NCGC National Clinical Guideline Centre

Crohn's disease

Appendix J

Clinical Guideline <...>

Review of Cochrane ASA review

10 October 2012

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1 Cochrane 5-ASA review

1.1 Introduction

In December 2010, "Aminosalicylates for induction of remission or response in Crohn's disease"[1] was published by the Cochrane collaboration. This review included 16 RCTs which evaluated the efficacy of sulfasalazine and mesalazine (mesalamine). The review differs from the NCGC Crohn's disease guideline review of 5-ASA for induction in the following ways:

1. The review was in adults only.
2. Sulfasalazine and mesalazine were assessed independently.
3. Oral sulfasalazine or oral mesalazine were compared alone to placebo, glucocorticosteroid and other aminosalicylates (alone or in combination).
4. 5-ASA dosages were compared.
5. The following studies were not included in the NCGC Crohn's disease guideline review. The reasons for exclusion are as follows:

a. Van Hees 1981[2] : Sulfasalazine vs. placebo; GDG criteria for assessment of remission not met (VHI used)
b. Rijk 1991[3] : comparison of two indices of remission (CDAI and VHI) (change in activity indices with mean CDAI change 50 points used)
c. Singleton 1994[4] : letter to editor; not fully published study
d. Saverymuttu 1986[5] : sulfasalazine + placebo vs. sulfasalazine vs. glucocorticosteroid; GDG criteria for assessment of remission not met (faecal granulocyte excretion used)
e. Crohn's III 1999[6] : not fully published
f. Maier 1985[7] and Maier 1990[8] : comparison of two 5-ASA treatments and dose; not GDG question
g. Wright 1995[9] : olsalazine vs. placebo, withdrawal rate > 50%.

The Cochrane review "Aminosalicylates for induction of remission or response in Crohn's disease"[1] was assessed. The evidence table and GRADE tables are presented below. Controlled-release refers to drugs such as Pentasa which consists of ethyl-cellulose-coated microgranules of 5-aminosalicylic acid, resulting in continuous release of the drug throughout the lumen of the small intestine. Delayed-release refers to drugs such as Asacol which comprises 5-aminosalicylic acid enclosed in a pH-dependent resin, Eudragit S. This coat disintegrates above pH7, which corresponds to the pH of the distal ileum and colon, releasing the 5-aminosalicylic acid contents.

1.2 Clinical evidence

Table 1: Evidence table for 5-ASA versus placebo to induce remission

Bibliographic reference	Study type	Study quality	Number of patients/studies	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID:6484 Lim et al, 2010[1] Cochrane review	SR	Moderate	16 studies	Inclusion: Adult patients with mild to moderate active Crohn's disease	Oral sulfasalazine or mesalazine	Placebo; glucocorticosteroid and other aminosalicylates (alone or in combination with glucocorticosteroid)	Not specified	A well-defined clinical endpoint of induction of remission or response to treatment	See effect size table	Not stated	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control RR	Heterogeneity
Sulfasalazine (2−6g) vs. placebo induction of remission (CDAI < 150), therapeutic response(VHI* decrease ≥ 25%) or clinical improvement)	3	RR 1.51 (0.97 to 2.35) NS	41%
Sulfasalazine vs. placebo Induction of remission (CDAI < 150)	2	RR 1.38 (1.02 to 1.87) S (favours sulfasalazine)	0.0%
Sulfasalazine vs. glucocorticosteroid Induction of remission (CDAI < 150)	2	RR 0.66 (0.53, to 0.81) S (favours glucocorticosteroid)	0.0%
Sulfasalazine vs. sulfasalazine and glucocorticosteroid Induction of remission (CDAI < 150)	1	RR 0.64 (0.47 to 0.86) S (favours sulfasalazine + glucocorticosteroid)	NA

Controlled-release mesalazine (1-2 g/day) vs. placebo Decrease in CDAI ≥ 50, HBI ≥ 2 or improvement/remission (as defined by Tvede et al**)	3	RR 1.07 (0.80 to 1.42) NS	0.0%
Controlled-release mesalamine (1.0 g/day) vs. placebo Decrease in CDAI ≥ 50, HBI ≥ 2 or improvement/remission (as defined by Tvede et al)	1	0.91 (0.56 to 1.46) NS	NA
Controlled-release mesalamine (1.5 g/day) vs. placebo Decrease in CDAI ≥ 50, HBI ≥ 2 or improvement/remission (as defined by Tvede et al)	2	1.47 (0.87 to 2.49) NS	0.0%
Controlled-release mesalamine (2.0 g/day) vs. placebo Decrease in CDAI ≥ 50, HBI ≥ 2 or improvement/remission (as defined by Tvede et al)	1	0.97 (0.60 to 1.55) NS	NA
Controlled-release mesalamine (1-2 g/day) vs. placebo Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 or as defined by Tvede et al)	2	1.46 (0.89 to 2.40) NS	0.0%
Controlled-release mesalamine (1 g/day) vs. placebo Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 or as defined by Tvede et al)	1	1.29 (0.59 to 2.82) NS	NA
Controlled-release mesalamine (1.5 g/day) vs. placebo Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 or as defined by Tvede et al)	1	2.16 (0.70 to 6.68) NS	NA
Controlled-release mesalamine (2 g/day) vs. placebo Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 or as defined by Tvede et al)	1	1.37 (0.63 to 3.00) NS	NA

