Title: Budesonide treatment for microscopic colitis: systematic review and meta-analysis.

Authors:

Sebastian S [1,2], Wilhelm A [3], Lisle Jessica [1], Myers S [1], Veysey M [2].

Author Affiliations:

1. IBD Unit, Hull and East Yorkshire NHS Trust, Hull, United Kingdom
2. Hull York Medical School, Hull, United Kingdom
3. Tillotts Pharma UK Ltd, Lincoln, United Kingdom

Corresponding author:

Professor Shaji Sebastian MD FRCP

IBD Unit

Department of Gastroenterology

Hull & East Yorkshire NHS Trust

Hull, United Kingdom

E: shaji.sebastian@hey.nhs.uk

Conflicts of interest:

Shaji Sebastian: Received travel grants, speaker and advisory board honoraria from Tillotts Pharma, Takeda, Merck, AbbVie, Janssen, Ferring, Pharmacosmos and Pfizer. Received research grants from Takeda, AbbVie, Merck and Warner Chilcott

Annika Wilhelm: Employee of Tillotts Pharma

Sally Myers, Jessica Lisle, Martin Veysey- No conflicts of interest to declare

This is a non-final version of an article published in final form in : Sebastian, S., Wilhelm, A., Lisle, J., Myers, S., & Veysey, M. (in press). Budesonide treatment for microscopic colitis: systematic review and meta-analysis. European Journal of Gastroenterology and Hepatology, https://doi.org/10.1097/MEG.0000000000001456

Abstract:

Microscopic colitis, encompassing lymphocytic and collagenous colitis, is a common cause for chronic non-bloody diarrhoea, which impacts significantly on the quality of life for patients. Despite increasing awareness of the condition and its treatment, there is considerable variation in therapeutic approaches.

To conduct a systematic review and meta-analysis on the efficacy and safety of budesonide in the treatment of microscopic colitis.

We searched MEDLINE, EMBASE and CENTRAL databases using predefined search methodology for randomised trials using budesonide in the treatment of microscopic colitis. We extracted data, on the efficacy and safety of budesonide, from studies identified that met the feasibility for analysis criteria. These data were pooled with a fixed effects model.

Nine studies met the inclusion criteria for analysis. The pooled odds ratios (OR) for response to budesonide therapy at induction and maintenance were 7.34 (95% CI 4.08 to 13.19) and 8.35 (95% CI 4.14 to 16.85) respectively. Histological response rates were superior in budesonide-treated patients compared to placebo following induction (OR 11.52, 95% CI 5.67 to23.40) and maintenance treatment (OR 5.88, 95% CI 1.90 to 18.17). There was no difference in adverse events. Significant relapse rates (>50%) were observed following treatment cessation with no difference noted between the budesonide or the placebo-treated patients

Budesonide is an effective treatment option for microscopic colitis for achieving induction and maintenance of both clinical and histological response. High relapse rates on treatment cessation were observed.

Short tile: Budesonide for microscopic colitis

Key words; microscopic colitis, lymphocytic colitis, collagenous colitis, therapies, meta-analysis, budesonide

Introduction

In the last two decades, microscopic colitis (MC) has emerged as a frequent cause of watery, non-bloody diarrhoea with some studies reporting incidence rates similar to ulcerative colitis and Crohn`s disease (1,2). The aetiology of MC is unknown and it is associated with other autoimmune diseases, including coeliac disease, polyarthritis, and thyroid disorders (3). The hallmark of MC is chronic, non-bloody, watery diarrhoea, with greater than three bowel movements per 24 hours (day and night). At colonoscopy, the mucosa appears normal or near normal but there are specific histopathological abnormalities on biopsy (4).

Microscopic colitis (MC) includes two sub-types: collagenous colitis (CC) and lymphocytic colitis (LC). The clinical features, symptoms and responses to treatment are similar for both LC and CC, therefore the two subtypes are often considered together as MC (5). LC typically has a shorter disease course (6,7) and is milder than CC. Diarrhoea persists on a continuous basis in 10 to 15% of cases (4).

While the symptoms of MC can be debilitating, the disease often has a benign course and is intermittent. It does not increase mortality or the risk of colorectal cancer and only rarely requires surgery (8). However, MC may lead to impaired health quality of life (QoL) and social handicap (9,11). Multiple medications have been trialled in the treatment of MC, with the aim of resolving symptoms, improving QoL, and preventing symptom relapse, while minimizing any adverse effects of the therapy (12,13). These medications, such as corticosteroids, mesalazine and anti-diarrheals, have variable response rates (14,15).

Budesonide is a topically acting steroid with extensive first pass metabolism and therefore low systemic exposure, (16). A number of uncontrolled studies and randomised placebo controlled trials have been performed recently using budesonide in both CC and LC. While the dose and duration of use has been variable in the reported studies, a response rate of up to 80% has been reported in MC using budesonide (17, 18, 19). Two separate Cochrane

Collaboration Systematic Literature Reviews and pooled meta-analyses were published for CC and LC documenting separately the evidence base to date for efficacy and safety for a range of interventions (20, 21). The review for CC concluded that budesonide was effective for inducing and maintaining clinical and histological response in patients with CC, while the evidence for all other agents was weak. The review for LC concluded that there is low quality evidence that budesonide may be effective for the treatment of active LC and recommended further research to broaden the evidence base. Beyond these reviews, there have been no other attempts to systematically compare the efficacy and safety of budesonide in the treatment of MC. These reviews did not include any uncontrolled studies.

In this review, we aimed to identify and summarize all the available evidence on the efficacy and safety of budesonide for MC, without distinguishing between CC and LC, and for the two available budesonide formulations (Entocort and Budenofalk).

Methods:

Search Strategy:

Medline, EMBASE, CENTRAL were searched using a pre-defined search strategy through OVID® until September 2018. We used the MESH terms: colitis, microscopic colitis, collagenous colitis, lymphocytic colitis, treatment, randomised, gluco-corticosteroids, glucocorticoids, steroids, budesonide, response, remission and relapse. The search string was combined for all three databases CENTRAL, EMBASE and MEDLINE.

Study Screening

The identified studies from search were screened against the pre-determined eligibility criteria by 2 independent researchers for Population, Intervention(s), Comparator(s), Outcome(s) and Study design (PICOS), presented in ~~Table 1 in~~ (**Supplement File 1)**. If exclusion of a record based on its title/abstract was not possible, the full publication was retrieved and evaluated against the eligibility criteria in the second stage of screening. This

second stage was also performed by two independent researchers. When consensus was not achieved a third researcher was involved. The inclusion and exclusion process were documented including reviewers' initials, the reason for exclusion (if applicable), and additional comments on the decision.

