The cost effectiveness of rofecoxib and celecoxib in patients with osteoarthritis or rheumatoid 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
Cyclooxgenase 2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs) were compared with standard NSAIDs. In particular, the COX-2 NSAIDs rofecoxib (25 mg four times daily) and celecoxib (100 or 200 mg twice daily) were compared with the standard NSAIDs naproxen (500 mg twice daily), ibuprofen (800 mg three times daily) and diclofenac (75 mg twice daily). The use of the proton-pump inhibitor (PPI) lansoprazole was also considered while the patient was on NSAIDs.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients suffering from osteoarthritis or rheumatoid arthritis, in whom a decision had been made to treat with NSAIDs and who no longer required low-dose aspirin.

Setting
The study setting was primary care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness and resource use date were derived from two randomised trials, both published in 2000, and a systematic review of the literature from 1990 to 2000. The price year was 1999.

Source of effectiveness data
Evidence for final outcomes was derived from two randomised trials and a systematic review of the medical literature. The randomised trials were the Celecoxib Long-Term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.

Modelling
The major clinical outcomes associated with treatment using both types of NSAIDs were summarised using a Markov model. This technique involved identifying clinically important gastrointestinal (GI) or cardiovascular events. The GI events included dyspeptic symptoms (symptoms severe enough to require a medical consultation, with/without prescription of antacids), clinical upper GI (UGI) events (symptomatic ulcers) and complicated UGI events (symptomatic ulcers with bleeding). Once started on a treatment, the patients moved cyclically from one event to another every 3 months, with the events experienced by each patient determining the subsequent Markov state. Patients
who experienced a symptomatic ulcer were considered high risk from then on and received a PPI while on NSAIDs. Average risk patients, not experiencing any UGI event in any one cycle, remained average risk in the next cycle. Those with a complicated UGI event were taken off NSAIDs. Patients experiencing a myocardial infarction (MI) were modelled to continue their respective NSAID with coprescription of low-dose aspirin.

Outcomes assessed in the review
The key estimates of event rates and the relative effectiveness of rofecoxib and celecoxib over naproxen, diclofenac and celecoxib, were derived from the CLASS and the VIGOR studies. These included:

- the number of clinical UGI events and clinical UGI events per 100 patient years;
- the number of complicated UGI events and complicated UGI events per 100 patient years;
- the number of MIs and MI events per 100 patient years.

The relative risk reductions (RRR) for clinical and complicated UGI events, and relative risk for MI events, were also derived from these two studies. The remaining estimates were obtained from the systematic review. These included:

- the RRR in clinical complicated UGI events due to PPIs;
- the RRR in antacid use due to COX-2 drugs;
- the proportion of dyspepsia cases requiring consultation;
- the proportion of hospitalisations due to an UGI event;
- the proportion of patients undergoing surgery if hospitalised;
- the mortality in patients with first UGI bleed;
- the surgery rate in patients with second UGI bleed;
- the rate in retrying NSAIDs after GI bleed;
- the relative risk increase due to a prior UGI event;
- mortality rates after experiencing nonfatal MIs; and
- the 3-month quality-adjusted life-years for life post-MI.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
MEDLINE was searched comprehensively for primary studies. The bibliographies of relevant articles were also searched.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
The authors judged studies including patients with osteoarthritis or rheumatoid arthritis, who were receiving long-term NSAIDs, to be relevant.

**Number of primary studies included**
Approximately 19 studies (including CLASS and the VIGOR study) were included in the analysis.

**Methods of combining primary studies**
If multiple studies were relevant, the study that provided evidence for the target population in a North American setting was used to support the baseline estimate. The 95% confidence intervals, or estimates from other studies, were used to support the lower and upper plausible range for each variable.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
From the VIGOR study:

- the RRR in clinical UGI events when comparing rofecoxib versus naproxen was 53.7%, (p<0.05), while the RRR in complicated UGI events was 56.9%, (p<0.05);

- the relative risk in MI events when comparing rofecoxib versus naproxen was 4.93, (p<0.05).

From the CLASS:

- the RRR in clinical UGI events was 2.5% when comparing celecoxib versus diclofenac, and 63.8% when comparing celecoxib to ibuprofen, (p<0.05);

- the RRR in complicated UGI events was 8.3% when comparing celecoxib to diclofenac, and 61.4% when comparing celecoxib to ibuprofen, (p<0.05);

- the relative risk in MI events was 1.39 when comparing celecoxib to diclofenac, and 1.44 when comparing celecoxib to ibuprofen.

The clinical data results (and plausible ranges) obtained from the review, which were used as estimates in the model, were reported in full in the paper.

