Drug Class Review
on
Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Final Report

May 2004

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TABLE OF CONTENTS

Evidence Tables

Appendices

Figures

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INTRODUCTION

Compared with placebo, non-steroidal anti-inflammatory drugs (commonly called NSAIDs) reduce pain significantly in patients with arthritis,[1] low back pain,[2] minor injuries, and soft tissue rheumatism. However, NSAIDs have important adverse effects, including gastrointestinal (GI) bleeding,[3] peptic ulcer disease, hypertension,[4] edema, and renal disease.

NSAIDs reduce pain and inflammation by blocking *cyclo-oxygenases (COX)*, enzymes that are needed to produce *prostaglandins*. Most NSAIDs block two different cyclo-oxygenases, called COX-1 and COX-2. COX-2, found in joint and muscle, contributes to pain and inflammation.

NSAIDs cause bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. In the US, complications from NSAIDs are estimated to cause about six deaths per 100,000 population, a higher death rate than that for cervical cancer or malignant melanoma.[5] A risk analysis[6] based on a retrospective case-control survey of emergency admissions for upper GI disease in two UK general hospitals provided useful estimates of the frequency of serious GI complications from NSAIDs.[7] In people taking NSAIDs, the 1-year risk of serious GI bleeding ranges from 1 in 2,100 in adults under age 45 to 1 in 110 for adults over age 75, and the risk of death ranges from 1 in 12,353 to 1 in 647:

Table 1. One year risk of GI bleeding due to NSAID

Age range (years)	Chance of GI bleed due to NSAID	Chance of dying from GI bleed due to NSAID
	Risk in any one year is 1 in:	
16-45	2100	12,353
45-64	646	3800
65-74	570	3353
≥ 75	110	647
Data are from Blower,[7] recalculated in Moore[6] and in Bandolier[8]		

NSAIDs differ in their selectivity for COX-2—how much they affect COX-2 relative to COX-1. An NSAID that blocks COX-2 but not COX-1 might reduce pain and inflammation in joints but leave the stomach lining alone. Appendix A[9] summarizes the NSAIDs and their selectivity based on assay studies (done in the laboratory instead of in living patients). The table gives an idea of how widely NSAIDs vary in their selectivity, but should be interpreted with caution. Different assay methods give different results, and no assay method can predict what will happen when the drug is given to patients. Clinical studies, rather than these assay studies, are the best way to determine whether patients actually benefit from using more selective NSAIDs.

Scope and Key Questions

1. In head-to-head comparisons, are there differences in effectiveness or safety between different COX-2 inhibitors?
2. Are there differences in effectiveness between coxibs and other NSAIDs?
3. Are there clinically important differences in safety or adverse effects between coxibs, other NSAIDs, and the combination of a nonselective NSAID plus antiulcer medication?
4. Are there subgroups of patients based on demographics, other medications, or

co-morbidities for which one medication is more effective or associated with fewer adverse effects?

Several aspects of the key questions merit comment:

1. Patients. We focused on patients with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, or back pain. We included ankylosing spondylitis. COX-2 inhibitors are also used to treat dysmenorrhea and acute pain (e.g., dental or surgical pain), and to prevent the formation of colorectal polyps. We did not examine studies of the use of coxibs for these indications.
2. Efficacy. The main efficacy measures are pain, functional status, and discontinuations due to lack of efficacy. Measures vary among studies. Frequently used measures are:
   - *Visual analogue scale* (VAS): The patient indicates their level of pain, function, or other outcome by making a mark on a scale labeled with numbers (such as 0 to 100) or descriptions (such as "none" to "worst pain I've ever had").
   - The *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC) is a 24-item questionnaire used to assess the functional status of patients with osteoarthritis of the knee and hip. A lower score indicates better function.
   - *Patient Global Assessment of Disease Status* and *Investigator Global Assessment of Disease Status.* The patient or investigator answers questions about the overall response to treatment, functional status, and pain response, using a VAS or Likert scale.
   - *American College of Rheumatology (ACR) criteria* measure disease activity and response to treatment. ACR 20, ACR 50, or ACR 70 reflect either an improvement to the 20%, 50%, or 70% level in the parameters outlined.
3. Safety and adverse effects. The following events were included in the review:
   a. Serious GI events (GI bleeding, symptomatic ulcer disease, perforation of the GI tract, and death).
   b. Serious cardiovascular events (myocardial infarction, angina, stroke, transient ischemic attack, cardiovascular death, and related measures).
   c. Tolerability and adverse events. We recorded discontinuation due to any adverse event, any serious adverse event, the overall rate of adverse events, the rate of GI adverse events, and the combined rate of adverse events related to renal and cardiovascular function, including increased creatinine, edema, hypertension, or congestive heart failure. We also recorded the frequency of, and discontinuations due to, abnormal laboratory tests, primarily elevated transaminases (liver tests).

Several types of adverse events were excluded:

d. The main non-clinical, or intermediate, outcome measure for GI adverse effect is *endoscopic ulcer.* Ulcers in the stomach or small intestine can be seen in up to 40% of patients taking NSAIDs.[10, 11] As many as 85% of these ulcers can only be found by endoscopy because they do not cause symptoms or bleeding. All three COX-2 inhibitors in the US market significantly reduce the incidence of these asymptomatic ulcers. Based on input from the subcommittee, we did

not include endoscopic ulcer as an outcome measure, since our focus is on clinically significant adverse events.

e. *Case reports.*

i. *Aseptic meningitis.* Near the end of March 2002, the Food and Drug Administration announced that rofecoxib use had been linked to seven cases of aseptic meningitis reported to the FDA's Spontaneous Reporting System. Authors from the FDA published an article reporting five of the cases.[12]

ii. *New case reports.* The May, 2003 searches identified 38 case reports involving the following adverse events:

a. Celecoxib: anaphylaxis,[13] fatal[14] and nonfatal allergic vasculitis,[15, 16] interstitial nephritis with[17] and without[18] nephritic syndrome, cholestatic hepatitis,[19] toxic epidermal necrolysis,[20-23] erythema multiforme,[24] migratory pulmonary infiltrates,[25] acute pancreatitis,[26] torsade de pointes,[27] and renal papillary necrosis.[28]

b. Rofecoxib: wrinkled palms,[29] acute pancreatitis,[30] acute colitis,[31-33] cholestatic hepatitis,[34] fatal[35] and nonfatal hyperkalemia,[36] fatal pulmonary hemorrhage,[37] erythema multiforme,[38] acute interstitial nephritis,[39] and gynecomastia.[40]

4. Drugs. We sought evidence about currently available coxibs (celecoxib [SC 58635], rofecoxib [MK 0966], valdecoxib) and NSAIDs.

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Database of Systematic Reviews (4th quarter, 2003), EMBASE (1st quarter, 2004), MEDLINE (1996 to January, week 1 2004), and Premedline. We used broad searches, only combining terms for drug names with terms for relevant research designs (see Appendix B for complete search strategy). Other sources of citations were EULAR 2001 abstracts, Bandolier and reference lists of review articles. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (http://www.ohsu.edu/drugeffectiveness/pharma/Final_Submission_Protocol_Ver1_1.pdf). All citations were imported into an electronic database (EndNote 6.0).

Study Selection

We included randomized controlled trials of at least 4 weeks' duration that compared a coxib or other NSAID with an active control group. We excluded trials in healthy volunteers and those that had only a placebo control group.

In contrast with many other drug classes, clinical trials of COX-2 inhibitors are

often designed to assess adverse events. We also identified several observational studies that assessed adverse event rates, but we excluded them as these offered no advantage over the randomized trials.

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to followup, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available.

Validity Assessment

We assessed the internal validity (quality) of systematic reviews and randomized trials based on the predefined criteria listed in Appendix C. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[41, 42] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials which met all criteria were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.

Overall quality ratings for an individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

RESULTS

Overview

Searches identified 748 publications: 135 from the Cochrane Library, 78 from MEDLINE, 421 from EMBASE and 114 from the combination of other sources listed above. 66 were included in the review. We included 49 randomized controlled trials, 5 systematic reviews and 2 observational studies. An additional 14 publications provided background information, including 8 meta-analyses. We excluded 72 publications for the reasons detailed in Figure 1. Excluded trial publications are listed in Appendix D.

Key Question 1. In head-to-head comparisons, are there differences in effectiveness or safety between different COX-2 inhibitors?

We found six published randomized, multicenter, fair-to-good quality trials that directly compared COX-2 inhibitors for osteoarthritis of the knee. [43-48] Pharmaceutical manufacturers were reported as funding sources in all but one study.[47] Three earlier studies funded by the maker of celecoxib[43-45], found no difference in efficacy between rofecoxib 25mg and celecoxib 200mg, but found a higher rate of adverse effects with rofecoxib. Another (VACT, for *Vioxx Acetominophen Celecoxib Trial*)[46], conducted by the maker of rofecoxib, found that rofecoxib 25mg was more effective than celecoxib 200mg, with no differences in rates of adverse effects. The more recent study funded by the maker of celecoxib[48]found no difference in either efficacy or adverse effects between celecoxib 200 mg and rofecoxib 25 mg (Evidence Tables 1 and 1a).

Efficacy results. Rofecoxib 25 mg and celecoxib 200 mg had similar effects on patients' pain intensity, 3-hour pain relief, global assessment of efficacy and rescue medication use in a fair-quality, 7-day study of 30 patients with osteoarthritis of the knee.[47] Three larger trials appeared to enroll patients with similar demographics and baseline levels of pain (see table below).[45, 46, 48, 49] All compared rofecoxib 25mg qd and celecoxib 200mg qd in patients with flare-ups of chronic osteoarthritis of the knee. All were 6-week trials.

Table 2. Comparison of rofecoxib and celecoxib in flare-ups of chronic osteoarthritis of the knee

Characteristic	McKenna	Geba	Gibofsky
Rofecoxib 25mg (n)	59	95	190
Celecoxib 200mg (n)	60	97	189
Aspirin 325 qd permitted	Yes	No	Yes
Mean age	62	62.6	62.9
Mean osteoarthritis duration	10.5 years	10 years	9 years
Percent white	80%	85%	NR
Baseline pain on walking (score)	72	72	68
Discontinued trial by 6 wks: Rofecoxib 25mg Celecoxib 200mg	 16% 22%	 19% 17%	 15% 16%

All were probably adequately randomized and blinded, and didn't have statistically significant differences in baseline characteristics. However, there were some discrepancies in McKenna and Geba. In McKenna, the proportion of patients with a past history of ulcers was higher for celecoxib (10% vs. 5%), and the proportion that had a past history of nonspecific GI symptoms was higher for rofecoxib (38% vs. 46%). The proportion of white patients was the same in the celecoxib and rofecoxib groups (84% vs. 85%), but was lower in the placebo group (73%). In Geba, the rofecoxib 25mg group had a higher proportion of women (72.6% vs. 64.9%) and a lower proportion of white subjects (82.1% vs. 87.6%) than the celecoxib 200mg group. The main article did not report the baseline WOMAC and global assessment scores of patients in the different treatment groups; a response to a letter to the editor states that the baseline WOMAC scores were similar.

More recently, Gibofsky hypothesized that perhaps neither McKenna nor Geba were powered sufficiently to measure differences between celecoxib and rofecoxib. Gibofsky described the McKenna study as being powered only to compare active treatments with placebo

and the Geba study as powered to compare rofecoxib with acetaminophen. Therefore, Gibofsky, along with some authors of the McKenna study, set out to conduct a study powered to compare celecoxib and rofecoxib, with a sample size based on results of the McKenna study.

Efficacy results are summarized in Table 3 below. Mean change in WOMAC VAS score for pain on walking was similar for celecoxib 200 mg and rofecoxib 25 mg across studies. Compared to celecoxib on other VAS scores reported in Geba, rofecoxib had significantly larger mean reductions in Rest Pain and Night Pain and a similar mean reduction in Morning Stiffness. Similar mean VAS reductions in Arthritis Pain were seen for celecoxib and rofecoxib in McKenna. WOMAC Composite Score results from Geba and Gibofsky are conflicting.

