

## Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials

Jonathan J Deeks, Lesley A Smith, Matthew D Bradley



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### Abstract

**Objective** To determine the efficacy, gastrointestinal safety, and tolerability of celecoxib (a cyclo-oxygenase 2 (COX 2) inhibitor) used in the treatment of osteoarthritis and rheumatoid arthritis.

**Design** Systematic review of randomised trials that compared at least 12 weeks' celecoxib treatment with another non-steroidal anti-inflammatory drug (NSAID) or placebo and reported efficacy, tolerability, or safety. Trials identified from manufacturer and by searching electronic databases and evaluated according to predefined inclusion and quality criteria. Data combined through meta-analysis.

**Participants** 15 187 patients with osteoarthritis or rheumatoid arthritis.

**Main outcome measures** Efficacy: Western Ontario and McMaster universities osteoarthritis index; American College of Rheumatology responder index and joint scores for rheumatoid arthritis. Tolerability: withdrawal rates for adverse effects. Gastrointestinal safety: incidence of ulcers, bleeds, perforations, and obstructions.

**Results** Nine randomised controlled trials were included. Celecoxib and NSAIDs were equally effective for all efficacy outcomes. Compared with those taking other NSAIDs, in patients taking celecoxib the rate of withdrawals due to adverse gastrointestinal events was 46% lower (95% confidence interval 29% to 58%; NNT 35 at three months), the incidence of ulcers detectable by endoscopy was 71% lower (59% to 79%; NNT 6 at three months), and the incidence of symptoms of ulcers, perforations, bleeds, and obstructions was 39% lower (4% to 61%; NNT 208 at six months). Subgroup analysis of patients taking aspirin showed that the incidence of ulcers detected by endoscopy was reduced by 51% (14% to 72%) in those given celecoxib compared with other NSAIDs. The reduction was greater (73%, 52% to 84%) in those not taking aspirin.

**Conclusion** Celecoxib is as effective as other NSAIDs for relief of symptoms of osteoarthritis and rheumatoid arthritis and has significantly improved gastrointestinal safety and tolerability.

### Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for the treatment of osteoarthritis and rheumatoid arthritis and provide effective relief from symptoms. However, serious gastrointestinal complications occur with their use. There are between 2000-2500 deaths annually in the United Kingdom due to use of NSAIDs.<sup>1 2</sup>

NSAIDs control pain and inflammation by inhibiting cyclo-oxygenase 1 and 2 (COX 1 and COX 2) enzymes. Inhibition of the COX 1 enzyme is responsible for the associated gastrointestinal toxicity. Celecoxib was developed as a COX 2 specific inhibitor to provide relief without the associated gastrointestinal complications.

We conducted a systematic review of all published and unpublished trials to determine if celecoxib is as effective as other NSAIDs for the treatment of osteoarthritis and rheumatoid arthritis and if there is evidence of greater gastrointestinal tolerability and safety.

### Methods

#### Inclusion criteria

We included randomised controlled trials if they were double blind, compared celecoxib at a licensed therapeutic dose for at least 12 weeks with placebo or another NSAID at a standard dose in patients with active rheumatoid arthritis or osteoarthritis, and reported efficacy, tolerability, or safety outcomes. In addition, to investigate safety we considered data on doses of celecoxib above those recommended for treatment. Placebo comparisons were included to demonstrate the sensitivity of efficacy outcomes and to investigate gastrointestinal toxicity.

#### Outcome measures

We present results of the Western Ontario and McMaster universities (WOMAC) osteoarthritis index for pain (scored 0 to 20), stiffness (scored 0 to 8), and physical function (scored 0 to 68). We used the American College of Rheumatology (ACR-20) responder index and evaluations of improvement in the numbers of painful or tender and swollen joints for trials of rheumatoid arthritis.

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Centre for Statistics  
in Medicine,  
Institute of Health  
Sciences,  
Headington,  
Oxford OX3 7LF

Jonathan J Deeks  
senior medical  
statistician

Lesley A Smith  
research fellow

Pfizer Global  
Research and  
Development,  
Sandwich, Kent  
CT13 9NJ

Matthew D Bradley  
associate director

Correspondence to:  
JJ Deeks  
[jon.deeks@  
cancer.org.uk](mailto:jon.deeks@<br/>cancer.org.uk)

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Drug tolerability was assessed by considering rates of withdrawal due to any adverse event at 12 weeks. Gastrointestinal safety was assessed by comparing the incidence of ulcers detected by routine endoscopy at 12 and 24 weeks and the incidence of symptomatic ulcers, perforations, bleeds, and obstructions up to 24 weeks.

