Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study

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Executive summary

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Background
Both oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat knee pain. However, oral NSAIDs are associated with gastric, renovascular and respiratory adverse effects, which are a particular risk for older people. If oral and topical NSAIDs are equally effective for chronic knee pain, and topical preparations produce fewer adverse effects than oral preparations, they may be preferred to oral preparations, even if they appear more expensive to purchase. Patient preference for route of administration may be an important factor influencing patient perception of effectiveness of the medication.

Objective
The objective of the study was to determine whether GPs should advise their older patients with chronic knee pain to use topical or oral NSAIDs.

Design
An equivalence study was designed to compare the effect of advice to use preferentially oral or topical ibuprofen (an NSAID) on knee pain and disability, NSAID-related adverse effects and NHS/societal costs, using a randomised controlled trial (RCT) and a patient preference study (PPS). Reasons for patient preferences for topical or oral preparations, and attitudes to adverse effects, were explored in a qualitative study.

Setting
The setting was 26 general practices in the UK.

Participants
Participants comprised 585 people with knee pain, aged 50 years or over; 44% were male, mean age 64 years. The RCT had 282 participants: 144 in the oral group and 138 in the topical group. The PPS had 303 participants: 79 in the oral group and 224 in the topical group.

Intervention
The intervention was advice to use preferentially oral or topical NSAIDs for knee pain.

Main outcome measures
The primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcome measures were the Short Form with 36 Items (SF-36), perceived troublesomeness of knee pain, satisfaction with health status, major adverse effects (unplanned hospital admissions and deaths) and minor adverse events over 12 months. The health economic analysis measured the comparative cost per quality-adjusted life-year (QALY) from both an NHS and a societal perspective over 24 months.

Results
Clinical outcomes
Changes in the global WOMAC score at 12-months were equivalent in both studies: topical – oral, RCT difference = 2 [95% confidence interval (CI) –2 to 6], PPS difference = 1 (95% CI –4 to 6). There were no differences in the secondary outcomes, except for a suggestion, in the RCT, that those in the topical group were more likely to have more severe overall pain and disability as measured by the chronic pain grade, and more likely to report changing treatment because of inadequate pain relief.

Adverse effects
There were no differences in the rate of major adverse effects. There were some differences in the number of minor adverse effects. In the RCT, 17% and 10% in the oral and the topical group, respectively, had a defined respiratory adverse effect (95% CI of difference –17% to –2.0%); after 12 months, the change in serum creatinine was 3.7 mmol/l (95% CI 0.9 to 6.5) less favourable in the oral than in the topical group, and 11% of
those in the oral group reported changing treatment because of adverse effects compared with 1% in the topical group ($p = 0.02$). None of these differences were seen in the PPS.

**Economic analysis**
Oral NSAIDs cost the NHS £191 and £72 more per participant over 1 year in the RCT and PPS, respectively. In the RCT the cost per QALY in the oral group, from an NHS perspective, was in the range £9000–12,000. In the PPS it was £2564 over 1 year, but over 2 years the oral route was dominant, that is, more cost-effective.

**Qualitative studies**
Patient preference for medication type was affected by previous experience of medication (including adverse reactions), other illness, pain elsewhere, anecdotes, convenience, severity of pain and perceived degree of degeneration. Lack of understanding about knee pain and the action of medication led to increased tolerance of symptoms. Symptoms such as indigestion, sensitive stomach and poor general well-being were normalised as an effect of age rather than medication. Potentially important symptoms may inadvertently have been disregarded, increasing participants’ risk of suffering a major adverse effect.

**Interpretation**
Clinical outcomes in the two groups were similar in almost every measure at every time-point. This finding was consistent across the RCT and PPS, suggesting that the two treatment strategies are either equally effective or equally ineffective. Although it is inconclusive, those in the RCT oral group appeared to have more minor adverse effects. Rigorous safety exclusion criteria meant that the impact of adverse effects on NHS costs and health utility may have been underestimated. Since the absolute differences in NHS costs and health utility were small, the cost per QALY may have been very sensitive to any such underestimate. In the PPS, participants with more severe widespread pain chose oral rather than topical ibuprofen. Furthermore, there was little difference in defined adverse effect rates in those who chose oral NSAIDs and those who were randomised to them, even though the PPS oral group took substantially more oral NSAIDs and were older than those in the RCT.

**Conclusions**
Advice to use either oral or topical preparations has an equivalent effect on knee pain, but oral NSAIDs appear to produce more minor adverse effects than topical NSAIDs. Generally, these results support advising older people with knee pain to use topical rather than oral NSAIDs. However, for patients who prefer oral NSAID preparations rather than a topical NSAID, particularly those with more widespread or severe pain, the oral route is a reasonable treatment option, provided that patients are aware of the risks of potentially serious adverse effects from oral medication.

**Implications for healthcare**
The evidence suggests that advice to use topical NSAIDs in preference to oral NSAIDs for treating knee pain in older people may be appropriate.

**Recommendations for research**
Further research is recommended in the following areas.

- Developing and testing strategies to change prescribing behaviour and ensure that older patients are aware of the potential risks and benefits of using NSAIDs.
- Observational studies to estimate rates of different predefined minor adverse effects associated with the use of oral NSAIDs in older people.
- Long-term studies of topical NSAIDs in those for whom oral NSAIDs are not appropriate, for example the very elderly.

**Publication**
The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

**Criteria for inclusion in the HTA journal series**

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA Programme as project number 01/09/02. The contractual start date was in July 2002. The draft report began editorial review in December 2006 and was accepted for publication in July 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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