Table 3. Head to head efficacy comparisons at 6 weeks (mean change from baseline)

	WOMAC VAS Scores					*WOMAC Composite Subscales*			
	Walking pain	Rest pain	Morning stiffness	Night pain	Arthritis pain	Pain	Stiffness	Function	Total
Geba									
Rofecoxib-42	-31.1*	-36.2	-32.7**	nr	-35.4*	-35*	-29.7	-26	
Celecoxib-36.2	-23.4	-29.1	-22.6	nr	-28.6	-27.9	-24.9	-26	
McKenna									
Rofecoxib-38	nr	nr	nr	-40	nr	nr	nr	nr	
Celecoxib-38	nr	nr	nr	-39	nr	nr	nr	nr	
Gibofsky									
Rofecoxib-29.2	nr	nr	nr	nr	-42.6	-34.7	-35.5	-20.1	
Celecoxib-31.5	nr	nr	nr	nr	-42.0	-36.7	-37.9	-22.1	

*p≤0.05
**p<0.001

Geba and his colleagues noted that, regarding the WOMAC scores, "There is no current consensus on the magnitude of effects that is clinically important." A 1992 consensus conference found that a difference of 15 to 20 points on a VAS for pain and global disease activity was "clinically significant," but this has never been validated in clinical studies.[50] A more recent analysis of data from randomized trials estimated that the minimal perceptible improvement for each WOMAC scale was 11 mm.[51] In the Geba trial, WOMAC scores differed by 8 points or less between celecoxib 200mg and rofecoxib 25mg.

Adverse events and safety. Proportion of tolerability questionnaire ratings of "good" or "excellent" were similar for rofecoxib and celecoxib patients in the 7-day trial.[47] The differences in rates of adverse effects across the three similar trials were striking. In McKenna, more rofecoxib than celecoxib patients experienced at least one GI adverse effect (34% vs. 11%, p=0.004), most of which were mild and involved diarrhea, dyspepsia, or abdominal pain. There were no differences between rofecoxib and celecoxib groups in rates of diarrhea, dyspepsia, or abdominal pain in Geba or Gibofsky.

It is difficult to explain the discrepancy of the adverse GI event rates in McKenna. One possible explanation is that McKenna's study may have included a broader spectrum of patients with respect to previous GI disease. In McKenna, patients who had previously had ulcer disease or other GI disorders were permitted to enter the study, and almost 50% had at least one GI disorder before the study began. In Gibofsky, only 7.4% had a history of either upper GI

bleeding or ulcer. It is not clear how many patients in Geba's study had a history of GI disorders. In contrast, concomitant aspirin use may be ruled out as another potential explanation, as both McKenna's and Gibofsky's studies permitted aspirin 325mg qd and occasional use of acetaminophen.

There were no differences in the percentage of patients who discontinued therapy by 6 weeks in the studies. In Geba, the proportion of patients who discontinued for lack of efficacy was 8.4% in the rofecoxib 25mg group and 9.2% in the celecoxib 200mg group (not significant).

Another two head-to-head trials (SUCCESS VI and SUCCESS VII) focused on adverse events in patients 65 or older who had osteoarthritis and well-controlled hypertension.[43, 44] Both of these 6-week trials compared rofecoxib 25mg qd to celecoxib 200mg qd.

In the first trial,[44] nearly twice as many rofecoxib-treated patients (n=399) as celecoxib-treated patients (n=412) experienced edema (9.5% vs. 4.9%, p = 0.014). Systolic blood pressure increased significantly in 17% of rofecoxib- compared with 11% of celecoxib-treated patients (p = 0.032) at any study time point. Diastolic blood pressure increased in 2.3% of rofecoxib-compared with 1.5% of celecoxib-treated patients (p = 0.44). At week 6, the change from baseline in mean systolic blood pressure was +2.6 mmHg for rofecoxib compared with -0.5 mmHg for celecoxib (p = 0.007).

In this trial, there was an important baseline difference in the proportion of patients who took an ACE inhibitor for hypertension (40% for celecoxib-treated patients vs. 29% for rofecoxib-treated patients, p=0.002). Although not statistically significant, at baseline fewer celecoxib-treated patients had angina (16.3% vs. 19.8%) or or a history of myocardial infarction (8% vs. 9.3%). These differences cast doubt on the quality of the trial: unbiased randomization is unlikely to have resulted in a baseline difference this large.

In the second trial,[43] the primary endpoints were 1) systolic blood pressure >140 mm Hg or elevation of 20 or more mm Hg from baseline 2) edema and 3) change from baseline in mean blood pressure. Aspirin use was permitted. The mean age of subjects was 73 years. At baseline, fewer celecoxib-treated patients had coronary disease (15.5% vs. 12.8%), but the proportions of patients taking different anti-hypertensive medications were similar. The baseline differences do not suggest that there was a major flaw in randomization.

A similar proportion of patients taking rofecoxib (53/543, 9.8%) and celecoxib (51/549, 9.3%) withdrew from the study because of adverse events, treatment failure, or other reasons. By 6 weeks, 14.9% of the rofecoxib patients and 6.9% of the celecoxib patients had systolic blood pressure elevations (p<0.0001). In a subgroup analysis, rofecoxib was more likely than celecoxib to cause systolic blood pressure elevation for patients taking an ACE inhibitor or a beta blocker, with or without a diuretic.

Two head-to-head trials have been reported in abstract form but have not been published fully and could not be included in this review. One,[52] funded by the maker of celecoxib, found that rofecoxib, but not celecoxib or naproxen, induced a significant increase in 24-hour ambulatory systolic blood pressure in diabetics taking ACE inhibitors. The other (VACT II), funded by the maker of rofecoxib, found no difference in clinically important hypertension adverse events for rofecoxib and celecoxib.[53]

Key Question 2. Are there differences in effectiveness between coxibs and other NSAIDs?

Celecoxib vs. NSAIDS. Nearly all of the available efficacy data comparing celecoxib to nonselective NSAIDs in osteoarthritis and rheumatoid arthritis come from a series of trials sponsored, designed, and analyzed by the maker of celecoxib. These trials were large (536 to 1,214 subjects) and were mostly short-term. As shown in the table, not all of these trials have been published:

Table 4. Trials of celecoxib versus NSAIDs

NSAID	Number of trials	Number published fully in peer-reviewed literature	Duration
naproxen	9	6	6-12 weeks
diclofenac	3	2	6-24 weeks
ibuprofen	2	1	12 weeks

The lack of complete reporting raises concern about publication bias. For example, of the two trials that compared celecoxib to naproxen in patients with osteoarthritis, the one that found celecoxib and naproxen to be equally effective has been published.[54, 55] The unpublished trial, which included 1191 subjects, found that naproxen was superior to celecoxib at 2 and 12 weeks.[56] Data from the unpublished studies have been reported, but not in detail, in several meta-analyses sponsored by the manufacturer of celecoxib.[56-61] After reviewing data from all the trials, the FDA found no difference in efficacy between celecoxib and nonselective NSAIDs.[62] These data are not completely available for critical appraisal, however.

In addition to the nine published trials in the series, there were two others. The CLASS trial had a total of 7,968 patients randomized to celecoxib, ibuprofen, or diclofenac.[63] CLASS focused on adverse effects rather than efficacy. A higher proportion of NSAID patients withdrew for lack of efficacy (14.8% vs. 12.6%, p=0.005), but no other efficacy results were reported. In the other trial, there were no statistically significant differences between celecoxib and ketoprofen in pain control or function in 246 patients with ankylosing spondylitis.[64]

The eleven published trials are summarized in Table 5.[54, 55, 65-73] In one of the studies (Emery), randomization did not appear to result in equivalent groups; this study was rated fair-to-poor while the others were rated good-quality. The published trials provide good overall evidence that celecoxib is equivalent to nonselective NSAIDs in efficacy for osteoarthritis, rheumatoid arthritis, and other soft-tissue pain.

Data from some of these studies.[54, 55, 65, 66, 68-70, 73], as well as two unpublished studies (Pharmacia Studies 054 and 071), were also analyzed in a good quality systematic review funded by the makers of celecoxib.[74] This review focused only on studies that were at least 12 weeks in duration. Results of this review are consistent with our findings that celecoxib and NSAIDs are equally efficacious in studies of patients with osteoarthritis and rheumatoid arthritis.

One meta-analysis of trials of celecoxib versus NSAIDs focused on efficacy in elderly patients.[59] Celecoxib 200mg and 400mg and naproxen 1000mg were similar in efficacy.

SUCCESS-1, a randomized trial of 13,274 patients with osteoarthritis, compared celecoxib to diclofenac and naproxen. The trial is not yet published, but the authors reported in an abstract that there were no differences in efficacy.[75-77]

Rofecoxib vs. NSAIDs. We were unable to determine whether all manufacturer-sponsored trials of rofecoxib versus NSAIDs have been published. The results of thirteen published trials are summarized in Table 6, where they are sorted by length of followup.[10, 11, 78-87] All but one of the trials included osteoarthritis patients, and all but two[83, 85] were supported by the manufacturer of rofecoxib. The published trials provide good overall evidence that rofecoxib is equivalent to nonselective NSAIDs in efficacy for OA. In addition, one large, good-quality trial indicates that rofecoxib is equivalent to nonselective NSAIDs in efficacy for rheumatoid arthritis.

Valdecoxib vs. NSAIDs. In clinical trials submitted to the FDA, valdecoxib was as effective as ibuprofen (800mg 3 times/day), diclofenac (75mg twice daily), and naproxen (500mg twice daily) in treating osteoarthritis symptoms. Three published trials found no difference in efficacy between valdecoxib and naproxen.[88-90] A fourth trial found no difference in efficacy between valdecoxib 20-40 mg and diclofenac 75 mg slow release in treating rheumatoid arthritis.[91]

NSAID vs NSAID. In double-blinded trials of meloxicam 7.5mg, 15mg, and 25mg versus other NSAIDs (Table 7) there were generally no differences in efficacy.[92-100] In two of the trials, however, patients taking nonselective NSAIDs were significantly less likely to withdraw due to lack of efficacy than patients taking meloxicam.[94, 99]

Several recent good-quality systematic reviews by the Cochrane Collaboration found no clear differences among nonselective NSAIDs in efficacy for treating knee,[101] back,[2] or hip pain.[102] These reviews did not include the COX-2 inhibitors.

Key Question 3. Are there clinically important differences in safety or adverse effects between coxibs, other NSAIDS, and the combination of a nonselective NSAID plus antiulcer medication?

Significant GI events (GI bleeding, hospitalization for GI bleeding, symptomatic ulcer disease, perforation of the GI tract, and death).

Coxibs. Three trials were sufficiently large to evaluate complications of peptic ulcer disease as a primary endpoint. The CLASS trial evaluated celecoxib versus ibuprofen and diclofenac;[63] the VIGOR trial evaluated rofecoxib versus naproxen.[81] The third trial compared celecoxib to the combination of dicoflenac plus omeprazole in patients who presented with a bleeding ulcer.[103] There are no trials of valdecoxib in this category.

VIGOR (Vioxx Gastrointestinal Outcomes Research) **Trial.** VIGOR, a randomized, double-blind trial, compared twice the highest recommended dose of rofecoxib to naproxen 500 mg twice a day in 8,076 patients with rheumatoid arthritis. VIGOR found a statistically significant reduction in complicated upper GI events (see Table 8). The number-needed-to-treat (NNT) to prevent a complicated, confirmed upper gastrointestinal event was 191.

