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Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review

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Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design and/or methodologic approaches do not necessarily represent the views of individual technical and content experts.

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Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review

Structured Abstract

Objectives: To update a previous report on the comparative benefits and harms of oral non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Data Sources: Ovid MEDLINE (1996–January 2011), the Cochrane Database (through fourth quarter 2010), and reference lists.

Review Methods: We included randomized trials, cohort studies, case-control studies, and systematic reviews that met predefined inclusion criteria. For each study, investigators abstracted details about the study population, study design, data analysis, followup, and results, and they assessed quality using predefined criteria. We assessed the overall strength of each body of evidence using predefined criteria, which included the type and number of studies; risk of bias; consistency; and precision of estimates. Meta-analyses were not performed, though pooled estimates from previously published studies were reported.

Results: A total of 273 studies were included. Overall, we found no clear differences in efficacy for pain relief associated with different NSAIDs. Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) compared to nonselective NSAIDs. Coprescribing of proton pump inhibitors, misoprostol, and H2-antagonists reduce the risk of endoscopically detected gastroduodenal ulcers compared to placebo in persons prescribed NSAIDs. Celecoxib and most nonselective, nonaspirin NSAIDs appeared to be associated with an increased risk of serious cardiovascular (CV) harms. There was no clear association between longer duration of NSAID use or higher doses and increased risk of serious CV harms. There were no clear differences between glucosamine or chondroitin and oral NSAIDs for pain or function, though evidence from a systematic review of higher-quality trials suggests that glucosamine had some very small benefits over placebo for pain. Head-to-head trials showed no difference between topical and oral NSAIDs for efficacy in patients with localized osteoarthritis, lower risk of gastrointestinal (GI) adverse events, and higher risk of dermatological adverse events, but serious GI and CV harms were not evaluated. No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs.

Conclusions: Each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. Choosing the optimal analgesic for an individual with osteoarthritis requires careful consideration and thorough discussion of the relevant tradeoffs.

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Executive Summary

Background

Osteoarthritis is a chronic condition involving degeneration of cartilage within the joints. It is the most common form of arthritis and is associated with pain, substantial disability, and reduced quality of life.[1] Surveys indicate that 5 to 17 percent of United States (U.S.) adults have symptomatic osteoarthritis of the knee, and 9 percent have symptomatic osteoarthritis of the hip.[2] Osteoarthritis is more common with older age. The total costs for arthritis, including osteoarthritis, may be greater than 2 percent of the gross domestic product, with more than half of these costs related to work loss.[3, 4]

Common oral medications for osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Patients with osteoarthritis also use topical agents, and over-the-counter oral supplements not regulated by the U.S. Food and Drug Administration (FDA) as pharmaceuticals, including glucosamine and chondroitin.[5] Opioid medications are also used for selected patients with refractory, chronic pain but are associated with special considerations related to their potential for addiction and abuse and were not included in this review.[6-8] Each class of medication or supplement included in this review is associated with a unique balance of risks and benefits. In addition, benefits and harms may vary for individual drugs within a class. Nonpharmacologic interventions (such as physical therapy, weight reduction, and exercise) also help improve pain and functional status in patients with osteoarthritis, but were outside the scope of this review.[5]

A challenge in treating osteoarthritis is deciding which medications will provide the greatest symptom relief with the least harm. NSAIDs decrease pain, inflammation, and fever by blocking cyclooxygenase (COX) enzymes. NSAIDs are thought to exert their effects primarily through blocking different COX isoenzymes, in particular COX-1 and COX-2. COX-1 mediates the mucosal protection of the gastrointestinal mucosa, including protection from acid and platelet aggregation. COX-2 is found throughout the body, including joint and muscle, and mediates effects on pain and inflammation. By blocking COX-2, NSAIDs reduce pain compared with placebo in patients with arthritis,[9] low back pain,[10] minor injuries, and soft-tissue rheumatism. However, NSAIDs that also block the COX-1 enzyme (also called "nonselective NSAIDs") can cause gastrointestinal (GI) bleeding. The number of deaths in the United States due to use of non-aspirin NSAIDs is not known with certainty. One study estimated the number at 3,200 annually in the 1990s[11], though other studies have reported higher estimates. Theoretically, NSAIDs that block only the COX-2 enzyme (also called "coxibs," "COX-2 selective NSAIDs," or "selective NSAIDs") should be safer with regard to GI bleeding, but were found to increase the risk of serious cardiovascular (CV) and other adverse events.

For this report, we defined the terms "selective NSAIDs" or "COX-2 selective NSAIDs" as drugs in the "coxib" class (celecoxib, rofecoxib, valdecoxib, etoricoxib, and lumiracoxib). We defined "partially selective NSAIDs" as other drugs shown to have partial in vitro COX-2 selectivity (meloxicam, etodolac, and nabumetone). However, whether partially selective NSAIDs are truly different from nonselective NSAIDs is unclear because COX-2 selectivity may be lost at higher doses and the effects of in vitro COX-2 selectivity on clinical outcomes are uncertain. Aspirin differs from other NSAIDs because it irreversibly inhibits platelet aggregation, and we considered the salicylic acid derivatives (aspirin and salsalate) a separate

subgroup. We defined "non-aspirin, nonselective NSAIDs" or simply "nonselective NSAIDs" as "all other NSAIDs."

The Agency for Healthcare Research and Quality (AHRQ) funded a comparative effectiveness review (CER) of analgesics for osteoarthritis that was published in 2006.[12] Since that time, additional research has become available to better understand the comparative efficacy and safety of oral and topical medications for osteoarthritis, and a study[13] commissioned by AHRQ on the need to update CERs assigned high priority to the previous report on analgesics for osteoarthritis based on an assessment of the number of potentially outdated conclusions and ongoing issues related to safety.

Objectives

The purpose of this comparative effectiveness review is to update the previous report[12] that assessed the comparative efficacy and safety of nonopioid oral medications (selective and nonselective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

The following Key Questions are the focus of our report:

Key Question 1

What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?

How do these benefits and harms change with dosage and duration of treatment?

The only benefits considered here are improvements in osteoarthritis symptoms. Evidence of harms associated with the use of NSAIDs includes studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.

Oral agents include:

- COX-2 selective NSAIDs:
  - o Celecoxib
- Partially selective NSAIDs:
  - o Etodolac
  - o Meloxicam
  - o Nabumetone
- Non-aspirin, nonselective NSAIDs:
  - o Diclofenac
  - o Diflunisal
  - o Fenoprofen
  - o Flurbiprofen
  - o Ibuprofen
  - o Indomethacin
  - o Ketoprofen
  - o Ketorolac
  - o Meclofenamate sodium
  - o Mefenamic acid
  - o Naproxen
  - o Oxaprozin

- o Piroxicam
- o Sulindac
- o Tolmetin
- Aspirin and salsalate:
  - o Aspirin
  - o Salsalate
- Acetaminophen and supplements:
  - o Acetaminophen
  - o Chondroitin
  - o Glucosamine

Key Question 2

Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients?

- Demographic subgroups: age, sex, and race
- Coexisting diseases: cardiovascular conditions, such as hypertension, edema, ischemic heart disease, heart failure, peptic ulcer disease, history of previous gastrointestinal bleeding (any cause), renal disease, hepatic disease, diabetes, obesity
- Concomitant medication use: antithrombotics, corticosteroids, antihypertensives, selective serotonin reuptake inhibitors (SSRIs).

Key Question 3

What are the comparative effects of coprescribing H2 receptor antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?

Key Question 4

What are the comparative benefits and harms of treating osteoarthritis with oral medications compared with topical preparations, or of different topical medications compared with one another?

For this comparative effectiveness review update, changes have been made to clarify the Key Questions, but these changes do not alter the meaning of each Key Question. Additional coexisting diseases and concomitant medications were included.

Analytic Framework

The analytic framework (Figure A) depicts the Key Questions within the context of the populations, interventions, comparators, outcomes, timing, and setting (PICOTS). In general, the figure illustrates how the nonopioid oral medications, over- the-counter supplements, and topical agents may result in outcomes such as improvements in osteoarthritis symptoms. Also, adverse events may occur at any point after the treatment is received.

Figure A. Analytic framework

Selection of candidates for therapy

Use of medications to treat osteoarthritis

Adults with osteoarthritis

Appropriate candidates for therapy

Not appropriate candidates for therapy

1, 2, 4

1, 3

Improvements in osteoarthritis symptoms

Adverse effects of medications
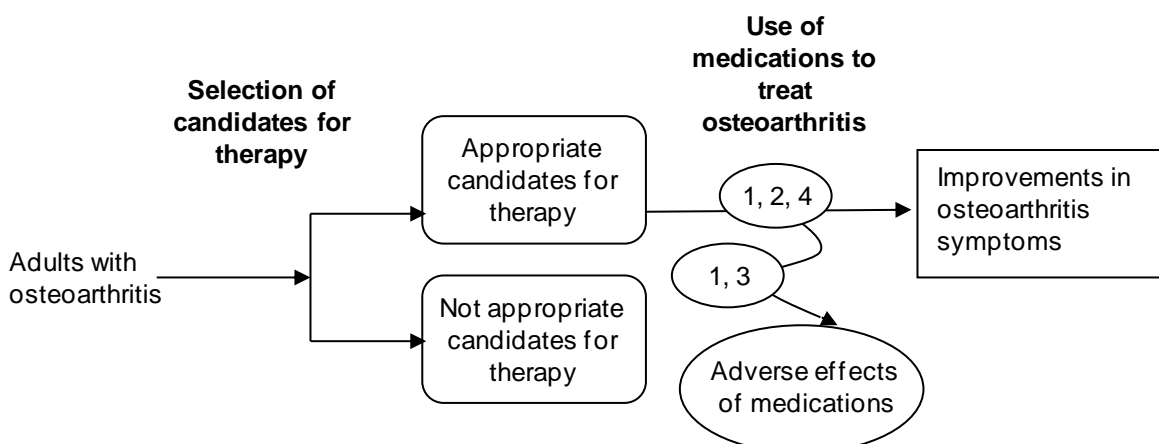
Methods

Input From Stakeholders

The topic for the original 2006 report[12] was nominated in a public process. The Key Questions for that report were developed by investigators from the Evidence-based Practice Center (EPC) with input from a Technical Expert Panel (TEP), which helped refine Key Questions, identify important issues, and define parameters for the review of evidence.

For the present report update, AHRQ proposed the same scope and Key Questions to the EPC. The EPC modified the Key Questions and list of included drugs after receiving input from a new TEP convened for this report update. Before participating in official TEP activities for this report, the TEP members disclosed all financial or other potential conflicts of interest with the topic and included drugs. The authors and the AHRQ Task Order Officer reviewed these conflicts and determined whether the disclosed potential conflicts of interest would compromise the report. The final TEP panel consists of individuals who did not have significant conflicts of interest.

Data Sources and Selection

We replicated the comprehensive search of the scientific literature conducted for the original CER, with an updated date range of 2005 to present to identify relevant studies addressing the Key Questions. We searched the Cochrane Database of Systematic Reviews (through January 2011) the Cochrane Central Register of Controlled Trials (through fourth quarter 2010) and Ovid MEDLINE (2005– January 2011). We used relatively broad searches, combining terms for drug names with terms for relevant research designs, limiting to those studies that focused on osteoarthritis and rheumatoid arthritis. Other sources include selected grey literature provided to the EPC by the Scientific Resource Center librarian, reference lists of review articles, and citations identified by public reviewers of the Key Questions. Pharmaceutical manufacturers were invited to submit scientific information packets, including citations and unpublished data.

We developed criteria for inclusion and exclusion of studies based on the Key Questions and the PICOTS approach. Abstracts were reviewed using abstract screening criteria and a two-pass process to identify potentially relevant studies. For the first pass, the abstracts were divided between three investigators. In the second pass, a fourth investigator reviewed all abstracts not

selected for inclusion in the first pass. Two investigators then independently reviewed all potentially relevant full text using a more stringent set of criteria for inclusion and exclusion.

As specified in the Key Questions, this review focuses on adults with osteoarthritis. We included studies that evaluate the safety, efficacy, or effectiveness of the included medications in adults with osteoarthritis. We also included studies that report safety in patients with rheumatoid arthritis or who were taking the drug for cancer or Alzheimer's prevention.

We considered studies that compared any of the oral and topical analgesics listed above to another included drug or placebo. For this report, we categorized NSAIDs as "COX-2 selective," "partially selective," salicylic acid derivatives, and "non-aspirin, nonselective" NSAIDs as described on p. ES-5. We excluded evidence on NSAIDs unavailable in the United States, leaving celecoxib as the only COX-2 selective NSAID included in this update.

We included studies that evaluate the safety, efficacy, or effectiveness of the previously mentioned medications. Primary outcomes include improvements in osteoarthritis symptoms and adverse events. Adverse events were evaluated from studies of the drugs used for osteoarthritis, rheumatoid arthritis, or cancer treatment. Specific adverse events evaluated include CV [stroke, myocardial infarction, congestive heart failure, hypertension, and angina]; GI [perforations, symptomatic gastroduodenal ulcers and upper GI bleeding (PUBs), obstructions, and dyspepsia]; renal toxicity; and hepatotoxicity. Other outcomes of interest were quality of life and sudden death.

We defined "benefits" as relief of pain and osteoarthritic symptoms and improved functional status. The main outcome measures for this review were pain, functional status, and discontinuations due to lack of efficacy. Frequently used outcome measures include visual and categorical pain scales.[14]

We included systematic reviews[15] and controlled trials pertinent to the Key Questions. We retrieved and evaluated for inclusion and exclusion any blinded or open, parallel, or crossover randomized controlled trial that compared one included drug to another, another active comparator, or placebo. We also included cohort and case-control studies with at least 1,000 cases or participants that evaluated serious GI and CV endpoints that were inadequately addressed by randomized controlled trials. We excluded non-English language studies unless they were included in an English language systematic review, in which case we relied on the data abstraction and results as reported in the systematic review. All 1,183 citations from these sources and the original report were imported into an electronic database (EndNote X3) and considered for inclusion.

Data Extraction and Quality Assessment

After studies were selected for inclusion based on the Key Questions and PICOTS, the following data were abstracted and used to assess applicability (see discussion below) (and quality of the study: study design; inclusion and exclusion criteria; population and clinical characteristics (including sex, age, ethnicity, diagnosis, comorbidities, concomitant medications, GI bleeding risk, CV risk); interventions (dose and duration); method of outcome ascertainment, if available; the number of patients randomized relative to the number of patients enrolled, and how similar those patients were to the target population; whether a run in period was used; the funding source; and results for each outcome, focusing on efficacy and safety. We recorded intention-to-treat results if available. Data abstraction for each study was completed by two investigators: the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness.

We assessed the quality of systematic reviews, randomized trials, and cohort and case control studies based on predefined criteria. We adapted criteria from the Assessment of Multiple Systematic Reviews (AMSTAR) tool (systematic reviews),[16] methods proposed by Downs and Black (observational studies),[17] and methods developed by the U.S. Preventive Services Task Force.[18] The criteria used are similar to the approach AHRQ recommended in the draft Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[19]

Individual studies were rated as "good," "fair" or "poor."[18] Studies rated "good" have the least risk of bias and results are considered valid. Good quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates, and clear reporting of dropouts; appropriate means for preventing bias; appropriate measurement of outcomes, and reporting results.

Studies rated "fair" are susceptible to some bias, but it is not sufficient to invalidate the results. These studies do not meet all the criteria for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The "fair" quality category is broad, and 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.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. We did not a priori exclude studies rated poor quality, but poor quality studies were considered to be less reliable than higher quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Studies could receive one rating for assessment of efficacy and a different rating for assessment of harms. Study quality was assessed by two independent investigators, and disagreements were resolved by consensus.

The applicability of trials and other studies 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, whether differences in outcomes were clinically (as well as statistically) significant, and whether the treatment received by the control group was reasonably representative of standard practice.[20] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as "high" or "low") because applicability may differ based on the user of this report.

We assessed the overall strength of evidence for a body of literature about a particular Key Question in accordance with AHRQ's Methods Guide for Comparative Effectiveness Reviews,[19] based on evidence included in the original CER,[12] as well as new evidence identified for this update. We considered the risk of bias (based on the type and quality of studies); the consistency of results within and between study designs; the directness of the evidence linking the intervention and health outcomes; the precision of the estimate of effect (based on the number and size of studies and the confidence intervals for the estimates); strength of association (magnitude of effect); and the possibility for publication bias.

We rated the strength of evidence for each Key Question using the four categories recommended in the AHRQ guide:[19] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect; a "moderate" grade indicates moderate confidence that the evidence reflects

the true effect and further research may change our confidence in the estimate of effect and may change the estimate; a "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; an "insufficient" grade indicates evidence either is unavailable or does not permit a conclusion.

Results

Table A provides a summary of the strength of evidence and brief results from this review, based on the evidence included in the original CER and new evidence identified for this update. Overall, we found no clear differences in efficacy of different NSAIDs, but there were potentially important differences in risk of serious harms. Celecoxib may be associated with decreased risk of serious GI events and a number of NSAIDs (selective and nonselective) appear to be associated with increased risk of serious CV risks. Furthermore, individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of an increase in CV risk, for example, could be an acceptable tradeoff for some patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and CV events), comorbid conditions, and concomitant medication use (such as aspirin and anticoagulation medications). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant tradeoffs.

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis

Key Question	Strength of Evidence	Conclusion
1. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?		
Benefits: Celecoxib vs. nonselective NSAIDs	High (consistent evidence from many randomized trials)	No clear difference in efficacy for pain relief, or withdrawals due to lack of efficacy.
Benefits: Partially selective NSAIDs vs. nonselective NSAIDs	High for meloxicam and etodolac (many randomized trials), low for nabumetone (2 short-term randomized trials)	Meloxicam was associated with no clear difference in efficacy compared to nonselective NSAIDs in 11 head-to-head trials of patients with osteoarthritis, but a systematic review that included trials of patients with osteoarthritis or rheumatoid arthritis found lesser effects on pain compared to nonselective NSAIDs (difference 1.7 points on a 10 point VAS pain scale) and withdrawals due to lack of efficacy (RR 1.5, 95% CI 1.2 to 1.7). Etodolac and nonselective NSAIDs were associated with no statistically significant differences on various efficacy outcomes in several systematic reviews of patients with osteoarthritis, with consistent results reported in 7 trials not included in the systematic reviews. Nabumetone was similar in efficacy to nonselective NSAIDs in two trials.

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
Benefits: Nonselective NSAID vs. nonselective NSAID	High (consistent evidence from many randomized trials)	No difference in efficacy between various non-aspirin, nonselective NSAIDs.
Benefits: Aspirin or salsalate vs. other NSAIDs	Low (one randomized trial)	No difference in efficacy between aspirin and salsalate in one head-to-head trial. No trial compared aspirin or salsalate vs. other NSAIDs.
GI and CV harms: Celecoxib	High for GI harms vs. nonselective NSAIDs (multiple systematic reviews and meta-analyses of mostly short-term trials, multiple observational studies; limited long-term data on serious GI harms) Moderate for CV harms vs. nonselective NSAIDs (multiple systematic review and meta-analyses of longer-term trials; some inconsistency between randomized trials and observational studies) Moderate for CV harms vs. placebo (multiple systematic reviews and meta-analyses; mostly from trials of colon polyp prevention)	GI harms: Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) and ulcer complications or symptomatic ulcers (RR 0.39, 95% CI 0.21-0.73) compared with nonselective NSAIDs in a systematic review of randomized trials. The systematic review included the pivotal, large, long-term CLASS study, in which celecoxib was superior to diclofenac or ibuprofen for ulcer complications or symptomatic ulcers at 6-month followup (2.1% vs. 3.5%, p=0.02), but not at 12-month followup. However, CLASS found difference in rates of ulcer complications alone at either 6 or 12 months. Other long-term followup data from randomized trials is lacking. A systematic review found celecoxib associated with a lower risk of upper GI bleeding or perforation compared to various nonselective NSAIDs based on 8 observational studies, though confidence interval estimates overlapped in some cases. CV harms: There was no increase in the rate of cardiovascular events with celecoxib vs. ibuprofen or diclofenac in CLASS (0.5% vs. 0.3%). In three systematic reviews of randomized trials, celecoxib was associated with increased risk of cardiovascular events compared to placebo (risk estimates ranged from 1.4 to 1.9). A systematic review of placebo-controlled trials with at least 3 years of planned followup found celecoxib associated with an increased risk of cardiovascular events (CV death, myocardial infarction, stroke, heart failure, or thromembolic event) compared to placebo (OR 1.6, 95% CI 1.1-2.3). About 3.7 additional cardiovascular events occurred for every 1,000 patients treated for one year with celecoxib instead of placebo, or 1 additional cardiovascular event for every 270 patients treated for 1 year with celecoxib instead of placebo. The risk was highest in patients prescribed celecoxib 400 mg twice daily compared to celecoxib 200 mg twice daily or 400 mg once daily. Much of the evidence for increased risks comes from two large colon polyp prevention trials. A network analysis of randomized trials and three large observational studies found celecoxib associated with no clear difference in risk of myocardial infarction compared to naproxen, ibuprofen, or diclofenac; a fourth observational study found celecoxib associated with lower risk than ibuprofen or naproxen. 11 of 13 large observational studies found celecoxib associated with no increased risk of myocardial infarction compared to nonuse of NSAIDs. An analysis of all serious adverse events in CLASS based on FDA data found no difference between celecoxib (12/100 patient-years), diclofenac (10/100 patient-years), and ibuprofen (11/100 patient-years). A retrospective cohort study found celecoxib and ibuprofen associated with neutral risk of hospitalization for acute myocardial infarction or GI bleeding compared to use of acetaminophen, but naproxen was associated with increased risk (HR 1.6, 95% CI 1.3 to 1.9).

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
GI and CV harms: Partially selective NSAIDs	GI harms: Moderate for meloxicam and etodolac (fewer trials with methodological shortcomings), low for nabumetone (sparse data)	GI harms: Meloxicam (primarily at a dose of 7.5 mg/day) was associated with a lower risk of ulcer complications or symptomatic ulcers compared to various nonselective NSAIDs in 6 trials included in a systematic review (RR 0.53, 95% CI 0.29 to 0.97), but the difference in risk of ulcer complications alone did not reach statistical significance (RR 0.56, 95% CI 0.27 to 1.2). Etodolac (primarily at a dose of 600 mg/day) was associated with a lower risk of ulcer complications or symptomatic ulcer compared to various nonselective NSAIDs in 9 trials included in a systematic review (RR 0.32, 95% CI 0.15 to 0.71), but the difference in risk of ulcer complications alone did not reach statistical significance (RR 0.39, 95% CI 0.12 to 1.2) and the number of events was very small. Evidence was insufficient to make reliable judgments about GI safety of nabumetone.
	CV harms: Insufficient for all (no trials, few large observational studies)	CV harms: Three observational studies found meloxicam associated with no increased risk of serious CV events relative to nonuse. One observational study evaluated etodolac and nabumetone, but estimates were imprecise.
GI and CV harms: Nonselective NSAIDs	GI harms: High for naproxen, ibuprofen, and diclofenac (consistent evidence from many trials and observational studies); insufficient for other nonselective NSAIDs (very little evidence)	GI harms: COX-2 selective NSAIDs as a class were associated with a similar reduction in risk of ulcer complications vs. naproxen (RR 0.34, 95% CI 0.24 to 0.48), ibuprofen (RR 0.46, 95% CI 0.30 to 0.71), and diclofenac (RR 0.31, 95% CI 0.06 to 1.6) in a systematic review of randomized trials. Evidence from randomized trials on comparative risk of serious GI harms associated with other nonselective NSAIDs is sparse. In large observational studies, naproxen was associated with a higher risk of serious GI harms than ibuprofen in 7 studies. Comparative data on GI harms with other nonselective NSAIDs was less consistent.
	CV harms vs. placebo: Moderate for ibuprofen, diclofenac, and naproxen (almost all evidence from observational studies, few large, long-term controlled trials, indirect evidence); insufficient for other nonselective NSAIDs (very little evidence) CV harms vs. selective NSAIDs: Moderate for ibuprofen, diclofenac, and naproxen (few large, long-term controlled trials, indirect evidence); insufficient for other nonselective NSAIDs (very little evidence)	CV harms: An indirect analysis of randomized trials found ibuprofen (RR 1.5, 95% CI 0.96 to 2.4) and diclofenac (RR 1.6, 95% CI 1.1 to 2.4), but not naproxen (RR 0.92, 95% CI 0.67 to 1.3) associated with an increased risk of myocardial infarction relative to placebo. 1 additional myocardial infarction occurred for about every 300 patients treated for 1 year with celecoxib instead of naproxen. A network analysis of randomized trials reported consistent results with regard to CV events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; ibuprofen: RR 2.3, 95% CI 1.1 to 4.9; diclofenac: RR 1.6, 95% CI 0.85 to 3.0 and naproxen: RR 1.2, 955 CI 0.78 to 1.9). An Alzheimer's disease prevention trial was stopped early due to a trend towards increased risk of myocardial infarction (HR 1.5, 95% CI 0.69 to 3.2) vs. placebo, but did not employ prespecified stopping protocols. In most large observational studies, naproxen was associated with a neutral effect on risk of serious CV events.

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
GI and CV harms: Aspirin	Moderate for GI and CV harms (many trials, but almost exclusively in patients receiving aspirin for cardiovascular disease prevention, usually at lower prophylactic doses)	GI harms: A systematic review of individual patient trial data found aspirin associated with increased risk of major GI and other extracranial bleeding when given for primary prevention of vascular events (RR 1.5, 95% CI 1.3 to 1.8, absolute risk 0.10% vs. 0.07%). Observational studies showed a similar risk of upper GI bleeding with aspirin and non-aspirin, nonselective NSAIDs. CV harms: Aspirin reduced the risk of vascular events in a collaborative meta-analysis of individual patient data from18 randomized controlled trials (0.51% aspirin vs. 0.57% control per year, p=0.0001 for primary prevention and 6.7% vs. 8.2% per year, p<0.0001 for secondary prevention).
GI and CV safety: Salsalate	Insufficient	No randomized trial or observational study evaluated risk of serious GI or CV harms with salsalate.
Mortality	Moderate (randomized trials with few events, and observational studies)	Large randomized trials and a meta-analysis of trials showed no difference between celecoxib and nonselective NSAIDs, but there were few events. One fair-quality cohort study found nabumetone associated with lower all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
HTN, CHF, and impaired renal function	Moderate (randomized trials and observational studies, but analyses limited by incomplete reporting of outcomes)	All NSAIDs are associated with deleterious effects on blood pressure, edema, and renal function. No clear evidence of clinically relevant, consistent differences between celecoxib, partially selective, and nonselective NSAIDs in risk of hypertension, heart failure, or impaired renal function.
Hepatotoxicity	High (many trials and large epidemiologic studies)	Several NSAIDs associated with high rates of hepatotoxicity have been removed from the market. A systematic review found clinically significant hepatotoxicity rare with currently available NSAIDs. A systematic review of randomized trials found no difference between celecoxib, diclofenac, ibuprofen, and naproxen in clinical hepatobiliary adverse events, though diclofenac was associated with the highest rate of hepatic laboratory abnormalities (78/1000 patient-years, vs. 16 to 28/1000 patient-years for the other NSAIDs). Another systematic review found diclofenac associated with the highest rate of aminotransferase elevations compared to placebo (3.6% vs. 0.29%, compared to <0.43% with other NSAIDs).

