had adequate allocation concealment, hence later rated as 'low' (McLeod 1995). The rest of the studies were assessed as having an inadequate description for allocation concealment, and were marked 'unclear' regarding risk of bias for allocation concealment (Ardizzone 2004; Brignola 1995; Caprilli 1994; Ewe 1989; Florent 1996; Lochs 2000; Reinisch 2010; Wenckert 1978).

Blinding

Blinding of participants and personnel

Three of the studies included had an open-label study design and were judged as being at high risk of bias for blinding (Ardizzone 2004; Caprilli 1994; Savarino 2013). All the remaining studies were described as double-blind. However, the method of blinding was not described clearly in four studies and these studies were marked as 'unclear' risk of bias (Caprilli 2003; Florent 1996; Hanauer 2004; Wenckert 1978). These studies either failed to report which parties were blinded or did not report that the placebo was identical to the intervention. Due to the adequate description of blinding methods for both participants and personnel, seven studies were rated as having low risk of bias (Brignola 1995; Ewe 1989; Herfarth 2006; Lochs 2000; McLeod 1995; Reinisch 2010; Sutherland 1997).

Blinding of outcome assessment

One study was judged as having high risk of detection bias as outcome assessors were aware of treatment assignment, which was confirmed by the lead author (Ewe 1989). Six studies were judged as unclear risk of bias, having failed to adequately describe blinding of outcome assessors (Ardizzone 2004; Florent 1996; Reinisch 2010; Savarino 2013; Sutherland 1997; Wenckert 1978). The remaining seven studies reported sufficient information regarding methods of outcome assessment blinding in order to be judged 'low risk' for detection bias (Brignola 1995; Caprilli 1994; Caprilli 2003; Hanauer 2004; Herfarth 2006; Lochs 2000; McLeod 1995).

Incomplete outcome data

Twelve studies were judged as 'low risk' of bias. Eleven studies reported attrition rates that were low and balanced across groups (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Florent 1996; Hanauer 2004; Lochs 2000; McLeod 1995; Reinisch 2010; Savarino 2013; Wenckert 1978), and in one study (Ewe 1989), although the overall attrition rate was high (37%), when compared to the event risk (60%), it was not sufficient to introduce bias. One study was judged to be at high risk of attrition bias due to a high discontinuation rate of 51% (Herfarth 2006). Sutherland 1997 was judged to be at 'unclear' risk of bias as attrition rates were not specifically reported for the sub-population of interest.

Selective reporting

None of the studies had a protocol or trial registration on www.clinicaltrials.gov or the WHO ICTRP with the exception of Reinisch 2010. Ten studies were judged as being at low risk of bias for reporting all outcomes prespecified in the methods section of the published manuscripts (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Hanauer 2004; Lochs 2000; McLeod 1995; Reinisch 2010; Savarino 2013; Sutherland 1997). Two studies were judged to be at 'high' risk of bias: one study failed to report on a prespecified outcome (Florent 1996); and the other study failed to report data on adverse events (Ewe 1989), which is considered a key outcome for a study of this type. Wenckert 1978 was judged 'unclear' as the results for adverse events were not reported clearly enough to allow analysis and permit a judgement. Herfarth 2006 was judged as 'unclear' because it was published as an abstract and as a letter and sufficient details about pre-specified outcomes were not available.

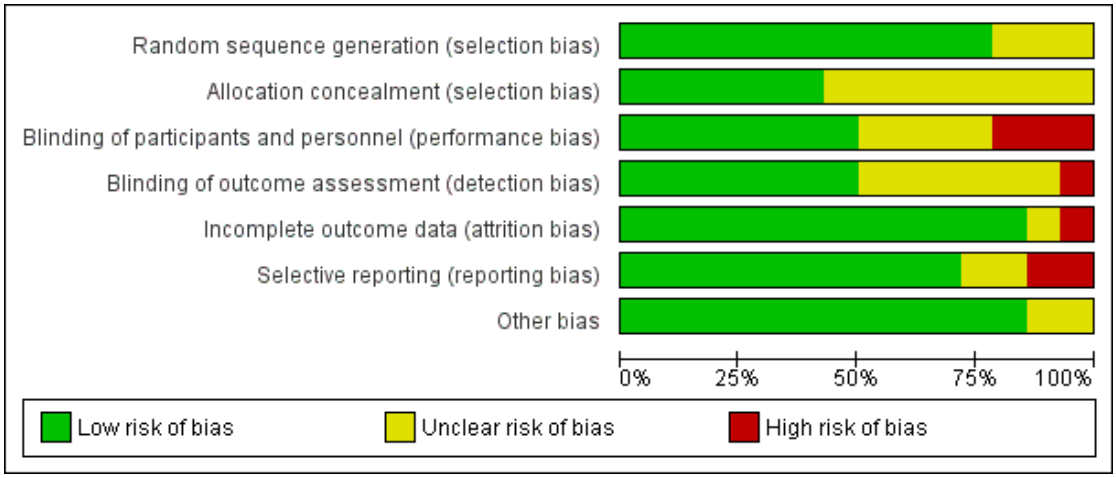
Other potential sources of bias

Twelve studies were judged as being at low risk of bias as there was no indication of other biases occurring (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; Ewe 1989; Florent 1996; Hanauer 2004; Lochs 2000; McLeod 1995; Reinisch 2010; Savarino 2013; Sutherland 1997). Wenckert 1978 was judged 'unclear' for failing to provide sufficient baseline characteristics of randomised patients, so the presence of any potential imbalances

between groups remained uncertain. Herfarth 2006 was judged as 'unclear' because it was published as an abstract and as a letter and sufficient details about other potential sources of bias were not described.

The risk of bias data as summary percentages across all included studies are presented in Figure 3.

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Effects of interventions

See: **Summary of findings for the main comparison** 5-ASA compared to no treatment for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 2** 5-ASAs compared to placebo for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 3** High dose 5-ASA compared to low dose 5-ASA for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 4** 5-ASA compared to purine antimetabolites for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 5** 5-ASAs compared to anti TNF-α for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 6** Sulphasalazine compared to placebo for maintenance of surgically-induced remission in Crohn's disease

Detailed information regarding interventions, treatments and key outcome definitions are presented on Table 2 and summarised below.

5-ASA versus no treatment

Caprilli 1994 was the only study that compared 5-ASA (2.4 g/day) to no treatment and a meta-analysis was not performed (110 participants; start of intervention: 0-2 weeks after surgery).

Primary outcome

Clinical relapse at 12 months was defined as a CDAI > 150, and a 100 point increase in CDAI from baseline. Thirty-six percent (20/55) of participants in the 5-ASA group relapsed at 12 months compared to 51% (28/55) in the no treatment control group (RR 0.71, 95% CI 0.46 to 1.10, 110 participants, low certainty evidence; See Analysis 1.1 and Summary of findings for the main comparison).

Secondary outcomes

Adverse events

The effects of 5-ASAs on adverse events and withdrawal due to adverse events compared to no treatment was uncertain (Analysis 1.2; Summary of findings for the main comparison). During the 24 month of intervention, 4% (2/55) of participants experienced adverse events classified as adverse reactions to mesalazine (skin rash, epigastric pain, vomiting, nausea) and they were withdrawn from the trial, compared to 0% (0/55) in the no treatment group (RR 5.00, 95% CI 0.25 to 101.81, 110 participants, 1 study; very low certainty evidence).

This study did not report on endoscopic recurrence, radiologic relapse, serious adverse events and HRQoL.

5-ASA versus placebo

Six studies (856 participants; start of intervention: < 8 weeks after surgery) comparing 5-ASAs (3 to 4 g/day) to placebo were identified (Brignola 1995; Florent 1996; Hanauer 2004; Lochs 2000; McLeod 1995; Sutherland 1997).

Primary outcome

Five studies reported on clinical relapse. However, the definition of relapse varied across the studies from CDAI > 150 (Brignola 1995; Sutherland 1997), to CDAI ≥ 250 or CDAI ≥ 200 with a minimum of 60 points increase for 2 weeks in Lochs 2000, a clinical recurrence score > 2 as defined by Hanauer 2004, to severe symptoms that warrant treatment plus radiological or endoscopic evidence of disease (McLeod 1995). There was moderate certainty evidence that 5-ASAs are more effective than placebo for preventing clinical relapse (Analysis 2.1, Summary of findings 2). During a follow-up period that ranged from 48 weeks to 72 months, 36% (131/361) of 5-ASA participants relapsed compared to 43% (160/369) of the placebo participants (RR 0.83, 95% CI 0.72 to 0.96, 730 participants, 5 studies, I^2 = 0%; moderate certainty evidence).

Secondary outcomes

Endoscopic recurrence

Endoscopic recurrence data were available for three studies. Florent 1996 defined endoscopic recurrence as a Rutgeerts score i ≥ 1. Lochs 2000 defined endoscopic recurrence as a Rutgeerts score i ≥ 2. Brignola 1995 defined endoscopic recurrence as a Rutgeerrts score i > 2. The effect of 5-ASAs on endoscopic remission was uncertain (Analysis 2.2, Summary of findings 2). After 12 weeks to 72 months of follow-up, 70% (183/263) of participants treated with 5-ASA had endoscopic recurrence compared to 73% (199/274) in the placebo arm (RR 0.83, 95% CI 0.56 to 1.24, 537 participants, 3 studies, I^2 = 84%; very low certainty evidence). Hanauer 2004 reported no difference in endoscopic recurrence rates (i ≥ 2) between the mesalamine (48%; 95% CI 30% to 70%) and placebo (42%; 95% CI 21% to 70%) groups at 24 months (reported: HR 1.10; 84 participants). However, the data were insufficient to be included in the meta-analysis.

The effect of 5-ASAs on radiologic relapse, adverse events, serious adverse events and withdrawals due to adverse events was uncertain (Summary of findings 2).

Radiologic relapse

Radiologic relapse rate defined as a radiographic recurrence grading score ≥*2* was reported in Hanauer 2004. After 24 months, 46% (95% CI, 29% to 66%) of participants treated with 5-ASA had radiologic relapse compared to 49% (95% CI, 30% to 72%) in the placebo group (reported: HR 0.61; 84 participants). McLeod 1995 reported combined endoscopic and radiologic relapse rate based on the presence of endoscopic or radiological evidence of disease in both symptomatic and asymptomatic patients. At 72 months, mesalamine was more effective in preventing endoscopic and radiologic relapse compared to placebo (RR 0.635, 95% CI 0.44 to 0.91; 169 participants).

Adverse events, serious adverse events and withdrawal due to adverse events

There was no clear difference in the number of participants who experienced adverse events, serious adverse events or were withdrawn from the trial due to adverse events when 5-ASAs were compared to placebo. Adverse events (Analysis 2.3) were reported in all but one study (Sutherland 1997). Ten per cent (23/241) of 5-ASA participants experienced at least one adverse event that was possibly related to treatment compared to 9% (20/225) of placebo participants (RR 1.07; 95% CI 0.60 to 1.91; 466 participants; 4 studies; I^2 = 0%; low certainty evidence). Reported adverse events included skin lesions, abdominal pain, diarrhoea , vomiting and nausea. Three studies reported serious adverse events that were possibly related to treatment (Hanauer 2004; Lochs 2000; McLeod 1995). Over a follow-up period of 52 weeks to 72 months, approximately an equal proportion of participants from the 5-ASA (3%; 9/286) and the placebo (3%; 9/291) groups experienced at least one serious adverse event (RR 1.06, 95% CI 0.44 to 2.59, 577 participants, I^2 = 0%, See Analysis 2.4; low certainty evidence). Reported serious adverse events included postoperative bowel obstruction and pancreatitis. Withdrawal due to adverse events (Analysis 2.5) was reported in three studies (Brignola 1995; Florent 1996; Hanauer 2004). Over a follow-up period ranging from 12 weeks to 24 months, the withdrawal rate due to adverse events was 10% (16/153) among 5-ASA participants compared to 7% (10/144) among placebo participants (RR 1.50, 95% CI 0.71 to 3.19, 297 participants, I^2 =0%; low certainty evidence). Adverse events leading to withdrawal included abdominal pain, pancreatitis and declining creatine clearance. McLeod 1995 reported the total number of withdrawn participants in both intervention arms (6/167) and as data could not be separated it was not included in the meta-analysis.

HRQoL

Health related quality of life using the IBDQ was evaluated in one study at week 48 (293 participants). However, there were no data reported for further analysis (Sutherland 1997).

High dose versus low dose 5-ASA

Caprilli 2003 was the only study that compared 5-ASA in doses of 4.0 g/day to 2.4 g/day (206 participants; start of intervention: 0 to 2 weeks after surgery).

Primary outcome

Clinical relapse was defined as a CDAI score higher than 150 or an increase in CDAI of more than 100 points from baseline. There was moderate certainty evidence for the efficacy of mesalamine for maintaining clinical remission when administered in doses of 4.0 g/day and 2.4 g/day (Analysis 3.1; Summary of findings 3). At 12 months, the proportion of participants with clinical relapse was

17% (17/101) among the 4 g/day mesalamine group compared to 26% (27/105) in the 2.4 g/day group (RR 0.65, 95% CI 0.38 to 1.13, 206 participants; moderate certainty evidence).

Secondary outcomes

Endoscopic recurrence

The definition for endoscopic recurrence was based on the presence of typical endoscopic Crohn's disease lesions in the terminal ileum or anastomosis, graded on the Rutgeer's score > 1. There was moderate certainty evidence regarding the effects of 4.0 g/day compared to 2.4 g/day mesalamine treatment for prevention of endoscopic recurrence (Analysis 3.2; Summary of findings 3). After 12 months, the proportion of participants with endoscopic recurrence was 45% (45/101) and 56% (59/105) in the 4.0 g/day and 2.4 g/day mesalamine treated participants respectively (RR 0.79, 95% CI 0.60 to 1.04, 206 participants; moderate certainty evidence).

Adverse events, serious adverse events and withdrawal due to adverse events

Regarging adverse events and withdrawal due to adverse events, the evidence was low certainty (Analysis 3.3; Summary of findings 3). At 12 months, approximately an equal proportion of participants from the 4.0 g/day (2%; 2/101) and the 2.4 g/day (2%; 2/105) groups experienced an adverse event and were withdrawn from the study (RR 1.04, 95% CI 0.15 to 7.24, 206 participants; low certainty evidence). Reported adverse events include severe dyspepsia, increase in transaminases and limb cramps.

Caprilli 2003 did not report on serious adverse events and HRQoL.

5-ASA versus purine antimetabolites

A total of five studies compared the efficacy of mesalamine (dose 3 to 4 g/day) to azathioprine (Ardizzone 2004; Herfarth 2006; Reinisch 2010; Savarino 2013), or 6-mercaptopurine (Hanauer 2004) agents (425 participants; start of intervention: within 4 weeks, except in Reinisch 2010 (6 to 24 months postoperatively)). Due to the specific inclusion/exclusion criteria in Reinisch 2010 (Characteristics of included studies), the clinical and endoscopic recurrence data of this study were not included in meta-analyses.

Primary outcome

Clinical relapse was reported in four studies, defined as clinical recurrence grading score ≥ 2 in Hanauer 2004 and Savarino 2013, as a CDAI > 150 plus a 100-point increase in CDAI from baseline in Herfarth 2006, or CDAI ≥ 200 in Ardizzone 2004.The effect of 5-ASA compounds in comparison to azathioprine or 6-mercaptopurine on clinical relapse was uncertain (Analysis 4.1.; Summary of findings 4). At the end of 24 months of treatment, 61% (103/170) of mesalamine treated participants clinically relapsed compared to 67% (119/177) of azathioprine participants (RR 0.90, 95% CI 0.76 to 1.07, 347 participants, 4 studies, I^2 = 38%; low certainty evidence).

Secondary outcomes

Endoscopic recurrence

Endoscopic recurrence defined as a Rugeerts score ≥ 2, was reported in one study and meta-analysis was not performed (Savarino 2013). The efficacy of 5-ASA in comparison to purine antimetabolites agents for preventing endoscopic recurrence was uncertain (Analysis 4.2; Summary of findings 4). After 24 months, 83% (15/18) of 5-ASA treated participants relapsed compared to 65% (11/17) in the purine analogues group (RR 1.29, 95% CI 0.86 to 1.94; very low certainty evidence).

Radiologic relapse

Radiologic relapse defined as a radiographic recurrence grading score ≥ 2, was reported in one study and meta-analysis was not performed (Savarino 2013). The effect of 5-ASA drugs on the radiologic relapse rate compared to purine analogues was uncertain (Analysis 4.3). At 24 months, 83% (15/18) of 5-ASA participants experienced radiologic relapse compared to 76% (13/17) of the purine antimetabolites group (RR 1.09, 95% CI 0.78 to 1.52; very low certainty evidence).

Endoscopic and radiologic relapse rates were reported by Hanauer 2004. However, the results lacked sufficient detail to be included in the meta-analysis. At 24 months (91 participants), the reported endoscopic and radiologic relapse rates were 48% (95% CI 30 to 70) and 46% (95 CI 29 to 66) in the mesalamine intervention group compared to 16% (95% CI 7 to 35) and 33% (95% CI 19 to 54) in the purine antimetabolites group respectively.

Surgical relapse

Surgical relapse defined as the need for another surgery was reported by Ardizzone 2004. The effect of 5-ASA compared to purine analogues on surgical relapse was uncertain (Analysis 4.4). During the follow-up period of two years, the proportion of participants with surgical relapse was 35% (26/71) in the 5-ASA group compared to 29% (21/71) in the purine analogues group (RR 1.24, 95% CI 0.77 to 1.98).

Adverse events, serious adverse events and withdrawal due to adverse events

Adverse events and withdrawal due to adverse were reported in five studies, while serious adverse events were reported in all studies except for Savarino 2013. The effect of 5-ASA drugs on safety when compared to the purine analogues was uncertain, as the quality of evidence ranged from low to very low (Summary of findings 4). During a follow-up period of 52 weeks to 24 months, the proportion of 5-ASA participants who experienced at least one adverse event (Analysis 4.5) was 52% (107/207) compared to 47% (102/218) of purine analogue participants (RR 1.11, 95% CI 0.97 to 1.27, 425 participants, 5 studies, I^2 = 0%; low certainty evidence). Reported adverse events include leukopenia, abdominal pain, nausea, nasopharyngitis, diarrhoea and headache. Four per cent (6/152) of patients treated with 5-ASA experienced serious adverse events compared to 17% (27/159) of the purine antimetabolites group (RR 0.30, 95% CI 0.11 to 0.80, 311 participants, 3 studies, I^2 = 9%; very low certainty evidence). The types of serious adverse events were not well described in the studies but included post-

operative bowel obstruction and acute pancreatitis. Eight per cent (17/207) of the 5-ASA group withdrew due to an adverse event during 52 weeks to 24 months of follow-up compared to 19% (42/218) of the purine analogues group (RR 0.48, 95% CI 0.28 to 0.83, 425 participants, 5 studies, I^2 = 0%; low certainty evidence). Adverse events leading to withdrawal included severe epigastric intolerance, increase in liver function test results, leukopenia, and acute pancreatitis.

HRQoL

Two studies with treatment duration of 52 weeks and 24 months reported on HRQoL based on the IBDQ score (Reinisch 2010; Savarino 2013). The effect of 5-ASA agents compared to purine analogues on HRQoL was uncertain. Savarino 2013 reported on the proportion of participants with an IBDQ score > 170 which is regarded as a symptomatic remission score (IBDQ scores ranged from 32 to 224). At 24 months of follow-up (Analysis 4.8), 17% (3/18) of 5-ASA treated participants reported an IBDQ score > 170 compared with 12% (2/17) in the azathioprine group (RR 1.42, 95% CI 0.27 to 7.46; very low certainty evidence). Reinisch 2010, assessed HRQoL based on the mean change in IBDQ scores compared to baseline (Analysis 4.9). The mean difference in IBDQ score at 52 weeks compared to baseline among the 5-ASA treated group was 5 (SD 27.4) compared to 9 (SD 17.7) in the purine analogue group (MD -4.00, CI -14.36 to 6.36; 78 participants).

5-ASAs vs anti-TNF-α

One study (34 participants; start of intervention: 2 to 4 weeks after surgery) compared mesalamine (3 g/day) to adalimumab (Savarino 2013). The effect of mesalamine in comparison to adalimumab on preventing postoperative clinical, endoscopic and radiologic recurrence was uncertain (Summary of findings 5).

Primary outcome

Clinical relapse was defined as clinical recurrence grading score ≥ 2 (Analysis 4.1). Over 24 months of follow-up, 50% (9/18) of 5-ASA participants had clinical relapse compared to 12% (2/16) in the anti TNF-α intervention (RR 4.00, 95% CI 1.01 to 15.84; very low certainty evidence).

