Rheumatology 2008;47:1077–1081
Advance Access publication 29 May 2008

doi:10.1093/rheumatology/ken128

Cost–effectiveness of advising the use of topical or oral ibuprofen for knee pain; the TOIB study [ISRCTN: 79353052]

E. Castelnuovo[1], P. Cross[1], S. Mt-Isa[2], A. Spencer[3] and M. Underwood[4] on behalf of the TOIB study team

Objective. Advice to use topical or oral NSAIDs is equally effective for the treatment of knee pain in older people. The ingredient cost of topical preparations is typically more than oral preparations, but could save costs because they have fewer adverse effects. A cost–utility study is needed to decide on their comparative cost effectiveness.

Methods. We recruited 585 people aged ≥50 yrs with knee pain; 282 participated in a randomized controlled trial and 303 in a patient preference study from 26 MRC General Practice Research Framework practices in the UK. They received advice to preferentially use topical or oral NSAIDs for knee pain. We calculated the comparative cost per quality-adjusted life year (QALY) from both a National Health Service (NHS) and a societal perspective over 12 and 24 months.

Results. Compared with the topical route, oral NSAIDs cost the NHS £191 and £72 more over 1 yr in the randomized trial and preference study, respectively. The cost per QALY, from an NHS perspective, was in the range of £9000–£12 000 in the randomized trial. In the preference study, it was £2564 over 1 yr, but over 2 yrs the oral route was dominant.

Conclusions. Our cost–effectiveness analysis supports the use of oral NSAIDs in selected patients. Nevertheless, deciding to recommend oral NSAIDs in preference to topical NSAIDs could have a substantial impact on NHS costs because of the uncertainty in the cost–effectiveness estimate.

Key words: Primary care, Knee pain, Osteoarthritis, Health economics, Non-steroidal anti-inflammatory drugs, Topical non-steroidal anti-inflammatory drugs.

Introduction

Knee pain, much of which is due to OA, is a common problem in older people, affecting a third of those aged ≥50 yrs. The annual cost of OA-related knee pain in the UK is £43 million for community care and £215 million for social care. Other costs of treating knee OA are not available; however the total cost to the National Health Service (NHS) of treating OA is around £675 million, a third of which is spent on NSAID prescriptions [1].

Around 60% of those treated in general practice for OA are offered symptomatic drug treatment. Oral and topical NSAIDs are widely used to treat knee pain in older people. We have shown that advice to use oral or topical NSAIDs as a treatment for knee pain in older people has an equivalent clinical effect over the long term [2]. The cost-effectiveness of topical NSAIDs is not well established [3–5]. Prescriptions for topical NSAIDs are typically more expensive than those for oral preparations, whilst oral NSAIDS are likely to have more costs associated with adverse effects than topical ones [6]. Thus, from a health economic perspective, the decision whether to preferentially advise oral or topical NSAIDs depends crucially on the balance between overall costs and benefits of topical or oral NSAIDs. In this article, we compare the costs and benefits of advising older people with knee pain to preferentially use topical or oral NSAIDs, from both an NHS and a societal perspective.

Methods

The methods used for the Topical or Oral Ibuprofen (TOIB) study are described in detail elsewhere [6]. Briefly, we recruited 585 people who had received treatment for chronic knee pain from 26 MRC General Practice Research Framework practices spread across the UK [7].

Participants were aged ≥50 yrs, had had troublesome pain in or around the knee on most days for at least a month as well as knee pain for >3 months in the preceding year; and had consulted or been prescribed treatment by the general practitioner for knee pain in the preceding 3 yrs. A radiological diagnosis of OA was not required. Potential participants with current or planned knee replacements and those who did not meet our safety criteria were excluded [2, 6].

We recruited 282 participants to a randomized controlled trial and 303, who met the same entry criteria, to a patient preference study. We compared advice to preferentially use either oral or topical NSAIDs; ibuprofen was our preferred NSAID. Follow-up was through postal questionnaires after 3, 6, 12 and 24 months, and nurse assessments at 12 and 24 months.

