

## Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials

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### Abstract

**Objective** To estimate the analgesic efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclo-oxygenase-2 inhibitors (coxibs), in patients with osteoarthritis of the knee.

**Design** Systematic review and meta-analysis of randomised placebo controlled trials.

**Studies reviewed** 23 trials including 10 845 patients, median age of 62.5 years. 7807 patients received adequate doses of NSAIDs and 3038 received placebo. The mean weighted baseline pain score was 64.2 mm on 100 mm visual analogue scale (VAS), and average duration of symptoms was 8.2 years.

**Main outcome measure** Change in overall intensity of pain.

**Results** Methodological quality of trials was acceptable, but 13 trials excluded patients before randomisation if they did not respond to NSAIDs. One trial provided long term data for pain that showed no significant effect of NSAIDs compared with placebo at one to four years. The pooled difference for pain on visual analogue scale in all included trials was 10.1 mm (95% confidence interval 7.4 to 12.8) or 15.6% better than placebo after 2-13 weeks. The results were heterogeneous, and the effect size for pain reduction was 0.32 (0.24 to 0.39) in a random effects model. In 10 trials that did not exclude non-responders to NSAID treatment the results were homogeneous, with an effect size for pain reduction of 0.23 (0.15 to 0.31).

**Conclusion** NSAIDs can reduce short term pain in osteoarthritis of the knee slightly better than placebo, but the current analysis does not support long term use of NSAIDs for this condition. As serious adverse effects are associated with oral NSAIDs, only limited use can be recommended.

### Introduction

Osteoarthritis of the knee is the most common type of osteoarthritis,<sup>1</sup> the prevalence of which is rising in parallel with the increasing age of the population.<sup>2</sup> The condition is associated with pain and inflammation of the joint capsule, impaired muscular stability, reduced range of motion, and functional disability. Treatment guidelines for knee osteoarthritis recommend

pharmacological intervention, initially with paracetamol and subsequently with a non-steroidal anti-inflammatory drug (NSAID).<sup>3</sup> In a recent UK survey, 15% of patients with osteoarthritis used paracetamol, whereas 50% reported regular use of NSAIDs. Of the latter, 32% were using traditional NSAIDs and 18% were using cyclo-oxygenase-2 inhibitors (coxibs).<sup>4</sup> This widespread use is one explanation for the interest in tolerability and efficacy issues regarding these drugs.<sup>3 5 6</sup> The recent introduction of coxibs seemed to promise a reduction in serious adverse events related to NSAIDs,<sup>6 7</sup> but this remains controversial.<sup>8-11</sup>

Guidelines state that both pharmacological and non-pharmacological interventions are needed for optimal treatment of knee osteoarthritis.<sup>12</sup> The various potentially effective pharmacological interventions at the clinicians' disposal<sup>12</sup> highlight the need for information regarding treatment efficacy.

We carried out a meta-analysis of published randomised placebo controlled trials to estimate the analgesic efficacy of NSAIDs, including coxibs, in patients with knee osteoarthritis.

### Methods

#### Protocol specification

We identified relevant randomised placebo controlled trials from Medline, Embase, and the Cochrane central register of controlled trials, and evaluated their methodological quality according to predefined criteria.<sup>13</sup> We calculated their pooled effect as the mean difference in change between NSAID groups and placebo groups in mm on a visual analogue scale and as a unitless effect size. Effect size measures the magnitude of a treatment effect independent of sample size.<sup>14</sup> There is no current operational definition for what constitutes a sufficiently large effect size for a therapeutic intervention to be considered as useful, but a value of 0.2 is usually considered small, 0.5 moderate, and 0.8 large.<sup>15</sup>

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The references for the studies included in the meta-analysis (w1-w23) can be found on [bmj.com](http://bmj.com)

Characteristics of trials of NSAIDs for pain relief in patients with knee osteoarthritis