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
Tolerability	High for celecoxib and nonselective NSAIDs, moderate for partially selective NSAIDs (fewer trials with some methodological shortcomings)	The most recent systematic review of randomized trials found celecoxib associated with a lower risk of GI-related adverse events (RR 0.75, 95% CI 0.70 to 0.80) and withdrawals due to GI adverse events (RR 0.45, 95% CI 0.33 to 0.56) compared to nonselective NSAIDs, but the difference in risk of any adverse event or withdrawal due to any adverse event did not reach statistical significance). Meloxicam was also associated with decreased risk of any adverse event (RR 0.91, 95% CI 0.84 to 0.99), any GI adverse events (RR 0.31, 95% CI 0.24 to 0.39), and withdrawals due to GI adverse events (RR 0.61, 95% CI 0.54 to 0.69) compared to nonselective NSAIDs, though there was no difference in risk of withdrawal due to any adverse event. Etodolac was associated with lower risk of any adverse event compared to nonselective NSAIDs (RR 0.83, 95% CI 0.70 to 0.99), but there was no difference in risk of GI adverse events, withdrawal due to adverse events, or withdrawal due to GI adverse events. A meta-analysis found nabumetone associated with similar GI adverse events (25% vs. 28%, p=0.007) compared to nonselective NSAIDs. In a systematic review of randomized trials, the only relatively consistent finding regarding the tolerability of different nonselective NSAIDs was that indomethacin was associated with higher rates of toxicity than other NSAIDs (statistical significant unclear).
Acetaminophen	High for benefits, moderate to low for harms (few trials, limited number of observational studies)	Acetaminophen is consistently modestly inferior to NSAIDs for reducing pain and improving function in randomized trials included in multiple systematic reviews. Acetaminophen is superior to NSAIDs for GI side effects (clinical trials data) and GI complications (observational studies). Some observational studies found acetaminophen associated with modest increases in blood pressure or higher risk of renal dysfunction compared to NSAIDs, but results may be susceptible to confounding by indication. One observational study found risk of acute myocardial infarction similar in users of acetaminophen compared to users of NSAIDs. Acetaminophen may cause elevations of liver enzymes at therapeutic doses in healthy persons; comparative hepatic safety has not been evaluated.

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
Glucosamine and chondroitin	High for glucosamine vs. oral NSAIDs (consistent evidence from multiple trials) Low for chondroitin vs. oral NSAIDs (one trial) High for glucosamine or chondroitin vs. placebo (consistent evidence from recent, higher quality trials)	Seven randomized trials showed no clear difference between glucosamine vs. oral NSAIDs for pain or function. One randomized trial showed no difference between chondroitin vs. an oral NSAID. A systematic review including recent, higher quality trials found glucosamine associated with statistically significant but clinically insignificant beneficial effects on pain (-0.4 cm on a 10 cm scale, 95% CI -0.7 to -0.1) and joint space narrowing (-0.2 mm, 95% CI -0.3 to 0.0) compared with placebo. The systematic review reported similar results for chondroitin. A recent large, good-quality NIH-funded trial found the combination of pharmaceutical grade glucosamine hydrochloride and chondroitin sulfate modestly superior to placebo only in an analysis of a small subset of patients with at least moderate baseline pain. Older trials showed a greater benefit with glucosamine or chondroitin, but were characterized by lower quality. For glucosamine, the best results have been reported in trials sponsored by the manufacturer of a European, pharmaceutical grade product (no pharmaceutical-grade glucosamine available in the United States).
1a. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?	High for effects of dose and duration (many trials and observational studies with some inconsistency); low for alternative dosage strategies (1 randomized trial)	Higher doses of NSAIDs were associated with greater efficacy for some measures of pain relief, and in some trials with greater withdrawals due to adverse events A meta-analysis of 41 randomized trials found no clear association between longer duration of therapy with COX-2 selective NSAIDs and increase in the relative risk of CV events. The meta-analysis found higher doses of celecoxib associated with increased risk of cardiovascular events, but most events occurred in the long-term polyp prevention trials. Almost all of the cardiovascular events in trials of celecoxib were reported in long-term trials of colon polyp prevention. Large observational studies showed no association between higher dose and longer duration of nonselective NSAID therapy and increased risk of cardiovascular events. Many observational studies found that risk of GI bleeding increased with higher doses of nonselective NSAIDs, but no clear association with duration of therapy. One small trial found continuous celecoxib slightly more effective than intermittent use on pain and function, and similar rates of withdrawals due to adverse events. No trial was designed to assess serious GI or CV harms associated with intermittent dosing strategies.

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?		
Demographic subgroups including age, sex, and race	Moderate for age (consistent evidence from observational studies) Insufficient for sex and race (most studies included a majority of women, but studies didn't evaluate whether comparative benefits and harms vary in men and women or in different racial groups)	The absolute risks of serious GI and CV complications increase with age. Large observational studies that stratified patients by age found no clear evidence of different risk estimates for different age groups. However, because the event rates increases in older patients, even if the relative risk estimates are the same, the absolute event rates are higher. There is insufficient evidence to determine the comparative benefits and harms of different selective and nonselective NSAIDs in men compared to women, or in different racial groups.
Preexisting disease including history of previous bleeding due to NSAIDs or peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure	Moderate for previous bleeding Moderate for hypertension, edema, ischemic heart disease, heart failure (observational studies and few randomized trials)	The risk of GI bleeding is higher in patients with prior bleeding. Two trials found high rates of recurrent ulcer bleeding in patients randomized to either celecoxib (4.9% to 8.9% with 200 mg twice daily) or a nonselective NSAID + PPI (6.3%). One trial found celecoxib plus high dose PPI associated with lower risk of bleeding compared with celecoxib alone (0% vs. 8.9%, p=0.0004). A systematic review of randomized trials of celecoxib found risk of CV events doubled in patients at moderate vs. low risk (HR 2.0, 95% CI 1.5 to 2.6) and doubled again in patients at high risk (HR 3.9 for high risk vs. low risk, 95% CI 2.3 to 6.7). Most large observational studies found an association between increased cardiovascular risk and increased risk of cardiovascular events in persons using NSAIDs. Following hospitalization for heart failure, one large observational study found celecoxib and diclofenac associated with a higher risk of death compared to ibuprofen or naproxen, and another large observational study found an increased risk of repeat heart failure admission with indomethacin compared to other nonselective NSAIDs, ibuprofen, acetaminophen, or celecoxib.
Concomitant anticoagulant use	Moderate overall: Primarily observational studies	Concomitant use of anticoagulants and nonselective NSAIDs increases the risk of GI bleeding three- to six-fold compared with anticoagulant use without NSAIDs. The risk with concomitant celecoxib is not clear due to conflicting findings among observational studies, but may be increased in older patients. Reliable conclusions about the comparative safety of nonselective, partially selective, and COX-2 selective NSAIDs with concomitant anticoagulants could not be drawn due to small numbers of studies with methodological shortcomings. Warfarin plus low-dose aspirin increased the risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis. Acetaminophen can increase INR levels, but effects on bleeding rates have not been studied.

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
Concomitant use of prophylactic-dose aspirin	High for GI harms: Consistent evidence from clinical trials and observational studies Moderate for CV harms: Subgroup analyses from few trials, few observational studies	Concomitant use of aspirin appears to attenuate or eliminate the GI benefits of selective NSAIDs, resulting in risks similar to nonselective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in patients on celecoxib and those on nonselective NSAIDs in one meta-analysis. Addition of a PPI may reduce the risk of GI harms associated with use of either celecoxib or nonselective NSAIDs plus low-dose aspirin. Evidence regarding the effects of concomitant aspirin use on CV risk associated with selective or nonselective NSAIDs is limited, though three polyp prevention trials of COX-2 selective NSAIDS found that concomitant aspirin use did not attenuate the observed increased risk of CV events. Observational studies did not find increased CV risk with the addition of nonselective NSAIDs as a class to low-dose aspirin. Limited evidence suggests an increased risk of mortality with aspirin and concomitant ibuprofen compared to aspirin alone among high risk patients (HR 1.9, 95% CI 1.3 to 2.9), but studies on effects of ibuprofen added to aspirin on MI risk in average risk patients were inconsistent and did not clearly demonstrate increased risk.
3. What are the comparative effects of coprescribing of H2-antagonists, misoprostol, or PPIs on the gastrointestinal harms associated with NSAID use?	High: Consistent evidence from good-quality systematic reviews and numerous clinical trials	Misoprostol was the only gastroprotective agent to reduce risk of ulcer complications compared to placebo in patients with average risk of GI bleeding prescribed nonselective NSAIDs, but was also associated with a higher rate of withdrawals due to adverse GI symptoms. Coprescribing of PPIs, misoprostol, and H2-antagonists all reduced the risk of endoscopically detected gastric and duodenal ulcers compared to placebo in patients prescribed a nonselective NSAID. In direct comparisons, coprescribing of PPIs in patients with increased risk of GI bleeding who were prescribed a nonselective NSAID was associated with a lower risk of endoscopically detected duodenal ulcers compared to misoprostol or H2-antagonists, a lower risk of endoscopically detected gastric ulcers compared to H2-antagonists, and a similar risk of endoscopically detected gastric ulcers compared to misoprostol. Coprescribing of misoprostol was associated with a lower risk of endoscopically detected gastric ulcers compared to ranitidine, and a similar reduction in risk of endoscopically detected duodenal ulcers. Compared to placebo, double (full) dose H2-antagonists may be more effective than standard dose for reducing endoscopically detected gastric and duodenal ulcers. Celecoxib alone was associated with fewer decreases in hemoglobin (> 2 g/dl) without overt GI bleeding compared with diclofenac plus a PPI. Celecoxib plus a PPI may reduce the risk of endoscopic ulcers and ulcer complications compared to celecoxib alone in average risk persons.

Table A. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
4. What are the comparative benefits and harms of treating osteoarthritis with oral medications compared with topical preparations?		
Topical NSAIDs: efficacy	Moderate (consistent evidence for topical diclofenac from three trials)	Three head-to-head trials found topical diclofenac similar to oral NSAIDs for efficacy in patients with localized osteoarthritis.
Topical NSAIDs: safety	Moderate (consistent evidence for topical diclofenac from three trials)	Topical NSAIDs were associated with a lower risk of GI adverse events and higher risk of dermatologic adverse compared to oral NSAIDs. There was insufficient evidence to evaluate comparative risks of GI bleeding or CV events. Other topical NSAIDs evaluated in head-to-head trials have not been FDA approved.
Topical salicylates and capsaicin	Insufficient for topical salicylates or capsaicin versus oral NSAIDs (no head-to-head trials) Low for topical salicylates or capsaicin versus placebo (some placebo-controlled trials)	No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs for osteoarthritis. Topical salicylates were no better than placebo in two trials of patients with osteoarthritis included in a systematic review, and associated with increased risk of local adverse events when used for any acute or chronic pain condition. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events (13% vs. 3%, RR 4.0, 95% CI 2.3 to 6.8).

CHF = congestive heart failure; CI = confidence interval; CLASS = Celecoxib Long-term Arthritis Safety Study; COX = cyclooxygenase; CV = cardiovascular; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; H2 = histamine 2; HR = hazard ratio; HTN = hypertension; INR = international normalized ratio; NIH = National Institutes of Health; NNT = number needed to treat; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; PPI = proton pump inhibitor; PUD = peptic ulcer disease; RR = relative risk; VAS = visual analogue scale

Discussion and Future Research

This report provides a summary of the evidence on the comparative benefits and harms of oral NSAIDs (celecoxib, partially selective, nonselective, aspirin, and salsalate), acetaminophen, certain over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs, salicylates, and capsaicin) that are commonly used for pain control and improvement of functional status in patients with osteoarthritis. At this time, no drug or supplement is known to modify the course of disease, though some data suggest potential effects of glucosamine or chondroitin on slowing progression of joint space narrowing.

Major new evidence included in this update include a large trial of celecoxib versus a PPI) plus naproxen and risk of GI bleeding, new placebo-controlled trials of glucosamine and chondroitin, and a new head-to-head trial of topical versus oral diclofenac. Other new evidence in this update includes large observational studies on serious GI and CV harms associated with NSAIDs, and a number of systematic reviews. Like the original CER, a limitation of this update is that studies have not used standardized methods for defining and assessing harms.

As in the original CER, evidence indicates that each of the analgesics evaluated in this report is associated with a unique set of risks and benefits. The role of selective, partially selective, and nonselective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence varies, no currently available analgesic reviewed in this report offers a clear overall advantage compared

with the others, which is not surprising given the complex trade-offs between many benefits (pain relief, improved function, improved tolerability, and others) and harms (CV, renal, GI, and others). In addition, individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of a small increase in CV risk, for example, could be an acceptable tradeoff for many patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and CV events), comorbid conditions, and concomitant medication use (such as aspirin and anticoagulation). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant tradeoffs.

The report identified a number of important areas for future research:

- Nearly all of the clinical trials reviewed in this report were "efficacy" trials conducted in ideal settings and selected populations. "Pragmatic" trials that allow flexible dosing or medication switches and other clinical trials of effectiveness would be very valuable for learning the outcomes of different analgesic interventions in real-world settings.
- The CV safety of nonselective NSAIDs has not been adequately assessed in large, long-term clinical trials. Naproxen in particular might have a different CV safety profile from other NSAIDs and should be investigated in long-term, appropriately powered trials.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms, but have generally had a narrow focus on single adverse events. More observational studies that take a broader view of all serious adverse events would be more helpful for assessing the overall trade-offs between benefits and harms.
- The CV risks and GI benefits associated with different COX-2 selective NSAIDs might vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.
- Meta-analyses of the risks associated with selective COX-2 inhibitors need to better assess for the effects of dose and duration, as most of the CV harms have only occurred with prolonged use and at higher doses.
- Large, long-term trials of the GI and CV safety associated with full-dose aspirin, salsalate, or acetaminophen compared with non-aspirin NSAIDs or placebo are lacking.
- Trials and observational studies evaluating comparative safety or efficacy should be sufficiently inclusive to evaluate whether effects differ by race or gender.
- Genetic testing could theoretically help predict patients who are at higher risk of CV complications from selective COX-2 inhibitors because of differences in the COX-2 gene promoter or other genes. This remains a promising area of future research.
- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been well studied. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once daily versus twice daily dosing of certain COX-2 inhibitors could affect CV risk; this hypothesis has not yet been tested in a clinical trial.
- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical-grade glucosamine not available in the United States and may not be applicable to currently available over-the-counter preparations. Large trials comparing

currently available over-the-counter preparations to oral NSAIDs are needed, as these are likely to remain available even if the FDA approves a pharmaceutical grade glucosamine. Additional long-term trials are also required to further evaluate effects of glucosamine on progression of joint space narrowing and to determine the clinical effects of any beneficial effects on radiographic outcomes.

- Head-to-head trials of topical versus oral NSAIDs have not been large enough to evaluate the risks of serious CV and GI harms. Additional head-to-head trials and large cohort studies may be required to adequately assess serious harms.

Glossary

For this report, we have defined the terms as follows:

- **All other NSAIDs:** Non-aspirin, nonselective NSAIDs, or simply nonselective NSAIDs.
- **Aspirin:** Differs from other NSAIDs, because it irreversibly inhibits platelet aggregation; salicylic acid derivatives (aspirin and salsalate) are considered a separate subgroup.
- **Partially selective NSAIDs:** Other drugs shown to have partial in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam).
- **Selective NSAIDs or COX-2 selective NSAIDs:** Drugs in the "coxib" class (celecoxib).

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Introduction

Background

Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life. Twenty-seven million adults in the United States are thought to have clinical osteoarthritis.[1] In large surveys, 5 percent to 17 percent of U.S. adults had symptomatic osteoarthritis of the knee, and 9 percent had symptomatic osteoarthritis of the hip.[1] Osteoarthritis is more common with increasing age. Osteoarthritis accounts for more disability in walking, stair climbing, and other tasks requiring use of the lower extremities than any other disease, particularly in the elderly.[2] The total costs for arthritis, including osteoarthritis, may be greater than 2 percent of the gross domestic product,[3] with more than half of these costs related to work loss.[2]

In addition to nonpharmacologic interventions (such as physical therapy, weight reduction, and exercise), numerous medications and over-the-counter supplements are available to treat pain and potentially improve functional status in patients with osteoarthritis.[4] Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may also vary for individual drugs within a class. Oral medications commonly used to treat osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Many are available at lower over-the-counter and higher prescription doses. A dose comparison table of available NSAIDs is available in Appendix A. Commonly used supplements sold over the counter and not regulated as pharmaceuticals by the U.S. Food and Drug Administration (FDA) include glucosamine and chondroitin. Topical agents used by patients with osteoarthritis include rubefacients (including salicylates and capsaicin) and NSAIDs. Opioid medications are also used for patients with chronic osteoarthritis pain, especially if it is refractory to other therapies, but recommendations suggest cautious use due to risks of addiction, tolerance, diversion, and other adverse events.[5-7]

NSAIDs exert analgesic, anti-inflammatory, and antipyretic effects by blocking cyclooxygenases (COX), enzymes that are needed to produce prostaglandins. Understanding of the pharmacology of NSAIDs continues to evolve, but it is thought that most NSAIDs block the COX-1 and COX-2 isoenzymes. COX-2 is found throughout the body, including joint and muscle, where it contributes to pain and inflammation. Because they block COX-2, NSAIDs reduce pain compared to placebo in patients with arthritis,[8] low back pain,[9] minor injuries, and soft-tissue rheumatism.

NSAIDs are also associated with important adverse effects. NSAIDs cause gastrointestinal (GI) bleeding because they also block the COX-1 enzyme, which mediates mucosal defense of the gastrointestinal tract, including protection from acid and platelet aggregation. The number of serious GI bleeds in the United States due to use of nonaspirin NSAIDs is not known with certainty. One study estimated 32,000 hospitalizations and 3,200 deaths annually in the 1990s, though other studies have reported higher estimates.[10] A risk analysis[11] based on a retrospective case-control survey of emergency admissions for upper GI disease in two United Kingdom general hospitals provided estimates of the frequency of serious GI complications from NSAIDs.[12] 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). In addition to age, prednisone use, disability level, and previous NSAID-induced GI bleed are risk factors for GI bleeding.

Table 1. One-year risk of gastrointestinal 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	2,100	12,353
45-64	646	3,800
65-74	570	3,353
> 75	110	647

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug
Note: Data are from Blower,[12] recalculated in Moore[11] and in Bandolier.[13]

NSAIDs differ in their selectivity for COX-2—how much they affect COX-2 relative to COX-1. Theoretically, an NSAID that blocks COX-2 but not COX-1 might reduce pain and inflammation in joints but not affect the gastrointestinal mucosa or cause platelet inhibition. Appendix B 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 assay method may not reliably 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.

In addition to their propensity to cause GI bleeding, NSAIDs are also associated with adverse effects on blood pressure, renal function, and fluid retention. Mechanisms may involve attenuation of prostaglandin-mediated vasodilation, promotion of sodium and water retention, increased vascular resistance, and increased renal endothelin-1 synthesis.[14-16] An association between COX-2 selective NSAIDs and increased rates of myocardial infarction was first observed in the large, pivotal Vioxx Gastrointestinal Outcomes Research (VIGOR) trial comparing high-dose rofecoxib (50 mg) to naproxen 1,000 mg.[17] Reasons for the increase in thromboembolic cardiovascular (CV) event risk are not completely understood. Initially, it was thought that the degree of COX-2 selectivity could predispose to CV events by suppressing endothelial-derived prostaglandin I2 formation, in the setting of unaffected platelet production of prothrombotic COX-1 mediated thromboxane A2.[18] However, subsequent in vitro studies have not definitively confirmed this hypothesis. Blood pressure elevations associated with COX-2 selective NSAIDs may play a role in increasing CV risk,[19] and CV events in VIGOR were also later found to be associated with a higher incidence of arrhythmias. On September 30, 2004, rofecoxib was withdrawn from the market after a long-term polyp prevention trial found an increased risk of myocardial infarction compared with placebo.[20] On December 9, 2004, the FDA issued a black-box warning for the selective COX-2 inhibitor valdecoxib for life-threatening skin reactions and increased CV risk. This drug was subsequently also withdrawn voluntarily by the manufacturer,[21] leaving celecoxib the only COX-2 selective NSAID available in the United States.

Aspirin, or acetylsalicylic acid, has long been known to have analgesic, antipyretic, and anti-inflammatory effects.[22] It is thought to be the most consumed medicinal drug in the world. Like the non-aspirin NSAIDs, aspirin's effects are due to blockade of cyclooxygenases. However, an important distinction between aspirin and non-aspirin NSAIDs is that aspirin also induces irreversible functional defects in platelets (although non-aspirin NSAIDs also have effects on platelet aggregation, they are short lived). Because of these antiplatelet effects, low-dose aspirin

is also used prophylactically to reduce the risk of thrombotic events.[23] However, even at doses of 325 mg daily or lower, the potential CV benefits must be balanced against dose-dependent risk of aspirin-induced adverse GI events. In addition, it is not known with certainty how frequently aspirin is used at the higher doses more effective for analgesia, where tolerability may be an issue. Salsalate, a nonacetylated salicylate, is a prodrug of salicylic acid, the active metabolite of aspirin. It is considered a relatively weak inhibitor of cyclooxygenases.[24]

Acetaminophen (also known as paracetamol) is an antipyretic and analgesic medication that is not thought to have significant anti-inflammatory properties. Although its mechanism of inducing analgesia is still not completely understood, it is thought to work in part by indirectly decreasing production of prostaglandins through inhibitory effects involving COX-2.[14, 25] Acetaminophen is frequently recommended as a first-line agent for osteoarthritis and other pain conditions because of its perceived favorable safety profile—particularly with regard to ulcer risk.[6]

Chondroitin sulfate and glucosamine sulfate are natural compounds found in cartilage. Both are marketed to patients who have osteoarthritis. The precise mechanisms of action are unknown, but may involve promotion of maintenance and repair of cartilage. Glucosamine, for example, has been shown to increase proteoglycan synthesis.[26] In the European Union countries, glucosamine is available as a prescription drug manufactured by the Rotta Pharmaceutical Company. In the United States, by contrast, glucosamine and chondroitin are considered dietary supplements and are not regulated as pharmaceuticals. Adequate standardization of glucosamine and chondroitin preparations is a significant concern. It has been shown that the actual content often varies substantially from what is stated on the label.[27] Such inconsistencies may have implications on estimates of efficacy and safety for different commercial preparations.

Topical administration of NSAIDs could theoretically result in local analgesic and anti-inflammatory effects by direct absorption through the skin, with reduced systemic adverse events compared with oral administration.[28] Research indicates that topical administration is associated with substantially higher concentrations of NSAIDs in soft tissue (particularly meniscus and cartilage) and lower peak plasma concentrations compared with oral administration.[29] For a topical NSAID to be effective, it has to reach the inflamed tissue in sufficient concentrations to produce analgesic and anti-inflammatory activity. The solubility of specific NSAIDs varies considerably, and is also affected by the carrier or formulation used.[28] Superior in vivo permeability characteristics, however, do not necessarily predict clinical effectiveness. At the time of the original comparative effectiveness review (CER), the FDA had approved no topical NSAID formulations, though compounding of oral NSAIDs into topical preparations was permitted. Since then, the FDA has approved several topical formulations of diclofenac.

In contrast to topical NSAIDs, whose mechanism of action involves inhibition of cyclooxygenase, topical rubefacients are thought to relieve pain through counter-irritation.[29, 30] Although the mechanism of action of topical preparations containing salicylate esters is unclear, they are now usually classified as rubefacients rather than topical NSAIDs because they may not work via inhibition of cyclooxygenase.[29, 31] Capsaicin, which may be classified as a rubefacient, is derived from the hot chili pepper (*Capsicum* species). It is applied topically and thought to work by stimulating the release of substance P and other neuropeptides from sensory nerve endings.[32] Although this release can initially lead to burning and pain, analgesia occurs after repeated and continued application, as substance P becomes depleted. Although a wide variety of other rubefacients are available, only topical salicylates and capsaicin were included in this review.

The Agency for Healthcare Research and Quality (AHRQ) funded a CER of analgesics for osteoarthritis that was published in 2006,[33] based on searches conducted through 2006. Since that time, additional research has become available to better understand the comparative efficacy and safety of oral and topical medications for osteoarthritis, and a study[34] commissioned by AHRQ on the need to update CERs assigned high priority to the previous report on analgesics for osteoarthritis, based on an assessment of the number of potentially outdated conclusions and ongoing issues related to safety.

Scope and Key Questions

The purpose of this report was to update a previous comparative effectiveness review funded by AHRQ[33] on the comparative efficacy and safety of nonopioid oral medications (selective and nonselective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis. The analytic framework and Key Questions guiding this report are described below.

Key Question 1

What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?

- How do these benefits and harms change with dosage and duration of treatment?

The only benefits considered here are improvements in osteoarthritis symptoms. Evidence of harms associated with the use of NSAIDs includes studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.

