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RESEARCH

Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study

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ABSTRACT

Objective To determine whether older patients with chronic knee pain should be advised to use topical or oral non-steroidal anti-inflammatory drugs (NSAIDs).

Design Randomised controlled trial and patient preference study.

Setting 26 general practices.

Participants People aged ≥50 with knee pain: 282 in randomised trial and 303 in preference study.

Interventions Advice to use topical or oral ibuprofen.

Primary outcome measures WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, major and minor adverse effects.

Results Changes in global WOMAC scores at 12 months were equivalent. In the randomised trial the difference (topical minus oral) was two points (95% confidence interval −2 to 6); in the preference study, it was one point (−4 to 6). There were no differences in major adverse effects in the trial or study. The only significant differences in secondary outcomes were in the randomised trial. The oral group had more respiratory adverse effects (17% *v* 7%,95% confidence interval for difference −17% to −2%), the change in serum creatinine was 3.7 mmol/l less favourable (0.9 µmol/l to 6.5 µmol/l); and more participants changed treatments because of adverse effects (16% *v* 1%, −16% to −5%). In the topical group more participants had chronic pain grade III or IV at three months, and more participants changed treatment because of ineffectiveness.

Conclusions Advice to use oral or topical preparations has an equivalent effect on knee pain over one year, and there are more minor side effects with oral NSAIDs. Topical NSAIDs may be a useful alternative to oral NSAIDs.

Trial registration ISRCTN 79353052.

INTRODUCTION

Around a third of people aged over 50 years have chronic knee pain.[1-4] Both oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat this and both have some short term beneficial effects.[5-9] If topical NSAIDs are as effective as oral NSAIDs for reducing knee pain but produce fewer adverse effects, then topical treatment might be preferred. As the route of administration is different, non-pharmacological factors may affect the response to treatment. Thus, patients' preferences for topical or oral treatment might have an important effect on perceived benefit and the incidence of subjective adverse effects and should be considered in the recommended route of administration. These preferences need to be considered in any pragmatic study comparing topical or oral administration. The popularity of comparatively expensive topical NSAIDs and the importance of adverse effects related to NSAIDs meant that the NHS Health Technology Assessment programme identified a comparison of oral and topical NSAIDs for osteoarthritis as a priority for research.

Here we compare the effect of advice to use oral or topical NSAIDs on knee pain and disability, minor adverse effects related to use of NSAIDs, overall pain, and health related quality of life.

METHOD

We have described our methods in detail elsewhere.[10]

Recruitment

We recruited general practices from the Medical Research Council general practice research framework (GPRF).[11] We sent postal invitations to patients who had consulted these practices with osteoarthritis or knee or leg pain in the preceding five years or who had had a prescription for a topical or an oral NSAID or a rubefacient over the preceding year. Research nurses based in the practices then confirmed whether potential participants met our eligibility and safety criteria and took blood samples for baseline laboratory tests (boxes 1 and 2). To be included participants had to be aged ≥50, have had troublesome pain in or around the knee on most days for at least a month as well as knee pain for more than three months in the preceding

Box 1 Criteria for exclusion on grounds of safety

- Peptic ulceration (past or current)
- Indigestion on most days in past three months
- Previous adverse reaction to NSAIDs
- Raised blood pressure ≥155/95 mm Hg (mean of three readings at study entry)
- Uncontrolled heart failure
- Serum creatinine concentration >140 µmol/l
- Abnormal liver function sufficient to contraindicate use of NSAIDs
- Taking anticoagulants or oral steroids
- Haemoglobin <124 g/l for men or <118 g/l for women
- Disseminated malignancy
- Request by general practitioner not to include potential participant for any other reason

year; have consulted or been prescribed treatment by the general practitioner for knee pain in the preceding three years; have no current or planned knee replacements; and meet our safety criteria (box1).[4 12] Each participant was assessed by a general practitioner who confirmed they were willing to prescribe NSAIDs for this participant and recorded the physical components of the American College of Rheumatologists' clinical criteria for knee osteoarthritis.[13] At a subsequent assessment at study entry the research nurses confirmed eligibility, obtained informed consent, and collected baseline data (box 1 and table 1). Potential participants were asked not to use any topical or oral NSAIDs for one week before the assessment at study entry. Participants were offered a choice of joining the randomised trial or the preference study. Participants in the randomised study were then randomised and those who joined the preference study selected their treatment. We provided participants with a starter pack of their chosen or allocated treatment. After this participants were either prescribed medication by the practice or they could purchase their own over the counter.

Quality control

All the research nurses had a full day of training in the study procedures and were visited at least once during the study by a regional training nurse or a senior research nurse from the general practice research framework to ensure that the protocol was being followed.

Assignment

We used a remote computer based telephone randomisation service to register participants and to allocate participants in the randomised study to treatment groups. Randomisation was stratified by practice and troublesomeness of knee pain.[14]

Participant flow and follow-up

We followed up participants with postal questionnaires at 3, 6, 12, and 24 months after study entry, with two reminders. There were nurse assessments and blood tests at 12 and 24 months. Because recruitment was slow, not all participants could be followed for 24 months; participants with 16-24 months of follow-up at the end of data collection underwent 24 month (end of study) assessments at this time; for those with 12-16 months of potential follow-up we did the end of study assessments after 12 months. We collected data on health service activity and prescribing from randomisation to 24 months or end of study.

Intervention

In the randomised trial we compared a recommendation to use either a topical or an oral NSAID, preferably ibuprofen, as required for knee pain. In the preference study the recommendation was to use the route of delivery preferred by the patient. The medication could be either prescribed or bought over the counter. If a change of medication was required, participants were encouraged, when appropriate, to use an alternative NSAID with the same route of administration.

Masking

The study was not blinded at the general practice or participant level. All other members of the study team involved in data collection were blind to the participants' chosen or allocated treatment.

