The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of cyclooxygenase-2 (COX-2) selective inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain associated with chronic arthritis. In particular, celecoxib (200 mg once daily) or rofecoxib (25 mg twice daily) were compared with a nonselective NSAID (i.e. naproxen, 500 mg twice daily).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with osteoarthritis, or rheumatoid arthritis, who were not taking concurrent aspirin and required long-term NSAID therapy for moderate to severe arthritis pain.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1987 and 2003. No explicit dates for the resource use data were reported. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A decision tree model was constructed to examine the costs and benefits of NSAIDs versus COX-2 inhibitors in a hypothetical cohort of 60-year-old patients with osteoarthritis or rheumatoid arthritis. The patients did not have GI symptoms. Those with a history of ulcer complications were not considered in the base-case, but were considered in an alternative scenario. The time horizon of the model was lifetime. The patients could either develop a GI complication (non-ulcer dyspepsia, symptomatic ulcer, ulcer haemorrhage, or ulcer perforation) or remain free of GI adverse events. Patients who remained free from GI side effects continued their therapy, while those who experienced complications required further evaluation (haemostasis, oesophagogastroduodenoscopy, or surgical repair). Patients developing upper-GI dyspeptic symptoms underwent upper endoscopy and were prescribed proton-pump-inhibitor (PPI) therapy for the remainder of their lifetime. All NSAID patients who developed an upper-GI dyspeptic symptom were also required to discontinue their therapy and switch to a COX-2 inhibitor. All patients who had an ulcer underwent endoscopy biopsy.
and a rapid urease test for Helicobacter pylori, and those testing positive received a course of eradication therapy. Only GI-related adverse events were considered. Such a structure of the model explicitly biased the analysis in favour of COX-2 inhibitors (coxibs).

**Outcomes assessed in the review**

The probabilities of the following were assessed in the review:

- upper-GI dyspeptic symptoms (based on the relative risk between coxibs and naproxen);
- non-ulcer dyspepsia or ulcer symptoms improved with trial of PPI therapy;
- clinically significant ulcer complications;
- clinically significant ulcer complication is a symptomatic ulcer, an ulcer haemorrhage, or an ulcer perforation;
- endoscopy for ulcer haemorrhage reveals low- or high-risk ulcer stigmata;
- recurrent haemorrhage for treated and untreated ulcer stigmata;
- endoscopically induced perforation or uncontrollable bleeding;
- perioperative death for surgical ulcer repair;
- developing moderate or severe side effects from antibiotics for Helicobacter pylori eradication.

The length of stay (LOS) for an ulcer haemorrhage or perforation, and utility values, were also estimated.

**Study designs and other criteria for inclusion in the review**

A systematic review of the literature was carried out to identify relevant primary studies providing values for the model inputs. The authors targeted randomised controlled trials. Where available, results of meta-analyses and systematic reviews were used.

**Sources searched to identify primary studies**

MEDLINE and handsearched published abstracts from two major journals were searched for primary studies published in English from January 1985 to December 2002.

**Criteria used to ensure the validity of primary studies**

The validity of the primary studies was ensured by the selection of randomised studies.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

Approximately 41 studies were included in the review.

**Methods of combining primary studies**

Some primary studies were combined using a narrative approach, while a meta-analysis was used for other estimates. The final choice for model parameters was based on the assumption of biasing the results in favour of coxibs.
Investigation of differences between primary studies
A test of homogeneity was carried out for those estimates that were combined using a meta-analysis.

Results of the review
The probabilities were as follows:

10.9% for upper-GI dyspeptic symptoms with naproxen and 8% with coxib (this was based on a relative risk between coxibs and naproxen of 0.74);

45% for non-ulcer dyspepsia improved with trial of PPI therapy;

80% for ulcer symptoms improved with trial of PPI therapy;

2.6% for clinically significant ulcer complications with naproxen during the first year and 7.2% over a lifetime horizon, and 1.04% with coxibs during the first year and 4.9% over a lifetime horizon;

74% that a clinically significant ulcer complication is a symptomatic ulcer, 25% that it is an ulcer haemorrhage, and 1% that it is an ulcer perforation;

66% and 34% that endoscopy for ulcer haemorrhage reveals, respectively, low- or high-risk ulcer stigmata;

2% for recurrent haemorrhage for untreated ulcer stigmata (clean-based ulcer) and 10% for recurrent haemorrhage for untreated ulcer stigmata (ulcer with overlying clot);

20% for recurrent haemorrhage for high-risk ulcer stigmata following endoscopic haemostasis;

70% for successful repeated haemostasis in patients with recurrent haemorrhage treated with a second round of endoscopy therapy;

0.02% for endoscopically induced perforation or uncontrollable bleeding;

10% for perioperative death for surgical ulcer repair;

0.05% for developing moderate side effects from antibiotics for Helicobacter pylori eradication; and

0.001% for developing severe side effects from antibiotics for Helicobacter pylori eradication.

The average LOS was 7 days for an ulcer haemorrhage and 10 days for an ulcer perforation.

The utility values were 0.87 for severe dyspepsia, 0.91 for moderate dyspepsia, 0.49 for an ulcer haemorrhage, and 0.46 for a complicated ulcer requiring surgery.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were obtained using a modelling approach. The utility weights were obtained from a published study. An annual discount rate of 3% was applied.