Oral agents include:
- COX-2 selective NSAIDs:
    - Celecoxib
- Partially selective NSAIDs:
    - Etodolac
    - Meloxicam
    - Nabumetone
- Non-aspirin, nonselective NSAIDs:
    - Diclofenac
    - Diflunisal
    - Fenoprofen
    - Flurbiprofen
    - Ibuprofen
    - Indomethacin
    - Ketoprofen
    - Ketorolac
    - Meclofenamate sodium
    - Mefenamic acid
    - Naproxen
    - Oxaprozin
    - Piroxicam
    - Sulindac

- o Tolmetin
- Aspirin and salsalate:
  - o Aspirin
  - o Salsalate
- Acetaminophen and supplements
  - o Acetaminophen
  - o Chondroitin
  - o Glucosamine

Key Question 2

Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients?

- Demographic subgroups: age, sex, and race
- Coexisting diseases: CV conditions, such as hypertension, edema, ischemic heart disease, heart failure; peptic ulcer disease; history of previous gastrointestinal bleeding (any cause); renal disease; hepatic disease; diabetes; obesity
- Concomitant medication use: antithrombotics, corticosteroids, antihypertensives, selective serotonin reuptake inhibitors (SSRI)

Key Question 3

What are the comparative effects of coprescribing H2 receptor antagonists, misoprostol, or proton pump inhibitors on the gastrointestinal harms associated with NSAID use?

Key Question 4

What are the comparative benefits and harms of treating osteoarthritis with oral medications compared with topical preparations, or of different topical medications compared with one another?

For the update of this comparative effectiveness review, changes have been made to clarify the Key Questions, but these changes do not alter the meaning of each Key Question. Additional coexisting diseases and concomitant medications were included.

Table 2 describes the characteristics and current indications for the drugs evaluated in this review.

Table 2. Indications and dosing for drugs included in the report

Drug		Labeled Indications	Dosing	Dose Adjustments for Special Populations
Oral drugs	Acetaminophen	Fever; pain	Pain: 650–1,000 mg up to 4 g/day	Pediatric patients (peds): 10–15 mg/kg/dose up to 5 doses/day
	Aspirin	Arthritis; cerebrovascular accident; transient ischemia; coronary artery bypass graft; disorder of joint of spine; fever; juvenile rheumatoid arthritis; myocardial infarction; prophylaxis; osteoarthritis; pain; percutaneous coronary intervention; pleurisy; systemic lupus erythematosus; rheumatoid arthritis; stable angina, chronic; unstable angina	OA and RA: 3g/day divided into 4 to 6 doses	Peds: 40–130 mg/kg/day, depending upon condition
	Celecoxib (Celebrex)	Ankylosing spondylitis; familial adenomatous polyposis; syndrome osteoarthritis; pain; primary dysmenorrhea; rheumatoid arthritis; juvenile rheumatoid arthritis	OA: 200 mg/day; RA: 200–400 mg/day	Renal impairment: reduce dose by 50%; elderly patients weighing < 50 kg: initiate at lowest dose
	Diclofenac	Ankylosing spondylitis; extraction of cataract; inflammatory disorder of eye; light intolerance; pain in eye; refractive keratoplasty; osteoarthritis; pain; rheumatoid arthritis	OA: delayed release, 100–150 mg/day in 2 to 3 doses; extended release, 100–200 mg/day; RA: delayed release, 100–200 mg/day in 3 to 4 doses; extended release, 75–225 mg/day	Renal impairment: initiate with lowest recommended dose, then monitor closely
	Diflunisal	Osteoarthritis; pain, mild to moderate; rheumatoid arthritis	OA and RA: 500–1000 mg/day in 2 equally divided doses; maximum dose, 1,500 mg/day	Renal impairment and elderly: initiate with lowest dose possible, then monitor closely
	Etodolac	Juvenile rheumatoid arthritis; osteoarthritis; pain, acute; rheumatoid arthritis	OA and RA initial treatment: immediate release, 300 mg 2–3x/day or 400–500 mg 2x/day; OA and RA maintenance: immediate release, 600–1,000 mg/day 2–4x/day with a maximum dose of 1,200 mg/day; extended release, 400–1,000 mg/day	Juvenile rheumatoid arthritis weighing 20 to 30 kg: extended release, 400 mg 1x/day; JRA weighing 31 to 45 kg: extended release, 600 mg 1x/day; JRA weighing 46 to 60 kg: extended release, 800 mg 1x/day; JRA, extended release, weighing >60 kg: extended release,1,000 mg 1x/day

Table 2. Indications and dosing for drugs included in the report (continued)

Drug		Labeled Indications	Dosing	Dose Adjustments for Special Populations
Oral drugs	Fenoprofen	Migraine; osteoarthritis; pain, mild to moderate; rheumatoid arthritis	OA and RA: 300–600 mg, 3 to 4x/day; maximum daily dose, 3,200 mg	Elderly: smaller dose recommended, 300 mg 3x/day; renal impairment: no dose adjustment necessary
	Flurbiprofen	Constricted pupil, intraoperative prophylaxis; osteoarthritis; rheumatoid arthritis	OA and RA: 200–300 mg/day in 2 to 4 divided doses; maximum dose, 300 mg/day	Renal impairment, liver disease, and geriatric patients: initiate with lowest recommended dose, then monitor closely
	Ibuprofen	Fever; juvenile rheumatoid arthritis; osteoarthritis; pain, minor; pain, mild to moderate; primary dysmenorrhea; rheumatoid arthritis	OA and RA: 1200–3200 mg/day in 3 to 4 divided doses	Renal impairment: initiate with lowest recommended dose, then monitor closely
	Indomethacin	Ankylosing spondylitis; bursitis of shoulder–pain, acute; gouty arthritis, acute; osteoarthritis; tendonitis of shoulder—pain, acute; patent ductus arteriosus; rheumatoid arthritis	OA and RA: immediate release, 25–50 mg 2 to 3x/day or a maximum dose of 100 mg 2x/day; sustained release product, 75 mg 1 to 2x/day	Severe renal impairment (CrCL < 15 mL/min), liver disease (Child-Pugh Class III), elderly, and peds: initiate with lowest recommended dose, then monitor closely
	Ketoprofen	Fever; osteoarthritis; pain, minor; pain, mild to moderate; rheumatoid arthritis	OA and RA: immediate release, 150–300 mg/day in 3 to 4 divided doses; extended release, 100–200 mg 1x/day	Mild renal impairment (CrCL > 25 mL/min): maximum, 150 mg/day; moderate renal impairment (CrCL < 25 mL/min): maximum, 100 mg/day; geriatric (>75 years): initiate with doses of 75-150 mg/day; liver disease and serum albumin < 3.5 g/dL: maximum initial dose, 100 mg/day
	Ketorolac	Extraction of cataract—inflammatory disorder of eye; light intolerance—pain in eye—refractive keratoplasty; pain, acute—moderate to severe; seasonal allergic conjunctivitis	Pain, acute—moderate to severe (<65 years of age): initiate with 20 mg, followed by 10 mg, every 4 to 6 hours; maximum, 40 mg/day	Peds: lowest effective dose for shortest possible duration; >65 years of age or weight <50 kg or renal impairment: 10 mg every 4 to 6 hours as needed; maximum, 40 mg/day
	Meclofenamate sodium	Dysmenorrhea; menorrhagia; osteoarthritis; pain; rheumatoid arthritis	OA and RA: 200–400 mg/day in 3 to 4 equally divided doses; maximum, 400 mg/day	Elderly and renal impairment: lowest effective dose for shortest possible duration
	Mefenamic acid	Dysmenorrhea; pain	Pain (children >14 years and adults): initiate with 500 mg, followed by 250 mg every 6 hours; use beyond 1 week is not recommended	Renal impairment: do not use; peds: use not studied

Table 2. Indications and dosing for drugs included in the report (continued)

Drug		Labeled Indications	Dosing	Dose Adjustments for Special Populations
Oral drugs	Meloxicam	Juvenile rheumatoid arthritis, polyarticular–pauciarticular juvenile rheumatoid arthritis; osteoarthritis; rheumatoid arthritis	OA and RA: 7.5 mg 1x/day; maximum, 15 mg 1x/day	Elderly, renal impairment, liver disease (Child-Pugh Class III): initiate with lowest recommended dose, then monitor closely
	Nabumetone	Osteoarthritis; rheumatoid arthritis	OA and RA: initial treatment, 1,000 mg/day in a single dose; maintenance, 1,000–2,000 mg 1x/day or in 2 equally divided doses	Renal impairment and liver disease: monitor closely and reduce dose if necessary
	Naproxen	Ankylosing spondylitis; bursitis; fever; gout, acute; juvenile rheumatoid arthritis; osteoarthritis; pain; pain, minor; primary dysmenorrhea; rheumatoid arthritis; tendinitis	OA and RA: 250–500 mg 2x/day, maximum, 1,500 mg/day ≤ 6 months; over-the-counter, ≤ 10 days	JRA: 10 mg/kg/day in 2 equally divided doses; renal impairment and liver disease: monitor closely and reduce dose if necessary
	Oxaprozin	Juvenile rheumatoid arthritis; osteoarthritis; rheumatoid arthritis	OA and RA: 1,200 mg 1x/day; maximum, 1,800 mg/day or 26 mg/kg/day	JRA, 22 to 31 kg: 600 mg 1x/ day; JRA, 32 to 54 kg: 900 mg 1x/day; JRA, >55 kg: 1,200 mg 1x/day; renal impairment or weight <50 kg: initiate with 600 mg 1x/day, then monitor closely
	Piroxicam	Osteoarthritis; rheumatoid arthritis	OA and RA: 20 mg/day 1x/day or 2 equally divided doses	Renal impairment or liver disease: monitor closely and reduce dose if necessary
	Salsalate	Inflammatory disorder of musculoskeletal system, rheumatic; osteoarthritis; rheumatoid arthritis	OA and RA: 3,000 mg/day in 2 to 3 equally divided doses	Elderly: lower doses may be required; peds: safety and efficacy not established
	Sulindac	Bursitis of shoulder—pain, acute; gouty arthritis, acute; osteoarthritis; tendonitis of shoulder—pain, acute; rheumatoid arthritis	OA and RA: 150 mg 2x/day; maximum 400 mg/day	Renal impairment and liver disease: monitor closely and reduce dose if necessary
	Tolmetin	Juvenile rheumatoid arthritis; osteoarthritis; rheumatoid arthritis	OA and RA: initial treatment, 400 mg 3x/day for 1 to 2 weeks; maintenance, 200–600 mg 3x/day; maximum, 1,800 mg/day	Renal impairment: initiate with lowest recommended dose, then monitor closely and reduce dose if necessary; juvenile rheumatoid arthritis, ≥2 years, initial treatment: 20 mg/kg/day divided into 3 to 4 doses; juvenile rheumatoid arthritis, ≥2 years, maintenance: 15–30 mg/kg/day divided into 3 to 4 doses

Table 2. Indications and dosing for drugs included in the report (continued)

Drug		Labeled Indications	Dosing	Dose Adjustments for Special Populations
Topical drugs	Diclofenac epolamine (Flector; one patch equals180 mg in an aqueous base)	Acute pain from minor strains, sprains, and contusions	1 patch to most painful area 2x/day	Patients with fluid retention or heart failure: use with caution
	Diclofenac sodium (Voltaren; 1% gel)	Osteoarthritis of joints amenable to topical treatment, such as knees and hands	Maximum, 32 g/day, over all affected joints; maximum, 16 g/day, to any single joint of lower extremities; maximum, 8 g/day to any single joint of upper extremities	Patients with fluid retention or heart failure: use with caution
	Diclofenac sodium (Pennsaid)	Osteoarthritis of knee	40 drops on each painful knee, 4x/day	Patients with fluid retention or heart failure: use with caution
	Capsaicin	Arthritis; diabetic neuropathy; postherpetic neuralgia	Arthritis: apply thin film 3 to 5x/day	Peds (>2 years): apply thin film 3 to 4x/day

CrCL = creatinine clearance; JRA = juvenile rheumatoid arthritis; OA = osteoarthritis; RA = rheumatoid arthritis

Methods

Topic Development

The topic for the original 2006 report[33] was nominated in a public process. The key questions for that report were developed by investigators from the Evidence-based Practice Center (EPC) with input from a Technical Expert Panel (TEP), which helped to refine key questions, identify important issues, and define parameters for the review of evidence.

For the present report update, the same scope and key questions were proposed to the EPC by Agency for Healthcare Research and Quality (AHRQ). The key questions and list of included drugs were modified by the EPC after receiving input from a new TEP convened for this report update. The revised key questions were then posted to a public Web site for comment. AHRQ and the EPC agreed upon the final key questions after reviewing the public comments and receiving additional input from the TEP.

Search Strategy

We updated the search conducted with the comparative effectiveness review (CER) for studies published in the years 2005–present. We searched the Cochrane Database of Systematic Reviews (through January 2011) the Cochrane Central Register of Controlled Trials (through fourth quarter 2010) and Ovid MEDLINE (2005–January 2011.) We used relatively broad searches, combining terms for drug names with terms for relevant research designs, limiting to those studies that focused on osteoarthritis and rheumatoid arthritis (see Appendix C for the complete search strategy). Other sources include selected grey literature provided to the EPC by the Scientific Resource Center librarian, reference lists of review articles, and citations identified by public reviewers of the Key Questions. Pharmaceutical manufacturers were invited to submit scientific information packets, including citations and unpublished data.

All 1,184 citations from these sources and the original report were imported into an electronic database (EndNote X3) and considered for inclusion.

Study Selection

We developed criteria for inclusion and exclusion of studies based on the key questions and the populations, interventions, comparators, outcomes, timing and setting (PICOTS) approach. Abstracts were reviewed using abstract screening criteria (Appendix D) and a two-pass process to identify potentially relevant studies. For the first pass, the abstracts were divided between three investigators. In the second pass, a fourth investigator reviewed all abstracts not selected for inclusion in the first-pass. Two investigators then independently reviewed all potentially relevant full text using a more stringent set of criteria for inclusion and exclusion (Appendix D).

Population and Condition of Interest

As specified in the Key Questions, this review focuses on adults with osteoarthritis. We included studies that evaluate the safety, efficacy, or effectiveness of the included medications in adults with any grade of osteoarthritis. We also included studies that report safety in patients with rheumatoid arthritis or who were taking the drug for cancer or Alzheimer's prevention.

Interventions and Comparators of Interest

We considered studies that compared any of the oral and topical analgesics listed in Table 2 to another included drug, or placebo.

Oral agents include:

- COX-2 selective NSAIDs:
    - celecoxib
- Partially selective NSAIDs:
    - etodolac
    - meloxicam
    - nabumetone
- Non-aspirin, nonselective NSAIDs:
    - diclofenac
    - diflunisal
    - fenoprofen
    - flurbiprofen
    - ibuprofen
    - indomethacin
    - ketoprofen
    - ketorolac
    - meclofenamate sodium
    - mefenamic acid
    - naproxen
    - oxaprozin
    - piroxicam
    - sulindac
    - tolmetin
- Aspirin and salsalate:
    - aspirin
    - salsalate
- Acetaminophen and supplements:
    - acetaminophen
    - chondroitin
    - glucosamine

For this report, we defined the terms "selective nonsteroidal anti-inflammatory drug (NSAID)" or "cyclooxygenase (COX)-2 selective NSAID" as drugs in the "coxib" class (e.g. celecoxib, rofecoxib, and valdecoxib). We grouped etodolac, nabumetone, and meloxicam into a separate category that we referred to as "partially selective NSAIDs," based on in vitro differences in COX-2 selectivity intermediate between COX-2 selective NSAIDs and nonselective NSAIDs. However, whether partially selective NSAIDs are truly different from nonselective NSAIDs is unclear because COX-2 selectivity may be lost at higher doses and the effects of in vitro COX-2 selectivity on clinical outcomes are uncertain.[35] The salicylic acid derivatives aspirin and salsalate were also considered a separate subgroup. We defined "non-aspirin, nonselective NSAIDs" or simply "nonselective NSAIDs" as all other NSAIDs. We excluded evidence on NSAIDs unavailable in the United States, leaving celecoxib as the only COX-2 selective NSAID included in this update.

Outcomes of Interest

We included studies that evaluate the safety, efficacy, or effectiveness of the previously mentioned medications. Outcomes include:

- Improvements in osteoarthritis symptoms
- Adverse events were evaluated from studies of the drugs used for osteoarthritis, rheumatoid arthritis, or cancer treatment
  - Cardiovascular (CV): stroke, myocardial infarction, congestive heart failure, hypertension, and angina
  - Gastrointestinal (GI): perforations, symptomatic gastroduodenal ulcers and upper GI bleeding (PUBs), obstructions, dyspepsia
  - Renal toxicity
  - Hepatotoxicity
- Other outcomes of interest: quality of life, sudden death

We defined "benefits" as relief of pain and osteoarthritic symptoms and improved functional status. The main outcome measures for this review were pain, functional status, and discontinuations due to lack of efficacy. Frequently used outcome measures include visual and categorical pain scales.[36]

Patients use visual analog scales (VAS) to indicate their level of pain, function, or other outcome by marking a scale labeled with numbers (such as 0 to 100) or descriptions (such as "none" to "worst pain I've ever had"). One study found minimum clinically important improvement thresholds of an absolute improvement from baseline for 15 to 20 points on a 0 to 100 VAS scale, or a relative improvement of 30 percent to 40 percent.[37]

Categorical pain scales consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must chose among categories that may not accurately describe their pain. A variety of disease-specific and nonspecific scales are used to assess these outcomes in patients with osteoarthritis. Commonly used categorical pain scales include:

- The *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC), a 24-item, disease-specific questionnaire used to assess the functional status of patients with osteoarthritis of the knee and hip. Separate scores can be calculated for pain (5 items, scored 0 to 20, 0 to 500, or 0 to 100), functional status (17 items, scored 0 to 68, 0 to 1700, or 0 to 100), and stiffness (2 items, scored 0 to 8, 0 to 200, or 0 to 100). For each subscale, the score is calculated by adding the scores for all the items together (in some cases translating to a 100 point scale). A lower score indicates better function.[38] One study found minimum clinically important improvement thresholds of an absolute improvement from baseline in the WOMAC total score of about 10 points (on a 0 to 100 scale) or a relative improvement of 25 percent.[37]
- The *Medical Outcomes Short Form-36 (SF-36)* health survey, an 8-item questionnaire for measuring health-related quality of life across different diseases. Each item is score from 0 to 100, with higher scores indicating better health. Physical and mental component summary scores can be calculated by combining results for several subscales.[39]
- *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 categorical scale. Thresholds for minimum clinically important improvements for global assessment of disease status were similar to those for pain, based on a 0 to 100 VAS.[37]

Another method for measuring outcomes is classifying patients dichotomously as "responders" or "nonresponders." Responders are often defined as patients with at least a 50 percent improvement in pain or function. The *Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria,* for example, were developed through a consensus process and classifies patients as responders if they meet specific predefined criteria (≥50% improvement in pain or function that was ≥20 mm on a 100-mm VAS, or a ≥20% improvement in at least two of pain, function, or patient global assessment that was ≥10 mm on a 100-mm VAS).[40]

"Harms" include tolerability (not having to stop the drug due to adverse effects); CV, hepato-, renal, and GI toxicity; and increased risk for hospitalizations, drug interactions, and death. For GI toxicity, we focused on serious complications associated with NSAIDs including perforation, bleeding ulcer, and gastric outlet obstruction, though we also evaluated other GI side effects (such as nausea, dyspepsia, and GI tolerability). We only considered rates of endoscopic ulcers when data on clinical ulcer complications were incomplete or not available.

Timing

We did not apply a minimum threshold for duration of intervention.

Setting

Studies conducted in primary care and specialty settings were included.

Types of Studies

We included systematic reviews[41] and controlled trials pertinent to the Key Questions. We retrieved and evaluated for inclusion and exclusion any blinded or open, parallel or crossover randomized controlled trial that compared one included drug to another, another active comparator, or placebo. We also included cohort and case-control studies with at least 1,000 cases or participants that evaluated serious GI and CV endpoints that were inadequately addressed by randomized controlled trials. We excluded non-English language studies unless they were included in an English-language systematic review, in which case we relied on the data abstraction and results as reported in the systematic review. A list of excluded studies can be found in Appendix E.

Figure 1. Analytic framework
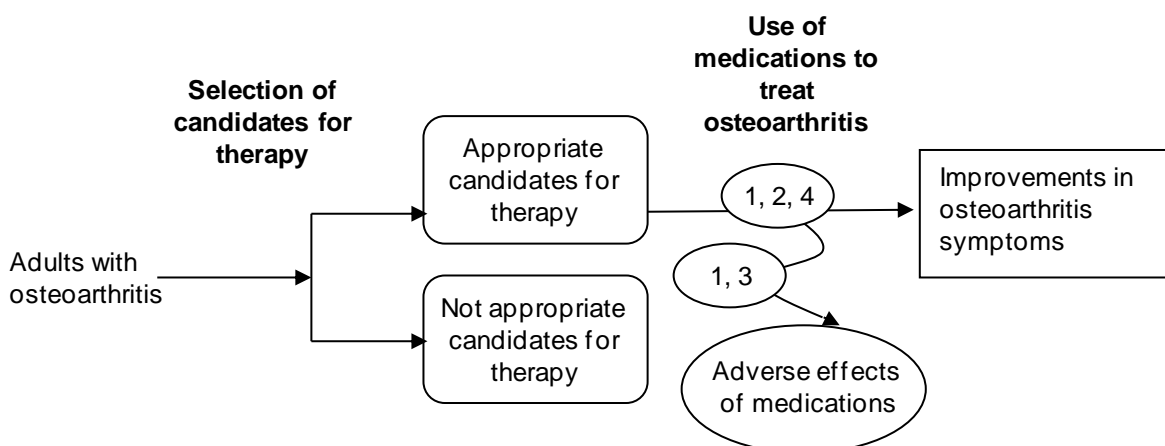
Figure 1 depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how the nonopioid oral medications, over-the-counter supplements, and topical agents may result in outcomes such as improvements in osteoarthritis symptoms. Also, adverse events (including, but not limited to, CV, GI, renal and hepatic events) may occur at any point after analgesics are received.

Data Extraction

After studies were selected for inclusion based on the key questions and PICOTS, the following data were abstracted and used to assess applicability and quality of the study: study design; inclusion and exclusion criteria; population and clinical characteristics (including sex, age, ethnicity, diagnosis, comorbidities, concomitant medications, GI bleeding risk, CV risk); interventions (dose and duration); method of outcome ascertainment, if available; the number of patients randomized relative to the number of patients enrolled, and how similar those patients were to the target population; whether a run-in period was used; the funding source; and results for each outcome, focusing on efficacy and safety. We recorded intention-to-treat results if available. Data abstraction for each study was completed by two investigators: the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness.

Quality Assessment

We assessed the quality of systematic reviews, randomized trials, and cohort and case control studies based on the predefined criteria listed in Appendix F. We adapted criteria from the Assessment of Multiple Systematic Reviews (AMSTAR) tool (systematic reviews),[42] methods proposed by Downs and Black (observational studies),[43] and methods developed by the US Preventive Services Task Force.[44] The criteria used is similar to the approach recommended by AHRQ in the Methods Guide for Comparative Effectiveness Reviews.[45]

We rated the quality of each controlled 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; the use of intention-to-treat analysis; and ascertainment of outcomes.[44]

Included systematic reviews also were rated for quality based on predefined criteria assessing whether they had a clear statement of the question(s), reported inclusion criteria, used an

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adequate search strategy, assessed validity, performed dual data abstraction, reported adequate detail of included studies, assessed for publication bias, and used appropriate methods to synthesize the evidence.[42] We included systematic reviews and meta-analyses that included unpublished data inaccessible to the public, but because the results of such analyses are not verifiable, we considered this a methodological shortcoming. For each systematic review included in this report, we considered their relevance to the key questions and scope, their quality, and how new evidence might affect conclusions.[41]

Large observational studies on serious harms associated with selective and nonselective NSAIDs have primarily relied on claims data or other administrative databases or on electronic medical record data collected in practice networks to identify cases, and prescription claims to determine exposure. A strength of these studies is that they evaluated much larger populations than could be enrolled into clinical trials.[46] In addition, they may reflect how NSAIDs are actually used in practice better than many clinical trials, which are usually short term, mandate rigid dosing regimens, limit the use of other drugs, and implement strategies to monitor and enhance compliance. Population- and practice-based studies may also better represent patients who would be excluded from randomized trials because of comorbidities, age, or other factors.

The most important weakness of observational studies is that patients are allocated treatment in a nonrandomized matter. This can lead to biased estimates of effects even when appropriate statistical adjustment on a variety of confounding variables is performed.[47] In addition, data sources often cannot reliably assess over-the-counter aspirin, NSAIDs, or acid-suppressing medication use,[46] and information on prescription fills may not always accurately correspond to the actual degree of exposure to the drugs.

For assessing the internal validity of cohort studies, we evaluated whether they used nonbiased selection methods to create an inception cohort; whether rates of loss to followup were reported and acceptable; whether they used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders.[43] For assessing the internal validity of case-control studies, we evaluated whether similar inclusion and exclusion criteria were applied to select cases and controls, whether they used accurate methods to identify cases, whether they used accurate methods for ascertaining exposures and potential confounders, and whether they performed appropriate statistical analyses of potential confounders.[43] We only included studies that performed adjustment for important confounders (such as age, sex, and markers of underlying risk) and only reported adjusted risk estimates.

Individual studies were rated as "good," "fair" or "poor" as defined below:[44]

Studies rated "good" have the least risk of bias and results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates, and clear reporting of dropouts; appropriate means for preventing bias; appropriate measurement of outcomes, and reporting results.

Studies rated "fair" are susceptible to some bias, but it is not sufficient to invalidate the results. These studies do not meet all the criteria for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The "fair" quality category is broad, and 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.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. We did not exclude studies rated poor quality a priori, but poor quality studies were considered to be less reliable than higher quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Studies could receive one rating for assessment of efficacy and a different rating for assessment of harms. Study quality was assessed by two independent investigators, and disagreements were resolved by consensus. Quality assessments for individual studies can be found in Appendix G.

Assessing Research Applicability

The applicability of trials and other studies 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, whether differences in outcomes were clinically (as well as statistically) significant, and whether the treatment received by the control group was reasonably representative of standard practice.[48] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as "high" or "low") because applicability may differ based on the user of this report.

Evidence Synthesis and Rating the Body of Evidence

We assessed the overall strength of evidence for a body of literature about a particular key question in accordance with AHRQ's Methods Guide for Comparative Effectiveness Reviews,[45] based on evidence included in the original CER,[32] as well as new evidence identified for this update. We considered the risk of bias (based on the type and quality of studies); the consistency of results within and between study designs; the directness of the evidence linking the intervention and health outcomes; the precision of the estimate of effect (based on the number and size of studies and confidence intervals for the estimates); strength of association (magnitude of effect); and the possibility for publication bias. We did not perform original meta-analyses. Rather, we relied on the results of existing individual studies and systematic reviews (including meta-analyses when available).