Controlled-release mesalamine (4 g/day) vs. placebo Mean change in baseline CDAI (Random effects model***)	3	MD (IV Random 95% CI) -19.76 (-46.22 to 6.70) NS (p = 0.14)	54%
Controlled-release mesalazine (4 g/day) vs. placebo Mean change in baseline CDAI (Fixed effects model***)	3	MD (IV, Fixed 95% CI) -17.54 (-33.00 to -0.08) S (p = 0.05)	54%
Delayed-release mesalazine (2 - 3.2 g/day) versus placebo Induction of remission or clinical improvement: olsalazine 2 g/day [9]	1	0.36 (0.18 to 0.71) S (favours placebo)	NA
Delayed-release mesalazine (2 - 3.2 g/day) versus placebo Induction of remission or clinical improvement: Asacol 3.2 g/day[10]	1	2.70 (1.06 to .88) S (favours mesalazine)	NA
Delayed-release mesalazine (2 - 3.2 g/day) versus placebo Induction of remission (CDAI < 150 + decrease ≥ 70): Asacol 3.2 g/day [10]	1	2.03 (0.75 to 5.45) NS	
Delayed-release mesalazine (3-4.5 g/day) versus glucocorticosteroid Induction of remission (CDAI < 150 with or without decrease of at least 60 points)	3	1.04 (0.7 to 1.36) NS	0.0%
Delayed-release mesalazine (3-4.5 g/day) versus glucocorticosteroid Induction of remission (CDAI < 150 with or without decrease of at least 60 points): 3 g/day	1	0.95 (0.49 to 1.85) NS	NA
Delayed-release mesalazine (3-4.5 g/day) versus glucocorticosteroid Induction of remission (CDAI < 150 with or without decrease of at least 60 points): 4 g/day	1	1.0 (0.61 to 1.64) NS	NA
Delayed-release mesalazine (3 - 4.5 g/day) versus glucocorticosteroid Induction of remission (CDAI < 150 with or	1	1.26 (0.82 to 1.92) NS	NA

without decrease of at least 60 points): 4 g/day microgranules			
Delayed-release mesalazine (3-4.5 g/day) versus glucocorticosteroid Induction of remission (CDAI < 150 with or without decrease of at least 60 points): 4.5 g/day	1	0.67 (0.30 to 1.46) NS	NA
Controlled-release mesalazine (4 g/day) versus budesonide Induction of remission (CDAI < 150)	1	0.56 (0.40 to 0.78) S (favours budesonide)	NA
Mesalazine versus sulfasalazine (alone or in combination with glucocorticosteroid) Induction of remission (CDAI < 150) or clinical improvement: Salofalk 1.5 g/day	1	0.85 (0.59 to 1.22) NS	NA
Mesalazine versus sulfasalazine (alone or in combination with glucocorticosteroid) Induction of remission (CDAI < 150) or clinical improvement: Salofalk 3.0 g/day	1	1.06 (0.85 to 1.33) NS	NA

**Van Hees Index.*
***Concentrations of plasma interleukins.*
**** If fixed effect and random effect meta-analyses give identical results then it is unlikely that there is important statistical heterogeneity.*

Table 2: Clinical evidence profile - sulfasalazine versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sulfasalazine	Placebo	Relative (95% CI)	Absolute	Quality
Induction of remission (CDAI or VHI); Malchow 1984, Summers 1979, Van Hees 1981 in Lim et al 2010											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/141 (47.5%)	46/148 (31.1%)	RR 1.51 (0.97 to 2.35)	159 more per 1000 (from 9 fewer to 420 more)	MODERATE
Induction of remission (CDAI); Malchow 1984, Summers 1979 in Lim et al 2010											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/128 (46.1%)	45/135 (33.3%)	RR 1.38 (1.02 to 1.87)	127 more per 1000 (from 7 more to 290 more)	MODERATE

[1] *Jadad scale used for quality assessment.*

Table 3: Clinical evidence profile - sulfasalazine versus conventional glucocorticosteroid

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sulfasalazine	Conventional Glucocorticosteroid	Relative (95% CI)	Absolute	Quality
Induction of remission (CDAI ≤ 150) Malchow 1984, Summers 1979 in Lim et al 2010											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/128 (46.1%)	90/132 (68.2%)	RR 0.66 (0.53 to 0.81)	232 fewer per 1000 (from 130 fewer to 320 fewer)	MODERATE