VIGOR met all but one of the criteria for a good-quality study. The one weakness was the number of subjects who had incomplete followup. VIGOR was designed to be a 13-month study, but half of the patients were followed up for 9 months or less, and only about 1,000 patients (13%) were followed up longer than 10 months. By 13 months,

about 29% of the subjects had discontinued the study drugs. Similar proportions discontinued naproxen or rofecoxib because of an adverse event (naproxen—16.1%, rofecoxib—16.4%).

In 2003, the VIGOR investigators published a *post hoc* analysis of lower GI events, defined as bleeding with a 2 g/dL drop in hemoglobin or hospitalization, or hospitalization for perforation, ulceration, diverticulitis, or obstruction.[104] There were 11 events in the rofecoxib group and 24 events in the naproxen group ($p<0.001$, NNT=309.)

CLASS (Celecoxib Long-term Arthritis Safety Study). CLASS combined two randomized trials: one compared celecoxib 400 mg twice a day with ibuprofen 800 mg three times a day, and the other compared celecoxib 400 mg twice a day with diclofenac 75 mg twice a day.[63] The main publication of the study in JAMA reported only 6 months of data and combined the ibuprofen and diclofenac results. Subsequently, additional details of the study have been made public on the FDA web site. The findings reported on the FDA site suggest that, as reported in the JAMA publication, the results of CLASS are incomplete and, in part, misleading.

There were 3,987 subjects in the celecoxib group and 3,981 subjects in the NSAID groups. For the primary endpoint of CLASS, confirmed serious ulcer complications, by 6 months there were more events in the celecoxib group[22] than in the NSAID groups,[13] but the difference was not statistically significant. Moreover, by 12 months, according to FDA documents, there was no longer a trend favoring celecoxib (see Figure 4, Shieman review).[105]

Twenty per cent of the patients in the CLASS trial took aspirin in addition to their study drug. When patients taking aspirin were excluded from the analysis, there were fewer confirmed serious ulcer complications in the celecoxib group than in the ibuprofen group ($p=0.03$). However, celecoxib was less likely to cause serious ulcer complications than ibuprofen, but was equivalent to diclofenac.[106]

In summary, celecoxib was unable to demonstrate a statistically significant advantage over either diclofenac or ibuprofen for the primary endpoint. Celecoxib was superior to ibuprofen, but not diclofenac, in the subgroup of subjects not taking aspirin.

The incidence of serious ulcer complications in CLASS was much higher than it had been in previous trials of celecoxib. A meta-analysis examined the endpoint of "UGI ulcer complications" in 14 RCTs of celecoxib versus placebo or nonselective NSAIDs (usually naproxen).[58] The trials ranged in duration from 2 to 24 weeks, with most lasting 6 or 12 weeks. The strength of this meta-analysis was that the endpoint was similar to those used in the VIGOR and CLASS trials. The endpoint consisted of upper GI bleeding with endoscopic findings of an ulcer or large erosion, perforation, or gastric outlet obstruction. Potential ulcer complications were adjudicated by a Safety Committee in a blinded manner. These endpoints were ascertained through a monitoring program which appears to have been superimposed on all of the trials; it is not clear how assiduously investigators complied with this program. As mentioned above, not all of these trials have been published, and their quality was not assessed as part of the meta- analysis.

In the 14 trials, there were 2/6,376 UGI ulcer complications in the celecoxib group (3 per 10,000) and 9/2,768 in the NSAIDs group (33 per 10,000) and none in the placebo group (0/1,864). This corresponded to annual rates of 2 per 1,000 per year for celecoxib and about 17 per 1,000 per year for NSAIDs ($p=0.002$). In the CLASS trial, the annualized rate of serious ulcer complications was 7.6 per 1,000 per year for

celecoxib and 14.5 per 1,000 per year for the two NSAIDs combined.

There are several possible reasons why rofecoxib, but not celecoxib, was found to reduce ulcer complications significantly. Patient populations and features of the study designs differed (Table 8). VIGOR included patients with rheumatoid arthritis over 50 years, while CLASS had a broader age range of patients with either osteoarthritis or rheumatoid arthritis. VIGOR prohibited the use of aspirin while CLASS did not. The rate of ulcers in the patients taking a control drug was almost 3 times as high in VIGOR as in CLASS, although rates of ulcer complications were similar.

In the **third major trial**, conducted in Hong Kong, patients who presented with a bleeding ulcer were randomized to the combination of celecoxib 200 mg twice a day plus placebo once daily (n=144) or to the combination of extended-release diclofenac 75 mg twice a day plus omeprazole 20 mg once daily (n=143). The primary endpoint was recurrent ulcer bleeding within six months.

By six months, there were 16 cases of recurrent bleeding: 7 (4.9%) in the celecoxib group and 9 (6.3%) in the diclofenac+omeprazole group (the difference, -1.5%, CI –6.8% to 3.8%, was not significant).[103] There were also no differences between the groups in other adverse events, including GI symptoms and renovascular complications. Overall 13.3% of celecoxib patients and 11.9% of diclofenac+omeprazole patients had discontinued medications because of adverse events or lack of efficacy (not significant.) It is not possible to determine whether (or by how much) celecoxib reduced the incidence of recurrent bleeding compared to what would be expected from using diclofenac alone. The high rates of recurrent bleeding in both the celecoxib-treated patients and in the diclofenac+omeprazole group—over 10 times as high as the rate in the CLASS trial— suggest that NSAIDs and coxibs should be used with caution, if at all, in patients who have a recent history of a bleeding ulcer.

COX-2 selective NSAIDs. Evidence that meloxicam and nabumetone prevent ulcer complications is weaker than that for coxibs. Meta-analyses have been performed of published and unpublished trials both of these agents. For nabumetone, a fair-quality meta-analysis included six nonendoscopic studies (five published and one abstract), the largest of which had 3,315 nabumetone patients and 1,096 NSAID patients. The studies had 3 to 6 months of followup. The main endpoint used in this meta-analysis was "PUB", meaning perforation, symptomatic ulcer, or bleeding. Because of the inclusion of symptomatic ulcer, this is a broader endpoint than that used in the VIGOR and CLASS trials or in the meta-analysis of celecoxib trials. The methods to ascertain the endpoint (that is, how well and consistently investigators identified complications) is unknown. There was one PUB event among 4,098 patients taking nabumetone versus 17 events among 1,874 nonselective NSAID patients; this was highly statistically significant. The rates per 1,000 patients per year were about 2 versus 6. (For comparison, in a similar meta-analysis of rofecoxib studies, the rates of PUBs per 1,000 patients per year were 13 for rofecoxib and 26 for NSAIDs.[107]) There was also a significant reduction in treatment-related hospitalizations in the nabumetone group (6.4 per 1,000 patients per year vs. 20.3 per 1,000 patients per year).

The meloxicam (7.5mg or 15mg) meta-analysis included seven double-blind trials, one single-blind trial, and two unblinded trials.[108] Most of the patients were followed for only 4 weeks. The main endpoint was "PUBs". The meta-analysis did not provide event rates, but reported that the rate of PUBs was reduced in the meloxicam patients (Odds ratio 0.52, 95% CI 0.28-0.96). Another double-blind trial of meloxicam 7.5, 15 and 22.5 mg and diclofenac 75

mg bid reporting 12-week PUB rates in RA patients (n=894) has been published since the Schoenfeld meta-analysis.[109] PUB rates of 1.1%, 0.5%, 0.6% and 0% were not significantly different between meloxicam 7.5, 15, and 22.5 mg and diclofenac 75 mg bid.

Because of the lack of detail about the quality and results of the studies included in the Schoenfeld (1999) meta-analysis and lack of a more stringent endpoint than PUBs in that and the Furst trial (2002) there is insufficient evidence to make any judgment about the safety of meloxicam. While the nabumetone meta-analysis is somewhat better, the results are unlikely to apply to actual practice: as for the celecoxib meta-analysis, the rates of events with nabumetone are probably underestimated, and the similarity of the subjects in the efficacy trials to a broader group of NSAID users was not addressed.

Misoprostol, PPIs, and H2 blockers. One good-to-fair-quality double-blind, randomized trial (MUCOSA) of 8,843 patients found that misoprostol 800µg/day prevented symptomatic ulcers and ulcer complications among patients taking nonselective NSAIDs.[110] As in the VIGOR trial, patients were older (> age 50) and had rheumatoid arthritis. Both the misoprostol and placebo groups took NSAIDs. Misoprostol reduced the frequency of gastric outlet obstruction and perforation but not the rate of serious bleeding. The NNT to prevent one serious ulcer complication was 263. Misoprostol was associated with high rate GI adverse effects, such as diarrhea, nausea, dyspepsia, and flatulence. These side effects were not correlated with serious GI events but led to a significantly higher rate of discontinuation of the drug than NSAID plus placebo (42%, vs. 36% in the placebo group).

Proton pump inhibitors (PPIs) and H2-receptor antagonists have also been used to prevent GI side effects in patients taking NSAIDs. A Cochrane review summarized four placebo-controlled trials of PPIs and seven placebo-controlled trials of H2-receptor antagonists.[111, 112] These trials provide strong evidence that PPIs and double-dose H2-receptor antagonists reduce the risk of endoscopic gastric and duodenal ulcers in patients taking NSAIDs, but the total number of subjects was too low to examine whether symptomatic ulcers or ulcer complications are reduced. Unlike misoprostol, PPIs and double-dose H2-receptor blockers also reduced GI symptoms.

No head-to-head comparisons of high-dose H2-receptor blockers vs. PPIs have been done. Since the Cochrane review was last updated, a trial comparing lansoprazole 15 or 30mg/day and misoprostol 800µg/day in patients who had a history of NSAID-induced ulcer has been published.[113] The outcomes were endoscopic ulcer and withdrawal due to adverse events. Withdrawals were much higher for misoprostol, due primarily to diarrhea. On an intention-to-treat basis, misoprostol and lansoprazole were equally efficacious in preventing recurrent endoscopic ulcers. This was because the higher rate of withdrawals was balanced by a lower rate of endoscopic ulcers among those who continued to take misoprostol. The incidence of GI symptoms and the amount of antacid use was significantly higher in the misoprostol group.

Cardiac risk.

The main publication of the VIGOR trial[81] reported that "the incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups." This corresponds to 1 additional heart attack for every 333 patients treated with rofecoxib instead of with naproxen. Blinded re-review of the VIGOR trial data classified

45/4047 (1 in every 90) rofecoxib patients and 20/4029 (1 in 201) naproxen patients as having serious thrombotic events (heart attack, stroke, unstable angina, transient ischemic attack, resuscitated cardiac arrest, and sudden death). This corresponds to one additional serious thrombotic event for every 162 patients taking rofecoxib. For patients who had an indication for aspirin prophylaxis, rofecoxib patients were 4.89 (95% CI, 1.41-16.88) times as likely to have a cardiovascular event than those who took naproxen. For the other, lower-risk subjects in VIGOR, rofecoxib patients were 1.89 (1.03 - 3.45) times as likely as naproxen patients to have a serious cardiovascular event.

An independent review article re-examined the findings of VIGOR, CLASS, and two unpublished trials of rofecoxib that reported cardiovascular outcomes.[114] The latter three trials all permitted patients to use low-dose aspirin, and none of them found an increase in cardiovascular events. Both rofecoxib patients (three trials) and celecoxib patients (CLASS) had annual rates of heart attacks higher than the average for the patients in several placebo-controlled studies of aspirin prophylaxis.

In October 2001, an article published in *Circulation*[115] reported a pooled analysis from 23 rofecoxib Phase IIb through V trials conducted by Merck. The investigators examined results by patient group (rheumatoid arthritis, osteoarthritis, or Alzheimer's disease) and by control group (placebo, naproxen, or non-naproxen NSAID). The risk of cardiovascular events was 1.69 times higher for rofecoxib than for naproxen, but was not elevated in trials comparing rofecoxib versus placebo or other NSAIDs. The authors hypothesized that rofecoxib might have been an "innocent bystander" in the VIGOR trial; that is, rather than rofecoxib increasing the rate of cardiovascular events, naproxen might have reduced it. They also criticized the Mukherjee article, correctly in our view, for comparing trials of patients under treatment for rheumatoid arthritis to an entirely different group of patients in studies of aspirin prophylaxis.

