Once-daily versus multiple-daily mesalamine for patients with ulcerative colitis: a meta-analysis
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CRD summary
The authors concluded that the efficacy and safety of once-daily mesalamine was comparable to multiple-daily mesalamine for the maintenance treatment of ulcerative colitis and was more effective for inducing remission in active ulcerative colitis. The evidence suggests that this conclusion may be reliable where it relates to quiescent ulcerative colitis, but subject to more uncertainty for active disease.

Authors’ objectives
To compare the efficacy and safety of once-daily mesalamine versus multiple-daily mesalamine for the treatment of ulcerative colitis.

Searching
MEDLINE, EMBASE, Science Citation Index, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2011; search terms were reported. Reference lists of retrieved articles and abstracts from the Digestive Disease Week and the United European Gastroenterology Week were hand searched over five years to locate further studies. Abstracts were included if they reported sufficient data.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared the effect of once-daily versus multiple-daily mesalamine in patients with active or quiescent ulcerative colitis. Therapy duration had to be at least two weeks for the induction of remission trials in active ulcerative colitis, and at least six months in the prevention of relapse trials in quiescent ulcerative colitis. Trials that administered any dose of mesalamine were eligible; the total daily dose of once-daily mesalamine had to equal the multiple-daily dose. Primary outcomes were failed remission in active ulcerative colitis, or relapse of disease in quiescent ulcerative colitis. Secondary outcomes included any adverse events during treatment, discontinuations due to adverse events, and compliance.

Included trials were conducted in the USA, the UK, Germany and Australia; most were multi-site trials. The mean age of patients ranged from 37.3 to 50.4 years. The proportion of men per trial arm ranged from 16.7% to 62.5% (where reported). Treatment duration ranged from eight weeks to 12 months. Total dosages for once-daily regimens and multiple-daily regimens ranged from 1.5g/day to 3g/day. Various criteria with various cut-off points were used to define relapse or remission.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Trial quality was assessed using the Jadad Scale on criteria of randomisation, blinding and withdrawals (on a scale from 1 to 5, where 5 was the highest score). Total scores under 3 were seen to indicate low quality.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Per-protocol and intention-to-treat data were extracted from once-daily and multiple-daily mesalamine groups to calculate risk ratios (RRs) and 95% confidence intervals (CIs).

Data were extracted independently by two reviewers; disagreements were resolved by discussion with a third reviewer.

Methods of synthesis
Risk ratios and 95% confidence intervals for rates of remission, relapse, adverse events, and compliance were pooled using fixed-effect or random-effects models. Intention-to-treat and per-protocol analyses were both performed using
data from the endpoint of each trial. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. Publication bias was investigated via Egger's regression test and construction of a funnel plot.

Results of the review
Ten RCTs were included in the review (3,410 patients). The number of patients per trial ranged from 20 to 1,023. Four trials scored 5 for quality on the Jadad scale, four trials scored 4, one trial scored 3, and one trial scored 2.

Efficacy of once-daily versus multiple-daily mesalamine for preventing relapse in quiescent ulcerative colitis: Intention-to-treat analysis revealed that 372 (26.3%) patients receiving once-daily doses of mesalamine relapsed compared with 384 (26.5%) patients receiving multiple doses a day; the difference between the groups was not statistically significant (RR 1.00, 95% CI 0.89 to 1.12; eight trials). Moderate statistical heterogeneity was shown ($I^2=41\%$). Similar results were shown with per-protocol analysis. Results of various sensitivity analyses were reported but did not materially alter the results of the analysis. No evidence of publication bias was found.

Efficacy of once-daily versus multiple-daily mesalamine for inducing remission in active ulcerative colitis: Intention-to-treat analysis revealed that remission was not observed in 82 (29.8%) patients receiving once-daily doses of mesalamine compared with 104 (37.8%) patients receiving multiple doses a day. Risk of failure to achieve remission was higher among multiple-daily patients compared with once-daily patients (RR 0.80, 95% CI 0.64 to 0.99; two trials), but this difference was of borderline statistical significance. Statistical heterogeneity was observed but was not substantial ($I^2=21.6\%$). Per-protocol analysis revealed this difference to be statistically non-significant.

Adverse events: No statistically significant differences were found between once-daily and multiple-daily regimens for the incidence of adverse events overall, serious adverse events, and discontinuations due to adverse events. Statistical heterogeneity for these analyses was not reported.

Compliance: No statistically significant difference was found between once-daily regimens and multiple-daily regimens for compliance.

Authors’ conclusions
The efficacy and safety of once-daily doses of mesalamine was comparable to multiple-daily doses for the maintenance treatment of ulcerative colitis, and was even more effective for inducing remission in active ulcerative colitis.

CRD commentary
The review question was clear. Inclusion criteria appeared to be sufficiently replicable. Relevant databases were searched. Attempts were made to reduce error and bias during the data extraction stage, but the potential for error and bias during other stages of the review process was unclear.

Quality of the included trials was assessed using a tool which contained some, but not all, relevant criteria; only a summary score was provided, which did not provide a clear picture of the methodological quality of trials. Adequate trial details were presented. Appropriateness of methods of synthesis was ambiguous because statistical heterogeneity was high in some cases and was not stated for other outcomes. The only statistically significant difference between remission rates of active ulcerative colitis for once-daily and multiple-daily groups was of borderline significance. Some trials also contained very small numbers of participants. Although statistical heterogeneity was high for remission efficacy of quiescent disease, the evidence appeared stronger than the evidence for active disease, due to a greater number of trials (and patients) and similar findings in both intention-to-treat and per-protocol analyses.

The authors’ conclusion may be reliable where it relates to quiescent ulcerative colitis, but subject to more uncertainty in relation to active disease.

Implications of the review for practice and research
The authors did not state any implications for practice and further research.

Funding
National Natural Science Foundation of China; Science and Technology Commission of Shanghai Municipality.

Bibliographic details

**PubMedID**
22435504

**DOI**
10.1111/j.1751-2980.2012.00576.x

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-Inflammatory Agents, Non-Steroidal /administration & dosage /adverse effects; Colitis, Ulcerative /drug therapy; Drug Administration Schedule; Humans; Mesalamine /administration & dosage /adverse effects; Secondary Prevention

**AccessionNumber**
12012018049

**Date bibliographic record published**
28/05/2012

**Date abstract record published**
11/10/2012

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.