We calculated quality-adjusted life years (QALYs) and cost of healthcare (in Sterling Pounds for the year 2005) for individuals advised to use topical or oral NSAIDs preferentially. We assessed the cost–utility of topical NSAIDs using the incremental cost–effectiveness ratio (ICER), the ratio of the difference in cost to the difference in QALYs with topical compared with oral NSAIDs, both from the UK NHS and societal perspectives [8].

To assess the implications of patients' treatment selection, we separately estimated cost–effectiveness for the randomized trial and patient preference study, over a 12-month time-horizon as our primary analysis. For completeness we also present the analysis at 24 months, although not all participants were able to complete 24 months of follow-up before the end of the study. A 3.5% discount rate, as per the UK Treasury Guidelines, was applied to both costs and QALYs during the second year [9].

[1]Centre for Health Sciences, [2]Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, [3]Department of Economics, Queen Mary University of London, London and [4]Clinical Trials Unit, Warwick Medical School, Coventry, UK.

Submitted 9 November 2007; revised version accepted 26 February 2008.

Correspondence to: M. Underwood, Clinical Trials Unit, Warwick Medical School, Gibbet Hill Road, Coventry CV4 7AL, UK.
E-mail: m.underwood@warwick.ac.uk

Outcome measure

We calculated QALYs for each participant using the 'area under the curve' [10] that is, the weighted average of time spent in the study and quality of life, obtained by inputting EQ-5D scores into a quality of life estimation model for the UK general population [11, 12].

Healthcare use

From general practice records we obtained type and number of primary care and outpatient consultations, physiotherapy services, diagnostic tests, hospital admissions and prescription data. Diagnostic tests included blood tests, X-rays and gastroscopies. Whilst blind to study allocation, two general practitioner members of the study team (M.U., P.C.) independently coded hospital admission using Healthcare Related Groups v3.5, conferring to resolve any disagreement [13]. From participant questionnaires, we obtained number and cost of equipment or other aids, privately acquired or dispensed by the NHS and private treatment, including GP and nurse consultations, referrals and hospital admissions, nursing or other help.

Healthcare costs

We used the sum of the number of healthcare contacts multiplied by their unit costs, derived from UK sources, to estimate the cost of care for each participant.

We used published unit costs for general practitioner and nurse consultations, other primary care services, counselling, outpatient, physiotherapy and rehabilitation consultations, and diagnostic tests and procedures [14–18]. When the latter costs were unavailable we used costs charged for tests carried out in the study.

Unit costs for elective and acute hospital admissions were obtained from the Reference Costs Database [18]. Drug costs were calculated from the 2004 Prescription Cost Analysis Database [15]. Costs were actualized for inflation using the Healthcare Price Index [14].

Total healthcare costs in the base-case included the cost of the drug starter pack provided at randomization and any costs plausibly related to knee pain, treatment or adverse effects of treatment.

Prescription costs were broken down into drug groups, and only those whose prescribing rate was most likely to be affected by treatment were included: any oral or topical NSAIDs, rubefacients, paracetamol, aspirin, opioids, cardiovascular drugs, indigestion remedies and respiratory drugs.

Since the trial did not require attendance or visits to clinics, all healthcare use, except for initial starter packs was patient initiated. For this reason, we did not attempt to exclude protocol-driven resource consumption and costs, with the exceptions of recruitment visits and blood tests conducted to follow-up participants.

Participants and family costs

We also calculated total costs from a societal perspective, encompassing the cost of any items and care purchased by patients and families and healthcare costs to the NHS. Participants' costs included supplementary private GP consultations, hospital admissions and equipment and aids privately purchased. These costs also covered domiciliary help for family care or other care and transport costs for treatment received. Participants' costs were the sum of quantity of items and services by price paid, as declared by participants. For individuals unable to recall this information, the mean unit price paid was extrapolated to estimate the cost of similar items. We did not include productivity costs relative to potential income losses for participants or their carers due to disease or treatment as many participants were retired.

Cost–utility

We used inverse probability weighted regressions of individual data in the randomized and preference study separately to estimate the cost–utility of advising topical NSAIDs [19]. First, we calculated the mean incremental cost of advising topical compared with advising oral ibuprofen by estimating the proportion of mean costs that could be attributed to the treatment allocation. Similarly, we calculated the mean incremental effects for topical compared with oral ibuprofen, using health utility data. We used these data to calculate the ICER.