Drug		No of patients (n=7767)	Method quality	Trial exclusion criteria	Mean baseline pain (mm VAS)	Mean difference (95% CI) of change over placebo (mm VAS)	No (%) of adverse events
Bensen <sup>w1</sup>	Celecoxib-naproxen	597	5	9	54.1	8.0 (2.3 to 13.7)	43 (5.4)
Case <sup>w2</sup>	Diclofenac	25	4	14	39.6	11.7 (6.2 to 17.2)	3 (12)
Dore <sup>w3</sup>	Naproxen-etodolac	168	3	12	NA	16.3 (4.8 to 27.7)	15 (8.9)
Ehrich <sup>w4</sup>	Rofecoxib	147	5	10	61.9	21.9 (15 to 28.7)	26 (17.6)
Fleischmann <sup>w5</sup>	Nabumetone-naprelan	185	3	14	59.9	1.3 (-7.0 to 10.5)	10 (5.4)
Gibofsky <sup>w6</sup>	Celecoxib-rofecoxib	379	5	14	67.7	11.6 (3.4 to 19.8)	21 (5.5)
Gottesdiener <sup>w7</sup>	Eterocoxib	326	5	21	68.4	18.4 (16.6 to 20.2)	17 (5.2)
Kivitz <sup>w8</sup>	Valdecoxib-naproxen	408	5	18	71.9	5.5 (2.3 to 8.8)	77 (10.5)
Kivitz <sup>w9</sup>	Rofecoxib-nabumetone	834	5	13	74.5	15.1 (4.9 to 25.3)	49 (5.8)
Lee <sup>w10</sup>	Diflunisal	279	3	4	57	8.5 (-2.9 to 19.5)	33 (11.8)
Lund <sup>w11</sup>	Meloxicam	134	3	Not stated	48.2	6.6 (1.4 to 11.8)	16 (5.8)
McKenna <sup>w12</sup>	Celecoxib-diclofenac	400	3	Not stated	69.1	8.8 (5.2 to 12.3)	36 (18)
McKenna <sup>w13</sup>	Celecoxib-rofecoxib	122	3	15	73.3	14.5 (2.7 to 26.3)	8 (6.6)
Schnitzer <sup>w14</sup>	Nabumetone-etodolac	180	3	19	57.5	13.2 (5.4 to 21)	18 (10)
Scott <sup>w15</sup>	Tiaprofenic acid	307	4	Not stated	55.1	4.1 (4.0 to 4.2)	61 (12)
Makarowski <sup>w16</sup>	Nabumetone-oxaprozin	231	3	17	NA	NA	20 (8.5)
Simon <sup>w17</sup>	Celecoxib	222	4	8	67.8	6.0 (-1.1 to 12.1)	6 (3.0)
Tannenbaum <sup>w18</sup>	Lumiracoxib-celecoxib	1459	4	Not stated	65.2	8.0 (2.7 to 13.3)	132 (9.1)
Uzun <sup>w19</sup>	Flurbiprofen-tiaprofenic acid	26	3	6	61	17.0 (3.9 to 37.9)	0
Weaver <sup>w20</sup>	Nabumetone-oxaprozin	219	3	15	NA	6 (-0.1 to 12.1)	11 (5.0)
Williams <sup>w21</sup>	Celecoxib	472	4	15	66.4	7.5 (2.9 to 12.1)	15 (3.5)
Williams <sup>w22</sup>	Etodolac	50	3	10	76	7.3 (0 to 14.6)	NA
Zhao <sup>w23</sup>	Celecoxib	597	5	9	53.9	7.5 (4.8 to 10.2)	70 (10.7)
Overall			3.8*	14†	64.1‡	10.1‡ (7.4 to 12.8)	687 (9.2)

VAS=visual analogue scale.

NA=not available.

\* Mean.

† Median.

‡ Weighted mean.

### Inclusion criteria

Trials had to study patients whose knee osteoarthritis had been verified by clinical examination according to the American College of Rheumatology criteria and by x ray. The symptoms had to have been present for more than three months. All trials had to be randomised, blinded, placebo controlled, and of parallel design. Pain intensity had to be scored on the subscale of pain on the osteoarthritis index of Western Ontario and McMaster Universities (WOMAC)<sup>16</sup> or on a 100 mm visual analogue scale for one or the mean score of two or more pain dimensions. Functional disability had to be measured on the WOMAC subscale for function.

The intervention groups had to have received matched placebo drug or adequate NSAID dose (see bmj.com).

## Results

### Included studies

We evaluated 268 randomised controlled trials and identified 23 trials that satisfied the inclusion criteria.<sup>w1-w23</sup> Of these, 16 were sponsored by the pharmaceutical industry,<sup>w1 w4-10 w12 w13 w16 w17 w18 w20 w21 w23</sup> while three others did not state sponsorship but gave an address of a pharmaceutical company as the workplace of most of the authors.<sup>w1 w3 w11</sup> The final sample included 10 845 patients, of whom 7767 received NSAIDs and 3078 received placebo (table).