#### Study identification

We aimed to include all randomised trials of celecoxib, regardless of whether or not they had been published. We obtained from the manufacturer reports from all industry sponsored randomised controlled trials that were completed by 25 May 2000 and that compared celecoxib with placebo or other NSAID in people with osteoarthritis and rheumatoid arthritis. We also searched Medline, Embase, and the Cochrane controlled trials register from 1998 to March 2001 using the search terms celecoxib, Celebrex, and SC-58635.

#### Trial quality and data abstraction

To assess the potential for bias we considered the method of randomisation, concealment of allocation, blinding of trial investigators and patients, completeness of follow up, and analysis according to intention to treat. Summary outcome data were extracted from the original company trial reports.

#### Data synthesis

Separate meta-analyses were undertaken for each comparison and outcome. We analysed efficacy data separately for osteoarthritis and rheumatoid arthritis. We analysed tolerability and safety data for the two diseases combined.

Dichotomous data were summarised as relative risks; continuous data were summarised as differences in means.

## Results

We obtained reports of 17 trials, nine of which (15 187 patients) fulfilled the inclusion criteria.<sup>3-11</sup> See the long version of this paper on [bmj.com](http://bmj.com) for full details of the studies. All nine trials were of high quality.

After 12 weeks of treatment, 56% of patients in the placebo group had dropped out due to poor efficacy or adverse events. Dropout rates in celecoxib and other NSAID groups were lower (39% on celecoxib 200 mg per day; 32% on celecoxib 400 mg per day; 39% on naproxen 1000 mg per day; 26% on diclofenac 150 mg per day).

#### Effectiveness of celecoxib for treatment at 12 weeks

**Rheumatoid arthritis**—Celecoxib provided significant improvement in all outcomes compared with placebo.<sup>4-9</sup> Three trials compared celecoxib with other NSAIDs (naproxen 500 mg twice daily in two trials<sup>4-9</sup> and diclofenac 75 mg twice daily in one<sup>7</sup>). There were no significant differences, with all drugs appearing equally effective for all outcomes. With celecoxib the ACR-20 responder rate was 4% higher (95% confidence interval -20% to 36%), 9% more (-10% to 32%) showed improvement in the number of painful or tender joints, and 2% more (-15% to 22%) showed improvement in the number of swollen joints (see also [bmj.com](http://bmj.com)).

**Osteoarthritis**—Compared with placebo celecoxib resulted in significant improvement in all components

of the WOMAC scale as well as the composite WOMAC score.<sup>3-10-11</sup> The same three trials compared celecoxib with naproxen 500 mg twice daily in 1917 patients. There were no significant differences between celecoxib and naproxen, with both drugs appearing equally effective for all components of the WOMAC scale: pain (mean difference 0.0, -0.7 to 0.7), stiffness (0.1, -0.1 to 0.2), and physical function (0.4, -1.0 to 1.8) and the composite WOMAC score (0.4, -1.5 to 2.3) (see [bmj.com](http://bmj.com)).

#### Tolerability

**Celecoxib versus placebo**—Withdrawal due to adverse events occurred more often on celecoxib than on placebo, both for any adverse event (relative risk 1.49, 1.15 to 1.92) and for all gastrointestinal adverse events (1.68, 1.07 to 2.65) (fig 1). However, withdrawals due to abdominal pain, diarrhoea, dyspepsia, nausea, or vomiting were not significantly increased with celecoxib compared with placebo.

**Celecoxib versus NSAID**—There was no significant difference between celecoxib and NSAID in the incidence of withdrawals for all adverse events (fig 1). However, there was a significant decrease in the number of withdrawals due to gastrointestinal adverse events, corresponding to a number needed to treat of 35 at three months. Of the specific gastrointestinal adverse events, there were significantly fewer withdrawals due to abdominal pain and dyspepsia in the celecoxib group compared with other NSAIDs. The incidence of withdrawals due to diarrhoea, nausea, or vomiting were not significantly different between celecoxib and other NSAIDs.