[1] *Jadad scale used for quality assessment.*

Table 4: Clinical evidence profile - sulfasalazine versus sulfasalazine plus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sulfasalazine	Sulfasalazine plus glucocorticosteroid	Relative (95% CI)	Absolute	Quality
Induction of remission; (CDAI < 150) Malchow 1984 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/54 (50%)	44/56 (78.6%)	RR 0.64 (0.47 to 0.86)	283 fewer per 1000 (from 110 fewer to 416 fewer)	MODERATE

[1] *Jadad scale used for quality assessment*

Table 5: Clinical evidence profile - controlled-release mesalazine 1-2 g/day versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Controlled-release mesalazine (1-2 g/day)	Placebo	Relative (95% CI)	Absolute	Quality
Decrease in CDAI ≥ 50, HB ≥ 2 or improvement/remission; Singleton 1993, Mahida 1990, Rasmussen 1987 in Lim et al 2010											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79/205 (38.5%)	48/137 (35%)	RR 1.07 (0.8 to 1.42)	25 more per 1000 (from 70 fewer to 147 more)	MODERATE
Decrease in CDAI ≥ 50, HBI ≥ 2 or improvement/remission as defined by Tvede et al 1 g/day; Singleton 1993 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/80 (36.3%)	16/40 (40%)	RR 0.91 (0.56 to 1.46)	36 fewer per 1000 (from 176 fewer to 184 more)	MODERATE
Decrease in CDAI ≥ 50, HBI ≥ 2 or improvement/remission as defined by Tvede et al 1.5 g/day; Mahida 1990, Rasmussen 1987 in Lim et al 2010											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/50 (42%)	16/57 (28.1%)	RR 1.47 (0.87 to 2.49)	132 more per 1000 (from 36 fewer to 418 more)	MODERATE
Decrease in CDAI ≥ 50, HBI ≥ 2 or improvement/remission as defined by Tvede et al 2 g/day; Singleton 1993 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/75 (38.7%)	16/40 (40%)	RR 0.97 (0.6 to 1.55)	12 fewer per 1000 (from 160 fewer to 220 more)	MODERATE
Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 or as defined by Tvede et al) 1-2g/day; Singleton 1993, Rasmussen 1987 in Lim et al 2010											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/185 (23.2%)	18/117 (15.4%)	RR 1.46 (0.89 to 2.4)	71 more per 1000 (from 17	MODERATE

										fewer to 215 more)	
Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 as defined by Tvede et al) 1 g/day; Singleton 1993 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/80 (22.5%)	7/40 (17.5%)	RR 1.29 (0.59 to 2.82)	51 more per 1000 (from 72 fewer to 318 more)	MODERATE
Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 as defined by Tvede et al) 1.5 g/day; Rasmussen 1987 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/30 (23.3%)	4/37 (10.8%)	RR 2.16 (0.7 to 6.68)	125 more per 1000 (from 32 fewer to 614 more)	MODERATE
Induction of remission (CDAI ≤ 150 + decrease of ≥ 50 as defined by Tvede et al) 2 g/day; Singleton 1993 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/75 (24%)	7/40 (17.5%)	RR 1.37 (0.63 to 3)	65 more per 1000 (from 65 fewer to 350 more)	MODERATE

[1] *Jadad scale used for quality assessment*

Table 6: Clinical evidence profile - controlled-release mesalazine 4 g/day versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Controlled-release mesalazine (4 g/day)	Placebo	Relative (95% CI)	Absolute	Quality
Mean change in baseline CDAI (Better indicated by lower values) (Random effects model); Singleton 1993 and 1994, Crohn III 1997 in Lim et al 2010											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none[3]	304	311	-	MD 19.76 lower (46.22 lower to 6.7 higher)	LOW
Mean change in baseline CDAI (Better indicated by lower values) (Fixed effects model) ;Singleton 1993 and 1994, Crohn III 1997 in Lim et al 2010											
3	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none[3]	304	311	-	MD 17.54 lower (35 to 0.08 lower)	LOW

[1] *Jadad scale used for quality assessment.*
[2] *Heterogeneity 54%.*
[3] *One study unpublished: Crohn III 1997.*

Table 7: Clinical evidence profile - delayed-release mesalazine 2 - 3.2 g/day versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed-release mesalazine (2-3.2 g/day)	Placebo	Relative (95% CI)	Absolute	Quality
Induction of remission or clinical improvement - olsalazine 2g/day; Wright 1995 in Lim et al 2010											
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/46 (17.4%)	22/45 (48.9%)	RR 0.36 (0.18 to 0.71)	313 fewer per 1000 (from 142 fewer to 401 fewer)	VERY LOW
Induction of remission or clinical improvement - Asacol 3.2g/day; Tremaine 1994 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/20 (60%)	4/18 (22.2%)	RR 2.7 (1.06 to 6.88)	378 more per 1000 (from 13 more to 1307 more)	LOW
Induction of remission (CDAI ≤ 150 + decrease ≥ 70) - Asacol 3.2 g/day; Tremaine 1994 in Lim et al 2010											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	9/20 (45%)	4/18 (22.2%)	RR 2.03 (0.75 to 5.45)	229 more per 1000 (from 56 fewer to 989 more)	MODERATE

