Economic evaluation of meloxicam (7.5mg) versus sustained release diclofenac (100mg) treatment for osteoarthritis: a cross-national assessment for France, Italy and the UK  
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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
Two non-steroidal anti-inflammatory drugs (NSAIDs) were evaluated: meloxicam (7.5 mg/day) versus sustained release (SR) diclofenac (comparator, 100 mg/day).

Type of intervention
Treatment, palliative care.

Economic study type
Cost-effectiveness analysis.

Study population
The target population was that of patients with OA.

Setting
The setting was primary and secondary care. The economic analysis was conducted in France, Italy and the UK.

Dates to which data relate
Effectiveness evidence was from 1986 and an undated reference. Resource use dates ranged from 1989 to 1996. The price year was 1995-6.

Source of effectiveness data
Effectiveness data were derived from a synthesis of previous studies and expert opinion.

Modelling
A decision tree was constructed for each country to model the costs of a 30-day treatment period for patients with OA treated with meloxicam or SR diclofenac. The clinical information (GI adverse events) was taken from a pooled analysis of double blind trials, whereas resource use and costs attached to these events were estimated separately for each country. Software used was DATA Treeage (USA).

Outcomes assessed in the review
Inputs to the model included probabilities of adverse GI events categorised as: no adverse event; adverse event not requiring treatment; minor adverse event with ambulatory treatment; ulcer with ambulatory treatment; ulcer requiring hospitalisation; haemorrhage requiring hospitalisation; and perforation requiring hospitalisation.
Study designs and other criteria for inclusion in the review
Data came from a Boehringer Ingelheim safety database of a subset of patients with OA from double-blind randomised studies that compared meloxicam at 7.5 mg/day with diclofenac retard at 100 mg/day.

Sources searched to identify primary studies
Not stated.

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

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

Number of primary studies included
The number of studies included in the company database was not stated, either in the paper or in the parent UK article (see Jansen et al in "Other Publications of Related Interest" below).

Methods of combining primary studies
The database aggregated primary safety data from clinical trials conducted during the development of meloxicam. Although not described in detail, it seems that a patient level analysis was conducted and a pooled analysis of adverse events was reported.

Investigation of differences between primary studies
Not reported. The authors stated that key demographic information was similar across both groups at baseline.

Results of the review
For patients taking meloxicam, 1.9% (6 of 309) experienced a minor GI effect in contrast to 2.8% in the diclofenac group (9 of 324).

Of the patients taking diclofenac, 0.3% (1) experienced an ulcer which required hospitalisation while no patients in the meloxicam group had such an event.

These probabilities were used to derive the different adverse events mentioned in the "outcomes assessed" field.

Methods used to derive estimates of effectiveness
To augment data derived from the literature the authors made a number of assumptions. A Delphi panel was used in France and Italy.

Estimates of effectiveness and key assumptions
The authors assumed that the GI adverse events reported simultaneously contributed to the probabilities in the model as if they were a single event, while GI adverse events reported for the same subject at different times were calculated as separate events. In the French model, some further assumptions were made regarding the inclusion of hospital-based gastroenterologists only for treatment of serious complications; and the definition of patients "at risk" of a GI side effect. In the Italian model, all patients were assumed to have had one initial general practitioner (GP) consultation as well as one with a rheumatologist.
Measure of benefits used in the economic analysis
No summary measure of benefit was produced. The health benefits are those associated with the avoidance of GI events as depicted in the model. Cost differences were derived from the different adverse events experienced in the intervention and comparator strategies. The study might best be described as a cost-consequences analysis.

Direct costs
Discounting was not carried out, and this was appropriate given the short time horizon of the model. Quantities and costs were analysed and reported separately for each country. Cost items included GP or specialist visits, hospitalisations, endoscopies, ulcer prophylaxis and treatment drugs, pain medication, and prescription fees. The quantity/cost boundary was that of the payer (the NHS in the UK; the French statutory health insurance; and the Italian NHS). The estimation of quantities was based on a local database, data from the literature and from expert opinion in the UK; data from expert interviews using a Delphi panel in France (1993); and on expert interviews and the literature in the case of Italy. The price year was 1995-6 and reflation was used when required. Unit cost sources came from published sources, and from Boehringer Ingelheim in the case of mecloxicam. In Italy, Diagnosis Related Group (DRG) reimbursement system was used to cost hospitalisation and ulcer treatment.

Statistical analysis of costs
Costs were treated in a deterministic way.

Indirect Costs
Indirect costs were not included in the study.

Currency
Costs were shown in national currencies (UK pound sterling (£), Italian Lira (L), and French Francs (Ffr)). Some summary results were also provided in US dollars (1 US dollar = 0.65, = L1519.3, = Ffr5.0600).

Sensitivity analysis
A one-way sensitivity analysis was performed for the different countries by modifying key probability variables over the range of their 95% confidence interval.

Estimated benefits used in the economic analysis
As previously stated, no summary measure of health benefit was used and a cost-minimisation analysis was undertaken.

Cost results
Average total 30 day costs per patient for mecloxicam and diclofenac SR were Ffr 201.94 versus Ffr 298.50 in France; L 131,873 versus L 138,474 in Italy; and 28.18 versus 37.14 in the UK respectively (the corresponding average figures in $ are $37.99 versus $56.15 in France; $86.80 versus $91.14 in Italy; and $43.69 versus $57.58 in the UK respectively).