#### Ulcers detected by endoscopy

**Celecoxib versus placebo**—Although there was no significant difference in the number of ulcers detected between the groups, the results were compatible with up to a threefold increase in the incidence of ulcers (1.53, 0.73 to 3.21).

**Celecoxib versus NSAID**—The incidence of ulcers was 71% (59% to 79%) lower in those taking celecoxib compared with other NSAIDs, corresponding to a number needed to treat of six at three months. The one study that reported ulcers detected by endoscopy at 24 weeks found a similar significant reduction, with incidence being 75% (47% to 88%) lower in those taking celecoxib.<sup>7</sup>

#### Ulcers, perforations, bleeds, and obstructions at 24 weeks

The CLASS study of 7968 patients investigated the incidence of serious upper gastrointestinal events (bleeds, perforations, obstructions) in those taking celecoxib (3987 given celecoxib 800 mg per day; above the recommended dose) compared with other NSAIDs (1985 took ibuprofen, 1996 took diclofenac).<sup>8</sup> Patients were monitored and withdrawn from the trial due to adverse events, if endoscopy indicated a symptomatic ulcer, if prolonged use of an ulcer healing treatment was required, or if treatment did not control the symptoms of arthritis. Outcomes at six months were considered as the overall rates of withdrawal were more comparable after six months (40% for celecoxib, 42% for diclofenac, and 47% for ibuprofen) than at the final follow up (55%, 53% and 65%). With celecoxib the incidence of bleeds, perforations, or obstructions

**Celecoxib v placebo**

	Celecoxib	Placebo
<b>Any adverse effects</b>		
Bensen 1999 <sup>3</sup>	58/439	17/219
Zhao 1999 <sup>10</sup>	39/476	14/247
Simon 1999 <sup>4</sup>	42/692	11/231
Zhao 2000 <sup>9</sup>	44/664	12/221
Study 054	52/420	16/217

RR =1.49 (1.15 to 1.92)  
Heterogeneity: Q=1.08, P=0.90

	Celecoxib	Placebo
<b>Any GI adverse effect</b>		
Bensen 1999 <sup>3</sup>	19/439	5/219
Zhao 1999 <sup>10</sup>	18/476	5/247
Simon 1999 <sup>4</sup>	16/692	3/231
Zhao 2000 <sup>9</sup>	16/664	4/221
Study 054	18/420	6/217

RR =1.68 (1.07 to 2.65)  
Heterogeneity: Q=0.32, P=0.99

	Celecoxib	Placebo
<b>Abdominal pain</b>		
Bensen 1999 <sup>3</sup>	4/439	1/219
Zhao 1999 <sup>10</sup>	7/476	1/247
Simon 1999 <sup>4</sup>	6/692	2/231
Zhao 2000 <sup>9</sup>	2/664	1/221
Study 054	4/420	0/217

RR =1.86 (0.75 to 4.60)  
Heterogeneity: Q=2.07, P=0.72

	Celecoxib	Placebo
<b>Diarrhoea</b>		
Bensen 1999 <sup>3</sup>	2/439	2/219
Zhao 1999 <sup>10</sup>	1/476	0/247
Simon 1999 <sup>4</sup>	2/692	0/231
Zhao 2000 <sup>9</sup>	2/664	0/221
Study 054	4/420	0/217

RR =1.45 (0.47 to 4.45)  
Heterogeneity: Q=1.78, P=0.78

	Celecoxib	Placebo
<b>Dyspepsia</b>		
Bensen 1999 <sup>3</sup>	6/439	1/219
Zhao 1999 <sup>10</sup>	4/476	2/247
Simon 1999 <sup>4</sup>	6/692	1/231
Zhao 2000 <sup>9</sup>	8/664	2/221
Study 054	9/420	3/217