Data Extraction

For both the systematic literature review update and studies from the Cochrane reviews, data extraction was performed using a standardized data extraction form. Data extraction of all studies found in the search were extracted from the original full text articles. All extraction was performed by one researcher and checked by an independent researcher. Any discrepancies were resolved by a third party. If multiple papers or conference abstracts referred to the same trial, these were grouped in data extraction, and all information was combined.

Extracted data included information on study and patient characteristics, as well as outcomes of interest. The definition of each outcome was extracted alongside summary statistics of interest and measures of uncertainty. The parameters extracted are reported in **supplementary file 2.**

Risk of Bias of Studies

All studies were critically appraised from the original articles using the Cochrane Risk of Bias Tool. This tool is a valid comparator and has been tested for internal consistency, reliability, and validity (22). The two-part tool addresses seven domains of potential bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. The first part of the tool describes how the study was conducted in sufficient detail to

support a judgment about the risk of bias. The second part of the tool assigns a judgment relating to the risk of bias for that study. Each study was judged by one reviewer and checked by a second reviewer. This judgement was achieved by assigning a rating of 'Low', 'High' or 'Unclear' risk of bias to each domain in the tool.

Feasibility and heterogeneity assessment

The feasibility of conducting a valid meta-analysis was assessed by a detailed assessment of heterogeneity in terms of outcome definitions. Heterogeneity was assessed based on Cochranes Q based on chi-square test and I^2 statistic with >75% considered as high heterogeneity. For each outcome, the outcome definitions from each study were presented in tables. Induction and maintenance were always reported separately. We assessed whether the outcome definitions were comparable. The outcome definitions of clinical induction, clinical maintenance, histological response, adverse events, serious adverse events and withdrawal due to adverse events were considered comparable.

Summary of analyses

Analyses were performed separately for induction and maintenance outcomes. The outcomes analyzed were: clinical induction, histological induction, clinical maintenance, histological maintenance, adverse events, withdrawals due to adverse events and relapse rates following stopping treatments. For these outcomes, the comparison of budesonide versus placebo was analyzed.

As all studies are estimating the same effect based on comparable data, we used a fixed effects model using Revman V 5.3 software. Mantel-Hansel odds ratios were used to calculate pooled effect estimates.

Results

1. Study selection

A PRISMA flow diagram of the studies included and excluded at each stage is provided in **Figure 1**. Ten RCTs, that met the pre-defined criteria for inclusion, were identified for final analysis (23-32).

2. Risk of bias

The Cochrane Risk of Bias Tool was used to assess the risk of bias in the included RCTs.

Figure 2 shows the risk of bias with respect to the checklist for each study. The reviewer evaluated every section of the critical appraisal and if the answer (or answers if there is more than one question per section) provided sufficient information results, were assessed as "low risk of bias" (green), for the insufficient data as "unclear" (yellow), and for not in line as "high risk of bias" (red).

All ten studies included in the meta-analysis used appropriate methods for random sequence allocation and there was no risk for other types of bias. Pardi et al (24) was unclear on performance bias, because the authors did not formally assess whether patients knew which treatment they received. Bonderup et al. (26) scored a high-risk on attrition bias and reporting bias, because there was no clear description of withdrawals and dropouts. Moreover, there was very limited information on the relapse of clinical symptoms in the eight weeks that patients were followed after ending treatment. Munch et al. (28) did not give information on the concealment of treatment allocation. It was unclear how the participants were blinded to the intervention. This study also scored a high risk on attrition bias and reporting bias, because the discontinuation of the study by participants was not equally

distributed over the budesonide and placebo group. In addition, the achievement of histological remission was not reported in the results section, even though this was a secondary endpoint in the study.

3. Main Results:

3:1: Induction of response

3:1:1: Clinical response at induction

Seven studies with a total of 256 participants compared budesonide with placebo (Baert et al (30), Miehlke et al.2002 (31), Miehlke et al. 2018 (32), Bonderup et al. (26), Miehlke et al.2009 (23), Pardi et al. (24) Miehlke et al. 2014 (29). After 6 to 8 weeks of treatment 105 of 128 patients (82.03%) treated with budesonide achieved a clinical response compared to 49 of 128 patients (38.28%) treated with placebo. The pooled odds ratio for response to budesonide therapy was 7.34 (95% CI 4.08 to 13.19) **(Figure 3)**

To test the influence of studies examining LC to CC, the meta-analysis for budesonide on clinical induction was split by MC type, results showed comparable odds ratios for both MC sub-types. The pooled odds ratio for response to budesonide therapy in LC studies was 8.05 (95% CI = 3.05, 21.26) **(Figure 4)** and in CC was 7.65 (95% CI = 3.66, 15.98) **(Figure 5).**

3:1:2: Histological response at induction

Seven studies with a total of 228 participants compared budesonide with placebo (Miehlke et al 2002 (31), Miehlke et al 2009 (23), Miehlke et al 2014 (29) Bonderup et al. (26), Pardi et al. (24) and Miehlke et al 2018 (32). Histological remission was achieved by 91 of 115 (79.13%) patients in the budesonide group and 36 of 113(31.85%) patients in the placebo

group. The pooled odds ratio for histological response was in favour of budesonide with an OR of 11.52 (95% CI 5.67,23.40) (**Figure 6)**

3:2: Maintenance of response

3:2:1: Maintenance of Clinical response

Three studies with a total of 172 participants compared budesonide with placebo (Bonderup et al. (27), Miehlke et al. (25), Munch et al. (28). These 172 participants were treated initially with open-label budesonide 4.5-9 mg/day for 6-8 weeks with a favourable response. 84 patients were then randomized to budesonide 4.5-6 mg/day and 88 were randomized to placebo for 6-12 months. At the end of the study period, 57 of 84 patients (67.9%) treated with budesonide and 18 of 88 patients (20.5%) treated with placebo had sustained their response. The pooled odds ratio was 8.35 (95% CI 4.14 to 16.85) **(Figure 7).**