We rated the strength of evidence for each Key Question using the four categories recommended in the AHRQ guide:[45] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or does not permit a conclusion.

Results

Overview

For the original comparative efectiveness review (CER), searches identified 2,789 publications: 1,522 from the Cochrane Central Register of Controlled Trials, 68 from the Cochrane Database of Systematic Reviews, 1,015 from MEDLINE and 184 from the combination of other sources listed above. There were also 59 studies not previously reviewed for inclusion that were suggested through peer review or public comment or published after the searches were conducted. Following application of inclusion criteria, 321 publications were included in the original CER.

For the update, searches identified 93 citations from the Cochrane Central Register of Controlled Trials, 52 from the Cochrane Database of Systematic Reviews, 579 from MEDLINE and 139 from other sources (including suggestions from experts, gray literature searches, and reviewing reference lists). We combined the publications found in the update searches with the publications included from the original report in the EndNote library. A total of 491 full-text articles were reviewed for inclusion in this update, with 273 publications determined to be eligible. There were 180 articles included in Key Question 1, 33 articles for Key Question 1a, 52 articles for Key Question 2, 41 articles for Key Question 3, and 19 articles for Key Question 4. Reasons for exclusion of studies can be found in the literature flow diagram (Figure 2) and a list of excluded studies can be found in Appendix E.

Few randomized trials met criteria to be considered effectiveness studies.[48] Almost all trials applied numerous exclusion criteria, used rigid dosing regimens. In addition, most trials were relatively short term. An exception was a new trial of topical versus oral ibuprofen that randomized patients to advice to use topical or oral ibuprofen without a fixed dosing regimen and followed patients through one year.[49] A number of large observational studies were population-based or evaluated patients followed in large practice databases and met many criteria for effectiveness studies.

Figure 2. Study flow diagram

Abstracts of potentially relevant articles reviewed: **1,184**
Identified through bibliographical databases: CCRCT, CDSR, MEDLINE, other sources (experts, reference lists and gray literature)

Articles included in previous report: **321**

Excluded abstracts: **693**

Full text articles reviewed for relevance to Key Questions: **491**

Articles excluded: total: **218**
- Used as background: **40**
- Foreign language article: **13**
- Outcomes not included in this review: **60**
- Drug not included in this review: **32**
- Population differs from those in this review: **27**
- Publication type not included in this review: **21**
- Study design not included in this review: **2**
- Study results included through another publication: **23**

Includes **273**

*The total number of articles for all of the key questions exceeds the number in the 'Includes' box because articles could be included in more than one key question

Included Articles:

Key Question 1.
1. 180 articles
1a. 33 articles

Key Question 2.
52 articles

Key Question 3.
41 articles

Key Question 4.
19 articles

Key Question 1. What are the Comparative Benefits and Harms of Treating Osteoarthritis With Oral Medications or Supplements?

Summary of Evidence

Benefits:
- Celecoxib versus nonselective nonsteroidal anti-inflammatory drugs (NSAIDs):
    - There were no clear differences between celecoxib and various nonselective NSAIDs in efficacy for pain relief or withdrawals due to lack of efficacy.
- Partially selective NSAIDs versus nonselective NSAIDs:
    - Meloxicam, etodolac, and nabumetone were associated with no clear differences in efficacy compared to nonselective NSAIDs in patients with osteoarthritis.
- Nonselective NSAIDs versus nonselective NSAIDs:
    - There were no clear differences in efficacy between various non-aspirin, nonselective NSAIDs
- Aspirin or salsalate versus other NSAIDs:
    - Sparse evidence of no difference in efficacy between aspirin and salsalate. No trials compared aspirin or salsalate versus other NSAIDs

Harms: gastrointestinal (GI) and cardiovascular (CV)
- Celecoxib:
    - In systematic reviews of arthritis trials, most of which evaluated short-term use, celecoxib was associated with fewer ulcer complications than nonselective NSAIDs.
    - It is not clear whether celecoxib is associated with fewer serious GI harms than nonselective NSAIDs when used longer than 3-6 months. In the only large, long-term trial (CLASS) designed to assess ulcer complications (perforation, obstruction, or bleeding), celecoxib at 800 mg daily did not decrease predefined ulcer complications compared with diclofenac and ibuprofen at 12 months; the risk of ulcer complications at 6 months was lower with celecoxib than with ibuprofen, but not diclofenac, in patients who did not use aspirin; and there was no reduction in ulcer complications at 12 months. The overall rate of serious adverse events with celecoxib was similar to the rate with ibuprofen and diclofenac.
    - Celecoxib was associated with an increased risk of CV events or trend towards increased risk (CV death, myocardial infarction, stroke, heart failure, or thromboembolic events) relative to placebo in systematic reviews of randomized controlled trials (RCTs). Most of the CV events with celecoxib were reported in two large polyp-prevention trials evaluating 200 mg or 400 mg twice daily, or 800 mg once daily.
        - One additional CV event occurred for about every 270 patients treated for one year with celecoxib compared to placebo.
        - Systematic reviews found no clear difference between celecoxib and nonselective NSAIDs in risk of CV events.

- Partially selective NSAIDs:
  - Meloxicam (relative risk [RR] 0.53, 95% confidence interval [CI] 0.29 to 0.97) and etodolac (RR 0.32, 95% CI 0.15 to 0.71) were associated with a lower risk of ulcer complications or symptomatic ulcers compared to nonselective NSAIDs in a systematic review of randomized, but differences in risk of ulcer complications alone did not reach statistical significance.
  - There was insufficient evidence to make reliable judgments about GI harms of nabumetone relative to nonselective NSAIDs, or CV harms of any partially selective NSAID.
- Nonselective NSAID versus nonselective NSAID or any cyclooxygenase (COX)-2 selective NSAID:
  - No clear difference in GI safety was found among nonselective NSAIDs at commonly used doses.
  - COX-2 selective NSAIDs as a class were associated with similar, lower risks of ulcer complications relative to naproxen (RR 0.34, 95% CI 0.24 to 0.48), ibuprofen (RR 0.46, 95% CI 0.30 to 0.71), and diclofenac (RR 0.31, 95% CI 0.06 to 1.6).
  - The CV safety of naproxen appeared moderately superior to that of any COX-2 selective NSAID in two systematic reviews of RCTs.
    - In a large systematic review of RCTs, one additional myocardial infarction occurred for about every 300 patients treated for 1 year with a COX-2 selective NSAID instead of naproxen.
  - Most observational studies showed similar estimates of CV risk for naproxen, COX-2 selective NSAIDs, and other nonselective NSAIDs.
  - The CV safety of nonselective NSAIDs other than naproxen (data primarily on ibuprofen and diclofenac) was similar to that of COX-2 selective NSAIDs in a large systematic review of randomized trials.
  - In two systematic reviews that included indirect analyses of randomized trials, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo (RR 0.92, 95% CI 0.67 to 1.3 and RR 1.2, 95% CI 0.78 to 1.9).
- Aspirin:
  - Aspirin is associated with a lower risk of serious cardiovascular events (0.51% aspirin vs. 0.57% control per year, p=0.0001 for primary prevention 6.7% vs. 8.2%, p<0.0001 for secondary prevention) and a higher risk of major GI and other extracranial bleeds (0.10% vs. 0.07%, p<0.0001) compared to placebo when given at long-term, primarily lower prophylactic doses.
  - There is insufficient evidence to assess the balance of GI and CV safety of higher dose aspirin as used for pain relief compared with nonaspirin NSAIDs.
- Salsalate:
  - Salsalate was associated with a lower risk of adverse events than other selective and nonselective NSAIDs using broad composite endpoints in older, poor-quality observational studies.
  - No randomized trial or observational study evaluated risk of serious GI or CV harms associated with salsalate.

Harms: mortality
- Individual trials and systematic reviews have recorded too few events to detect differences in mortality between different NSAIDs.
- In one fair-quality cohort study, nabumetone was associated with a lower risk of all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.

Harms: hypertension, congestive heart failure (CHF), or impaired renal function
- All COX-2 selective and nonselective NSAIDs can cause or aggravate hypertension, congestive heart failure, and impaired renal function.
- Short-term trials showed that, on average, nonselective NSAIDs raised mean blood pressure by about 5.0 mm Hg (95% CI 1.2 to 8.7).
- There was no clear evidence of clinically relevant, consistent differences between celecoxib, partially selective, and nonselective NSAIDs in risk of hypertension, congestive heart failure, or impaired renal function.

Harms: hepatotoxicity
- Clinically significant hepatotoxicity was rare.
- Among currently marketed NSAIDS, diclofenac was associated with the highest rate of hepatic laboratory abnormalities (78/1,000 patient-years with diclofenac vs. 16 to 28/1,000 for other NSAIDs in one systematic review; 3.6% vs. <0.43% in another systematic review).

Tolerability
- Relative to nonselective NSAIDs, COX-2 selective and partially selective NSAIDs were better or similarly tolerated.
- There were no clear differences in tolerability between nonselective NSAIDs.
- Two of three short-term trials found salsalate less well tolerated than nonselective NSAIDs, but older, flawed observational studies found salsalate better tolerated than nonselective NSAIDs.

Other oral agents: benefits and harms
- Acetaminophen
  - Acetaminophen was modestly inferior to NSAIDs for pain and function in four systematic reviews.
    - Pain severity ratings averaged less than 10 points higher for acetaminophen compared to NSAIDs on 100-point visual analogue scales.
  - Compared with NSAIDs, acetaminophen had fewer GI side effects (clinical trials data) and serious GI complications (observational studies).
  - Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies).
  - One good-quality, prospective observational study found an increased risk of CV events with heavy use of acetaminophen that was similar to the risk associated with heavy use of NSAIDs.
  - Acetaminophen may cause elevations of liver enzymes at therapeutic doses even in healthy persons.

- Glucosamine and chondroitin
  - Seven randomized trials showed no clear difference between glucosamine and oral NSAIDs for pain or function.
  - One randomized trial showed no clear difference between chondroitin and an oral NSAID for pain or function.
  - A systematic review including recent, higher-quality trials found glucosamine associated with statistically significant but clinically insignificant beneficial effects on pain (-0.4 cm on a 10 cm scale) and joint space narrowing (-0.2 mm, 95% CI -0.3 to 0.0) compared to placebo.
  - Similar results were reported for chondroitin.
  - Glucosamine and chondroitin were tolerated similarly to placebo and no serious adverse events were reported in randomized trials.

Detailed Analysis

Benefits

Celecoxib

Two systematic reviews included in the original CER evaluated the efficacy of celecoxib versus nonselective NSAIDs.[50, 51] We identified two fair-quality head-to-head trials of celecoxib versus diclofenac (n=925 and n=249) published since the original CER (Appendix H).[52, 53]

A good-quality systematic review (published in 2002) funded by the makers of celecoxib found similar effects on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores associated with celecoxib and nonselective NSAIDs based on data from published and unpublished randomized trials of at least 12 weeks' duration in patients with either osteoarthritis (OA) or rheumatoid arthritis (RA).[50] A more recent systematic review (published in 2005) with access to all unpublished manufacturer-held clinical trial reports found celecoxib at doses of 200-400 mg associated with slightly higher rates of withdrawals due to lack of efficacy compared to nonselective NSAIDs (RR 1.1; 95% CI 1.0, 1.2), based on data from 31 primarily short-term (≤12 weeks) trials.[51]

The two largest head-to-head trials of celecoxib versus nonselective NSAIDs are the Celecoxib Long-term Arthritis Safety Study (CLASS)[54] and the Successive Celecoxib Efficacy and Safety Study-1 (SUCCESS-1).[55] Both systematic reviews included CLASS (n=7,968), a pivotal, long-term (6 to 13 months) trial of celecoxib versus the nonselective NSAIDs ibuprofen or diclofenac for rheumatoid and osteoarthritis.[54] The nonselective NSAIDs were associated with a slightly higher (but statistically significant) likelihood of withdrawal due to lack of efficacy compared to celecoxib (15% vs. 13%, p=0.005). CLASS focused on assessment of adverse events rather than efficacy, and other efficacy results were not reported. The Moore et al. systematic review[51] included the large (n=13,274), Successive Celecoxib Efficacy and Safety Study (SUCCESS-1), which found no clinically meaningful (and mostly statistically nonsignificant) differences after 12 weeks in efficacy (pain, global assessment of arthritis, or WOMAC total score) between celecoxib 100 mg or 200 mg twice daily and the nonselective NSAIDs diclofenac and naproxen in patients with osteoarthritis.[55] Withdrawals due to lack of efficacy were not reported.

A new, fair-quality trial (high loss to followup) found no differences between celecoxib 200 mg once daily and diclofenac 50 mg twice daily in pain scores, global assessment of arthritis, or

patient satisfaction through 52 weeks of followup in older (≥60 years) patients (n=925) with osteoarthritis.[52] Withdrawals due to adverse events were slightly less frequent with celecoxib compared with diclofenac, but the difference was not statistically significant (27% vs. 31%, RR 0.87, 95% CI 0.71-1.1). Another new, fair-quality trial (high loss to followup, allocation concealment method not described, failure to report intention-to-treat analysis) reported results inconsistent with other trials.[53] It failed to demonstrate noninferiority of celecoxib 200 mg compared to diclofenac 50 mg three times daily on pain at 6 weeks (mean difference between drugs in change from baseline 12 mm on a 0 to 100 visual analogue scale (VAS), 95% CI 5.8 to 18) or 12 weeks (10 mm, 95% CI 2.8 to 17) in patients with hip osteoarthritis requiring joint replacement surgery. Withdrawals due to lack of efficacy were similar (13 percent vs. 11 percent).

Partially Selective NSAIDs

Three systematic reviews included in the original CER evaluated the efficacy of the partially selective NSAIDs etodolac or nabumetone versus nonselective NSAIDs.[9, 56, 57] One new, good-quality systematic review evaluated comparative efficacy of the partially selective NSAIDs for osteoarthritis or rheumatoid arthritis (Appendix H).[58] We identified no new head-to-head trials of partially selective NSAIDs versus nonselective NSAIDs published since the original CER.

Eleven randomized, double-blinded trials of meloxicam 7.5 mg, 15 mg, or 25 mg versus other NSAIDs for osteoarthritis found no clear or consistent differences in efficacy.[59-69] In two of the trials, meloxicam was associated with a greater likelihood of withdrawal due to lack of efficacy than nonselective NSAIDs.[63, 68] The new systematic review, which included trials of patients with osteoarthritis or rheumatoid arthritis, found meloxicam associated with lower efficacy compared to nonselective NSAIDs for pain (difference 1.7 points on a 10-point VAS pain scale, 95% CI 0.8 to 2.7) and withdrawals due to lack of efficacy (RR 1.5, 95% CI 1.2 to 1.7).[58]

The original CER included several good-quality Cochrane systematic reviews of randomized trials that found no difference between etodolac and various nonselective NSAIDs for OA of the hip (trials published through 1994),[70] back (through 1998),[9] or knee (through 1997).[57] In seven trials published after or not included in the Cochrane reviews, there were also no differences between sustained-release etodolac and diclofenac[71] or tenoxicam;[72] or between standard-formulation etodolac and piroxicam (2 trials[73, 74]), naproxen (2 trials[75, 76]), or nimesulide[77] for OA of the knee, hip, or foot. The new systematic review found no differences between etodolac and various nonselective NSAIDs for pain (mean difference 2.1, 95% CI -2.1 to 6.2) or withdrawals due to lack of efficacy (RR 1.0, 95% CI 0.85 to 1.2) in patients with osteoarthritis or rheumatoid arthritis.[58]

The Cochrane review of NSAIDs for knee osteoarthritis found nabumetone similar in efficacy to the nonselective NSAIDs diclofenac SR[78] and etodolac[79] in two 4-week trials.[57]

Nonselective NSAIDs

The original CER included several good-quality systematic reviews by the Cochrane Collaboration of trials that compared various nonselective NSAIDs for OA of the hip (trials published through 1994),[70] back (through 1998),[9] or knee (through 1997).[57] These reviews found no clear differences in efficacy between non-aspirin, primarily nonselective NSAIDs. We identified no new head-to-head trials comparing efficacy of one non-aspirin, nonselective

NSAID versus another. The large SUCCESS-1 trial included diclofenac and naproxen arms, but only reported combined efficacy results for these two nonselective NSAIDs.[55]

Aspirin or Salsalate

We identified no new head-to-head trials comparing efficacy of aspirin or salsalate versus other NSAIDs. A head-to-head trial included in the original CER found salsalate 3 g once daily and aspirin 3.6 g once daily associated with similar efficacy in patients with OA after 2 weeks of treatment.[80]

Safety: Serious Gastrointestinal and Cardiovascular Harms

Randomized Controlled Trials

Celecoxib: GI Harms

One systematic review of randomized trials of serious GI harms associated with celecoxib versus nonselective NSAIDs was included in the original CER (Appendix H).[51] We included another fair-quality systematic review that only had preliminary results available at the time of the original CER (Appendix H).[81] We identified one new pooled analysis of three similarly designed, 12-week trials of celecoxib versus diclofenac[82] and one other new head-to-head trial of celecoxib versus diclofenac,[52] but they either did not report serious GI events[82] or reported too few events (two GI ulcers in nearly 1,000 patients)[52] to affect the conclusions of the systematic reviews.

The systematic reviews both included the pivotal CLASS trials (n=7,968),[54] which compared the risk of serious GI harms associated with celecoxib versus nonselective NSAIDs for osteoarthritis or rheumatoid arthritis. CLASS was designed as two trials with separate patient recruitment and randomization procedures: 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. The prespecified primary outcome was ulcer-related complications, defined as gastric or duodenal perforation, gastric outlet obstruction, or upper GI bleeding (POBs).[83] Another prespecified outcome was ulcer related complications plus symptomatic ulcers (PUBs). The planned maximum duration of the trials were 15 and 12 months, respectively, or until at least 20 ulcer-related complications occurred in each trial, or 45 in both trials combined.[84] The prespecified criteria to conclude superiority of celecoxib was statistically significant differences between celecoxib and each of the comparators, as well as between celecoxib versus the comparator groups combined.

CLASS was stopped early after reaching a predefined threshold of ulcer complications. The main publication in the Journal of the American Medical Association (JAMA) reported 6-month results even though the median duration of followup was 9 months (the rationale for reporting truncated data was high attrition), and combined the ibuprofen and diclofenac results without reporting the results of the two trials separately.[54] Additional details of the study were subsequently made public on the Food and Drug Administration (FDA) Web site.[84]

CLASS randomized 3,987 subjects to celecoxib and 3,981 subjects to nonselective NSAIDs. The JAMA article reported celecoxib associated with fewer PUBs (a secondary outcome) compared to the combined nonselective NSAIDs (32/3,987 vs. 51/3,981, annualized incidence rates 2.1% vs. 3.5%, p=0.02),[54] while the rates of POBs (the primary outcome) were not significantly different (13/3,987 vs. 22/3,981, annualized incidence rates 0.76% vs. 1.4%,

p=0.09). By 12 months, according to FDA documents (see Table 13, FDA Medical Officer Review)[84] there was no longer a trend favoring celecoxib for POBs (17/3987 [0.43%] events with celecoxib vs. 21/3,981 [0.53%] with the nonselective NSAIDs,[84] relative risk 1.1, 95% CI 0.47 to 2.6[85, 86], also see Figure 4, Scheiman review[87]). For the individual comparisons between celecoxib and ibuprofen or diclofenac, which were not reported in the JAMA article, there was no difference in the rate of ulcer complications at either 6 months or the end of followup.[85] For the secondary outcome of PUBs, celecoxib was superior to ibuprofen, but not to diclofenac at 6 months and the end of followup.[85] Celecoxib was also associated with a lower risk of hemoglobin (>2 g/dL) and/or hematocrit drops (≥0.10), among all patients (2.4% vs. 4.4% and 5.7% for celecoxib, diclofenac, and ibuprofen, respectively.[84]

About 20 percent of the patients in the CLASS trial took aspirin in addition to their study NSAID. 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).[84, 85] However, serious ulcer complications were equivalent for celecoxib and diclofenac after exclusions of patients taking aspirin.

The new, fair-quality, nonmanufacturer-funded systematic review found celecoxib associated with a lower risk of POBs compared to nonselective NSAIDs (3 trials, RR 0.23, 95% CI 0.07 to 0.76) as well as a lower risk of PUBs (4 trials, RR 0.39, 95% CI 0.21-0.73).[81] Use of 12-month instead of 6-month CLASS data did not significantly alter the pooled estimates. The systematic review also found selective COX-2 inhibitors as a class associated with lower risk of GI adverse events and withdrawal due to GI adverse events compared to nonselective NSAIDs, but did not report separate analyses for celecoxib.

The largest study in the Rostom et al. review was a manufacturer-funded combined analysis by Goldstein et al. of 14 randomized controlled trials (RCTs) of celecoxib (not including CLASS) versus placebo or nonselective NSAIDs (usually naproxen).[88] The trials ranged in duration from 2 to 24 weeks, with most lasting 6 or 12 weeks. The definition of ulcer complications (POBs) was similar to the one used in CLASS, and in all trials a blinded Safety Committee adjudicated potential ulcer complications. Not all of the included trials have been published, and their quality was not assessed by Goldstein et al. In addition, data were pooled across trials without regard to randomization, duration of therapy, or which comparator NSAID was evaluated. In the 14 trials, there were 2 POBs among 6,376 patients in the celecoxib group (3 per 10,000) and 9 among 2,768 in the NSAIDs group (33 per 10,000). This corresponded to annual rates of 2 per 1,000 patient-years for celecoxib and about 17 per 1,000 patient-years for NSAIDs (p=0.002). Rostom et al. found that excluding this study eliminated heterogeneity from the pooled analyses, but celecoxib was still associated with a lower risk of POBs (RR 0.42, 95% CI 0.22 to 0.80) and PUBs (RR 0.34, 95% CI 0.22 to 0.80) compared to nonselective NSAIDs.[81]

A systematic review by Moore et al. included in the original CER was funded by Pfizer and the Oxford Pain Relief Trust.[51] The authors obtained a declaration from Pfizer that they had received information on all completed clinical trials of celecoxib and could publish whatever results they found, but much of the data on which this meta-analysis was based is not publicly accessible. Thus, although the meta-analysis methods appeared appropriate, it is impossible to verify the reproducibility of the meta-analysis. Rather than including the pooled analysis by Goldstein et al.,[88] Moore et al. appeared to have access to the individual trial methods and data.

All 18 trials of celecoxib versus nonselective NSAIDs included in the systematic review were rated 5 out of 5 on the Jadad quality scale, and 16 out of 16 on an 8-item validity scale.[51] Only 2 of the 31 trials were longer than 12 weeks in duration. Although POBs was not evaluated

as an outcome, celecoxib was associated with a lower risk of clinical ulcers and bleeds than nonselective NSAIDs in 18 trials (RR 0.61, 95% CI 0.46 to 0.81). When the analysis was limited to trials evaluating doses of 200 or 400 mg daily of celecoxib (excluding CLASS), the benefit was more pronounced (RR 0.35, 95% CI 0.22 to 0.56). The meta-analysis also found celecoxib associated with a lower risk of hemoglobin fall of 20 g/L or more (RR 0.72, 95% CI 0.56 to 0.92) and hematocrit fall of 5% or more (RR 0.78, 95% CI 0.69 to 0.89) compared with nonselective NSAIDs.[51]

In addition to having access to the individual trials included in Goldstein et al., another difference between the systematic review by Moore et al. and the one by Rostom et al. is that the latter did not include results of SUCCESS-1, the largest (N=13,274) randomized controlled trial of celecoxib.[55] SUCCESS-1 found celecoxib associated with a lower risk of POBs than naproxen or diclofenac after 12 weeks in patients with osteoarthritis (0.1% vs. 0.8%, odds ratio [OR] 0.14, 95% CI 0.03 to 0.68). Post hoc analysis of nonaspirin users found nonselective NSAIDs associated with a significantly higher risk of ulcer complications compared to celecoxib, though the estimate was very imprecise (OR 12, 95% CI 1.4 to 100).[55]

There are several possible reasons why the results of the systematic reviews differed from those of CLASS, which did not clearly show a decreased risk of POBs for celecoxib compared to nonselective NSAIDs. First, the incidence of POBs in CLASS was relatively high.[54] In the CLASS trials, the annualized rate of POBs was 0.8/100 patient-years for celecoxib and 1.4 per 100 patient-years for nonselective NSAIDs,[54] compared to 0.1/100 patient-years and 0.8/100 patient-years, respectively, in SUCCESS-1.[55] The high rate of POBs in the CLASS trials could be due in part to enrollment of a higher-risk population, the use of concomitant medications, or other factors. In CLASS, 20 percent of patients randomized to celecoxib were on aspirin and 31 percent on corticosteroids,[54] whereas in SUCCESS-1, 7 percent were on aspirin and corticosteroid use was not permitted.[55] In addition, antiulcer medications (except for occasional antacids) were prohibited in CLASS, but used in 16 percent of celecoxib patients in the Goldstein et al. combined analysis.[88] Another potential explanatory factor is that the high dose of celecoxib used in CLASS—400 mg twice daily—was evaluated in few other trials, and could be associated with an increased risk of bleeding compared to lower doses. Finally, different comparator NSAIDs could be associated with different risks of GI complications. Pooling data from trials evaluating different comparator NSAIDs could obscure differential effects on GI safety if they were present.

Partially Selective NSAIDs

Five systematic reviews included in the original CER evaluated the comparative risks of serious GI harms associated with partially selective compared to nonselective NSAIDs.[89-93] We identified one new systematic review (Appendix H).[58] We identified no new head-to-head trials comparing serious GI harms of partially selective versus nonselective NSAIDs.