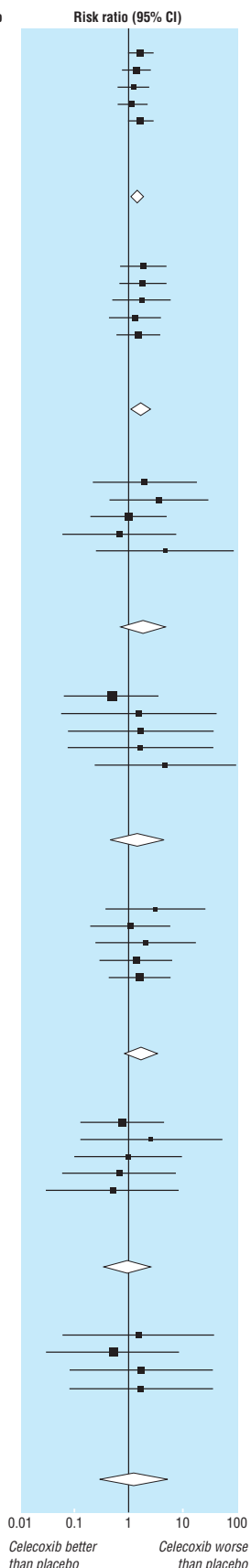
RR =1.60 (0.77 to 3.34)  
Heterogeneity: Q=0.69, P=0.95

	Celecoxib	Placebo
<b>Nausea</b>		
Bensen 1999 <sup>3</sup>	3/439	2/219
Zhao 1999 <sup>10</sup>	2/476	0/247
Simon 1999 <sup>4</sup>	3/692	1/231
Zhao 2000 <sup>9</sup>	2/664	1/221
Study 054	1/420	1/217

RR =0.90 (0.33 to 2.49)  
Heterogeneity: Q=0.74, P=0.95

	Celecoxib	Placebo
<b>Vomiting</b>		
Bensen 1999 <sup>3</sup>	1/439	0/219
Zhao 1999 <sup>10</sup>	1/476	1/247
Simon 1999 <sup>4</sup>	2/692	0/231
Zhao 2000 <sup>9</sup>	2/664	0/221
Study 054	0/420	0/217

RR =1.20 (0.28 to 5.16)  
Heterogeneity: Q=0.46, P=0.93



**Celecoxib v NSAID**

	Celecoxib	NSAID
<b>Any adverse effects</b>		
Study 071 (D)	11/183	37/387
Study 071 (I)	11/183	37/346
Bensen 1999 <sup>3</sup> (N)	58/439	18/216
Zhao 1999 <sup>10</sup> (N)	39/476	30/233
Simon 1999 <sup>4</sup> (N)	42/692	12/225
Zhao 2000 <sup>9</sup> (N)	44/664	16/218
Study 054 (N)	52/420	29/207
Study 062 (N)	19/269	24/267

RR =0.86 (0.72 to 1.04)  
Heterogeneity: Q=10.86, P=0.15

	Celecoxib	NSAID
<b>Any GI adverse effect</b>		
Study 071 (D)	6/183	22/387
Study 071 (I)	5/183	26/346
Bensen 1999 <sup>3</sup> (N)	19/439	13/216
Zhao 1999 <sup>10</sup> (N)	18/476	18/233
Simon 1999 <sup>4</sup> (N)	16/692	11/225
Zhao 2000 <sup>9</sup> (N)	16/664	9/218
Study 054 (N)	18/420	17/207
Study 062 (N)	11/269	16/267

RR =0.54 (0.42 to 0.71)  
Heterogeneity: Q=1.99, P=0.96

	Celecoxib	NSAID
<b>Abdominal pain</b>		
Study 071 (D)	2/183	6/387
Study 071 (I)	1/183	3/346
Bensen 1999 <sup>3</sup> (N)	4/439	5/216
Zhao 1999 <sup>10</sup> (N)	7/476	4/233
Simon 1999 <sup>4</sup> (N)	6/692	4/225
Zhao 2000 <sup>9</sup> (N)	2/664	4/218
Study 054 (N)	4/420	9/207
Study 062 (N)	3/269	6/267

RR =0.41 (0.26 to 0.67)  
Heterogeneity: Q=4.30, P=0.75

	Celecoxib	NSAID
<b>Diarrhoea</b>		
Study 071 (D)	0/183	4/387
Study 071 (I)	0/183	0/346
Bensen 1999 <sup>3</sup> (N)	2/439	3/216
Zhao 1999 <sup>10</sup> (N)	1/476	0/233
Simon 1999 <sup>4</sup> (N)	2/692	1/225
Zhao 2000 <sup>9</sup> (N)	2/664	0/218
Study 054 (N)	4/420	0/207
Study 062 (N)	1/269	0/267

