Choice of NSAID and management strategy in rheumatoid arthritis and osteoarthritis: the impact on costs and outcomes in 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

Non-steroidal anti-inflammatory drugs (NSAIDs) for the management of rheumatoid arthritis and osteoarthritis: nabumetone (between 1,000 and 2,000 mg per day), diclofenac (100-200 mg per day), ibuprofen (1,200-3,200 mg per day), piroxicam (10-20 mg per day) and naproxen (500-1000 mg for patients with osteoarthritis and 1,500 mg per day for those with rheumatoid arthritis).

Type of intervention

Treatment.

Economic study type

Cost-effectiveness analysis.

Study population

Patients at least 18 years of age with either rheumatoid arthritis or osteoarthritis. Individuals were excluded if they had either a history of liver disease, blood dyscrasia, uncontrolled hypertension, abnormal laboratory values, recent myocardial infarction, heart failure, functional class IV arthritis, pregnancy or lactating, recent gastrointestinal bleeding or peptic ulcer. In additions others were excluded if they were not using contraception, were sensitive to aspirin or NSAIDs, or needed coumadin, anticonvulsants, hydantoins or multiple NSAIDs.

Setting

Community and hospital. The economic analysis was conducted in Sheffield, South Yorkshire, United Kingdom.

Dates to which data relate

Effectiveness data and some resource data were taken from a three month clinical trial published in 1993. Additional resource data were taken from 1994 and 1995 publications. 1995 prices were used.

Source of effectiveness data

Effectiveness data were derived from a single study and a review of the literature

Link between effectiveness and cost data

Cost data were not collected from the same population sample as that used in the effectiveness analysis.

Study sample

Patients were randomised on a 3:1 ratio between nabumetone and the other four NSAIDS. Specifically there were 3,315 patients in the nabumetone group (between 1,000 and 2,000 mg per day), 296 received diclofenac (100-200 mg per

day), 235 ibuprofen (1,200-3,200 mg per day), 286 piroxicam (10-20 mg per day) and 279 naproxen (500-1000 mg for patients with osteoarthritis and 1,500 mg per day for those with rheumatoid arthritis). Power calculations were not reported as having been used to determine the sample size.

Study design

This was a multi-centre open label randomised controlled trial. The duration of follow up was 12 weeks or until withdrawal. Withdrawal rates in the five NSAID groups respectively were nabumetone 10.7%, diclofenac 10.1%, naproxen 11.5%, ibuprofen 8.1% and piroxicam 9.1%. These withdrawal rates were not significantly different.

Analysis of effectiveness

The analysis of effectiveness was based on intention to treat. The primary health outcomes measured were the incidence of minor and major adverse effects, including gastric bleeding and peptic ulcers. At baseline all groups were similar in demographic and clinical characteristics.

Effectiveness results

Overall there were no significant differences in the rate of adverse events reported in the five groups, with 33.3% of those receiving nabumetone reporting adverse events, and similarly 38.9% of those on diclofenac, 33.7% for the naproxen group, 25.5% for ibuprofen and 25.9% for piroxicam. However, there were significant differences between the different NSAIDs for specific adverse events. Significantly more patients on diclofenac experienced abdominal pain (8.8%) compared with the nabumetone group (4.3%) ($P<0.002$) and they also experienced more abnormal hepatic function events than all other NSAIDs combined, ($P<0.01$). The incidence of gastritis was also significantly higher at 1.7% compared with 0.4 in the nabumetone group, ($P<0.02$). The incidence of diarrhoea was, however, significantly higher at 7% in the nabumetone group, compared with naproxen, ibuprofen and piroxicam. Dyspepsia was more common in the naproxen group (12.2% versus 6.6% for nabumetone and 4.3 % for ibuprofen), ($P<0.002$). The incidence of perforations, ulcer and bleeds in the nabumetone group (1 (0.03%)) was significantly lower than that for the other NSAIDs combined (6 (0.5%)), ($P=0.001$).

Clinical conclusions

Nabumetone is as safe as the other four NSAIDs compared and may be preferable for some patients due to the lower rates of gastric events compared with some of the other NSAIDs.

Modelling

Two decision analysis models were used to combine data on effectiveness from the published clinical trial with UK resource and cost data to determine costs per life year gained. In the first model individuals were prescribed one of the NSAIDs for a period of three months. If there were minor adverse events additional treatment would be prescribed, whereas if there were major adverse events, treatment with NSAIDs would be terminated. In the second model if patients experienced minor adverse events they would be switched to the NSAID with the lowest risk for those adverse events; switching would take place after four weeks. If patients then continue to experience minor adverse events, these are treated with additional medication. As in the first model patients experiencing major adverse events had NSAID treatment stopped and received treatment for the adverse event.

Outcomes assessed in the review

Mortality rates due to gastric bleeding were assessed by a review of the literature.

Study designs and other criteria for inclusion in the review

Not stated.

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
3 studies were included.