Four systematic reviews of short-term trials reported PUBs associated with meloxicam.[58, 91-93] The meta-analyses mainly included in the same trials, and reported fairly consistent results. A new, good-quality systematic review, funded by UK Health Technology Assessment Programme, found meloxicam (primarily at a dose of 7.5 mg/day) associated with a lower risk for PUBs compared to various nonselective NSAIDs (6 trials, RR 0.53, 95% CI 0.29 to 0.97, p for heterogeneity=0.77), but the difference in risk of POBs did not reach statistical significance (6 trials, RR 0.56, 95% CI 0.27 to 1.2, p for heterogeneity=0.95).[58] Results were mainly driven by short-term (4 week) trials of low-dose (7.5 mg) meloxicam. An earlier systematic review of

10 trials found the risk of PUBs reduced with meloxicam (OR 0.52, 95% CI 0.28 to 0.96) compared to nonselective NSAIDs.[92] The third meta-analysis was funded by the manufacturer of meloxicam and used manufacturer-held documents from 28 trials.[93] It found a dose-response relationship between meloxicam and PUBs (ascertained by a blinded, external adjudication committee). Meloxicam 7.5 mg was associated with lower PUB rates during the first 60 days compared to diclofenac, piroxicam, or naproxen, but the 15 mg dose was only associated with lower PUB rates than piroxicam. Finally, a good-quality systematic review found meloxicam associated with no increased risk of a composite GI outcome (including GI tolerability, PUBs, GI hospitalization, or GI-related death) compared to nonuse (RR 1.2, 95 % CI 0.98 to 1.6), and a similar risk compared to nonselective NSAIDs.[91] Estimates for GI hospitalizations or GI-related deaths alone were not reported.

The new systematic review found etodolac (primarily at a dose of 600 mg/day) associated with a lower risk of PUBs compared to various nonselective NSAIDs (9 trials, RR 0.32, 95% CI 0.15 to 0.71, p for heterogeneity=0.87).[58] The difference in risk of POBs was not statistically significant (6 trials, RR 0.39, 95% CI 0.12 to 1.2) but the number of events was very small (1 in the etodolac arms and 7 in the nonselective NSAID arms).

For nabumetone, a fair-quality meta-analysis included in the original CER of 6 short-term (3 to 6 months) studies (5 published and 1 abstract) found 1 PUB event among 4,098 patients taking nabumetone versus 17 events among 1,874 nonselective NSAID patients; this difference was highly statistically significant.[89] The absolute PUB rates were about 2 versus 6 per 1,000 patient-years. For comparison, in a similar meta-analysis, the PUB rates per 1,000 patients per year were 13 for rofecoxib and 26 for NSAIDs.[90] It is not clear why the rates of PUBs were so much lower in the nabumetone trials. There was also a significant reduction in treatment-related hospitalizations in the nabumetone group (6.4 per 1,000 patient-years versus 20 per 1,000 patients-years). Risks of POBs were not reported. A problem in interpreting these results is that the methods used to ascertain the endpoints in the trials were not described in enough detail to determine whether they were accurate or applied consistently.

Nonselective NSAIDs

Two systematic reviews evaluated comparative risks of serious GI harms associated with nonselective NSAIDs.[91, 94] One was included in the original CER.[91] We also included final results from a fair-quality systematic review which only had preliminary results[94] at the time of the original CER (Appendix H).[81] It found COX-2 inhibitors as a class (celecoxib, rofecoxib, valdecoxib, lumiracoxib, and meloxicam) associated with a similarly decreased risk of POBs compared to naproxen (RR 0.34, 95% CI 0.24 to 0.48), ibuprofen (RR 0.46, 95% CI 0.30 to 0.71), and diclofenac (RR 0.31, 95% CI 0.06 to 1.6).[81] The systematic review did not include the large SUCCESS-1 study, which found no statistically significant difference in risk of POBs between naproxen (4 events, 1.83/100 patient-years) and diclofenac (3 events, 0.41/100 patient-years), though analyses were limited by the small number of events.[55]

The results of the new systematic review are consistent with a previous meta-analysis which found similarly increased risks of GI complications (major plus minor) for different NSAIDs relative to nonuse: indomethacin (RR 2.2, 95% CI 1.0 to 5.1), naproxen (RR 1.8, 95% CI 1.2 to 2.7), diclofenac (RR 1.7, 95% CI 1.2 to 2.5), piroxicam (RR 1.7, 95% CI 1.1 to 2.4), tenoxicam (RR 1.4, 95% CI 0.40 to 5.1), and ibuprofen (RR 1.2, 95% CI 0.93 to 1.5).[91]

Aspirin and Salsalate

We identified no new trials or systematic reviews on risk of ulcer complications in patients prescribed aspirin or salsalate at doses effective for analgesia. As noted in the original CER, randomized controlled trials assessing the risk of upper GI bleeding with aspirin have mainly been conducted in populations receiving aspirin as prophylaxis for thrombotic events. The populations evaluated in these trials may differ in bleeding risk compared to patients who take aspirin for arthritis. In these studies, the dose of aspirin varied widely and was generally lower (75 mg to 500 mg daily in most trials) than the doses considered effective for analgesia and anti-inflammatory effects, and patients typically received aspirin for prolonged periods. In a good-quality meta-analysis of 24 randomized trials with nearly 66,000 participants, the risk of GI hemorrhage was 2.5 percent with aspirin compared with 1.4 percent with placebo (OR 1.7, 95% CI 1.5 to 1.9), based on an average of 28 months therapy.[95] A good-quality collaborative meta-analysis of individual patient data from randomized trials (over 110,000 participants) found aspirin associated with increased risk of GI and other extracranial bleeding when given for primary prevention (RR 1.5, 95% CI 1.3 to 1.8, absolute risk 0.10% vs. 0.07%) or secondary prevention (RR 2.7, 95% CI 1.2 to 5.8; absolute difference not estimated due to incomplete reporting).[96]

No randomized trial reported risk of ulcer complications associated with salsalate.

Observational Studies

One new systematic review[97] and five systematic reviews[10, 98-101] included in the original CER evaluated serious GI harms associated with various NSAIDs.

The new, fair-quality (did not assess quality of included studies) systematic review (by Massó González et al.) found celecoxib associated with an increased risk of upper GI bleeding or perforation compared to nonuse (four studies, RR 1.4, 95% CI 0.85 to 2.4), but the risk was lower than for nonselective NSAIDs as a group (eight studies, RR 4.5, 95% CI 3.8 to 5.3) as well as for individual nonselective NSAIDs, though confidence interval estimates overlapped in some cases (Table 3, Appendix H).[97]

Table 3. Risk of upper gastrointestinal bleeding or perforation with use of an NSAID compared with nonuse of NSAIDs, systematic review of observational studies[97]

NSAID	Number of Studies	Pooled Estimate (95% CI)
Celecoxib	4	1.4 (0.85 to 2.4)
Meloxicam	4	4.2 (2.6 to 6.6)
Naproxen	6	5.6 (3.8 to 8.3)
Ibuprofen	5	2.7 (2.2 to 3.3)
Diclofenac	6	4.0 (3.4 to 4.7)
Indomethacin	5	5.4 (4.2 to 7.0)
Ketoprofen	5	5.6 (3.9 to 7.9)
Piroxicam	5	9.9 (6.0 to 16)
Ketorolac	2	15 (5.9 to 36)

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug

Meta-analyses of observational studies included in the original CER reported similar findings. In a collaborative meta-analysis of cohort and case-control studies published between 1985 and 1994, use of all nonselective NSAIDs were associated with significantly increased risks of peptic ulcer complication hospitalizations relative to nonuse.[100] As in the Massó

González et al. review, ibuprofen was associated with the lowest risk of peptic ulcer complication-related hospitalizations compared to other nonselective NSAIDs.[95] In two other meta-analyses of cohort and case-control studies published between 1990 and 1999, however, risk of upper GI bleeds was no lower for ibuprofen compared to any other non-aspirin, nonselective NSAID when results were stratified by low to medium (RR 2.1 vs. nonuse, 95% CI 1.6 to 2.7) or high dose (RR 5.5 vs. nonuse, 95% CI 3.0 to 10) (Table 4).[98, 101] A systematic review of observational studies published through 2002 also found GI bleeding risk increased for all nonselective NSAIDs, with risk appearing related more to dose than to the specific drug evaluated.[10]

Eight large case-control (>1,000 cases) or cohort (n>100,000) studies reported risks of serious upper GI complications associated with various NSAIDs (Table 4, Appendix H).[98, 102-108] Two of the studies were published after the original CER,[102, 108] and all but two were included in the new systematic review.[103, 108] Three studies used a cohort design[106-108] and the remainder used a case-control (or nested case-control) design. Two case-control studies were rated good quality[102, 104] and the remainder of the observational studies rated fair quality (Appendix G). The most common methodological shortcomings in the fair-quality case-control studies were failure to report the proportion of patients who met inclusion criteria who were excluded from the study and unclear accuracy of methods used to ascertain exposures and potential confounders. The most common methodological shortcomings in the fair-quality cohort studies were noncomparability of groups at baseline, unclear blinding status of outcomes assessors and data analysts, and failure to report attrition from a defined inception cohort.
Four of the observational studies found celecoxib associated with an no increased risk of upper GI complications compared to nonuse[103, 104, 106] or acetaminophen use.[108] A fifth study found celecoxib associated with an increased risk of upper GI perforation or bleeding compared to nonuse, but risk estimates were similar or lower than those for nonselective NSAIDs.[102]

The partially selective NSAID meloxicam was evaluated in four of the large observational studies.[98, 102, 104, 105] Meloxicam was associated with a risk of upper GI bleeding relative to nonuse of NSAIDs that was generally in the midrange of risks reported for various nonselective NSAIDs. Only one study reported risks associated with other partially selective NSAIDs, and estimates were imprecise.[98]

For various nonselective NSAIDs, the observational studies generally showed increased risk of GI bleeding relative to nonuse.[98, 102, 103, 105-107] Naproxen was associated with a higher risk than ibuprofen in seven studies,[98, 102-105, 107, 108] though the risk estimates were relatively close in two of them.[103, 107] Comparative data for other nonselective NSAIDs was less consistent. For example, diclofenac was associated with similar or lower risk compared to ibuprofen in three studies, [103, 104, 108] but higher in four others.[98, 102, 105, 107]

The risk of upper GI bleeding was similar with aspirin compared to non-aspirin, nonselective NSAIDs in one large nested case-control study.[103] Systematic reviews of observational studies included in the original CER found that aspirin increases risk of serious GI events relative to placebo or nonuse, at a rate similar to that of other nonselective NSAIDs.[99, 100]

Serious GI event rates (bleeding, perforation, obstruction) associated with salsalate were reported in one smaller cohort study (n=1,198) of long-term care residents in Indiana.[109] The number of cases of GI-related hospitalizations associated with salsalate (1, 5.9 percent) after 14 months was similar to that of other selective and nonselective NSAIDs.

Table 4. Serious gastrointestinal events in observational studies

Author, Year Study Design Sample Size	Mean age (yrs) Country	Outcome	Main Findings
Garcia Rodriguez, 2007[102] Nested case-control Cases: 1561	NR UK (The Health Improvement Network database)	Upper GI perforation or bleeding	*NSAID use vs. nonuse of NSAIDs (CI's not reported and difficult to estimate from graph)* Celecoxib: RR 2.7 Ibuprofen: RR 2.0 Meloxicam: RR 2.7 Diclofenac: RR 3.7 Ketoprofen: RR 5.4 Indomethacin: RR 7.2 Naproxen: RR 8.1
Garcia Rodriguez, 2001[98] Nested case-control Cases: 2105	NR UK (GPRD)	Upper GI perforation or bleeding	*NSAID use vs. nonuse of NSAIDs* Ibuprofen: RR 2.5 (95% CI 1.9 to 3.4) Etodolac: RR 2.2 (95% CI 0.4 to 11) Fenbufen: RR 1.1 (95% CI 0.2 to 5.1) Mefenamic acid: RR 2.7 (95% CI 0.8 to 9.4) Ketoprofen: RR 3.3 (95% CI 1.9 to 5.9) Nabumetone: RR 3.4 (95% CI 1.1 to 11) Tenoxicam: RR 3.4 (95% CI 0.9 to 13) Meloxicam: RR 3.8 (95% CI 0.8 to 17) Naproxen: RR 4.0 (95% CI 2.8 to 5.8) Diclofenac: RR 4.6 (95% CI 3.6 to 5.8) Flurbiprofen: RR 4.6 (95% CI 2.0 to 11) Indomethacin: RR 5.2 (95% CI 3.2 to 8.3) Piroxicam: RR 6.2 (95% CI 3.7 to 10)
Hippisley-Cox 2005[103] Nested case-control Cases: 9407	NR; ≥ 25 UK	Complicated GI Event	*NSAID use within 90 days vs. no prescription for 3 years* Celecoxib: OR 1.2 (95% CI 0.91 to 1.7) Ibuprofen: OR 1.6 (95% CI 1.4 to 1.8) Diclofenac: OR 2.1 (95% CI 1.8 to 2.4) Naproxen: OR 2.0 (95% CI 1.5 to 2.6) Aspirin: OR 1.8 (95% CI 1.6 to 1.9)
Lanas, 2006[104] Case-control Cases: 2777	NR Spain	Hospitalization for upper G I bleeding	Celecoxib use vs. nonuse of selective NSAID: RR 1.0 (95% CI 0.4 to 2.1) *NSAID use vs. nonuse of nonselective NSAID* Ibuprofen: RR 4.1 (95% CI 3.1 to 5.3) Diclofenac: RR 3.1 (95% CI 2.3 to 4.2) Aceclofenac: RR 2.6 (95% CI 1.5 to 4.6) Naproxen: RR 7.3 (95%CI 4.7 to 11) Piroxicam: RR 13 (95% CI 7.8 to -20) Indomethacin: RR 9.0 (95% CI 3.9 to 21) Meloxicam: RR 9.8 (95% CI 4.0 to 24) Ketorolac: RR 14 (95% CI 5.2 to 50) Lornoxicam: RR 7.7 (95% CI 2.4 to 24) Ketoprofen: RR 8.6 (95% CI 2.5 to 29)
Laporte 2004[105] Case-control Cases=2,813	NR; ≥ 18 Spain and Italy	Upper GI bleeding	*NSAID use vs. nonuse of NSAIDs* Aspirin: OR 8.0 (95% CI 6.7 to 9.6) Dexketoprofen: OR 4.9 (95% CI 1.7 to 14) Diclofenac: OR 3.7 (95% CI 2.6 to 5.4) Ibuprofen: OR 3.1 (95% CI 2.0 to 4.9) Indomethacin: OR 10 (95% CI 4.4 to 23) Ketoprofen: OR 10 (95% CI 3.9 to 26) Ketorolac: OR 25 (95% CI 8.0 to 77) Meloxicam: OR 5.7 (95% CI 2.2 to 15) Naproxen: OR 10 (95% CI 5.7 to 18) Nimesulide: OR 3.2 (95% CI 1.9 to 5.6) Piroxicam: OR 16 (95% CI 10 to 24)

Table 4. Serious gastrointestinal events in observational studies (continued)

Author, Year Study Design Sample Size	Mean age (yrs) Country	Outcome	Main Findings
Mamdani 2002[106] Cohort n=143,969	75.7 Canada	Upper GI hemorrhage	*NSAID use vs. no use of NSAIDs* Celecoxib: HR 1.0 (95% CI 0.7 to 1.6) Diclofenac + misoprostol: HR 3.0 (95% CI 1.7 to 5.5) Nonselective NSAIDs: HR 4.0 (95% CI 2.3 to 6.9) *NSAID use vs. celecoxib* Diclofenac + misoprostol: HR 3.2 (95% CI 1.6 to 6.5) Nonselective NSAIDs: HR 4.4 (95% CI 2.3 to 8.5)
Mellemkjaer, 2002[107] Cohort n=156,138 NSAID users	NR Denmark	Hospitalization for GI bleeding	*NSAID use vs. no use of NSAIDs* Diclofenac: RR 4.9 (95% CI 3.5 to 6.6) Ibuprofen: RR 2.4 (95% CI 2.0 to 2.9) Indomethacin: RR 4.3 (95% CI 2.9 to 6.0) Ketoprofen: RR 6.3 (95% CI 4.5 to 8.5) Naproxen: RR 3.0 (95% CI 2.1 to 4.2) Piroxicam: RR 5.0 (95% CI 3.3 to 7.2)
Rahme, 2007[108] Retrospective cohort N=510,871	NR; ≥65 Canada	Hospitalization for GI bleeding	*NSAID use vs. acetaminophen use* Celecoxib: HR 0.82 (95% CI 0.66 to 1.0) Ibuprofen: HR 1.1 (95% CI 0.56 to 2.2) Diclofenac: HR 1.2 (95% CI 0.86 to 1.6) Naproxen: HR 2.8 (95% CI 2.0 to 3.7)

CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; RR = relative risk; UK GPRD = United Kingdom General Practice Research Database

Cardiovascular Harms

Randomized Controlled Trials

Celecoxib

Four systematic reviews or meta-analyses included in the original CER (one as an earlier version available only as an FDA briefing document[110]) evaluated risk of serious CV events in randomized controlled trials of celecoxib (Table 5, Appendix H).[51, 111-113] Two new systematic reviews were identified for this update (Table 5, Appendix H).[114, 115] We identified one new placebo-controlled Chinese trial of celecoxib for prevention of gastric cancer that reported serious CV events,[116] and one head-to-head trial of celecoxib versus diclofenac for osteoarthritis.[52]

The systematic reviews all included CLASS.[54] Six-month data from CLASS showed no association between celecoxib and risk of myocardial infarction or any CV event (stroke, myocardial infarction, or angina) compared with the nonselective NSAIDs (myocardial infarctions 0.3% [10/3987] vs. 0.3% [11/3981]).[54] A subsequent analysis based on complete followup data also showed no differences in the rates of any significant CV event for the overall sample (0.5% [19/3987] vs. 0.3% [13/3981]) or for the subgroup who did not use aspirin.[117] Approximately 2,770 subjects in CLASS (about one-third of the sample) had at least 9 months of followup, and 1,126 had at least 12 months of followup.

Three systematic reviews provided the best information on CV risks associated with long-term use of celecoxib.[111, 114, 115] All included preliminary or published results from trials of celecoxib for prevention of colon polyps or Alzheimer's disease (Adenoma Prevention with

Celecoxib trial [APC], Alzheimer's Disease Anti-Inflammatory Prevention Trial [ADAPT], Prevention of Colorectal Sporadic Adenomatous Polyps [PreSAP]). Two systematic reviews were rated fair-quality due to failure to adequately assess trial quality[111, 114] or report statistical heterogeneity.[114] The third systematic review was rated good quality.[115] All of the meta-analyses excluded a number of short-term trials,[111, 114, 115] one of the meta-analyses excluded trials that did not have at least two arms with at least 100 patient years of followup,[115] and one of the meta-analyses[111] excluded trials without publicly available information on CV events. Although excluding short-term trials limited conclusions regarding short-term risks, data on long-term harms may be more relevant for patients using NSAIDs for chronic conditions such as osteoarthritis.

One of the two systematic reviews was a new study which limited inclusion to randomized, double-blind, placebo-controlled trials with planned followup of at least 3 years.[114] It included 6 trials (3,664 people randomized to celecoxib), none of which evaluated patients with osteoarthritis. Three trials evaluated celecoxib for colon polyp prevention (APC, PreSAP, and the Celecoxib/Selenium trial), one for prevention of Alzheimer's disease (ADAPT), one for prevention of recurrent breast cancer (MA27), and one for treatment of retinopathy (CDME). Relative to placebo, the overall risk of a CV event (CV death, myocardial infarction, stroke, heart failure, or a thromboembolic event) in patients randomized to celecoxib at any dose was increased (hazard ratio [HR] 1.6, 95% CI 1.1 to 2.3). The absolute difference in risk of a CV event was 3.7/1000 patient-years (11.2/1000 patient-years with celecoxib vs. 7.5/1000 patient-years with placebo), or 1 additional CV event for about every 270 patients treated with celecoxib instead of placebo for 1 year. However, the risk appeared to vary at different doses, and was lowest for celecoxib 400 mg once daily (HR 1.1, 95% CI 0.6 to 2.0), intermediate for celecoxib 200 mg twice daily (HR 1.8, 95% CI 1.1 to 3.1), and highest for celecoxib 400 mg twice daily (HR 3.1, 95% CI 1.5 to 6.1). In subgroup analyses, patients at higher baseline risk were at disproportionately increased risk of CV events compared to those at lower baseline risk (p-value for interaction 0.003).

The second systematic review, which was also a new study, limited inclusion to trials with at least 100 patient years of followup and performed a network analysis to incorporate indirect evidence into pooled estimates.[115] It included 31 trials of various NSAIDs versus placebo or other NSAIDs, with 6 trials of celecoxib versus placebo (12,799 patient years), including ADAPT, APC, and PreSAP (these three trials accounted for 6,801 patient-years of celecoxib exposure). It found celecoxib associated with a nonstatistically significant trend toward increased risk of myocardial infarction (RR 1.4, 95% CI 0.7 to 2.7) and composite cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, RR 1.4, 95% CI 0.94 to 2.2). Results were insensitive to a variety of sensitivity analyses based on methodological factors (such as use of independent adjudication of harms) or dose. There was no difference in risk of myocardial infarction between celecoxib and naproxen, ibuprofen, or diclofenac.

The third systematic review, which was included in the original CER, limited its analysis to trials that were at least 6 weeks in duration and reported CV events in published articles or publicly available material.[111] It found the risk of myocardial infarction increased in three trials (APC, ADAPT, PreSAP; none evaluated arthritis patients) that compared celecoxib to placebo (OR 2.3, 95% CI 1.0 to 5.1) and in five trials (APC, CLASS, ADAPT, PreSAP, VACT; the latter two evaluated arthritis patients) that compared celecoxib to placebo, diclofenac, ibuprofen, or paracetamol (OR 1.9, 95% CI 1.2 to 3.1). No heterogeneity was present. There was no association between celecoxib use and either cerebrovascular events, CV death, or composite CV

events. The meta-analysis did not include the large (N=13,274), 12-week SUCCESS-I Study, which reported results consistent with its findings (10 myocardial infarctions or 0.55/100 patient-years in the combined celecoxib arms versus 1 myocardial infarction or 0.11/100 patient-years in the combined nonselective NSAID arms).[55]

Neither of the systematic reviews included a new, fair-quality head-to-head trial (n=916) that found no difference in risk of myocardial infarction after 1 year in 916 patients randomized to celecoxib versus diclofenac for osteoarthritis (0.9% vs. 1.3%, RR 0.67, 95% CI 0.19 to 2.35),[52] or a new, fair-quality Chinese trial (n=1,024) that found no difference in risk of CV events (defined as fatal or nonfatal myocardial infarction, and ischemic or hemorrhagic stroke) between celecoxib 200 mg twice daily and placebo after 1.5 years in patients at high risk for gastric cancer (0.86% vs. 1.1%, OR 0.84, 95% CI 0.23 to 3.2).[116] In both trials, the number of events was small (9 or 10 total), and it was unclear if myocardial infarctions were subject to blinded adjudication.

Table 5. Meta-analyses of serious cardiovascular events in trials of celecoxib

Study, Year Time Period Covered	Number of Studies (Number Randomized to Celecoxib)	Includes Trials of Colorectal Cancer or Alzheimer's Prevention*	Risk of Cardiovascular Events	Quality
White, 2003[112] Search dates not reported	15 (18,942)	No	Antiplatelet Trialists' Collaboration composite CV events (cardiovascular, hemorrhagic, and unknown deaths; nonfatal MI; or nonfatal stroke) <u>All patients</u> Celecoxib vs. placebo: RR 0.85 (95% CI 0.23 to 3.15) Celecoxib vs. NSAIDs: RR 1.06 (95% CI 0.70 to 1.61) Celecoxib vs. naproxen: RR 0.85 (95% CI 0.29 to 2.46) <u>Aspirin nonusers</u> Celecoxib vs. placebo: RR 0.60 (95% CI 0.11 to 3.29) Celecoxib vs. NSAIDs: RR 0.86 (95% CI 0.48 to 1.56) Celecoxib vs. naproxen: RR 0.82 (95% CI 0.18 to 2.46)	Poor
Moore, 2005[51] Trials completed by December 2003	31 (22,192)	No	Myocardial infarction Celecoxib vs. placebo: RR not reported (10 events) Celecoxib 200–400 mg vs. NSAID to maximum daily dose: RR 1.9 (95% CI, 0.87 to 4.1) Celecoxib any dose vs. NSAID to maximum daily dose: RR 1.6 (95% CI 0.93 to 2.6)	Fair
Caldwell, 2006[111] Searches through April 2005	6 (6,859)	Yes	Celecoxib vs. placebo Myocardial infarction: RR 2.3 (95% CI 1.0 to 5.1) Cerebrovascular event: RR 1.0 (95% CI 0.51 to 1.8) Cardiovascular death: RR 1.1 (95% CI 0.38 to 3.0) Composite cardiovascular events: RR 1.38 (95% CI 0.91 to 2.1) Celecoxib vs. placebo, diclofenac, ibuprofen, or paracetamol Myocardial infarction: RR 1.9 (95% CI 1.2 to 3.1) Cerebrovascular event: RR 0.73 (95% CI 0.42 to 1.3) Cardiovascular death: RR 1.0 (95% CI 0.52 to 2.0) Composite cardiovascular events: RR 1.2 (95% CI 0.92 to 1.6)	Fair

Table 5. Meta-analyses of serious cardiovascular events in trials of celecoxib (continued)

Study, Year Time Period Covered	Number of Studies (Number Randomized to Celecoxib)	Includes Trials of Colorectal Cancer or Alzheimer's Prevention*	Risk of Cardiovascular Events	Quality
White, 2007[113] Trials completed by October 2004	41 (23,030)	No	Celecoxib 200–800 mg vs. placebo Antiplatelet Trialists' Collaboration composite CV events: RR 1.1 (95% CI 0.47 to 2.7) CV deaths: RR 1.3 (95% CI 0.33 to 4.8) Nonfatal MI: RR 1.6 (95% CI 0.21 to 12) Nonfatal stroke: RR 0.80 (95% CI 0.19 to 3.3) Celecoxib 200–800 mg vs. nonselective NSAIDs Antiplatelet Trialists' Collaboration composite CV events: RR 0.90 (95% CI 0.60 to 1.3) CV deaths: RR 0.57 (95% CI 0.28 to 1.1) Nonfatal MI: RR 1.8 (95% CI 0.93 to 3.4) Nonfatal stroke: RR 0.51 (95% CI 0.23 to 1.1)	Poor
Solomon, 2008[114] Search dates not reported	6 (3664)	Yes	Cardiovascular death, MI, stroke, heart failure, or thromboembolism Celecoxib any dose vs. placebo: HR 1.6 (95% CI 1.1 to 2.3) Celecoxib 400 mg qd vs. placebo: HR 1.1 (95% CI 0.6 to 2.0) Celecoxib 200 mg bid vs. placebo: HR 1.8 (95% CI 1.1 to 3.1) Celecoxib 400 mg bid vs. placebo: HR 3.1 (95% CI 1.6 to 6.1)	Fair

bid = twice daily; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction;
NSAID = nonsteroidal anti-inflammatory drug; qd = once daily; RR = relative risk
* Colon polyp prevention trials: PreSAP, APC; Alzheimer's prevention: ADAPT

Three meta-analyses included in the original CER found no increased risk of serious CV events with celecoxib versus placebo.[51, 112, 113] However, these meta-analyses did not include trials completed after 2004, including two large, long-term trials of colon polyp prevention (APC and PreSAP).[118, 119] These two trials account for a high proportion of the myocardial infarctions in the celecoxib trials (70 events in persons randomized to celecoxib, compared with 31 in one of the meta-analyses[113]). The pooled relative risk from these trials for celecoxib versus placebo was 1.9 (95% CI 1.1 to 3.1, no heterogeneity) for the composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or heart failure.[120] Rates of fatal or nonfatal myocardial infarction were 1.6 percent (22/1356) versus 0.4 percent (3/679) in the APC trial and 9/933 (1.0 percent) versus 4/628 (0.6 percent) in PreSAP. The meta-analyses also focused almost exclusively on short-term trials, with the proportion 12 weeks or shorter in duration ranging from 87 percent to 94 percent.[51, 112, 113] In addition, two of the meta-analyses were rated poor quality, in part due to failure to assess study quality and because they pooled raw event rates for a particular drug and dose across studies,[112, 113] resulting in loss of randomization effects, and making it impossible to evaluate heterogeneity across studies.