The problem with the Konstam analysis[115] is that the non-naproxen studies and naproxen studies are not directly comparable. VIGOR, the only COX-2 trial to demonstrate a significant reduction in serious GI events, used a supratherapeutic dosage of rofecoxib (50mg), prohibited aspirin, and followed patients for 9 months. All but one of the non-naproxen-controlled studies were shorter than 6 weeks in duration or used lower doses of rofecoxib. The one exception is a combination of data from eight phase IIb/III trials in osteoarthritis patients (see below). The data presented in the meta-analysis are also inadequate to judge the quality of the included studies and how concomitant aspirin use might have affected rates of cardiovascular events.

A subsequent meta-analysis provided a more detailed analysis of the subjects in the eight phase IIb/III trials mentioned in the Konstam analysis.[116] The total number of subjects in the eight trials is given as 5,435, versus 5,505 in the Konstam analysis; the reason for the discrepency is unclear and the second analysis does not provide a detailed accounting of the excluded subjects. The mean duration of treatment was 3½ months.

The conclusion of the analysis--that there were no significant differences between rofecoxib and placebo or non-naproxen NSAIDs—is valid for this set of studies, but does not address the more general question of whether rofecoxib is safe at the dosage proven to reduce serious GI events. The analysis combined data from all rofecoxib doses (12.5, 25, and 50mg/day); only 545 of the patients received the 50mg/day dose. The issue of dosage is important because only the 50mg dose has been shown to prevent GI adverse events. It is possible that lower doses do not increase cardiovascular events compared with non-naproxen NSAIDs, but the benefit of lower, conventional doses are uncertain.

The original publication of the CLASS trial found that celecoxib had no effect on the rate

of cardiovascular events compared with diclofenac and ibuprofen. The CLASS data on thrombotic events were recently analyzed in more detail.[117] There were no differences in the rates of any significant cardiovascular event for the overall sample and for the subgroup who did not use aspirin. In their analysis, White and colleagues pooled the data from the ibuprofen and diclofenac groups. In fact, more detail is needed about the duration of the CLASS trial to judge the validity of these results. While the original publication reported results at 6 months,[63] a concurrent publication by the Director of Clinical Research at Pfizer[118] stated that "CLASS…consisted of two trials lasting 1 year." The recent analysis by White seems to contradict this statement, saying: "After all patients had the opportunity to participate for at least 6 months, a monthly blinded review of ulcer complications by the CLASS oversight committees indicated a marked decrease and then cessation in the accrual rate. After two successful reviews with no further complications noted, the oversight committee voted to terminate the study." This may mean that the study was terminated after all patients had the opportunity to be followed for 8 months, which may not be long enough to assess cardiovascular risk. At 8 months in the VIGOR trial there was no significant difference between rofecoxib and naproxen in the cumulative incidence of events. From 8 to 12 months, the incidence of events in the rofecoxib group rose sharply (Figure 1 of Mukherjee[114]), while that of naproxen did not. Based on this pattern in VIGOR, if celecoxib were associated with an increased risk of cardiovascular events, it would probably not be seen until 10 or 12 months of followup. In the VIGOR trial, 2,140 subjects, about one-fourth of the original sample, were available for 10 months of followup, and 1,045 were available for 12 months. Comparable data are not available for CLASS, so it is difficult to know whether the analysis had sufficient power to detect a difference.

The authors of the study argue that their results show that celecoxib is safer than rofecoxib. To support this point, they note that the annualized rate of all cardiovascular thromboembolic events in the naproxen group in the VIGOR trial and the non-aspirin users in the CLASS trial were similar. However, this comparison of rates across the VIGOR and CLASS studies is imprecise. After 8 months in the VIGOR trial, about 0.4% of naproxen patients had experienced an event; after 8 months in CLASS, about 0.8% of non-aspirin users had. It is not clear whether or not this is a clinically or statistically significant difference.

New analyses of the CLASS and VIGOR data. One meta-analysis from Canadian used FDA materials to analyze the rates of serious adverse events, defined as death, hospitalization, "any life-threatening event, or event leading to severe disability."[119](see also http://www.cfpc.ca/cfp/2002/sep/vol48-sep-critical-2.asp) This measure combines the rates of serious upper GI complications (in which coxibs are expected to have an advantage over NSAIDs) with other serious adverse events. The numbers of all serious adverse events shown in the following table were drawn directly from FDA materials, pages 7 and 57.[120]

In the Canadian re-analysis, shown in the table, the rates are calculated using the number of patients as the denominator. These simple rates are compared with the number of serious upper GI events, which constitute only about 10% of all serious adverse events (the 2 columns to the right in the table). Using the data from the table, the number-needed-to-harm 1 person was 82 for celecoxib vs. diclofenac, 129 for celecoxib vs. ibuprofen, 100 for celecoxib vs. diclofenac and ibuprofen, and 65 for rofecoxib vs. naproxen. The Canadian authors pooled the results for celecoxib and rofecoxib, assigning more weight to VIGOR, which had a longer duration than CLASS. In the pooled analysis, the number needed to harm was 78 and was statistically significant.

Table 9. Re-analysis of the CLASS and VIGOR Trials

Trial	ALL SERIOUS ADVERSE EVENTS		SERIOUS UPPER GI EVENTS	
	Treatment	Control	Treatment	Control
CLASS	270/3987 (6.8%)	230/3981(5.8%)	20/3987	24/3987
VIGOR	378/4047 (9.3%)*	315/4029 (7.8%)	16/4047*	37/4029

*statistically significant vs. control group.

For the VIGOR trial, the FDA calculated rates of serious adverse events in exactly the same manner as the Canadian investigators. The FDA noted that the rates of each serious adverse event (except GI adverse events) were higher for rofecoxib than for naproxen. For the CLASS trials, the FDA used normalized patient-years as the denominator instead of a simple proportion to calculate rates of serious adverse events. (This approach was used because the 2 trials that make up CLASS had different durations.) In the FDA analysis, the rates of all serious adverse events combined were 11.6 per 100 patient-years for celecoxib; 10.3 per 100 patient-years for diclofenac, and 10.6 per 100 patient-years for ibuprofen. The FDA interpreted these differences as being insignificant.

In summary, the FDA data clearly show that these 2 coxibs, *in doses higher than those used in practice,* do not reduce the overall rate of serious adverse events, and may have increased them. It should also be noted that not all serious adverse events are equal in importance to patients and physicians. A reduction in the rate of one kind of adverse event might be considered more important than an increase in another one.

In October 2003, an article published in *Annals of Internal Medicine*[87] reported results from the more recent **ADVANTAGE** (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness) **Trial**. ADVANTAGE, a randomized, double-blind trial, compared rofecoxib 25 mg to naproxen 500 mg twice a day in 5,557 patients with osteoarthritis of the knee, hip, hand or spine. This 12-week trial evaluated GI tolerability as the primary end point. Incidence of PUBs and thrombotic cardiovascular events (cardiovascular, hemorrhagic, and unknown deaths; nonfatal myocardial infarction; nonfatal stroke) were also evaluated. The ADVANTAGE trial found that conventional dosing of rofecoxib didn't significantly increase rates of combined cardiovascular events [10/2785(0.4%) vs 7/2772(0.3%); p>0.2], myocardial infarctions [5/2785(0.2%) vs 1/2772(0.04%); p>0.2] or strokes [0 vs 6/2772(0.2%); p=0.015] compared to naproxen 500 mg. This evidence isn't directly comparable to results of the VIGOR trial, in which higher CV event rates were only found after following patients for 9 months. This trial also does not answer the question regarding the benefit of rofecoxib 25 mg in reducing serious GI events, however, as only rates of PUBs were reported [2/2799(0.07%) vs 9/2787(0.3%); RR=0.22; p=0.038).

Observational studies. Two retrospective cohort studies focused on the cardiovascular complications of coxibs. In both studies, rofecoxib 25 mg or less, naproxen, and celecoxib were not associated with an increased rate of cardiac events. In one of the studies, rofecoxib 50 mg, the dose studied in the VIGOR trial, was associated with an increased risk of cardiac events.

One of these examined a database from a Medicaid population in Tennessee.[Ray, 2002 #1169] In an earlier publication, the investigators had examined the effects of different NSAIDs on cardiac events in the era before coxibs became available. In the more recent article, the authors added rofecoxib and celecoxib use to their analysis. The investigators compared rates of

cardiovascular events within one year of starting one of several NSAIDs or one of the 2 coxibs, versus not taking any NSAID or coxib, as identified by pharmacy benefit claims. The unit of analysis was the patient-year: over the course of the study, a particular patient could be in the same group several times, or in several different groups. For example, if a patient had the following history:

Year 1 No NSAID or coxib
Year 2 No NSAID or coxib
Year 3 Took rofecoxib
Year 4 No NSAID or coxib
Year 5 Took celecoxib

she could be in the control group for year 2, the rofecoxib group for year 3, the control group again for year 4, and the celecoxib group for year 5. The investigators attempted to adjust for baseline cardiovascular risks using a patient's inpatient diagnostic codes and medication history.

The subjects mean age was 61 years. Approximately 42% of rofecoxib and celecoxib users had a history of treatment for major cardiovascular diseases, as estimated by the claims information. The main findings of the study was an increased adjusted 1-year risk of a cardiovascular event (death or myocardial infarction) in patients taking more than 25 mg of rofecoxib daily. Rates for patients taking ibuprofen, naproxen, rofecoxib 12.5 mg or 25 mg daily, or celecoxib were not different from the rate in nonusers of NSAIDs or coxibs.

The other study, from Ontario, Canada, used similar methods.[121] It found no difference in 1-year rates of cardiovascular events between nonusers of NSAIDs and patients taking various NSAIDs, rofecoxib, or celecoxib. It did not specifically examine patients taking doses of rofecoxib greater than 25 mg daily.

The strength of these studies is that they reflect how coxibs are actually used in practice. The studies have important weaknesses. Perhaps the most serious weakness of these two observational studies is that they did not report serious GI events. Doing so would have provided a sense of the balance of benefits and harms of using the coxibs in these populations.

Inadequate data were available to control for confounders in a convincing manner. Neither study could control for (or estimate the degree of use of) over-the-counter aspirin and ibuprofen. The lack of information about aspirin use makes it even more important to report the frequency of GI adverse events. and the methods used to estimate baseline cardiovascular risk were crude.

The clinical information available from claims was insufficient and, possible, unreliable. For example, in the earlier of the two Tennessee reports, 22% of NSAID users and 22% of the nonuser controls were described as having "serious cardiovascular disease in the past year" at baseline In the 2nd report, 43% of coxib users, 38% of NSAID users, and 34% of nonusers were described as having "major cardiovascular disease" in the past year by similar criteria. In the first report, 67% of NSAID users took a cardiovascular drug in the previous year; in the 2nd report, 82% did. In the 2nd report, although only 3 to 5% of the subjects had rheumatoid arthritis, 30% of the patients taking coxibs, 24% of the patients taking naproxen or ibuprofen, and 16% of the controls had been prescribed oral corticosteroids within the past year. These examples underscore

that, when a study relies on claims data, it may not be able to provide a meaningful, consistent sense of the type, severity, and frequency of cardiovascular morbidity and comorbidity in the compared groups.