3:2:2: Maintenance of histological remission

Two studies with a total of 80 participants compared budesonide with placebo (Bonderup et al (27). 2008, Miehlke et al. (25). These 80 participants were treated with open-label budesonide 9 mg/day for 6 weeks and responded to the treatment. Forty patients were randomized to budesonide 6 mg/day and 40 were randomized to placebo for 6 months. At the end of the 6 months, 25 patients treated with budesonide and 19 patients treated with placebo, all with a maintained clinical response, underwent a follow up colonoscopy or sigmoidoscopy. Nineteen of 25 patients treated with budesonide and 6 of 19 patients treated with placebo had a maintained histological response. The pooled odds ratio was 5.88 (95% CI 1.90, 18.17) (**Figure 8)**

3:3 Relapse following discontinuation of treatment

Twelve months of follow-up, after cessation of treatment in the trials, was evaluated in four studies (Bonderup et al (26), Miehlke et al 2008 (25), Miehlke et al 2009 (23), Munch et al

(28) and Miehlke et al 2018 (32) involving 147 patients. Overall, more than 50% of patients relapsed following cessation of treatment with budesonide. The pooled odds ratios for relapse were not different between those who received budesonide or placebo at randomisation (OR 1.02, 95% CI 0.52-2.01). **(Figure 9).** However, there was significant heterogeneity between the studies with different durations of follow up following treatment cessation with longer follow up studies showing higher relapse rates.

3:4: Adverse Events

Adverse events were recorded in eight of the studies. In total 81 of 191 patients who received budesonide in these trials had an adverse event when compared to 75 of the 199 patients who received placebo. The difference in pooled risk ratio for adverse events between budesonide and placebo was not significant (OR 1.32, 95% CI 0.86,2.03) **(Figure 10).** The most common adverse event recorded in the budesonide group was headache. Withdrawal from the study due to adverse events was recorded to be 12 and 11 patients receiving budesonide or placebo respectively (pooled OR 1.16, 95% CI 0.51,2.64) **(Figure 11).**

3:5: Quality of life

Two studies reported on quality of life after induction phase of treatment. Miehlke et al 2002. (31) compared budesonide with placebo and reported the QoL with the GIQLI. The mean change from baseline in the budesonide group was 25, whereas the mean change from baseline in the placebo group was 2. Miehlke et al. 2009 (23) compared budesonide with placebo and reported the QoL with the SF-36- mental and SF-36 – physical. The mean change from baseline on the SF-36 – mental scale was 0.4 for the budesonide group and 0.1 for the placebo group (p= 0.01). The mean change from baseline on the SF-36 – physical

scale was 7 for the budesonide group and 3.9 for the placebo group (p=0.01). No pooled analysis was possible because of inconsistency in reported outcomes.

Among the studies reporting maintenance treatment Munch et al. (28) reported QoL with 4 SHS scales and 1 PGWBI score. The mean change from baseline on the SHS score symptom burden scale was 0 for the budesonide group and 69 for the placebo group. The mean change from baseline on the SHS score social function score was 0 in the budesonide group and 57 in the placebo group. The mean change from baseline on the SHS score disease-related worry scale was 1 in the budesonide group and 33 in the placebo group. The mean change in baseline on the SHS score general well-being scale was -8 in the budesonide group and 24 in the placebo group (p=0.001). The mean change from baseline on the PGWBI global score was -5.4 for the budesonide group and -13.6 for the placebo group (p=0.03).

Discussion

The pooled analyses for clinical induction showed good evidence that budesonide is an effective treatment option for clinical induction for MC. All studies within the analyses showed efficacy levels that were comparable in direction and magnitude. As an exploratory analysis the contribution of budesonide to LC and CC was examined separately to compare the magnitude of efficacy between these two MC subtypes. Pooled analyses showed comparable findings for clinical induction, irrespective of MC type. Furthermore, histological response rates showed that budesonide was significantly more effective than placebo.

Budesonide was also shown to be a good intervention for clinical and histological maintenance, although, it needs to be kept in mind that only studies examining CC contributed to this analysis. However, given that for clinical induction CC and LC had a comparable contribution, and their aetiologies are comparable, it is not unreasonable to

assume that this level of efficacy for budesonide may be seen across all sub-types of MC with respect to clinical and histological maintenance.

In terms of adverse events (induction and maintenance) and withdrawals due to adverse events (maintenance), there were no significant differences between budesonide and placebo. These data suggest that budesonide treatment is well-tolerated for MC. Serious adverse events (maintenance) and withdrawals due to adverse events (induction) could not be pooled.

The two previous reviews in this area looked at LC and CC independently. The review for CC (21) concluded that budesonide was effective for inducing and maintaining clinical and histological response in patients with CC, while the evidence for all other compared agents was weak. The review for LC (20) concluded that there is low quality evidence that budesonide may be effective for the treatment of active LC and recommended further research, to broaden the evidence base. The current study sought to summarise the efficacy of budesonide on MC without reference to sub-type.

The current pooled analysis reports high recurrence rates following cessation of budesonide therapy. Relapse of the symptoms of microscopic colitis was reported in four of the studies included in the meta analysis. In the Bonderup study (26), 80% (8 out of 10) of patients randomised to budesonide relapsed within eight weeks after stopping treatment. In the Munch et al study (28) after the double-blind phase of one year, treatment free follow up of six months was done in 28 patients and 23 of them relapsed (82%) with median time to relapse of 40 days. On multivariate analysis, the relapse rate was associated with increased age and an increased number of stools per day at inclusion. In a randomised placebo controlled cross-over design study, Miehlke and colleagues showed a relapse rate of 61% after a mean interval of ten weeks. Patients older than 60 years, at inclusion, were identified as most likely to relapse. 80% of the relapsed patients were re-treated with budesonide and all responded. In

the 54 patients who were followed up following completion of treatment , relapse was observed in 19 patients (35%) with a mean time to relapse of 58 days. Once again a significant proportion (14/19) achieved remission on re-treatment. Similar relapse rates were also noted in the cohort studies indicating that the majority of patients relapse following cessation of budesonide treatment.

