Cost-effectiveness analysis of NSAIDs, NSAIDs with concomitant therapy to prevent gastrointestinal toxicity, and COX-2 specific inhibitors in the treatment of 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
The study examined the use of non-steroidal anti-inflammatory agents (NSAIDs) with and without concomitant therapy to prevent gastrointestinal (GI) toxicity, in comparison with cyclooxygenase-2-specific (COX-2) inhibitors in the treatment of rheumatoid arthritis (RA). The prophylactic agents for GI toxicity were misoprostol and a proton-pump inhibitor (PPI).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The hypothetical study population comprised 50-year-old patients with RA, with a female-to-male ratio of 2.5:1

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

Dates to which data relate
The effectiveness data referred to 1991 to 2000, while the resource use data related to 1989 to 1999. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, and authors' assumptions.

Modelling
A Markov model was used to extrapolate the costs and benefits to a lifetime horizon. The model had a cycle length of 1 year. The model included health states for RA, dyspepsia, GI complications, acute hepatic failure, acute renal failure and death. Patients experiencing a first GI complication entered a post GI complication health state where the risk of further events was increased. Acute hepatic failure and acute renal failure due to NSAIDs were modelled as temporary states. The model assumed that NSAIDs or COX-2 inhibitors would be discontinued immediately following an adverse event, and resumed the following year.

Outcomes assessed in the review
The review was used to determine the transition probabilities for the Markov model. The outcomes assessed included mortality and the risk of adverse events.

**Study designs and other criteria for inclusion in the review**
The review included randomised controlled studies, life table analyses and cohort studies. The authors stated that the study population for papers included in the review had to be similar to the hypothetical cohort simulated in the model.

**Sources searched to identify primary studies**
The authors searched MEDLINE (from 1966 to 2000) and the bibliographies of identified studies.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
At least 11 primary studies were included in the review of effectiveness.

**Methods of combining primary studies**
The authors stated that no attempt was made to combine data from multiple studies.

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

**Results of the review**
The annual probability of dyspepsia was 0.29 with NSAIDs alone or NSAIDs and misoprostol, 0.125 for NSAIDs with PPI, and 0.182 for COX-2 inhibitors.

The annual probability of serious GI complication was 0.0190 with NSAIDs alone, 0.0118 with NSAIDs and misoprostol, 0.0053 with NSAIDs and PPI, and 0.0020 with COX-2 inhibitors.

The annual probability of death following admission for a GI complication was 0.12.

**Methods used to derive estimates of effectiveness**
The authors assumed that the four treatment strategies were equally effective for controlling RA on the basis of published studies.

**Estimates of effectiveness and key assumptions**
The response rate to each strategy for the control of RA was assumed to be 60%.

**Measure of benefits used in the economic analysis**
The measure of health benefit was the quality-adjusted life-years (QALYs). Estimates of the relative utility decrement associated with adverse events were derived from published studies (utility adjustments were given in the paper). It was
assumed that each disease state reduced the patient's utility by the same percentage, irrespective of the presence of concomitant disease.

**Direct costs**
The cost estimates were taken from published studies and published pricing lists. The resource use quantities were not reported separately from the costs, but were given in terms of the cost per event or time period. The cost data were not reported in sufficient detail to know whose direct costs were included in the analysis. The direct costs were for RA treatment, the four additional treatment strategies, and the treatment of adverse events. Drug prices were based on average wholesale prices. The costs were discounted at a rate of 3% per annum. The study reported the average costs in 1999 US dollars.

**Statistical analysis of costs**
Sampled data were not available for the costs.

**Indirect Costs**
The indirect costs do not appear to have been included in the analysis.

**Currency**
US dollars ($). The costs were updated to 1999 using the medical care component of the Consumer Price Index.

**Sensitivity analysis**
The generalisability of the results was explored in one-way sensitivity analyses by varying the medication costs of NSAIDs, misoprostol, PPIs and COX-2 inhibitors. The authors did not specify the rationale used to determine the ranges explored.