Methods of combining primary studies
Not combined.

Investigation of differences between primary studies
Not stated.

Results of the review
Mortality rates ranged from 4 to 14% in the literature and, based on these estimates, a rate of 10% was used in the decision analysis model.

Measure of benefits used in the economic analysis
The benefit measure was life years gained.

Direct costs
Costs of NSAID treatment in addition to treatment for minor and major adverse events and their long term consequences were estimated. The cost of a three month NSAID course was taken from the 1994 Drug Tariff and the May 1995 Chemist and Druggist Monthly Price List. Adverse event costs were taken from published Extra Contractual Referral prices for the NHS Trent region. Maintenance therapy requirements to prevent re-bleeding were taken from the recommendations of the English Royal College of Physicians. Maintenance therapy was assumed to last 55 weeks. Costs were determined from the perspective of the UK National Health Service. 1995 price years were used. All costs were for a duration of three months only with the exception of maintenance therapy for gastric bleeding which was assumed to last for 55 weeks. Costs and benefits were not discounted due to the short duration of the model.

Indirect Costs
Not included.

Currency
UK pounds sterling ().

Sensitivity analysis
Analysis of extremes multi-way sensitivity analysis was carried out. In sensitivity analysis the mortality rate associated with gastric bleeding was varied to upper and lower thresholds of 20% and 5% respectively because of uncertainty over

the baseline estimate of 10% used in the model. Adverse events rates were also varied to the values at the upper and lower confidence intervals. Similarly costs due to treating major adverse events were also halved and doubled.

Estimated benefits used in the economic analysis

Note: In this paper although all five NSAIDs were considered in the economic analysis, only results comparing nabumetone with ibuprofen were reported. For the first decision scenario considered (without switching, co-prescribe drugs to treat minor adverse events) in hypothetical cohorts of 100,000 patients receiving either of these two NSAIDs there would be an additional 82 deaths in the ibuprofen group (85 deaths, 95% CI: 10-307) compared with the nabumetone group (3 deaths, 95% CI: 0-17). Similarly there would be an additional 821 major adverse events in the ibuprofen group (851 events, 95% CI: 102-3070) compared with the nabumetone group (30 events, 95% CI: 0-168). For the second decision scenario considered (allowing switching between NSAIDs after four weeks in the event of minor adverse events) in hypothetical cohorts of 100,000 patients receiving either of these two NSAIDs there would be an additional 69 deaths in the ibuprofen group (93 deaths, 95% CI: 10-408) compared with the nabumetone group (24 deaths, 95% CI: 2-121). Similarly there would be an additional 689 major adverse events in the ibuprofen group (929 events, 95% CI: 103-4081) compared with the nabumetone group (240 events, 95% CI: 17-1213).

Cost results

The costs per patient (including adverse events) for all patients initiated on nabumetone and ibuprofen in the first decision scenario were 75.99 (95% CI: 74.10-80.16) and 35.17 (95% CI: 16.99-86.12) respectively. The incremental cost of treatment initiated by nabumetone was 40.82. The costs per patient (including adverse events) for all patients initiated on nabumetone and ibuprofen in the second decision scenario were 64.20 (95% CI: 59.61-83.11) and 41.67 (95% CI: 17.61-109.34) respectively. The additional incremental cost of treatment initiated by nabumetone was 22.53.

Synthesis of costs and benefits

The incremental cost per life year gained using nabumetone rather than ibuprofen was 2,517 (95% CI: -104 - 28,346) in the first scenario without switching and 1,880 (95% CI: -463 - 24,566) in the second scenario where switching to the alternative NSAID with the lowest risk of minor adverse events experienced would be permitted.

Authors' conclusions

The authors concluded that the additional cost of nabumetone may represent good value for money compared with other health care interventions, although this new NSAID was unlikely to be cost saving compared to the older NSAIDs. Furthermore, many additional factors including the management of minor and major adverse events also influence costs and outcomes of NSAIDs and these also need to be taken into account.

CRD COMMENTARY - Selection of comparators

ustification was provided by the authors for the comparators used. The four older NSAIDs compared with nabumetone are reported to be in wide use, and all five NSAIDs have been shown to be efficacious.

Validity of estimate of measure of benefit

efits used in the decision analysis models were taken largely from a large open label multi-centre randomised controlled trial, reducing the potential for bias. The estimate of mortality due to gastric bleeding used in the model was based on results reported in the literature. It is unclear how these references were identified, which may possibly bias the estimate used in the model, although the authors did account for this in their sensitivity analys

Validity of estimate of costs

quate details of costs were provided by the authors, and resources used in treatment were assumed to be the same as in the clinical trial. Future analyses may also wish to consider costs to others in society such as patients and their caregivers.

Other issues
t estimates in this analysis are not generalisable to contexts outside the UK national health service. Estimates of benefits and adverse events were obtained from a trial of three months duration only and additional studies may be required to determine longer term outcomes and costs associated with the newer NSAIDs.

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