Incremental analysis including NSAIDs costs showed that mecloxicam was cost-saving in all countries ($18.16 (32%) in France; $4.34 (5%) in Italy and $13.89 (24%) in the UK).

Substantial differences in resource use existed between countries, and hospitalisation was the most expensive unit cost in all of them.

Although rare, hospitalisation had a strong impact on the average treatment costs in the diclofenac SR arm (there were no side effects requiring hospitalisation in the mecloxicam arm) and especially in France due to the elevated country specific costs.
In the sensitivity analysis, the greatest impact on savings was hospitalisation in the diclofenac SR arm.

Excluding perforations, ulcer and bleeding (PUBs) as well as the costs of NSAIDs, 30 days cost saving per patient of meloxicam was reduced to $0.84 in France; $1.23 in Italy and $2.11 the UK.

In the French model, variation of GI side effect probabilities did not alter the results, but the model was sensitive to PUBs.

In the Italian model, some variation of GI side effect probabilities did alter the results, and the model was also sensitive to PUBs.

Lower savings in Italy are thought to have been due to the higher standard cost of OA patients as well as the costing methodology (DRGs).

In the UK model, meloxicam was always associated with cost savings (it was also the only country in which daily meloxicam cost was cheaper than diclofenac).

Synthesis of costs and benefits
Costs and benefits were not combined.

Authors' conclusions
Differences in treatment practices for NSAID-induced GI adverse events are prevalent among countries. The improved safety profile of meloxicam (7.5 mg daily) consistently resulted in potential savings for an OA population over 30 days when compared with diclofenac SR (100 mg daily).

CRD COMMENTARY - Selection of comparators
The authors did not explicitly report the reason for the selection of the comparator, as many other NSAIDs with inhibition of both type 1 and 2 cyclo-oxygenase inhibitors, and thus more prone to GI adverse events, exist. A previous UK study by the same group of authors used the same comparator. You should decide if this is the appropriate comparator and represents current practice in your setting.

Validity of estimate of measure of effectiveness
Side effect incidence and severity was pooled from a subgroup of patients with OA from a manufacturer database of double-blind trials conducted during the development of meloxicam. The authors stated that the patients were comparable at analysis, and further details of the pooled analysis methodology were not given, but a reference was given to a previous economic evaluation (see Koller in "Other Publications of Related Interest" below). From the 633 patients included only 1 of the 324 subjects taking diclofenac had an ulcer which required hospitalisation. Although the clinical and statistical significance of this difference between the groups was not discussed, hospitalisation differences had an important influence on the results, and an analysis excluding hospitalisations alone was not reported and would probably show that cost savings of meloxicam would diminish.

Validity of estimate of measure of benefit
The authors stated that the drugs had similar effectiveness and thus did not derive a summary measure of health benefit. The health benefits were reflected in the side-effects profile of each drug from which probabilities were derived to populate the decision tree. This was an appropriate approach in light of the study question.

Validity of estimate of costs
Relevant categories of costs were included for the perspective adopted, and relevant costs in each category were also included. As the authors stated, only direct medical costs were included, and inclusion of indirect costs could lead to a
larger differential in favour of meloxicam. Costs and quantities were reported separately, which helps readers in other settings to consider generalisability issues. Resource use was assessed through experts in all countries; in the UK a linked database was also used; and in the UK and France data from the literature were also used. A Delphi approach with eleven physicians was conducted in France; in Italy a panel of four experts was used but the methodology was not stated; and in the UK the method was not stated. A sensitivity analysis of quantities was not reported, but it was conducted for side effect probabilities and severity, which helps to evaluate the robustness of the findings. Official published prices and other published sources were used in all countries and the source was the manufacturer in the case of meloxicam for UK and Italy (the source was not stated for France). A sensitivity analysis of prices was not conducted. Discounting was unnecessary as the time horizon of the study was one month.

Other issues
The authors made comparisons with another study carried out in the UK by the same group. Generalisability was specifically addressed for each country setting, using local estimates of resource use and costs. The authors appear to have presented their results somewhat selectively, and they omitted to present an analysis excluding hospitalisation costs only (the increase in hospitalisation with diclofenac does not appear to be clinically or statistically significant), which may have changed the results. The only analysis presented that omitted hospitalisations also omitted drug costs, and this could potentially mislead the reader.

Implications of the study
As the authors state, assuming relevance of the models to the clinical population, meloxicam, an efficacious treatment for OA, was shown to be economically viable due to its reported GI tolerability, although the impact differs due to country specific treatment practices. If results are confirmed in practice or in a wider population it can be hypothesized that the costs associated with adverse effects of OA treatment could be considerably reduced.

Source of funding
Grants from Boehringer Ingelheim.

Bibliographic details

Other publications of related interest

Koller C. Meloxicam (UH - AC 62 XX): Summary of safety. Medical Data Services, Thomae.

Indexing Status
Subject indexing assigned by CRD

MeSH
Anti-Inflammatory Agents, Non-Steroidal /adverse effects /therapeutic use /economics; Clinical Trials as Topic; Costs and Cost Analysis; Databases; Diclofenac /adverse effects /therapeutic use /economics /administration & dosage; Drug Costs; France; Great Britain; Humans; Italy; Osteoarthritis /drug therapy; Randomized Controlled Trials as Topic

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