[1] *Jadad scale used for quality assessment and missing data.*
[2] *Small sample size.*

Table 8: Clinical evidence profile - delayed-release mesalazine 3-4.5 g/day versus glucocorticosteroid

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed-release mesalazine (3-4.5 g/day)	Glucocorticosteroid	Relative (95% CI)	Absolute	Quality
Induction of remission (CDAI ≤ 150 with or without decrease of at least 60 points) 3-4.5 g/day; Martin 1990, Prantera 1999, Gross 1995 in Lim et al 2010											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/102 (56.9%)	40/76 (52.6%)	RR 1.04 (0.79 to 1.36)	21 more per 1000 (from 111 fewer to 189 more)	MODERATE
Induction of remission (CDAI ≤ 150 with or without decrease of at least 60 points) 3 g/day; Martin 1990 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/22 (40.9%)	12/28 (42.9%)	RR 0.95 (0.49 to 1.85)	21 fewer per 1000 (from 219 fewer to 364 more)	LOW
Induction of remission (CDAI ≤ 150 with or without decrease of at least 60 points) 4 g/day; Prantera 1999 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/35 (60%)	9/15 (60%)	RR 1 (0.61 to 1.64)	0 fewer per 1000 (from 234 fewer to 384 more)	LOW
Induction of remission (CDAI ≤ 150 with or without decrease of at least 60 points) 4 g/day microgranules; Prantera 1999 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/28 (78.6%)	10/16 (62.5%)	RR 1.26 (0.82 to 1.92)	162 more per 1000 (from 113 fewer to 575	LOW

										more)	
Induction of remission (CDAI ≤ 150 with or without decrease of at least 60 points) 4.5 g/day; Gross 1995 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/17 (35.3%)	9/17 (52.9%)	RR 0.67 (0.3 to 1.46)	175 fewer per 1000 (from 371 fewer to 244 more)	LOW

[1] *Jadad scale used for quality assessment.*
[2] *Small sample size.*

Table 9: Clinical evidence profile - controlled-release mesalazine 4 g/day versus budesonide

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Controlled-release mesalazine (4 g/day)**	**Budesonide**	**Relative (95% CI)**	**Absolute**	**Quality**
Induction of remission (CDAI ≤ 150); Thomsen 1998 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/89 (33.7%)	56/93 (60.2%)	RR 0.56 (0.4 to 0.78)	265 fewer per 1000 (from 132 fewer to 361 fewer)	LOW

[1] *Jadad scale used for quality assessment.*
[2] *Small sample size.*

Table 10: Clinical evidence profile - mesalazine versus sulfasalazine (alone or in combination with glucocorticosteroid)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine	Sulfasalazine (alone or in combination with glucocorticosteroid)	Relative (95% CI)	Absolute	Quality
Induction of remission (CDAI ≤ 150) or clinical improvement - Salofalk (mesalazine) (1.5 g/day); Maier 1985 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/15 (73.3%)	13/15 (86.7%)	RR 0.85 (0.59 to 1.22)	130 fewer per 1000 (from 355 fewer to 191 more)	LOW
Induction of remission (CDAI ≤ 150) or clinical improvement - Salofalk (mesalazine)(3.0 g/day); Maier 1990 in Lim et al 2010											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/26 (88.5%)	20/24 (83.3%)	RR 1.06 (0.85 to 1.33)	50 more per 1000 (from 125 fewer to 275 more)	LOW

[1] *Jadad scale used for quality assessment.*
[2] *Small sample size.*

1.2.1 Evidence statements – clinical

- In a Cochrane meta-analysis of sulfasalazine versus placebo, sulfasalazine 2-6 g/day was effective for induction of remission by CDAI score < 150 (RR 1.38 [1.02 to 1.87]).[1][MODERATE QUALITY]
- In a Cochrane meta-analysis of controlled-release mesalazine versus placebo, mesalazine 1-2 g/day for induction of remission by CDAI score < 150 was not shown to be superior to placebo, (RR 1.46 [0.89 to 2.4]).[11-13][MODERATE AND LOW QUALITY]
- Two studies of delayed release mesalazine and olsalazine 2-3.2 g/day showed opposite effects.[9,10] [LOW QUALITY]
- Higher doses of delayed-release mesalazine 3-4.5 g/day also did not show greater efficacy than placebo in inducing remission in Crohn's disease.[10][LOW QUALITY]
- Olsalazine was shown to be less effective than placebo in inducing remission in Crohn's disease.[9][VERY LOW QUALITY]
- Glucocorticosteroid treatment was shown to be more effective than sulfasalazine at inducing remission in Crohn's disease.[14,15][MODERATE QUALITY]
- In two studies there was no significant difference in induction of remission between Salofalk 1.5-3 g/day compared with sulfasalazine alone or in combination with glucocorticosteroid treatment.[7,8][LOW QUALITY]