Outcome measures

For our primary efficacy analyses we used follow-up questionnaires at 12 months. Our primary efficacy outcome measure was the WOMAC (Western Ontario and McMaster Universities) VA 3.1 questionnaire,

Box 2 Criteria for minor adverse effects*

Gastrointestinal

- Haemoglobin concentration <113 g/l (male)*
- Haemoglobin concentration <106 g/l (female)*
- Fall in haemoglobin concentration ≥16 g/l
- Ferritin concentration below lower limit of normal
- Indigestion more than occasionally
- Increase in indigestion by ≥ one category†

Renovascular

- Creatinine concentration ≥152 µmol/l*
- Increase in creatinine concentration ≥20 µmol/l*
- Increase in systolic blood pressure ≥20 mm Hg
- Increase in diastolic blood pressure ≥10 mm Hg
- New diagnosis of heart failure

Respiratory

- New diagnosis of asthma or COPD
- New treatment for asthma or COPD
- ≥15% fall in peak flow

* This includes tests done as part of routine care within 18 months of randomisation, but excludes those done after one year nurse assessment had been completed.

†Categories: no days; few days (occasionally); more than occasionally, but fewer than half the days; most days (half or more of the days); every day.

which measures knee pain and disability in the preceding 48 hours and produces individual measures of pain, stiffness, and physical function and a global assessment.[15] For our secondary efficacy outcome measures we used the postal version of the chronic pain grade, which measures overall pain and disability related to pain over the preceding six months,[16 17] and the SF-36v2, a well established measure of health related quality of life over the preceding four weeks, reported as physical and mental component scores.[18 19]

Adverse effects

We defined a major adverse effect as an unplanned hospital admission or death during follow-up. We identified deaths from practice records and from flagging participants at the NHS central registry. Practices provided copies of participants' hospital discharge letters during the study period. Two members of the study team (MU, PC) who were blind to allocation independently coded these as planned or unplanned admissions, conferring only to resolve any disagreements.

We defined a minor adverse effect as a change in one or more selected variables that a Delphi panel of general practitioners considered serious enough to entail advising a change of treatment (box2).[20] We also report the differences in clinical and laboratory study measures, participants' reports of changing treatment because of adverse effects, and, when appropriate, the results of laboratory tests initiated by the practice. We used questionnaire data at 3, 6, and 12 months, results of blood tests taken up to and including those taken at the 12 month nurse assessment (so long as these were collected within 18 months), and medical record data up to 12 months.

Prescribing data

We calculated the number of defined daily doses of oral ibuprofen, other oral NSAIDs, rescue analgesia (paracetamol or opioids), treatments for dyspepsia, and respiratory and cardiovascular drugs (except aspirin) prescribed with standardised values.[21] For oral ibuprofen the defined daily dose is 1.2 g. For topical NSAIDs and rubefacients we defined a daily dose for one knee as 1.5g.[20] All analyses on prescribing data are based on prescriptions issued in the first year after participants joined the study.

Sample size

Our hypothesis was that there would be equivalence in means between groups for the WOMAC score. Typically, standard deviations for the WOMAC in knee osteoarthritis trials are around 22 mm. We defined equivalence as 95% confidence that the difference between groups lay within 10 mm. To show this with 80% power and 5% significance, assuming 25% loss to follow-up, we needed 275 participants in the randomised trial. Early recruitment data indicated a 3:1 preference for topical compared with oral treatment in the preference study and a 2:1 preference for joining the preference study, which compromised the original sample size calculations.[10] To ensure recruitment to the randomised trial the last seven practices to join the study recruited only to the randomised trial. Allowing for the unequal group size, we needed 368 participants in the preference study.

Analysis

We analysed the two studies separately. When appropriate we adjusted for baseline values using regression models. For other analyses we used *t* tests, differences

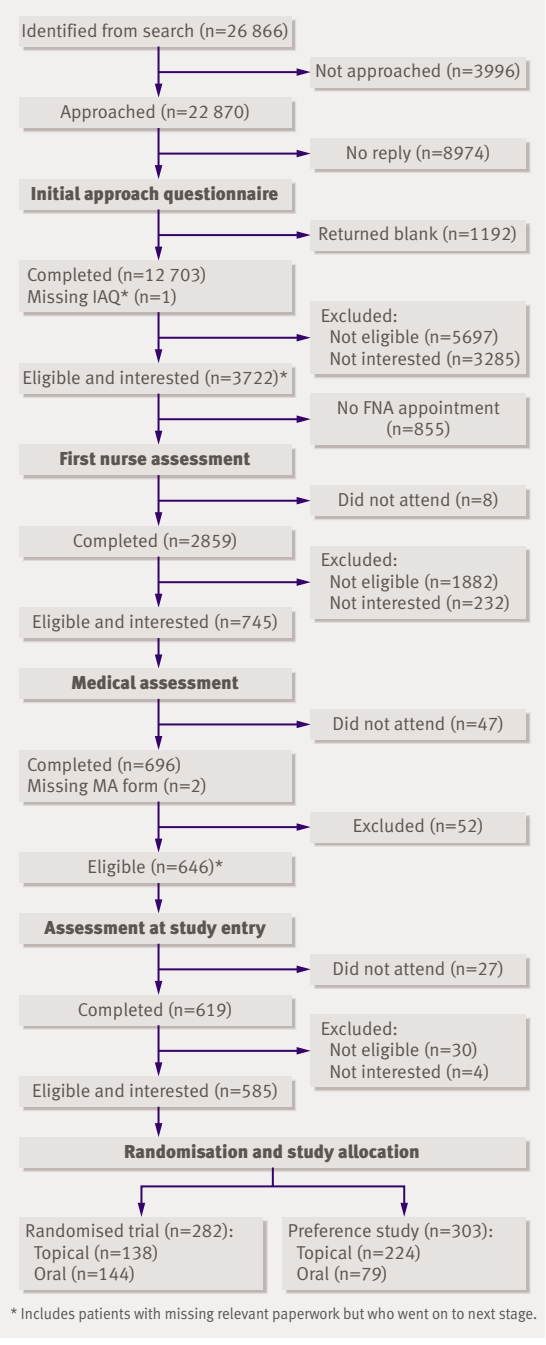

Fig 1 Flow chart of recruitment to both studies

Table 1 | **Baseline characteristics of participants in randomised trial and preference study according to treatment with oral or topic NSAIDs for knee pain. Figures are means (SDs) unless stated otherwise**