We used inverse probability weighting since, as different patients accrue costs and QALYs at different rates, potential imbalances may arise during follow-up in costs and quality of life between arms of a study. In addition, although potential imbalances at baseline should be resolved in the randomized trial, they were likely to be present in the preference study. Using a regression framework, we adjusted the cost–effectiveness using health utility at baseline, age (above median age) and gender (males) in the estimation of QALYs, and age and gender in the estimation of incremental costs.

We investigated variation around the incremental cost–effectiveness ratio using non-parametric bootstrapping, selecting 10 000 random samples of costs and QALYs of the same number of participants in each study and treatment [20]. We then estimated cost–effectiveness acceptability curves (CEACs), showing the probability that advising topical NSAIDs was cost-effective over a willingness to pay between £0 and £40 000 per QALY [21, 22].

We did sensitivity analyses considering unit costs and cost of admissions based on actual length of stay reported in discharge notes, excluding high-cost individuals (95th percentile of total cost of care at 12 months) and increasing the discount rate to 6%. We then conducted a sensitivity analysis including the total cost of any drug prescribed to assess the robustness of assumptions around which costs were related to knee pain.

Finally, we calculated the expected value of information, which is a measure of the degree of uncertainty about what is the most cost-effective treatment. The expected value of perfect information represents the maximum societal return to additional investigation, and can be used to identify those clinical decision problems which should be regarded as priorities for further research. In this cost–effectiveness study, there is uncertainty arising from imprecise information on the risk of side-effects in individuals with OA, the reduction of adverse effects from using topical NSAIDs and other events that were not observed with sufficient precision in the study. Given that the expected value of information is proportional to the population eligible to be treated with ibuprofen we estimate the expected value for two eligible populations:

(1) All individuals in the UK reporting moderate and severe knee OA.
(2) Sixty percent of all individuals with knee OA [1, 23].

In both the populations, we calculate the expected value of information for a 10-yr time horizon.

Ethical review and funding

Ethical approval for the study was obtained by Northern and Yorkshire multi-centre research ethics committee (MREC 2/3/1) and 28 local research ethics committees. All participants gave informed consent to join the study.

TABLE 1. Utility scores during follow-up, randomized trial and preference study

	Oral	Topical	Difference	*n*
Utility scores, randomized trial, mean, (S.E.)				
Baseline	0.649 (0.02)	0.670 (0.01)	+0.022	278
3 months	0.659 (0.02)	0.660 (0.02)	+0.003	259
6 months	0.653 (0.02)	0.637 (0.02)	−0.016	243
12 months	0.663 (0.02)	0.650 (0.02)	−0.012	235
24 months	0.676 (0.02)	0.684 (0.02)	+0.008	159
Utility scores, preference study, mean, (S.E.)				
Baseline	0.633 (0.03)	0.656 (0.01)	+0.023	298
3 months	0.647 (0.03)	0.647 (0.02)	+0.001	265
6 months	0.634 (0.03)	0.637 (0.02)	+0.003	261
12 months	0.643 (0.03)	0.630 (0.02)	−0.013	253
24 months	0.622 (0.03)	0.607 (0.02)	−0.015	223

Results

Health outcomes

Though not statistically significant, in both studies the topical group had fewer QALYs over both the 12- and 24-month horizons (Table 1). The differences were slightly larger in the preference study. Any differences were small or very small in both studies, but such small differences may still have an impact on cost–effectiveness ratios.

Healthcare resource consumption

Resource consumption was similar in all groups, although individuals with longer follow-up tended to have fewer primary care consultations. The majority of consultations took place in the NHS. Admissions to NHS hospitals were frequent, one in four patients over 12 months and one in three over 24 months; private admissions were rare, one in the randomized trial and three in the preference study.

Healthcare costs

In the randomized trial, the mean cost of care was lower in the topical treatment group, over both 12 and 24 months. In the preference study, the cost of care was lower for individuals in the topical group over 12 months, but not over 24 months. The cost of all major groups of healthcare consumption was lower in the topical group, except for the cost of general practice and outpatient consultations, equipment and aids, and in the randomized trial, diagnostic tests. These differences were very small in absolute values. None of these differences were statistically significant.