1.3 Subgroup analysis of GDG data:

Drug type was not included as a potential confounder in the original GDG protocol for review of 5-aminosalisylates. There was no heterogeneity identified in the initial 5-ASA versus placebo induction of remission meta-analysis. See original results below.

Figure 1: 1. Guideline analysis (Singleton 4 g/day)

	5-ASA		placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Mahida 1980	8	20	7	20	9.5%	1.14 [0.51, 2.55]	
Malchow 1984	27	54	22	58	28.8%	1.32 [0.86, 2.01]	
Rasmussen 1987	13	30	9	37	10.9%	1.78 [0.88, 3.59]	
Singleton 1993	32	75	14	80	18.4%	2.44 [1.42, 4.20]	
Summers 1979	28	74	20	77	26.6%	1.46 [0.90, 2.35]	
Tremaine 1994	9	20	4	18	5.7%	2.02 [0.75, 5.45]	
Total (95% CI)		**273**		**290**	**100.0%**	**1.64 [1.29, 2.07]**	
Total events	117		76				

Heterogeneity: Chi² = 4.30, df = 5 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.09 (P < 0.0001)

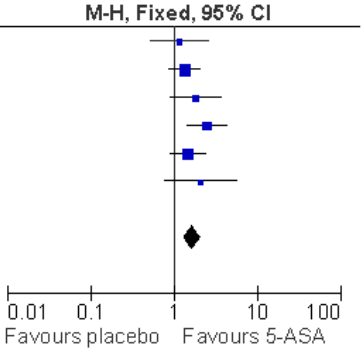
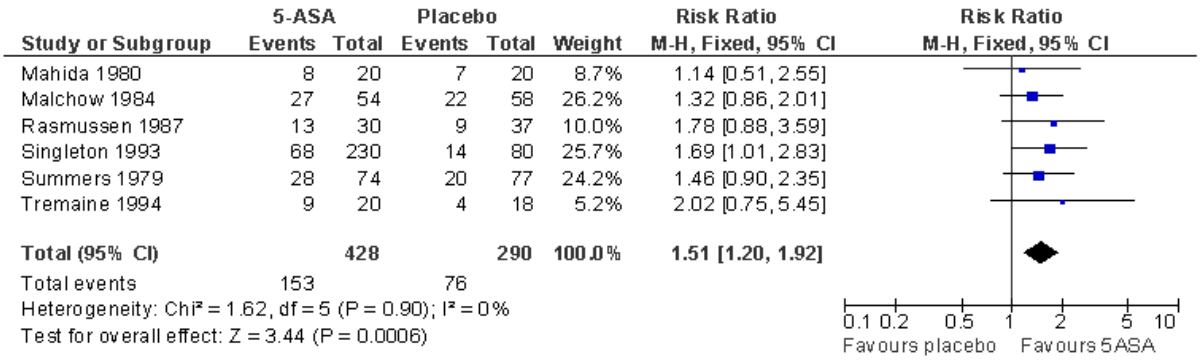


Figure 2: Guideline analysis with full Singleton results



Before running a *post-hoc* subgroup analysis by drug type, all potential sources of heterogeneity which were identified by the GDG prior to the review were investigated. These are presented in the table below:

Potential source of heterogeneity	Result of analysis
Disease severity • mild-moderate active disease • moderate-severe active disease • severe-fulminating active disease OR • active • quiescent	All six studies identified patients with mild-moderate active disease. There was no variability in the aspect of patient selection, so disease severity did not explain the heterogeneity.
Concurrent medications	There were no concurrent medications being taken by patients during the study period in any of the included studies.
Age (adults/children)	Five of six studies included patients over the age of 18. One study included patients from age 15 onward.
Disease location • Small bowel • Colon • Small bowel and colon	Results were reported by disease location in five of six studies. The reports varied by outcome measures and statistical methods and could not be combined in a subgroup meta analysis. The results are as follows: Mahida 1990, improvement on Pentasa (mesalazine) as defined by fall in HBI score by 2 or more points: Ileal 33% Pentasa (3/9) vs. 38% placebo (5/13); Ileo-colonic 40% Pentasa (2/5) vs. 0% placebo (0/1); Colonic 67% Pentasa (4/6) vs. 33% placebo (2/6). Malchow 1984, improvement on sulfasalazine (SS) as defined by CDAI < 150: Small bowel 50% SS (5/10) vs. 56% placebo (9/16); Small and large bowel SS 58% (18/31) vs. 39% placebo (11/28); Colon SS 31% (4/13) vs. 14% placebo (2/14). Rasmussen 1987, data not provided. Authors state, 'No difference was seen in the results (of Pentasa vs. placebo) between patients with exclusively small