Tolerability. Tables 10 and 11 summarize tolerability information from 11 published randomized trials. There was no difference between celecoxib versus NSAIDs or rofecoxib versus NSAIDs in withdrawals due to adverse events, with one exception. A 2003 publication of a 12-week trial in 660 RA patients reported significantly less discontinuations due to adverse events for rofecoxib 50 mg than naproxen 500 mg (5.0% vs 9.1%; $p<0.05$).[122] In general total adverse events were similar for coxibs and nonselective NSAIDs, but celecoxib was better than ibuprofen 800mg tid or diclofenac 75mg bid in the largest celecoxib study.[63] GI adverse events, primarily abdominal pain, diarrhea, and nausea, were consistently lower for coxibs than for nonselective NSAIDs, even in studies which permitted the use of H2 blockers in the NSAID group. In most studies these adverse events are described as mild or moderate because they did not result in discontinuation of the drug. The magnitude of difference is probably one GI adverse event for every 20 patients treated. Coxibs may be associated with a lower incidence of anemia than nonselective NSAIDs, but because only a few studies report this outcome publication bias cannot be ruled out.

Results of a good quality systematic review[74] of five trials published prior to April 2001 [54, 55, 66, 69, 70, 73] and two unpublished trials (Pharmacia studies 062 and 071) were also available. Their pooled analysis suggests that there was one fewer withdrawal due to GI adverse events after 3 months for every 35 patients treated with celecoxib instead of NSAIDs.

The effects of celecoxib on renal function were reviewed in a meta-analysis of manufacturer's data; the overall incidence was similar to that of nonselective NSAIDs.[61] In the CLASS trial, there was one fewer episode of edema, hypertension, or increased creatinine for every 62 patients treated with celecoxib instead of ibuprofen 800mg tid or diclofenac 75 bid. Data on renal events of rofecoxib are less well-reported, there were no differences in the studies that reported these events, but many studies did not report them. As discussed earlier, one head-to-head trial found higher rates of these complications with rofecoxib than with celecoxib.[44]

There is some evidence that meloxicam (7.5mg or 15mg) is better tolerated than nonselective NSAIDs. The meta-analysis of meloxicam studies mentioned earlier found lower rates of any gastrointestinal event, dyspepsia, and withdrawals due to GI events compared with NSAIDs, but as mentioned before it included some inadequately blinded studies; only blinded studies are reliable for assessing withdrawals and attributing the cause of adverse events. The double-blind trial of meloxicam 7.5, 15 and 22.5 mg and diclofenac 75 mg bid mentioned earlier[109] found no significant differences between the treatments in rates of withdrawals due to adverse events or in incidence of overall and gastrointestinal tolerability. In the nabumetone meta-analysis, the incidence of GI adverse events was significantly different (25.3% vs. 28.2%, p=.007), corresponding to about 1 fewer event for every 34 patients treated with nabumetone.

FDA information A warning was added to the valdecoxib product label in Nov, 2002. It was prompted by reports of cases of serious anaphylactic reactions and serious dermatologic adverse events in postmarketing surveillance.[123]

A November, 2003 publication reported that a January, 2003 search of the FDA Adverse Event Reporting System (AERS) found 13 cases of lithium toxicity for rofecoxib and 5 for celecoxib.[124]

Key Question 4. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication is more effective or associated with fewer adverse effects?

An original data meta-analysis of three celecoxib trials found that, in the elderly, celecoxib 200mg/day or 400mg/day and naproxen 1,000mg/day were similar in WOMAC scores and SF-36 scores.[59] For the SF-36, there were no statistically significant differences: naproxen scored better than celecoxib 200mg on four of 10 components of the SF-36, while celecoxib 200mg scored better on six, including general health. Celecoxib 200mg was significantly better than placebo on nine of the 10 components, while naproxen was significantly better than placebo on seven. The study confirmed that, as discussed above, the overall incidence of GI adverse events was lower with celecoxib; the difference was about one event in 20 patients for celecoxib 200mg and one in 10 for celecoxib 400mg.

A July 2003 publication reported results from an open, crossover trial of celecoxib 200 mg and rofecoxib 25 mg in 18 patients with OA, RA, or chronic pain who were stable (three consecutive INRs within 15% of each other) on warfarin therapy.[125] The trial was designed to measure mean change in INR and safety parameters. Similar rates of edema, heart failure and other adverse events were found for celecoxib and rofecoxib.

In most of the published trials, a majority of subjects were women. We did not find any publications focusing on the differential efficacy or safety of coxibs in African-Americans, Hispanics, or other ethnic minorities.

SUMMARY

The table below summarizes the strength of evidence and results for each key question. Publication bias is an issue for all of these questions, because we do not know the complete results of unpublished trials submitted to the FDA or trials that have been done but not published or submitted to the FDA

Table 12. Strength of evidence by key question

Key Question	Level of Evidence	Conclusion
1. In head-to-head comparisons, are there differences in efficacy or safety between different COX-2 inhibitors?	Overall grade: fair. Grade for valdecoxib: poor. There are no head-to-head comparisons involving valdecoxib.	The trials had conflicting results on efficacy and on GI adverse effects. Two trials found that in patients 65 years or older, rates of edema and hypertension were higher for rofecoxib than for celecoxib (Number-needed-to-harm(NNH)) was 21 for edema and 26 for hypertension).
2. Are there differences in efficacy between coxibs and NSAIDS		
a. celecoxib or rofecoxib vs. NSAIDs	Good. Consistent evidence from many published trials.	No difference
b. valdecoxib vs NSAIDs	Fair. (1 published and several unpublished trials)	No difference
c. NSAID vs. NSAID	Good. Consistent evidence from many published trials and several good-quality systematic reviews	No difference

Key Question	Level of Evidence	Conclusion
3. Are there clinically important differences in safety or adverse effects between coxibs, COX-2 selective NSAIDs, nonselective NSAIDs, and the combination of a nonselective NSAID plus antiulcer medication?		
a. Significant GI events (GI bleeding, hospitalization for GI bleeding, symptomatic ulcer disease, perforation of the GI tract, and death).	Good for rofecoxib (1 fair quality RCT)	Rofecoxib significantly reduced symptomatic ulcers and serious ulcer complications in patients with RA. NNT was 62 to prevent one symptomatic ulcer and 191 to prevent one serious complication.
	Fair for celecoxib (subgroup analysis in an RCT; fair quality meta analysis)	Celecoxib did not significantly reduce ulcer complications in a large, fair-to-poor quality trial, but did reduce them in the subgroup of patients who did not take aspirin.
	Insufficient evidence for valdecoxib.	Valdecoxib has not been shown to reduce ulcer complications.
	Fair-poor for nabumetone.	Nabumetone reduced PUBs and hospitalizations in a fair-quality meta-analysis, but the results are unlikely to apply to practice.
	Insufficient for meloxicam.	Meloxicam reduced PUBs poor quality meta-analysis; the results are unlikely to apply to practice.
	Good for misoprostol (1 good-quality RCT)	Misoprostol prevented serious ulcer complications (perforations and gastric outlet obstruction, but not bleeding); NNT 263.
	Good for omeprazole vs. celecoxib. No data for high-dose H2 blockers.	The combination of a PPI plus diclofenac was equivalent to celecoxib. High-dose H2 blockers were associated with fewer endoscopic ulcers, but there are no data regarding serious ulcer complications.
b. Cardiac risk	Fair-quality for rofecoxib.	Rofecoxib: An unplanned endpoint in a good-quality trial found an increased risk of serious thromboembolic events, primarily myocardial infarction, in patients using rofecoxib 50 mg daily. Observational cohort studies of short-term use found no relationship for doses of 25 mg daily or lower.
	Fair-to-poor-quality for celecoxib	Celecoxib: A meta-analyses and a re-analysis of a good-quality trial found no risk, but these analyses were flawed.
	No data for valdecoxib, meloxicam and nabumetone.	

Key Question	Level of Evidence	Conclusion
c.1. Tolerability: discontinuations due to adverse effects	Good. (consistent results from randomized trials)	In all but 1 trial, discontinuations were lower for celecoxib or rofecoxib vs NSAIDs
c. 2. Tolerability: total adverse effects	Fair	In most trials total adverse events were not lower with coxibs. Total serious adverse events were as high or higher for coxibs than for NSAIDs.
c.3. Tolerability: GI adverse effects and GI adverse events leading to discontinuation	Fair-to-good. (celecoxib and rofecoxib, certain measures)	Celecoxib consistently reduced the frequency of GI adverse events vs NSAIDs. NNT to prevent one event was about 20. Rofecoxib reduced the frequency of withdrawals for GI adverse events in one good-quality trial (for overall GI adverse events, data are insufficient).
	Insufficient. (valdecoxib)	
	Fair-to-poor. (meloxicam, nabumetone)	
c.4. Elevated creatinine or blood pressure, edema, CHF, and abnormal LFTs (coxibs vs. nonselective NSAIDs).	Fair	Trial data comparing celecoxib to nonselective NSAIDs are inconsistent. Data comparing rofecoxib and valdecoxib to NSAIDs are insufficient. (see Key Question 1 for coxib vs. coxib comparisons.)
4. Are there differences in efficacy or safety of COX-2 inhibitors in different demographic groups (age, sex, race)?	Good (age, sex). Poor (race).	Most studies included a majority of women. The data that coxibs are safe and efficacious in different racial groups have been presented to the FDA, but no differences have been described in the peer-reviewed literature.

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Table 5. Efficacy in trials of celecoxib versus NSAIDs

Trial	Subjects	Celecoxib doses (mg)	NSAIDs (mg)	Number of subjects*	Duration (weeks)	Aspirin permitted?	Efficacy measures	Results
Ekman	Ankle sprain	400 mg daily	ibuprofen 2400 mg daily	445	10 days	Yes	Pain (VAS); PGA	No difference
Bertin	Acute shoulder pain	400 mg daily	naproxen 100 mg daily	203	14 days	nr	Improvement in maximum pain	No difference
Dougados	Ankylosing spondylitis with flare	100 bid	ketoprofen 100 bid	170	6	?	PGA, Sleep, BASFI	Trend favoring celecoxib
McKenna	OA of the knee with flare	100 bid	diclofenac 50 tid	400	6	Yes	Index joint pain, WOMAC	No difference
Goldstein	OA and RA with no ulcer on EGD; many had a history of GI disease	200 bid	naproxen 500 bid	537	12	Yes	PGA, withdrawals	No difference
Bensen/Zhao	OA of the knee with flare	50, 100, or 200 bid	naproxen 500 bid	1004	12	Yes	PGA, WOMAC, withdrawals	No difference
Simon/Zhao	RA with flare and no ulcer on EGD	100, 200, or 400 bid	naproxen 500 bid	918	12	Yes	PGA, pain, duration of morning stiffness	No difference
Kivitz	OA	100-400 mg daily	naproxen 100 mg daily	1061	12	Yes	PGA, WOMAC	No difference

PGA - patient global asssessment; BASFI - Bath Ankylosing Spondylitis Functional Index; WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; OA - osteoarthritis; RA -rheumatoid arthritis; EGD - esophagogastroduodenoscopy; GI - gastrointestinal; ACR-20 - American College of Rheumatology criteria

HAQ - Health Assessment Questionnaire; FDI - Functional Disability Index

*Excludes subjects randomized to placebo

Table 5. Efficacy in trials of celecoxib versus NSAIDs

Trial	Subjects	Celecoxib doses (mg)	NSAIDs (mg)	Number of subjects*	Duration (weeks)	Aspirin permitted?	Efficacy measures	Results
Simon	RA	100-400 mg bid	naproxen 500 mg bid	1149	12	Yes	PGA; arthritis pain (VAS); complete count of tender/painful joints and swollen joints; duration of morning stiffness; HAQ; FDI	No difference
Emery	RA	200 bid	diclofenac 75 bid	655	24	No	PGA, ACR-20	No difference except significantly more improvement in morning stiffness
Silverstein (CLASS)	OA and RA	400 bid	ibuprofen 800 tid or diclofenac 75 bid	7968	24	Yes	No efficacy measures reported except withdrawal	Not reported

PGA - patient global asssessment; BASFI - Bath Ankylosing Spondylitis Functional Index; WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; OA - osteoarthritis; RA -rheumatoid arthritis; EGD - esophagogastroduodenoscopy; GI - gastrointestinal; ACR-20 - American College of Rheumatology criteria

