Flurbiprofen in the symptomatic management of rheumatoid arthritis: a valuable alternative
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CRD summary
The authors concluded that flurbiprofen may be an alternative to other non-steroidal anti-inflammatory drugs for the symptomatic management of rheumatoid arthritis. Poor reporting of review methods and study quality, differences between the studies and the reliance upon predominantly short-term studies mean that the authors’ conclusion may not be reliable.

Authors’ objectives
To evaluate the efficacy and safety of flurbiprofen in the management of symptoms in patients with rheumatoid arthritis.

Searching
MEDLINE, PREMEDLINE, BIOSIS Previews, HealthSTAR, EMBASE, the Cochrane CENTRAL Register, Current Contents, EBM Reviews and the Internet were searched for studies realised and/or published between 1975 and January 2006. In addition, the reference lists of reports were screened. Only reports written in English were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared oral flurbiprofen (100 to 300 mg) with placebo, aspirin, indomethacin, naproxen, ibuprofen or ketoprofen were eligible for inclusion. The included studies evaluated the following median daily dose of the specified drugs: 200 mg flurbiprofen, 4,000 mg aspirin, 150 mg indomethacin, 750 mg naproxen and 1,800 mg ibuprofen. The median duration of treatment was 4 weeks (range: 1 to 52).

Participants included in the review
Studies of patients with rheumatoid arthritis were eligible for inclusion. In the included studies, the patients had a mean age of 49 years and had suffered rheumatoid arthritis for varying durations (where reported, it ranged from more than 6 months to 7 years).

Outcomes assessed in the review
Studies that assessed pain, articular swelling, global efficacy or tolerance were eligible for inclusion. The review assessed all symptomatic outcomes combined, pain at rest/mobilisation, articular swelling, articular stiffness, patient preference, physician opinion, global safety and gastrointestinal tolerance.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity. However, they did report the level of blinding in tables.

Data extraction
Two reviewers independently extracted the data. Intention-to-treat data were extracted, where possible, otherwise per-protocol data were extracted.

Methods of synthesis
How were the studies combined?
The data were pooled using random-effect models where heterogeneity was significant \( (p<0.1) \), otherwise fixed-effect models were used. Flurbiprofen was compared with each of the comparators by combining data from all reported symptomatic outcome measures. In this analysis, individual studies could provide more than one comparison. Flurbiprofen was also compared with comparators by pooling data for specified outcomes. Although not explicitly stated, it appears that pooled effect sizes \( (ES) \) with 95\% confidence intervals \( (CIs) \) were calculated to assess treatment effects. Publication bias was assessed using a funnel plot, the fail-safe \( N \), the regression asymmetry test of Egger and a rank correlation test.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using Cochran’s \( Q \) statistic. The authors stated that sensitivity analysis was performed by excluding extreme values, weighting studies by methodological quality, and using the trim-and-fill method. However, no details of the methodological weighting were reported. Meta-regression was used to examine the effects of study duration on global safety.

**Results of the review**
Fourteen RCTs \( (n=2,432) \) were included, four of which were crossover RCTs.

Ten of the RCTs were double-blinded.

For all symptomatic outcomes combined, flurbiprofen was significantly superior to placebo \( (ES \ 3.13, \ 95\% \ CI: \ 1.70, 4.55, \ p<0.001; \ based \ on \ 3 \ studies \ providing \ 7 \ outcomes \ measures) \), naproxen \( (ES \ 0.41, \ 95\% \ CI: \ 0.22, 0.60, \ p<0.001; \ based \ on \ 3 \ studies \ providing \ 8 \ outcome \ measures) \) and indomethacin \( (ES \ 0.30, \ 95\% \ CI: \ 0.15, 0.44, \ p<0.001; \ based \ on \ 6 \ studies \ providing \ 15 \ outcome \ measures) \). There was no significant difference between flurbiprofen and aspirin \( (3 \ studies \ providing \ 8 \ outcome \ measures; \ ES \ 0.10, \ 95\% \ CI: \ -0.02, 0.21, \ p=0.11) \) or ibuprofen \( (3 \ studies \ providing \ 6 \ outcome \ measures; \ ES \ 0.13, \ 95\% \ CI: \ -0.01, 0.27, \ p=0.06) \).