RR =0.88 (0.37 to 2.11)  
Heterogeneity: Q=4.04, P=0.67

	Celecoxib	NSAID
<b>Dyspepsia</b>		
Study 071 (D)	1/183	7/387
Study 071 (I)	0/183	3/346
Bensen 1999 <sup>3</sup> (N)	6/439	2/216
Zhao 1999 <sup>10</sup> (N)	4/476	8/233
Simon 1999 <sup>4</sup> (N)	6/692	5/225
Zhao 2000 <sup>9</sup> (N)	8/664	3/218
Study 054 (N)	9/420	3/207
Study 062 (N)	2/269	3/267

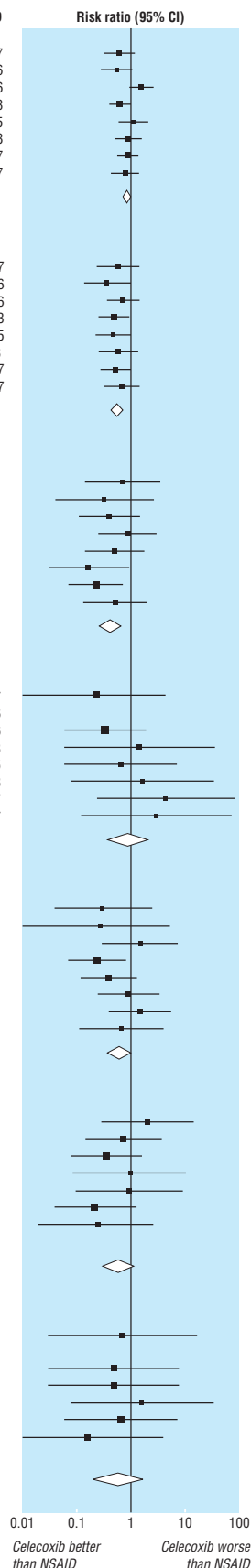
RR =0.59 (0.36 to 0.98)  
Heterogeneity: Q=6.80, P=0.45

	Celecoxib	NSAID
<b>Nausea</b>		
Study 071 (D)	2/183	2/387
Study 071 (I)	2/183	5/346
Bensen 1999 <sup>3</sup> (N)	3/439	4/216
Zhao 1999 <sup>10</sup> (N)	2/476	1/233
Simon 1999 <sup>4</sup> (N)	3/692	1/225
Zhao 2000 <sup>9</sup> (N)	2/664	3/218
Study 054 (N)	1/420	2/207
Study 062 (N)	0/269	0/267

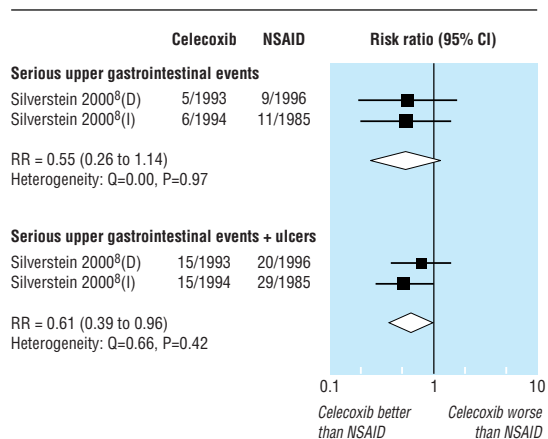
RR =0.58 (0.30 to 1.14)  
Heterogeneity: Q=4.17, P=0.65

	Celecoxib	NSAID
<b>Vomiting</b>		
Study 071 (D)	0/183	1/387
Study 071 (I)	0/183	0/346
Bensen 1999 <sup>3</sup> (N)	1/439	1/216
Zhao 1999 <sup>10</sup> (N)	1/476	1/233
Simon 1999 <sup>4</sup> (N)	2/692	0/225
Zhao 2000 <sup>9</sup> (N)	2/664	1/218
Study 054 (N)	0/420	1/207
Study 062 (N)	0/269	0/267

RR =0.57 (0.19 to 1.74)  
Heterogeneity: Q=1.09, P=0.96



**Fig 1** Withdrawals from celecoxib, placebo and NSAIDs at 12 weeks attributed to adverse effects. D=diclofenac 75 mg twice daily, I=ibuprofen 800 mg thrice daily, N=naproxen 500 mg twice daily