It is important to highlight that many of the studies included in the current evidence base are small RCT's, with relatively short follow-up periods. Thus, the generalizability of the studies and power to detect long-term efficacy and safety may be limited. Two important aspects in relation to efficacy remain unclear. Firstly, what is the optimal duration and dose of treatment when first diagnosed with MC and, secondly, should patients be treated with repeated short courses of budesonide and if so what dosing schedules and duration should be used. Munch et al (28) indicated that long-term treatment up to one year using low dose budesonide at 4.5mg per day was effective in maintaining remission in 61% of patients. However, this is less than the 84% response following induction with 9mg budesonide in their study. In the two other maintenance studies (25,27), the dose used was 6 mg and there were higher response rates of 76.5% and 73.9%. This suggests that there is a dose effect in maintenance of response rates. Furthermore, even after one year of treatment the majority of the patients (82.1%) relapsed indicating that prolonged treatment does not reduce risk of relapses on treatment cessation. The majority of relapses occurred within three months of stopping treatment and it is not clear whether intermittent short retreatment with doses ranging between 4.5 to 9mg is a viable and well-tolerated option for patients with recurrent flares (34,35,36). One recent cohort study, with long-term follow-up, reported the requirement of high dose budesonide for maintaining remission (37). No new safety signals were noted in the study with longest follow up (28). Despite inconsistent data in literature suggesting long-term treatment with budesonide in MC patients may lead to adverse effects (38,39), there is currently no solid

evidence for an increased risk of adverse events in long-term treatment with low-dose budesonide. Interventions such as immunomodulatory agents (thiopurines, methotrexate, biologics) are used to maintain remission in ulcerative colitis and Crohn`s disease has yielded mixed results in microscopic colitis (40,41,42) although there are no placebo-controlled trails in this setting.

Furthermore, the current indicators of a relapse and hence the prompt to restart treatment are symptoms, as there is no biomarker-based monitoring for MC (43). This may be relevant as recent data suggest that there is a significant overlap between symptoms of irritable bowel syndrome (44,45). Up to one third of patients, with microscopic colitis, have co-existent symptoms and risk factors for irritable bowel syndrome (45). Indices to predict microscopic colitis which have been recently developed (46,47) may be useful in future once they have been fully validated in multiple cohorts and this has led to the development of clinical decision tools (48).

While histological response with budesonide was noted in the studies included in the review, the impact of histological healing in microscopic colitis on disease course, similar to that in ulcerative colitis and Crohn`s disease has not been extensively evaluated. In one study, histology for baseline and at the end of budesonide treatment was included in the analysis on risk factors for clinical relapse (33) and suggested that histology appears not to be a risk factor for relapse. As a consequence, there is currently no recommendation for histological follow-up in MC. Future studies should assess the impact of mucosal healing and make recommendations to standardise histological assessment in MC (48).

Prior exposure to certain commonly used drugs, such as non-steroidal anti-inflammatories and proton pump inhibitors, which some authors have suggested may trigger MC (50,51), and the impact of their cessation and reintroduction could not be determined from the studies in

this review. There is a suggestion that patients on offending drugs should be excluded from clinical trials of MC (52,53) but as these drugs are so widely used this may prove difficult to do.

Finally, while the quality of life assessment was done in some of the studies included in this meta-analysis and these suggested that there was an improvement in quality of life measures, no economic analysis has been done. Direct and indirect costs to the patients and health economy should be assessed in future prospective studies.

Conclusions

In summary, our review and meta-analysis has provided comprehensive evidence that budesonide should be considered as an effective treatment option for clinical induction and maintenance of remission in patients with MC. The safety profile appears favourable but the relapse rates are high. Randomised controlled trials with additional interventions for maintaining long term remission and reducing the risk of relapses are required. Further prospective real-world studies to evaluate diagnostic and early treatment pathways are also recommended.

References

1. Agnarsdottir M, Gunnlaugsson O, Orvar KB, et al. Collagenous and lymphocyitic colitis in Iceland. Dig Dis Sci 2002;47:1122-8.
2. Pardi DS, Loftus EV Jr, Smyrk TC, et al. The epidemiology of micoscopic colitis:a population based study in Olmsted County,Minnesota. Gut 2007;56:504-8.

3. Vigren L, Tysk C, Strom M, et al. Celiac disease and other autoimmune diseases in patients with collagenous colitis. Scand J Gastroenterol 2013;48:944–950.
4. Munch A, Langner . Microscopic colitisc: linical and pathologic perspectives. Clinical Gastroenterology and Hepatology 2015; 13:228–236.
5. Pardi DS, Tremaine WJ, Carrasco-Labra A . American Gastroenterological Association Institute Technical Review on the Medical Management of Microscopic Colitis." Gastroenterology 2016;150(1): 247-274.e211.
6. Rasmussen, M. A. and L. K. Munck. Systematic review: are lymphocytic colitis and collagenous colitis two subtypes of the same disease - microscopic colitis?" Alimentary pharmacology and therapeutics 2012;36: 79-90.
7. Colussi D, Salari B, Stewart KO, Lauwers GY, et al. Clinical characteristics and patterns and predictors of response to therapy in collagenous and lymphocytic colitis. Scandinavian Journal of Gastroenterology 2015;50: 1382-1388.
8. Yen EF, Pokhrel B, Bianchi LK, et al. Decreased colorectal cancer and adenoma risk in patients with microscopic colitis. Dig Dis Sci 2012;57(1):161-9
9. Hjortswang H, Tysk C, Bohr J, et al. Health-related quality of life is impaired in active collagenous colitis. Dig Liver Dis 2011; 43(2): 102-109.
10. Roth B, Ohlsson B. Gastrointestinal symptoms and psychological well-being in patients with microscopic colitis. Scand J Gastroenterol. 2013 ;48(1):27-34.
11. Nyhlin N, Wickbom A, Montgomery SM, et al Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case-control study. Aliment Pharmacol Ther. 2014 ;39(9):963-72.
12. Cotter TG, Kamboj AK, Hicks SB et al Immune modulator therapy for microscopic colitis in a case series of 73 patients. Aliment Pharmacol Ther. 2017 ;46(2):169-174