### Patients and possible selection bias

The included patients had a median age of 62.5 years, and three trials had an upper age limit of 75 years.<sup>w2 w10 w22</sup> There were more women (67.9%) than

men, and the median duration of symptoms was 8.2 years. Most trials excluded individuals with concomitant health disorders by a median of 14 exclusion criteria. All trials had a minimum limit for pain intensity or disease activity for inclusion, and they all used a pretreatment washout period of 3-14 days for previous pharmacotherapy. Thirteen trials used an additional criterion by requiring a predefined minimum flare of symptoms when NSAID treatment was discontinued in the pretreatment wash out period.<sup>w1 w2 w4 w6 w7 w9 w12 w13 w16 w17 w20 w21 w23</sup> Five of these trials reported the proportion of regular NSAIDs users, ranging from 66% to 100% (median 90.5%).<sup>w2 w7 w9 w12 w13</sup>

### Trial quality

The methodological quality was adequate or good (table). All trials were randomised and double blinded, but adequate randomisation procedure, concealed allocation to groups, and blinding procedure were described satisfactorily in only eight studies.<sup>w1 w4 w6-9 w21-w23</sup> All trials described dropouts and withdrawals well, but one trial did not perform intention to treat analyses.<sup>w22</sup>

### Effect size for reduction in functional disability and pain

We excluded from analysis six intervention groups (n=867) in five trials because patients did not receive an adequate NSAID dose.<sup>w1 w2 w7 w8 w23</sup> As most trials with multiple time points showed rather stable results from 2-13 weeks, we pooled data. Eleven trials with 7433 patients provided separate scores for reduction in functional disability,<sup>w1 w2 w4 w6 w8 w9 w11 w12 w18 w21 w23</sup> and their combined effect size was 0.29 (95% confidence

interval 0.18 to 0.40) in a random effects model. One trial reported long term effects on pain but found no significant difference between tiaprofenic acid and placebo at one, two, three, and four years after start of treatment.<sup>w15</sup> For short term effects (2-13 weeks) the pooled effect size of all included trials was 10.1 mm on visual analogue scale (7.4 to 12.8) or 15.6% better than placebo, and the effect size was 0.32 (0.24 to 0.39) in a random effects model (figure).

For the subgroup of 10 trials (n = 4565) that did not require patients to have a minimum flare of symptoms after treatment with NSAIDs was stopped before the trial, trial results were homogeneous both for function and pain.<sup>w3 w5 w8 w10 w11 w14 w15 w18 w19 w23</sup> For pain reduction, we used a fixed effect model to calculate a pooled effect size of 0.23 (0.16 to 0.31) or 5.9 mm on visual analogue scale (3.8 to 7.9).

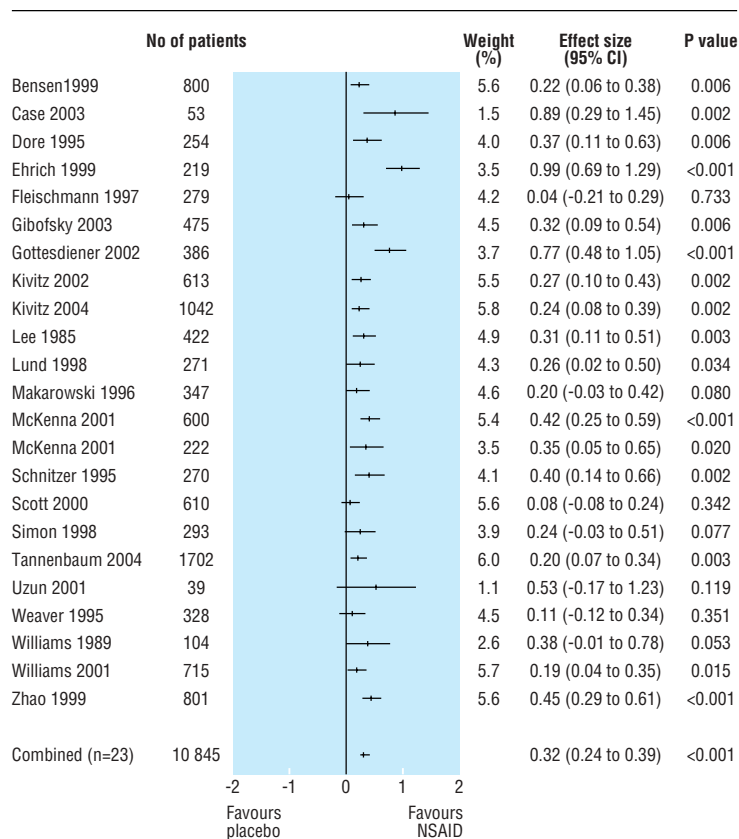
## Discussion

NSAIDs can reduce short term pain in osteoarthritis of the knee slightly better than placebo, but the current analysis does not support the long term use of these drugs. Several NSAIDs, of which rofecoxib is the most recent example, have been withdrawn because of adverse effects.<sup>17</sup> We initially included rofecoxib in our investigation, but did not include it in the final subgroup analysis. As use of oral NSAIDs may incur serious adverse effects, they can only be recommended for limited use in osteoarthritis of the knee. Although NSAIDs have been used for nearly three decades, most trials included in this review were from the past decade. This is mainly due to the inclusion in older studies of patients with multiple joint osteoarthritis and the lack of separate data for osteoarthritis of the knee.