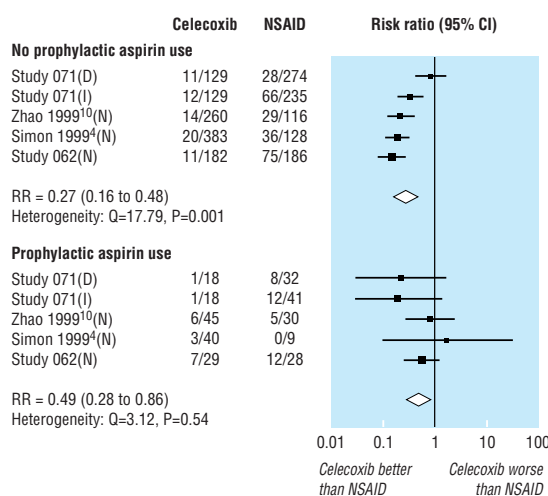
**Fig 2** Incidence of symptomatic ulcers, perforations, bleeds, and obstructions after 24 weeks' treatment with celecoxib 400 mg twice daily, diclofenac 75 mg twice daily (D) or ibuprofen 800 mg thrice daily (I). Trial stratified into two parts as designed

(n=11) was nearly half that with the other NSAIDs (n=20), but this difference was not significant (fig 2).

Among the participants withdrawn from the trial for safety reasons, 19 patients taking celecoxib were found to have ulcers on endoscopy compared with 29 patients taking other NSAIDs. When ulcers were included within the definition of serious adverse events, the reduction of serious adverse events with celecoxib decreased to 39% (corresponding to a number needed to treat of 208 at six months) but became significant (fig 2).

**Benefits of celecoxib in patients receiving low dose aspirin**

Four trials compared celecoxib with other NSAIDs and showed that the incidence of ulcers detected by routine endoscopy were significantly reduced both in patients taking and not taking aspirin (up to 325 mg/day).<sup>4-5 10</sup> The benefit of celecoxib seemed greater in those not taking aspirin, although the difference between subgroups was not significant (P=0.18, fig 3).



**Fig 3** Impact of prophylactic aspirin on incidence of ulcers detected by routine endoscopy after 12 weeks' treatment. D=diclofenac 75 mg twice daily, I=ibuprofen 800 mg thrice daily, N=naproxen 500 mg twice daily

In the CLASS study the reduction in the incidence of clinical ulcers, perforation, bleeds, and obstructions was also smaller in those taking aspirin (19% reduction, -63% to 60%) than in those not taking aspirin (50% reduction, 8% to 72%).<sup>8</sup> This difference between the subgroups was not significant (P=0.44).

**Discussion**

In this review of randomised controlled trials we have shown that celecoxib is as effective as other NSAIDs for the relief from symptoms of osteoarthritis and rheumatoid arthritis. The confidence intervals around the point estimates of efficacy were reasonably narrow, which mean that it is unlikely that there were clinically important differences.

Our findings are robust and unlikely to be influenced by bias. Beyond the stated involvement of MDB, the industrial sponsors had no involvement in the review process once the protocol had been agreed. We included published and unpublished studies, and we insisted that the companies involved provided a signed legal statement confirming that they had made available data from all celecoxib trials that were completed before our inclusion date. We evaluated the impact of including unpublished studies by sensitivity analyses for main outcomes (see bmj.com); our findings and interpretation did not change. Results of further phase 4 trials (the Success trial) have recently been partially published in abstract form since we completed our search. We did not add these to our review as they are incomplete and could introduce bias.<sup>12</sup>

As we abstracted data directly from original trial reports we minimised the effects of missing data and errors in transcription. Access to individual patient data would have allowed us to investigate further any variation in treatment effect with patient characteristics.

All included trials were designed and executed to meet standards required for licensing. Although withdrawals were common, the potential biases due to unequal withdrawals act in a conservative direction.

For most analyses we did not detect any heterogeneity, which supports pooling of different doses of drugs and disease states. Each analysis comprised large numbers of patients, baseline characteristics were similar, all patients had active disease at the start of the study, and efficacy outcomes assessed were those routinely required for licensing of drugs for osteoarthritis and rheumatoid arthritis (WOMAC and ACR-20). Additional efficacy outcomes that we investigated but have not reported here showed similar patterns of benefit.