	Randomised trial		Preference study	
	Oral	Topical	Oral	Topical
No of participants	144	138	79	224
Demographic data				
No (%) of men	63 (44)	68 (49)	31 (39)	95 (42)
Mean age at randomisation (median, IQR)	63 (60, 56-69)	63 (60, 56-68)	64 (64, 57-72)	66 (66, 60-72)
No (%) with occupational codes 1-3[30] *	54 (38)	39 (28)	24 (30)	53 (24)
No (%) who met clinical criteria for osteoarthritis[13]	140 (98)	134 (97)	79 (100)	217 (97)
Mean BMI (median, IQR)	31 (29, 26-34)	30 (29, 26-32)	30 (29, 27-33)	29 (28, 26-32)
Pain/wellbeing				
WOMAC (each scale range 0-100†):				
No of participants with data	144	135	76	216
Pain score	39 (21.5)	39 (19.3)	39 (19.3)	41 (20.1)
Stiffness	47 (25.7)	50 (24.6)	50 (22.4)	49 (24.9)
Difficulty	38 (23.1)	37 (18.3)	41 (20.2)	40 (20.4)
Global	39 (22.0)	38 (17.6)	41 (18.7)	41 (19.4)
EQ-5D utility score:				
No of participants with data	140	138	78	219
Score	0.65 (0.22)	0.67 (0.19)	0.63 (0.23)	0.66 (0.19)
Chronic pain grade:				
No of participants with data	141	136	78	219
Pain intensity	52.6 (19.9)	52.0 (18.2)	54.9 (18.3)	51.9 (18.4)
Disability	38.5 (27.3)	34.5 (23.4)	37.6 (23.3)	35.3 (25.7)
No (%) with grade III or IV	50 (35)	35 (26)	26 (33)	68 (31)
SF-36 (SD):				
No of participants with data	138	136	74	209
Physical component score	39.0 (9.7)	39.2 (8.9)	37.7 (7.8)	38.5 (9.4)
Mental component score	52.0 (10.2)	53.7 (9.6)	51.7 (10.4)	52.0 (10.0)
No (%) with very/extremely troublesome knee pain[14]	45/144 (31)	45/138 (33)	26/79 (33)	66/224 (29)
No (%) with indigestion in past 3 months:				
No of participants with data	144	138	78	224‡
None	86 (60)	78 (57)	47 (59)	106 (47)
A few days or occasionally	50 (35)	54 (39)	28 (35)	106 (47)
Over occasional-less than 50% of time	8 (6)	6 (4)	3 (4)	11 (5)
No (%) who used NSAIDs in past year:				
No of participants with data	141	138	78	223
Used neither oral nor topical	34 (24)	20 (14)	8 (10)	64 (29)
Used oral only	59 (41)	81 (59)	49 (62)	82 (37)
Used topical only	9 (6)	8 (6)	1 (1)	40 (18)
Used both topical and oral	39 (27)	28 (20)	21 (27)	37 (17)
No (%) with other pain:				
No of participants with data	143	138	79	221
At least one more area of at least moderately troublesome pain[14]	101 (71)	97 (71)	66 (84)§	160 (73)§
Expectation (%):				
How helpful do you think tablets will be? (very, helpful, not helpful)	30, 63, 7 (n=144)	28, 64, 8 (n=136)	44, 54, 1 (n=79)	11, 59, 30 (n=222)
How helpful do you think ointment will be? (very, helpful, not helpful)	30, 59, 10 (n=138)	16, 67, 17 (n=135)	7, 48, 45 (n=71)	30, 69, 1 (n=216)
Blood pressure (average of three readings before study entry¶)				
No of participants with data	142	138	76	222
Systolic (mm Hg)	134 (15)	131 (15)	135 (15)	132 (15)
Diastolic (mm Hg)	74 (10)	75 (10)	73 (9)	71 (8)
Lung function (best of three readings at study entry assessment) and blood results				
No of participants with data	143	135	78	223
PEF (l/min)	380 (126)	388 (125)	365 (105)	345 (114)
FEV_1 (l)	2.36 (0.69)	2.42 (0.72)	2.40 (0.71)	2.24 (0.65)

	Randomised trial		Preference study	
	Oral	Topical	Oral	Topical
Hb (g/l)	141 (11)	141 (11)	139 (10)	139 (13)
Creatinine (μmol/l)	86 (15)	88 (16)	88 (17)	88 (15)
Ferritin (μg/l)	120 (94)	127 (106)	117 (92)	106 (92)
$\log_e$ (ferritin (μg/l)	4.5 (0.8)	4.5 (0.8)	4.5 (0.8)	4.4 (0.8)

BMI=body mass index; IQR=interquartile range, PEF=peak expiratory flow, FEV_1=forced expiratory volume in one second.
*Managers and senior officials, professionals, and associate professional and technical, better of self or partner.[30]
†0=no symptoms, 100=maximum symptoms.
‡One person included in error with pain › half the days.
§95% CI for difference −1% to −21%.
¶Excluding seven participants with higher than eligible mean BP recorded.

in proportions, and rates with 95% confidence intervals with corrections for small numbers. STATA 9 was used for all the analyses (StataCorp, College Station, TX).