13. Cotter TG, Pardi DS. Current Approach to the Evaluation and Management of Microscopic Colitis Curr Gastroenterol Rep. 2017 ;19(2):8.
14. Nyhlin N, Bohr J, Eriksson S, Tysk C. Systematic review: microscopic colitis. Aliment Pharmacol Ther. 2006 ;1;23(11):1525-34.
15. Park T, Cave D, Marshall C. Microscopic colitis: A review of aetiology, treatment and refractory disease. World J Gastroenterol 2015 21(29): 8804-8810.
16. Spenser CM, McTavish D. Budesonide: A review of its pharmacological proprerties and therapeutic efficacy in inflammatory bowel disease. Drugs 1995;50:854-72.
17. Chande N, McDonald JW, Macdonald JK. Interventions for treating collagenous colitis. Cochrane Database Syst Rev 2008 (2a): CD003575.
18. Chande N, McDonald JW, Macdonald JK. Interventions for treating lymphocytic colitis. Cochrane Database Syst Rev 2008 (2b): CD006096.
19. Chande N, MacDonald JK, McDonald JW. Interventions for Treating Microscopic Colitis: A Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Review Group Systematic Review of Randomized Trials. Am J Gastroenterol 2009;104:235-241.
20. Chande N, Bhanji N, Nguyen T, et al. Interventions for treating lymphocytic colitis. Cochrane Database of Systematic Reviews 2017 (7) (CD006096).
21. Kafil TS, Nguyen TM, Patton PH, et al Interventions for treating collagenous colitis. Cochrane Database Syst Rev. 2017 ;11:CD003575.
22. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]." from http://handbook.cochrane.
23. Miehlke S, Madisch A, Karimi A, et al. Budesonide Is Effective in Treating Lymphocytic Colitis: A Randomized Double-Blind Placebo-Controlled Study. Gastroenterology 2009;136(7): 2092-2100

24. Pardi DS, Tremaine EV, Sandborn WJ. etal. A randomized, double-blind, placebo-controlled trial of budesonide for the treatment of active lymphocytic colitis. Gastroenterology 2009 ;1: A519-A520
25. Miehlke S, Madisch A, Bethke B, et al. Oral Budesonide for Maintenance Treatment of Collagenous Colitis: A Randomized, Double-Blind, Placebo-Controlled Trial. Gastroenterology 2008;135(5): 1510-1516.
26. Bonderup OK, Hansen JB, Birket-Smith L et al. Budesonide treatment of collagenous colitis: a randomised, double blind, placebo-controlled trial with morphometric analysis. Gut 2003;52(2): 248-251.
27. Bonderup OK, Hansen JB, Teglbjaerg PS, et al. Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. Gut 2009; 58(1): 68-72.
28. Munch A, Bohr J, Miehlke S, etal. Low-dose budesonide for maintenance of clinical remission in collagenous colitis: A randomised, placebo-controlled, 12-month trial. Gut 2016; 65(1): 47-56.
29. Miehlke S, Madisch A, Kupcinskas L et al. Budesonide is more effective than mesalamine or placebo in short-term treatment of collagenous colitis. Gastroenterology 2014;146(5): 1222-1230.
30. Baert F, Schmit A, D'Haens D, et al. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. Gastroenterology 2002;122(1): 20-25.
31. Miehlke S, Heymer P, Bethke B, et al. Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicentre trial. Gastroenterology 2002;123(4): 978-984

32. Miehlke S, Aust D, Mihaly E, et al. Efficacy and Safety of Budesonide, vs Mesalazine or Placebo, as Induction therapy for Lymphocytic Colitis. Gastroenterology 2018; 155(6):1795-1804.
33. Miehlke S, Hansen JB, Madisch A, et al. Risk factors for symptom relapse in collagenous colitis after withdrawal of short-term budesonide therapy. Inflamm Bowel Dis. 2013 ;19(13):2763-7.
34. Miehlke S, Madisch A, Voss C, et al. Long-term follow-up of collagenous colitis after induction of clinical remission with budesonide. Aliment Pharmacol Ther. 2005 ;22(11-12):1115-9.
35. Miehlke S, Madisch A, Bethke B, Stolte M. Time to remission with budesonide in collagenous colitis. Aliment Pharmacol Ther. 2005 15;21(12):1507-8
36. Fernández-Bañares F, Salas A, Esteve M, et al. Collagenous and lymphocytic colitis. evaluation of clinical and histological features, response to treatment, and long-term follow-up. Am J Gastroenterol. 2003 ;98(2):340-7.
37. Fernandez-Bañares F, Piqueras M, Guagnozzi D, et al. Collagenous colitis: Requirement for high-dose budesonide as maintenance treatment. Dig Liver Dis. 2017 ;49(9):973-97.
38. Wildt S, Munck LK, Becker S, Risk of osteoporosis in microscopic colitis. Postgrad Med. 2018 ;130(3):348-354
39. Tripathi K, Dunzendorfer T.Budesonide-Related Iatrogenic Cushing's Syndrome in Microscopic Colitis. ACG Case Rep J. 2017 4;4: e5
40. Cotter TG, Kamboj AK, Hicks SB, et al. Immune modulator therapy for microscopic colitis in a case series of 73 patients. Aliment Pharmacol Ther. 2017 ;46(2):169-174.

41. Münch A, Fernandez-Banares F, Munck LK. Azathioprine and mercaptopurine in the management of patients with chronic, active microscopic colitis. Aliment Pharmacol Ther. 2013 ;37(8):795-8
42. Münch A, Bohr J, Vigren L, Tysk C, Ström M. Lack of effect of methotrexate in budesonide-refractory collagenous colitis. Clin Exp Gastroenterol. 2013; 30(6):149-52
43. Pisani LF, Tontini GE, Marinoni B, et al Biomarkers and Microscopic Colitis: An Unmet Need in Clinical Practice. Front Med (Lausanne). 2017;10; 4:54.
44. Guagnozzi D, Arias Á, Lucendo AJ. Systematic review with meta-analysis: diagnostic overlap of microscopic colitis and functional bowel disorders. Aliment Pharmacol Ther. 2016 ;43(8):851-862.
45. Kane JS, Irvine AJ, Derwa Y, et al. High prevalence of irritable bowel syndrome-type symptoms in microscopic colitis: implications for treatment. Therap Adv Gastroenterol 2018 ;21; 11:1756284818783600.
46. Kane JS, Sood R, Law GR, et al. Validation and modification of a diagnostic scoring system to predict microscopic colitis. Scand J Gastroenterol. 2016 ;51(10):1206-12
47. Cotter TG, Binder M, Loftus EV Jr, et al. Development of a Microscopic Colitis Disease Activity Index: a prospective cohort study. Gut. 2018 ;67(3):441-446.
48. American Gastroenterological Association. AGA Institute Guideline on the Management of Microscopic Colitis: Clinical Decision Support Tool. Gastroenterology. 2016 ;150(1):276.
49. Langner C, Aust D, Ensari A, et al. Histology of microscopic colitis-review with a practical approach for pathologists. Histopathology. 2015 r;66(5):613-26.
50. Lucendo AJ. Drug Exposure and the Risk of Microscopic Colitis: A Critical Update Drugs R D. 2017 r;17(1):79-89

51. Verhaegh BP, de Vries F, Masclee AA, et al. High risk of drug-induced microscopic colitis with concomitant use of NSAIDs and proton pump inhibitors. Aliment Pharmacol Ther. 2016 ;43(9):10
52. Beaugerie L, Pardi DS Review article: drug-induced microscopic colitis - proposal for a scoring system and review of the literature. Aliment Pharmacol Ther. 2005 ;15;22(4):277-84.
53. Beaugerie L, Pardi DS Patients with drug-induced microscopic colitis should not be included in controlled trials assessing the efficacy of anti-inflammatory drugs in microscopic colitis. Gastroenterology. 2009; 137(4):1535-6.