Secondary outcomes

Endoscopic and radiologic recurrence

Endoscopic recurrence was defined as Rutgeert's score ≥ 2 (Analysis 5.2), while radiologic relapse was defined as a radiographic recurrence score ≥2 (Analysis 5.3). The proportions of participants with endoscopic and radiologic recurrence within the mesalamine and adalimumab groups were equal. Namely, 83% (15/18) of mesalamine treated participants and 6% (1/16) of adalimumab participants had both endoscopic and radiologic recurrence after a follow-up of 24 months (RR 13.33, 95% CI 1.98 to 89.95; very low certainty evidence for both outcomes).

Adverse events, serious adverse events and withdrawal due to adverse events

The effect of oral 5-ASA compounds compared to anti TNF-α on adverse events (Analysis 5.4), and withdrawal due to adverse events (Analysis 5.5), was uncertain (Summary of findings 5). After 24 months, the proportion of participants who experienced adverse events in the 5-ASA group was 78% (14/18) compared to the 69% (11/16) of the adalimumab group (RR 1.13, 95% CI 0.75 to 1.71; very low certainty evidence). Reported adverse events include bronchitis, nasopharyngitis, abdominal pain, arthralgia and exacerbation of Crohn's disease. Over 24 months of follow-up, 0% (0/18) of 5-ASA participants withdrew from the study due to adverse events compared to 6% (1/16) of adalimumab participants (RR 0.30, 95% CI 0.01 to 6.84; very low certainty evidence). Adverse events leading to withdrawal included atopic dermatitis and severe exacerbation of Crohn's disease.

HRQoL

The effect of 5-ASA compared to adalimumab on HRQoL was uncertain (Analysis 5.6; Summary of findings 5). At 24 months, an IBDQ > 170 was reported in 17% (3/18) of 5-ASA participants compared to 88% (14/16) of adalimumab participants (RR 0.19, 95% CI 0.07 to 0.54; very low certainty evidence).

Sulphasalazine versus placebo

There were two studies (298 participants; start of intervention: 0 to 4 weeks after surgery) that compared sulphasalazine (3 g/day) with placebo (Ewe 1989; Wenckert 1978).

Primary outcome

Clinical relapse defined as 'proven radiological, endoscopic or operation findings' (Ewe 1989), or as a scoring system developed for the study that considered symptoms, signs and impact (Wenckert 1978), was reported in both studies. The effect of sulphasalazine compared to placebo for maintaining surgically-induced remission in Crohn's disease is uncertain due to low certainty evidence (Analysis 6.1; Summary of findings 6). After 18 to 36 months of follow-up, 66% (95/143) of sulphasalazine participants relapsed compared with 71% (110/155) of placebo participants (RR 0.88, 95% CI 0.56 to 1.38, I^2 = 38%; low certainty evidence).

Secondary outcomes

The certainty of the evidence regarding adverse events of sulphasalazine is very low (Analysis 6.2, Summary of findings 6). Adverse events were reported only in Wenckert 1978 and meta-analysis was not performed. After 18 months of follow-up, one participant belonging to the placebo group (3%; 1/34) experienced nausea caused by a parallel consumption of acetylsalicylic acid and was withdrawn from the study, compared to none in the sulphasalazine group (0%; 0/32) (RR 0.35, 95% CI 0.01 to 8.38; very low certainty evidence).

Endoscopic recurrence, radiological relapse, adverse events, serious adverse events and HRQoL were not reported on in either study.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

5-ASAs compared to placebo for maintenance of surgically-induced remission in Crohn's disease

Patient or population: people with surgically-induced remission in Crohn's disease
Setting: outpatients
Intervention: 5-ASA (3 to 4 g/day)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with 5-ASA				
Clinical relapse Follow-up: 48 weeks to 72 months	434 per 1,000	360 per 1,000 (312 to 416)	RR 0.83 (0.72 to 0.96)	730 (5 studies)	⊕⊕⊕◯ MODERATE [1]	Clinical relapse defined as CDAI >150 (Brignola 1995; Sutherland 1997) ; CDAI ≥ 250 (Lochs 2000); clinical recurrence score > 2 (Hanauer 2004); severe symptoms that warrant treatment plus radiological/endoscopic evidence (McLeod 1995)
Endoscopic recurrence Follow-up:12 weeks to 72 months	726 per 1,000	603 per 1,000 (407 to 901)	RR 0.83 (0.56 to 1.24)	537 (3 studies)	⊕◯◯◯ VERY LOW [2,3]	Enodscopic recurrence defined as Rutgeerts score i ≥1 (Florent 1996), Rutgeerts score i ≥ 2 (Lochs 2000), Rutgeerrts score i > *2* (Brignola 1995)
Radiologic relapse	Outcome not reported					Not reported

Adverse events Follow-up:12 weeks to 72 months	89 per 1,000	95 per 1,000 (53 to 170)	RR 1.07 (0.60 to 1.91)	466 (4 studies)	⊕⊕◯◯ LOW [3]	Reported adverse events included skin lesions, abdominal pain, diarrhea , vomiting and nausea
Serious adverse events Follow-up:48 weeks to 72 months	31 per 1,000	33 per 1,000 (14 to 80)	RR 1.06 (0.44 to 2.59)	577 (3 studies)	⊕⊕◯◯ LOW [4]	Reported serious adverse events included postoperative bowel obstruction and pancreatitis
Withdrawal due to adverse events Follow-up:12 weeks to 72 months	69 per 1,000	104 per 1,000 (49 to 222)	RR 1.50 (0.71 to 3.19)	297 (3 studies)	⊕⊕◯◯ LOW [5]	Adverse events leading to withdrawal included abdominal pain, pancreatitis and declining creatine clearance
Health related quality of life	Outcome not reported					Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious imprecision (291 events)
[2] Downgraded one level due to high risk of reporting bias and unclear risk of selection bias and outcome assessment
[3] Downgraded two levels due to substantial heterogeneity (I^2 = 84%)
[4] Downgraded two levels due to very serious imprecision (43 events)
[5] Downgraded two levels dur to due to very serious imprecision (18 events)

[6] Downgraded two levels due to very serious imprecision (26 events)

High compared to low dose 5-ASAs for maintenance of surgically-induced remission in Crohn's disease

Patient or population: people with surgically-induced remission in Crohn's disease
Setting: outpatient
Intervention: high dose 5-ASAs (4.0 g/day)
Comparison: low dose 5-ASAs (2.4 g/day)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low dose 5-ASA	Risk with high dose 5-ASA				
Clinical relapse Follow-up:12 months	257 per 1,000	167 per 1,000 (98 to 291)	RR 0.65 (0.38 to 1.13)	206 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	Clinical relapse reported as CDAI > 150 or increase of 100 points from baseline (Caprilli 2003)
Endoscopic recurrence Follow-up:12 months	562 per 1,000	444 per 1,000 (337 to 584)	RR 0.79 (0.60 to 1.04)	206 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	Endoscopic recurrence reported as Rutgeer's score >1 (Caprilli 2003)
Radiologic relapse	Outcome not reported					Not reported
Adverse events Follow-up:12 months	19 per 1,000	20 per 1,000 (3 to 138)	RR 1.04 (0.15 to 7.24)	206 (1 RCT)	⊕⊕◯◯ LOW [3]	Reported adverse events include severe dyspepsia, increase in transaminases and limb cramps
Serious adverse events	Outcome not reported					Not reported

Withdrawal due to adverse events Follow-up: 12 months	19 per 1,000	20 per 1,000 (3 to 138)	RR 1.04 (0.15 to 7.24)	206 (1 RCT)	⊕⊕◯◯ LOW [3]	Reported adverse events include severe dyspepsia, increase in transaminases and limb cramps
Health related quality of life	Outcome not reported					Not reported

*__The risk in the intervention group__ (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious imprecision (44 events)
[2] Downgraded one level due to due to serious imprecision (104 events)
[3] Downgraded two levels due to due to very serious imprecision (4 events)

5-ASA compared to purine antimetabolites for maintenance of surgically-induced remission in Crohn's disease

Patient or population: people with surgically-induced remission in Crohn's disease
Setting: outpatient
Intervention: 5-ASA (3-4 g/day)
Comparison: purine antimetabolites

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with purine antimetabolites	Risk with 5-ASA				
Clinical relapse Follow-up:24 months	672 per 1,000	605 per 1,000 (511 to 719)	RR 0.90 (0.76 to 1.07)	347 (4 studies)	⊕⊕◯◯ LOW [12]	Clinical relapse defined as a clinical grading score ≥ 2 (Hanauer 2004;Savarino 2013) CDAI ≥ 200 (Ardizzone 2004) CDAI > 200 plus a 100-point increase in CDAI from baseline (Herfarth 2006)
Endoscopic recurrence Follow-up:24 months	647 per 1,000	835 per 1,000 (556 to 1,000)	RR 1.29 (0.86 to 1.94)	35 (1 study)	⊕◯◯◯ VERY LOW [13]	Endoscopic recurrence defined as Rugeerts score ≥ 2 (Savarino 2013)
Radiologic relapse Follow-up:24 months	765 per 1,000	834 per 1,000 (596 to 1,000)	RR 1.09 (0.78 to 1.52)	35 (1 study)	⊕◯◯◯ VERY LOW [14]	Radiologic relapse defined as a radiographic grading score ≥ 2 (Savarino 2013)

Adverse events Follow-up:52 weeks-24 months	468 per 1,000	519 per 1,000 (454 to 594)	RR 1.11 (0.97 to 1.27)	425 (5 studies)	⊕⊕◯◯ LOW [15]	Reported adverse events included leukopenia, abdominal pain, nausea, nasopharyngitis, diarrhoea.and headache
Serious adverse events Follow-up:52 weeks to 24 months	170 per 1,000	51 per 1,000 (19 to 136)	RR 0.30 (0.11 to 0.80)	311 (3 studies)	⊕◯◯◯ VERY LOW [16]	Reported serious adverse events included postoperative bowel obstruction and pancreatitis
Withdrawal due to adverse events Follow-up:52 weeks to 24 months	193 per 1,000	92 per 1,000 (54 to 160)	RR 0.48 (0.28 to 0.83)	425 (5 studies)	⊕⊕◯◯ LOW [17]	Adverse events leading to withdrawal included severe epigastric intolerance, increase in liver function test results, leukopenia, acute pancreatitis
Health related quality of life Follow-up: 24 months	1118 per 1,000	167 per 1,000 (32 to 878)	RR 1.42 (0.27 to 7.46)	35 (1 study)	⊕◯◯◯ [18] VERY LOW	Health related quality of life defined as IBDQ score > 170

*__The risk in the intervention group__ (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to to high risk of performance bias

[2] Downgraded one level due to serious imprecision (222 events)
[3] Downgraded two levels due to serious imprecision (26 events)
[4] Downgraded two levels due to serious imprecision (28 events)
[5] Downgraded one level due to serious imprecision (209 events)
[6] Downgraded two levels due to very serious imprecision (33 events)
[7] Downgraded one level due to serious imprecision (59 events)
[8] Downgraded two levels due to very serious imprecision (5 events)

5-ASAs compared to anti TNF-α for maintenance of surgically-induced remission in Crohn's disease

Patient or population: people with surgically-induced remission in Crohn's disease
Setting: outpatient
Intervention: 5-ASAs (3 g/day)
Comparison: anti TNF-α

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with anti TNF-α	Risk with 5-ASAs				
Clinical relapse Follow-up: 24 months	126 per 1,000	500 per 1,000 (126 to 1,000)	RR 4.00 (1.01 to 15.84)	34 (1 study)	⊕◯◯◯ VERY LOW [12]	Clinical relapse defined as a grading score ≥ 2 (Savarino 2013)
Endoscopic recurrence Follow-up: 24 months	63 per 1,000	833 per 1,000 (124 to 1,000)	RR 13.33 (1.98 to 89.95)	34 (1 study)	⊕⊕◯◯ VERY LOW [13]	Endoscopic recurrence defined as a Rutgeert's score ≥2 (Savarino 2013)
Radiologic relapse Follow-up: 24 months	63 per 1,000	833 per 1,000 (124 to 1,000)	RR 13.33 (1.98 to 89.95)	34 (1 study)	⊕◯◯◯ VERY LOW [13]	Radiologic relapse defined as a score ≥2 (Savarino 2013)
Adverse events Follow-up: 24 months	688 per 1,000	777 per 1,000 (516 to 1,000)	RR 1.13 (0.75 to 1.71)	34 (1 study)	⊕⊕◯◯ VERY LOW [14]	Reported adverse events included bronchitis, nasopharyngitis, abdominal pain, arthralgia and exacerbation of Crohn's disease
Serious adverse events	Outcome not reported					Not reported

Withdrawal due to adverse events Follow-up: 24 months	63 per 1,000	19 per 1,000 (0 to 428)	RR 0.30 (0.01 to 6.84)	34 (1 study)	⊕◯◯◯ VERY LOW [15]	Adverse events leading to withdrawal included atopic dermatitis and severe exacerbation of Crohn's disease
Health related quality of life Follow-up: 24 months	875 per 1,000	166 per 1,000 (61 to 473)	RR 0.19 (0.07 to 0.54)	34 (1 study)	⊕◯◯◯ VERY LOW [16]	Health related quality of life defined as (IBDQ >170)

*__The risk in the intervention group__ (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; __OR:__ Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to high risk of performance bias and unclear risk of outcome assessment bias
[2] Downgraded two levels due to very serious imprecision (10 events)
[3] Downgraded two levels due to very serious imprecision (16 events)
[4] Downgraded two levels due to very serious imprecision (25 events)
[5] Downgraded two levels due to very serious imprecision (1 event)
[6] Downgraded two levels due to very serious imprecision(17 events)

Sulphasalazine compared to placebo for maintenance of surgically-induced remission in Crohn's disease

Patient or population: people with surgically-induced remission in Crohn's disease
Setting: outpatient
Intervention: Sulphasalazine (3 g/day)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Sulphasalazine				
Clinical relapse Follow-up:18 to 36 months	710 per 1,000	625 per 1,000 (397 to 979)	RR 0.88 (0.56 to 1.38)	298 (2 studies)	⊕⊕◯◯ LOW [12]	Clinical relapse was proven by radiological, endoscopic, or operation findings (Ewe 1989) Clinical relapse was measured by a scoring system that considered symptoms, signs and impact (Wenckert 1978)
Endoscopic recurrence	Outcome not reported					Not reported
Radiologic relapse	Outcome not reported					Not reported
Adverse events	Outcome not reported					Not reported
Serious adverse events	Outcome not reported					Not reported
Withdrawal due to adverse events Follow-up:18 months	29 per 1,000	10 per 1,000 (0 to 246)	RR 0.35 (0.01 to 8.38)	66 (1 RCT)	⊕◯◯◯ VERY LOW [34]	Adverse events leading to withdrawal included nausea

Health related quality of life (HRQL)	Outcome not reported	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for limitation due to high risk of reporting and detection bias
[2] Downgraded one level due to serious imprecision (205 events)
[3] Downgraded one level due to unclear risk of bias for several domains
[4] Downgraded two levels due to very serious imprecision (1 event)

DISCUSSION

Summary of main results

This updated review includes 14 studies (1867 participants) investigating the use of 5-ASA agents for maintenance of remission in Crohn's disease after surgery. Sulphasalazine agents, the earliest class of 5-ASA drug, have not shown efficacy compared to placebo for preventing clinical relapse (low certainty evidence), although there were just two older studies for this comparison. Similarly for 5-ASA versus no treatment, efficacy was not demonstrated, although again there was just a small number of participants in one study. Both of these results were judged to be of low certainty evidence due to quality issues and imprecision.

5-ASA agents when compared with placebo were efficacious for the prevention of clinical relapse and this result was rated as moderate certainty evidence on GRADE analysis, with five studies included in this analysis. The number needed to treat to prevent one relapse was 13. Endoscopic recurrence was not as consistently reported with only three studies included in the analysis. The effect of 5-ASA on endoscopic recurrence is uncertain due to very low certainty evidence due to substantial heterogeneity and high risk of bias.

5-ASA agents compared to purine analogues were also investigated. There was no difference between 5-ASA agents and purine analogues in preventing clinical relapse, although this outcome was reported as low certainty evidence due to risk of bias and imprecision. The secondary outcome of preventing endoscopic recurrence was also analysed and no difference in efficacy between the agents was found, however this outcome was rated as very low certainty evidence due to a high risk of bias and very serious imprecision.

A single study compared two different dosing regimens of the same 5-ASA agent (4 g/day versus 2.4 g/day), but found no difference in preventing clinical relapse.The certainty of evidence was reported as moderate due to imprecision from the small event numbers.

One study compared 5-ASA with an anti TNF-α agent (adalimumab) and found 5-ASA to be inferior compared to adalimumab for prevention of clinical relapse. However, this outcome was rated as very low certainty evidence due to risk of bias and very serious imprecision.

The effect of 5-ASA on adverse events was uncertain. The overall certainty of the evidence for adverse event outcomes ranged from very low to low due to serious imprecision and high risk of bias. 5-ASA did not appear to increase the risk of adverse events, serious adverse events or withdrawal due to adverse events when compared with placebo, no treatment or adalimumab. 5-ASA participants had fewer serious adverse events and withdrawals due to adverse events than participants who received purine antimetabolites.

5-ASA preparations are ineffective for maintenance of medically-induced remission in Crohn's disease (Akobeng 2016). It is not clear why the evidence suggests a difference in efficacy for 5-ASA agents in patients with medically- and surgically-induced remission. One possibility could be that disease activity levels at study entry may not be comparable. The limitations of a CDAI score within clinical trials has previously been noted (Caprilli 1994), and most of the clinical trials performed to evaluate the role of 5-ASA in the maintenance of medically-induced remission defined remission using the CDAI score. As most of the trials involved in this review used surgical resection of macroscopically diseased bowel as inclusion criterion, it follows that many of these participants may have less active disease at study entry compared to participants in trials of medically-induced remission. This may explain the observed difference in efficacy of 5-ASA agents.

It is also possible that the length of time in remission may partly explain this difference in efficacy. Many of the studies in the review of medically-induced remission included patients who had been in remission for significant periods of time prior to study entry (Akobeng 2016). By contrast, most of the studies in this review required entry and initiation of therapy within 12 weeks of surgery. Evidence obtained from studies with a follow-up of greater than 12 months still favoured the use of 5-ASA agents, but as the longest study follow-up was 36 months, it is possible that if a longer follow-up was used this effect would not be sustained.

Overall completeness and applicability of evidence

With the increase of studies in this updated review, the overall volume and utility of the synthesised data has improved. This has facilitated meaningful comparisons. Moderate certainty evidence indicates that 5-ASA is superior to placebo for maintaining surgically-induced remission in Crohn's disease. The effect of 5-ASA on endoscopic recurrence was uncertain as the certainty of the evidence was very low, so this would be an outcome of interest if further studies do occur in this context.

The evidence is less complete when 5-ASA agents are compared with the two key medication classes that are routinely considered in the post-surgical setting (i.e. purine analogues and anti TNF-α agents). The evidence shows no difference in efficacy when 5-ASA is compared with purine analogues. There was a difference in safety favouring 5-ASA over purine analogues. As these results were rated as very low or low certainty predominantly due to issues with imprecision, this is an area that needs to be addressed. Similarly, there is just one trial with 34 patients comparing 5-ASA with anti TNF-α agents and therefore further research is warranted.

The longest follow-up period was six years, with the majority of trials following participants for less than three years and again this further limits the applicability of the evidence to clinical practice. Time-to-event data would be useful as this would allow better insights on the efficacy of 5-ASA for preventing relapse in post-surgical Crohn's disease.

The reporting of adverse events was a source of significant heterogeneity. The terminology used to describe adverse events in the included studies was not consistent. Terms used included minor adverse events, adverse events, side effects, major side effects, serious adverse events, serious events attributable to medication and withdrawals due to adverse events. Across studies, the reporting of adverse events was not consistent, with some studies reporting total event numbers, rather than the number of events per participants and some studies included treatment failure as an adverse event. There is now clear guidance on the reporting of adverse event outcomes in IBD trials and we strongly advise future studies to align with this.

Quality of the evidence

The included studies were inconsistent in terms of quality. The risk of bias was judged to be low in one study, unclear in seven studies and high in six studies. For the comparison of 5-ASA to placebo, there was moderate certainty evidence of the efficacy of 5-ASA for preventing clinical relapse in post-surgical Crohn's disease. Whilst this has added to our confidence in the effect estimate, this is not the case for other comparisons and outcomes assessed in this review. In particular, the studies comparing 5-ASA with purine analogues had issues with performance bias and sparse data. Additionally, there is just one trial comparing 5-ASA with anti TNF-α agents. This led to other results being of very low or low certainty. Nonetheless, it is worth noting that there was little statistical heterogeneity noted across the comparisons. There was no indirectness as the included studies were all within the scope of the review. However, the limited number of studies precluded an assessment of publication bias.

Potential biases in the review process

We acknowledge that there are certain decisions which were made during the review process which may have introduced bias in the results. It was decided that sulphasalazine as a pharmacologically different 5-ASA should be analysed separately, a decision that was not made for the previous version of the review. It is worth noting, however, that if 5-ASA and sulphasalazine studies are combined, the results do not change.