It is usual in equivalence studies to carry out an on-treatment analysis. As this study was testing two approaches to managing knee pain, however, we used an intention to treat approach for all our analyses.

For the 12 month analyses we used the data collected between 6 and 18 months that were closest to 12 months. For the 24 month analyses, we used data collected between 18 months and end of study closest to 24 months. Additionally, we carried out an end of study analysis using the last follow-up data collected on each participant, including end of study questionnaire data on some participants that was collected between 12 and 18 months and subsequent to their 12 month assessment.

RESULTS

Participant recruitment

We recruited 25 practices plus two pilot practices. There were no changes in protocol between the pilot and main studies so the pilot data contributed to our analyses. We excluded data from one pilot practice in which participants had also taken part in a nested qualitative study.[22] The 26 practices had a registered population of 233 558 with mean list size of 8983 (range 2922-16 100); their geographic distribution was broadly representative of the UK.

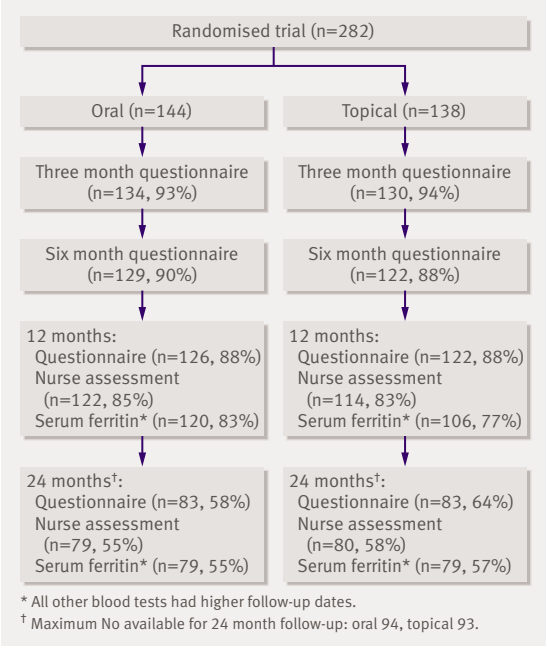

Fig 2 Participant follow-up in randomised trial

Recruitment took place from April 2003 to May 2005. The follow-up finished in May 2006. We approached 22 870 (89%) of the 26 866 potential participants identified. We assessed 2859 of these who seemed eligible: 913 (32%) did not meet the entry criteria for knee pain; 230 of the remaining 1946 (12%) did not meet the consultation criteria; 25/1716 had had a knee replacement; 609/1691 (36%) failed the clinical history safety criteria; 10/1075 (1%) failed other entry criteria; 86/1065, 8% of the remainder, failed the safety criteria for hypertension. Finally two participants were excluded because of poor understanding of English. Of those eligible and interested at the end of the first assessment, 585/745 (79%) eventually joined the study; 282 joined the randomised trial and 303 the preference study (fig 1).

Ten participants were entered into the study in error: one had dyspepsia; two had failed the consultation criteria; and seven had a mean recorded blood pressure at the study entry assessment that was slightly higher than allowed and missing repeat blood pressure record before study entry. They are included in the analyses, except that we did not use follow-up blood pressure data in those who failed the safety criteria for hypertension. Another participant who had a knee replacement was initially entered into the study but later removed.

Baseline characteristics

Participants' mean age was 64 years (SD 8.5) and median 64 years (range 50-89). Participants in the topical group in the preference study, but not those in the oral group, were older and of lower social class than those in the controlled trial. The remainder of participants' main baseline characteristics were broadly similar across all four groups. In particular, there were no differences between the two randomised groups except for some differences in their use of topical and oral NSAIDs in the previous year. In the preference study 89% of the oral group had used oral

NSAIDs and 28% had used topical NSAIDs in the previous year, while in the topical group the rates of use of oral and topical drugs were 56% and 35%, respectively. In the randomised trial, the attitude to topical treatment was less favourable in the topical group. Participants in the preference study generally expected their chosen medication to be effective or very effective. More participants in the preference study who chose to use oral NSAIDs had at least moderately troublesome pain in one or more additional body area (difference topical minus oral 11% (95% confidence interval −21% to −1%) (table 1).

Follow-up

We obtained at least an 83% response to follow-up questionnaires, nurse assessment, and blood test data at 12 months. We obtained at least 55% of these data at 24 months (82% of those eligible for a 24 month follow-up) (figs 2 and 3).

Primary outcome

WOMAC scores changed little between baseline and the 12 month follow-up. For the global scores these were −0.5 (SD 17) in the oral group and 1.1 (SD 17) in the topical group in the randomised trial and 0.1 (SD 18) and 1.1 (SD17), respectively, in the preference study. Only for pain at 24 months in the randomised trial did the limits of the confidence intervals for the difference between oral and topical groups exceed our predefined limits for equivalence. We found no significant differences in the WOMAC global score changes between topical and oral groups in either study. For the WOMAC pain scores in the randomised trial 24 month and end of study analyses, there was a difference of borderline significance in favour of oral medication (table 2).

Adverse effects

We found no differences in major adverse effects. There were two deaths before the end of follow-up, both in the topical group in the preference study. One participant in the oral group in the preference study had an upper gastrointestinal haemorrhage during a planned admission to hospital.

The only difference in defined minor adverse effects was that fewer participants in the topical group in the randomised trial had a respiratory adverse effect −9% (−17% to −2%). This was primarily explained by the higher proportion in the oral group whose peak expiratory flow dropped by 15% or more (22 (18%) *v* 9 (8%)). There were no differences in the proportions of participants having one or more defined adverse effects. The only significant mean difference in our clinical and laboratory measurements was in the randomised trial, where the change in creatinine concentrations at 12 months in the topical group was more favourable by 3.7 µmol/l (0.9 µmol/l to 6.5 µmol/l) (table 3).