A meta-analysis[121] that was included in the original report was excluded from this section because it pooled risks of different COX-2 selective NSAIDs together. Based on published and unpublished data from 121 RCTs, including the polyp prevention trials previously mentioned, the relative risk for any vascular event with COX-2 selective NSAIDs as a class compared to

placebo was 1.4 (95% CI 1.1 to 1.8). Much of the association appeared to be related to an increased risk of myocardial infarction (RR 1.9, 95% CI 1.3 to 2.6), with no increased risk of stroke (RR 1.0, 95% CI 0.71 to 1.5). From 41 trials, the raw event rate for myocardial infarction in patients randomized to celecoxib was 0.5 percent (44/8976 person-years) compared to 0.2 percent (9/4953 person-years) in those randomized to placebo. Based on the forest plot presented with the meta-analysis, the point estimate for celecoxib was similar to the overall pooled estimate for all COX-2 selective NSAIDs, and just met criteria for statistical significance. A trend towards increased risk of vascular events (p=0.03) with higher doses of celecoxib was observed, but nearly all of the events at the highest (800 mg daily) dose occurred in the polyp prevention trials. Analyses on the effects of duration and independent event adjudication were not stratified by specific COX-2 inhibitor, nor were estimates of CV risk with specific COX-2 inhibitors relative to naproxen or nonnaproxen NSAIDs.

In summary, celecoxib appears to be associated with an increased risk of myocardial infarctions or thromboembolic CV events compared to placebo. Much of the evidence for increased CV risk comes from two large, long-term polyp prevention studies that compared celecoxib 200 or 400 mg twice daily, or 400 mg once daily, to placebo.

Other NSAIDs

One systematic review included in the original CER evaluated risk of serious CV events associated with nonselective NSAIDs.[121] We identified one new systematic review[115] Two trials included in the original CER and not included in the systematic review also reported serious CV events in patients prescribed naproxen.[55, 122]

A new, good-quality systematic review by Trelle and colleagues of 31 trials (with at least two arms with at least 100 patient-years of followup) compared CV risks associated with various nonselective NSAIDs, based on a network analysis.[115] It found ibuprofen associated with increased risk of composite cardiovascular outcomes (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) compared with placebo (RR 2.3, 95% CI 1.1 to 4.9) and diclofenac associated with a trend towards increased risk (RR 1.6, 95% CI 0.85 to 3.0). Among the nonselective NSAIDs, with respect to specific CV outcomes, diclofenac was associated with the highest risk of stroke (RR 2.9, 95% CI 1.1 to 8.4) and cardiovascular death (RR 4.0, 95% CI 1.5 to 13). Naproxen was associated with only a slight, nonsignificant trend toward increased risk (RR 1.2, 95% CI 0.78 to 1.9). There were no statistically significant differences in risk of composite CV outcomes between naproxen, ibuprofen, and diclofenac.

A fair-quality systematic review included in the original CER by Kearney and colleagues of 91 trials (mostly ranging from 4 to 13 weeks in duration) evaluated risks associated with any nonselective NSAID (33,260 person-years of exposure) compared to any COX-2 selective NSAID (23,325 person-years of exposure).[121] Most of the trials evaluated naproxen (42 trials), ibuprofen (24 trials), and diclofenac (26 trials); only 7 evaluated other nonselective NSAIDs. Generalizability to usual practice could be limited because the majority of the trials evaluated higher than standard doses of NSAIDs. Much of the data regarding CV event rates were obtained by requesting unpublished data from trial sponsors.

Table 6 shows estimates of risk for different CV outcomes with COX-2 inhibitors relative to nonselective NSAIDs. Risk of myocardial infarction was similar with COX-2 inhibitors and nonnaproxen NSAIDs, but about twofold as great for COX-2 inhibitors compared with naproxen (0.6% or 99/16360 vs. 0.3% or 30/10,978, RR 2.0, 95% CI 1.4 to 3.0). This is equivalent to about 1 additional myocardial infarction for every 300 patients treated for 1 year with a COX-2

inhibitor instead of naproxen. COX-2 inhibitor use was also associated with a lower risk of stroke relative to nonnaproxen NSAIDs (RR 0.62, 95% CI 0.41 to 0.95). In subgroup analyses of specific nonselective NSAIDs (ibuprofen, diclofenac, other nonselective NSAIDs), the difference in stroke risk was only observed with diclofenac, which was usually evaluated at high doses (RR 0.48, 95% CI 0.27 to 0.83). There was insufficient data to analyze the effects of lower doses on estimates of risk.

Table 6. Rate ratios (95% CI)*: COX-2 inhibitor relative to nonselective NSAID[121]

NSAID Group	Vascular Events	Myocardial Infarction	Stroke	Vascular Death
Any nonselective NSAID	1.2 (0.97 to 1.4)	1.5 (1.2 to 2.0), p=0.0009	0.83 (0.62 to 1.1)	0.97 (0.69 to 1.4)
Any nonnaproxen, nonselective NSAID	0.88 (0.69 to 1.1)	1.2 (0.85 to 1.7)	0.62 (0.41 to 0.95), p=0.03	0.67 (0.43 to 1.1)
Naproxen	1.6 (1.2 to 2.0)	2.0 (1.4 to 3.0), p=0.0002	1.1 (0.73 to 1.6)	1.5 (0.90 to 2.4)

CI = confidence interval; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug
*Rate ratios below 1 favor COX-2 inhibitors, and rate ratios above 1 favor NSAIDs

Kearney et al. found insufficient data to directly estimate risks of nonselective NSAIDs from placebo-controlled trials. Indirect analyses (based on trials of nonselective NSAIDs versus COX-2 inhibitors and trials of COX-2 inhibitors vs. placebo) suggested an increased risk of vascular events with ibuprofen (RR 1.5, 95% CI 0.96 to 2.4) and diclofenac (RR 1.6, 95% CI 1.1 to 2.4) relative to placebo, but not with naproxen (RR 0.92, 95% CI 0.67 to 1.3). However, indirect analyses should be interpreted with caution because they can give discrepant results compared to head-to-head comparisons.[123]

The Kearney meta-analysis did not include results of the large SUCCESS-1 trial, which reported 0.61 MIs/100 patient-years with naproxen (n=905), and no cases of MI in diclofenac users (n=3489).[55] It also didn't include the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which was terminated early in December 2004 because of an "apparent increase in CV and cerebrovascular events among the participants taking naproxen when compared with those on placebo."[124] Results from ADAPT showed a nonsignificant increased in risk of CV deaths (HR 1.5, 95% CI 0.30 to 7.3), myocardial infarction (HR 1.5, 95% CI 0.69 to 3.2), or stroke (HR 2.1, 95% CI 0.81 to 5.6).[122] Naproxen was associated with an increased risk based on the composite outcome of CV death, myocardial infarction, stroke, congestive heart failure, or transient ischemic attack (HR 1.6, 95% CI 1.0 to 2.6). The decision to terminate ADAPT has been criticized because rigorous stopping protocols were not used, the increased risk associated with naproxen for individual and most composite CV outcomes did not reach statistical significance, the events were not adjudicated, and the number of events was small.[125]

Aspirin and Salsalate

Aspirin is known to be protective against occlusive vascular events because of its irreversible antiplatelet effects. In a collaborative meta-analysis of infidel patient data from 22 randomized trials (over 110,000 participants), lower doses of aspirin (primarily less than 325 mg daily) were associated with decreased risk of serious vascular events when given for primary prevention (0.51% aspirin vs. 0.57% control per year, p=0.0001) or secondary prevention (6.7% vs. 8.2%, p<0.0001).[96] The populations evaluated in these trials probably varied substantially from trials of patients with arthritis.

Observational Studies

Three systematic reviews evaluated CV risk associated with various NSAIDs.[126-128] Two were included in the original CER and focused on risks associated with naproxen.[126, 127] The third was a new, good-quality systematic review of CV risk (primarily myocardial infarction) from 23 observational studies that was published too late to be included in the original CER, though results were summarized in a brief addendum (Appendix H).[128] We also identified four large observational studies not included in the original CER.[108, 129-131]

The new systematic review included a total of 23 observational studies (16 case-control and 7 cohort studies).[128] It found diclofenac associated with the highest risk, followed by indomethacin and meloxicam (Table 7). Celecoxib, naproxen, piroxicam, and ibuprofen were not associated with increased risks. For all NSAIDs, increases in risk were modest (RR <1.5), and all of the main analyses were characterized by substantial between-study heterogeneity.

Table 7. Rate ratios for cardiovascular events (95% CI)*: NSAID use compared with nonuse of NSAIDs[128]

NSAID	Number of Studies	Risk of Cardiovascular Events
Celecoxib	11	1.1 (0.91 to 1.2)
Meloxicam	3	1.2 (1.0 to 1.6)
Naproxen	15	0.97 (0.87 to 1.1)
Diclofenac	9	1.4 (1.2 to 1.7)
Ibuprofen	16	1.1 (0.97 to 1.2)
Indomethacin	6	1.3 (1.1 to 1.6)
Piroxicam	4	1.1 (0.70 to 1.6)

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug

Nineteen large observational studies (case-control studies with >1000 cases or cohort studies with >100,000 subjects) evaluated risk of CV events associated with various NSAIDs (Table 8, Appendix H).[108, 129-146] All of these studies except for four[108, 129-131] were included in the original CER. Seven studies[108, 129-132, 141, 146] not included in the systematic review of observational studies.[128] Six studies used a cohort design[108, 130, 131, 140, 146, 147] and the remainder a case-control (or nested case-control) design. Three studies evaluated the UK General Practice Research Database[133, 134, 143] and three evaluated the same Canadian (Quebec) database.[108, 130, 141] Only one study was rated good quality,[139] the remainder were rated fair quality. The most common methodological shortcoming in the fair-quality case-control studies was failure to report the proportion of patients who met inclusion criteria who were excluded from the study. The most common methodological shortcomings in the fair-quality cohort studies were unclear blinding status of outcomes assessors and data analysts, and failure to report attrition from a defined inception cohort. Interpretation of the studies was complicated by the use of different study designs, adjustment for different numbers and types of confounders, and evaluation of different populations and outcomes.

Sixteen observational studies evaluated risk of serious CV events (primarily myocardial infarction) associated with celecoxib.[108, 129-132, 135-140, 145-149] Three studies found celecoxib associated with similar risk of CV events compared to naproxen, ibuprofen, or diclofenac.[130, 145, 146] A fourth study found ibuprofen (OR 1.3, 95% CI 1.0 to 1.6) and naproxen (OR 1.4, 95% CI 1.1 to 1.8) associated with a higher risk of acute MI requiring admission or sudden cardiac death than celecoxib.[135] Twelve studies found no increased risk of serious CV events with celecoxib relative to nonuse of NSAIDs.[108, 129, 131, 135, 136, 138-140, 145-148] Three studies found current (RR 1.6,

95% CI 1.2 to 2.0),[132] new (RR 2.1, 95% CI 1.4 to 3.1),[137] or any (HR 1.5, 95% CI 0.99 to 2.2)[149] use of celecoxib associated with increased risk compared to nonuse of NSAIDs. In these studies, the increased MI risk was either time-[137] or dose-dependent.[132]

Table 8. Cardiovascular events in observational studies

Author, Year Data Source Sample size	Mean age Country	Rate of Aspirin use	Main Findings
Andersohn 2006[132] Nested case-control Cases=3,643	69 UK	NR	***Acute MI, death from acute MI, or sudden death from CHD*** *Current NSAID use vs. nonuse of NSAIDs: RR (95% CI)* Celecoxib: 1.6 (1.2 to 2.0) Diclofenac: 1.4 (1.2 to 1.6) Ibuprofen: 1.0 (0.86 to 1.2) Naproxen: 1.2 (0.84 to 1.6) Other nonselective NSAIDs: 1.1 (0.98 to 1.2)
Cunnington, 2008 [148] Cohort n=71, 026	<65 years old: 52% USA	NR	***MI or ischemic stroke*** *Chronic NSAID use vs. nonchronic or nonuse: HR (95% CI)* Celecoxib: 1.0 (0.91 to 1.2) Naproxen: 0.99 (0.64 to 1.5)
Fischer, 2005[133] Nested case-control Cases=8,688	NR UK (GPRD)	NR	***Acute MI*** *Current NSAID use vs. nonuse of NSAIDs: OR (95% CI)* Diclofenac: 1.2 (1.0 to 1.5) Ibuprofen: 1.2 (0.92 to 1.5) Naproxen: 0.96 (0.66 to 1.4) Indomethacin: 1.4 (0.82 to 2.2) Piroxicam: 0.95 (0.53 to 1.7) Ketoprofen: 0.86 (0.44 to 1.7) Fenbufen: 3.1 (1.2 to 8.1) Nabumetone: 0.62 (0.25 to 1.5) Mefenamic acid: 2.3 (0.79 to 6.7) Etodolac: 1.1 (0.40 to 3.2) Tiaprofenic acid: 0.65 (0.17 to 2.5)
Fosbol, 2009[149] Cohort n=1,028,437	43 (median) Denmark	NR	***MI or death*** *NSAID use vs. nonuse of NSAIDs: HR (95% CI)* Celecoxib: 1.5 (0.99 to 2.2) Diclofenac: 1.6 (1.3 to 1.9) Ibuprofen: 0.88 (0.74 to 1.1) Naproxen: 0.85 (0.49 to 1.5)
Garcia Rodriguez, 2004[134] Nested case-control Cases: 4,975	NR UK (GPRD)	NR	***MI*** *NSAID use vs. nonuse of NSAIDs: OR (95% CI)* Naproxen: 0.89 (0.64 to 1.2) Ibuprofen: 1.1 (0.87 to 1.3.) Diclofenac: 1.2 (0.99 to 1.4) Ketoprofen: 1.1 (0.59 to 2.0) Meloxicam: 0.97 (0.60 to 1.6) Piroxicam: 1.2 (0.69 to 2.2) Indomethacin: 0.86 (0.56 to 1.3)
Graham 2005[135] Nested case-control Cases=8,143	NR: 18-84 USA	Telephone interview subgroup (n=817): 23%	***Acute MI requiring admission or sudden cardiac death*** *Current NSAID use vs. remote use: OR (95% CI)* Celecoxib: 0.84 (0.67 to 1.0) Ibuprofen: 1.1 (0.96 to 1.2) Naproxen: 1.1 (1.0 to 1.3) *Current NSAID use vs. celecoxib use: OR (95% CI)* Ibuprofen: 1.3 (1.0 to 1.6) Naproxen: 1.4 (1.1 to 1.8)

Table 8. Cardiovascular events in observational studies (continued)

Author, Year Data Source Sample size	Mean age Country	Rate of Aspirin use	Main Findings
Helin-Salmivaara, 2006[129] Case-control Cases=33,309	NR Finland	NR	***First time MI*** *Current NSAID use vs. nonuse of NSAIDs: OR (95% CI)* Indomethacin: 1.6 (1.2 to 2.0) Ibuprofen: 1.4 (1.3 to 1.6) Diclofenac: 1.4 (1.2 to 1.5) Naproxen: 1.2 (1.0 to 1.4) Piroxicam: 1.4 (0.92 to 2.0) Ketoprofen: 1.1 (0.94 to 1.3) Tolfenamic acid: 1.4 (0.90 to 2.2) Nimesulide: 1.7 (1.4 to 2.0) Etodolac: 1.4 (0.44 to 4.2) Nabumetone: 1.3 (0.59 to 2.7) Meloxicam: 1.2 (0.99 to 1.6) Celecoxib: 1.1 (0.83 to 1.3) *Recent (within 30 days) NSAID use vs. nonuse of NSAIDs: OR (95% CI)* Indomethacin: 1.5 (1.0 to 2.1) Ibuprofen: 1.1 (0.94 to 1.3) Diclofenac: 0.93 (0.77 to 1.1) Naproxen: 1.3 (1.0 to 1.7) Piroxicam: 0.89 (0.49 to 1.6) Ketoprofen: 1.3 (1.0 to 1.7) Tolfenamic acid: 1.3 (0.74 to 2.3) Nimesulide: 1.1 (0.91 to 1.4) Etodolac: 0.95 (0.23 to 4.0) Nabumetone: 3.0 (0.96 to 9.4) Meloxicam: 1.0 (0.77 to 1.4) Celecoxib: 0.95 (0.65 to 1.4)
Hippisley-Cox 2005[136] Nested case-control Cases: 9,218	NR; aged 25-100 UK	NR	***First ever MI*** *NSAID use within 3 months vs. no prescription for 3 years: OR (95% CI)* Celecoxib: 1.2 (0.96 to 1.5) Ibuprofen: 1.2 (1.1 to 1.4) Diclofenac: 1.6 (1.4 to 1.7) Naproxen: 1.3 (1.0 to 1.6) Other nonselective NSAIDs: 1.2 (1.0 to 1.4)
Johnsen 2005[137] Case-control Cases=10,280	70 Denmark	7% high-dose	***Acute MI*** *Current NSAID use vs. nonuse of NSAIDs: RR (95% CI)* Celecoxib: 1.2 (0.97 to 1.6) Naproxen: 1.5 (0.99 to 2.3) Other nonaspirin NSAID: 1.7 (1.5 to 1.8) *New NSAID use vs. nonuse of NSAIDs: (95% CI)* Celecoxib: 2.1 (1.4 to 3.1) Naproxen: 1.6 (0.57 to 4.8) Other nonaspirin NSAID: 2.6 (2.0 to 3.5)
Kimmel 2005[138] Case-control Cases: 1,718	NR; aged 40 to 75 USA	34%	***Nonfatal MI*** *NSAID use vs. nonuse of NSAIDs: OR (95% CI)* Celecoxib: 0.43 (0.23 to 0.79) Nonselective NSAID: 0.61 (0.52 to 0.71)

Table 8. Cardiovascular events in observational studies (continued)

Author, Year Data Source Sample size	Mean age Country	Rate of Aspirin use	Main Findings
Levesque 2005[139] Nested case-control Cases: 2,844	NR; ≥ 66 Canada	22%	***Acute MI, fatal or nonfatal*** *NSAID current use vs. nonuse of NSAIDs: RR (95% CI)* Celecoxib: 0.99 (0.85 to 1.2) Naproxen: 1.2 (0.75 to 1.8) Meloxicam: 1.1 (0.49 to 2.3)
Mamdani 2003[140] Cohort n=166,964	NR; ≥ 66 Canada	15%	***Hospitalization for acute MI*** *NSAID user vs. nonuser control: RR (95% CI)* Celecoxib: 0.9 (0.7 to 1.2) Naproxen: 1.0 (0.7 to 1.7) Nonnaproxen nonselective NSAIDs: 1.2 (0.9 to 1.4)
Rahme, 2002[141] Case-control Cases=4163	NR (older than 65 years) Canada	NR	***Hospitalization for acute MI*** Exposure to naproxen vs. exposure to other NSAIDs: OR 0.79 (95% CI 0.63 to 0.99)
Rahme, 2007[130] Retrospective cohort N=283,799	NR (>65 years) Canada	24%	***Acute myocardial infarction hospitalization*** Celecoxib vs. diclofenac/ibuprofen: 0.90 (0.76 to 1.1)
Rahme, 2007[108] Retrospective cohort N=510,871	NR; ≥65 Canada	22%	***Acute myocardial infarction*** *NSAID use vs. acetaminophen use: HR (95% CI)* Celecoxib: 0.97 (0.86 to 1.1) Ibuprofen: 1.0 (0.68 to 1.6) Diclofenac: 1.2 (0.96 to 1.4) Naproxen: 1.2 (0.89 to 1.5)
Ray 2002[147] Cohort n=378,776	61.5 USA	NR	***Serious CHD (hospital admission for acute MI or death from CHD)*** *Current NSAID use vs. nonuse of NSAIDs: RR (95% CI)* Celecoxib: 0.96 (0.76 to 1.2) Naproxen: 0.93 (0.82 to 1.1) Ibuprofen: 0.91 (0.78 to 1.1) *New NSAID use vs. nonuse of NSAIDs: RR (95% CI)* Celecoxib: 0.88 (0.67 to 1.2) Naproxen: 0.92 (0.73 to 1.2) Ibuprofen: 1.0 (0.77 to 1.3)
Schlienger, 2002[143] Nested case-control Cases=3,319	NR UK (GPRD)	NR	***First acute MI*** *NSAID use vs. nonuse of NSAIDs: OR (95% CI)* Ibuprofen: 1.2 (0.87 to 1.6) Diclofenac: 1.4 (1.1 to 1.8) Piroxicam: 1.6 (0.78 to 3.5) Fenbufen: 2.1 (0.80 to 5.3) Ketoprofen: 1.4 (0.77 to 2.5) Indomethacin: 1.0 (0.58 to 1.8) Flurbiprofen: 2.3 (0.93 to 5.5) Naproxen: 0.68 (0.42 to 1.1)
Solomon, 2002[144] Case to control Cases=4,425	NR USA	NR	***Hospitalization for MI*** *NSAID use vs. nonuse of NSAIDs: RR (95% CI)* Naproxen: 0.84 (0.72 to 0.98) Ibuprofen: 1.0 (0.88 to 1.2) *NSAID use vs. ibuprofen use: RR (95% CI)* Naproxen: 0.82 (0.67 to 1.0)

Table 8. Cardiovascular events in observational studies (continued)

Author, Year Data Source Sample size	Mean age Country	Rate of Aspirin use	Main Findings
Solomon 2004[145] Case-control Cases=10,895	NR; > 80 USA	NR	**_Acute MI_** Celecoxib use vs. no celecoxib use: OR 0.93 (95% CI 0.84 to 1.0) Celecoxib use vs. naproxen use: OR 0.95 (95% CI 0.74 to 1.2) Celecoxib use vs. ibuprofen use: OR 0.98 (95% CI 0.76 to 1.3) Celecoxib use vs. other NSAID use: OR 0.95 (95% CI 0.82 to 1.1)
Solomon, 2008[131] Cohort n=175,654	80 years USA	NR	**_MI, stroke, CHF, and out-of-hospital death attributable to cardiovascular disease_** _NSAID use vs. nonuse of NSAIDs: HR (95% CI)_ Celecoxib: 0.89 (0.83 to 0.94) Diclofenac: 1.2 (1.1 to 1.3) Ibuprofen: 0.96 (0.83 to 1.1) Naproxen: 0.79 (0.67 to 0.93) Other nonselective NSAIDs: 0.87 (0.79 to 0.96)
Velentgas 2006[146] Cohort n=424,584	NR (40-64 years) USA	NR	**_Acute coronary syndrome or MI_** _Current NSAID use vs. current ibuprofen use: RR (95% CI)_ Celecoxib: 1.0 (0.83 to 1.3) Naproxen: 1.1 (0.93 to 1.4)

CHD = coronary heart disease; CHF = congestive heart failure; HR = hazard ratio; MI = myocardial infarction; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; RR = relative risk; UK GPRD = United Kingdom General Practice Research Database

The nonselective NSAID naproxen has received additional scrutiny since the VIGOR trial[17] showed an increased risk of CV events with rofecoxib versus naproxen, due to the hypothesis that naproxen might be protective against myocardial infarction. In addition, a systematic review[121] of randomized trials (described earlier) found that naproxen was not associated with the same increased in CV risk as other nonselective and selective NSAIDs. In addition to the new systematic review of observational studies described above (which found a neutral effect of naproxen on CV risk),[128] two systematic reviews included in the original CER specifically focused on CV risks associated with naproxen.[126, 127] The first, a meta-analysis of 11 observational studies of naproxen (four based on the General Practice Research Database) found naproxen associated with a small cardioprotective effect (OR 0.86, 95% CI 0.75 to 0.99), with Merck-funded studies reporting larger effect sizes.[127] Nine observational studies published after this systematic review showed no cardioprotective effect associated with naproxen,[108, 129, 132, 135-137, 139, 148, 149] though one other study showed a modest protective effect (HR 0.79, 95% CI 0.67 to 0.93).[131] An FDA review included in the original CER concluded no cardioprotective effect of naproxen after taking into account various methodological issues.[126]

Large observational studies found no other nonselective NSAID consistently associated with increased risk of CV events compared to nonuse of NSAIDs.[129, 131-137, 139, 140, 142-144] For example, ibuprofen was associated with a modest increased risk (OR 1.4, 95% CI 1.3 to 1.6 and OR 1.2, 95% CI 1.1 to 1.4) of serious CV events compared to nonuse of NSAIDs in two[129, 136] studies, but no increased risk in nine others.[131-135, 143, 144, 147, 149]

Partially selective NSAIDs have not been well studied in large observational studies. Three studies found no increased risk of serious CV events with meloxicam compared to nonuse.[129, 134, 139] One study found no increased risk of acute myocardial infarction with use of etodolac or nabumetone versus nonuse of NSAIDs, but estimates were imprecise.[133]

In April 2005, after reviewing the available observational data, the FDA issued a Public Health Advisory stating, "Long-term controlled clinical trials have not been conducted with most of these (nonselective) NSAIDs. However, the available data suggest that use of these drugs may increase CV risk. It is very difficult to draw conclusions about the relative CV risk among the COX-2 selective and nonselective NSAIDs with the data available. All sponsors of nonselective NSAIDs will be asked to conduct and submit to FDA a comprehensive review and analysis of available controlled clinical trial databases pertaining to their NSAID product(s) to which they have access to further evaluate the potential for increased CV risk."[150] The FDA also required labeling changes to both prescription and nonprescription nonselective NSAIDs warning about potential CV risks.