In the randomized trial, the total cost of drugs was lower in participants randomized to the topical group. The cost of both oral and topical ibuprofen was a relatively modest proportion of the total cost of drugs over the course of the study. Nevertheless, the initial lower cost of oral ibuprofen was displaced by the higher cost of other drugs, particularly cardiovascular and gastrointestinal drugs.

In the preference study, there was no difference in drug costs over 12 months since the higher cost of other oral NSAIDs in the oral arm displaced the savings made with oral ibuprofen. However, over 24 months, the cost of drugs for individuals in the topical group in the preference was higher, albeit non-significantly so, due to increased costs of cardiovascular and indigestion drugs.

Participant and family costs

Patient and family costs were substantial, in spite of excluding loss of income. Over 12 months, these costs ranged between £180 and £300, and were greater in the oral group [costing an additional £53 in the oral group in the randomized trial, and an additional £100 in the preference study (Table 2)].

Cost–utility

NHS perspective. Over 12 months, the incremental cost–effectiveness ratio for oral NSAIDs compared with topical NSAIDs was £9114 in the randomized trial and £2564 in the preference study (Table 2). These show that the lower costs in the topical group did not compensate for the reduction of health utility from using topical preparations.

Over 24 months the two studies produced different results. In the randomized trial, oral treatment continued to improve quality of life at an increased cost, producing an incremental cost–effectiveness ratio of £11 976 per QALY. However, in the preference study, as a result of increased costs associated with topical NSAIDs over this time-horizon, oral NSAIDs became dominant; that is, oral NSAIDs improved health utility and were less costly.

Societal perspective. Using a societal perspective the incremental costs with the topical route were −£244.8 and −£815.5 in the randomized trial, at 12- and 24-months, and −£171.7 in the preference study at 12 months. At 24 months, the cost of care remained higher in the topical group compared with oral group (+£175.9). The incremental cost–effectiveness ratio became less favourable to the oral group in the randomized trial, £11 657 and £21 461 over 12 and 24 months, respectively and in the preference study over 12 months, £6132. In the preference study, the oral route remained dominant over 24 months (see supplementary data Figs 1w and 2w at *Rheumatology* Online).

Sensitivity analyses. The cost-effectiveness of the oral route was robust in both time-horizons to the assumptions underpinning the calculation of costs. Including the total cost of drugs, increasing discount rate and excluding high-cost individuals did not change the results at 12 months. However, the oral route became cost-effective at £3738, rather than dominant, over the 24-month horizon when using the actual length of stay for hospital admissions (Table 2).

CEACs. Over the 12-month horizon, our primary analysis, CEACs for the randomized trial indicate that the probability that advising patients to use oral rather than topical NSAIDs is cost-effective approaching 80% at a threshold of £30 000, whilst in the preference study, the probability that advising oral ibuprofen is cost-effective is 80% at a threshold of £20 000. Over 24 months in the randomized trial, the probability that the oral route is cost-effective decreases with 55% at a threshold of £30 000. In the preference study, oral ibuprofen is dominant for any threshold of cost–effectiveness at 24 months (Figs 1w and 2w).

Expected Value of Perfect information. Based on population survey data, the number of individuals with moderate to severe knee OA aged 45–64 yrs is 91 000 and aged ≥65 yrs is 370 000 [1, 23]. If we apply these estimates to the national age distribution from the Office of National Statistics we calculate that 412 000 people aged ≥50 yrs have moderate to severe knee OA and that 3 600 000 individuals are affected by knee OA of any severity [24]. If drugs for symptom relief are offered to 60% of these, drug treatment for OA-related knee pain is used by I ~2 160 000 people in the UK.

Expected value of Perfect Information (EVPI) over 10 yrs for cost–effectiveness thresholds range from £0–£40 000. There is a high degree of uncertainty about which is the most cost-effective treatment (see supplementary data Figs 3w and 4w available at *Rheumatology* online). For example, at a cost–effectiveness threshold of £30 000, the EVPI over 10 yrs in the randomized trial based on 12-month data is ~£170 million if we assume that the use of ibuprofen is restricted to those with moderate to severe knee OA, and increases to than £1000 million if these drugs are used by 60% of all those aged ≥50 yrs with knee OA. The same