Secondary outcomes

We found no significant differences in the overall proportion with chronic pain grade III or IV at any time point or in the SF-36 physical component scores. In the preference study there was a difference of borderline significance in the SF-36 mental component score at three months that favoured oral treatment.

There were some differences in the disability component of the chronic pain grade at three months and in the end of study analyses in the randomised trial. Those in the oral group had slightly less pain related disability at three months and in the end of study analysis but not at 12 months. After we corrected for baseline differences there was a difference in the odds of having chronic pain grade III or IV at three months and in the end of study assessment, but not at 12 months, favouring the oral group (table 4).

Adherence with treatment route

There were no significant differences in the proportions in either study who reported in the 12 month questionnaire that they had changed treatment. In the randomised trial this apparent similarity masks

Table 2 | Mean difference (95% CI for difference) in change in WOMAC* from baseline, for topical minus oral treatment with NSAIDs for knee pain in elderly people (adjusted by regression for baseline values)

	3 months	6 months	12 months	24 months	End of study†
Randomised trial					
No in oral/topical group‡	133/129	128/121	125/121	80/87	139/132
Pain	−2 (−6 to 2)	1 (−3 to 5)	1 (−4 to 6)	6 (0 to 12)	5 (0 to 9)
Stiffness	−3 (−8 to 2)	−4 (−9 to 1)	0 (−6 to 5)	−1 (−8 to 6)	−2 (−7 to 4)
Difficulty	−2 (−5 to 2)	1 (−3 to 5)	3 (−2 to 7)	5 (−1 to 10)	3 (−2 to 7)
Global	−2 (−5 to 2)	0 (−3 to 4)	2 (−2 to 6)	4 (−1 to 10)	3 (−1 to 7)
Preference study					
No in oral/topical group‡	71/198	66/194	70/184	65/162	75/209
Pain	−2 (−7 to 3)	−2 (−7 to 3)	−1 (−7 to 4)	0 (−6 to 6)	−1 (−7 to 5)
Stiffness	0 (−6 to 6)	−3 (−9 to 3)	−2 (−8 to 4)	−2 (−9 to 5)	−3 (−9 to 3)
Difficulty	2 (−3 to 6)	3 (−2 to 7)	2 (−3 to 7)	1 (−5 to 7)	1 (−4 to 6)
Global	1 (−3 to 5)	1 (−3 to 5)	1 (−4 to 6)	0 (−6 to 6)	0 (−5 to 5)

*Each WOMAC score has potential range of 0-100; 0=no symptoms, 100=maximum symptoms. Positive differences favour oral treatment.
†End of study value is last value carried forward or 24 month follow-up.
‡No of analysable WOMAC questionnaires.

important differences: 11% (95% confidence interval 2% to 20%) more of the topical group reported changing treatment because of inadequate pain relief and 10% (5% to 16%) more of the oral group reported changing treatment because of adverse effects. This was not seen in the preference study (table 5).

Over 80% of participants received prescriptions for their chosen or allocated treatment (table 6).

Only 5% of those randomised to the oral group, and nobody who chose oral treatment, had any prescriptions for topical NSAIDs. More of the topical group had prescriptions for oral NSAIDs (37% in the randomised trial and 26% in the preference study). The average number of days' worth of oral NSAIDs prescribed in the randomised study was 139 and 61, respectively, in the oral and topical groups. In the preference study these were 159 and 28, respectively. We found no significant differences in the number of days' worth of "rescue medication" or drugs for adverse effects prescribed in either study. In the preference study, however, more of the oral group were prescribed "rescue medication"; this difference approaches significance (−14%, −26% to 0.4%) (table 6).

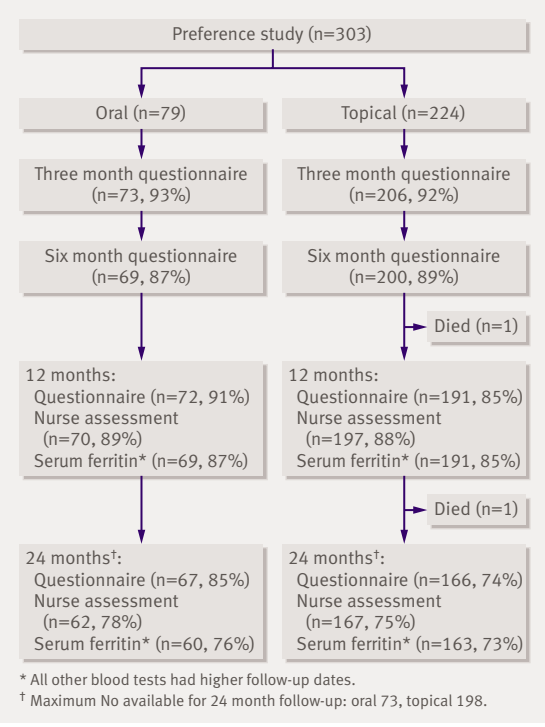

Fig 3 Participant follow-up in preference study

DISCUSSION

Main findings

We found that advising patients to use either oral or topical NSAIDs produced equivalent clinical outcomes for knee pain over one year in both studies. Only for the pain subscale in the randomised trial at 24 months did limits of the confidence interval breech our definition of equivalence; this may be because of small numbers. There were no differences in the secondary patient centred outcomes except for suggestions, in the randomised trial, that those in the topical group were more likely to have more severe overall pain and disability as measured by the chronic pain grade at three months and in the end of study analysis adjusted for the baseline values, and that more people in the topical group stopped treatment because it was ineffective.