HAQ - Health Assessment Questionnaire; FDI - Functional Disability Index

*Excludes subjects randomized to placebo

Table 6. Efficacy in trials of rofecoxib versus NSAIDs

Study	Subjects	Rofecoxib doses (mg)	NSAIDs (mg)	Number of subjects*
Niccoli	OA of the hand, hip or knee	25	diclofenac 50 mg tid	90
Chrubasik	Low back pain	12.5	Assalix 1 qid †	228
Acevado	OA, negative FOBT	12.5	diclofenac 50/misoprostol 200 mcg bid	483
Saag	OA of knee or hip and flare (for NSAID users) or acetominophen user. Excluded aspirin 81mg users.	12.5, 25	ibuprofen 800 tid	667
Day	OA of knee or hip and flare (for NSAID users) or acetominophen user.	12.5, 25	ibuprofen 800 tid	735
Truitt	OA of knee or hip	12.5, 25	nambumetone 1500 qd	341
Myllykangas-Luosujarvi	OA of knee or hip	12.5	naproxen 500 tid	944
Lisse	OA of the knee, hop, hand, or spine	25	naproxen 500 tid	5557
Hawkey	OA with no ulcer on EGD	25, 50	ibuprofen 800 tid	581
Laine (044)	OA with no ulcer or esophagitis on EGD	25, 50	ibuprofen 800 tid	565
Bombadier (VIGOR)	RA, negative FOBT	50	naproxen 500 bid	8076
Cannon (035)	OA of knee or hip and flare (for NSAID users) or acetominophen user.	12.5, 25	diclofenac 50 tid	784
Saag	OA of knee or hip and flare (for NSAID users) or acetominophen user. Excluded aspirin 81mg users.	12.5, 25	diclofenac 50 tid	693

OA - osteoarthritis; FOBT - fecal occult blood test; PGA - patient global assessment;
WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis
* Excludes subjects randomized to placebo
** If underlined, for lack of efficacy; otherwise, for all reasons
†Willow bark extract containing 15% salicin, total dose 240mg of salicin a day

Table 6. Efficacy in trials of rofecoxib versus NSAIDs (continued)

Study	Duration (weeks)	Aspirin permitted?	Efficacy measures	Withdrawals**		Other outcomes
				Rofecoxib	NSAIDs	
Niccoli	2	nr	PGA, pain	nr	nr	No difference
Chrubasik	4	Yes	Pain	21%	18.0%	No difference
Acevado	6	No	PGA	7%	10.80%	No difference
Saag	6	No	WOMAC, PGA, pain while walking	7.8% (12.5 mg) 4.0% (25 mg)	8.6%	No difference
Day	6	No	WOMAC, PGA, pain while walking	3.5% (12.5 mg) 2.8% (25 mg)	3%	No difference in 3 primary endpoints, but trend favored rofecoxib 25 mg for 2 of the 3.
Truitt	6	No	PGA, WOMAC	1.7% (12.5 mg) 0% (25 mg)	1.7%	No differences
Myllykangas-Luosujarvi	6	No	PGA, WOMAC	27.20%	28.4%	No difference
Lisse	12	No	PGA, SF-36	11.30%	12.9%	No difference
Hawkey	24	No	PGA	3% (12.5 mg) 1.6% (25 mg)	5%	No difference
Laine (044)	24	No	PGA	3% (12.5 mg) 2.1% (25 mg)	4.9%	No difference
Bombadier (VIGOR)	52	No	PGA	6.30%	6.50%	No difference
Cannon (035)	52	No	WOMAC, PGA, pain while walking	13.9% (12.5 mg) 21.8% (25 mg)	16%	Trend favoring diclofenac for 2 of 3 primary measures
Saag	52	No	WOMAC, PGA, pain while walking	12.1% (12.5 mg) 11.2% (25 mg)	7.0%	No difference

OA - osteoarthritis; FOBT - fecal occult blood test; PGA - patient global assessment;
WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis
* Excludes subjects randomized to placebo
** If underlined, for lack of efficacy; otherwise, for all reasons
†Willow bark extract containing 15% salicin, total dose 240mg of salicin a day

Table 7. Efficacy in trials of NSAIDs versus NSAIDs

Trial	Subjects	Meloxicam doses (mg)	NSAIDs (mg)	Number of subjects*	Duration (weeks)	Aspirin permitted?	Efficacy measures	Withdrawals**		Other outcomes
								Meloxicam	NSAID	
Valat	OA lumbar spine	7.5	diclofenac 100	229	2	unclear	pain on motion	0.0%	0.0%	No difference
Linden§	OA hip	15	piroxicam 20		6					No difference
Hawkey (Melissa)	OA hip, knee, hand, or spine	7.5	diclofenac 100	9323	4	unclear	pain, PGA, withdrawals	**1.7%**	**1.0%**	No difference, trend slightly favored meloxicam
Dequeker (Select) †	OA hip, knee, hand, or spine	7.5	piroxicam 20	8656	4	unclear	pain, PGA, withdrawals	1.7%	1.6%	No difference
Goei The	OA knee	7.5	diclofenac 100	258	6	yes	pain during active movement, PGA, acetominophen use.	3.9%	2.3%	No difference, trend favored meloxicam
Furst	RA	7.5, 15, 22.5	diclofenac 150	894	12	no	PGA, pain, painful/tender joints, physical functioning	25.7% (7.5 mg); 24.5% (15 mg); 20.9% (22.5 mg)	14.4%	No differences
Hosie 1996	OA hip or knee	7.5	diclofenac 100	336	24	unclear	pain, quality of life	4%	4%	No difference
Hosie 1997§	OA hip or knee	15	piroxicam 20	455			overall pain, pain on movement, joint stiffness, global efficacy and quality of life			No difference
Wojtulweski	RA	7.5	naproxen 750	379	24	no	PGA, several others	**23.6%**	**14.4%**	No difference, trend favored naproxen

Bold type - statistically significant; OA - osteoarthritis; PGA - patient global assessment; RA - rheumatoid arthritis

* Excludes subjects randomized to placebo

**If underlined, for lack of efficacy; otherwise for all reasons

§review incomplete at time of draft

†design identical to Hawkey et al

Table 8. Comparison of the VIGOR and CLASS Trials

a) Evidence table

Trial	Sites	Patients	Aspirin use	Definition of significant GI events	Number screened/ enrolled	Number analyzed	Withdrew for lack of efficacy (Coxib group / NSAID groups)*
VIGOR (rofecoxib 50mg qd)	301 centers, 22 countries	RA, over 50	Not allowed	Perforation, obstruction, upper GI bleeding, or symptomatic ulcer	9539/8076	8076	6.3% / 6.5%
CLASS (celecoxib 400mg bid)	386 centers, US and Canada	RA or OA, 18 or older	20%	Perforation, obstruction, upper GI bleeding	9764/8059	7968	12.6% / 14.8%

* In VIGOR, there was no difference

b) Comparison of outcomes

	VIGOR NSAID group**	CLASS NSAID group†	VIGOR NNT	CLASS NNT †
ulcers	0.030	0.011	62	265
perforation	0.001	0.000	no effect	no effect
obstruction	0.000	0.000	no effect	no effect
bleeding from an ulcer	0.008	0.008	268	199
Complicated confirmed UGI events	0.009	0.008	191	199

RA - rheumatoid arthritis; GI - gastrointestinal; OA - osteoarthritis; NNT - number needed to treat; UGI - upper gastrointestinal

**average 9 months of followup

† adjusted to replicate 9 months of followup

Table 10. Tolerability in randomized controlled trials

Trial	Focus	Subjects	Coxib dose	NSAIDs (mg)	Number of subjects*	Duration (weeks)
Celecoxib						
Ekman	efficacy and tolerability	Ankle sprain	400 mg daily	ibuprofen 2400 mg daily	445	10 days
Bertin	efficacy and tolerability	Acute shoulder pain	400 mg daily	naproxen 100 mg daily	203	14 days
Dougados	efficacy	Ankylosing spondylitis with flare	100 bid	ketoprofen 100 bid	170	6
McKenna	efficacy and tolerability	OA of the knee with flare	100 bid	diclofenac 50 tid	400	6
Bensen/Zhao	efficacy	OA of the knee with flare	200 bid	naproxen 500 bid	1004	12
Goldstein	endoscopic ulcers	OA and RA with no ulcer on EGD	200 bid	naproxen 500 bid	537	12
Simon/Zhao	efficacy and endoscopic ulcers	RA with flare and no ulcer on EGD	100, 200, or 400 bid	naproxen 500 bid	918	12
Emery	endoscopic ulcers	RA	200 bid	diclofenac 75 bid	655	24
Silverstein (CLASS)	serious GI events	OA and RA	400 bid	ibuprofen 800 tid or diclofenac 75 bid	7968	24
Kivitz	efficacy and tolerability	OA	100-400 mg daily	naproxen 100 mg daily	1061	12

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; OA - osteoarthritis;
EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis; FOBT-fecal occult blood test; LFT - liver function test
*Excludes subjects randomized to placebo
**inadequately reported

Table 10. Tolerability in randomized controlled trials (continued)

Trial	Withdrawals due to adverse events		Total adverse events		GI adverse events		Elevated creatinine, HTN, CHF, or edema		Comment
	coxib	NSAID	coxib	NSAID	coxib	NSAID	coxib	NSAID	
Celecoxib									
Ekman	<1%	0%	24.0%	27.0%	Total GI nr	Total GI nr	nr	nr	
Bertin	nr	nr	40.4%	44.7%	20.2%	25.2%	nr	nr	
Dougados	6.3%	1.1%	68.0%	60.0%	32.2%	33.8%	nr	nr	
McKenna	7.0%	11.0%	50.0%	54.0%	18.0%	25.0%	5.0%	3.0%	**
Bensen/Zhao	10.0%	8.0%	65.0%	63.0%	24.0%	32.0%	4.0%	1.0%	
Goldstein	7.0%	9.0%	70.0%	70.0%	34.0%	40.0%	nr	nr	
Simon/Zhao	5.5%	5.3%	62%-68%	65.0%	26.0%	31.0%	2.0%	2.0%	
Emery	nr	nr	68.0%	73.0%	36.0%	48.0%	nr	nr	5 NSAID patients admitted for adverse events. Lower hematocrits and higher LFTs in the NSAID group.
Silverstein (CLASS)	18.4%	20.6%	48.5%	56.8%	31.4%†	36.8%	5%†	6.6%	
Kivitz	8% (100 mg); 13% (200 mg); 12% (400 mg)	14%	58% (100 mg); 66% (200 mg); 62% (400 mg)	63.0%	17% (100mg); 29% (200mg); 30% (400mg)	35.0%	Edema 1% (100mg); 1% (200mg); 5% (400mg)	Edema 3%	

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; OA - osteoarthritis;
EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis; FOBT-fecal occult blood test; LFT - liver function test
*Excludes subjects randomized to placebo
**inadequately reported

Table 10. Tolerability in randomized controlled trials (continued)

Trial	Focus	Subjects	Coxib dose	NSAIDs (mg)	Number of subjects*	Duration (weeks)
Simon	efficacy and tolerability	RA	100-400 mg bid	naproxen 500 mg bid	1149	12
Rofecoxib						
Niccoli	tolerability	OA of hand, hip or knee	25 mg	diclofenac 50 tid	90	2
Acevado	adverse events	OA, negative FOBT	12.5 mg	diclofenac 50 mg/misoprostol 200 mcg bid	483	6
Saag	efficacy and tolerability	OA of knee or hip with flare (for NSAID users) or acetominophen user. Excluded aspirin 81mg users.	25 mg	ibuprofen 800 tid	667	6
Day	efficacy and tolerability	OA of knee or hip with flare (for NSAID users) or acetominophen user	25	ibuprofen 800 tid	735	6
Truitt	efficacy and tolerability	OA knee or hip with flare, >80 years old	25	nabumetone 1500	250	6

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; OA - osteoarthritis;
EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis; FOBT-fecal occult blood test; LFT - liver function test
*Excludes subjects randomized to placebo
**inadequately reported
§ Reported GI adverse events leading to discontinuation, but did not report total GI adverse events
†statistically significant

Table 10. Tolerability in randomized controlled trials (continued)

Trial	Withdrawals due to adverse events		Total adverse events		GI adverse events		Elevated creatinine, HTN, CHF, or edema		Comment
	coxib	NSAID	coxib	NSAID	coxib	NSAID	coxib	NSAID	
Simon	5% (100mg); 7% (200mg); 6% (400mg)	5%	68% (100mg); 63% (200 mg); 62% (400mg)	65.0%	28% (100mg); 25% (200mg); 26% (400mg)	31.0%	Edema 1% (100mg); 2% (200mg); 2% (200mg) HTN 0% (100mg); <1% (200mg); <1% (400mg)	Edema 2% HTN <1%	
Rofecoxib									
Niccoli	11.7%	3.2%	33.3%¦	26.6%¦	nr	nr	24%‖, nr, nr, nr	5.7%‖, nr, nr, nr	
Acevado	4.1%	9.1%	52.9%†	73.0%	28.9%	48.5%	nr	nr	
Saag	no difference (numbers not given)		nr	nr	3.5%	3.2%	5.3%	2.3%	
Day	3.7%	8.4%	53.3%	51.8%	higher for NSAID (numbers not given)		no difference (numbers not given)		
Truitt	8.9%	7.0%	nr	nr	nr	nr	incompletely reported; probably no difference.		