There were also significant problems classifying adverse events, as stated above. For the purposes of maintaining as homogenous reporting as possible, it was decided that we would not report on minor adverse events. Additionally, when considering the remaining adverse events, disease worsening or treatment failure were removed from the counting of adverse events. This was done for two reasons. Firstly, it was of concern that such patients may have already been included in the original relapse figures and be counted twice and whilst we tried to confirm this with authors, it was not always possible. Secondly, it was felt that such outcomes should be considered a natural result of treatments that do have a variable efficacy, it was not appropriate to consider these events as adverse events. However, it is possible such judgements may be a source of bias.

Agreements and disagreements with other studies or reviews

Since the original publication of this review (Gordon 2011), the UK National Institute for Health and Care Excellance guidance was updated to now consider 5-ASA as a treatment in this context (NICE 2012). However, the most recent NICE guidelines that were updated in May 2019 removed the recommendation stating that 5-ASA had not been shown to be clinically or cost effective in terms of endoscopic relapse rates (NICE 2019). However, the NICE systematic review excluded studies with less than 12 months follow-up and did not include abstracts. This led to several studies being excluded from the NICE guideline that have contributed to this review (Florent 1996; Herfarth 2006; Reinisch 2010; Sutherland 1997), and a reduction in the size of the evidence base.

An additional concern is that the NICE systematic review used a network meta-analysis methodology. However, several included studies that exerted influence on the network included non-randomised active agents, specifically metronidazole. This does not meet the stringent requirement of transitivity for network meta-analysis and therefore limits the conclusions that can be made from the NICE meta-analysis.

The most recent American Gastroenterological Association guideline does not recommend the use of 5-ASA in this setting, citing the low GRADE rating on their committee analysis and so this review is not in agreement with this guideline (Nguyen 2017). The European Crohn's and Colitis Organisation guidelines are older and include far fewer studies in their analysis, but conclude that while 5-ASA is effective, it is less effective than purine analogues with no difference in safety (Van Assche 2010). This is also in contrast with the findings of this review.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate certainty evidence suggests that 5-ASA preparations are superior to placebo for the maintenance of surgically-induced clinical remission in patients with Crohn's disease. The number needed to treat to prevent one relapse was 13 patients. However, the effect of 5-ASA on endoscopic remission was uncertain. These findings require careful consideration given that endoscopic recurrence has been shown to precede clinical relapse. There was no evidence of a difference in the rate of adverse events, serious adverse events or

withdrawals in the 5-ASA or placebo groups, but this was rated as low certainty evidence. The analysis of the studies comparing sulphasalazine to placebo did not demonstrate superiority, but this result was of low or very low certainty due to sparse data and risk of bias. This was also the case for the one study that compared 5-ASA with no treatment. There was no difference between 5-ASA (mesalamine) and purine analogues (azathioprine) in efficacy, but there was evidence of lower rates of serious adverse events and withdrawals due to adverse events with 5-ASA agents. However, the evidence was rated as low or very low certainty. Finally, in one study 5-ASA was inferior to anti TNF-α agents, although the evidence was rated as very low certainty.

Implications for research

Further studies investigating the efficacy of 5-ASA for maintenance of endoscopic remission may be required. However, given that the current international guidance recommends post-surgical prophylaxis over no intervention (Nguyen 2017), it is proposed that further studies would be best placed to investigate both endoscopic and clinical outcomes for 5-ASA when compared with purine analogues and anti TNF-α . Key to these studies is the need to address both design and reporting issues that have been identified in both versions of this review, as well as enrolling enough participants to allow for adequate statistical power.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ardizzone 2004

Methods	**Study design:** RCT, single centre **Setting:** University "L.Sacco" Hospital (Milan, Italy), 1994-2001
Participants	**Inclusion:** Adult (18-70yrs) patients who underwent surgery for symptomatic intestinal stenosis or occlusion, which is clinically quiescent (CDAI $\leq$ 150 CD) able to start oral nutrition and oral medication within the first 2 postoperative weeks **Exclusion:** Contraindications for use of mesalamine or AZA and pre-existing hepatic disease, renal dysfunction, clinically important lung disease, systemic infection, short-bowel syndrome, presence of alcoholic stoma, history of cancer, hypersensitivity to mesalamine or AZA, erythrocyte macrocytosis, use of immunosuppressive drugs in the past 3 months; patients who had received treatment with anti-TNF α within the 6 months before surgery; pregnancy/breastfeeding; patients who had undergone surgical procedures other than conservative surgery or for perianal disease only; history of corticosteroid-dependent disease **Age (IG1 / IG2)mean:** 38.4 yrs mean overall **Sex (M:F):** 95: 52 overall; (45:26) vs. (50:26) **Type of surgery:** Stricturoplasty- 36; Minimal bowel resection- 70; Minimal bowel resection stricturoplasty-36 **Previous surgery (IG1+IG2):** 69/142 overall (38/71) vs. (31/71) **Start of intervention after surgery:** <2 weeks **Medication use (IG1+ IG2):** Mesalamine or sulphasalazine: 62; Corticosteroids: 41; Immunosuppressants: 9; None: 30 **Smoker (IG1 / IG2):** (28/71) vs. (36/71) **Number randomised (n = 142):** 71 vs. 71 **Number analysed (n = 138):** ITT: (69/71) vs. (69/71); Per protocol: 50/71 vs. 61/71 **Post-randomisation exclusion (n = 11)**: (6/71) vs. (5/71); Did not start the treatment: 3 (2 vs. 1); lost to follow-up:8 (4 vs. 4)
Interventions	**Group 1:** Azathioprine administered at a dosage of 2 mg/kg/day **Group 2:** Mesalamine was administered at a dosage of 3 g/day divided into 3 doses **All participants:** treatment with aminosalicylates, metronidazole, and any other CD-specific treatment had to be discontinued. Corticosteroids were allowed to be tapered by standardized stepwise dose reductions within 6 weeks after surgery at the latest. Symptomatic treatment with antacids, antidiarrhoeal agents, or spasmolytic agents was allowed but had to be scrupulously recorded. Compliance with treatment was evaluated by a simple questionnaire in which adverse events were also recorded. Patients receiving AZA were regularly assessed by total blood cell count and serum transaminase values to monitor any myelotoxicity and hepatotoxicity of the treatment. Patients were seen at baseline and every 6 months

Outcomes	**Duration of study:** 24 months 1. **Clinical relapse** defined as the presence of symptoms related to CD, variably associated with radiologic, endoscopic, and laboratory findings, with a CDAI score >200, which is considered severe enough to warrant treatment with a systemic corticosteroid at a medium-high dose 2. **Surgical Relapse d**efined as the presence of symptoms refractory to medical treatment or complications requiring another surgical procedure (e.g., occlusive disease, intra-abdominal abscesses, or high-flow fistulas) 3. Adverse events
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Sample size:** Based on a maximum relapse rate at 2 years of 45% mesalamine, 62 patients per treatment group was considered sufficient to detect a difference of ≥25% for the AZA treatment group (type 1 error of 5%). The number of patients in each group was increased to 68 to compensate for an anticipated drop out rate of 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After surgery, patients who met the inclusion criteria and who agreed to enter the study were randomised to receive mesalamine or AZA by a computer-generated list" and "Randomization was performed in blocks of 10" Comment: computer generated block randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the study is open-label and blinding is not performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgment, however it is unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotes: "In the intention-to-treat analysis, all randomised patients who received at least one dose of the study drug and were subjected to the baseline evaluation were considered for the analysis."and "Outcome measures were analysed in all randomised patients who had taken at least one dose of the study medication (intention-to-treat population)…"

Ardizzone 2004 (*Continued*)

		Comment: withdrawals were low and balanced across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all outcomes stated in the method section were assessed and reported
Other bias	Low risk	Quote: "No significant differences were observed between the 2 treatment groups regarding age, sex, duration of disease, location of disease, fistula and abscess at surgery, surgical procedure, previous operations, and CD therapy during the previous 6 months" Comment: baseline characteristics well balanced across groups

Brignola 1995

Methods	**Study design:** RCT, multicentre **Setting:** Italy, 8 centres, 1990-1992 enrolment
Participants	**Inclusion:** Patients with so-called curative resection, such as those who have undergone removal of all macroscopic disease in the ileal or ileocaecal region **Exclusion:** Patients with localization of CD in another region or having resection of >100 cm were excluded **Age (IG1 / IG2) mean (SD):** 36.5 ±14 overall; (39 ± 17) vs. (34 ± 10) **Sex (M:F):** 42:45 overall; (22:22) vs. (20:23) **Type of surgery:** Not reported **Previous surgery (IG1+IG2):** 24 overall; (13/44) vs. (11/43) **Start of intervention after surgery:** ≤ 1 month **Medication use (IG1+ IG2):** Not reported **Smoker (IG1 / IG2):** 44 overall (22/44) vs. (22/43) **Number randomised (n = 87):** 44/43 **Number analysed (n = 85):** (43/44) vs. (42/43) **Post-randomisation exclusion (n = 2)**: (1/44) vs. (1/43); Lost to follow up: 1 (1 vs 0); protocol violation:1 (0 vs 1)
Interventions	**Group 1:** Mesalamine tablets 3 g/day for 12 months (2 tablets Pentasa (500-mg) 3 times a day) **Group 2:** Identical placebo tablets **All participants:** Laboratory tests performed at baseline after 1 month and then every 3 months for evaluation of hematologic, renal, and hepatic function
Outcomes	**Duration of study:** 12 months 1. **Clinical recurrence** defined as worsening of the symptoms by at least 100 CDAI points above the patient's level at the previous visit and attainment of a CDAI score of more than 150

Brignola 1995 (*Continued*)

	2. **Endoscopic recurrence** based on a standardised form for description of endoscopic lesions by type (aphthous lesion, large ulcer, nodule, or narrowing) and characteristics (number, size, and whether a diffuse or skip lesion 3. **Severe endoscopic recurrences** (i score of 3 and 4) 4. **Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Sample size**: The severe endoscopic recurrence (score 3-4) rate in the placebo group was estimated to be 50%. The decision was made to enrol 80 patients (40 per group) to detect a significant difference in comparison with the active group (30% recurrence) (one-tailed test; α level, 5%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each center received material for at least 4 cases labelled with a patient code number according to a randomization made in balanced blocks" Comment: block random sequence generation, but method not described
Allocation concealment (selection bias)	Unclear risk	"Each center received material for at least 4 cases labelled with a patient code number according to a randomization made in balanced blocks" Comment: Unclear whether drug containers were identical.Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The treatment blinding code was broken in September 1993 when all the assessments were finished; no serious adverse event necessitated breaking of the code beforehand" Comment: It is a double-blind trial, patients were receiving placebo tablets which were identical to the study intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Endoscopists, unaware of the treatment that the patient had received, recorded on a standardized form a description of endoscopic lesions by type...At the end of the trial, two investigators not previously involved in the patients' follow-up and unaware of which treatment the patients had received and also of the overall

Brignola 1995 (*Continued*)

		assessments provided by each center, independently evaluated all of the standardized forms with a description of endoscopic and radiological responses; their assessments were then compared with those furnished by the investigators from the original center...The treatment blinding code was broken in September 1993 when all the assessments were finished; no serious adverse event necessitated breaking of the code beforehand. " Comment: blinding maintained till after assessments were finished
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were low and balanced across groups with reasons reported
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all outcomes stated in the method section reported
Other bias	Low risk	Quote: "Clinical characteristics that were considered in our trial were well balanced between the mesalamine group and the placebo" Comment: Groups well balanced at baseline. No other apparent biases

Caprilli 1994

Methods	**Study design:** RCT, multicentre, **Setting:** Italy, 15 collaborating centres, 1990-1992 enrolment
Participants	**Inclusion:** Age between 18 and 65 years for both sexes, disease limited to the terminal ileum with or without involvement of caecum-ascending colon : resection had to be the first one and judged to be 'radical' (complete removal of the macroscopically involved intestinal segment) by the surgeon during operation: absence of skip lesions; diagnosis of Crohn's disease confirmed macroscopically and microscopically by standard criteria **Exclusion:** Localization of the disease to the jejunum, proximal ileum, left colon or anorectum: known side-effects from sulphasalazine or salicylates; severe diseases unrelated to Crohn's disease (for example, renal or liver dysfunction); treatment with drugs that may alter intestinal pH (H,-receptor antagonists, omeprazole); pregnancy ; questionable ability to co-operate and give consent **Age (IG1 / IG2) mean (range):** 35.5 (16-61)) vs. 33.7 (16-58) **Sex (M:F):** 55:40 overall; (32:15) vs. (23:25) **Type of surgery:** Elective-71; Emergency-24 **Previous surgery (IG1+IG2):** Not reported **Start of intervention after surgery:** $\leq$ 2 weeks

	Medication use (IG1+ IG2): Mesalazine-46; corticosteroids-59; cetronidazole-25; sulphasalazine-21 **Smoker (IG1 / IG2):** Not reported **Number randomised (n = 110):** 55/55 **Number analysed (n = 95):** (47/55) vs. (48/55) **Post-randomisation exclusion (n = 17)**: (9/55) vs. (8/55); randomised, no endoscopy at base: 15 (8 vs. 7); drop-out: 2 (1 vs. 1)
Interventions	**Group 1:** 2.4 g/day of Eudragit-S coated mesalazine **Group 2:** No treatment **All participants:** Patients were seen for clinical and laboratory assessment at 2 weeks after surgery, at 3, 6, and 12 months, and annually thereafter. Colon-ileoscopy was performed at 6 and 12 months, and annually thereafter. Clinical, laboratory and endoscopic examination were brought forward if symptoms recurred. Patients requiring corticosteroids or surgery were withdrawn from the study. Patients who stopped the treatment for more than 2 weeks, or who presented with severe side-effects, were considered to be drop-outs. Adverse events and reported compliance with the drug were recorded at each visit
Outcomes	**Duration of study:** 24 months 1. **Clinical relapse:** Patients in whom CDAI was > 150, and who presented 100 points over their previous value, were considered to be relapsed 2.**Recurrence** defined as the presence of typical endoscopic Crohn's disease lesions in the neoterminal ileum and/or anastomosis according to the criteria proposed by Rutgeerts et al. (judged as no, mild or severe) 3. **Adverse events** (skin rash, epigastric pain, nausea, vomiting) 4.**Withdrawal due to adverse events**
Notes	**Funding source:** Supported in part by Bracco SpA (Milan) **Conflict of interest:** Not reported **Sample size**: The study entailed the enrolment of 55 consecutive patients in each arm of the trial, a number sufficient to demonstrate a fall in the recurrence rate from 90 to 80% with a power of 0.90 and a 0.05 one-sided type I error. Only the 95 patients with almost 6 months of observation were considered in the statistical analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomly allocated to receive 2.4 g/day of Eudragit-S coated mesalazine (Asacol, Bracco SPA, Italy) or no treatment at all" Comment: insufficient information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This multicentre study was not blind" Comment: Study is open-label design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "On the first occasion, the endoscopist was unaware of the treatment; on the second, the tapes were shown with a different sequence and the endoscopist was informed of treatment... The variability sources of the recurrence classification were evaluated... However, the results of the reliability study suggest that lack of blindness in the endoscopists collaborating on the trial was no relevant. In fact, we found that the endoscopists were not in disagreement in the assessment of recurrence nor was the diagnosis of recurrence affected by endoscopists' awareness of the kind of treatment" Comment: There was some form of blind outcome assessment and the reliability study comparing blind versus unblind assessment showed that the lack of blinding had no effect on outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The cumulative proportions of symptomatic recurrence and asymptomatic recurrence were estimated by the life table method on the intention-to-treat principle" Comment: Attrition rate was low and balanced across groups
Selective reporting (reporting bias)	Low risk	All outcome data stated in the method section were reported
Other bias	Low risk	Quote: "the groups were homogenous for age, duration of the disease, site and extent of the lesions, clinical course perforating or non-perforating), previous treatment, indication and type of surgery, and CDAI score at operation. Males more common in MEZ group" Comment: groups well balanced at baseline. No other apparent sources of bias detected

Caprilli 2003

Methods	**Study design:** RCT, multicentre, **Setting:** Italy, 17 collaborating centres, Italy, enrolment 1997-2000
Participants	**Inclusion:** Adults (18-65 years) with CD limited to the terminal ileum (lesions not exceeding 1 m), with or without involvement of the caecum/ascending colon, evaluated by colonoscopy and small bowel follow-through within 1 month before surgery; first or second resection, and considered by the surgeon during the operation to be 'radical' (complete removal of the macroscopically involved intestinal segment); absence of skip lesions; diagnosis of CD confirmed macroscopically and microscopically by standard criteria **Exclusion:** Localization of the disease to the jejunum, proximal ileum, transverse colon, left colon or ano-rectum; small bowel resection exceeding 1 m; known side-effects from sulphasalazine or salicylates; severe diseases unrelated to Crohn's disease (e.g. renal or liver dysfunction); treatment with drugs likely to affect intestinal pH ; pregnancy; questionable ability to co-operate; inability to give informed consent **Age (IG1 / IG2) mean:** 33.8 vs 36.4; overall age not reported **Sex (M:F):** 114:93 overall; (49:52) vs (64/41) **Type of surgery:** Emergency: 45; Elective: 161 **Previous surgery (IG1+IG2):** First- 166; second-40 **Start of intervention after surgery:** $\leq$ 2 weeks **Medication use (IG1+ IG2):** Mesalamine-153; Steroids-123; Antibiotics-71; Immunosuppressants-20 **Smoker (IG1 / IG2):** (21/ 101) vs (27/105) **Number randomised (n = 206):** 101/105 **Number analysed (n = 206):** (99/101) vs (103/105) **Post-randomisation exclusion (n = 61)**: (23/101) vs (38/105); Withdrawals from clinical control -20 (6 vs 14); withdrawals from endoscopy -41 (17 vs. 24)
Interventions	**Group 1:** 4.0 g/day of oral Eudragit-S-coated mesalazine (Asacol). Patients received five tablets of mesalazine (800 mg) divided into three doses (1 + 2 + 2 tablets) **Group 2:** 2.4 g/day of oral Eudragit-S-coated mesalazine (Asacol). Patients received three tablets of mesalazine (800 mg) divided into three doses (1 + 1 + 1 tablets) plus two tablets of placebo identical in appearance **All participants:** No other pharmacological treatment was given, with the exception of anti-diarrhoeal drugs on demand. Patients were seen for clinical and laboratory assessment 2 weeks after surgery, and then at 6 and 12 months. Colon ileoscopy was performed at 12 months. Clinical, laboratory and endoscopic examinations were brought forward if the recurrence of symptoms was reported before the scheduled follow-up. Adverse events and reported compliance with the drug were recorded at each visit
Outcomes	**Duration of study:** 12 months 1. **Endoscopic recurrence** defined as the presence of typical endoscopic CD lesions in the neoterminal ileum and/or anastomosis, and was graded according to the criteria of Rutgeerts et al. Three different degrees of endoscopic recurrence were evaluated: (i) an endoscopic score of > 0; (ii) an endoscopic score of > 1; and (iii) an endoscopic score of > 2 (severe recurrence) 2. **Clinical recurrence** defined as CDAI > 150 points or an increase in CDAI score of > 100 points 3. **Adverse events**

	4. **Withdrawals due to adverse events**
Notes	**Funding source:** supported by a grant from Giuliani SpA, Milan, Italy **Conflict of interest:** Not reported **Sample size**: Assuming that mesalazine, 2.4 g/day, would reduce severe endoscopic recurrence from 70% to 55% at 1 year of follow-up, it was hypothesized that mesalazine, 4.0 g/day, would reduce the rate of severe endoscopic recurrence to 30%. The number of patients needed to ensure a type 1 and type 2 error level of 5% calculated was 85 patients per group plus 25% drop-outs (i.e. a further 43 patients). Therefore, the total number of patients required was 213

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized in blocks of four according to a computer-generated randomization scheme provided by an independent institution at the beginning of the trial and forwarded to the Department of Clinical Trials at Giuliani SpA. " Comment: computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Quote: "...provided by an independent institution at the beginning of the trial and forwarded to the Department of Clinical Trials at Giuliani SpA" Comment: Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "All patients and investigators were blind with regard to treatment allocation" Comment: double-blinded RCT, but no explanation how were the conditions of blinding achieved. Given the variation in doses between study groups (5 vs. 3 tablets) , blinding is unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatment blinding code was broken in June 2000 when all assessments had been completed" Comment: assessors were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Outcome measures were analysed in all randomized patients who had taken at least one dose of the study medication (intention-to-treat population)"

		Comment: Attrition rates were similarly low and balanced across groups except for the endoscopy outcome where attrition rates were about 20%
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all outcomes stated at the method section reported adequately
Other bias	Low risk	Groups well balanced at baseline, compliance satisfactory; no other apparent sources of bias detected