TABLE 2. Incremental costs and QALYs, topical NSAIDs, 12- and 24-month randomized trial and preference study

Incremental costs, QALY and cost–effectiveness ratios, adjusted by age and gender, base case

	Randomized trial 12 months	Preference study 12 months	Randomized trial 24 months	Preference study 24 months
NHS perspective				
Incremental costs, topical ibuprofen (£)	−191.4	−71.8	−455.1	+33.1
Incremental effects, topical ibuprofen	−0.021	−0.028	−0.038	−0.037
ICER, oral ibuprofen (£)	9114	2564	11 976	Oral dominant
Social perspective				
Incremental costs, topical ibuprofen (£)	−244.8	−171.7	−815.5	+175.9
Incremental effects, topical ibuprofen	−0.021	−0.028	−0.038	−0.037
ICER, oral ibuprofen (£)	11 657	6132	21 461	Oral dominant
Sensitivity Analyses (NHS perspective)				
Cost of admissions based on actual length of stay (£)	11 584	6632	31 501	3738
Including all prescriptions (£)	11 227	435	19 155	Oral dominant[a]
Excluding high-cost individuals (>95th percentile) (£)	9099	2125	16 069	Oral dominant[b]
Discount rate (6%) (£)	9020	2211	18 010	Oral dominant[c]

[a]Topical, +£222, −0.037 QALYs; [b]Topical, +£167, −0.037 QALYs; [c]Topical, +£146, −0.037 QALYs.

estimates based on 24-month data are £1000 million and £6000 million, respectively. In the preference study, the expected value of perfect information is between £150 million and £800 million based on 12 months data and between £400 million and £2500 million based on 24 months data.

The EVPI suggests that there is a high degree of uncertainty about whether oral is indeed the most cost-effective treatment. The high uncertainty surrounding this estimate suggests that by preferentially advising oral ibuprofen, the NHS may face a higher cost per QALY than those in our cost–effectiveness calculation. For example, if we consider the annual EVPI estimate, which is simply the expected value for information for 10 yrs divided by 10, the annual expected value of information at a cost–effectiveness threshold of £30 000 is between £17 million and £600 million (as measured in the randomized trial) or between £15 million and £250 million (as measured in the preference study). Based on the randomized trial data, therefore, prescribing oral ibuprofen may be less cost-effective to the NHS than expected, with unforeseeable opportunity costs of £17 million–£600 million per year, arising from uncertainty in our analysis.

Additional information

The following additional supplementary figures (Figs 1w–4w) and tables (Tables 1w–4w) are available as supplementary data at *Rheumatology* Online: CEAC; EVPI; unit costs used; resource use; and healthcare costs.

Discussion

Main findings

We found participants in both studies had slightly, but not statistically significantly, higher health utility if they were allocated to, or chose, oral NSAIDs using both 12- and 24-month horizons. This result is in keeping with the findings from the main clinical results paper where we found that although the outcome from knee pain was equivalent whether oral or topical NSAIDs were advised, the oral route was slightly more effective for overall pain [2].

In the randomized trial, healthcare costs were consistently lower for the topical group across both time horizons and in our sensitivity analyses. The bulk of this difference appears to be due to reduced cost of prescribing of cardiovascular and gastroprotective drugs. Prima facie, this suggests that if purchasers are prepared to pay over £9000–£12 000 for an additional QALY then advising oral NSAIDs will be preferred over advising topical preparations; however, we will return the interpretation of this result in a following section.

The results of the preference study seem to be even more in favour of recommending oral ibuprofen. At 12 months, oral NSAIDs appear to be cost-effective at quite a modest cost per QALY, of £2500–£6000. However, over 24 months topical NSAIDs were dominated in all but one sensitivity analysis. This suggests that for those patients who wish to use them, oral NSAIDs, are a 'good buy' for the NHS in the 12-month analysis, becoming clearly preferable in the 24-month analysis, whether from an NHS or a societal perspective. Overall, considering participants' strong preference for topical rather than oral preparations (2.5 : 1 in our preference study), oral NSAIDs appear surprisingly cost-effective.

Strengths and weaknesses

Some important caveats should be considered that could question whether the cost per QALY in this analysis justifies the routine use of oral rather than topical NSAIDs.