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; OA - osteoarthritis;
EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis; FOBT-fecal occult blood test; LFT - liver function test
*Excludes subjects randomized to placebo
**inadequately reported
§ Reported GI adverse events leading to discontinuation, but did not report total GI adverse events
†statistically significant

Table 10. Tolerability in randomized controlled trials (continued)

Trial	Focus	Subjects	Coxib dose	NSAIDs (mg)	Number of subjects*	Duration (weeks)
Myllykangas-Luosujarvi	efficacy and tolerability	OA of the knee or hip	12.5	naproxen 500 bid	944	6
Lisse	efficacy and tolerability	OA of the knee, hip, hand, or spine	25	naproxen 500 bid	5557	12
Hawkey	tolerability	RA	50	naproxen 500 bid	660	12
Hawkey	endoscopic ulcers	OA with no ulcer on EGD	25	ibuprofen 800 tid	581	18
Laine (044)	endoscopic ulcers	OA with no ulcer or esophagitis on EGD	25, 50	ibuprofen 800 tid	565	24
Bombadier (VIGOR)	serious GI events	RA, negative FOBT	50	naproxen 500 bid	8076	52
Cannon (035)	efficacy	OA of knee or hip with flare (for NSAID users) or acetominophen user	25	diclofenac 50 tid	784	52
Saag	efficacy and tolerability	OA of knee or hip with flare (for NSAID users) or acetominophen user. Excluded aspirin 81 mg users.	25	diclofenac 50 tid	693	52
Valdecoxib						
Makarowski	efficacy and tolerability	OA of the hip	5, 10	naproxen 500 bid	349	12
Pavelka	efficacy and tolerability	RA	20, 40	diclofenac 75 mg SR bid	722	26

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; OA - osteoarthritis;
EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis; FOBT-fecal occult blood test; LFT - liver function test
*Excludes subjects randomized to placebo

Table 10. Tolerability in randomized controlled trials (continued)

Trial	Withdrawals due to adverse events		Total adverse events		GI adverse events		Elevated creatinine, HTN, CHF, or edema		Comment
	coxib	NSAID	coxib	NSAID	coxib	NSAID	coxib	NSAID	
Myllykangas-Luosujarvi	nr	nr	43.3%	48.2%	13.4%†	24.1%	nr; 1.9%; nr; 3.4%(lower extremity), 0.2% (peripheral)	nr; 1.7%; nr; 2.3%(lower extremity), 1.4% (peripheral)	
Lisse	nr	nr	30.0%	30.0%	5.9%§†	8.1%§	nr, 2.9%, nr, 3.5%	nr, 2.4%, nr, 3.8%	
Hawkey	5%†	9.1%	62.1%	66.4%	3.7%§	6.8%§	nr, 6.4%, 0.5%, 1.4%	nr, 0.9%, 0.0%, 0.0%	
Hawkey	5.6%	9.8%	80.1%	80.0%	no difference		nr	nr	
Laine (044)	10.3%	14.0%	78.3%	74.7%	nr	nr	nr	nr	
Bombadier (VIGOR)	16,4%	16.1%			3.5%§†	4.9%	1.2%	0.9%	
Cannon (035)	12.5%	15.3%	84.0%	86.2%	no difference (numbers not given)		no differences		
Saag	significantly higher for NSAID (numbers not given)		nr	nr	5.2%	8.3%	no difference (numbers not given)		Discontinuation for elevated ALT higher in NSAID group.
Valdecoxib									
Makarowski	9%	12.70%	53%	60.20%	no difference		nr	nr	
Pavelka	9.8%, 10.5%	15.20%	67%, 65%	73.0%	39.4%†, 40.1%	49.4%	nr	nr	

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; OA - osteoarthritis;

EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis; FOBT-fecal occult blood test; LFT - liver function test

*Excludes subjects randomized to placebo

Table 11. Tolerability in trials of meloxicam vs. NSAID

Trial	Focus	Subjects	Meloxicam dose	NSAIDs (mg)	Number of subjects*	Duration (weeks)
Furst	efficacy and tolerability	RA	7.5, 15, 22.5	diclofenac 150	894	12

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; RA - rheumatoid arthritis

Table 11. Tolerability in trials of meloxicam vs. NSAID (continued)

Trial	Withdrawals due to adverse events		Total adverse events		GI adverse events		Elevated creatinine, HTN, CHF, or edema	
	Meloxicam	Other NSAID	Meloxicam	Other NSAID	Meloxicam	Other NSAID	Meloxicam	Other NSAID
Furst	10.3%, 7.6%, 8.5%	11%	56%, 58.2%, 62.1%	61.90%	25.7%, 27.2%, 27.1%	32%	nr	nr

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; RA - rheumatoid arthritis

Evidence Table 1. Characteristics and results of head to head randomized trials of coxibs

Author Year (Quality Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period	Allowed other medications/ interventions
Bianchi 2003 (Fair)	Outpatients aged 18 years or older were eligible to participate in the study if they fulfiled the American College of Rheumatology criteria for a diagnosis of OA evident for 3 months or longer; visual analogue scale (VAS) score of 40mm for the basal assessment of pain associated with walking	Nimesulide 100 mg Celecoxib 200 mg Rofecoxib 25 mg 7 days	None	Paracetamol 500 mg daily
Gibofsky 2003 (Fair)	Adults (≥40 years old) with OA of the knee, diagnosed accordine to ACR criteria; functional capacity class rating of I, II, or III at the time of screening; OA in a flare state at baseline	Celecoxib 200 mg Rofecoxib 25 mg Placebo 6 weeks	2-14 day washout for patients receiving NSAIDs or analgesic therapy at screening	Aspirin ≤ 325 mg daily Occasional use of acetaminophen Antacids

NR = not reported

Evidence Table 1. Characteristics and results of head to head randomized trials of coxibs (continued)

Author Year (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Bianchi 2003 (Fair)	Pain intensity (rated on 10-cm VAS scale with endpoints 'no pain' and 'worst pain') x 0.25, 0.5, 1, 2, 3 and 12 hours post-dose Total pain relief over 3 hours (TOPAR3) post-dose=sum of pain relief scores over 3 hours Global assessment of analgesic efficacy questionnaire (5-point scale: none, mild, moderate, good, very good) at day 7 Rescue medication use at 12 hours post-dose	Mean age=69.0 (SEM=1.18) 90% female Ethnicity nr	Mean OA duration nr Baseline basal VAS range: 42-95mm	NR/NR/30	1(3.2%) withdrawn/0/nr
Gibofsky 2003 (Fair)	OA pain (100 mm visual analog scale (VAS)): Weeks 3 and 6 Pain on walking (100 mm VAS): Weeks 3 and 6 Patient/Physician Global Assessment of arthritis (1=very good to 5=very poor): Weeks 3 and 6 OA severity index (0-24 with lower scores indicating a better condition): Weeks 3 and 6 Western Ontario and McMaster Universities Osteoarthritis (WOMAC): Weeks 3 and 6 Patient satisfaction assessment (scale of 1=very dissatisfied to 10=very satisfied): Week 6	Mean age=62.9 67.1% female Ethnicity NR	Mean OA duration 8.6 years Baseline OA pain score (mean VAS): 70.8	NR/NR/477	94(19.7%) withdrawn/2(0.4%) lost to fu/475 analyzed

Evidence Table 1. Characteristics and results of head to head randomized trials of coxibs (continued)

Author Year (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Bianchi 2003 (Fair)	Mean VAS at days 1 and 7 (at 15, 30, 60, 120, and 180 minutes post-dose): celecoxib=rofecoxib TOPAR: celecoxib=rofecoxib Global assessment of analgesic efficacy(% patients with ratings of 'good' or 'very good'): celecoxib=46.7%, rofecoxib=50%; NS Rescue medication use (% patients with use of >/= 1 tablet in 7 days): celecoxib=13.3%, rofecoxib=13.3%; NS	Tolerability questionnaire (5-point scale: very poor, poor, fair, good, very good) on day 7	Tolerability (% patients with 'good' or 'excellent' ratings): celecoxib=70%, rofecoxib=76.7%; NS	NR
Gibofsky 2003 (Fair)	Arthritis pain (mean change from baseline): celecoxib= -34.0 mm, rofecoxib= -31.6 mm; NS WOMAC (mean change from baseline): celecoxib= -22.1, rofecoxib= -20.1; NS Rescue medication use (% patients): celecoxib=6.4%, rofecoxib=6.8%; NS Pain on walking (mean change from baseline in VAS): celecoxib= -31.5, rofecoxib= -29.2; NS Patient global assessment (% reduced by at least 2 grades): celecoxib=48%; rofecoxib=43%; NS Physician global assessment (% reduced by at least 2 grades): celecoxib=49%, rofecoxib=43%; NS	NR	Any adverse event: celecoxib=43%; rofecoxib=42%	Adverse event causing withdrawal: celecoxib=6%; rofecoxib=5%

Evidence Table 1a. Quality assessment of head to head randomized controlled trials of coxibs

Internal Validity

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?
Bianchi 2003	Yes	NR	N/A-crossover	Yes	NR	NR	NR	NR	No/No	No
Gibofsky 2003	Yes	NR	Yes	Yes	NR	NR	NR	NR	No/No	ITT analysis excluded 2 patients that did not take study medication

Evidence Table 1a. Quality assessment of head to head randomized controlled trials of coxibs (continued)

Internal Validity ***External Validity***

Author Year	Post-randomization exclusions?	Quality Rating	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Bianchi 2003	No	Fair	nr/nr/31	Concurrent arthritic disease or laboratory test results outside normal reference ranges, a history of allergy to study drugs or hypersensitivity to any other NSAID; gastrointestinal tract ulceration within 30 days of receiving study medication; bleeding disorders	No	No	Yes	NR	Yes
Gibofsky 2003	No	Fair	nr/nr/477	Inflammatory arthritis or acute joint trauma in the index knee; recent corticosteroid (previous 8 weeks) or hyaluronic acid (previous 6 months) injection; NSAID use within previous 2 days; active malignancy or a history of mmalignancy; upper gastrointestinal ulceration within the past 30 days; active GI disease; chronic or acute renal or hepatic disorder, or significant coagulation defect	No/Yes	No	Yes	Pharmacia	Yes

Appendix A.