**Estimated benefits used in the economic analysis**
Treatment with NSAIDs without prophylaxis was estimated to result in 11.46 QALYs per patient. The addition of misoprostol increased the estimated QALY gain to 11.55 per patient. The addition of a PPI increased the estimated QALY gain to 11.79 per patient. Treatment with COX-2 inhibitors was estimated to result in 11.77 QALYs per patient. The health benefits were discounted at a rate of 3% per annum. Side effects from treatment were one of the main considerations of the analysis.

**Cost results**
The average lifetime cost of treatment with NSAIDs without prophylaxis was $45,317, compared with $56,105 for treatment with NSAIDs and misoprostol, $62,939 for COX-2 inhibitors, and $68,773 for NSAIDs with PPI. The costs were discounted at a rate of 3% per annum.

**Synthesis of costs and benefits**
The costs and benefits were combined to calculate the cost per QALY gained. The incremental cost-effectiveness ratios were calculated according to standard methods, eliminating strategies ruled out by dominance or extended dominance. The strategy of NSAIDs with misoprostol was ruled out by extended dominance. The cost per QALY gained with COX-2 inhibitors compared with NSAIDs without prophylaxis was $56,751. The cost per QALY gained with NSAIDs and PPI compared with COX-2 inhibitors was $355,747. The costs and health benefits were discounted at a rate of 3% per annum. The results were sensitive to variations in the cost of PPI, the risk of serious GI complications with NSAIDs without prophylaxis, and the risk of dyspepsia with COX-2 inhibitors. In these sensitivity analyses, the optimal treatment strategy could change from COX-2 inhibitors to NSAIDs with PPI.
Authors' conclusions
Cyclooxygenase-2-specific (COX-2) inhibitors were the most cost-effective treatment option among the strategies analysed.

CRD COMMENTARY - Selection of comparators
The comparator was chosen to represent current practice in the study setting. You should consider whether the included treatment strategies are relevant alternatives in your own setting.

Validity of estimate of measure of effectiveness
The authors stated that a detailed review of the literature had been undertaken. The sources searched and the inclusion criteria for the review were satisfactorily reported. However, the methods used to determine the validity of the primary studies and to extract the data were not reported in detail. The authors made no attempt to combine data from the primary studies, and so made selective use of the available data. The authors did not consider the impact of differences between the primary studies when estimating effectiveness. This is important as the effectiveness data might have been based on non-randomised trials, or extracted from single arms of randomised trials, which would introduce the possibility of bias into the study results.

Validity of estimate of measure of benefit
The estimation of health benefits was modelled using a Markov model, to extrapolate the effectiveness data to a lifetime horizon and to combine it with estimates of the relative utility decrement associated with adverse events. The utility estimates were derived from published studies and authors' assumptions. The authors acknowledged that the fact that some utility estimates were not derived in the appropriate RA study population was a limitation of the study.

Validity of estimate of costs
Although the authors stated that the study adopted a societal perspective, they did not include the indirect costs. They stated that data on the indirect costs were not available from the included clinical trials. They did not search for alternative sources of data on the indirect costs, thus it is possible that these omissions might have affected the study conclusions. The cost data were based on published studies and on published prices. There was limited information on the cost estimates, which restricts the generalisability of the study results. However, one-way sensitivity analyses were conducted to explore variation in the costs of the study drugs. The authors used appropriate methods to inflate the costs to the reported study price year, and discounted appropriately.

Other issues
The authors made appropriate comparisons of their results with the findings from other studies. The issue of generalisability to other settings was addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively. The authors concluded that COX-2 inhibitors are the optimal treatment strategy, despite their concerns that the incremental cost-effectiveness ratio exceeded $50,000 per QALY, a common threshold for cost-effectiveness. Were the authors to use a cost-effectiveness threshold of $50,000 per QALY, the optimal treatment strategy would instead be NSAIDs without prophylaxis. The authors acknowledged that the omission of cardiovascular adverse events associated with COX-2 inhibitors might have affected the study results. The authors highlighted limitations of the study, such as simplifications in the model's structure, in their discussion.

Implications of the study
The authors suggested that the results of this study may be applicable to other inflammatory arthritides that require the use of NSAIDs or COX-2 inhibitors. No recommendations for further research were made.

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