Potential source of heterogeneity	Result of analysis
	bowel disease and those with small bowel and colorectal disease risk(36 vs. 31 patients respectively).' Singleton 1993, data for Pentasa activity by location not provided. Authorsstate, '...no significant difference in response to therapy (Pentasa) was observed for various subgroup populations (disease location, etc).' Summers 1979, a comparison of Wilcoxon Rank Sum outcomes for sulfasalazine in small bowel, colon and both small bowel and colonic sites was significant in colon only. Tremain 1994, data not reported for Asacol

A *post-hoc* subgroup analysis of the original guideline analysis was carried out based on drug type. The results are presented below:

Figure 3: Induction of remission: sulfasalazine versus placebo

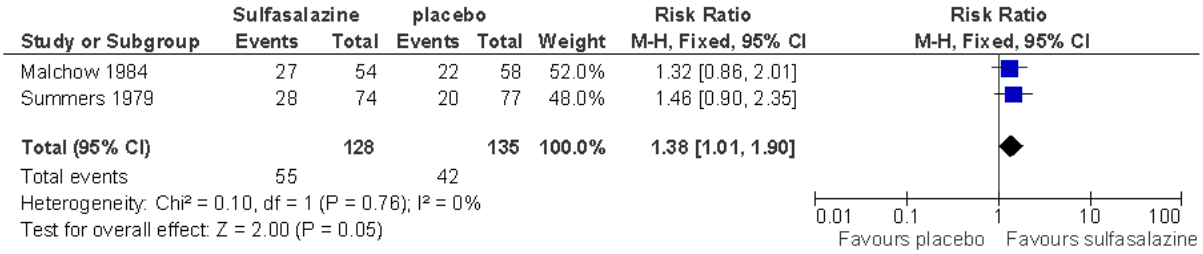


Figure 4: Induction of remission: Pentasa 1-2 g (controlled-release) versus placebo (Note heterogeneity)

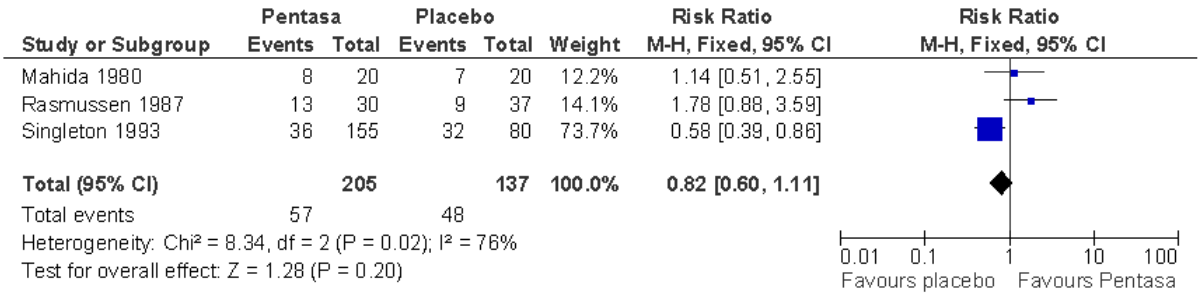


Figure 5: Induction of remission: Pentasa 4 g (controlled-release) versus placebo

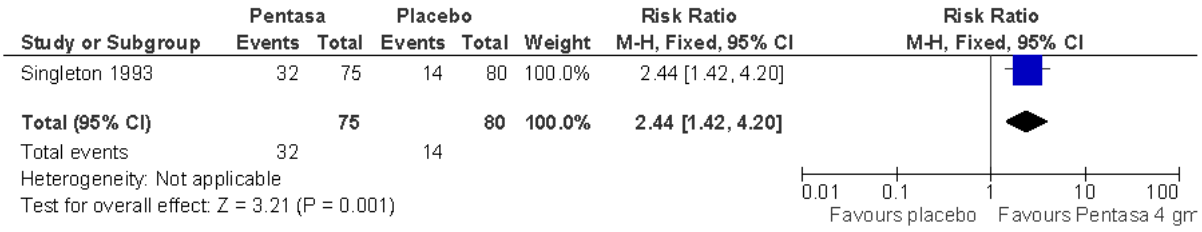


Figure 6: Induction of remission: Pentasa (controlled release - highest dose in study: Mahida and Rasmussen 1-2 g and Singleton 4 g) versus placebo