Ewe 1989

Methods	**Study design:** RCT, multicentre **Setting:** Germany / 16 surgical and medical centres; study period not reported
Participants	**Inclusion:** Adult patients resected for CD by one of the medical centres; resection had to be curative with no macroscopically inflamed intestine left; diagnosis of CD had to be confirmed macro and microscopically **Exclusion:** Patients not resected according to the standard policy of the individual (radical or non-radical); inability/refusal to give written consent; questionable ability to cooperate; age less than 18 **Age (IG1 / IG2) median (range):** 31 (15-66) overall; 32 (16-66) vs 30 (15-62) **Sex (M:F):** 113:119 overall; (48:63) vs (65:56) **Type of surgery:** Not reported **Previous surgery (IG1+IG2):** 94 (48/46) **Start of intervention after surgery:** Immediately postoperatively **Medication use (IG1+ IG2):** Not reported **Smoker (IG1 / IG2):** Not reported **Number randomised (n = 232):** 111/121 **Number analysed (n = 206):** (101/101) vs (105/105) **Post-randomisation exclusion (n = 88)**: (47/111) vs (41/121); Noncoop-57 (31 vs 26) ; technical-18 (8 vs 10); medical-13 (8 vs 5)
Interventions	**Group 1:** Sulfasalazine 3 g daily for 3 years **Group 2:** Similar placebo (size, colour, form) **All participants:** Medication initiated while in hospital. Control visits at 3 months and every 6 months thereafter. Colonoscopy not obligatory, although encouraged
Outcomes	**Duration of study:** 3 years 1. **Recurrence of CD** proven by radiology, endoscopy or operation (>3 months, >1 year, >2 years, 3 years)
Notes	**Funding source:** supported by Deutsche Forschungsgemeinschaft grant Ew 4/12,14, 16/1-3 **Conflict of interest:** Not reported **Power calculation**: Not reported

Ewe 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Yes, we carried out random allocation. We got the key from our statistical department" Comment: Whilst the medical treatment part of the study is reported as randomised and double blind, there was no further information on this in the trial. However, based on correspondence on the 11/10/2018 with the lead author (Professor Ewe) , the review authors conclude that random allocation was probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medical treatment part of the study is reported as randomised and double blind. Dummy tablet similar to SZ has been used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote "Yes, the people who assessed the outcomes were aware of the intervention patients were allocated to" Comment: Confirmed via correspondence on the 11/10/2018 with the lead author (Professor Ewe)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition rate was around 37%, however, compared to the event risk (60%) , it was not sufficient to introduce bias
Selective reporting (reporting bias)	High risk	Trial registration is not available and adverse events outcome was not reported
Other bias	Low risk	Baseline characteristics appear to be balanced across groups

Florent 1996

Methods	**Study design:** RCT, multicentre **Setting:** France and Belgium;12 medical centres; 1989-1991
Participants	**Inclusion:** All patients treated by 'curative' resection for CD and whose anastomosis was within the reach of colonoscopy were eligible for the study. Crohn's disease diagnosis was established by the convergence of clinical, radiological, endoscopic and histological data

Florent 1996 (*Continued*)

	Exclusion: Pregnant or breastfeeding women, women of childbearing potential not receiving effective contraception, patients with a permanent stoma, subjects having undergone a small intestinal resection of more than 100 cm prior to the pretrial operation, and patients having a history of peptic ulcer, a known hypersensitivity to salicylates or a significant renal, hepatic or haematological disorder **Age (IG1 / IG2) mean (SD):** 33.5±12 overall; 35±13 vs 32±11; overall age not reported **Sex (M:F):** 56:70 overall; (23:42) vs (33:28) **Type of surgery:** Emergency: 45; Elective: 161 **Previous surgery (IG1+IG2):** First- 166; second-40 **Start of intervention after surgery:** ≤ 15 days **Medication use (IG1+ IG2):** Mesalamine-153; Steroids-123; Antibiotics-71; Immunosuppressants-20 **Smoker (IG1 / IG2):** (17/ 65) vs (22/61) **Number randomised (n = 126):** 65/61 **Number analysed (n = 106):** (55/65) vs (51/61) **Post-randomisation exclusion (n = 14)**: (8/65) vs (6/61); Lost to follow-up -5 (0 vs 5) ; Intercurrent pathology-2 (1 vs 1); Protocol violation-3 (2 vs 1); Error of inclusion-1 (0 vs 1); Colonoscopy failure/refusal-3 (0 vs 3)
Interventions	**Group 1:** Claversal, two 500 mg tablets three times daily **Group 2:** Placebo, two 500 mg tablets three times daily **All participants:** Metronidazole and antibiotics were allowed within the perioperative period. Sulfasalazine, corticosteroids (except for substitutive doses of hydrocortisone in patients with post-steroid adrenal insufficiency) and immunosuppressive agents were not allowed during the trial
Outcomes	**Duration of study:** 12 weeks 1. **Endoscopic recurrence** defined as the presence of ulcerative lesions at the anastomotic level (aphthous, superficial or deep) owing to its poor reproducibility, classified according to Rutgeerts et al. (i ≥ 1) 2. **CDAI score**
Notes	**Funding source:** Supported by a grant from SmithKline Beecham Laboratories **Conflict of interest:** Not reported **Power calculation:** An assumption was made that 80% of participants on placebo would have an endoscopic relapse. A reduction of 30% in the relapse rate in the Claversal group was considered as the minimal clinical significant decrease. The number of patients required was 50 per arm. Estimating that 20% of patients would prove to be non evaluable a total of 126 patients were randomised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"Randomization was carried out using a permutation table within each centre" Comment: Patients were classified into three categories and it seems stratified randomisation using permuted blocks has

Florent 1996 (*Continued*)

		been used. However no further details provided
Allocation concealment (selection bias)	Unclear risk	Quote: "The treatment was started as soon as feeding was resumed, and no later than the 15th postoperative day, and was administered blindly over 12 weeks Comment: Insufficient information to make judgment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The treatment was started as soon as feeding was resumed, and no later than the 15th postoperative day, and was administered blindly over 12 weeks." Comment: Study is placebo controlled, but no information regarding the placebo tablet provided and whether interventions were sufficiently identical to ensure blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rates and reasons for attrition were balanced across groups
Selective reporting (reporting bias)	High risk	Data on CDAI reported as means ±SD. Clinical relapse CDAI≥200 as one of reasons for withdrawal not reported, although it should have been as CDAI was assessed at 12 weeks
Other bias	Low risk	Groups balanced at baseline, except for ESR which was significantly higher in the MES group. The authors did not consider this sufficient to introduce bias. No other apparent sources of bias detected

Hanauer 2004

Methods	**Study design:** RCT, multicentre **Setting:** USA and Belgium / 5 centres; 1992 - 1996
Participants	**Inclusion:** Patients 18 and 65 years of age, with diagnosis of CD for at least 6 months and scheduled for curative ileo-caecal resection; ability to start oral nutrition within 7 days of operation, need for curative ileo-caecal resection, and resection margins free of inflammation **Exclusion:** Active perianal disease or any active disease in other segments of the intestine,

	anti-TNF_, and/or investigational treatment within 4 months prior to surgery; current treatment with 5-ASA, azathioprine/6MP, or methotrexate; bowel surgery performed less than 3 months previously; history of colostomy or ileostomy; infections, neoplasia, or uncontrolled diseases; or anticipation of noncompliance with protocols. Subjects who were receiving steroids preoperatively were tapered and weaned according to a strict schedule **Age (IG1 / IG2) mean (SD):** 34.4 ±11.0 overall; 34.9 ±11.5 vs 34.1 ±10.9 vs 34.2 ±10.9 **Sex (M:F):** 60:71 overall; (23:24) vs (19:25) vs (18:22) **Type of surgery:** Not reported **Previous surgery (IG1+IG2): 18** (7/11) **Start of intervention after surgery:** Therapy initiated before postoperative hospital discharge **Medication use (IG1+ IG2):** Not reported **Smoker (IG1 / IG2):** Not reported **Number randomised (n = 131):** 47/44/40 **Number analysed (n = 131):** (47/131) vs (44/131) vs (40/131) **Post-randomisation exclusion (n = 27)**: (12/47) vs (7/44) vs (8/40); Withdrew consent -5 (1 vs 2 vs 2); Surgical complication -3 (2 vs 0 vs 1); Noncompliance-9 (2 vs 4 vs 3); Lost to follow-up -10 (4 vs 2 vs 4)
Interventions	**Group 1:** 50 mg of 6-mercaptopurine (Purinethol) once daily **Group 2:** 3 g of Mesalamine (Pentasa); 4 capsules of 250mg, 3 times daily **Group 3**: Identical matching placebo **All participants:** Presurgical therapy, including aminosalicylates, antibiotics, or immunomodulators, was discontinued before surgical resection and was not allowed during the postoperative trial. Preoperative treatment with corticosteroids was completely tapered by 3 months after hospital discharge at a rate determined by the treating physician. No concurrent treatment for Crohn's disease, aside from topical therapy for perianal disease, was allowed during the duration of the trial. Continuous use of nonsteroidal anti-inflammatory drugs was not allowed during the study. If the white blood cell count and platelet counts fell below 4500/L or 150,000/L, respectively, the dosage of 6-MP was reduced by one half
Outcomes	**Duration of study:** 24 months 1. **Endoscopic recurrence** defined as i ≥ 1 according to the Rutgeerts scoring system: i1-i2 mild to moderate; i3-i4 severe. Relapse defined as i ≥1 2. **Clinical recurrence** defined as CDAI > 150 points or an increase in CDAI score of > 70 points or higher from baseline 3. **Histological score** assessed by the Geboes scoring system **4. Adverse events** **5. Serious adverse events** **6. Withdrawal due to adverse events**
Notes	**Funding source:** Not reported; However, authors contacted by email on 02/08/2018 and declared none **Conflict of interest:** Not reported; However, authors contacted by email on 02/08/2018 stating that study was funded by Crohn's and Colitis Foundation **Power calculation**: Sample size calculations were performed for the endoscopic criteria,

	using 2-sided of 0.05 and 80% power, based on a predicted endoscopic recurrence of 75% at 1 year in the placebo group. A sample size of 50 in each group allows sufficient power to detect a 40% reduction in mild Crohn's disease lesions and a 75% reduction in more severe lesions at 1 year

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: Patients were randomized by a central computer by permuted blocks of 6 (unknown to investigators) per center to receive mesalamine (Pentasa; Marion Merrill Dow, Kansas City, MO) 3 g daily, 6-MP (Purinethol; Burroughs Wellcome, Research Triangle Park, NC) 50 mg daily, or placebo Comment: Computer generated random sequence
Allocation concealment (selection bias)	Low risk	Quotes: "Medications were prepared and dispensed by an assigned pharmacist at each site's investigational pharmacy who was not directly involved in the care of the patients" Comment: Treatment controlled by pharmacies at each centre
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quotes: "Medications were prepared and dispensed by an assigned pharmacist at each site's investigational pharmacy who was not directly involved in the care of the patients" and "An evaluating (treating) physician followed up each patient and was blinded as to the study drug and laboratory results" Comment: Placebo-controlled, double-blind RCT. However, it is unclear whether both study drugs were sufficiently identical with the placebo to blind study participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "Patient evaluation consisted of assessments of clinical, endoscopic, and radiographic disease activity at each study site by the blinded physician" and "Colonoscopic examinations with endoscopic descriptions and photography of the anastomosis and pre-anastomotic ileum were performed by the blinded investigators (all gastroenterologists) at months 6, 12, and 24" and "Radiographic interpretations

Hanauer 2004 (*Continued*)

		were performed by the blinded inflammatory bowel disease radiologist at each institution" Comment:Assessors blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotes: "The clinical recurrence rates were determined using ITT" Comment: ITT analysis applied, attrition low, similar and balanced across groups
Selective reporting (reporting bias)	Low risk	Comment: All outcomes stated in the method section reported
Other bias	Low risk	Quote: "There were no statistical differences in patient age, sex, disease duration, indications for surgical resection, or preoperative disease activity among the 3 groups" Comment: Groups well balanced at baseline. No other apparent sources of bias detected

Herfarth 2006

Methods	**Study design:** Multicentre RCT **Setting:** Not stated (multicentre RCT)
Participants	**Inclusion:** People with Crohn's who had undergone resective surgery **Exclusion:** Homozygous TPMT **Age:** Not reported **Sex:** Not reported **Type of surgery:** Not reported **Previous surgery:** Not reported **Start of intervention after surgery:** within 2 weeks postoperative **Medication use (IG1+ IG2):** **Smoker (IG1 / IG2): Not reported** **Number randomised (n = 79): 42/37** **Number analysed (n = 37): 18/19** **Post-randomisation exclusion (n = 42)**
Interventions	**Group 1:** 2.0 to 2.5 mg/g body weight/day azathioprine **Group 2:** 5-ASA 4 g/day **All participants: Not stated**
Outcomes	**Duration of study:** 1 year (study was discontinued after one year) 1. Treatment failure (due to severe endoscopic recurrence, lack of efficacy and AE related to study drug) 2. Clinical or severe endoscopic relapse 3. Severe endoscopic relapse 4. Clinical relapse (reviewer calculated: clinical or severe endoscopic relapse minus severe

	endoscopic relapse) 5. Adverse events 6. Withdrawal due to adverse events
Notes	**Funding source:** Dr. Falk Pharma GmbH, Freiburg, Germany **Conflict of interest:** Not reported **Power calculation:** Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients in the present study were assigned to one of the two treatment groups (5-ASA or azathioprine) at random For creation of the randomisation list the programme "Rancode +" (version 3.6) of IDV, Gauting (Germany) was used. The randomisation into two treatment groups was performed in blocks of four. After voluntary written informed consent was obtained and basic selection criteria were checked, the investigator requested the allocation of a unique patient code number (randomisation number, consecutively allocated to each patient), and received medication packs with the randomisation number for the patient" Comment: Confirmed by correspondence from Muller R (2/5/2012)
Allocation concealment (selection bias)	Low risk	"The randomization code was prepared and stored by a statistician from a CRO, who was not involved in the conduct nor in the analysis of the study. The Qualified Person of the Sponsor and the contract manufacturer responsible for the preparation of the double-dummy patients sets received a copy of the randomization list, which was safely stored at both sites, without allowing access by other people. Neither the investigator nor the study team from the clinical operation from the sponsor nor the CRO had access to the random list" Comment: Confirmed by correspondence from Muller R (2/5/2012)
Blinding of participants and personnel (performance bias)	Low risk	"This was a double-blind, double-dummy study. Patients randomized to administer

Herfarth 2006 (*Continued*)

All outcomes		5-ASA had to take 5-ASA VERUM tablets AND azathioprine PLACEBO tablets. Patients randomized to receive azathioprine had to administer azathioprine VERUM tablets AND 5-ASA PLACEBO tablets Therefore, neither the investigator, nor the patients, nor the sponsor were ware of the TX a patient received until the database was clean, closed, and the code was broken" Comment: Confirmed by correspondence from Muller R (2/5/2012)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"This was a double-blind, double-dummy study. Patients randomized to administer 5-ASA had to take 5-ASA VERUM tablets AND azathioprine PLACEBO tablets. Patients randomized to receive azathioprine had to administer azathioprine VERUM tablets AND 5-ASA PLACEBO tablets Therefore, neither the investigator, nor the patients, nor the sponsor were ware of the TX a patient received until the database was clean, closed, and the code was broken" Comment: Confirmed by correspondence from Muller R (2/5/2012)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The study was stopped prematurely after an interim-analysis due to a high therapy failure rate. 38 patients (AZA 18 pat.; 5-ASA 20 pat.) completed the study and could be evaluated regarding the primary endpoint therapy failure. The other pat. terminated the trial prematurely due to the study stop, but were also evaluated for adverse events (AE) and adverse drug reactions (ADR)" Comment: 51% of randomised participants discontinued. High risk for primary outcome and low risk for AE and withdrawal due to AE
Selective reporting (reporting bias)	Unclear risk	Insufficient information as trial registration was not available and study was published as abstract
Other bias	Unclear risk	Insufficient information as study was published as abstract

Lochs 2000

Methods	**Study design:** RCT, multicentre **Setting:** Austria, Denmark, Germany, Norway, Sweden, and Switzerland, 29 university/ teaching hospitals; 1992-1996
Participants	**Inclusion:** Adults (18-70 years) who underwent a resective surgical procedure (radical or nonradical) for a CD-specific lesion at 1 of the participating centers; diagnosis of CD established by generally accepted endoscopic, histological, and/or radiological criteria at least 6 months before surgery; evaluation of disease location by a complete investigation of the gastrointestinal tract (gastroscopy, colonoscopy, and small bowel radiography) within a maximum of 1 year before the index surgery; and ability to start oral nutrition (and, thus, oral medication) within the first 10 postoperative days **Exclusion:** Exclusion criteria included contraindications for use of mesalamine; pregnancy or intention of pregnancy within the next 18 months; nursing; short bowel syndrome; clinically significant lactase deficiency; any severe additional disease; diagnosis of primary sclerosing cholangitis; presence of an ileocolonic stoma; more than 3 surgeries preceding the index surgery; and failure to obtain informed consent **Age (IG1 / IG2) mean (SD):** 33.6 ± 10.1 overall; 33.5 ± 10.0 vs 33.8 ± 10.2 **Sex (M:F):** 156:162 overall; (71:81) vs (85:81) **Type of surgery:** radical - 244 (121/123); nonradical-75 (35/40) **Previous surgery (IG1+IG2): 18** (7/11) **Start of intervention after surgery:** ≤ 10 days **Medication use (IG1+ IG2):** Sulfasalazine- 190 (96/94); Metronidazole -32 (10/22); Immunosuppressants-18 (8/10);Corticosteroids-187 (86/101); TPN-35 (16/19) **Smoker (IG1 / IG2):** not reported **Number randomised (n = 324):** 154/170 **Number analysed (n = 318):** (152/154) vs (166/170) **Post-randomisation exclusion (n = 20)**: (7/154) vs (13/170); Lost to follow-up-14 (5 vs 9); did not start treatment-6 (2 vs 4)
Interventions	**Group 1:** 4 g mesalamine (Pentasa) per day divided into 3 doses (1.5, 1, and 1.5 g) or placebo. One tablet of Pentasa contains 500 mg encapsulated in ethylcellulose microgranules and pressed to form a tablet with microcrystalline cellulose **Group 2:** Placebo tablets of identical appearance and consistency containing additional microcrystalline cellulose to compensate for the mesalamine microgranules **All participants:** Corticosteroids were allowed to be tapered by standardized stepwise dose reductions within 6 weeks. Concomitant medication such as glucocorticoids with the exception of initial tapering, nonsteroidal anti-inflammatory drugs, immunosuppressive drugs, metronidazole, methotrexate, sulphasalazine, and other 5-aminosalicylates were not allowed. Symptomatic treatment with antidiarrhoeal, antacid, or spasmolytic medication was allowed but had to be thoroughly documented for calculation of the CDAI. Similarly, patients were requested to report precisely any other concomitant medication in their diary. Patients were supplied with study medication for the subsequent 3 months at each follow-up visit. Any tablets not used had to be returned. Mesalamine and acetylmesalamine were determined in blood samples drawn at each visit. Patients were considered noncompliant if medication was interrupted for a total of >10% of their individual trial course. Endoscopic evaluation of the colon and, if possible, of the anastomosis was recommended at 6 weeks and 18 months after surgery or at the time of clinical relapse

Lochs 2000 (*Continued*)

Outcomes	**Duration of study:** 18 months 1. **Endoscopic recurrence** defined as i ≥ 1 defined by Rutgeerts et al 2. **Clinical recurrence** defined by 1 of the following: increase in CDAI above 250; increase in CDAI above 200 but by a minimum of 60 points over the lowest postoperative value for 2 consecutive weeks, indication for surgery; development of a new fistula; and occurrence of a septic complication 3. **Adverse events** **4. Withdralwal due to adverse events**
Notes	**Funding source:** not reported **Conflict of interest:** Not reported **Power calculation**: Based on a maximum relapse rate with placebo of 50% and an absolute effect size of 15% with the active drug, a sample size of 150 patients per treatment group was calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization scheme was provided by the Institut fur Medizinische Dokumentation und Statistik at the University of Koln at the beginning of the trial and forwarded to the Department of Galenics at Ferring A/S, Denmark. Randomization was performed in blocks of 10 for each of the participating centers" Comment: Computer generated random sequence
Allocation concealment (selection bias)	Unclear risk	Quote: " "In addition, each center retained sealed opaque envelopes containing patient numbers and treatment allocations, which were only allowed to be opened in case of a serious adverse event that necessitated disclosure of the type of treatment" Comment: Unclear whether envelops were sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo tablets of identical appearance and consistency contained additional microcrystalline cellulose to compensate for the mesalamine microgranules.. . All patients and investigators were blinded regarding treatment allocation" Comment: Placebo blinded