Although we found no differences in the overall numbers having major or defined minor adverse effects in either study, in the randomised trial we found an excess of respiratory adverse effects and a less favourable change in creatinine concentration in the oral group. These may be chance findings caused by multiple comparisons or they may represent real differences. The size of these differences could be clinically important; 9% more in the oral group had an adverse respiratory effect that could justify stopping NSAIDs. At a population level, a difference in creatinine of 3.7 μmol/l might have important health consequences.[23] Participants' reports in the randomised study showed that 11% of those in the oral group stopped taking NSAIDs because of adverse effects. Our data suggest that in the randomised trial oral NSAIDs caused more adverse effects. These differences were not seen in the preference study, even though the differences in daily doses of oral NSAIDs prescribed between the oral and topical groups were much greater than in the randomised trial. Possibly participants who chose oral treatment did so because of previous experience and so were more likely to tolerate adverse effects.

Preferences

Participants who wanted a choice predominantly selected topical rather than oral treatment, although those with more severe or widespread pain chose oral rather than topical treatment. Those who chose topical treatment tended to be older and of lower social class than those in the other three groups. There are likely to be other unmeasured differences between those in the preference study and the controlled trial, if only in the strength of their preferences for different treatments.

Those who chose oral NSAIDs seemed to be more tolerant of their adverse effects than those randomly allocated to the oral group, even though the oral group in the preference study took substantially more oral NSAIDs. In the nested qualitative study more widespread or chronic pain was perceived to be "more serious" and to require oral rather than topical medication.[22] Thus participants in our preference study seemed to be making logical choices as to which administration route to use; this should perhaps be expected given that most of the participants had experienced knee pain for some time.

Applicability to routine practice

Our results are highly relevant to the management of knee pain in primary care. All our participants were receiving care from their general practitioner for knee

Table 3 | Adverse effects* in elderly patients with knee pain according to NSAID treatment

	Oral	Topical	Difference (topical-oral) (95% CI)
Total (rate per 100 per year) with first unplanned hospital admission†			
Randomised trial:			
0-12 months	2 (1.4)	6 (4.5)	3.1 (−1.0 to 7.2)
0-24 months	6 (2.6)	10 (4.6)	2.0 (−1.5 to 5.5)
Preference study:			
0-12 months	4 (5.2)	11 (5.1)	−0.1 (−6.1 to 5.8)
0-24 months	6 (4.3)	19 (4.9)	0.6 (−3.5 to 4.7)
No (%) with defined minor adverse effects before 1 year			
Randomised trial:			
No with data	144	138	—
Gastrointestinal	57 (40)	58 (42)	2% (−9% to 14%)
Renovascular	22 (15)	22 (16)	1% (−8% to 9%)
Respiratory	24 (17)	10 (7)	−9% (−17% to −2%)
Any minor adverse effect	80 (56)	77 (56)	0 (−11% to 12%)
Preference study:			
No with data	79	224	—
Gastrointestinal	29 (38)	82 (37)	−1% (−13% to 12%)
Renovascular	15 (19)	34 (15)	−4% (−14% to 6%)
Respiratory	14 (18)	34 (15)	−3% (−13% to 7%)
Any minor adverse effect	45 (57)	118 (53)	−4% (−17% to 8%)
Other measures of potential adverse effects; changes are one year minus baseline‡			
Randomised trial:			
Change in haemoglobin (g/l)	0.2 (6.6)	0.7 (7.7)	0.5 (−1.3 to 2.3)
Change in $\log_e$ (ferritin µg/l)	-0.04 (0.50)	0.50 (0.59)	0.08 (−0.07 to 0.0.22)
Change in systolic blood pressure (mm Hg)	2.5 (14)	4.4 (14)	1.9 (−1.7 to 5.5)
Change in diastolic blood pressure (mm Hg)	−1.0 (8)	−0.5 (7)	0.5 (−1.3 to 2.4)
Change in serum creatinine (µmol/l)	2.4 (11)	−1.3 (10)	−3.7 (−6.5 to −0.9)
Change in PEF (l/min)	−3 (69)	4 (58)	8 (−9 to 24)
No (%) liver enzyme ≥ upper limit of normal[30]	3 (2.2)	3 (2.7)	0.4% (−3.4% to 4.3%)
Preference study:			
Change in haemoglobin (g/l)	0.06 (6.3)	0.02 (7.9)	−0.04 (−2.1 to 2.0)
Change in $\log_e$ (ferritin µg/l)	0.03 (0.37)	0.09 (0.47)	−0.07 (−0.06 to 0.19)
Change in systolic blood pressure (mm Hg)	1.3 (14)	1.4 (14)	0.2 (−3.8 to 4.2)
Change in diastolic blood pressure (mm Hg)	0.6 (8)	0.3 (8)	−0.3 (−2.4 to 1.8)
Change in serum creatinine (µmol/l)	0.3 (11)	−1.7 (11)	−1.9 (−4.8 to 1.0)
Change in PEF (l/min)	−4 (68)	−1 (63)	3 (−15 to 20)
No (%) liver enzyme ≥ upper limit of normal[30]	2 (3)	2 (1)	−1.7% (−5.7% to 2.2%)

*Participants were included in denominator for specific category of side effect provided there was at least one instrument from which adverse effect in that category could be identified. Denominators may be lower for individual outcomes.
†First unplanned admission in each person only. Subsequent admissions are not counted.
‡Blood result, either study or practice initiated, closest to one year and taken between six and 18 months. Mean time to follow-up blood test 1.04 years (SD 0.10).

pain, and their general practitioner would still have considered prescribing NSAIDs if the study were not taking place. Further, as the choice of treatment in routine practice is not random but is affected by preferences of the clinician and patient, the preference study arm increases the relevance of our findings to routine practice.