This review was limited to assessing only upper gastrointestinal safety. Recently the VIGOR (Vioxx gastrointestinal outcomes research) trial of rofecoxib has raised concerns about serious cardiovascular effects with the use of COX 2 inhibitors.<sup>13</sup> While it is important to evaluate this concern, this was not possible here as the celecoxib trials we included did not report outcomes comparable with those assessed in VIGOR (all trials started recruitment before publication of VIGOR). This issue should be a priority for a future systematic review when adequate data on both celecoxib and rofecoxib are available.

### What is already known on this topic

Long term NSAID use is associated with the development of peptic and duodenal ulcers

COX 2 specific inhibitors are claimed to cause fewer gastrointestinal complications

The National Institute for Clinical Excellence has recently recommended that COX 2 specific inhibitors are used in patients with arthritis who are at risk of gastrointestinal complications but not in those taking prophylactic aspirin

### What this study adds

Systematic review of randomised trials shows that celecoxib is as effective as other NSAIDs for osteoarthritis and rheumatoid arthritis

Celecoxib has significantly improved gastrointestinal safety and tolerability compared with standard NSAIDs

An improvement in gastrointestinal safety was still evident in patients who were also taking aspirin

Aspirin is commonly prescribed to prevent cardiovascular disease, and, like NSAIDs, it inhibits COX 1 thus increasing the risk of a gastrointestinal event. The present weight of evidence does not suggest that celecoxib should be withheld from aspirin users as currently recommended by the National Institute for Clinical Excellence (NICE), but further research should clarify the size of the possible reduction in efficacy in this group.

In conclusion, this meta-analysis provides strong evidence of the effectiveness of celecoxib for relief of pain and inflammatory symptoms of osteoarthritis and rheumatoid arthritis, the level of effectiveness being equivalent to that of other NSAIDs. However, the tolerability and gastrointestinal safety of celecoxib is substantially superior.

Mark Layton (Pfizer) and Anne Hopkins (Searle) provided input into the review protocol and facilitated access to the full trial reports.

Contributors: See bmj.com

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**Competing interests:** The review was undertaken independently at the Centre for Statistics in Medicine. LAS is employed on a fellowship funded by Pfizer. JJD has acted as a paid consultant to Pfizer and Pharmacia. MDB is an employee of Pfizer. The review was prepared as part of the submission to the UK National Institute of Clinical Excellence for appraisal of COX 2 selective inhibitors.

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### Bedsore, what bedsore?

When I was 19 I went down to Cambridge to play soccer for my hospital against one of the colleges. My right arm was in plaster from an earlier rugby injury. It was a rough game, and in the changing room I peed what looked like pure blood. This led to seven days' flat bed rest in Addenbrooke's Hospital. Twice a day I was rolled on my side and my back and heels were washed, rubbed with alcohol, creamed, and powdered. I got no bedsore.

When I was 28 I worked in a west country casualty department. We had our fracture ward upstairs full of cases immobilised in full plaster casts. When one of these patients developed a bedsore all hell broke loose. Two nurses were moved off the ward, and we were all up in front of Matron in a drumhead court. It was the only case in the six months that I was there.

When I was 47 I came back from overseas and joined a practice in the west country. I was astonished to see patients coming out of hospital with big infected bedsore. There was no explanation or

apology for this. Our district nurse, old and wise, cured them all with some difficulty.

When I was 74 I had a total hip replacement. During the operation, I lost four pints of blood, which were not replaced for two days. Until then, I was feeble and immobile, and I got a bedsore on my heel. After I got home, the bedsore turned green and grew *Staphylococcus aureus*. I got a massive infection in the surgical wound, softening the muscles, and eventually I dislocated the new hip. Back into hospital on full bed rest. This time my wife insisted on a ripple bed, and she herself did a full alcohol rub, cream, and powder on my heels twice a day. No bedsore that time.

The nurses, mostly middle aged, asked what she was doing. They had never been taught to do this. I suppose it's a shortage of young, active, and trained nurses. Until they arrive, how many patients less stroppy than me plus wife will get bedsore and maybe die of the infection?