Lochs 2000 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization was performed in blocks of 10 for each of the participating centers. This information was kept confidential at the Department of Quality Assessment at Ferring and the statistical center in Cologne and was only available to the Department of Galenics [...] An Endpoint Committee consisting of 2 physicians and 1 surgeon, not participating in the trial, made a final decision about questionable cases of protocol violations and relapses" Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotes: "Outcome measures were analyzed in all randomized patients who had taken at least 1 dose of study medication (intention-to-treat population)" Comment: Attrition rates and reasons were balanced across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all outcomes stated in the method section reported
Other bias	Low risk	Quote: "No significant differences were detected between the 2 treatment groups for any of the parameters investigated" Comment: Groups well balanced at baseline. No additional sources of bias detected

McLeod 1995

Methods	**Study design:** RCT, multicentre **Setting:** Canada; 1986-1993
Participants	**Inclusion:** All patients who had undergone a surgical resection for Crohn's disease at one of the participating hospitals and who had no gross residual disease were eligible for entry provided they were randomized within 8 weeks of the date of surgery **Exclusion:** Patients with residual Crohn's disease (including gastroduodenal Crohn's disease) with the exception of asymptomatic anal skin tags or anal stenosis; abnormal renal function with a serum creatinine level >130 μmol/dL or 1.5 mg/dL; if they were taking prednisone, sulphasalazine, metronidazole, or imuran and these drugs could not be discontinued **Age (IG1 / IG2) mean (SD):** 38.0 ± 13.1 overall; 38.9 ± 13.1 vs 38.9 ± 13.2 **Sex (M:F):** 98:65 overall; (49:38) vs (49:27) **Type of surgery:** Small bowel resection-15(8/7); Terminal ileal/ileocolic resection-109 (59/ 50); Segmental colon resection- 7 (7/0); Total abdominal colectomy-3 (1/2); Proctocolectomy-25 (13/12);Proctectomy-10 (3/7)

	Previous surgery (IG1+IG2): 179 surgical resections performed in the 163 patients **Start of intervention after surgery:** ≤ 8 week **Medication use (IG1+ IG2):** not reported **Smoker (IG1 / IG2):** not reported **Number randomised (n = 169):** 88/81 **Number analysed (n = 163):** (87/88) vs (76/81) **Post-randomisation exclusion (n = 21)**: (8/88) vs (13/81); Randomised but did not give consent-6 (1 vs 5); refused follow-up because of personal reason-11; death of multiple myeloma-1; moved to Europe - 1; bowel resection (suspected Crohn's disease, but resected specimen was pathologically normal) -2 [reasons not reported separately]
Interventions	**Group 1:** 3 g/ day of mesalamine taken as six 250-mg tablets twice daily **Group 2:** six identical-looking placebo tablets twice daily **All participants:** Study medication was mailed to the patient every 3 months. At 3-month intervals, all patients were interviewed by telephone by a research nurse to determine their clinical status, ensure they were not taking any other prescribed medications, and assess their compliance. At yearly intervals, all subjects were assessed by an investigator and appropriate radiological or endoscopic investigations performed. If endoscopy could not be performed, then an air contrast barium enema or ileostomy injection was performed. Once patients were judged to have symptoms caused by Crohn's disease that required treatment and there was radiographic or endoscopic confirmation of disease, they were considered a failure. Further treatment was at the discretion of their attending physician or surgeon. Compliance was determined by questioning the subjects and by pill counts of all medication returned at the annual visit
Outcomes	**Duration of study:** follow-up period 72 months max 1. **Symptomatic Recurrence** defined as symptoms compatible with Crohn's disease that were severe enough to warrant treatment in the opinion of the investigator plus radiological or endoscopic evidence of disease using the criteria outlined criteria (at least one of the following features had to be present to make the diagnosis of recurrent disease: aphthous ulcers; longitudinal or punched out ulcers; cobblestoning or nodularity of the bowel; stricture of the bowel associated with edema, ulceration, or erythema of the mucosa; pseudopolyps; or mucosal bridging) 2. **Endoscopic and radiologic relapse rate d**efined as the presence of endoscopic or radiological evidence of disease and included both asymptomatic and symptomatic patients. At least one of the following features had to be present to make the diagnosis of recurrent disease: aphthous ulcers; longitudinal or punched out ulcers; cobblestoning or nodularity of the bowel; stricture of the bowel associated with edema, ulceration, or erythema of the mucosa; pseudopolyps; or mucosal bridging. a septic complication 3. **Adverse events** **4. Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: Based on a review of retrospective studies in the literature, it was estimated that the symptomatic recurrence rate in the control group would be 12.5% per year. Using a sample size calculation based on survival analysis for two independent groups with censoring, it was estimated that 178 patients would have to be accrued during a period of 3 years and followed up for a maximum of 6 years to detect a 50%

	decrease in recurrence (6.25% per year) in the treatment group with a one-tail 06 of 0. 05 and power of 0.80

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ""The randomization scheme was computer generated by the Clinical Research Support Unit, University of Toronto, and maintained by the pharmacies at the Toronto Hospital, General Division, and St. Mary's Hospital, Rochester" Comment: Computer generated random sequence
Allocation concealment (selection bias)	Low risk	Quote:"All investigators and patients were blinded with respect to treatment allocation" Comment: No further details provided, however, author contacted 27 November 2009 and confirmed that central allocation was used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Subjects in the control group took six identical-looking placebo tablets twice daily" Comment:Patients and investigators were blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"All patient records were reviewed by an adjudication committee of five investigators (R.S.M., B.G.W., A.H.S., P.W.C., and K.O.) blinded to patient treatment allocation." And "The charts of patients who were noncompliant were reviewed by two blinded gastroenterologists (A.H.S. and P. W.C.), who determined whether noncompliance was secondary to adverse effects potentially related to the medication" Comment:Blinding of assessors performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were low and reasons for withdrawal were balanced across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all outcomes stated in method section reported

McLeod 1995 (*Continued*)

Other bias	Low risk	Quote: "The characteristics of the two groups, which are listed in Table 1, were similar" Comment:Groups balanced at baseline. No other apparent sources of bias detected

Reinisch 2010

Methods	**Study design:** RCT, multicentre **Setting:** Austria, the Czech Republic, Germany and Israel ; 21 centers, 2002-2007
Participants	**Inclusion:** Male or female patients aged 18-70 years with a diagnosis of CD confirmed by endoscopy and histology were eligible for screening if they had (1) undergone resection of the terminal ileum and partial colectomy with ileocolonic resection for complications of ileal CD with construction of an ileocolonic anastomosis in the preceding 6-24 months; (2) not experienced clinical recurrence due to CD since resection; and (3) a Crohn's disease activity index (CDAI) score <200 in the preceding 1-2 weeks. Patients with moderate endoscopic recurrence (Rutgeerts grade i2a: >5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions) or severe endoscopic recurrence (i3-i4: diffuse aphthous ileitis with diffusely inflamed mucosa, or diffuse inflammation with larger ulcers, nodules and/or narrowing) were recruited into the study **Exclusion:** Patients with a short bowel syndrome, an ileocolonic stoma, a thiopurine methyltransferase genotype, patients who had received treatment with immunosuppressant agents (methotrexate, ciclosporin, 6-MP, azathioprine or 6-thioguanine (6-TG) or anti-tumour necrosis factor a (TFNa) since resection, corticosteroids or oral antibiotics (e.g. metronidazole or ciprofloxacin) for >4 weeks since resection, non-steroidal anti-inflammatory drugs (NSAIDs) within the preceding 2 weeks (other than paracetamol or low-dose acetylsalicylic acid); patients who currently had strictureplasty (unless the present stricture plasty macroscopically showed no inflammation at the time of the index operation) or had serum creatinine >130 μmol/l. Patients were excluded if endoscopy revealed no lesions (grade i0), <5 aphthous lesions (grade i1) and/or if lesions were confined to the ileocolonic anastomosis (i.e. <1 cm long) (grade i2b). Patients in the latter category (grade i2b) were excluded since this presentation is associated with a lower risk of clinical recurrence **Age (IG1 / IG2) mean:** 35.8 ± 12.08 overall; 35.5 ± 13.6 vs 36.0 ± 10.7 **Sex (M:F):** 44: 34 overall; (24:17) vs (20/17) **Type of surgery:** Not reported **Previous surgery (IG1+IG2):** 1 or 2 surgeries-114 (63/51)); >2 surgeries -12 (4/8) **Start of intervention after surgery:** 6-24 months **Medication use (IG1+ IG2):** Mesalazine - 54 (28/26); Sulfasalazine- 5 (4/1); Budesonide- 22 (9/13); Corticosteroids- 39 (23/16); Azathioprine- 14 (6/8); Infliximab-3 (2/1); Other - 12 (6/6) **Smoker (IG1 / IG2):** 37 (17/20) **Number randomised (n = 78):** 41/37 **Number analysed (n = 78):** (41/41) vs (37/37) **Post-randomisation exclusion (n = 9)**: (4/41) vs (5/37) ; Lack of cooperation-7 (4 vs 3); lack of efficacy-2 (0 vs 2)

Reinisch 2010 (*Continued*)

Interventions	**Group 1:** Azathioprine 2.0 - 2.5 mg/kg/day (Azafalk 50 mg tablets) + placebo mesalazine tablets **Group 2:** Mesalazine 4 g/ day (Eudragit L-coated 500 mg tablets (Salofalk)) + placebo azathioprine tablets **All participants:** Medications prohibited during the study: immunosuppressants other than study drug, allopurinol, oxipurinol or thiopurinol, azathioprine-containing or mesalazine containing drugs other than study drug, anti-TNFa therapy, oral antibiotics for >4 weeks or more than three cycles of 2 weeks, NSAIDs for >2 weeks, corticosteroids and cimetidine
Outcomes	**Duration of study:** 52 weeks 1. **Therapeutic failure (Clinical relapse)** defined as CDAI score ≥200 and an increase of ≥60 points from baseline or study drug discontinuation due to lack of efficacy or an intolerable adverse drug reaction 2. **Endoscopic recurrence** defined by endoscopic Rutgeerts score ≥i2 only (endoscopic recurrence data were excluded from the analysis as the inclusion criteria suggest that people with moderate to severe endoscopic relapse were included) 3. **Health-related quality of life** based on IBDQ score at 12 months 4. **Adverse events** **5. Clinical recurrence follow-up** defined as a Rutgeerts score between i2-i4 within 24 months after the 1-year treatment
Notes	**Funding source:** Dr Falk Pharma GmbH, Freiburg, Germany **Conflict of interest:** WR has received an unrestricted grant from Dr. Falk Pharma. EFS and KRH have received speaker's honoraria. KD, RG and RM are employees of Dr. Falk Pharma. SA, WP, OS, ML, SB-M, AT, ES and MS have no conflicts of interest to declare. In part, AT, ES and MS are supported by the Robert Bosch Foundation, Stuttgart, Germany **Power calculation:** The sample size calculation for the primary end point estimated that 62 evaluable patients (31 per treatment arm) were needed to have 80% power to detect a difference of 35% in favour of azathioprine versus mesalazine for the reduction in the 1 year therapeutic failure rate (one-sided α = 0.025). To allow for non-evaluable patients, a population size of 76 patients (38 per treatment arm) was planned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "..a central randomisation was performed via five computer-generated randomisation lists (using the program 'Rancode +' (version 3.6) of IDV, Gauting, Germany), which were generated for the five body weight classes (40-50 kg, 51-60 kg, 61-75 kg, 76-100 kg and 101-128 kg), each in blocks of four, with medication distributed to each centre according to this list"

Reinisch 2010 (*Continued*)

		Comment: Centralised randomisation in blocks of 4
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To maintain investigator and patient blinding, patients randomised to azathioprine received verum azathioprine tablets and placebo mesalazine tablets; those randomised to mesalazine received verum mesalazine tablets and placebo azathioprine tablets" Comment: a double-blind, double-dummy RCT
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The intention-to-treat (ITT) population was defined as all randomised patients who received 1 dose of study medication" Comment:The intention-to-treat (ITT) population was defined as all randomised patients who received 1 dose of study medication
Selective reporting (reporting bias)	Low risk	Trial registration available (NCT00946946) and all prespecified outcomes were reported
Other bias	Low risk	Quote: "Baseline characteristics were similar between treatment groups apart from a lower mean CDAI value in the azathioprine cohort (70 vs 102 in the mesalazine arm) and a higher proportion of azathioprine patients with a penetrating disease behaviour (66% vs 43%)" Comment: Some differences at baseline; study supported by Falk Pharma but conflict of interest declared. No other apparent sources of bias detected

Savarino 2013

Methods	**Study design:** RCT, single **Setting:** Italy; University Hospital of Genoa; 2008-2010
Participants	**Inclusion:** Adult patients with ileal or ileocolonic CD within 4 weeks of resection of macroscopically diseased bowel with anastomosis between normal ileum and colon **Exclusion:** Patients with (i) more than 10 years of CD requiring first resective surgery for short (10 cm) fibrostenotic stricture, (ii) macroscopically active disease not resected at the time of surgery, and (iii) presence of a stoma **Age (IG1 / IG2) median (range):** not reported, overall >18; 45 (22 - 66) vs 46 (25 - 65) **Sex (M:F):** 25:26 overall; (8:8) vs (9:8) vs (8:10) **Type of surgery:** Not reported **Previous surgery (IG1+IG2):** one-40 (12/15/13); two-9 (3/2/4); three-2 (1/0/1) **Start of intervention after surgery:** 2-4 weeks **Medication use (IG1+ IG2):** Not reported **Smoker (IG1 / IG2):** 19 (9/4/6) **Number randomised (n = 51):** 16/17/18 **Number analysed (n = 78):** (16/16) vs (17/17) vs (18/18) **Post-randomisation exclusion (n = 5)**: (1/16) vs (2/17) vs (2/18) (unclear)
Interventions	**Group 1:** Adalimumab subcutaneous injections 160 / 80 mg at 0 and 2 weeks, followed by 40 mg every 2 weeks for 2 years **Group 2:** Azathioprine (Azafor, Sofar S.P.A., Milan, Italy), at the dose of 2 mg / kg every day for 2 years **Group 3:** Mesalamine (Pentasa, Ferring S.P.A., Milan, Italy), at the dose of 3 g / day divided in 3 doses for 2 years **All participants:** Patients on antibiotics or immunomodulators at entry into the study discontinued these medications 12 weeks before surgery. Continuous use of nonsteroidal anti-inflammatory drugs was not allowed during the study. No other medications were prescribed except for occasional tablets of paracetamol or tramadol. Patients were subjected to endoscopy at 12 and 24 months; small bowel enteroclysis or magnetic resonance imaging at 12 and 24 months; physical examination with interviews, together with an extensive battery of blood tests weekly for the first 4 weeks and then every 2 months, and completed an IBD-Q at 1 month before surgery and at 12 and 24 months aft er surgery. The CDAI was determined at each study visit. In addition, adverse events were ascertained at each visit
Outcomes	**Duration of study:** 2 years 1. **Clinical recurrence** d defined as a score of ≥ 2 on the clinical recurrence grading scale 1-4 proposed by Hanauer et al 2. **Clinical recurrence** based on CD activity index (CDAI) was calculated for each patient and recurrence was set in case of a score > 200, whereas clinical remission was defined by a CDAI score of < 150 2. **Endoscopic recurrence** defined by a Rutgeerts score of ≥ i2 3. **Radiologic recurrence** defined as a score of ≥ 2 on the radiographic recurrence grading scale (where 1 indicates normal; 2, mucosal edema / aphthoid ulcers; 3, linear ulcers / cobblestoning; and 4, strictures / fistulas / inflammatory mass) 4. **Health-related quality of life** 5. **Median Lémann Index** 5. **Adverse events**

Notes	**Funding source:** Supported by research funds of the university **Conflict of interest:** Authors declare no conflict of interest **Power calculation**: We considered reasonable to hypothesize an endoscopic recurrence rate of ~ 80% and 15% and a clinical recurrence rate of ~ 65% and 5% for the mesalamine and adalimumab groups, respectively, at 2 years of follow-up. This estimation has been supported by the results shown in previous trials on postoperative CD relapse. Thus, based on these data, 13 patients per treatment group resulted to be sufficient to detect a difference of at least 65 % for endoscopic recurrence and 60 % for clinical recurrence in favour of the adalimumab group with a power of 80 % (global type I error of 5 %). Th e number of patients in each group was increased to 16 to compensate for an anticipated dropout rate of 15%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible and consenting patients were assigned randomly using a computer-generated sequence (www. randomizer.org) to a regimen of…" Comment: Computer generated random sequence
Allocation concealment (selection bias)	Low risk	Quote: "Patient allocation was concealed and performed by an independent nurse not involved with the trial" Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study is open-label design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: ""A blinded investigator (P.D.) reviewed each patient's video-recorded procedure and provided a separate endoscopic score" and "At the conclusion of the study, the principal investigator (E.S.) re-scored each patient by re-reviewing the video recordings in a random and blinded manner" Comment: Assessors were blinded for endoscopic assessments only. However, no information on clinical assessment of relapse
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Statistical analysis was conducted according to the intention-to-treat principle." Comment: ITT analysis applied. Withdrawals and reasons reported

Savarino 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all outcomes stated in the method section reported
Other bias	Low risk	Quote: "Characteristics were similar for sex, age, smoking, duration of CD, disease behavior, disease location, prior medication exposure, including IFX, and prior surgical resection." Comment: Groups well balanced at baseline; no other apparent sources of bias detected

Sutherland 1997

Methods	**Study design:** RCT, multicentre **Setting:** Italy; University Hospital of Genoa; 2008-2010
Participants	**Inclusion:** Adult patients (18+) with ileal or ileocolonic CD CD location restrictions not mentioned. CD in remission for 1 month, but at least 2 flare-ups within the last 4 years, one within the last 18 months or a recent resection. Remission defined as CDAI<150 at baseline and no symptoms within last 30 days. No steroid use within a month of study **Exclusion:** CDAI >150; previous total proctocolectomy, short-bowel syndrome, more than 3 resections within 10 years, chronic perianal disease, ulcer colitis, stool positive for pathogens, parasites or toxins; drug or alcohol abuse, clinically significant hepatic neurological, endocrine, renal, or other major systemic disease that would make implementation or interpretation of the protocol or results difficult; any history of cancer, allergy to aspirin or Mesalamine; patients on immunosuppressants therapy within last 90 days, or corticosteroids within last 30 days or Mesalamine/metronidazole within last 7 days before resection **Age (IG1 / IG2) mean (±SE):** 36.5 (0.7) overall; 29.7 (1.1) vs 29.0 (1.0) **Sex (M:F):** 106:140 overall; (48:70) vs (58:70) **Type of surgery:** not reported **Previous surgery (IG1+IG2):** not reported **Start of intervention after surgery:** 2-4 weeks **Medication use (IG1+ IG2):** Not reported **Smoker (IG1 / IG2):** not reported **Number randomised (n = 66):** 31/35 (total number of randomised is 293 of which 180 have medically induced remission and 66 with surgically-induced remission; data presented for the later only) **Number analysed (n = 66):** (31/31) vs (35/35) **Post-randomisation exclusion (n = 7)**: not presented separately for patients with surgical remission
Interventions	**Group 1:** 3 capsules of 250 mg Mesalamine 4 times a day **Group 2:** 3 capsules of 250 mg Placebo 3g/day for 4 times a day **All participants:** No steroid, other mesalamine preparations, aspirin or other nonsteroidal anti-inflammatory drugs; immunosuppressives, narcotics except codeine or lop-

	eradime, antibiotics for longer than 14 days
Outcomes	**Duration of study:** 12 months 1. **Clinical recurrence** defined as first occurrence of a CDAI that was >150 as well as the absolute value of at least 60 points higher than baseline or where physician diagnosed a flare-up of disease but a full diary card was not available for the calculation of the final CDAI
Notes	**Funding source:** supported by research funds of the university **Conflict of interest:** Authors declare no conflict of interest **Power calculation**: It was hypothesized that the relapse rate for mesalamine-treated patients would be 25%. Assuming an α of 0.05 and a β of 0.20 (power of 0.80), a two-tailed sample size calculation determined that 150 patients were required for each treatment group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed according to a computer generated randomisation scheme by the study sponsor Comment: Computer generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Quote:"For each patient, the identity of the study medication was concealed in an individual sealed envelope sent with the drug supplies" "Medication was packaged by the sponsor and dispensed to each centre on coded identical-appearing boxes" Comment: sequentially numbered drug packages of identical appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Medication was packaged by the sponsor and dispensed to each centre on coded identical-appearing boxes" Comment: double blinded placebo controlled trial. Probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates were not specifically reported for the sub-population of interest in our review (surgical group)

Sutherland 1997 (*Continued*)

Selective reporting (reporting bias)	Low risk	Although adverse event data were not available for the sub-population of interest in our review (surgical group), all expected outcomes appear to have been reported for the entire population
Other bias	Low risk	The demographic characteristics and disease milestones for the patients are shown in Table 2. There were no significant differences between the mesalamine and placebo treated groups.Supported by a grant by Marrion Merrill Dow. Author contacted and confirmed company had no part in the design, analysis or write up