**Measure of benefits used in the economic analysis**
The measures of health benefit in the economic analysis were the life-years (LYs) and QALYs. Utilities were elicited from the general public by surveying a randomly selected sample of 60 residents in Sudbury, Ontario, using rating scale and standard gamble methods. Short-term health state utilities were elicited by comparing the best (arthritis without UGI events) and worst (a complicated UGI event requiring surgery) health states. The short-term health states were dyspepsia, symptomatic ulcer, and a complicated UGI event requiring medical treatment. These same methods were used to elicit the long-term utility for moderate arthritis with reference to perfect health and immediate death. The 3-month QALY values elicited (range: 0 - 0.25; QALY for 3 months in full health is 0.25) were:

- for arthritis with no UGI events, 0.172 (range: 0.159 - 0.185);

- for dyspepsia, 0.126 (range: 0.108 - 0.145);

- for symptomatic ulcers, 0.095 (range: 0.080 - 0.112);
for complicated UGI event requiring medical treatment, 0.078 (range: 0.062 - 0.096);
for complicated UGI event requiring surgery, 0; and
for nonfatal MI, 0.

Direct costs
The resource quantities were not reported, although the authors reported the unit costs of each item. The direct costs of
the third-party payer were included in the analysis. These were for hospitalisation, ambulatory care, physician billing,
and the drug costs allowed under the Ontario benefit Olan scheme. The hospitalisation episode costs were derived from
the national list of provincial cost for health care in Canada. The ambulatory care costs were derived from the 1999
Annual Report of Ambulatory Care costing results for Alberta. The costs for all physician billing were derived from the
1999 Ontario Ministry of Health Schedule of benefits. The costs for acute coronary artery disease were derived from
published cost estimates, and also determined from physician focus groups. The future costs were appropriately
discounted at an annual rate of 5% (as recommended by Canadian guidelines), as the model had a 5-year time horizon.
The price year was 1999.

Statistical analysis of costs
The costs were treated as point estimate, that is, the data were deterministic.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A series of one-way sensitivity analyses was carried out to investigate the discount rates, costs, patient age, prices and
estimates of effectiveness. The clinically plausible range of each variable was used in the sensitivity analysis.

Estimated benefits used in the economic analysis
For average risk patients, the average discounted LYs and QALYs gained were:

for those on naproxen, 4.3580 LYs and 2.8983 QALYs;
for those on rofecoxib, 4.3615 LYs and 2.8997 QALYs;
for those on ibuprofen, 4.3598 LYs and 2.8990 QALYs;
for those on diclofenac, 4.3654 LYs and 2.9104 QALYs; and
for those on celecoxib, 4.3651 LYs and 2.9095 QALYs.

For high-risk patients, the average discounted LYs and QALYs gained were:

for those on rofecoxib, 4.3545 LYs and 2.8851 QALYs;
for those on naproxen plus a PPI, 4.3519 LYs and 2.8816 QALYs;
for those on rofecoxib plus a PPI, 4.3587 LYs and 2.8936 QALYs;
for those on celecoxib, 4.3599 LYS and 2.9003 QALYs;
for those on ibuprofen plus a PPI, 4.3544 LYS and 2.8894 QALYs;
for those on diclofenac plus a PPI, 4.3631 LYS and 2.9064 QALYs; and
for those on celecoxib plus a PPI, 4.3630 LYS and 2.9057 QALYs.

Cost results
For average risk patients, the average total discounted costs were:
for those on naproxen, Can$1,576;
for those on rofecoxib, Can$3,173;
for those on ibuprofen, Can$1,141;
for those on diclofenac, Can$2,570; and
for those on celecoxib, Can$3,371.
For high-risk patients, the average total discounted costs were:
for those on rofecoxib, Can$4,090;
for those on naproxen plus a PPI, Can$4,766;
for those on rofecoxib plus a PPI, Can$6,486;
for those on celecoxib, Can$4,327;
for those on ibuprofen plus a PPI, Can$4,414;
for those on diclofenac plus a PPI, Can$5,980; and
for those on celecoxib plus a PPI, Can$6,746.

Synthesis of costs and benefits
The costs and benefits were synthesised by calculating the cost-effectiveness ratio (CER) for the additional cost required per LY and the cost-utility ratio (CUR) for the additional cost required per QALY. For patients at average risk, the use of rofecoxib over naproxen was associated with an incremental CUR of Can$271,188/QALY and an incremental CER of Can$455,071/LY. For the same group of patients, diclofenac and celecoxib were dominated by ibuprofen, even though they were more effective than ibuprofen, as it was the less costly strategy.

In patients at high risk (those with a history of clinical UGI events), rofecoxib alone was found to be both less costly and more effective than naproxen coprescribed with a PPI. Similarly, celecoxib alone was less costly and more effective than ibuprofen plus a PPI and in celecoxib in combination with a PPI. For the same group of patients, the use of celecoxib alone over diclofenac plus a PPI was associated with an incremental CUR of Can$271,066/QALY and an incremental CER of Can$518,339/LY. Adding a PPI to rofecoxib yielded an incremental CUR of Can$281,244/QALY and an incremental CER of Can$567,820/LY.