For pain at rest or mobilisation, flurbiprofen was associated with significant improvements compared with placebo \( (p<0.001; \ 3 \ studies) \) and ibuprofen \( (p=0.02; \ 2 \ studies) \), but there was no significant difference between flurbiprofen and aspirin \( (p=0.09) \), indomethacin \( (p=0.33) \) or naproxen \( (p=0.31) \).

For articular swelling, flurbiprofen was associated with significant improvements compared with placebo \( (p=0.045; \ 2 \ studies) \) and indomethacin \( (p<0.001; \ 3 \ studies) \), but there was no significant difference between flurbiprofen and aspirin \( (p=0.54) \), ibuprofen \( (p=0.72) \) or naproxen \( (p=0.72) \).

For articular stiffness, flurbiprofen was associated with significant improvements compared with indomethacin \( (p=0.03; \ 5 \ studies) \), ibuprofen \( (p=0.048; \ 2 \ studies) \), naproxen \( (p<0.001; \ 2 \ studies) \) and placebo \( (p<0.001; \ 2 \ studies) \), but there was no significant difference between flurbiprofen and high-dose aspirin \( (p=0.52) \).

For patient preference, flurbiprofen was associated with significant superiority compared with placebo \( (p<0.001) \), but there was no significant difference between flurbiprofen and aspirin, indomethacin, ibuprofen or naproxen.

For physician opinion, flurbiprofen was associated with significant superiority compared with indomethacin \( (p=0.046) \) and naproxen \( (p=0.01) \).

Flurbiprofen was associated with a significant increase in global safety compared with aspirin \( (p<0.001) \) and indomethacin \( (p<0.001) \), but there was no significant difference between flurbiprofen and ibuprofen \( (p=1) \), naproxen \( (p=0.14) \) or placebo \( (p=0.72) \).

Flurbiprofen was associated with a significant increase in gastrointestinal tolerance compared with aspirin \( (p<0.001) \), but there was no significant difference between flurbiprofen and indomethacin \( (p=0.95) \), ibuprofen \( (p=0.69) \) or naproxen \( (p=0.09) \).

Funnel plots for symptoms suggested the possibility of publication bias, whereas funnel plots of tolerance did not.
Authors’ conclusions
Flurbiprofen may be an alternative to other non-steroidal anti-inflammatory drugs for the symptomatic management of rheumatoid arthritis.

CRD commentary
The review question was clear with respect to the participants, intervention, outcomes and study design. Several relevant sources were searched but the review was restricted to studies published in English, so there is a possibility of language and publication bias. Methods were used to minimise reviewer error and bias in the extraction of data, but it is not clear whether similar steps were taken when selecting the studies. Study validity was not formally assessed; in particular, the validity and reliability of the methods used to measure outcomes and the comparability of cointerventions between treatment groups were not assessed. In addition, outcomes such as global safety and gastrointestinal tolerance were not defined. These limitations mean that the results from these studies and any synthesis may not be reliable. However, double-blinding was noted in the tables and attempts were made to extract intention-to-treat data.

For the main analyses, in which all symptomatic outcomes measures were pooled, there was no adjustment for multiple ES from individual studies and this potentially undermines the reliability of results from these analyses. Statistical heterogeneity was assessed but the results were not reported (other than indicating the use of a random-effects model), and some forest plots suggested differences in treatment effects between studies, thus it is not entirely clear whether it was appropriate to pool the data. In addition, most studies, as the authors acknowledged, were short-term (half of the studies lasted less than 1 month). Incomplete reporting of review methods and study quality, differences between the studies, and the reliance upon predominantly short-term studies mean that the authors’ conclusion may not be reliable.

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

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