Table 1. Cyclooxygenase Selectivity of 25 Nonsteroidal Anti-Inflammatory Drugs*

Nonsteroidal Anti-Inflammatory Drug	Ratio†	Reference‡
Flurbiprofen	10.27	4, 20, 21
Ketoprofen	8.16	4
Fenoprofen	5.14	4
Tolmetin	3.93	4, 20
Aspirin	3.12	4
Oxaprosin	2.52	4
Naproxen	1.79	4, 20, 21
Indomethacin	1.78	4, 20, 21
Ibuprofen	1.69	4
Ketorolac	1.64	4, 20, 21
Piroxicam	0.79	4, 20, 21
Nabumetone, 6-MNA	0.64	4, 21
Etodolac	0.11	4, 25
Celecoxib	0.11	Cryer B, Feldman M. Unpublished data
Meloxicam	0.09	21
Mefenamic acid	0.08	4
Flurbinitroxybutylester	0.08	22
NS-398	0.07	4, 20
Diclofenac	0.05	4, 20, 21
DuP-697	0.05	20
Rofecoxib	0.05	19
Nimesulide	0.04	4
Flosulide (CGP 28238)	0.02	20
SC-58125	0.007	20, 21
L-745,337	0.004	23

* Modified from reference 4.
† Expressed as the ratio of the 50% inhibitory concentration of cyclooxygenase-2 to the 50% inhibitory concentration of cyclooxygenase-1 in whole blood. Nonsteroidal anti-inflammatory drugs with a ratio <1 indicate selectivity for cyclooxygenase-2.
‡ If more than one study determined a ratio, the median ratio was used.

From:

Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? Annals of Internal Medicine 2000;132:134-43.

Appendix B. Search strategies

Ovid Technologies, Inc. Email Service

Search for: 13 and (200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).ed.
Citations: 1-22

Database: Ovid MEDLINE(R) <1996 to January Week 1 2004>
Search Strategy:
---
1 rofecoxib.mp. (701)
2 celecoxib.mp. (928)
3 valdecoxib.mp. (75)
4 meloxicam.mp. (374)
5 1 or 2 or 3 or 4 (1671)
6 limit 5 to (human and english language) (1100)
7 exp Randomized Controlled Trials/ (21953)
8 "Clinical Trial [Publication Type]"/ (0)
9 "Review [Publication Type]"/ (0)
10 Meta-Analysis/ (3140)
11 7 or 10 (24161)
12 5 and 11 (102)
13 limit 12 to (human and english language) (76)
14 13 and (200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).ed. (22)
15 from 14 keep 1-22 (22)

Ovid Technologies, Inc. Email Service

Search for: 5 and 18
Citations: 1-2

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 14, 2004>
Search Strategy:
---
1 rofecoxib.mp. (75)
2 celecoxib.mp. (105)
3 valdecoxib.mp. (12)
4 meloxicam.mp. (25)
5 1 or 2 or 3 or 4 (176)
6 limit 5 to (human and english language) [Limit not valid; records were retained] (166)
7 [exp Randomized Controlled Trials/] (0)

8 ["Clinical Trial [Publication Type]"/] (0)
9 ["Review [Publication Type]"/] (0)
10 [Meta-Analysis/] (0)
11 7 or 10 (0)
12 5 and 11 (0)
13 limit 12 to (human and english language) [Limit not valid; records were retained] (0)
14 13 and (200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).ed. (0)
15 randomized controlled trial.mp. [mp=title, abstract] (316)
16 controlled clinical trial.mp. [mp=title, abstract] (80)
17 meta-analysis.mp. [mp=title, abstract] (467)
18 15 or 16 or 17 (854)
19 5 and 18 (2)
20 from 19 keep 1-2 (2)

Ovid Technologies, Inc. Email Service

Search for: 5
Citations: 1-266

Database: CCTR, CDSR
Search Strategy:
---
1 rofecoxib.mp. (93)
2 celecoxib.mp. (78)
3 valdecoxib.mp. (20)
4 meloxicam.mp. (102)
5 1 or 2 or 3 or 4 (266)
6 limit 5 to (human and english language) [Limit not valid in: CCTR,CDSR; records were retained] (266)
7 exp Randomized Controlled Trials/ (4161)
8 "Clinical Trial [Publication Type]"/ (0)
9 "Review [Publication Type]"/ (0)
10 Meta-Analysis/ (138)
11 7 or 10 (4247)
12 5 and 11 (1)
13 limit 12 to (human and english language) [Limit not valid in: CCTR,CDSR; records were retained] (1)
14 13 and (200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).ed. (0)
15 randomized controlled trial.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (15521)
16 controlled clinical trial.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (3745)
17 meta-analysis.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (2789)
18 15 or 16 or 17 (21162)
19 5 and 18 (36)

20 from 19 keep 1-2 (2)
21 5 (266)
22 from 21 keep 1-266 (266)

Database: EMBASE Drugs & Pharmacology <1991 to 1st Quarter 2004>
Search Strategy:
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1 'rofecoxib'/exp 2,186
2 'valdecoxib'/exp 232
3 'celecoxib'/exp 2,784
4 'meloxicam'/exp 1,107
5 random* OR control* 2,867,144
6 #1 OR #2 OR #3 OR #4 4,266
7 #5 AND #6 AND [clinical trial]/lim AND [english]/lim AND [humans]/lim 590
8 #7 AND [01-05-2003]/sd 99 hits

Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of

study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix D. Excluded trial publications

Blardi P, Gatti F, Auteri A, et al. Effectiveness and tolerability of nimesulide in the treatment of osteoarthritic elderly patients. International Journal of Tissue Reactions 1992;14(5):263-268.

Burke TA, Zabinski RA, Pettitt D, et al. A framework for evaluating the clinical consequences of initial therapy with NSAIDs, NSAIDs plus gastroprotective agents, or celecoxib in the treatment of arthritis. Pharmacoeconomics 2001;19(SUPPL. 1):33-47.

Calligaris A, Scaricabarozzi I and Vecchiet L. A multicentre double-blind investigation comparing nimesulide and naproxen in the treatment of minor sport injuries. Drugs 1993;46(SUPPL.1):187-190.

Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. New England Journal of Medicine 2001;345(25):1809-17.

Ding C, Xu S and Li C. A randomized, controlled clinical trial of nimesulide in the treatment of 171 cases of rheumatoid anthritis. [Korean]. Chinese Pharmaceutical Journal 1998;33(12):752-755.

Dreiser RL and Riebenfeld D. A double-blind study of the efficacy of nimesulide in the treatment of ankle sprain in comparison with placebo. Drugs 1993;46(SUPPL.1):183-186.

Dreiser RL and Riebenfeld D. Nimesulide in the treatment of osteoarthritis: Double-blind studies in comparison with piroxicam, ketoprofen and placebo. Drugs 1993;46(SUPPL.1):191-195.

Ehrich EW, Bolognese JA, Watson DJ, et al. Effect of rofecoxib therapy on measures of health-related quality of life in patients with osteoarthritis. American Journal of Managed Care 2001;7(6):609-616.

Ehrich EW, Schnitzer TJ, McIlwain H, et al. Effect of specific COX-2 inhibition in osteoarthritis of the knee: A 6 week double blind, placebo controlled pilot study of rofecoxib. Journal of Rheumatology 1999;26(11):2438-2447.

Kapicioglu S, Baki AH, Sari M, et al. Does nimesulide induce gastric mucosal damage? 'A double-blind randomized placebo-controlled trial'. Hepato Gastroenterology 2000;47(34):1183-1185.

Kellner H. Selective cox-2-inhibition by rofecoxib reduces the risk of severe gastrointestinal complications by 50%. [German]. Zeitschrift fur Gastroenterologie 2001;39(5):443-445.

Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis & Rheumatism 2000;43(7):1478-1487.

Leese PT, Hubbard RC, Karim A, et al. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: A randomized, controlled trial. Journal of Clinical Pharmacology 2000;40(2):124-132.

Lemmel EM, Bolten W, Burgos-Vargas R, et al. Efficacy and safety of meloxicam in patients with rheumatoid arthritis. Journal of Rheumatology 1997;24(2):282-290.

Lipsky PE and Isakson PC. Outcome of specific COX-2 inhibition in rheumatoid arthritis. Journal of Rheumatology 1997;24(SUPPL. 49):9-14.

Lucker PW, Pawlowski C, Friederich I, et al. Double-blind, randomised, multi-centre clinical study evaluating the efficacy and tolerability of nimesulide in comparison with etodalac in patients suffering from osteoarthritis of the knee. European Journal of Rheumatology & Inflammation 1994;14(2):29-38.

Lund B, Distel M and Bluhmki E. A double-blind, randomized, placebo-controlled study of efficacy and tolerance of meloxicam treatment in patients with osteoarthritis of the knee. Scandinavian Journal of Rheumatology 1998;27(1):32-37.

Mandell BF. Cox-2 inhibitors and cardiovascular risk: point and counterpoint. Cleveland Clinic Journal of Medicine 2001;68(11):957-60.

Patoia L, Santucci L, Furno P, et al. A 4-week, double-blind, parallel-group study to compare the gastrointestinal effects of meloxicam 7.5 mg, meloxicam 15 mg, piroxicam 20 mg and placebo by means of faecal blood loss, endoscopy and symptom evaluation in healthy volunteers. British Journal of Rheumatology 1996;35(SUPPL. 1):61-67.

Porto A, Reis C, Perdigoto R, et al. Gastroduodenal tolerability of nimesulide and diclofenac in patients with osteoarthritis. Current Therapeutic Research, Clinical & Experimental 1998;59(9):654-665.

Quattrini A and Paladin S. A double-blind study comparing nimesulide with naproxen in the treatment of osteoarthritis of the hip.

Clinical Drug Investigation 1995;10(3):139-146.

Sad Neto M. Treatment of mechanical dorsolumbar pain: A double blind, randomized, comparative study of nimesulide and naproxene. [Portuguese]. Revista Brasileira de Medicina 1995;52(3):220-225.

Sarzi-Puttini P, Santandrea S, Boccassini L, et al. The role of NSAIDs in psoriatic arthritis: Evidence from a controlled study with nimesulide. Clinical & Experimental Rheumatology 2001;19(1 SUPPL. 22):S17-S20.

Schnitzer TJ, Truitt K, Fleischmann R, et al. The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis. Clinical Therapeutics 1999;21(10):1688-1702.

Shah AA, Thjodleifsson B, Murray FE, et al. Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: A comparison of nimesulide and naproxen. Gut 2001;48(3):339-346.

Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor. Efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis & Rheumatism 1998;41(9):1591-1602.

Swan SK, Rudy DW, Lasseter KC, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. [see comments.]. Annals of Internal Medicine 2000;133(1):1-9.

Valdes EF. Comparative evaluation of nimesulide in the treatment of low back pain. [Spanish]. Prensa Medica Argentina 1992;79(7):469-473.

Williams GW, Egglinger RE, Ruderman EM, et al. Treatment of Osteoarthritis with a once-daily dosing regimen of celecoxib. J Clin Rheumatol 2000;6(2):65-74.

Williams GW, Hubbard RC, Yu SS, et al. Comparison of once-daily and twice-daily administration of celecoxib for the treatment of osteoarthritis of the knee. Clinical Therapeutics 2001;23(2):213-227.

Wober W, Rahlfs VW, Buchl N, et al. Comparative efficacy and safety of the nonsteroidal anti-inflammatory drugs nimesulide and diclofenac in patients with acute subdeltoid bursitis and bicipital tendinitis. International Journal of Clinical Practice 1998;52(3):169-175.

Yocum D, Fleischmann R, Dalgin P, et al. Safety and efficacy of meloxicam in the treatment of osteoarthritis: A 12-week, double-blind, multiple-dose, placebo-controlled trial. Archives of Internal Medicine 2000;160(19):2947-2954.

Figure 1. Results of literature search