Authors' objectives
To assess the efficacy and safety of sulfasalazine (SSZ) compared to placebo and other disease-modifying drugs.

Searching
MEDLINE (1966-1998), Excerpta Medica (1974-1998) and Derwent Drug File (1964-1998) were searched using the following keywords: 'azulfidine', 'rheumatoid arthritis', 'arthritis', 'sulfasalazine', 'sulphasalazine', 'entabs', 'spondyloarthropathies', 'methotrexate', 'hydroxychloroquine (HCQ)', 'gold', 'penicillamine', and 'combination therapy'. Additional articles were identified from meta-analyses, literature reviews and the personal library of one of the reviewers. Only articles published in peer reviewed journals were included in the review. Abstracts and technical reports were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) comparing at least two single drug treatments. Studies where only combination treatments were used were excluded.

Specific interventions included in the review
Sulfasalazine (SSZ; on average 2g/day) was compared to control groups including hydroxychloroquine (HCQ; on average 350mg/day), penicillamine (D-Pen; on average 667mg/day), gold sodium thiomalate (GST; on average 25mg/day) and placebo. Exact dose regimens were not stated.

Participants included in the review
Individuals with rheumatoid arthritis (RA). Studies of juveniles with rheumatoid arthritis were excluded.

Outcomes assessed in the review
Erythrocyte sedimentation rate (ESR), morning stiffness duration, pain visual analogue scale, articular index, number of swollen joints, number of painful joints, patient global assessment, physician global assessment, adverse effects and study drop-outs (due to adverse effects and lack of efficacy).

How were decisions on the relevance of primary studies made?
Two teams of two independent reviewers examined the studies. When two independent reviewers disagreed their reasons were discussed and conflicting choices resolved.

Assessment of study quality
The authors did not state that they assessed quality. However, only RCTs were included in the review and the number of double-blind trials was reported.

Data extraction
Two teams of two independent reviewers extracted the data. One reviewer from each team examined the other teams data extractions and where a discrepancy occurred the reviewers referred to the original article for clarification.

Methods of synthesis
How were the studies combined?
Studies were combined in a meta analysis. Effect sizes were calculated and pooled using a fixed-effect model; and 'd' statistics with 95% confidence intervals (95% CI) reported. For continuously scaled outcome measures the treatment
effect sizes were reported as the percentage change from baseline. Data were considered statistically significant where \( p \) was less than or equal to 0.05. A statistical trend was defined as 0.05 < \( p \) ≤ 0.10 and a weak trend was defined as 0.10 < \( p \) ≤ 0.20.

How were differences between studies investigated?
A statistical test of homogeneity was performed.

**Results of the review**
Fifteen RCTs (twelve of which were double-blinded) were included.

1. **SSZ versus placebo** (8 studies, n=552 SSZ and n=351 placebo):
   - Withdrawals due to adverse effects (8 studies) \( d = 0.44 \) (95% CI: 0.30, 0.50); homogeneity test=0.67.
   - Withdrawals due to lack of effectiveness (7 studies) \( d = -0.44 \) (95% CI: -0.61, -0.28); homogeneity test=0.21.
   - ESR (5 studies) \( d = 0.53 \) (95% CI: 0.31, 0.75); homogeneity test=0.72. Morning stiffness duration (5 studies) \( d = 0.28 \) (95% CI: 0.07, 0.49); homogeneity test=0.21. Pain visual analogue scale (4 studies) \( d = 0.56 \) (95% CI: 0.30, 0.82); homogeneity test=0.56.
   - Articular Index (3 studies) \( d = 0.66 \) (95% CI: 0.35, 0.97); homogeneity test=0.37. No. of swollen joints (3 studies) \( d = 0.37 \) (95% CI: 0.11, 0.62); homogeneity test=0.54.
   - No. of painful joints (4 studies) \( d = 0.35 \) (95% CI: 0.11, 0.59); homogeneity test=0.31. Patient global assessment (3 studies) \( d = 0.28 \) (95% CI: 0.04, 0.52); homogeneity test=0.11. Physician global assessment (3 studies) \( d = 0.17 \) (95% CI: -0.07, 0.42); homogeneity test=0.31.

2. **SSZ versus HCQ** (2 studies, n=59 SSZ and n=61 HCQ):
   - Withdrawals due to adverse effects (2 studies) \( d = 0.20 \) (95% CI: -0.16, 0.56); homogeneity test=0.37.
   - Withdrawals due to lack of effectiveness (1 study) \( d = -0.51 \) (95% CI: -1.02, 0.005).
   - ESR (2 studies) \( d = 0.33 \) (95% CI: -0.07, 0.74); homogeneity test=0.19. Morning stiffness duration (2 studies) \( d = 0.35 \) (95% CI: -0.06, 0.75); homogeneity test=0.15. Pain visual analogue scale (1 study) \( d = 0.36 \) (95% CI: -0.16, 0.89).
   - Articular Index (1 study) \( d = 0.03 \) (95% CI: -0.48, 0.55). No. of swollen joints (2 studies) \( d = 0.18 \) (95% CI: -0.22, 0.58); homogeneity test=0.47.
   - Patient global assessment (3 studies) \( d = 0.49 \) (95% CI: -0.15, 1.13).