Our participants had substantial problems with their knee pain, with nearly a third reporting that it was very or extremely troublesome. The mean WOMAC function/difficulty scores for each group were in the range 38-41 compared with the score of 31 suggested as the limit of symptoms acceptable to patients.[24] They may differ from typical patients presenting in general practice in two important and related areas. Firstly, although we had no upper age limit for recruitment there was a preponderance of participants from younger age groups, so our results may not be directly applicable to the very elderly. Secondly, although most participants were identified because they had used NSAIDs, nearly half (763/1691, 45%) of those we assessed were deemed ineligible because they failed our safety criteria. The selection procedure may have produced a study population with a comparatively low risk of adverse effects related to NSAID use. Our results may not therefore be directly applicable to those who have most to gain from avoiding the toxicity of oral NSAIDs. The counterargument is that in very

Table 4 | Secondary outcome measures in elderly patients with knee pain

	3 months	6 months	12 months	24 months	End of study*
Mean difference in SF-36 (topical-oral) in change from baseline† (95% CI for difference)					
Randomised trial:					
No with data (topical/oral)	123/122	118/116	115/119	72/85	127/129
Physical component score	−0.1 (−1.7 to 1.8)	−0.4 (−2.0 to 1.3)	−1.6 (−3.5 to 0.3)	−0.7 (−3.0 to 1.5)	−0.7 (−2.5 to 1.2)
Mental component score	−1.2 (−3.3 to 0.9)	−1.7 (−3.9 to 0.4)	−1.0 (−3.4 to 1.3)	−0.4 (−2.8 to 2.1)	−0.5 (−2.6 to 1.7)
Preference study:					
No with data (topical/oral)	69/179	62/177	63/169	60/143	70/189
Physical component score	0.5 (−1.2 to 2.1)	0.8 (−1.2 to 2.7)	0.0 (−2.0 to 1.9)	−0.6 (−2.8 to 1.6)	0.4 (−1.6 to 2.3)
Mental component score	−2.4 (−4.8 to −0.1)	−0.5 (−2.9 to 1.9)	−0.3 (−2.7 to 2.0)	−1.8 (−4.4 to 0.9)	−1.1 (−3.5 to 1.3)
Mean difference in change in chronic pain grade (topical minus oral) from baseline (95% CI of mean difference in change)					
Randomised trial:					
No with data (topical/oral)	131/128	124/119	122/121	79/87	137/131
Pain intensity	0.1 (−3.8 to 4.1)	1.1 (−3.1 to 5.3)	2.1 (−2.7 to 7.0)	0.4 (−6.1 to 6.8)	2.8 (−2.2 to 7.8)
Disability	4.9 (0.2 to 9.6)	4.4 (−0.9 to 9.7)	4.7 (−1.2 to 10.7)	3.6 (−3.3 to 10.5)	6.5 (0.9 to 12.4)
Odds ratio for high CPG†	2.3 (1.1 to 4.5)	1.3 (0.7 to 2.5)	1.3 (0.7 to 2.5)	2.1 (1.0 to 4.5)	2.0 (1.1 to 3.7)
Preference study:					
No with data (topical/oral)	73/201	69/195	70/189	67/161	76/208
Pain intensity	1.2 (−3.0 to 5.4)	2.5 (−2.6 to 7.6)	4.3 (−0.6 to 9.1)	2.0 (−3.9 to 7.8)	0.4 (−4.9 to 5.7)
Disability	3.8 (−1.4 to 8.9)	0.7 (−5.1 to 6.4)	1.4 (−4.6 to 7.4)	6.5 (−0.6 to 13.5)	5.2 (−1.0 to 11.3)
Odds ratio for high CPG‡	1.5 (0.71 to 3.2)	0.8 (0.39 to 1.6)	1.1 (0.5 to 2.1)	1.7 (0.8 to 3.4)	1.4 (0.7 to 2.7)

CPG=chronic pain grade.
*End of study value is last value carried forward or 24 month follow-up.
†Lower scores on SF-36 indicate worse health state, negative values favour oral treatment.
‡Topical *v* oral, adjusted for baseline. Odds ratio ›1.0 favours oral treatment.

elderly people and those who would fail our safety criteria the risks of using oral NSAIDs are always too great.

Setting these concerns about generalisability to routine practice into context, our participants' physical health as measured by the SF-36 physical component score for each group in our study was in the range 37.7-39.0. This compares with mean values of 32.0,[25] 35.9,[26] and 43.6[27] found in observational studies of patients with osteoarthritis of the knee.

Participants' choices about joining the study may have been influenced by their past experience of NSAID use so we mainly recruited people who were tolerant of related adverse effects. In the nested qualitative study, however, we found that participants had different ideas from general practitioners about what these adverse effects were.[22] Indeed some participants were willing to endure a great deal of discomfort before alerting their general practitioner to their problems. As well as our findings on minor adverse effects, the well known risks of serious related adverse effects need to be included in any consideration of the comparative risk of oral and topical treatment.

Table 5 | Changes reported by patients between treatments over 12 months*. Denominator for (percentages) is all participants

	Oral	Topical	Difference (topical minus oral)
Randomised trial			
No with data	144	138	
Taking other mode of NSAID for more days in previous month	7 (5)	22 (16)	11% (4% to 18%)
Patient reported change in treatment	41 (28)	44 (32)	4% (−6% to 15%)
Changed because of inadequate pain relief	18 (13)	32 (23)	11% (2% to 20%)
Changed because of any adverse effects	16 (11)	1 (1)	−10% (−16% to −5%)
Changed for other reasons	9 (6)	11 (8)	−2% (−8% to 4%)
Preference study			
No with data	79	224	
Taking other mode of NSAID for more days in previous month	1 (1)	23 (10)	9% (4% to 14%)
Patient reported change in treatment	23 (29)	45 (20)	−9% (−20% to 2%)
Changed because inadequate pain relief	10 (13)	22 (10)	−3% (−11% to 5%)
Changed because of any adverse effects	7 (9)	8 (4)	−5% (−12% to 1.4%)
Changed for other reasons	6 (8)	16 (7)	−0.5% (−7% to 6%)

*Data come from 3, 6, and 12 month questionnaires. Only first recorded change used.