Wenckert 1978

Methods	**Study design:** RCT, multicentre **Setting:** Sweden and Denmark
Participants	**Inclusion:** No age restrictions mentioned. CD of small and / or large bowel, first resection and supporting histological evidence of active CD in resected specimens. ESR had to return to normal within 6 weeks of operation, no further remission criteria defined. No steroid use allowed **Exclusion:**Treatment with a by-pass, doubtful diagnosis, allergy on salazopyrin or acetylsalicylic acid, abnormal ESR 6 weeks after operation, lack of cooperation, treatment with corticosteroids or immunosuppressive drugs **Age (IG1 / IG2) median:** 24.5 overall **Sex (M:F):** 33:33 overall **Type of surgery:** Not reported **Previous surgery (IG1+IG2):** n/a **Start of intervention after surgery:** 2-4 weeks **Medication use (IG1+ IG2):** Not reported **Smoker (IG1 / IG2):** Not reported **Number randomised (n = 66):** 32/34 **Number analysed (n = 66):** (32/32) vs (34/34) **Post-randomisation exclusion (n = 4/66)**: (2/32) vs (2/36)
Interventions	**Group 1:** Salazopyrin 3 g/day for 18 months **Group 2:** placebo 3 g/day for 18 months **All participants:** Other specific treatment was avoided. Relapse free patients were observed for 24 months
Outcomes	**1. Relapse** was defined clinically, based on the information from special control charts on the presence/absence of fever, diarrhoea, rectal bleeding, abdominal pain, extra-intestinal manifestations, palpable abdominal masses, fistulae, abscesses and possible loss of working days. The relapses were not based on index calculation

Wenckert 1978 (*Continued*)

Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The experimental design was double blind multicentre trial with block-randomisation, and no cross-over." Comment: insufficient data to make judgement. However, author contacted and confirmed that block randomisation described was carried out in accordance with established acceptable randomisation methodology
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient data to make judgement The author was contacted, but was not able to give further details on this issue
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient data to make judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient data to make judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for those missing, balanced between study groups, reasons for withdrawal unlikely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	The study includes results for adverse events, but these are not reported clearly enough to allow analysis and permit a judgement as to the risk of bias to be made
Other bias	Unclear risk	Insufficient information to ascertain whether baseline characteristics were balanced

ADA: Adalimumab;AZA; Azathioprine;CD: Crohn's disease; CDAI: Crohn's disease activity index; cm: centimetre;dL; decilitre; ESR: erythrocyte sedimentation rate; F: female; g: gram; IFX: Infliximab; ITT: intention-to-treat; IBDQ: inflammatory bowel disease questionnaire; IG; intervention group; kg: kilogram; L; litres; M: male; MES; mesala(m/z)ine; mg: miligram; m: month; SD: standard deviation SE: standard error; μmol: micromole; y: years

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dumois 2001	Not randomised controlled trial - comment on already published trial
Ewe 1981	Not randomised controlled trial
ISRCTN84003996	Wrong population - medically-induced not surgically-induced remission
McLeod 1997	Not randomised controlled trial; non-randomised follow-up of included study
NCT00225810	Wrong population - active disease
NCT00245505	Study terminated due to lack of eligible participants
NCT00300118	Wrong population - active disease
NCT01696942	Terminated, lack of accrual
Orlando 2012	Not a randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00976690

Methods	RCT
Participants	Adults (> 18 years) with Crohn's disease who had ileocolonic or colon resection 21 days before inclusion, must have clinical remission at inclusion (CDAI < 150) Resection > 50 cm or subtotal colectomy with ileorectal anastomosis
Interventions	Azathioprine : 2 mg/kg/day Mesalazine : 4 g/day
Outcomes	Clinical and endoscopic recurrence at 12 and 24 months
Notes	Study completed, authors were contacted, report in preparation for publication

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. 5-ASA versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse events at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Withdrawals due to adverse events at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. 5-ASA versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse at 48 weeks to 72 months	5	730	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.72, 0.96]
2 Endoscopic recurrence at 12 weeks to 72 months	3	537	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.56, 1.24]
3 Adverse events at 12 weeks to 72 months	4	466	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.60, 1.91]
4 Serious adverse events at 48 weeks to 72 months	3	577	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.44, 2.59]
5 Withdrawal due to adverse events at 12 weeks to 72 months	3	297	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.71, 3.19]

Comparison 3. High versus low dose 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Endoscopic recurrence at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse events at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events leading to withdrawal at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 4. 5-ASA versus purine antimetabolites

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse at 24 months	4	347	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
2 Endoscopic recurrence at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Radiologic relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Surgical relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Adverse events at 52 weeks to 24 months	5	425	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.97, 1.27]
6 Serious adverse events at 52 weeks to 24 months	3	311	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.11, 0.80]
7 Withdrawal due to adverse events at 52 weeks to 24 months	5	425	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.28, 0.83]
8 HRQoL (IBDQ score >170 at 24 months)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 HRQoL (mean IBDQ score change at 52 weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 5. 5-ASA versus anti TNF-

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Endoscopic recurrence at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Radiologic relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Withdrawal due to adverse events at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 HRQoL (IBDQ >170)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 6. Sulphasalazine versus placebo

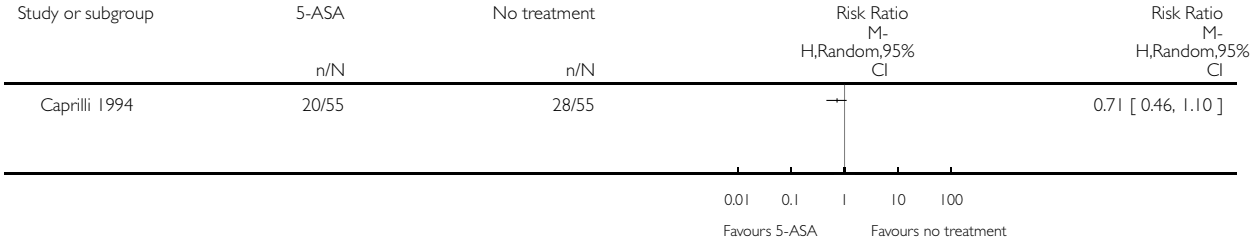
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse at 18 to 36 months	2	298	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.56, 1.38]
2 Withdrawal due to adverse events at 18 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 5-ASA versus no treatment, Outcome 1 Clinical relapse at 12 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 1 5-ASA versus no treatment

Outcome: 1 Clinical relapse at 12 months

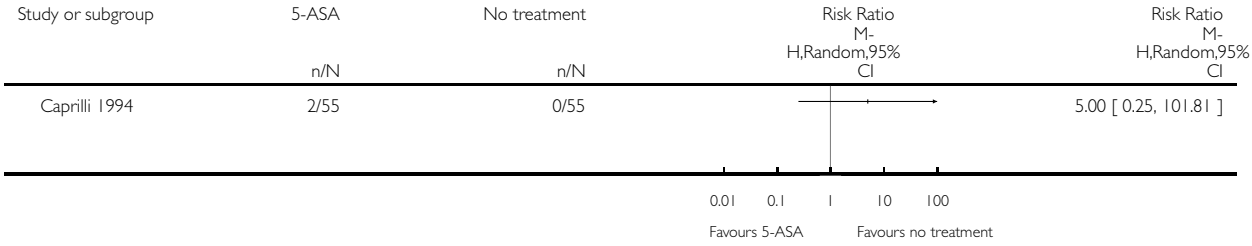


Analysis 1.2. Comparison 1 5-ASA versus no treatment, Outcome 2 Adverse events at 12 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 1 5-ASA versus no treatment

Outcome: 2 Adverse events at 12 months

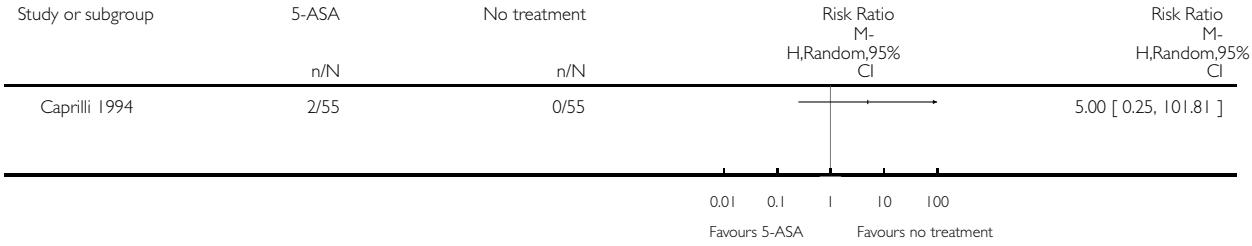


Analysis 1.3. Comparison 1 5-ASA versus no treatment, Outcome 3 Withdrawals due to adverse events at 12 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 1 5-ASA versus no treatment

Outcome: 3 Withdrawals due to adverse events at 12 months

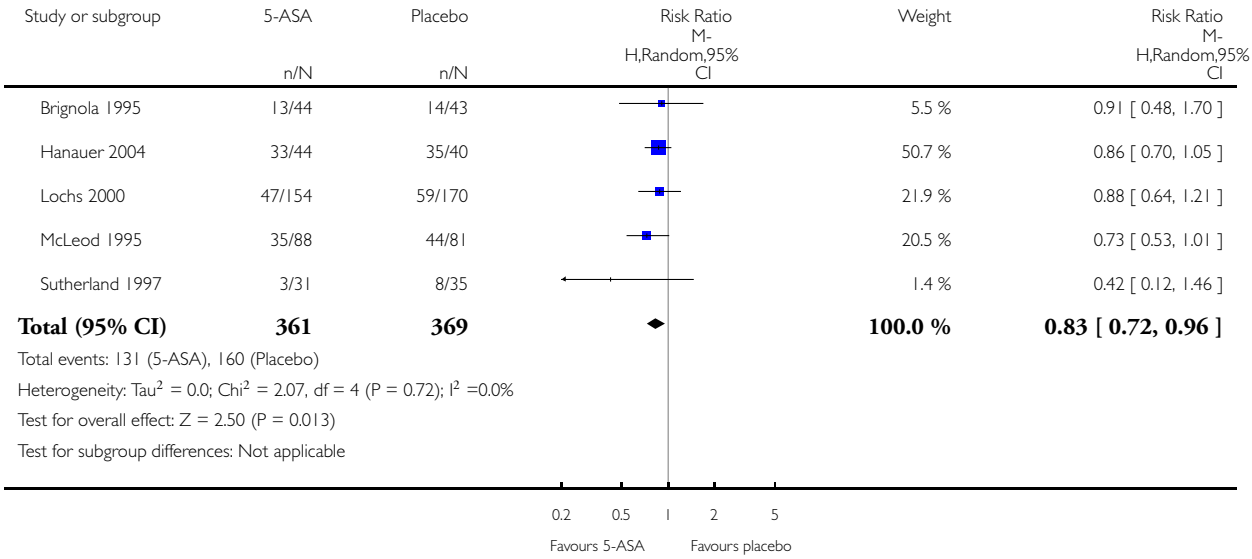


Analysis 2.1. Comparison 2 5-ASA versus placebo, Outcome 1 Clinical relapse at 48 weeks to 72 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 2 5-ASA versus placebo

Outcome: 1 Clinical relapse at 48 weeks to 72 months



Analysis 2.2. Comparison 2 5-ASA versus placebo, Outcome 2 Endoscopic recurrence at 12 weeks to 72 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 2 5-ASA versus placebo

Outcome: 2 Endoscopic recurrence at 12 weeks to 72 months

Study or subgroup	5-ASA n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brignola 1995	12/44	25/43		23.5 %	0.47 [0.27, 0.81]
Florent 1996	38/65	40/61		35.2 %	0.89 [0.68, 1.17]
Lochs 2000	133/154	134/170		41.3 %	1.10 [0.99, 1.21]
Total (95% CI)	**263**	**274**		**100.0 %**	**0.83 [0.56, 1.24]**

Total events: 183 (5-ASA), 199 (Placebo)

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 12.85$, df = 2 (P = 0.002); $I^2 = 84\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 5-ASA versus placebo, Outcome 3 Adverse events at 12 weeks to 72 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 2 5-ASA versus placebo

Outcome: 3 Adverse events at 12 weeks to 72 months

Study or subgroup	5-ASA n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brignola 1995	5/44	3/43		18.1 %	1.63 [0.41, 6.40]
Florent 1996	5/65	3/61		17.6 %	1.56 [0.39, 6.27]
Hanauer 2004	6/44	4/40		23.9 %	1.36 [0.41, 4.48]
McLeod 1995	7/88	10/81		40.3 %	0.64 [0.26, 1.61]
Total (95% CI)	**241**	**225**		**100.0 %**	**1.07 [0.60, 1.91]**

Total events: 23 (5-ASA), 20 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.98$, df = 3 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 0.22 (P = 0.83)

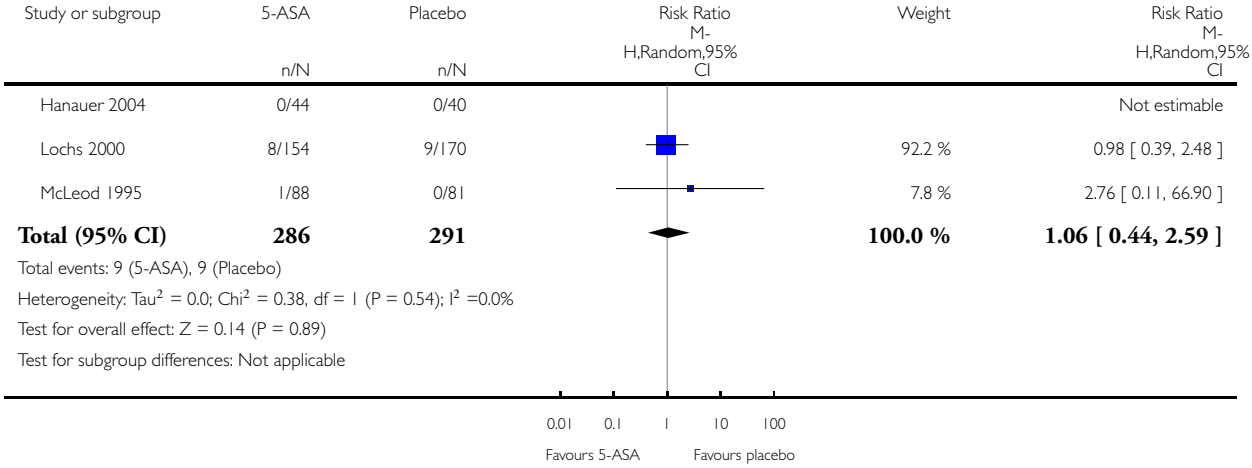
Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 5-ASA versus placebo, Outcome 4 Serious adverse events at 48 weeks to 72 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 2 5-ASA versus placebo

Outcome: 4 Serious adverse events at 48 weeks to 72 months

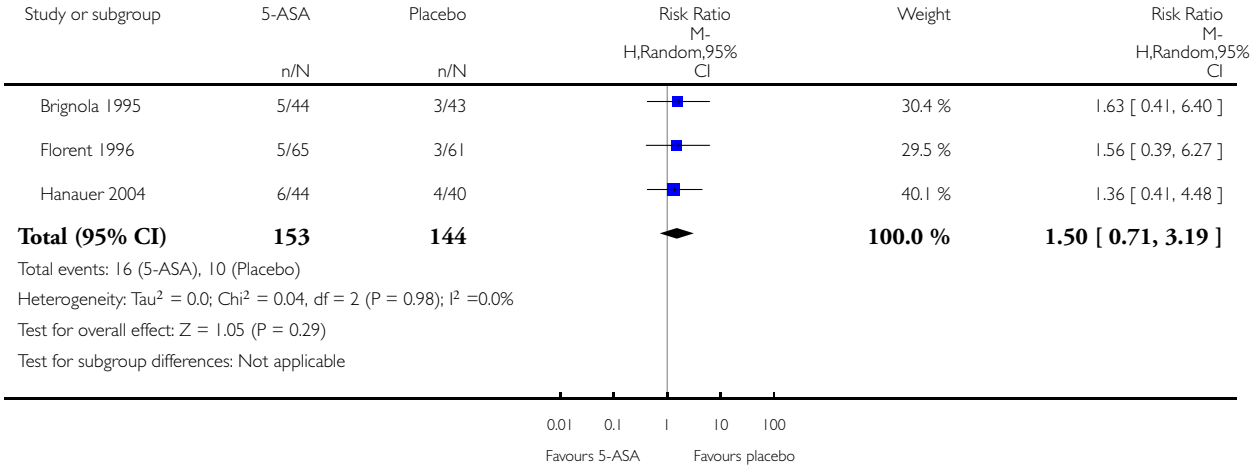


Analysis 2.5. Comparison 2 5-ASA versus placebo, Outcome 5 Withdrawal due to adverse events at 12 weeks to 72 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 2 5-ASA versus placebo

Outcome: 5 Withdrawal due to adverse events at 12 weeks to 72 months

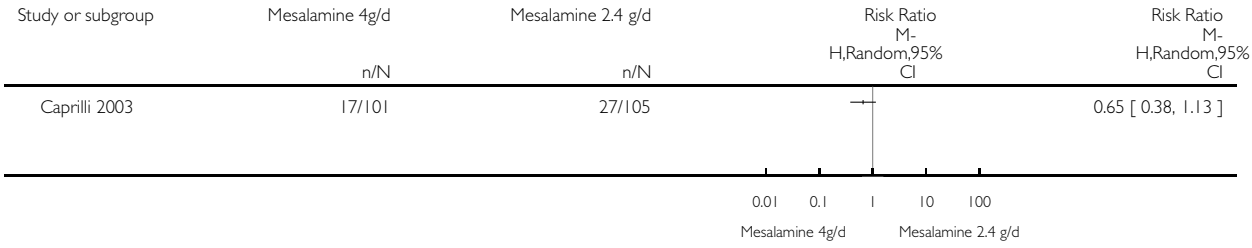


Analysis 3.1. Comparison 3 High versus low dose 5-ASA, Outcome 1 Clinical relapse at 12 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 3 High versus low dose 5-ASA

Outcome: 1 Clinical relapse at 12 months

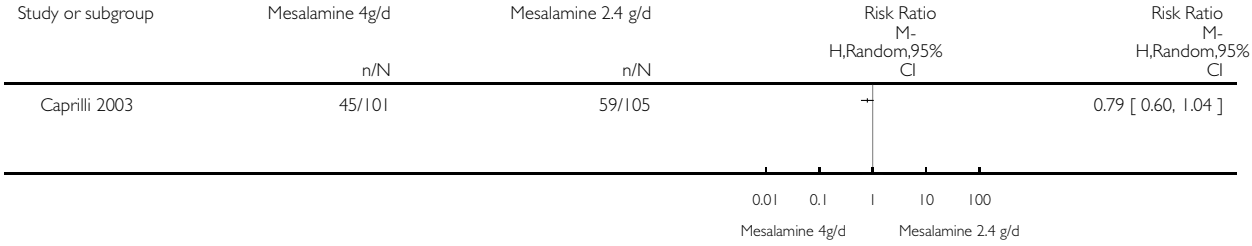


Analysis 3.2. Comparison 3 High versus low dose 5-ASA, Outcome 2 Endoscopic recurrence at 12 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 3 High versus low dose 5-ASA

Outcome: 2 Endoscopic recurrence at 12 months

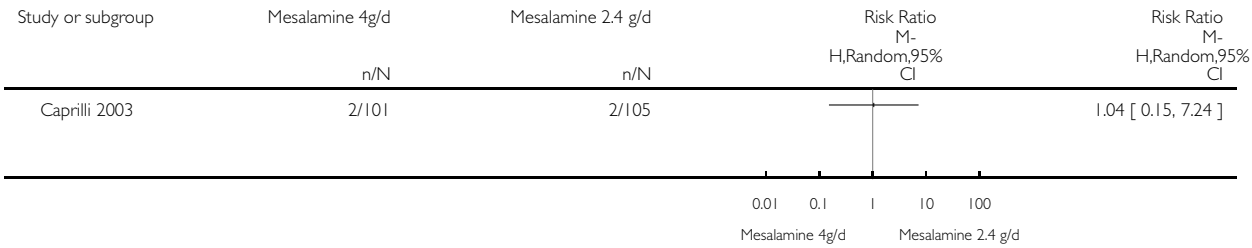


Analysis 3.3. Comparison 3 High versus low dose 5-ASA, Outcome 3 Adverse events at 12 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 3 High versus low dose 5-ASA

Outcome: 3 Adverse events at 12 months

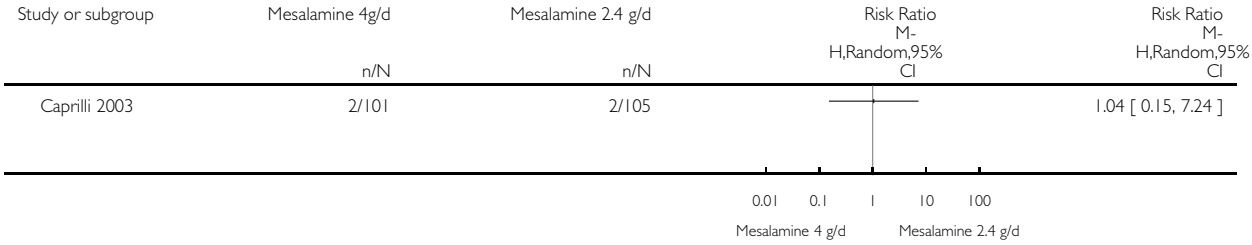


Analysis 3.4. Comparison 3 High versus low dose 5-ASA, Outcome 4 Adverse events leading to withdrawal at 12 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 3 High versus low dose 5-ASA