Direct costs
Discounting was relevant as the lifetime costs were estimated, and an annual discount rate of 3% was applied. In general, the unit costs were presented, but information on resource consumption was less clear. A detailed breakdown of the cost items was provided. The health services included in the economic evaluation were:

office visit,
diagnostic upper endoscopy (including endoscopist and facility fees, biopsy and urease test of Helicobacter pylori),
inpatient stay for ulcer haemorrhage or perforation (including professional and facility fees, and further follow-up services),
inpatient and outpatient care for myocardial infarction (including professional and facility fees, diagnostic tests, and medications),
naproxen,
coxibs, and
PPI therapy.

The cost/resource boundary of the third-party payer was adopted. The costs were mainly derived from typical Medicare sources and average wholesale prices. The source of the resource use data was less clear but was presumably based on typical patterns of care. The price year was 2002.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Multivariable sensitivity analyses were carried out to examine the robustness of the estimated cost-utility ratios to variations in model inputs, owing to uncertainty in some data. Univariate sensitivity analyses were then carried out on the most influential model inputs identified. The ranges of values used were mainly derived from the literature. Further, a probabilistic sensitivity analysis was performed using 1,000 simulations. Four alternative scenarios were considered. First, the costs were discounted at an annual rate of 5%. Second, cardiovascular events were considered by incorporating into the model, the cost, probability values and utility estimates that reflected a higher rate of cardiovascular events associated with coxibs. Third, lower drug acquisition costs were used as a proxy for discounts achieved by large buying consortiums. Fourth, an alternative cohort of patients at high-risk for ulcer complications was considered.

**Estimated benefits used in the economic analysis**
In the base-case analysis, the QALYs gained were 15.2613 with naproxen and 15.3033 with coxib.

**Cost results**
In the base-case analysis, the estimated costs per patient were $4,859 with naproxen and $16,443 with coxib.

**Synthesis of costs and benefits**
Incremental cost-utility ratios were calculated to combine the costs and QALYs of the alternative strategies under evaluation. In the base-case analysis, the incremental cost per QALY gained with coxib over naproxen was $275,809. Similar results were obtained in the other scenarios considered in the sensitivity analysis. When the costs were discounted using a 5% annual rate, the incremental cost per QALY was $274,555. When cardiovascular events were
considered, the incremental cost per QALY was $395,374. When lower drug acquisition costs were included, the incremental cost per QALY was $142,095. However, when a high-risk cohort (prior ulcer haemorrhage) was considered, the incremental cost per QALY gained with coxib over naproxen fell to $55,803.

The results of the other sensitivity analyses showed that wide variations in base-case model inputs were required for coxib to be the preferred strategy. The Monte Carlo simulation revealed that the median incremental cost per QALY gained with coxib over naproxen was $268,000 (2.5th and 97.5th percentiles: $146,000 and $633,000). The proportions of simulations below the $200,000, $150,000, $100,000 and $50,000 willingness-to-pay thresholds were 19.5%, 4.3%, 0.1% and 0%, respectively.

Authors’ conclusions
Compared with nonselective non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors were not cost-effective for the treatment of pain due to osteoarthritis and rheumatoid arthritis in patients at average risk for ulcer complications. This unfavourable result was due to the impact of cardiovascular events associated with the use of coxibs. However, COX-2 inhibitors could be cost-effective from a payer perspective in the sub-group of patients at high-risk for ulcer complications.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as naproxen was compared with COX-2 inhibitors, which were supposed to overcome the main side effects of nonselective NSAIDs (i.e. GI events). Dosages and administration patterns were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were mainly derived from a systematic review of the literature. The authors reported details of the methods and conduct of the review. The selection of clinical trials and meta-analyses as sources of evidence ensured the validity of the estimates used in the model. Some estimates were calculated using a meta-analytical approach, which further enhances the robustness of the clinical inputs. The authors chose to bias the final estimates used in the model in favour of coxibs, so as to present a best case for these drugs. The issue of uncertainty was extensively addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit in the economic evaluation was appropriate because QALY capture the impact of the interventions on the two most relevant aspects of patient health, that is, survival and quality of life. Discounting was applied, as recommended in US guidelines. The source of the utility weights was reported. The authors discussed the reasons for their choice of the utility weights. QALYs are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The analysis was carried out from the perspective of the service payer. As such, it appears that all the relevant categories of costs have been included in the analysis. Generally, the unit costs were presented. However, the quantities of resources used were presented for some items only. The economic data were derived from standard payer sources. The costs were treated deterministically in the base-case. The impact of using lower costs for large buyers was investigated in the sensitivity analysis. The price year was reported, which aids reflation exercises in other settings.

Other issues
The authors examined the results of a published study, reporting different findings, which showed that coxibs were cost-effective. However, the authors noted some biased assumptions had been used in the published model. The issue of the generalisability of the study results to other settings was not explicitly addressed, but extensive sensitivity analyses were carried out. This enhances the external validity of the analysis. The authors stated that their analysis had the typical
limitations associated with modelling studies, which usually rely on estimates derived from published sources. However, such issues were extensively addressed in the deterministic and probabilistic sensitivity analysis. In addition, the use of meta-analyses for estimating key model inputs partially overcomes this limitation. It was also noted that the model assumptions were explicitly biased in favour of coxibs. The authors stressed that their results were applicable to a population of patients suffering from osteoarthritis and rheumatoid arthritis who were not taking concurrent aspirin. Therefore, caution is required when extrapolating the study results to other patient populations.

Implications of the study

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