Table 6 | All drugs prescribed over 12 months of follow-up

	No (%) prescribed drug			Mean (SD) daily doses prescribed per participant*		
	Oral	Topical	95% CI†	Oral	Topical	95% CI†
Randomised trial						
No with data	130	124	—	130	124	—
All oral NSAIDs	119 (92)	46 (37)	−64% to −45%	139 (116)	61 (126)	−109 to −49
All topical NSAIDs	6 (5)	103 (83)	71% to 86%	7 (40)	211 (249)	161 to 248
"Rescue medication"‡	55 (42)	57 (46)	−9% to 16%	43 (107)	34 (67)	−31 to 13
Cardiovascular drugs	58 (45)	46 (37)	−20% to 5%	265 (448)	181 (355)	−183 to 17
Indigestion drugs	21 (16)	27 (22)	−4% to 15%	26 (81)	27 (78)	−19 to 20
Respiratory drugs	5 (4)	8 (6)	−3% to 8%	19 (132)	16 (87)	−31 to 25
Preference study						
No with data	76	210	—	76	210	—
All oral NSAIDs	67 (88)	55 (26)	−71% to −53%	159 (132)	28 (73)	−155 to −107
All topical NSAIDs	0 (0)	170 (81)	76% to 86%	0 (0)	245 (279)	182 to 308
"Rescue medication"‡	40 (53)	84 (40)	−26% to 0.4%	49 (89)	40 (76)	−31 to 11
Cardiovascular drugs	32 (42)	79 (38)	−17% to 8%	246 (497)	256 (481)	−118 to 138
Indigestion drugs	10 (13)	32 (15)	−7% to 11%	18 (74)	16 (51)	−17 to 14
Respiratory drugs	7 (9)	33 (16)	−2% to 15%	75 (483)	43 (157)	−107 to 42

*Denominator is all participants.
†For difference.
‡Total defined daily doses of paracetamol and opioid analgesics.

Statistical power

Good recruitment and follow-up rates, and the fact that the final imbalance between oral and topical in the preference study was less than anticipated, means that we had ample power for our primary effectiveness analyses at 12 months. The conclusions for 24 months, however, are weaker, particularly in the randomised trial, because of the smaller numbers available for follow-up.

Potential for bias

We did not attempt to blind the participants or practices. This was deliberate as we wanted to compare two forms of usual treatment, but it might have introduced bias in the questionnaires as these mostly asked participants for subjective judgments. The measurements taken by the research nurses and the data from medical records should be less prone to bias.

Use of prescribed medication

The amount of NSAID consumed in this trial was lower than in many controlled trials; most trials of NSAIDs use high dose regimens and expect good adherence to treatment—for example, in the VIGOR (Vioxx gastrointestinal outcomes research) study 71% of participants continued medication during follow-up, 99% of whom took at least 75% of the doses intended.[28 29] Thus, the clinical effects and rates of adverse effects observed in some other trials may overestimate what happens when these drugs are used in routine practice. The pattern of drug use we observed is more likely to be representative of how NSAIDs are prescribed in routine practice. One caveat when interpreting these prescribing data is that we were not able to measure the use of topical or oral NSAIDs purchased over the counter, nor to estimate the proportion of prescribed medication the participants actually used.

Meaning of the study

What is clear is that the outcome for knee pain at one year is equivalent, whether patients are initially advised to use oral or topical treatment. This is a consistent finding in both the randomised trial and the preference study.

Though we carried out multiple comparisons at different time points, the only comparisons that indicated a difference in effectiveness were the change in chronic pain grade III/IV at three months and at the end of the study in the randomised trial, and the fact that more participants reported changing treatment because of inadequate pain relief, again in the randomised trial. Both changes favoured oral treatment. Those in the topical groups who had inadequate pain relief might subsequently have obtained adequate pain relief from other, probably oral, drugs.

We have compared advice to use one of two active preparations, neither of which is known to have long term efficacy. We cannot use these data to conclude that advice to use either preparation is superior to

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) have short term beneficial effects for people with osteoarthritis

Oral NSAIDs have a high incidence of adverse effects

WHAT THIS STUDY ADDS

Advice to use oral or topical NSAIDs has an equivalent effect on knee pain in the long term

Topical NSAIDs may be a useful alternative to oral NSAIDs

paracetamol, placebo, or no treatment. Indeed, the absence of clear change in WOMAC scores between baseline and follow-up, in both arms of either study, is consistent with several hypotheses including the notion that neither preparation is particularly effective. Advice to use topical NSAIDs might, however, be a useful alternative to advice to use oral NSAIDs for knee pain in older people.

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Contributors: MU was the principal investigator, was primarily responsible for the original grant application, and led the trial team. He contributed to analysing and interpreting the data, wrote the first draft, and is guarantor. DA was study statistician and contributed to the analysis plan and analyses. PC was the clinical research fellow and led on developing the study paperwork, assisted with management, and liaised with laboratories and general practices on medical matters. She wrote the MIQUEST searches and worked with the practice research nurses to identify participants. EH produced the analysis plan and statistical analyses and is guarantor for statistical aspects. LL was responsible for all nursing activity, contributed to implementation of design, selecting and recruiting participants, and developing trial documentation, and managed the recruitment of participating practices. JM was one of the original applicants and contributed to development of protocol and procedures and developed fieldwork costings and was responsible for quality control of the fieldwork. SMtl contributed to the statistical analysis plan and carried out statistical analyses. SP was one of the original applicants, was a member of the project board, and contributed to the study design and development of the protocol. MV was one of the original applicants, contributed to the original design and procedures and had overall responsibility for trial fieldwork and management. She was a member of the project board and the trial steering committee. KW was the study manager.
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