None of the parameters in the sensitivity analysis had a significant impact on the CER or CUR for patients at average risk. However, the sensitivity analysis limited to high-risk patients revealed that the CURs were sensitive to the price of omeprazole and the percentage of patients receiving rofecoxib plus a concomitant PPI. These calculations also revealed that, compared with naproxen, rofecoxib would be cost-saving at a price of around Can$0.33 per dose and would have
cost utility thresholds of below Can$50,000/QALY (Can$0.50 per dose) and Can$100,000/QALY (Can$0.67 per dose).
It was also revealed that, compared with ibuprofen, celecoxib would be cost-saving at a price of Can$0.25 per dose and below thresholds of Can$50,000/QALY (Can$0.50 per dose) and Can$100,000/QALY (Can$0.70 per dose).

Authors’ conclusions
Prescribing celecoxib or rofecoxib in patients without a prior clinical upper gastrointestinal (UGI) event was not economically attractive as the cost per quality-adjusted life-year (QALY) gained exceeded thresholds of Can$100,000/QALY. However, both rofecoxib and celecoxib were economically attractive for high-risk patients.

CRD COMMENTARY - Selection of comparators
A justification was given for using naproxen, ibuprofen and diclofenac as the comparators. These NSAIDs were widely prescribed to patients with conditions as diverse as dysmenorrhoea, acute pain episodes, lower-back pain, rheumatoid arthritis and osteoarthritis. You should decide whether they represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The authors pointed out that the findings of this study were closely influenced by the rates of clinical and complicated UGI events reported in the CLASS and VIGOR studies. Both these studies were randomised controlled trials, the 'gold' standard study design when comparing different health technologies. In addition, in the VIGOR study all of the outcome differences between rofecoxib and naproxen were found to be statistically significant. However, osteoarthritis and rheumatoid arthritis were not observed together, as the VIGOR study only included patients with rheumatoid arthritis, whereas 72% of patients in the CLASS suffered from osteoarthritis. This raises the possibility, as the authors acknowledged, that differences between the two studies are entirely due to NSAID dosages and regimes.

Other necessary data to complete the model were obtained from a systematic review of the literature. However, it was unclear whether the review was conducted in a truly systematic way to identify relevant studies and minimise biases. If multiple studies were found to be relevant, the value of the study with a North American setting was used as the baseline estimate, with data from other studies being used to estimate a plausible range. An inherent problem with this method is that it does not weight studies according to their sample sizes or the quality of the study. However, uncertainty in the data was appropriately explored in the sensitivity analysis, which would tend to minimise this limitation.

Validity of estimate of measure of benefit
The measures of health benefit were obtained through modelling parameters. The authors disaggregated life expectancy from quality-adjusted life, enhancing generalisability to other settings or countries. The methods of derivation were clearly described with utility values being elicited from the general public. The LY gained and QALYs were both appropriately discounted at a rate of 5%, following Canadian guidelines. However, guidelines on the discount rate that should be applied vary from country to country.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted appear to have been included in the analysis. For each category of cost, all the relevant costs were, again, included in the analysis. The authors did not report the costs and the quantities separately, which will hamper the generalisability of their results to other settings. However, this limitation is minimised, as the authors did not report the unit costs. The cost estimates were derived from official statistics from Ontario or the province of Alberta. Sensitivity analyses of the prices were conducted to deal with uncertainty and variability in the data. Since the costs were incurred over 5 years, discounting was necessary and the costs were appropriately discounted at 5% per annum. The dates to which the prices related were appropriately reported (1999), making it possible to perform reflationary exercises.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. Worthy of note is the comparison with a large multinational randomised controlled trial (published in abstract form at the time of publication of VIGOR and CLASS) that compared celecoxib to naproxen and diclofenac. This study found that the event rates were lower than in the CLASS. If it had been used in the authors’ model, it would have led to higher CERs for celecoxib. The authors do not appear to have presented their results selectively. Their conclusions reflected the scope of the analysis since patients with osteoarthritis and rheumatoid arthritis were included in the model. The issue of generalisability to other settings was addressed through the sensitivity analysis and by including studies from other countries in the literature review. The authors reported a further limitation to their study in that the extrapolation to patients taking aspirin is uncertain, as the assumption that aspirin increases bleeding risk was based on the results from a small subgroup of CLASS.

Implications of the study
Although not explicitly stated, the authors appear to imply that COX-2 drugs should be made readily available to high-risk patients suffering from osteoarthritis or rheumatoid arthritis due to their cost-effectiveness. For average risk-patients, COX-2 drugs should only be prescribed to patients in certain age groups.

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