Outcome: 4 Adverse events leading to withdrawal at 12 months

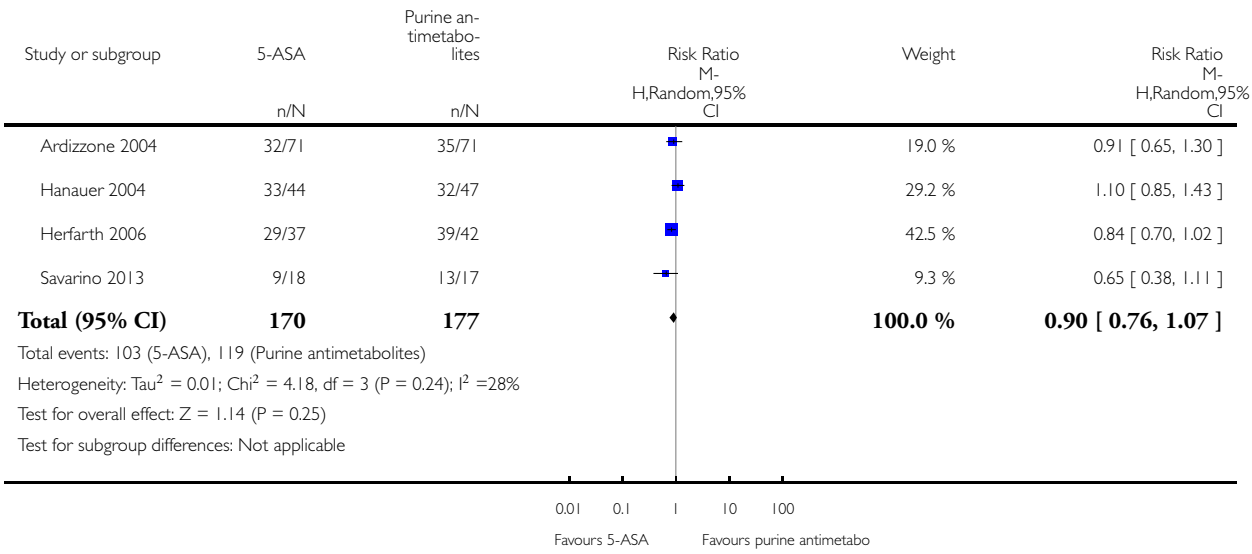


Analysis 4.1. Comparison 4 5-ASA versus purine antimetabolites, Outcome 1 Clinical relapse at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 1 Clinical relapse at 24 months

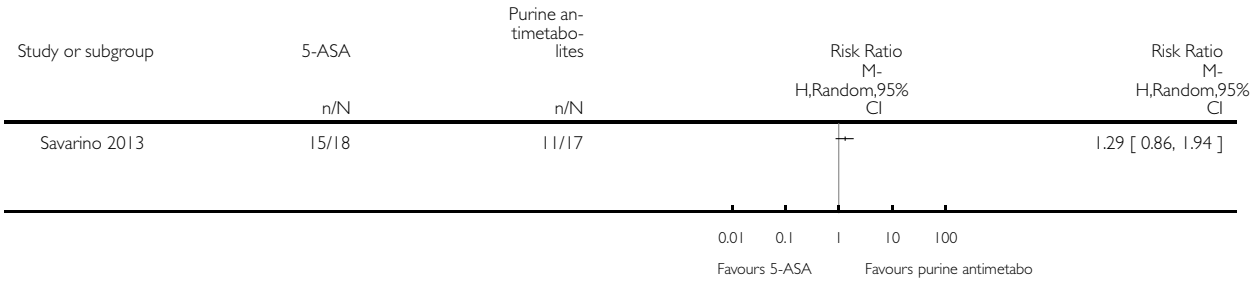


Analysis 4.2. Comparison 4 5-ASA versus purine antimetabolites, Outcome 2 Endoscopic recurrence at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 2 Endoscopic recurrence at 24 months

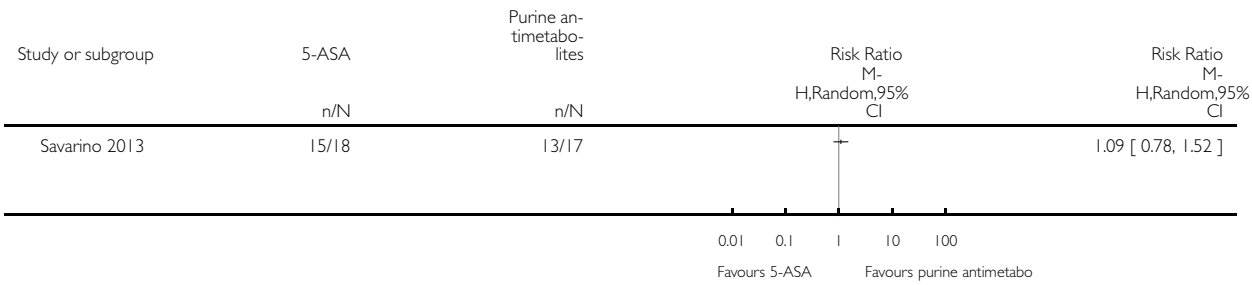


Analysis 4.3. Comparison 4 5-ASA versus purine antimetabolites, Outcome 3 Radiologic relapse at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 3 Radiologic relapse at 24 months

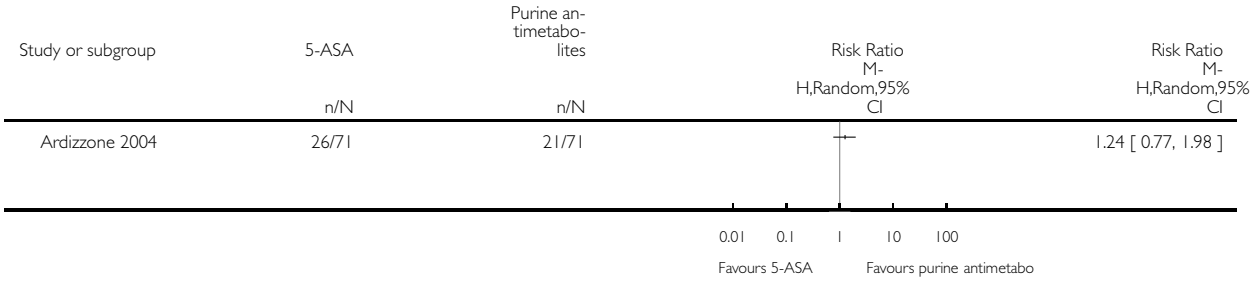


Analysis 4.4. Comparison 4 5-ASA versus purine antimetabolites, Outcome 4 Surgical relapse at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 4 Surgical relapse at 24 months

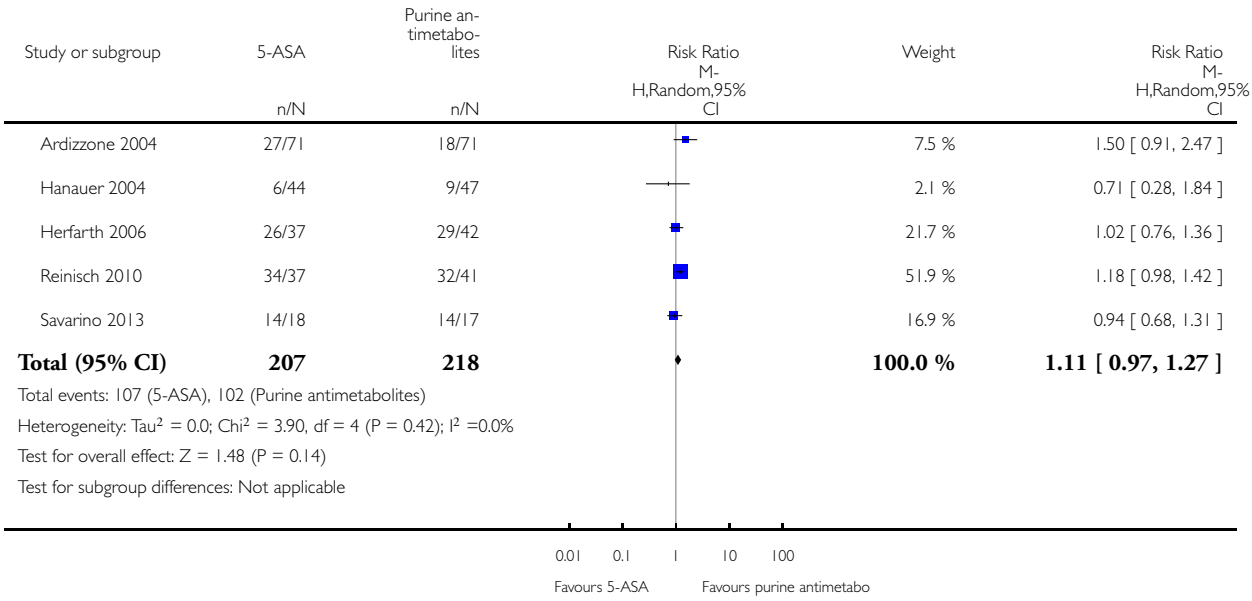


Analysis 4.5. Comparison 4 5-ASA versus purine antimetabolites, Outcome 5 Adverse events at 52 weeks to 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 5 Adverse events at 52 weeks to 24 months



Analysis 4.6. Comparison 4 5-ASA versus purine antimetabolites, Outcome 6 Serious adverse events at 52 weeks to 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 6 Serious adverse events at 52 weeks to 24 months

Study or subgroup	5-ASA n/N	Purine antimetabolites n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ardizzone 2004	6/71	15/71		77.9 %	0.40 [0.16, 0.97]
Hanauer 2004	0/44	2/47		10.3 %	0.21 [0.01, 4.32]
Reinisch 2010	0/37	10/41		11.8 %	0.05 [0.00, 0.87]
Total (95% CI)	**152**	**159**		**100.0 %**	**0.30 [0.11, 0.80]**

Total events: 6 (5-ASA), 27 (Purine antimetabolites)

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 2.20$, df = 2 (P = 0.33); $I^2 = 9\%$

Test for overall effect: Z = 2.41 (P = 0.016)

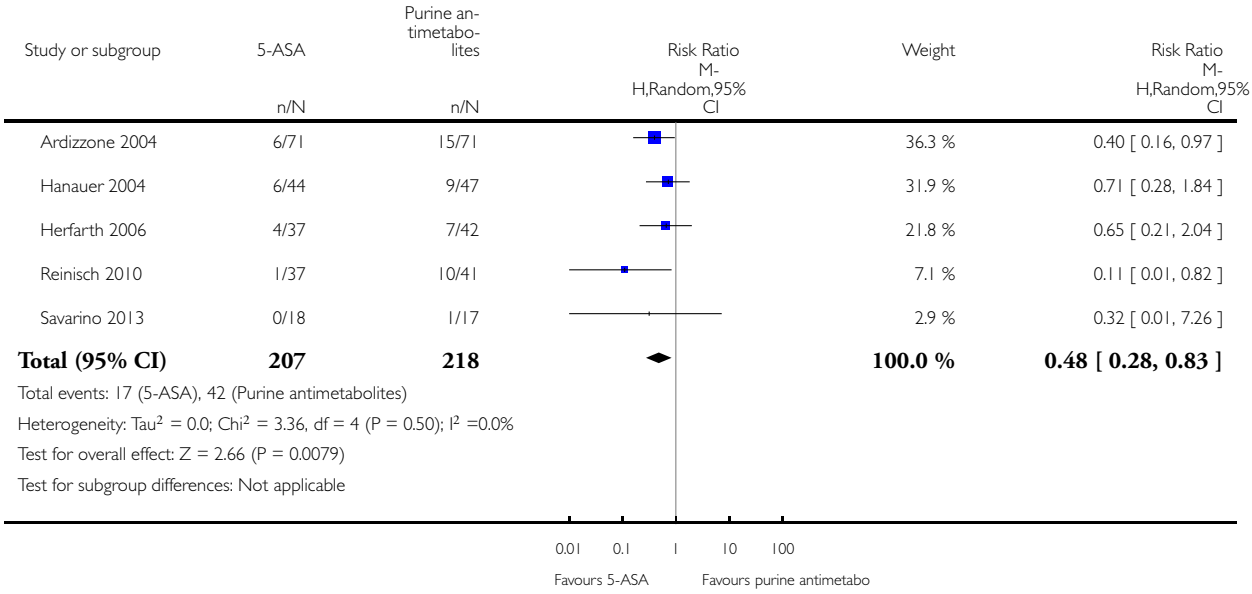
Test for subgroup differences: Not applicable

Analysis 4.7. Comparison 4 5-ASA versus purine antimetabolites, Outcome 7 Withdrawal due to adverse events at 52 weeks to 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 7 Withdrawal due to adverse events at 52 weeks to 24 months

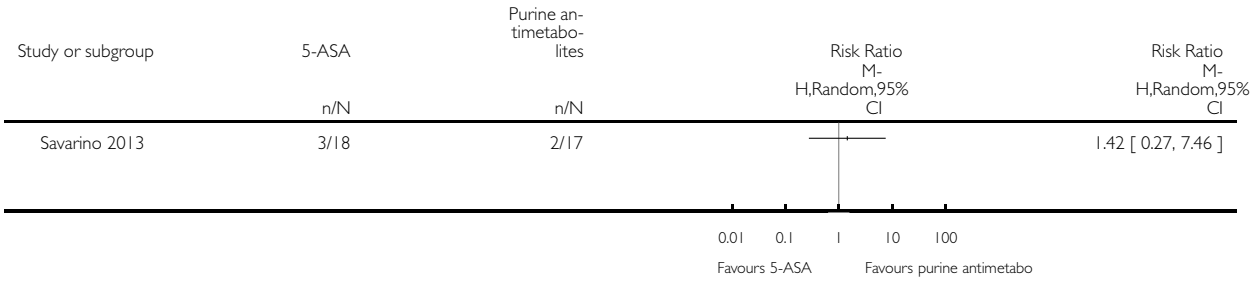


Analysis 4.8. Comparison 4 5-ASA versus purine antimetabolites, Outcome 8 HRQoL (IBDQ score >170 at 24 months).

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 8 HRQoL (IBDQ score >170 at 24 months)

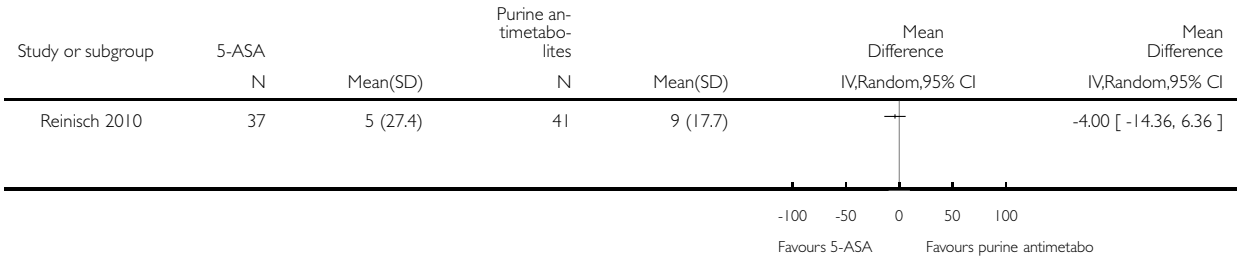


Analysis 4.9. Comparison 4 5-ASA versus purine antimetabolites, Outcome 9 HRQoL (mean IBDQ score change at 52 weeks).

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 4 5-ASA versus purine antimetabolites

Outcome: 9 HRQoL (mean IBDQ score change at 52 weeks)

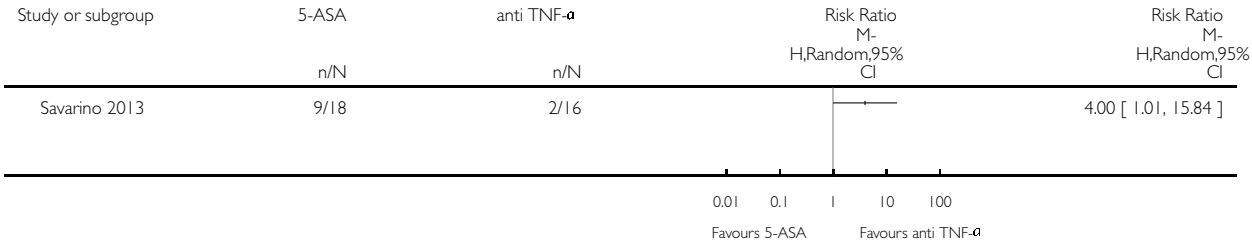


Analysis 5.1. Comparison 5 5-ASA versus anti TNF-α, Outcome 1 Clinical relapse at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 5 5-ASA versus anti TNF-α

Outcome: 1 Clinical relapse at 24 months

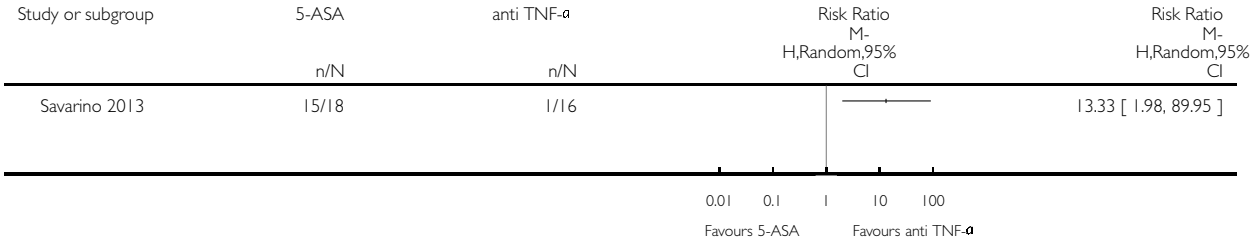


Analysis 5.2. Comparison 5 5-ASA versus anti TNF-α, Outcome 2 Endoscopic recurrence at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 5 5-ASA versus anti TNF-α

Outcome: 2 Endoscopic recurrence at 24 months

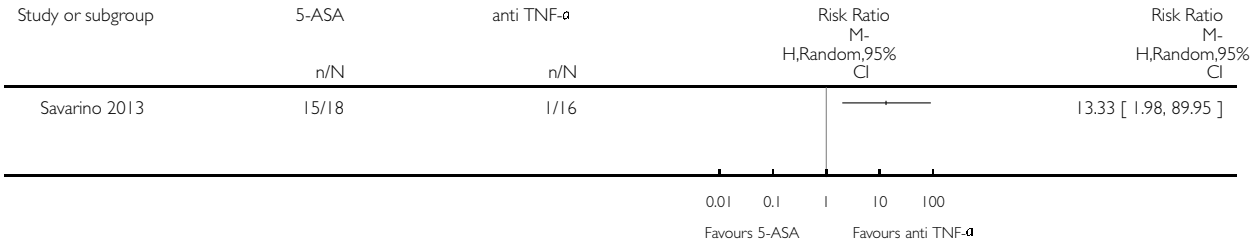


Analysis 5.3. Comparison 5 5-ASA versus anti TNF-α, Outcome 3 Radiologic relapse at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 5 5-ASA versus anti TNF-α

Outcome: 3 Radiologic relapse at 24 months

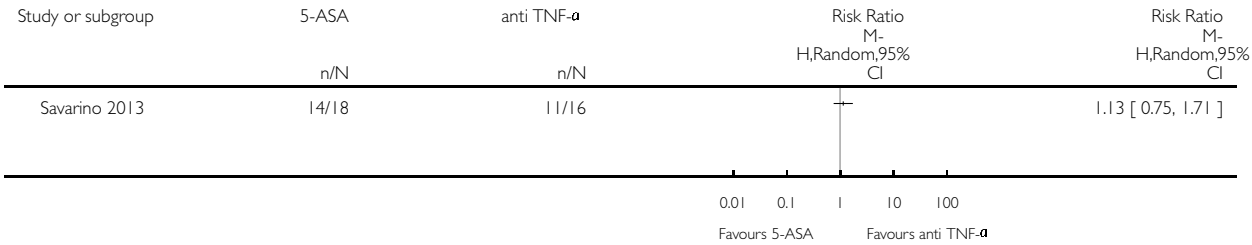


Analysis 5.4. Comparison 5 5-ASA versus anti TNF-α, Outcome 4 Adverse events at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 5 5-ASA versus anti TNF-α

Outcome: 4 Adverse events at 24 months

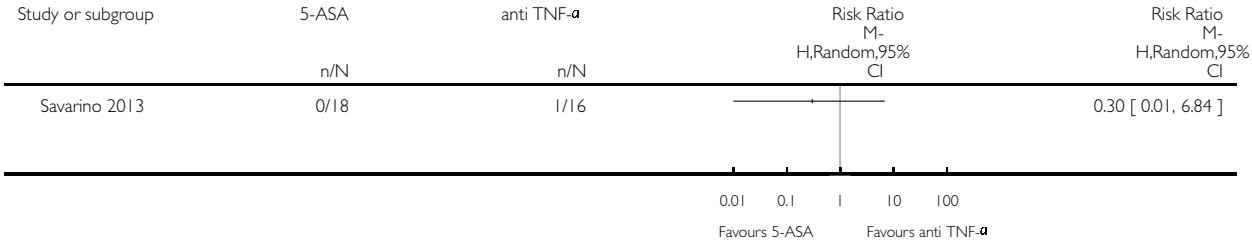


Analysis 5.5. Comparison 5 5-ASA versus anti TNF-α, Outcome 5 Withdrawal due to adverse events at 24 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 5 5-ASA versus anti TNF-α

Outcome: 5 Withdrawal due to adverse events at 24 months

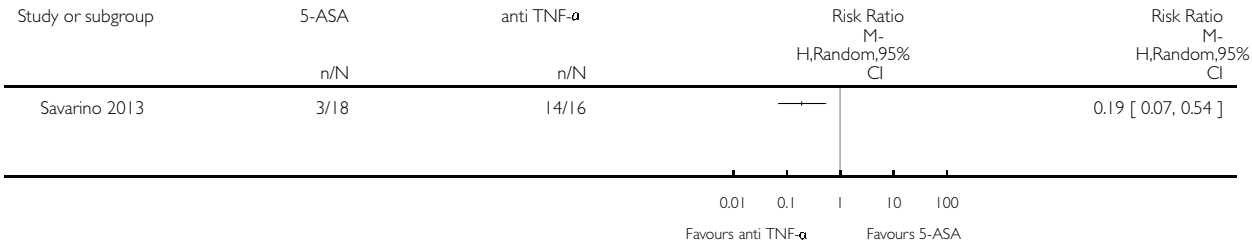


Analysis 5.6. Comparison 5 5-ASA versus anti TNF-α, Outcome 6 HRQoL (IBDQ >170).