Figure Legends

Figure 1: PRISMA Flow Chart

Figure 2: Risk Bias Assessment of selected studies

Green: No bias, Low risk of bias. Red: High risk of bias. Yellow: Unclear risk of bias

Figure 3: Clinical response induction

Figure 4: Clinical response at induction Lymphocytic colitis

Figure 5: Clinical response at induction Collagenous colitis

Figure 6: Histologic response at induction

Figure 7: Maintenance of clinical remission

Figure 8: Maintenance of histologic remission

Figure 9: Relapse rates following discontinuation of treatment

Figure 10: Adverse Events

Figure 11: Treatment withdrawal due to adverse events

Figure 1

Figure 1: PRISMA FLOW CHART

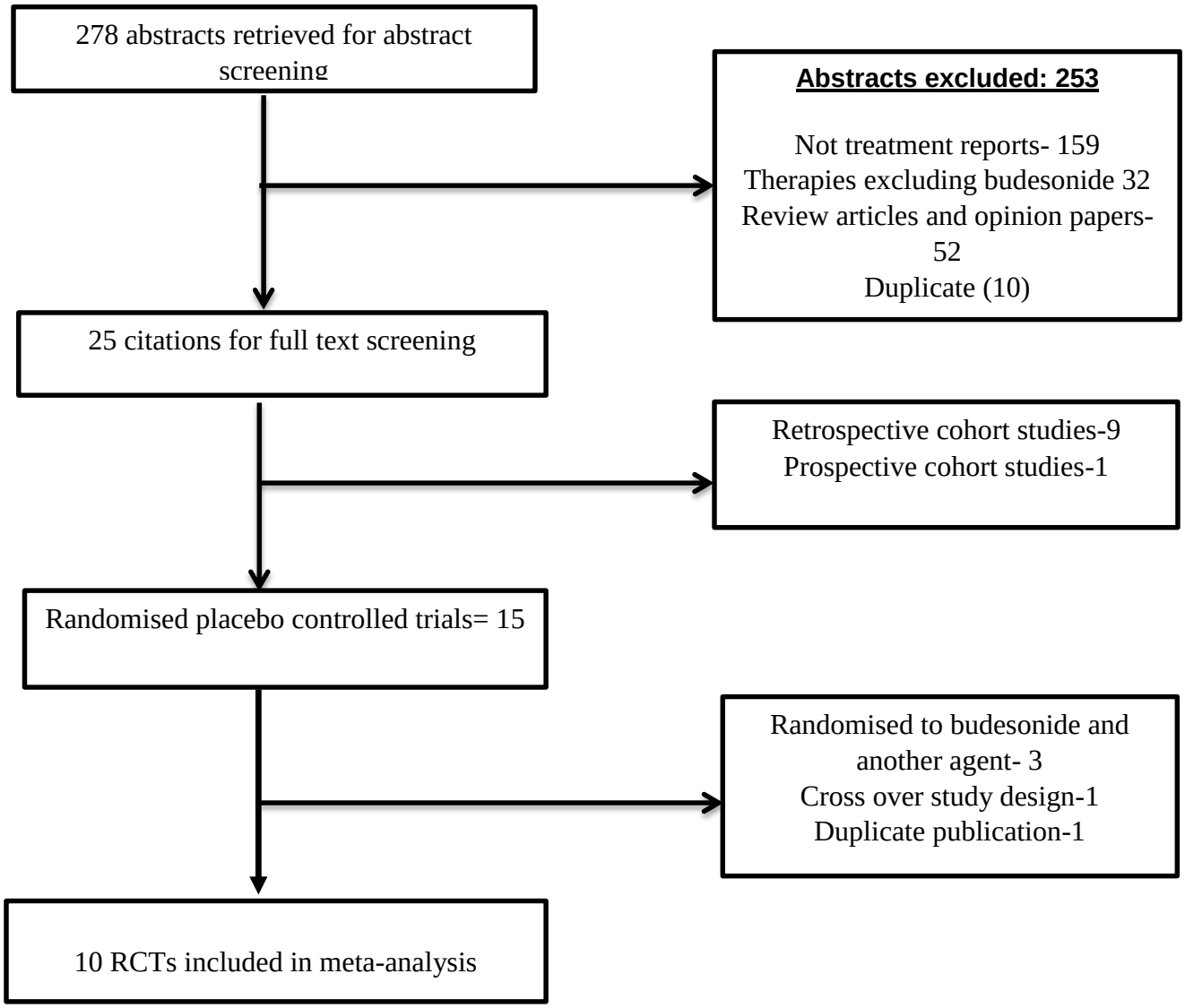
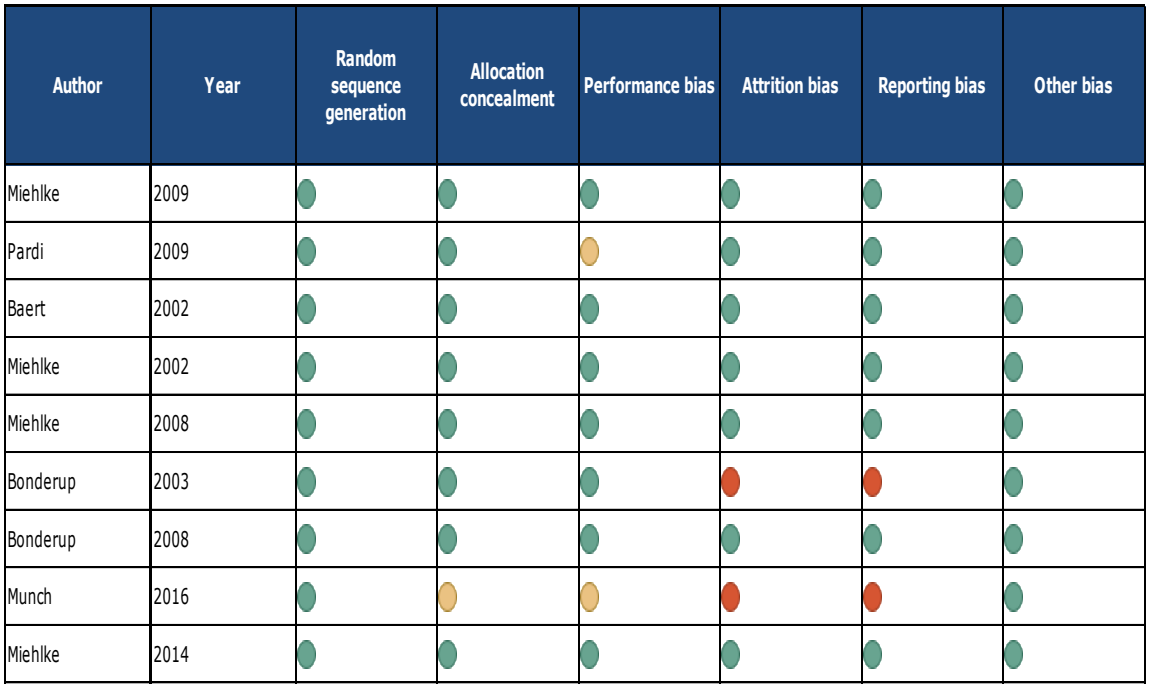


