Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic review of randomized controlled trials

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Authors' objectives
To review the frequency and severity of adverse gastrointestinal (GI) events among patients using meloxicam, a cyclooxygenase (COX)-2-selective nonsteroidal anti-inflammatory drug (NSAID).

Searching
Two independent searches of MEDLINE (1990 to 1998) were made using the MeSH terms: 'meloxicam', 'NSAIDs', 'GI bleeding', 'ulcer', 'dyspepsia', 'GI complication', 'randomized (pt)', 'meta-analysis (pt)', and 'clinical trial'. The authors also scanned the bibliographies of all retrieved studies and searched the abstracts of the American Gastrointestinal Association and the American Society for Gastrointestinal Endoscopy from 1996 to 1998 for additional relevant studies. The searches were limited to English language publications. No attempt was made to obtain unpublished data from Boehringer Ingelheim, Inc., the manufacturer of meloxicam.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) using a parallel design or a cross over design with washout period. Study duration ranged from 27 days to 6 months.

Specific interventions included in the review
Meloxicam 7.5 or 15 mg/day, a cyclooxygenase (COX)-2-selective nonsteroidal anti-inflammatory drug (NSAID compared with another NSAID (either piroxicam 20 mg/day, diclofenac 100 mg/day, or naproxen 750 mg/day).

Participants included in the review
Adult patients with acute lumbago or osteoarthritis or rheumatoid arthritis.

Outcomes assessed in the review
Adverse GI events, including dyspepsia, nausea/vomiting, abdominal pain, diarrhea, perforations, ulcers, and bleeds (PUBs), and frequency of withdrawal of medication because of adverse GI event. Adverse events were coded using the World Health Organization's Adverse Reaction Terminology List (WHO-ARTL). The category of PUBS is broadly defined to include an episode of gastric perforation, endoscopically diagnosed ulcer in a patient with dyspepsia or abdominal pain, and/or GI bleeding. The category of GI bleeding may or may not be consistent with a hemodynamically significant bleed.

How were decisions on the relevance of primary studies made?
One author reviewed the titles and abstracts and, subsequently, the full articles for inclusion.

Assessment of study quality
Whilst the authors did not formally assess quality, one reviewer assessed randomisation, blinding and withdrawals as part of the data extraction process.

Data extraction
A single reviewer extracted data using a standardised form for the categories of: randomisation process; blinding of physicians, patients, and outcome adjudicators; patient population; duration of study; and frequency of total adverse GI events. Specific data about the frequency of dyspepsia, frequency of PUBs, and frequency of withdrawal of medication because of adverse GI events were also extracted.
Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

How were differences between studies investigated?
The Breslow-Day test of homogeneity was used to assess heterogeneity between trials, defined as \( p < 0.05 \).

Results of the review
Twelve studies met the inclusion criteria but only 10 (all of parallel design) were used in the main analysis with 20,374 participants (352 with acute lumbago, 379 with rheumatoid arthritis, and 19,643 with osteoarthritis).

Patients using meloxicam had fewer GI adverse events compared with non-COX-2-selective NSAIDs (OR 0.64, 95% CI: 0.59, 0.69). Test of homogeneity, \( p = 0.58 \).

Patients using meloxicam experienced less dyspepsia (OR 0.73, 95% CI: 0.64, 0.84, test for homogeneity \( p = 0.62 \)), fewer PUBs (OR 0.52, 95% CI: 0.28, 0.96, test for homogeneity \( p = 0.69 \)) and less frequent discontinuation of NSAID because of adverse GI events (OR 0.59, 95% CI: 0.52, 0.67, test for homogeneity \( p = 0.09 \)) compared with non-COX-2 selective NSAIDs.

Results from two additional trials using endoscopy to assess the affect of meloxicam on gastric mucosa of healthy volunteers suggested that piroxicam caused no greater mucosal damage than meloxicam.

Authors' conclusions
The authors state that meloxicam, a COX-2-selective NSAID, appears to cause fewer adverse GI events than standard, non-COX-2-selective NSAIDs. However, the generalisability of these data may be limited by the low dose of meloxicam used in most trials and the use of the WHO-ARTL to code adverse events. The authors also state that the true question may be whether the therapeutic benefit justifies the additional cost of these drugs.

CRD commentary
A good review on adverse effects of a treatment. The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search could have been more comprehensive because only one database and U.S. journals were searched for publications. The search was also restricted to English language publications.

The quality of the included studies was not formally assessed, although it was addressed in the data extraction process and discussed in the review. The authors have reported how the articles were selected, and who performed the selection of articles, although this was done by only one reviewer.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a statistical meta-analysis and heterogeneity was assessed and its possible effects discussed in the review.

The authors' conclusions appear to follow from the results but, as the authors themselves state, these should be viewed with caution because of the relatively broad choice of outcome measures, the use of the WHO-ARTL criteria, and the limitations in the review process resulting from a limited search strategy, use of only one reviewer for selection and extraction of data and the lack of formal quality assessment of included studies.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.

Research: The authors state that future head-to-head trials of meloxicam versus non-COX-2-selective NSAIDs should provide specific data about haemodynamically significant GI bleeding and hospitalisations from GI complications, and assess dyspepsia with validated questionnaires. However, such studies would require tens of thousands of participants and might not produce statistically significant results.
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Other publications of related interest
This additional published commentary may also be of interest. Nabumetone and meloxicam gastrointestinal safety. Bandolier 2000;76:7.

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