The absolute differences in QALYs were small or very small, making our analyses very sensitive to minor changes. Participants reported fewer major adverse events than expected [2]. This was probably because of our rigorous safety exclusion criteria, which included a history of gastrointestinal events and raised blood pressure. For this reason, we may have underestimated both the negative effect on quality of life and increased health costs of NSAID-related adverse effects in routine practice. For example, a previous study estimated that, when considering major side-effects of treatment, oral NSAIDs brought about a loss of between 0.029 and 0.044 QALYs compared with placebo [4]. This suggests that the apparent gain in health utility from oral NSAIDs could be, at least partially, negated by unmeasured serious adverse effects.

Another problem is that many of those randomized to oral NSAIDs had stopped taking them at the end of 1 yr, reducing the occurrence of adverse events or changes in quality of life. Despite these findings there remains ample evidence, external to this study, of the overall risks associated with oral NSAID use.

In sensitivity analyses over 24 months, the ICER was in the range £18 000–£31 000. The uncertainty in our analysis summarized in the CEAC and value of information curves was low over 12 months, but increased over the longer term and remained large over the range of willingness to pay considered by policy makers [22]. For these reasons, our cost–effectiveness estimate of £9000–£12 000 per QALY from preferring oral NSAIDs in the randomized trial may be at the lower end of the likely range of true values.

Our expected value of perfect information calculation suggests that if we were to recommend oral ibuprofen in preference to topical ibuprofen based on our study results, the NHS could face a higher cost per QALY than expected, with unforeseeable costs of

£17 million to £600 million per year, which are the unforeseeable opportunity costs arising from uncertainty in our analysis.

These amounts are also the maximum resources that the NHS should invest in further research to reduce uncertainty in the adoption decision for oral NSAIDs. As the cost of research is likely to be lower than the smallest of these estimates we conclude that further research is needed to improve cost–effectiveness estimates of topical compared with oral NSAIDs. A new randomized trial powered to address this question is likely to be large and time-consuming, and may exclude those at highest risk of adverse effects from oral NSAIDs. What is needed is work to combine secondary data sources using modelling techniques to estimate the likely effects of a change in practice [25]. This would allow us to infer the impact of the uncertainty that arises from imperfect information on the risk of side-effects in individuals with OA and the effectiveness and the reduction of side-effects from using topical rather than oral NSAIDs.

Interpreting the results

Advising oral treatment was cost-effective for the participants in our randomized trial. Given the uncertainty surrounding the cost–effectiveness of oral ibuprofen in the randomized trial and the likely underestimation of major adverse events, it seems unjustified to strongly recommend oral ibuprofen on the grounds of cost–effectiveness for the general population in the absence of further confirmatory research. In particular, we may have underestimated the effect of NSAID-related adverse effects on both health utility and NHS costs.

In the preference study, oral treatment is cost-effective at quite a modest cost per QALY at 1 yr and dominates topical in the long term: that is, it is cheaper, more effective and more likely to be cost-effective at all levels of willingness to pay.

This produces an interesting conundrum. Based on the preference study data there appears to be a cost–effectiveness argument for preferring oral NSAIDs. However, the results of the cost–effectiveness analysis in the preference study have been driven both by the effects of the medications and the baseline characteristics of the participants. If, as seems likely, patients selected oral NSAIDs because they responded to and tolerated oral NSAIDs well, this could explain why oral NSAIDs were much more cost-effective in this small group of older people with knee pain who chose to use them.

Conclusion

In the randomized trial, oral NSAIDs are a cost-effective alternative to topical preparations, at a willingness to pay of £9000–£12 000 per QALY. In the preference study, oral NSAIDs appear to represent much better value for money, dominating in the 24-month analysis.

Rheumatology key messages

- The cost per QALY from advising oral rather than topical NSAIDs is £9114.
- The additional NHS cost of advising oral NSAIDs could be £17 million to £600 million per year.

Acknowledgements

We are grateful to Lynette Edwards for comments on earlier drafts of this article and to Dawn Carnes for assistance in preparing this article. The funders have not been involved in the production of this article.

Funding: This study was commissioned by the NHS Health Technology Assessment Programme (Project reference 01/09/02). Goldshield Pharmaceuticals supplied the starter packs of topical ibuprofen.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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