Figure 2

Figure 2: Risk Bias Assessment



Author	Year	Random sequence generation	Allocation concealment	Performance bias	Attrition bias	Reporting bias	Other bias
Miehlke	2009						
Pardi	2009						
Baert	2002						
Miehlke	2002						
Miehlke	2008						
Bonderup	2003						
Bonderup	2008						
Munch	2016						
Miehlke	2014						

Green: No bias, Low risk of bias . Red: High risk of bias. Yellow: Unclear risk of bias

Figure 3

Figure 3: Clinical response induction

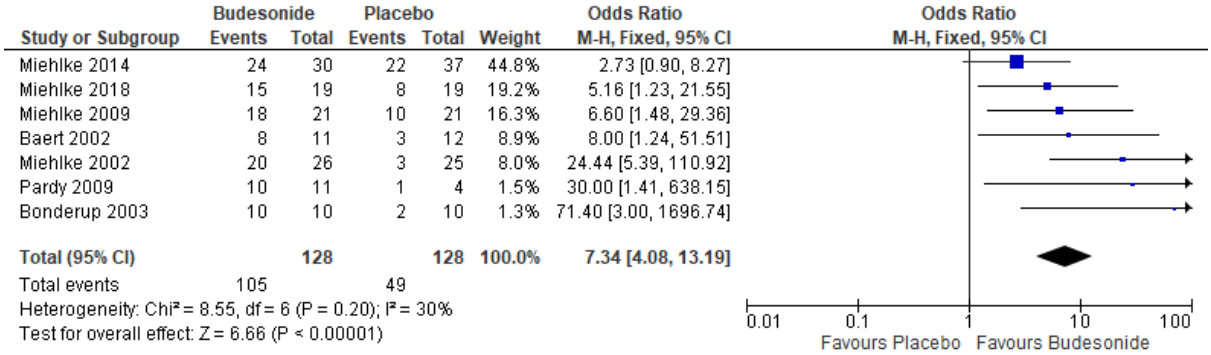


Figure 4

Figure 4: Clinical response at induction Lymphocytic colitis

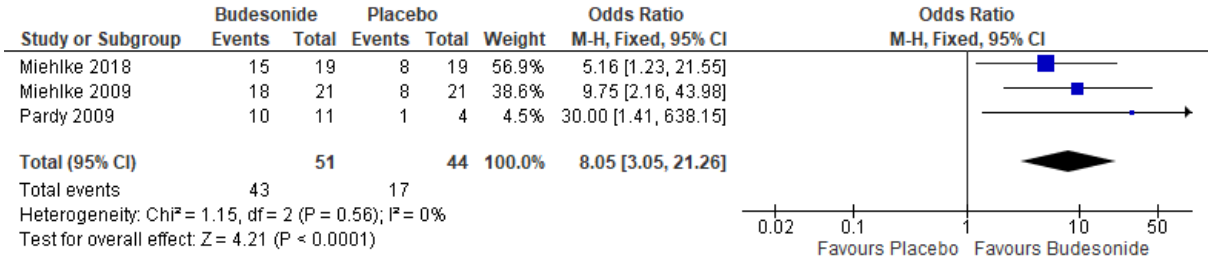


Figure 5