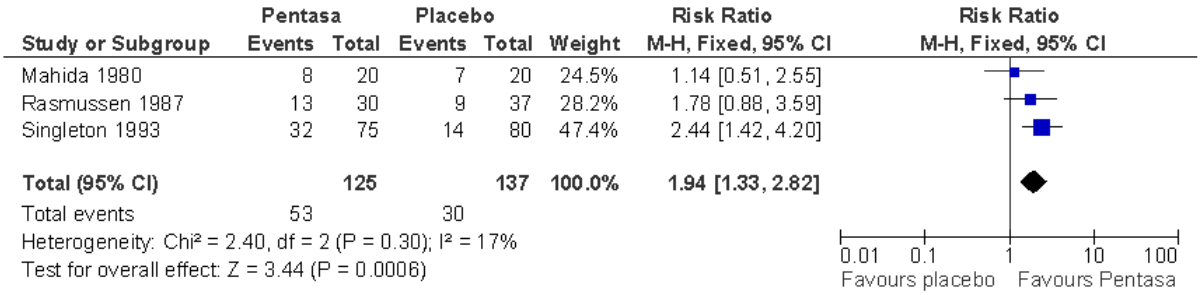
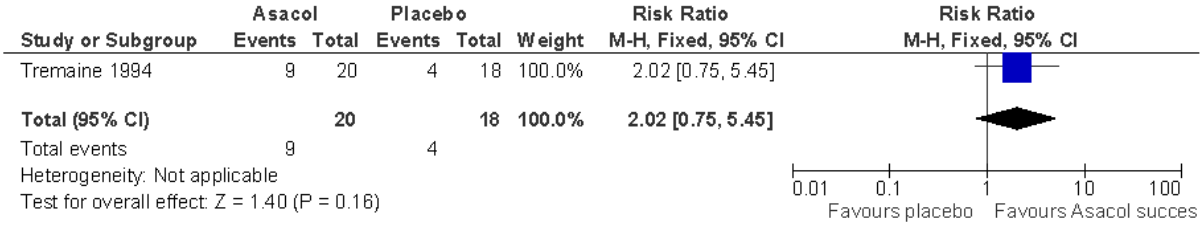


Figure 7: Induction of remission: Asacol 3.2 gm/day (delayed release - complete success CDAI < 150 with > 70 points reduction) versus placebo



In order to evaluate subgroup interaction it was necessary to plot all the subgroups on the same forest plot in order to pool data across groups. Inverse variance rather than the Mantel-Haenszel test used to calculate risk ratio in this analysis.

Figure 8: *Post-hoc* sub group analysis for Guideline analysis (Singleton 4 g/day) based on drug delivery mechanism