Overall Rate of Serious Adverse Events

Because use of different NSAIDs could be associated with different tradeoffs for serious CV and GI harms (for example, reducing serious GI harms but increasing serious CV harms), analyses that evaluate the risk of all serious harms simultaneously could be helpful for understanding overall comparative risks. However, 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.

Analyses of all serious adverse events in CLASS were included in the original CER. A Canadian analysis used data from FDA documents[84] to analyze serious adverse events, defined as death, hospitalization, or "any life-threatening event, or event leading to severe disability.[151] It found similar rates of all serious adverse events between celecoxib and ibuprofen or diclofenac (6.8 percent vs. 5.8 percent). An FDA analysis of CLASS found 12 serious adverse events/100 patient-years for celecoxib; 10/100 patient-years for diclofenac, and 11/100 patient-years for ibuprofen, a difference that was not statistically significant.[84]

A fair-quality retrospective cohort study not included in the original CER evaluated risk of first hospitalization for acute myocardial infarction or GI bleeding in a Canadian cohort of patients 65 years or older.[108] For the combined outcome, naproxen use was associated with the largest risk compared to acetaminophen use (HR 1.6, 95% CI 1.3 to 1.9). Celecoxib (HR 0.93, 95% CI 0.83 to 1.0) and ibuprofen (HR 1.0, 95% CI 0.74 to 1.5) were associated with neutral risk, and diclofenac with an intermediate but nonstatistically significant increased risk (HR 1.2, 95% CI 0.99 to 1.4)

Other Adverse Events Associated With Selective and Nonselective NSAIDs

Mortality

We identified no new studies evaluating mortality associated with different NSAIDs. Large clinical trials included in the original CER did not show differences in mortality between different NSAIDs.[54, 152] In CLASS, mortality rates were 0.47%, 0.37%, and 0.45% for celecoxib, diclofenac, and ibuprofen, respectively.[84] In SUCCESS-1, 5 deaths (0.06 percent) were observed after 12 weeks in the celecoxib group and 5 (0.11 percent) in the nonselective NSAIDs group.[55] A meta-analysis that included unpublished company clinical trial data (including CLASS and SUCCESS-1) found no significant difference in rates of death in patients randomized to

celecoxib compared with nonselective NSAIDs, though there were few events (0.03% or 6/18,325 in the celecoxib arms vs. 0.11% or 14/12,685 in the NSAID arms).[51]

One retrospective cohort study of Saskatchewan health-services databases that followed patients from 6 months following prescription until death found nabumetone associated with significantly lower rates of all-cause mortality compared with diclofenac (OR 2.0; 95% CI 1.2 to 3.1) and naproxen (OR 3.0, 95% CI 1.9 to 4.6).[153] However, we found no other studies that replicated this finding.

Hypertension, CHF, Edema, and Renal Function

Six systematic reviews or meta-analyses included in the original CER evaluated comparative risks of hypertension, CHF, edema, and renal function associated with various NSAIDs.[19, 51, 110, 154-156] A seventh systematic review was published too late to be fully included in the original CER, but described in an appendix.[157] It was rated fair quality because it did not assess the quality of included studies. Two new observational studies evaluated risk of congestive heart failure in high risk patients.[158]

All NSAIDs appear to be associated with increases in blood pressure. However, evidence regarding differential effects of specific NSAIDs is somewhat conflicting. One meta-analysis included in the original CER found that nonselective NSAIDs raised mean blood pressure by an average of about 5.0 mm Hg (95% CI 1.2 to 8.7).[154] Piroxicam produced the most marked elevation in blood pressure compared to placebo. In head-to-head trials, there were no significant differences between indomethacin and sulindac (10 trials), indomethacin and salicylate (1 trial), diclofenac and sulindac (1 trial), ibuprofen and sulindac (1 trial), and naproxen and sulindac (3 trials). Another meta-analysis found that piroxicam and ibuprofen had negligible effects on blood pressure, and that indomethacin and naproxen were associated with the largest increases.[155] In both meta-analyses, aspirin and sulindac were associated with minimal hypertensive affect. More than half of the published NSAID trials did not report hypertension rates as an outcome.[155]

Several meta-analyses of celecoxib included in the original CER found no increased risk of hypertension compared to nonselective NSAIDs.[19, 51, 110] A fair-quality meta-analysis found celecoxib (dose not specified) not associated with an increased risk of hypertension compared to either placebo (RR 0.81, 95% CI 0.13 to 5.21) or nonselective NSAIDs (RR 0.82, 95% CI 0.68 to 1.00).[19] A Pfizer-funded meta-analysis submitted to the FDA found an increased risk of developing hypertension with celecoxib at any dose compared to placebo (1.1% vs. 0.7%, p=0.02), though the risk was lower than for nonselective NSAIDs (1.5% vs. 2.0%, p=0.002).[110] A third meta-analysis, funded in part by the manufacturer, reported similar findings for risk of hypertension (celecoxib vs. nonselective NSAID, RR 1.1, 95% CI 0.90 to 1.3).[51] The fourth meta-analysis, which was included as an appendix in the original CER, found celecoxib associated with slightly lower risk of hypertension (RR 0.83, 95% CI 0.71 to 0.97) compared with control treatments (placebo, other NSAID, or mixed/other).[157] Most of the trials included in the meta-analyses were short-term and only one meta-analysis[51] evaluated the quality of the trials.

Results from large trials of celecoxib are mostly consistent with the meta-analyses. In CLASS (median duration of followup 9 months), celecoxib was associated with a similar rate of hypertension (new-onset and aggravated preexisting) compared with diclofenac (2.7 percent vs. 2.6 percent), and a lower rate compared with ibuprofen (2.7 percent vs. 4.2 percent).[117] In the shorter-term (12 weeks) SUCCESS-I trial (N=13,274), rates of hypertension were similar with celecoxib 100 or 200 mg twice a day compared with either diclofenac or naproxen (RR 0.86,

95% CI 0.62 to 1.20).[55] The APC polyp prevention trial found celecoxib associated with greater systolic blood pressure elevations compared to placebo at 1 and 3 years at either 200 mg twice daily (2.0 mm Hg at 1 year and 2.6 mm Hg at 3 years) and 400 mg twice daily (2.9 mm Hg at 1 year and 5.2 mm Hg at 3 years).[120] On the other hand, the PreSAP polyp prevention trial found no difference in systolic blood pressure increases between celecoxib 400 mg once daily and placebo.[120]

With regard to renal dysfunction, it is unclear whether COX-2 selective NSAIDs as a class are associated with clinically important differences in risk compared to nonselective NSAIDs. A systematic review included in the original CER of five small (sample size range 15 to 67), short-term (28 days or less) trials found that COX-2 selective NSAIDs had similar effects on glomerular filtration rate and creatinine clearance compared to nonselective NSAIDs in three trials, and were modestly superior in two.[156] The clinical effects of the modest differences observed in the latter two trials were unclear. Another systematic review found no difference in risk of creatinine increase greater than 1.3 times the upper limit of normal with celecoxib at 200 to 400 mg compared with nonselective NSAIDs (RR 0.78, 95% CI 0.46 to 1.3).[51] CLASS showed no differences in the risk of experiencing an increase in serum creatinine >1.0 mg/dl with celecoxib (0.2 percent), diclofenac (0.1 percent), or ibuprofen (0.2 percent), though the nonselective NSAIDs were associated with slightly greater increases in serum creatinine, particularly in patients with prerenal azotemia at baseline.[159] A systematic review of randomized trials included as an appendix in the original CER found celecoxib associated with lower risk of renal dysfunction (RR 0.61, 95% CI 0.40 to 0.94) compared to control treatments (placebo, other NSAID, or mixed/other), but no difference for composite renal events (RR 0.97, 95% CI 0.84 to 1.1).[157]

Two systematic reviews of randomized controlled trials included in the original CER found no clear difference between celecoxib and nonselective NSAIDs in risk of heart failure. In one systematic review, heart failure was more frequent with celecoxib than with placebo (13 of 8,405 vs. 1 of 4,057, p=0.05), though not compared with nonselective NSAIDs (0.1% vs. 0.2%, p=0.06).[110] A second meta-analysis also found no significant difference between celecoxib and nonselective NSAIDs in risk of heart failure (RR 0.70, 95% CI 0.43 to 1.1).[51] Similar results were observed in large trials of celecoxib. In CLASS, CHF rates were similar with celecoxib versus ibuprofen or diclofenac (0.3 percent vs. 0.3 percent).[117], and withdrawals due to heart failure rare with all three NSAIDs (0.1% vs. <0.1% vs. 0.3%).[159] The APC polyp prevention trial found no difference in rates of heart failure between celecoxib versus placebo, though event rates were low (five cases of heart failure among 1,356 subjects).[119]

The risks of hypertension and heart failure with celecoxib and nonselective NSAIDs were evaluated in several observational studies. A new Danish cohort study of patients who had been hospitalized for congestive heart failure found use of celecoxib, ibuprofen, diclofenac, or naproxen at any dose associated with similar risk of hospitalization due to congestive heart failure (HR estimates ranged from 1.2 to 1.4), though celecoxib and diclofenac were associated with greater risk of death (HR 1.8, 95% CI 1.6 to 1.9 and HR 2.1, 95% CI 2.0 to 2.2, respectively) compared with ibuprofen and naproxen (HR 1.3, 95% CI 1.2 to 1.4 and HR 1.2, 95% CI 1.1 to 1.4, respectively).[160] A new nested case-control study found indomethacin associated with increased risk of heart failure compared to celecoxib (OR 2.0, 95% CI 1.2-3.6) in patients older than 66 years recently hospitalized for heart failure.[158] There was no difference in risk of heart failure between other nonselective NSAIDs (diclofenac [OR 0.82, 95% CI 0.51 to 1.3] and ibuprofen [OR 1.5, 0.66 to 3.2]) or acetaminophen (OR 1.2, 95% CI 0.92 to 1.4) relative

to celecoxib. A retrospective cohort study included in the original CER based on the same Canadian database found nonselective NSAIDs associated with an increased risk of death (HR 1.5, 95% CI 1.2 to 2.0), recurrent heart failure (HR 1.2, 95% CI 0.92 to 1.6), or either (HR 1.3, 95% CI 1.0 to 1.6) in similarly high risk patients.[161] Another retrospective cohort study included in the original CER found nonselective NSAIDs (RR 1.4, 95% CI 1.0 to 1.9) but not celecoxib (RR 1.0, 95% CI 0.8 to 1.3) associated with increased risk of heart failure admission compared to nonuse.[162] A case-control study based on data from the General Practice Research Database found nonselective NSAIDs associated with an increased risk of newly diagnosed heart failure compared to nonuse of NSAIDs (RR 1.6, 95% CI 1.2 to 2.1).[163]

A fair-quality systematic review included as an appendix in the original CER found no difference between celecoxib and controls (placebo, other NSAIDs, or mixed/other) in risk of arrhythmia, but the number of events was small (RR 0.84, 95% CI 0.45 to 1.6) and most trials didn't report arrhythmias.[157]

Hepatotoxicity

One systematic review[164] included in the original CER and one new meta-analysis[165] evaluated randomized controlled trials reporting hepatotoxicity associated with various NSAIDs. Another systematic review included in the original CER evaluated observational studies.[166] We identified one new randomized controlled trial of celecoxib versus diclofenac that reported rates of hepatic adverse events,[52] and a report of hepatotoxicity from the diclofenac arm of a large randomized trial.[167]

The new meta-analysis included 41 randomized trials involving celecoxib.[165] It found risk of hepatobiliary abnormalities (clinical or laboratory) similar for celecoxib (276/24933 or 1.1 percent), ibuprofen (38/2484 or 1.5%, p=0.06 vs. celecoxib), and placebo (36/4057 or 0.89%, p=0.21 vs. celecoxib); slightly lower rate for naproxen (0.68%, p=0.03 vs. celecoxib); and slightly higher for diclofenac (324/2618 or 4.24%, p<0.0001 vs. celecoxib). No patient randomized to an NSAID met Hay's rule (elevation of alanine aminotransferase ≥3 times the upper limit of normal with an elevation of bilirubin ≥2 times the upper limit of normal), and no cases of liver failure or drug-related liver transplant were reported. The rate of alanine aminotransferase (ALT) abnormalities was higher with diclofenac (78/1000 patient-years) compared with the other NSAIDs or placebo (16 to 28/1000 patient-years). Four deaths occurred (2 in patients randomized to celecoxib, 1 naproxen, and 1 diclofenac), but none were considered related to drug treatment. A systematic review included in the original CER reported similar findings.[164] Based on 67 published articles and 65 studies accessible from the FDA archives, it found diclofenac (3.6%, 95% CI 3.1% to 4.0%) associated with higher rates of aminotransferase elevations greater than 3 times the upper limit of normal compared with placebo (0.29%; 95% CI 0.17% to 0.51%) and other NSAIDs (all ≤ 0.43 percent), and a higher rate of liver-related discontinuations compared to placebo (2.2%, 95% CI 1.8 to 2.6). Serious complications related to liver toxicity were rare: only one liver-related hospitalization (among 37,671 patients) and death (among 51,942 patients) occurred in a patient on naproxen in a trial of rofecoxib versus naproxen. Data from the diclofenac arm (n=17,289) of a randomized trial showed similar results.[167] The rate of aminotransferase elevation greater than three times the upper limit of normal was 3.1 percent, with four cases of liver-related hospitalizations (0.023 percent) and no cases of liver failure, death, or transplant.

Large trials that have evaluated diclofenac also suggested an increased risk of hepatotoxicity compared to other NSAIDs. In CLASS, celecoxib was associated with a lower risk of elevation

in serum ALT (0.6 percent vs. 2.2 percent), serum AST (0.5 percent vs. 1.8 percent), and withdrawals due to hepatic enzyme elevations (<0.1 percent vs. 1.2 percent) compared to diclofenac or ibuprofen.[54] In SUCCESS-1, rates of increase in ALT levels were 0.5 percent with celecoxib versus 1.3 percent with diclofenac or naproxen (p<0.001).[55] A smaller (n=916), new trial comparing celecoxib versus diclofenac also found a lower risk of hepatic function abnormalities with celecoxib compared to diclofenac (0.6 percent vs. 3.5 percent).[52]

A systematic review of seven population-based epidemiological studies found a similarly low risk of serious hepatic toxicity associated with NSAIDs.[166] In those studies, the excess risk of liver injury associated with current NSAIDs ranged from 4.8 to 8.6/100,000 person-years of exposure compared with past use. There were zero deaths from liver injury associated with NSAIDs in more than 396,392 patient-years of exposure. A recent cohort study from Italy found that nimesulide, an NSAID not available in the United States, was associated with a higher incidence of serious liver injury compared with other NSAIDs.[168] None of the other NSAIDs, including celecoxib, were associated with an increased risk of serious liver injury. An earlier review of five population-based studies found sulindac associated with a five- to tenfold higher incidence of hepatic injury compared with other NSAIDs.[169] Diclofenac was associated with higher rates of aminotransferase elevations compared with users of other NSAIDs, but not with a higher incidence of serious liver disease.

Tolerability

Celecoxib

Two systematic reviews[50, 51] included in the original CER and one new systematic review[58] evaluated the relative tolerability of celecoxib compared to nonselective NSAIDs (Table 9). We also identified one new pooled analysis of randomized trials from the Pfizer registry,[170] one randomized trial not included in the original CER,[52] and one pooled analysis of three similarly designed trials.[82]

The new systematic review found no differences between celecoxib and nonselective NSAIDs in the risk of any adverse event (RR 0.96, 95% CI 0.91 to 1.0), GI adverse events (RR 0.90, 95% CI 0.78 to 1.0), or withdrawals due to adverse events (RR 0.86, 95% CI 0.73 to 1.0).[58] However, celecoxib was associated with a lower likelihood of withdrawals due to GI adverse events (RR 0.45, 95% CI 0.35 to 0.56). A systematic review included in the original CER reported found celecoxib associated with decreased risk of withdrawal due to adverse events (RR 0.86, 95% CI 0.81 to 0.91), withdrawal due to GI adverse events (RR 0.75, 95% CI 0.70 to 0.80), or any GI adverse event (RR 0.85, 95% CI 0.82 to 0.88).[51] The risk of serious adverse events (RR 1.0, 95% CI 0.91 to 1.2) and any adverse event (RR 0.96, 95% CI 0.94 to 0.98) were similar. An older systematic review reported results consistent with the other two systematic reviews.[50] All of the systematic reviews included the large and longer-duration CLASS trial, which reported lower risks of withdrawal due to adverse events (18 percent vs. 21 percent) and withdrawal due to GI adverse events (8.7 percent vs. 11 percent) with celecoxib compared to diclofenac or ibuprofen.[54]

Table 9. Systematic review of tolerability of COX-2s compared with NSAIDs

Review	AE incidence		Withdrawals	
	Overall RR (95% CI)	GI-related RR (95% CI)	Any AE RR (95% CI)	GI-related RR (95% CI)
Celecoxib vs. NSAIDs for OA/RA				
Deeks 2002[50]	-	-	0.86 (0.72, 1.04)	**0.54 (0.42, 0.71)**
Moore 2005[51]	**0.96 (0.94, 0.98)**	**0.84 (0.81, 0.87)**	**0.86 (0.81, 0.91)**	**0.75 (0.7, 0.8)**
Chen, 2008[58]	0.96 (0.91, 1.0)	0.75 (0.70, 0.80)	0.86 (0.73, 1.0)	0.45 (0.35, 0.56)

AE = adverse event; CI = confidence interval; COX = cyclooxygenase; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; RR = relative risk

A meta-analysis of 21 randomized trials from the Pfizer registry reported results that were generally consistent with the systematic reviews.[170] It found celecoxib associated with lower risk of GI adverse events (20 percent) compared to naproxen (32 percent), ibuprofen (31 percent), or diclofenac (24 percent), as well as lower likelihood of withdrawal due to GI adverse events (4.2% vs. 5.0% to 8.5%). However, this study was rated poor quality, in part because it did not assess study quality and because raw event rates were pooled across studies, resulting in loss of randomization.

One new randomized trial (n=925) found celecoxib and diclofenac associated with no difference in risk of withdrawal due to adverse events (27% vs. 31%, respectively, p=0.22) or withdrawal due to GI adverse events (15 percent vs. 14 percent).[52] A pooled analysis from three similarly designed trials of patients in Asia (total n=880) found no difference between celecoxib and diclofenac in risk of withdrawal due to adverse events (3.4% vs. 6.1%, p>0.05).[82]

Partially Selective NSAIDs

Two systematic reviews[89, 92] of randomized trials included in the original CER and one new systematic review[58] evaluated the tolerability of meloxicam, etodolac, or nabumetone compared to nonselective NSAIDs. The new systematic review found meloxicam associated with decreased risk of any adverse event (RR 0.91, 95% CI 0.84 to 0.99), any GI adverse event (RR 0.31, 95% CI 0.24 to 0.39), and withdrawals due to GI adverse events (RR 0.61, 95% CI 0.54 to 0.69), though there was no difference in the risk of withdrawal for any adverse event (RR 0.92, 95% CI 0.66 to 1.3).[58] The median Jadad quality score for the trials included in the systematic review was three (maximum five), indicating moderate overall quality. A meta-analysis of meloxicam studies included in the original CER reported similar findings, with lower risks of any GI event (OR 0.64; 95% CI 0.59 to 0.69) and withdrawals due to GI events (OR 0.59; 95% CI 0.52 to 0.67) with meloxicam compared with nonselective NSAIDs.[92]

The new systematic review also evaluated tolerability of etodolac.[58] It found etodolac associated with a lower risk of any adverse event (RR 0.83, 95% CI 0.70 to 0.99) compared to nonselective NSAIDs, but there was no difference in risk of GI adverse events (RR 0.77, 95% 0.55 to 1.1), withdrawal due to adverse events (RR 0.93, 95% CI 0.77 to 1.1), or withdrawal due to GI adverse events (RR 0.95, 95% CI 0.54 to1.6). Only two of 29 trials of etodolac scored 5 out of 5 on the Jadad quality scale; 7 received only 2 points.

In a meta-analysis included in the original CER, the incidence of GI adverse events was slightly but statistically significantly lower with nabumetone compared to nonselective NSAIDs

(25 % vs. 28%, p=.007), corresponding to about one fewer event for every 34 patients treated with nabumetone.[89]

Nonselective NSAIDs

A Cochrane review included in the original CER evaluated the tolerability of different NSAIDs.[56] The only relatively consistent finding was that indomethacin was associated with higher rates of toxicity than other NSAIDs, but it was not clear if these differences were statistically significant.

Aspirin and Salsalate

Five randomized trials (all included in the original CER) evaluated the efficacy or safety of aspirin or salsalate compared with nonaspirin NSAIDs in patients with arthritis.[80, 171-174] All were short-term ($\leq$ 12 weeks) and involved a total of 471 patients; of the subjects enrolled, only 4 had osteoarthritis of the hip/knee for every 100 patients with rheumatoid arthritis. Aspirin was associated with higher incidence of overall adverse events than salsalate (70% vs. 40%, p<0.05)[80] and diclofenac (61% vs. 46%; p<0.05);[173] these led to higher rates of withdrawals due to adverse events for aspirin compared with diclofenac (23% vs. 6%; p<0.05). Salsalate was associated with a higher incidence of overall adverse events compared to other nonselective NSAIDs in two[171, 174] of three trials, but the actual rates were not reported.

The overall safety profile of salsalate has also been evaluated in the rheumatoid arthritis population using the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) databases. These studies reported summary measures of drug toxicity based on tabulations of mean frequencies of overall adverse events per patient years, weighted by severity, and adjusted for differences in demographic factors. Numerically larger index scores indicate greater levels of toxicity. The summary index score takes into account symptoms from all body systems, laboratory abnormalities, and all-cause hospitalizations.[175-178] Symptoms were assessed every 6 months using patient self-report in response to open-ended questions. Hospitalizations and deaths were ascertained from discharge summaries and death certificates. Descriptions of study methods varied, but the ARAMIS studies were somewhat vague with regard to patient selection and ascertainment methods; adverse events were not clearly defined or prespecified; exposure duration and length of followup were unclear; and adjustments were made only for demographic factors such as age and gender. Because the results of these studies are more subject to recall bias and had other methodological shortcomings, the findings that aspirin, salsalate, and ibuprofen were the least toxic among the NSAIDs studied (Table 10) are less convincing than if they were reported in more rigorously designed observational studies.

Table 10. Toxicity index scores from ARAMIS database studies

Study	Aspirin	Ibuprofen	Salsalate	Others (Range)
Fries 1991[177]	1.19	1.94	1.28	2.17 (naproxen) to 3.99 (indomethacin)
Fries 1993[176]	1.33	1.89	NR	1.90 (naproxen) to 2.86 (tolmetin)
Fries 1996[175]	1.77	2.68	2.00	1.63 (sulindac) to 3.09 (ketoprofen)
Singh 1997[178]	2.25	1.95	1.79	3.29 (naproxen) to 5.14 (meclofenamate)

ARAMIS = Arthritis, Rheumatism, and Aging Medical Information System; NR = not reported

Acetaminophen

Four systematic reviews included in the original CER evaluated the efficacy and safety of acetaminophen compared with NSAIDs (selective or nonselective) for osteoarthritis.[179-182] We

identified no new systematic reviews. One new randomized trial compared acetaminophen versus naproxen for osteoarthritis.[183] One new observational study evaluated risk of acute myocardial infarction associated with various NSAIDs compared to acetaminophen.[108]

The systematic reviews generally met all criteria for good-quality systematic reviews, except that three[180-182] did not provide sufficient detail about trials that were excluded. The overall conclusion from the reviews was that NSAIDs were modestly superior to acetaminophen for general or rest pain (Table 11). For pain on motion and overall assessment of clinical response, NSAIDs also appeared modestly superior, though the differences were not always statistically significant.[180, 181] Only two reviews assessed functional disability; neither found clear differences.[180, 181]

Table 11. Pain relief in systematic reviews of acetaminophen compared with NSAID

Systematic Review	Date of Last Search	Number of Head-to-Head Trials Included	Main Results for Outcome of General or Rest Pain
Towheed, 2006[180]	Through 7/05	12 (4 trials evaluated coxibs)	NSAIDs superior for rest pain (3 trials, SMD 0.20, 95% CI 0.03 to 0.36), overall pain (8 trials, SMD 0.25, 95% CI 0.17 to 0.33), WOMAC pain (2 trials, SMD 0.24, 95% CI 0.09 to 0.38), WOMAC stiffness (2 trials, SMD 0.20, 95% CI 0.05 to 0.34), WOMAC function (2 trials, SMD 0.25, 95% CI 0.11 to 0.40), and global assessment of efficacy (2 trials, RR 1.2, 95% CI 1.1 to 1.4)
Zhang, 2004[182]	Through 7/03	8 (3 trials evaluated coxibs)	NSAIDS superior using WOMAC scale (SMD 0.3, 95% CI 0.17 to 0.44) and clinical response rate (RR 1.24, 95% CI 1.08 to 1.41)
Lee, 2004[179]	Through 2/03	6 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (weighted mean difference 6.33, 95% CI 3.41 to 9.24)
Wegman, 2004[181]	Through 12/01	3 (no trials evaluated coxibs)	NSAIDs superior for general/rest pain (SMD 0.33, 95% CI 0.15 to 0.51)

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; RR = relative risk; SMD = standardized mean difference; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

The risk of adverse events with acetaminophen versus NSAIDs was assessed in three systematic reviews (Table 12).[179, 180, 182] In two reviews, there were no differences in withdrawal due to any adverse event.[179, 180] Acetaminophen was associated with lower risk of GI adverse events compared with nonselective NSAIDs in two systematic reviews (though not compared with coxibs)[180, 182] and lower risk of withdrawals due to GI adverse events in one systematic review.[180] One systematic review found no difference between NSAID and acetaminophen in serious GI, renal, or CV harms, but found few events in the primarily small, short-term trials (data not provided).[180]

Table 12. Adverse events in systematic reviews of acetaminophen compared with NSAID

Systematic Review	Withdrawal due to Adverse Events	GI Adverse Events
Towheed, 2006[180]	NSAID vs. acetaminophen: RR 0.79 (95% CI 0.59 to 1.0)	Withdrawal due to GI adverse event Nonselective NSAIDs vs. acetaminophen: RR 2.0 (95% CI 1.0 to 3.8) Any GI adverse event Nonselective NSAID vs. acetaminophen: RR 1.5 (95% CI 1.1 to 2.0) COX-2 selective NSAID vs. acetaminophen: RR 0.98 (95% CI 0.80 to 1.2)
Zhang, 2004[182]	NR	GI discomfort Nonselective NSAID vs. acetaminophen: RR 1.4 (95% CI 1.1 to 1.8) COX-2 selective NSAID vs. acetaminophen: RR 0.65 (95% CI 0.17 to 2.52)
Lee, 2004[179]	NSAID vs. acetaminophen: OR 1.4, 95% CI 0.93 to 2.3)	NR

CI = confidence interval; COX = cyclooxygenase; GI = gastrointestinal; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; RR = relative risk

A new, fair-quality (high loss to followup) randomized trial found no differences in withdrawal due to lack of efficacy or WOMAC scores between acetaminophen 4 g once daily and naproxen 750 mg once daily for osteoarthritis after 6 months (n-=105) or 1 year (n=476).[183] Acetaminophen and naproxen were also associated with similar rates of withdrawal due to adverse events (25% vs. 22%, NS), serious adverse events (3.5 percent vs. 2.5 percent), any adverse event (72 percent vs. 74 percent), renal adverse events (three total), or hepatic enzyme increases (three in acetaminophen group vs. zero in the naproxen group). Naproxen was associated with an increased risk of constipation (9.9% vs. 3.1%, p<0.002) and peripheral edema (3.9% vs. 1.0%, p<0.033) compared to acetaminophen.

