Coxibs versus combination NSAID and PPI therapy for chronic pain: an exploration of the risks, benefits, and costs

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CRD summary
This review compared cyclooxygenase-2 inhibitors (coxibs) with non-selective non-steroidal anti-inflammatory drugs plus a proton-pump inhibitor for patients with chronic musculoskeletal pain. The authors concluded that coxibs provide comparable pain control and produce fewer gastrointestinal complications, although the risk of cardiovascular events is unknown. The presence of several methodological flaws in the review process mean that the reliability of these conclusions is unclear.

Authors' objectives
To compare the risks and benefits of cyclooxygenase-2 inhibitors (coxibs) with combined non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and proton-pump inhibitor (PPI) therapy for chronic musculoskeletal pain.

Searching
MEDLINE (1985 to November 2005) and the Cochrane Library were searched for relevant studies published in the English language; the search terms were reported. References lists were screened for further articles of interest.

Study selection
Study designs of evaluations included in the review
Clinical trials were eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing coxib with combined non-selective NSAID-PPI therapy were eligible for inclusion. To be eligible for the measurement of pain control, the studies had to compare at least one coxib with a non-selective NSAID. For the measurement of gastrointestinal (GI) events, the initial selection criteria specified the comparator as a combination treatment of non-selective NSAIDs plus a PPI. This was subsequently amended (for lower GI complications only) to include studies of coxibs with NSAIDs alone. When measuring cardiovascular events (CVEs), studies of coxibs compared with non-selective NSAIDs as well as placebo, were eligible for inclusion. The coxibs included were celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib and parecoxib. The included NSAIDs were diclofenac, naproxen, nabumetone, acetaminophen and ibuprofen. The included PPI was omeprazole. A range of doses and administration regimens was reported in the paper.

Participants included in the review
Studies of patients with chronic musculoskeletal pain were eligible for inclusion. The majority of those included suffered from osteoarthritis or rheumatoid arthritis. The studies were conducted in different clinical settings across many countries of the world.

Outcomes assessed in the review
Studies that focused on pain control, GI complications and risk of CVEs were eligible for inclusion. Studies of short-term pain control (e.g. for dental or surgical procedures) were excluded. A range of measurement tools for pain control was reported in the paper.

How were decisions on the relevance of primary studies made?
Two reviewers independently performed the searches to minimise the chance of overlooking relevant articles. No further details of the study selection process was supplied.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Overall study conclusions (i.e. study groups comparable or more effective) were recorded for studies of pain control. Percentage incidences of GI complications were reported, with p-values where available. CVEs were reported as relative risks (RRs) with 95% confidence intervals (CIs) where possible.

Methods of synthesis
How were the studies combined?
The studies were grouped by outcome measure and combined in a narrative.

How were differences between studies investigated?
Some differences between the studies were evident from the data tables whilst others were discussed in the text.

Results of the review
Thirty-two trials (n=72,584) were included in the review. Two of the trials were analysed in more than one outcome category. The majority of the trials were randomised and controlled, but the specific design of those addressing risk of CVEs was not given (8 studies).

Pain control.
Three (n=5,838) of the 22 trials examining this outcome showed coxibs to be significantly more effective for pain control than non-selective NSAIDS. Two of the trials compared rofecoxib with nabumetone and showed statistically significant improvements in response rates (p<0.003) and mean walking pain (p=0.031). The other trial comparing etoricoxib with naproxen demonstrated improvements in pain control and tolerability (p<0.05). The remaining 19 trials showed comparable or non significantly different results.

GIs.
Three trials examined the risk of GIs, of which one (n=287) directly compared the upper GI event rate of celecoxib with a combination treatment of non-selective NSAID (diclofenac) and PPI (omeprazole). At the 6-month follow-up, there were no significant differences between the treatments for recurrent ulcer bleeding or endoscopically-determined ulcers. Another trial (n=356) compared celecoxib with naproxen plus omeprazole, and with placebo. The incidence of lower GI (small bowel) events was significantly lower amongst the coxib treatment group (p<0.001). This trend was confirmed in a further trial (n=8,076) of rofecoxib compared with naproxen, but without a PPI (p=0.032).

CVEs.
Trials comparing coxibs with placebo provided the strongest evidence that coxibs may significantly increase the risk of CVEs. Unpublished data suggested that the risk may be dose-related. Of the 8 trials in this outcome category, the results of one (n=1,671) (in which CVEs were used as the primary measure) suggested a statistically significantly elevated risk of CVE following parecoxib and valdecoxib compared with placebo (RR 3.7, 95% CI: 1.0, 13.5). This trend was demonstrated in another 2 trials. The first (n=2,586) compared rofecoxib with placebo and found a two-fold increase in risk (RR 1.92, 95% CI: 1.19, 3.11). The second (n=2,035) found a three-fold increase in risk (RR 3.4, 95% CI: 1.4, 7.8) when a higher dose of celecoxib was compared with placebo.

The evidence was less strong when coxibs were compared with non-selective NSAIDS. One trial (n=8,076) found a four-fold elevated risk of myocardial infarction associated with rofecoxib (0.4% versus 0.1% with naproxen) but the difference was not significant. Another trial (n=8,059) found no statistically significant increase associated with
celecoxib when compared with ibuprofen or diclofenac. A larger trial (n=18,325) also found no significant increase in CVEs when lumiracoxib was compared with naproxen or ibuprofen.

**Cost information**
The authors gave comparative costs for the drugs (reported in the paper), showing that most of the non-selective NSAID-PPI combinations would be less costly than coxib therapy. The exception to this was if prescription omeprazole and/or diclofenac were used as the comparators.

**Authors’ conclusions**
In comparison with non-selective NSAIDs and PPI as combination treatment, coxibs provide comparable pain control and may produce a lower level of GI tract complications. However, the unknown risk of CVEs and higher cost of coxibs mean that this conclusion should be interpreted cautiously.

**CRD commentary**
The review question and inclusion criteria were clear. The database search strategy was limited but adequate. Although there was no documented search for unpublished data, there was some recognition of preliminary trial results in the review findings. The restriction to English language papers might have introduced language bias. The lack of details of the review process mean that errors and biases cannot be ruled out. In addition, the absence of a validity assessment precludes any confirmation of study reliability. The apparent considerable variation amongst the included studies was not fully explored in the context of the review findings. The authors’ conclusions reflect the synthesis presented but (given the limitations above) it is unclear to what extent they are reliable.

**Implications of the review for practice and research**
Practice: The authors stated that health care providers should be aware that there are unknown risks and increased costs associated with prescribing coxibs as an equivalent pain control treatment for chronic musculoskeletal pain. Prescription should take account of individual patient characteristics.

Research: The authors stated that future research should examine the possibility of combination therapy comprising coxibs plus a PPI in terms of the impact on GI outcomes. Future research that allows risk stratification according to patient characteristics would be beneficial in allowing a quantitative risk-benefit and cost-effectiveness analysis to be conducted.

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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.