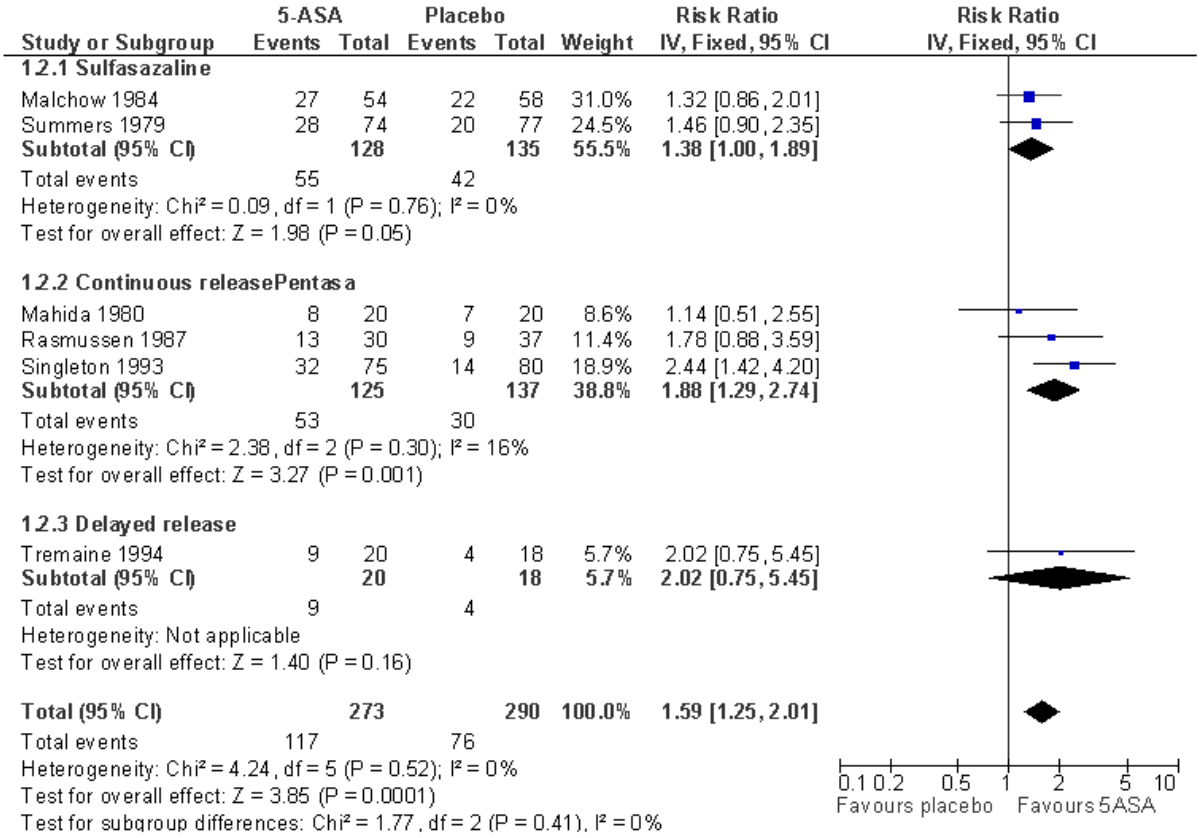
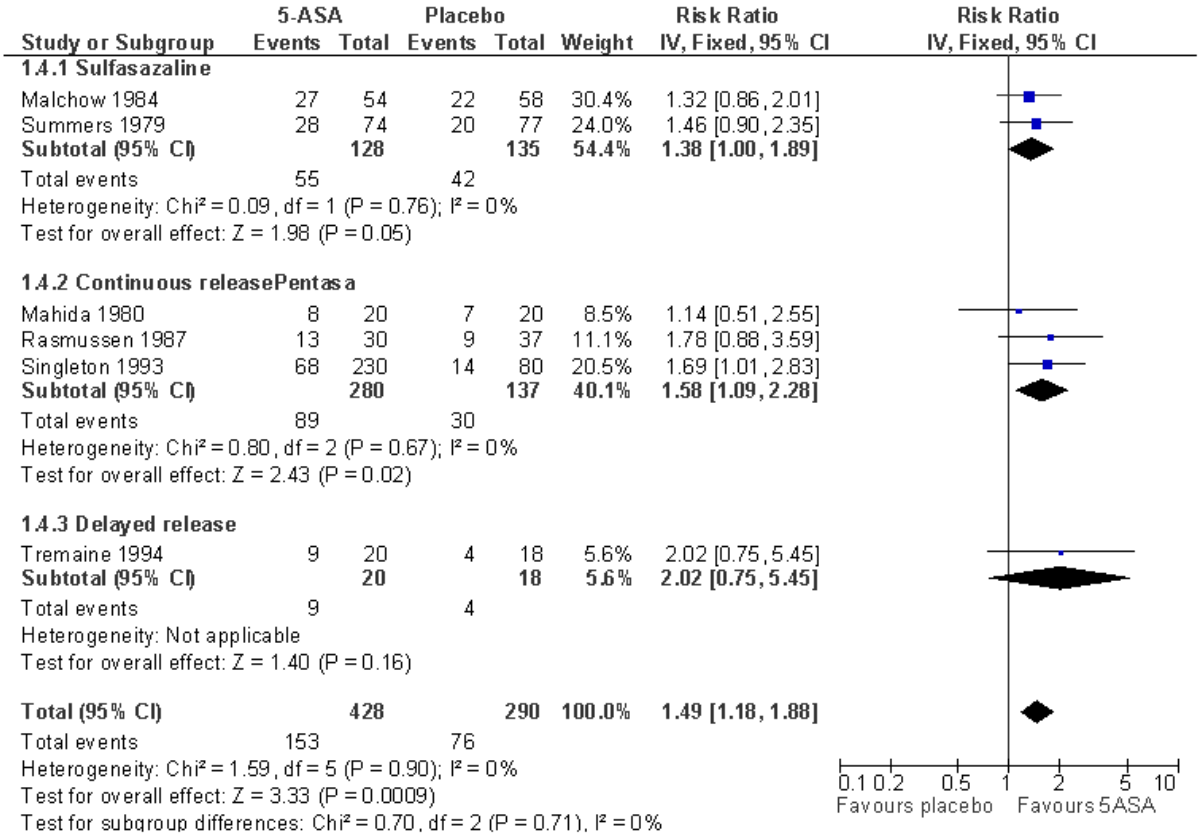


Figure 9: *Post hoc* Sub group analysis for Guideline analysis based on drug delivery mechanism



1.4 Evidence Summary

After applying a methodologically-rigorous approach to a *post-hoc* subgroup analysis, a test for interaction between groups of different drug delivery mechanisms did not show an interaction with the outcome, induction of remission. Therefore unless there are important differences in adverse events or costs, the recommendation should be for the 5-ASA class as a whole and the relative risk should be that for the whole meta-analysis. This analysis showed an effect which favoured 5-ASA s versus placebo for induction of remission in Crohn's disease. The current recommendation for use in individuals who are not able to tolerate glucocorticosteroid may represent an indirect comparison with the general population.

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