3. **SSZ versus D-Pen** (3 studies, n=111 SSZ and n=97 D-Pen):
   - Withdrawals due to adverse effects (3 studies) \( d = -0.07 \) (95% CI: -0.34, 0.20); homogeneity test=0.87.
   - Withdrawals due to lack of effectiveness (3 studies) \( d = -0.08 \) (95% CI: -0.35, 0.20); homogeneity test=0.64.
   - ESR (3 studies) \( d = 0.01 \) (95% CI: -0.28, 0.30); homogeneity test=0.51.
   - Morning stiffness duration (2 studies) \( d = -0.07 \) (95% CI: -0.47, 0.33); homogeneity test=0.51. Pain visual analogue scale (2 studies) not combined.
   - Articular Index (2 studies) \( d = 0.08 \) (95% CI: -0.32, 0.48); homogeneity test=0.79. No further outcomes reported.
4. SSZ versus GST (4 studies, n=181 SSZ and n=196 GST):

Withdrawals due to adverse effects (3 studies) d=-0.42 (95% CI: -0.62, -0.22); homogeneity test=0.42.

Withdrawals due to lack of effectiveness (3 studies) d=0.29 (95% CI: 0.08, 0.49); homogeneity test=0.01.

ESR (2 studies) d=0.08 (95% CI: -0.19, 0.36); homogeneity test=0.41. Morning stiffness duration (1 study) d=0.12 (95% CI: -0.22, 0.45).

Pain visual analogue scale (1 study) d=-0.04 (95% CI: -0.48, 0.40).

No. of swollen joints (1 study) d=0.00 (95% CI: -0.34, 0.34).

No. of painful joints (2 studies) d=0.08 (95% CI: -0.16, 0.31); homogeneity test=0.54.

Patient global assessment (1 study) d=0.00 (95% CI: -0.34, 0.34).

Physician global assessment (1 study) d=0.00 (95% CI: -0.34, 0.34).

No further outcomes reported.

4. 3g of SSZ versus placebo:

Withdrawals due to adverse effects (2 studies) d=0.62 (95% CI: 0.28, 0.95); homogeneity test=0.59.

Withdrawals due to lack of effectiveness (2 studies) d=-0.55 (95% CI: -0.88, -0.21); homogeneity test=0.08.

ESR (1 study) d=0.39 (95% CI: -0.04, 0.83).

Morning stiffness duration (1 study) d=0.60 (95% CI: 0.09, 1.10).

Pain visual analogue scale (1 study) d=0.84 (95% CI: 0.32, 1.36).

No. of swollen joints (1 study) d=0.70 (95% CI: 0.18, 1.21).

No. of painful joints (1 study) d=0.45 (95% CI: -0.06, 0.95).

Authors' conclusions

This meta analysis of the randomised trials published to date with SSZ in RA shows that there is a significant improvement in RA activity compared to placebo in randomised placebo-controlled studies. A significant improvement in disease activity, i.e. number of painful and swollen joints, patient global assessments, and ESR was observed with SSZ. In addition, the withdrawal rate due to lack of efficacy favoured SSZ compared to placebo. There were more withdrawals due to adverse events with SSZ in the placebo-controlled studies.

CRD commentary

This review is based on clear inclusion criteria and uses a reasonable search of the literature. However, relevant unpublished literature may have been excluded and so publication bias could be a problem. Various methodological details about the review were reported and all stages of the review process involved multiple reviewers in order to reduce the effects of error and bias. Only randomised controlled trials were included in the review and the number of double-blinded studies was reported. However the quality of the individual studies was not assessed.

It is difficult to assess the clinical validity of pooling the studies, as the details of individual studies were not reported. However, a statistical test for homogeneity was reported and, where significant, heterogeneity was identified, analyses were re-run without the outliers. It would appear from the data presented that intervention and control groups were pooled across the different studies rather than comparing the difference between the intervention and control groups.
within studies, and then pooling the differences in effects across the different studies. This effectively breaks the randomisation within studies and may lead to bias in the final estimates of treatment differences. Therefore the final treatment differences could be affected by differences between the study populations, rather than purely differences between the effects of the intervention and control treatments. In addition the authors rely on the across study pooled treatment effect estimates for the treatment and control groups (with the associated p value) in order to support their conclusions. Although the d statistic (with 95% CI) and treatment differences are quoted in the tables they are not discussed in the text of the report or used to summarise the overall study findings. In view of these concerns about the analyses and the presentation of data, the results of the review should be treated with great caution.

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

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