### Strengths and weaknesses of analysis

The strengths of the present study include the acceptable methodological quality of the separate trials on which the analysis is based, as well as the considerable number of trials and patients included. We also translated categorical WOMAC data and P values, *t* test results, standard error of mean values, and before and after values to mean differences in change between groups to avoid bias. For instance, we excluded all groups with less than adequate NSAID doses from the efficacy calculations.

One possible limitation of our study is that we included nine trials in which outcomes were recorded with fewer than the five pain dimensions covered by the WOMAC pain subscale.<sup>w3 w5 w9-w11 w13-w15 w22</sup> We thought that this, as well as the different time points in the individual studies (2, 3, 4, 6, 12, and 13 weeks) for registering outcome measures, could explain the heterogeneity that was found in the trial results, but heterogeneity persisted after we performed relevant subgroup analyses. Heterogeneity was not apparent, however, when we performed a subgroup analysis of trials that did not exclude non-responders to NSAIDs. The validity of requiring a certain increase in symptoms after discontinuation of NSAIDs before inclusion in an NSAID trial seems dubious. Indeed, our results show that this procedure significantly inflates effect sizes in favour of the trial drug. In a clinical setting, it may nevertheless be useful to have information about the magnitude of effect to be expected in patients who are



Effect size (pain) for all trials on NSAID use in knee osteoarthritis

known responders to NSAIDs. In comparisons of various treatments, however, the selective exclusion of people who do not respond to NSAIDs among patients given this type of therapy will introduce bias in favour of NSAID efficacy and may hence be inappropriate.

Another possible source of selection bias in patients is that the average age of the participants was low (62.5 years) for people with osteoarthritis of the knee, reflecting the exclusion of patients above 75 years of age in some trials.<sup>w2 w10 w22</sup> Data on efficacy and tolerability as a function of age were reported in only one comparatively small trial.<sup>w22</sup>

### Benefits of NSAIDs

NSAIDs significantly reduce pain in acute conditions.<sup>18 19</sup> In chronic conditions, however, patients have reported that pain has to be reduced by about 30% to be considered meaningful.<sup>20</sup> For knee osteoarthritis in particular, an effect size of 0.4 or 17-22% change from baseline has been calculated from empirical data and suggested as the minimal clinically important change.<sup>21</sup> Other authors have found that the least perceptible change in pain from osteoarthritis of the knee is 9.7 mm measured by the WOMAC subscale for pain.<sup>22</sup> In accordance with this, the effect size of 0.32 or 10.1 mm on visual analogue scale for pain reduction and the effect size of 0.29 for disability reduction may be considered too small to be clinically significant. This may in turn explain non-compliance with prescribed drug therapy in 29% of patients and the use of non-conventional drug therapy by one in four patients with osteoarthritis.<sup>4</sup>

The widespread and long term use of NSAIDs among elderly people with osteoarthritis is associated

### What is already known on this topic

Current guidelines recommend the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of osteoarthritis of the knee

Oral NSAIDs are used regularly by half of all patients with painful osteoarthritis

### What this study adds

The advantage of oral NSAIDs over placebo for short term pain relief is small and probably clinically insignificant

Evidence of long term effects from oral NSAIDs is still lacking

with considerable side effects. NSAIDs cause serious gastrointestinal complications such as bleeding or perforation in one in 50-100 patient years, and this risk increases with age, concurrent use of other medications, and probably also duration of treatment.<sup>5</sup> Substantial epidemiological and experimental data show that NSAIDs may increase blood pressure,<sup>23</sup> and NSAID use has been linked to the development and acceleration of congestive heart failure.<sup>24</sup> Elderly patients also have an increased risk for development of associated renal failure.<sup>25</sup> In addition, NSAID users are at risk of interactions, including pharmacodynamic interactions with antihypertensive drugs<sup>23</sup> and pharmacokinetic interactions with compounds eliminated by renal excretion, such as lithium.<sup>26</sup> These important caveats were not considered in the short term studies of NSAIDs that we included. Thus, it may be reasonable to assume that the benefits of NSAIDs may be less and the harmful effects more common in an unselected population of patients with knee osteoarthritis compared with the patients in these studies.

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