Figure 5: Clinical response at induction Collagenous colitis

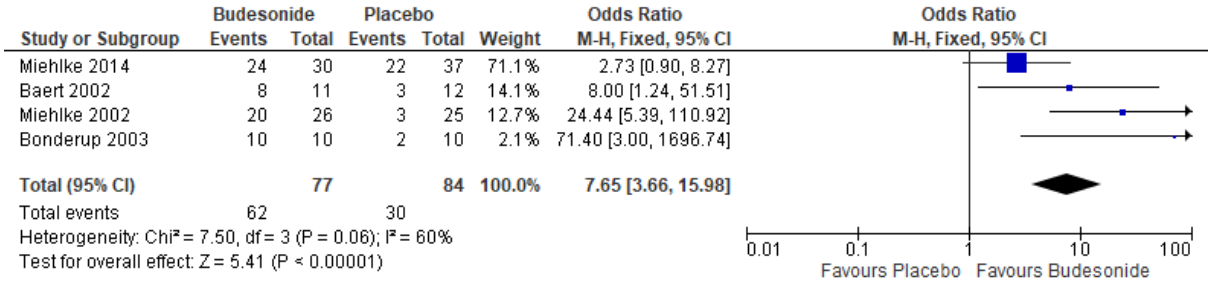


Figure 6

Figure 6: Histologic response at induction

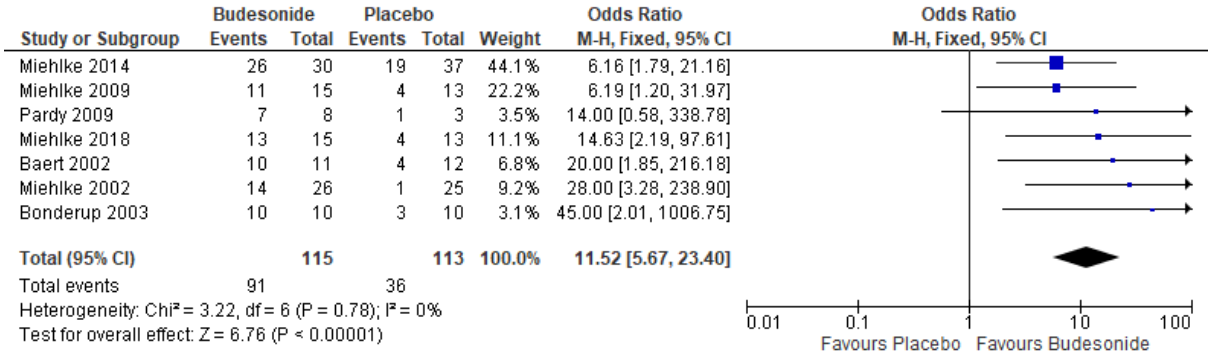


Figure 7

Figure 7: Maintenance of clinical remission

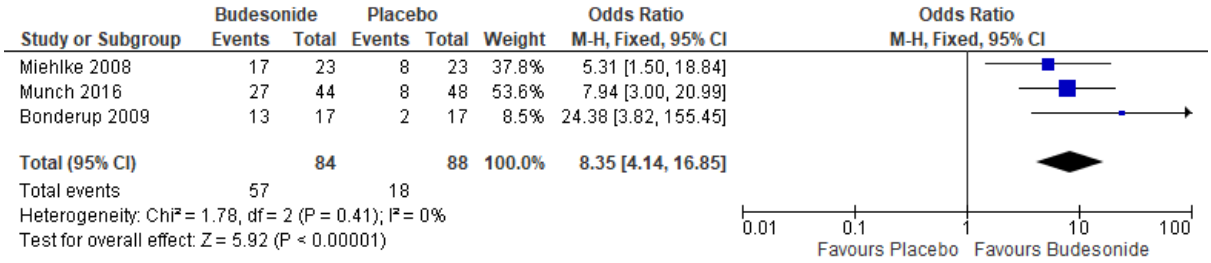


Figure 8

Figure 8: Maintenance of histologic remission

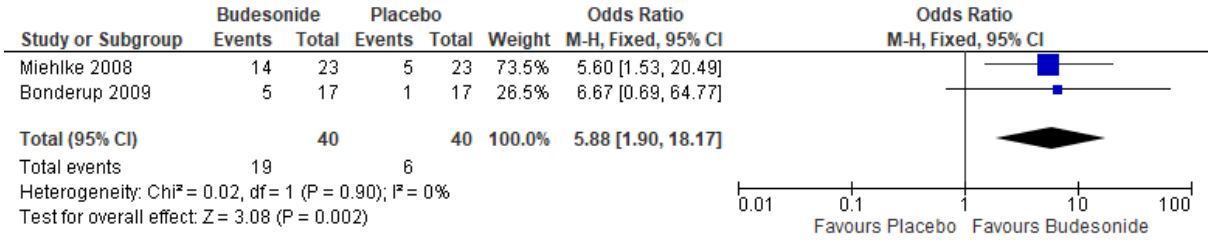


Figure 9

Figure 9: Relapse rates following discontinuation of treatment

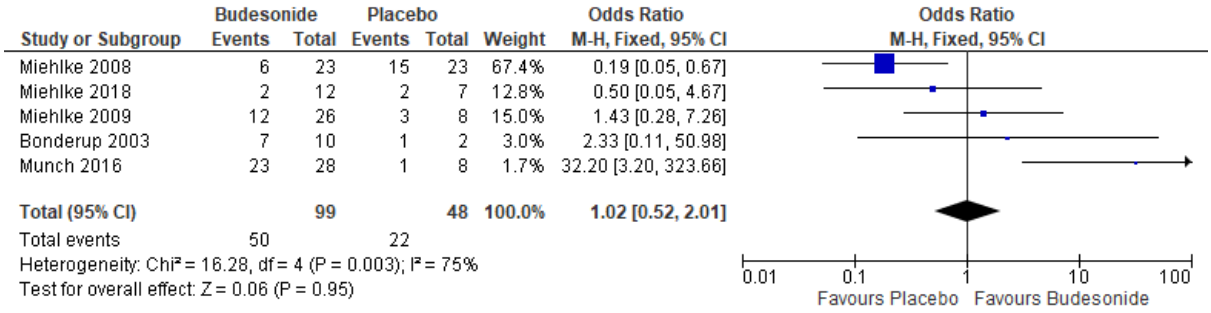


Figure 10: Adverse Events

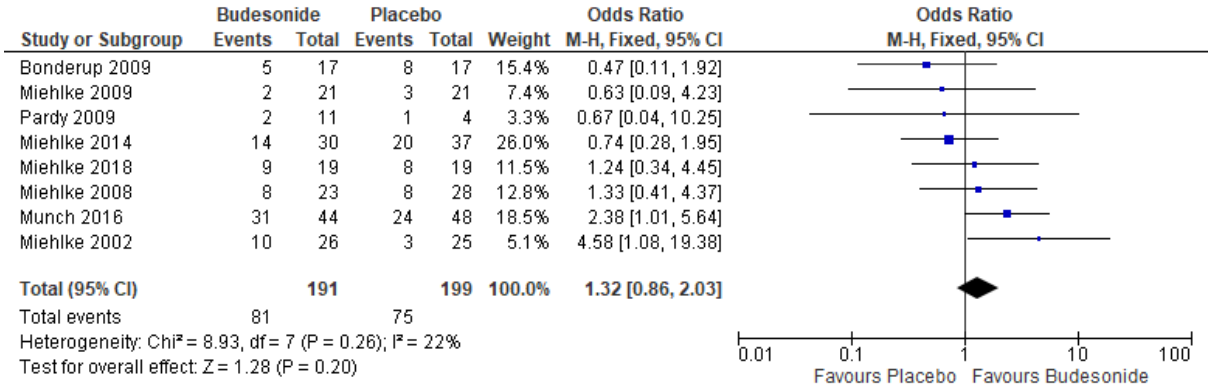


Figure 11

Figure 11: Treatment withdrawal due to adverse events