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 5 5-ASA versus anti TNF-α

Outcome: 6 HRQoL (IBDQ >170)

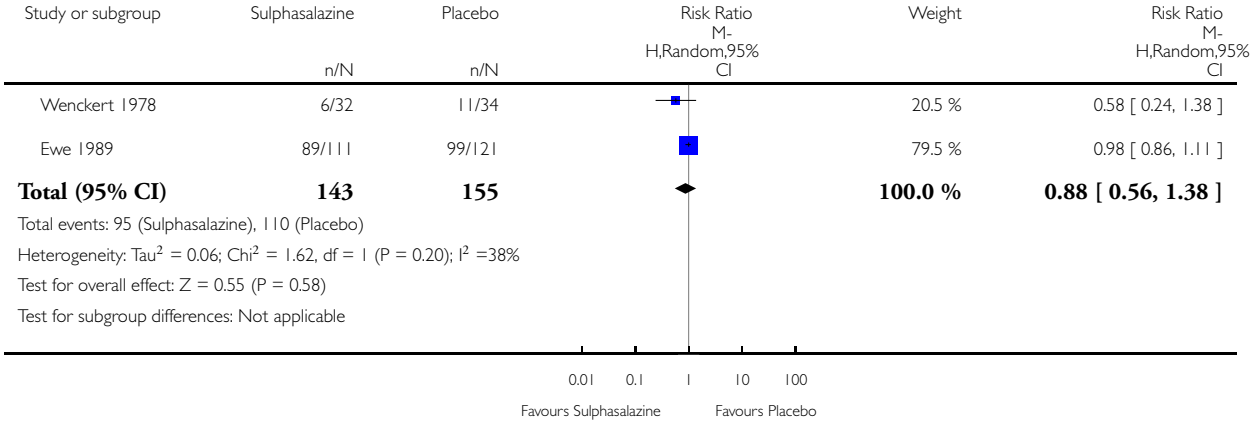


Analysis 6.1. Comparison 6 Sulphasalazine versus placebo, Outcome 1 Clinical relapse at 18 to 36 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 6 Sulphasalazine versus placebo

Outcome: 1 Clinical relapse at 18 to 36 months

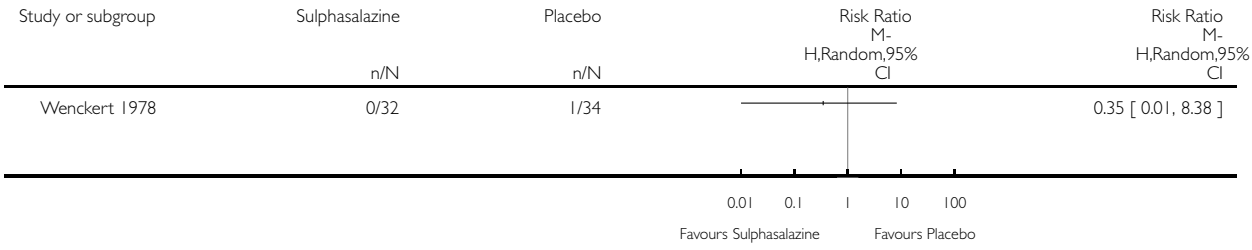


Analysis 6.2. Comparison 6 Sulphasalazine versus placebo, Outcome 2 Withdrawal due to adverse events at 18 months.

Review: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease

Comparison: 6 Sulphasalazine versus placebo

Outcome: 2 Withdrawal due to adverse events at 18 months



ADDITIONAL TABLES

Table 1. Summary of interventions and outcomes

Study ID	Group 1	Group 2	Group 3	Relapse	Health-related quality of life definition	Adverse Events/ Serious adverse events/ Withdrawal	
Ardizzone 2004	Mesalamine (3 g/day)	Azathioprine (2 mg/kg/day)		**Clinical:** 32/71 vs. 35/71 **Surgical:** 25/71 vs. 18/71		**AE:** 27/71 vs. 18/71 **SAE:** 6/71 vs. 15/71 **Withdrawal:** 6/71 vs. 15/71	
Brignola 1995	Mesalamine (3 g/day)	Placebo tablets		**Clinical:** 13/44 vs. 14/43		5/44 vs. 3/43	
Caprilli 1994	Mesalamine (2.4 g/day)	No treatment		**Relapse:** 20/55 vs. 28/55		**Withdrawal:** 2/55 vs. 2/55	
Caprilli 2003	Mesalazine (4 g/day)	Mesalazine (2.4 g/day)		**Clinical:** 17/101 vs. 27/101 **Endoscopic >1:** 45/101 vs. 59/105		**Withdrawal:** 2/101 vs. 2/105	
Ewe 1989	Sulfasalazine (3 g/day)	Placebo		**Relapse:** Total 0-36 months: 89/111 vs. 99/121		N/A	
Florent 1996	Claversal (1000 mg/day)	Placebo (1000 mg/day)		**Endoscopic:** 38/65 vs. 40/61		**Withdrawal:** 5/65 vs. 3/61	
Hanauer 2004	6-Mercaptopurine (50 mg/day)	Mesalamine (3 g/day)	Placebo	**Clinical:** 32/47 vs. 33/44 vs.35/40 **Endoscopic rate:** % (CI) **Radiographic rate:** % (CI)		**AE:** 9/47 vs. 6/44 vs. 4/40 **SAE:** 2/47 vs. 0/44 vs. 0/40	
Lochs 2000	Mesalamine (4 g/day)	Placebo		**Clinical:** 47/154 vs. 59/170		**SAE:** 8/154 vs. 9/170	

Table 1. Summary of interventions and outcomes (*Continued*)

				Endoscopic: 133/154 vs. 134/170			
McLeod 1995	Mesalamine (3 g/day)	Placebo		**Symptomatic relapse:** 35/88 vs. 44/81 **Endoscopic and radiologic rate:** significantly decreased in Group1		**AE:** 7/88 vs. 10/81 **SAE:** 1/88 vs. 0/81	
Reinisch 2010	Azathioprine (2.0 to 2.5 mg/kg/day) + Placebo mesalazine	Mesalazine (4 g/day) + Placebo azathioprine		Not included	Mean IBDQ change compared to baseline	**AE:** 34/37 vs. 32/41 **SAE:** 0/37 vs. 10/41 **Withdrawal:** 1/37 vs. 10/41	
Savarino 2013	Adalimumab (160 mg at week 0, 80 mg at 2 weeks and 40 mg/week thereafter)	Azathioprine (2 mg/kg/day)	Mesalamine (3 g/day)	**Clinical by CDAI:** 1/16 vs.12/17 vs. 9/18 **Endoscopic:** 1/16 vs. 11/17 vs. 15/18 **Radiologic:** 1/16 vs. 13/17 vs. 15/18	IBDQ >170: 14/16 vs 2/17 vs 3/18	**AE:**11/16 vs. 14/17 vs. 14/18 **Withdrawal:** 1/16 vs. 1/17 vs. 0/18	
Sutherland 1997	Mesalamine (3 g/day)	Placebo		**Clinical:** 3/31 vs.8/35	IBDQ score: significant decline in both groups	N/A	
Wenckert 1978	Suphasalazine (3 g/day)	Placebo		**Clinical:** 6/32 vs. 11/34		**Withdrawal:** 0/32 vs. 1/34	

AE = adverse events; CDAI = Crohn's disease activity index; ; g = gram; IBDQ = inflammatory bowel disease questionnaire; mg = milligram; N/A = not applicable; SAE = serious adverse events;

Table 2. Key study characteristics

Comparison	Study	Time from surgery till recruitment	Site of surgery % / *exclusion criteria	Clinical relapse definition	Endoscopic / histological recurrence definition/ other
Sulfasalazine vs Placebo					
SFZ 3 g/day	Ewe 1989	Immediately after surgery	Ileocolon 92; Ileum 2; colon 6 *non-standard policy resection (radical or non-radical)	Proven by radiology, endoscopy or operation	N/A
SFZ 3 g/day vs. placebo	Wenckert 1978	2-4 weeks	N/A	Special control charts	N/A
5-ASA vs no treatment					
MES 2.4 g/day (24 mo)	Caprilli 1994	2 weeks	Not reported *disease localisation to the jejunum, proximal ileum, left colon or ano-rectum	CDAI >150	N/A
5-asa vs placebo					
MES 3 g/day vs. placebo	Brignola 1995	≤ 1 month	Ileum 56, ileocaecal 46 *surgery other than in ileal or ileocaecal region	CDAI >150	Standardised form for description of endoscopic lesions by type and characteristics
MES 1.5 g/day vs. Placebo	Florent 1996	2 weeks	Ileal 44 ; colonic 6; ileocolonic 48; Anoperineal lesion 12. * permanent stoma, small intestinal resection of more than 100 cm prior to the pretrial operation	N/A	Rutgeerts i ≥ 1
MES 3 g/day vs. placebo	Hanauer 2004	Before postoperative hospital discharge	Not reported * Active perianal disease or any active disease in other segments of the intestine	Clinical recurrence grading >2	Rutgeerts i > 2 **Radiographic relapse:** radiographic recurrence grading > 2

Table 2. Key study characteristics (*Continued*)

MES 4 g/day vs. placebo	Lochs 2000	< 10 days	Ileal 49; ileocolonic 56, colonic 5. * short bowel syndrome, presence of an ileocolonic stoma, more than 3 surgeries	CDAI > 250 and CDAI >200 but min 60 points increase for 2 weeks	Rutgeerts i ≥ 2
Ileum 50, MES 3 g/day vs. placebo	McLeod 1995	≤ 8 week	Ileal 21; ileocolonic 46, colonic 33.	Severe symptoms to warrant treatment and radiological or endoscopic evidence of disease	Presence of endoscopic or radiological evidence of disease and included both asymptomatic and symptomatic patients
MES 3 g/day vs. placebo	Sutherland 1997	2-4 weeks	Ileal 49, ileocolonic 50, unknown 1	CDAI >150 as well as the absolute value of at least 60 points higher than baseline	N/A **HRQL: IBDQ**
5-ASA vs AZA or 6-MP					
MES 3 mg/kg/day vs. AZA 2 mg/kg/day	Ardizzone 2004	Max 2 weeks	Small bowel only 25.3; Colon 5.6; Small bowel and colon 9.8; upper gastrointestinal tract 16.2 *surgical procedures other than conservative surgery or for perianal disease only	CDAI >200	N/A **Surgical relapse:** need for another surgical procedure
MES 3 g/day vs. 6-MP 50 mg/day	Hanauer 2004	before postoperative hospital discharge	Not reported * Active perianal disease or any active disease in other segments of the intestine	Clinical recurrence grading >2 (Hanauer et al)	Rutgeerts i ≥ 2 **Radiographic relapse:** radiographic recurrence grading > 2
MES 4g/day vs. AZA 2 mg/kg/day (52 weeks)	Reinisch 2010	6-24 months	Not reported * Short bowel syndrome, an ileocolonic stoma	CDAI >200	Rutgeerts i ≥ 2 **HRQL: IBDQ**
MEZ 3 g/day vs. AZA 2 mg/kg/day	Savarino 2013	2-4 weeks	Ileum 49, Ileocolonic 51 * fibrostenotic stricture, macroscop-	1. ≥ 2 clinical recurrence grading scale (Hanauer et al) 2. CDAI > 200	Rutgeerts i ≥ 2 **Radiologic relapse**: ≥ 2 radiographic recur-

Table 2. Key study characteristics (*Continued*)

			ically active disease not resected at the time of surgery, and presence of a stoma		rence grading scale **HRQL:** IBDQ > 170
5-ASA vs anti TNF-α					
MEZ 3 g/day vs. Adalimumab	Savarino 2013	2-4 weeks	Ileum 49, Ileocolonic 51 * fibrostenotic stricture, macroscopically active disease not resected at the time of surgery, and presence of a stoma	1. ≥ 2 on the clinical recurrence grading scale by Hanauer 2. CDAI >200	Rutgeerts i ≥ 2 **Radiologic relapse**: ≥ 2 radiographic recurrence grading scale **HRQL:** IBDQ > 170
5-ASA VS 5-ASA					
4.0 g/day MES vs. 2.4 g/day MES (12 months)	Caprilli 2003	2 weeks	Ileum 64; Ileum/caecum/ascending colon 36 * disease localization to jejunum, proximal ileum, transverse colon, left colon or anorectum	CDAI > 150 points or an increase in CDAI score of + 100 points from baseline	Rutgeerts i ≥ 1

g = gram; mg = milligram; kg = kilogram; SFZ = sulphasalazine; MES = mesalamine; MEZ = mesalazine; 6-MP = 6-mercaptopurine; IBDQ = inflammatory bowel disease questionnaire; HRQL = health related quality of life; N/A = not applicable
AZA = azathioprine; CDAI = Crohn's disease activity index

APPENDICES

Appendix 1. Search strategies

Embase
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 Crohn disease/
20 exp Inflammatory bowel diseases/
21 exp ileitis/
22 regional enteritis.mp.
23 or/19-22
24 exp mesalamine/
25 exp Sulfasalazine/
26 (aminosalicylic acid OR aminosalicylate).mp.
27 (mesalazine OR mesalamine).mp.
28 5-ASA.mp.
29 olsalazine.mp.
30 balsalazide.mp.
31 sulfasalazine.mp.
32 or/24-31
33 (surgery OR surgical OR surgically).mp.
34 surgic*.mp.
35 (post-surgical OR post-surgery).mp.
36 (postoperative OR post-operative).mp.
37 resection*.mp.
38 operation*.mp.
39 or/33-38
40 18 and 23 and 32 and 39

MEDLINE

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. randomized controlled trial/
14. or/1-13
15 exp Crohn disease/
16 exp Inflammatory bowel diseases/
17 exp ileitis/
18 regional enteritis.mp.
19 or/15-18
20 exp mesalamine/
21 exp sulfasalazine/

22 (aminosalicylic acid OR aminosalicylate).mp.
23 (mesalazine OR mesalamine).mp.
24 5-ASA.mp.
25 olsalazine.mp.
26 balsalazide.mp.
27 sulfasalazine.mp.
28 or/20-27
29 (surgery OR surgical OR surgically).mp.
30 surgic*.mp.
31 (post-surgical OR post-surgery).mp.
32 (postoperative OR post-operative).mp.
33 resection*.mp.
34 operation*.mp.
35 or/29-34
36 14 and 19 and 28 and 35

CENTRAL

#1 MeSH descriptor: [Crohn's Disease] explode all trees
#2 MeSH descriptor: [Ileitis] explode all trees
#3 MeSH descriptor: [Inflammatory Bowel Disease] explode all trees
#4 Regional enteritis
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Mesalamine] explode all trees
#7 aminosalicylic acid OR aminosalicylate* OR 5-ASA OR 5ASA OR mesalazine OR mesalamine
#8 olsalazine OR balsalazide OR sulfasalazine
#9 #6 or #7 or #8
#10 surgery OR surgic*
#11 post-surgical OR post-surgery
#12 post-operative OR postoperative
#13 resection* OR operation*
#14 #10 or #11 or #12 or #13
#15 #5 and #9 and #14

Cochrane IBD Group Specialized Register

Title and abstract search (Aminosalicylate and Crohn's Disease OR Mesalazine and Crohn's Disease OR 5-ASA and Crohn's Disease)

Clinicaltrials.gov

1. Aminosalicylate and Crohn's Disease
2. Mesalazine and Crohn's Disease

WHO trial registry

1. Aminosalicylate and Crohn's Disease
2. Mesalazine and Crohn's Disease

WHAT'S NEW

Date	Event	Description
16 July 2018	New search has been performed	New search and new studies added
16 July 2018	New citation required but conclusions have not changed	Updated review with new authors

HISTORY

Protocol first published: Issue 3, 2010

Review first published: Issue 1, 2011

Date	Event	Description
3 December 2010	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Teuta Gjuladin-Hellon performed screening of abstracts and titles, data extraction, risk of bias assessments, statistical analyses, manuscript preparation, GRADE analysis, critical revision for the manuscript and approval of the final manuscript.

Morris Gordon provided methodological expertise and performed screening of abstracts and titles, screening of full-text articles and was involved with adjudication of GRADE analysis, manuscript preparation, data interpretation, critical revision of the manuscript, and approval of the final manuscript.

Anthony K Akobeng provided methodological expertise and was involved with checking the data analyses, critical revision for the manuscript, and approval of the final manuscript.

Zipporah Iheozor-Ejiofor performed adjudication in the screening and data extraction phases, data extraction, communication with primary study authors, risk of bias assessments, GRADE analysis, manuscript preparation, critical revision for the manuscript and approval of the final manuscript.

DECLARATIONS OF INTEREST

Teuta Gjuladin-Hellon: None known.

Morris Gordon has received travel fees to attend international scientific and training meeting such as DDW, Advances in IBD, ESPGHAN, BSPGHAN and Cochrane focused international events from companies including: Abbott, Nutricia, Biogaia, Ferring, Allergan, and Tillots.

Zipporah Iheozor-Ejiofor: None known.

Anthony K Akobeng: None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the original review in 2011 (Gordon 2011), several elements have been refined. These are primarily to reflect developments in Cochrane methods, to ensure consistency across the Cochrane IBD group portfolio and ensure clinically appropriate synthesis.

- A minimum period of three months from start of therapy was sufficient to allow judgement of maintenance of remission (previously defined as six months in the first version of the review: Gordon 2011)

- We have allowed the inclusion of no treatment control groups in this updated review with plans to analyse separately from placebo-controlled studies.

- Sulfasazine was previously pooled with other 5-ASA agents. However, the authors discussed with the central editors of the group and it was decided that given the specific and rationale differences in such preparations, particularly the goal of reducing side effects, these should be treated separately. However, all other 5-ASA formulations have still been considered together for the primary analysis.

- Gordon 2011 lists endoscopic recurrence as a primary outcome, however, we decided to report it as a secondary outcome in this review update to ensure consistency across the Cochrane IBD group portfolio.

- We also reported adverse event data as a composite outcome not individually as proposed in Gordon 2011 to ensure consistency across the Cochrane IBD group portfolio.

- The following secondary outcomes have been added: quality of life, radiologic relapse, serious adverse events and withdrawal due to adverse events.

- Surgical relapse has been included as a post-hoc secondary outcome.

- For the previously published version of this review we contacted leaders in the field and 5-ASA manufacturers to identify additional studies. We did not do this for the updated review.

- For the 'Summary of findings' tables, we included the following outcomes: clinical relapse, endoscopic recurrence, radiologic relapse, adverse events, serious adverse events, study withdrawal due to adverse events and health-related quality of life. We did not pre-specify these outcomes in the published protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Crohn Disease [*drug therapy; *surgery]; Mesalamine [*administration & dosage]; Randomized Controlled Trials as Topic; Remission Induction [methods]

MeSH check words

Humans