Clinical trials of acetaminophen have not been large enough to assess serious but less common complications such as PUBs, myocardial infarction, acute renal failure, or hypertension. Several observational studies included in the original CER provide some additional information about the safety of acetaminophen relative to NSAIDs. A fair-quality nested case-control study of 1,197 cases and 10,000 controls from a population-based cohort of 458,840 people in the General Practice Research Database found current acetaminophen use associated with a lower risk for symptomatic peptic ulcer (adjusted RR 1.9, 95% CI 1.5 to 2.3) than NSAID use (adjusted RR 4.0, 95% CI 3.2 to 5.1) when each was compared with nonuse.[184] There was no clear relationship between higher acetaminophen dose and increased risk for symptomatic ulcers. An earlier analysis on the same database also found current acetaminophen use associated with a lower risk for upper GI bleeds or perforations (adjusted RR 1.3, 95% CI 1.1 to 1.5) than current NSAID use (adjusted OR 3.9, 95% CI 3.4 to 4.6), each compared with nonuse.[98] A retrospective cohort study of elderly patients found that patients using lower doses of acetaminophen (<2,600 mg once daily) had lower rates of GI events (defined as GI-related hospitalizations, ulcers, and dyspepsia) compared with users of NSAIDs (RR 0.73, 95% CI 0.67 to 0.80 for 1,951 to 2,600 mg once daily), but the risks were similar at higher doses (RR 0.93 to 0.98).[185] Although GI hospitalization rates were not reported separately, the authors noted that dyspepsia was responsible for most of the increase in GI events in the high-dose acetaminophen groups. A meta-analysis on individual patient data from three earlier retrospective case-control studies (2472 cases) was consistent with the above studies.[186] It found acetaminophen associated with a minimal increase in the risk for serious upper GI bleeding (OR 1.2, 95% CI 1.1 to 1.5). By

contrast, nonselective NSAIDs were associated with higher risks, though estimates of risk varied considerably for different NSAIDs (OR 1.7 for ibuprofen to 35 for ketoprofen).

No randomized trial evaluated the association between acetaminophen use and myocardial infarction or other thromboembolic CV events. An analysis from the large, prospective Nurses' Health Study found heavy use of acetaminophen (more than 22 days/month) associated with an increased risk of CV events (RR 1.4, 95% CI 1.1 to 1.6) similar to that with heavy use of NSAIDs (RR 1.4, 95% CI 1.3 to 1.6).[187] Dose- and frequency-dependent effects were both significant. A new retrospective cohort study found no difference in risk of acute myocardial infarction between celecoxib, ibuprofen, diclofenac, or naproxen versus acetaminophen (Table 13, Appendix H).[108]

The association between renal failure and acetaminophen use was evaluated in several case-control studies included in the original CER. Interpretation of these studies is difficult because many had important flaws (such as failure to identify patients early enough in the course of their disease to ensure that the disease had not led to a change in the use of analgesics, failure to specify diagnostic criteria, failure to adjust for the use of other analgesics, incompleteness of data on exposure, and use of proxy respondents) in the collection or analysis of data.[188] The largest (926 cases) case-control study was designed to try to avoid many of these flaws, though results remain susceptible to confounding by indication.[189] It found regular use of acetaminophen associated with an increased risk for chronic renal failure (Cr >3.8 for men and >3.2 for women) compared with nonuse (OR 2.5, 95% CI 1.7 to 3.6). Use of NSAIDs was not associated with an increased risk (OR 1.0). A prospective cohort study of 1,697 women in the Nurses' Health Study found increased lifetime acetaminophen exposure associated with a higher risk of decline in glomerular filtration rate of 30% or greater (p<0.001), though NSAIDs were not (p=0.88).[190] The absolute risk of renal function decline, however, was modest, even in women reporting high amounts of lifetime acetaminophen use. Compared with women consuming less than 100 g of cumulative acetaminophen, the odds of a decline in GFR of at least 30 mL/min per 1.73 m^2 for women consuming more than 3,000 g was 2.04 (95% CI, 1.28 to 3.24). By contrast, analyses of men in the Physicians' Health Study found no association between acetaminophen or NSAIDs and change in kidney function.[191, 192]

The risk of heart failure associated with acetaminophen has not been well studied. In a single study using the General Practice Research Database, current use of acetaminophen was associated with a higher risk of newly diagnosed heart failure compared with nonuse (RR 1.3, 95% CI 1.1 to 1.7), though the risk was lower compared with current use of NSAIDs (RR 1.6, 95% CI 1.2 to 2.0).[163]

The risk of hypertension has been evaluated using data from the Nurses' Health Studies[193-195] and the Physicians' Health Study.[196] In the Nurses' Health Studies, acetaminophen and NSAIDs were associated with similar increases in risk of incident hypertension (Table 13). In the Physicians' Health Study, there was no association between NSAID or acetaminophen use and hypertension.

Table 13. Incidence of hypertension in the Nurses' Health Study and Physicians' Health Study according to use of acetaminophen or NSAIDs

Study	Acetaminophen use vs. Nonuse: Odds Ratio (95% CI)	NSAID use vs. Nonuse: Odds Ratio (95% CI)
Nurses' Health Study I (women 51 to 77 years old)[195]	1.9 (1.3 to 2.9)	1.8 (1.2 to 2.6)
Nurses' Health Study II (women 34 to 53 years old)[195]	2.0 (1.4 to 2.8)	1.6 (1.1 to 2.3)
Physicians' Health Study[196]	1.1 (0.87 to 1.3)	1.0 (0.89 to 1.2)

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug

Glucosamine and Chondroitin

Five new systematic reviews (Appendix I)[197-201] and four systematic reviews [202-205] included in the original CER evaluated benefits and harms of glucosamine and chondroitin. New trials identified for this update include one trial of glucosamine versus acetaminophen and placebo,[206] two trials of glucosamine versus placebo,[207, 208] four trials of chondroitin versus placebo,[209-212] and one trial of the combination of glucosamine and chondroitin versus placebo (Table 14, Appendix I).[213] We also identified two followup analyses from the previously included Glucosamine/chondroitin Arthritis Intervention Trial (GAIT).[214, 215]

Glucosamine

The most promising results for glucosamine have been reported in trials evaluating a pharmaceutical grade glucosamine not available in the United States, and sponsored by its European manufacturer (the Rotta Corporation). Because the content and purity of over-the-counter glucosamine preparations vary substantially, the results of trials that evaluated pharmaceutical grade glucosamine may not be directly applicable to over-the-counter preparations available in the U.S.[216]

The original CER included a good-quality Cochrane review (searches through November 2004) with four short-term (4 to 8 weeks) head-to-head trials of glucosamine versus an oral NSAID (ibuprofen or piroxicam).[205] Two of the trials were rated 5 out of 5 on the Jadad scale, and the other two were rated 3 or 4 out of 5. Three of the trials were sponsored by the European manufacturer; the fourth[217] was also conducted in Europe, but funding information was not reported. One of the trials has only been published as an abstract,[218] with analyses based on data from an unpublished manuscript. Two of the four trials found glucosamine superior to oral NSAIDs for efficacy,[217, 218] and two found no difference.[219, 220] In pooled analyses, glucosamine was superior to an oral NSAID for improving pain (three trials, standardized mean difference –0.40, 95% CI –0.60 to –0.19), but not for improving function measured with the Lequesne Index (two trials, standardized mean difference [SMD] –0.36, 95% CI –1.07 to 0.35). Glucosamine was also associated with fewer adverse events (RR 0.29, 95% CI 0.19 to 0.44) and withdrawals due to toxicity (RR 0.06, 95% CI 0.01 to 0.25).

Three head-to-head trials[221-223] included in the original CER were not included in the Cochrane review. The large, (n=1,583), NIH-funded, good-quality GAIT trial compared glucosamine versus celecoxib, as well as placebo, chondroitin, and the combination of glucosamine plus chondroitin (Tables 14 and 15, Appendix I).[221] GAIT evaluated pharmaceutical-grade glucosamine hydrochloride (over-the-counter supplements commonly

available in the United States are typically glucosamine sulfate) and chondroitin sulfate under an investigational new drug application. It found no differences between glucosamine and celecoxib in the proportion of responders defined by those with at least a 20 percent decrease in WOMAC pain score (70% vs. 64%, RR 0.91 [95% CI 0.82 to 1.02]), or as defined using Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria (67% vs. 61%, RR 0.90 [95% CI 0.80 to 1.01]). There were also no differences in change from baseline on WOMAC scores, SF-36 Mental or Physical Component summary scores, or the Health Assessment Questionnaire. The number of withdrawals due to adverse events was similar (2.8 percent vs. 2.2 percent), with no serious GI adverse events or deaths in either group. One patient randomized to glucosamine had chest pain and one patient randomized to celecoxib had a stroke. The celecoxib group experienced a nonsignificant but higher incidence of "cardiac" events compared to patients randomized to other treatments, though these were predominantly arrhythmias (palpitations and atrial fibrillation) rather than ischemic events (data not reported). Two small (n=40 and n=45), 12-week Canadian trials (not funded by the European manufacturer of pharmaceutical grade glucosamine) found no differences between glucosamine and ibuprofen for general osteoarthritis pain[222] or temporomandibular joint osteoarthritis.[223] Only limited details of the study design were reported for the first trial, though the second met all criteria for a good-quality study.

Table 14. Response rates in the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)[224]

Intervention	All Patients	Moderate-Severe Baseline Pain (WOMAC Pain Score 301-400 mm)	Mild Baseline Pain (WOMAC Pain Score 125-300)
Placebo	60.1%	54.3%	61.7%
Celecoxib	70.1% (p=0.008 vs. placebo)	69.4% (p=0.06 vs. placebo)	70.3% (p=0.04 vs. placebo)
Glucosamine	64.0% (p=0.30 vs. placebo)	65.7% (p=0.17 vs. placebo)	63.6% (p=0.67 vs. placebo)
Chondroitin	65.4% (p=0.17 vs. placebo)	61.4% (p=0.39 vs. placebo)	66.5% (p=0.27 vs. placebo)
Glucosamine + chondroitin	66.6% (p=0.09 vs. placebo)	79.2% (p=0.002 vs. placebo)	62.9% (p=0.80 vs. placebo)

GAIT = Glucosamine/chondroitin Arthritis Intervention Trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

One new, fair-quality trial sponsored by the European manufacturer of pharmaceutical grade glucosamine found no difference between glucosamine and acetaminophen in improvements from baseline on the Lequesne Index (-3.1 [95% CI -3.8 to -0.8) vs. -2.7 [95% CI -3.3 to -2.1], respectively), the WOMAC total score (-13 [95% CI -16 to -10] vs. -12 [95% CI -15 to -10.0]), the WOMAC pain score (-2.7 [95% CI -3.3 to -2.1] vs. -2.4 [-3.0 vs. -1.8]), and the WOMAC function score (-9.2 [-11 vs. -7.2] vs. -8.7 [-11 vs. -6.8]).[206] There was also no difference in the proportion of responders based on OARSI-A criteria (40 percent vs. 33 percent). Adverse events were similar.

Four systematic reviews not included in the original CER focused on evaluations of glucosamine versus placebo (Appendix I).[197, 198] The first, fair-quality systematic review, by Bjordal et al., was based on 7 randomized trials (sample size range 10 to 126, median 46, total n=401).[197] It found glucosamine associated with a statistically significant but clinically nonsignificant beneficial effect on pain compared to placebo (mean difference 4.7 points on a 100-point scale, 95% CI 0.3 to 9.1). The second, good-quality systematic review, by Wandel et al., differed from the first in that in focused on larger (n>200) randomized trials (7 trials of glucosamine, 1,939 patients randomized to glucosamine vs. placebo), included more recently

published trials, and conducted network analysis to incorporate indirect evidence.[198] It also found a statistically significant but clinically nonsignificant beneficial effect of glucosamine on pain (-0.4 cm on a 10 cm scale, 95% credible interval -0.7 to -0.1) and joint space narrowing (-0.2 mm, 95% CI -0.3 to 0.0) compared to placebo. No differences were found when trials were stratified according to whether they evaluated glucosamine hydrochloride or sulfate. There was no difference between glucosamine and placebo in withdrawals due to adverse events. A third, good-quality systematic review (by Vlad et al.) of 15 randomized trials (sample size range 24 to 630, median 155, total n=2,613) found glucosamine associated with an SMD of 0.35 (95% CI 0.14 to 0.56), based on the primary outcome reported in each study.[201] However, the overall estimate was associated with substantial statistical heterogeneity (I^2=80 percent). In stratified analyses, there was no statistically significant effect and heterogeneity was absent in subgroups of trials without industry funding (four trials, SMD 0.05, 95% CI -0.32 to 0.41), those that did not evaluate a Rottapharm produce (seven trials, SMD 0.11, 95% CI -0.16 to 0.38), and those with adequate allocation concealment (five trials, SMD 0.09, 95% CI -0.24 to 0.42). A fourth, fair-quality systematic review by Lee et al. found glucosamine associated with decreased joint space narrowing (SMD 0.43, 95% CI 0.23 to 0.63) and decreased risk of >0.5 mm joint space narrowing (OR 0.36, 95% CI 0.20 to 0.64), but results were based on only two trials.[200]

Other systematic reviews[202, 204, 205] included in the original CER are now outdated, as they excluded recent good-quality and relatively large trials. The Cochrane review included in the original CER found higher trial quality and evaluation of non-Rotta brand glucosamine associated with lower estimates of benefits.[205] Other older systematic reviews also found important methodological flaws in the glucosamine trials that could have exaggerated estimates of effect.[202, 204]

The previously described, good-quality GAIT trial is the largest trial of glucosamine.[224] It found no difference between glucosamine and placebo in the likelihood of experiencing a >20% improvement in WOMAC pain score after 24 weeks (64% vs. 60%, RR 1.1 [95% CI 0.94 to 1.2]), or various WOMAC, SF-36, and Health Assessment Questionnaire scores. There was also no difference in joint space width narrowing,[214] likelihood of achieving a 20 percent reduction in WOMAC pain (OR 1.2, 95% CI 0.65 to 2.0), or improvement in WOMAC function after 24 months.[215]

Three trials of glucosamine versus placebo have been published since the original CER.[206-208] All except one[208] were included in the Wandel et al. systematic review.[198] Of the three new trials, two were rated good quality.[207, 208] Both found no differences on outcomes related to pain, function, or (in one trial) radiographic narrowing between glucosamine and placebo for hip osteoarthritis[207] or low back pain with degenerative osteoarthritis.[208] The hip osteoarthritis trial also found no differences in efficacy in subgroups defined by radiographic severity, type of osteoarthritis (localized or generalized), level of pain, and other factors.[207] The third, fair-quality trial (high attrition) found glucosamine more effective than placebo in improving the Lequesne score (difference in mean change from baseline -1.2 [95% CI -2.3 to -0.8] on a 24 point scale), WOMAC Function score (difference -3.7 [95% CI -6.9 to -0.5] on a 68-point scale), and in the proportion experiencing an OARSI response (40% vs. 21%, RR 1.9 [95% CI 1.2 to 2.9]).[206] In all three trials, withdrawals due to adverse events and specific adverse events were similar with glucosamine and placebo.

Chondroitin

The only trial that compared chondroitin to an NSAID was the GAIT trial.[224] It found no difference between chondroitin and celecoxib in the proportion of patients with a 20 percent decrease in WOMAC pain score (65% vs. 70%, RR 0.93 [95% CI 0.84 to 1.0]), response based on OMERACT-OARSI criteria, or mean changes in WOMAC, SF-36, or Health Assessment Questionnaire Scores.

For chondroitin versus placebo, a good-quality systematic review by Wandel et al. found chondroitin associated with a borderline statistically significant (but clinically insignificant) effect on pain versus placebo (-0.3 cm on a 10 cm scale, 95% CI -0.7 to 0.0).[198] There was no effect on radiological joint space narrowing (mean difference -0.1 mm, 95% CI -0.3 to 0.1). The analysis was restricted to trials with sample sizes >200 subjects (four studies). There was no difference between chondroitin and placebo in withdrawals due to adverse events. A fair-quality systematic review by Hochberg et al. that focused on effects of chondroitin versus placebo on joint space narrowing in trials with longer (2 years) followup reported a point estimate similar to Wandel et al., but result were statistically significant (3 trials, mean difference 0.13 mm, 95% CI 0.06 to 0.19 mm). Another fair-quality systematic review also found chondroitin associated with less joint space narrowing compared to placebo (2 trials, SMD 0.26, 95% CI 0.13 to 0.39).[199, 200]

Systematic reviews[202, 204, 225] included in the original CER are now outdated as they do not include several recently published, larger trials.[202, 204, 225] In addition, two of the systematic reviews did not evaluate effects of trial quality,[204, 225] and one did not evaluate effects of chondroitin separately from glucosamine.[204] One of the systematic reviews found that lower quality and smaller trials reported larger effects compared to higher quality and larger trials.[202]

The good-quality, large GAIT trial (included in the original CER and the Wandel et al. systematic review) provides the strongest evidence on efficacy of chondroitin versus placebo.[224] It found no differences between chondroitin and placebo for experiencing a >20% improvement in WOMAC Pain score after 24 weeks (65% vs. 60%, RR 1.1, 95% CI 1.0 to 1.2) or various WOMAC, SF-36, and Health Assessment Questionnaire scores. There was also no difference in joint space width narrowing,[214] WOMAC pain, or WOMAC function after 24 months.[215] Adverse events with chondroitin and placebo were similar.

Three new fair-quality trials included in the Wandel et al. systematic review[198] (unclear allocation concealment methods in all three trials,[209-211] and high attrition in two of the three trials[209, 211]) found no clear benefit from chondroitin versus placebo for knee osteoarthritis on most clinical outcomes (pain or function) for knee osteoarthritis, though the two trials[209, 211] that evaluated radiographic outcomes found chondroitin associated with less joint space narrowing. One of the trials found chondroitin associated with no benefit on the primary outcomes of pain and function, but a higher likelihood of an OMERACT-OARSI response (68% vs. 56%, RR 1.2 [95% CI 1.0 to 1.5]).[210] In all three trials, adverse events with chondroitin and placebo were similar.[209-211] One other new fair-quality trial not included in the Wandel et al. systematic review found chondroitin associated with decreased pain (mean difference -12 on a 0 to 100 mm VAS, 95% CI -20 to -3.7) and improved Lequesne index (mean difference -1.7 points on a 0 to 24 scale, 95% CI -3.0 to -0.4) compared to placebo in patients with osteoarthritis of the knee and psoriasis.[212] There were no differences in SF-36 physical or mental component scores.

Glucosamine Plus Chondroitin

The GAIT trial also evaluated the combination of glucosamine plus chondroitin.[224] It found no differences between the combination and placebo in the likelihood of achieving a clinical

response after 24 weeks. Followup analyses at 24 months found no differences between the combination and placebo in joint space narrowing,[214] WOMAC pain, or WOMAC function.[215] In a post hoc analysis, the combination was superior to placebo for achieving a clinical response at 24 weeks in an analysis of a small (20 percent of enrollees) subgroup of patients with moderate to severe (WOMAC 301 to 400 mm) baseline pain (79% vs. 54.3%, RR 1.5 [95% CI 1.1 to 1.9]). The authors postulated that the lack of effect in the mild baseline pain group could have been due in part to floor effects. Adverse events were similar in the combination and placebo groups. A new, fair-quality trial (unclear randomization and allocation concealment methods) found no difference between the combination of glucosamine and chondroitin in patients with osteoarthritis of the knee, in combination with exercise or as a standalone treatment.[213] Adverse events were not reported.

Table 15. Efficacy, glucosamine and chondroitin trials

Author, Year Quality	Condition Number Enrolled	Comparison Duration of Study	Main Results
		Glucosamine Trials	
Herrero- Beaumont, 2007[204] Fair	OA of knee 318	Glucosamine sulfate 1500 mg powder for oral solution qd Acetaminophen 1 gm po tid Placebo 6 months	Glucosamine sulfate vs. acetaminophen vs. placebo Change from baseline: Lequesne Index (0 to 24): -3.1 vs. -2.7 vs. -1.9; p=0.032 for difference vs. placebo WOMAC total (0 to 100): -12.9 vs. -12.3 vs. -8.2; p=0.039 for difference vs. placebo WOMAC pain (0 to 100): -2.7 vs. -2.4 vs. -1.8; NS WOMAC function (0 to 100): -9.2 vs. -8.7 vs. -5.5; p=0.022 for difference vs. placebo OARSI-A responders: 40% vs. 21.2% for placebo, p= 0.004
Rozendaal, 2008[205] Rozendaal, 2009 Good	OA of hip 222	Glucosamine sulfate 1500 mg po qd or bid Placebo 24 months	Glucosamine sulfate vs. placebo Change from baseline: WOMAC pain (0 to 100): -1.90 ± 1.6 vs. -0.30 ± 1.6, adjusted difference -1.54 (-5.43 to 2.36) WOMAC function (0 to 100): -1.69 ± 1.3 vs. 0.38 ± 1.3, adjusted difference -2.01 (95% CI -5.38 to 1.36) JSN, mm adjusted difference: Minimal: -0.029 (95% CI -0.122 to 0.064) Lateral: -0.017 (95% CI -0.121 to 0.088) Superior: 0.016 (95% CI -0.079 to 0.111) Axial: -0.005 (95% CI -0.118 to 0.108)

Table 15. Efficacy, glucosamine and chondroitin trials (continued)

Author, Year Quality	Condition Number Enrolled	Comparison Duration of Study	Main Results
Wilkens, 2010[206] Good	Degenerative lumbar OA 250	Glucosamine sulfate 1500 mg po qd or tid Placebo 6 months	Glucosamine sulfate vs. placebo Treatment Effect at 1 year (negative values favor glucosamine): RMDQ (0 to 24): -0.8 (95% CI -2.0 to 0.4), p=0.50 NRS LBP (0 to 10): -0.3 (95% CI -0.8 to 0.3). p=.85 Global perceived effect, No. (%):* 34 (30.9%) vs. 32 (29.4%), p=.30
Chondroitin Trials			
Kahan, 2009[207] Fair	OA of knee 622	Chondroitin sulfates 4 & 6 800 mg every evening Placebo 2 years	Chondroitin sulfate vs. placebo At 6 months: WOMAC pain score decrease ≥40%: 41% vs. 34%, p=0.05 No difference in WOMAC total, stiffness, or function At 24 months: minimum JSW loss (mean ± SEM): -0.07 ± 0.03 mm vs. -0.31 ± 0.04 mm Hodges-Lehmann estimator of median effect of treatment: -0.14 (95% CI 0.06 – 0.21 mm, p<0.0001)
Mazieres, 2010[208] Fair	OA of knee 307	Chondroitin sulfate 500 mg po bid Placebo 24 weeks	Chondroitin sulfate vs. placebo Change from baseline to week 24, M (SD): Lequesne Index, (0 to 24): -2.4 (3.4) vs. -1.7 (3.3), p=0.109 VAS pain, mm: -26.2 (24.9) mm vs. -19.9 (23.5) mm, p= 0.029 OMERACT-OARSI responders: 68% vs. 56% (p=0.03)
Michel, 2005[209] Fair	OA of knee 300	Chondroitin sulfates 4 & 6 800 mg po qd Placebo 2 years	Chondroitin sulfate vs. placebo Changes in WOMAC: Total: -3.9% vs. 2.1% Pain: -11.0% vs. -6.2% Stiffness: -7.8% vs. -4.6% Function: -0.8% vs. 5.9% JSN Minimum difference: 0.12 (95% CI 0.00 to 0.24), p=0.05 JSM Mean difference: 0.14 (95% CI 0.01 to 0.27), p =0.04

Table 15. Efficacy, glucosamine and chondroitin trials (continued)

Author, Year Quality	Condition Number Enrolled	Comparison Duration of Study	Main Results
Moller, 2010[210] Fair	OA of knee (in patients with psoriasis) 129	Chondroitin sulfate 800 mg po qd Placebo 3 months	Chondroitin sulfate vs. placebo (mean differences at 3 months) Pain intensity (0 to 100 mm VAS): -12 (95% CI -20 to -4) Lequesne Index (0 to 24): -1.7 (95% CI -3.0 to -0.4) SF-36 physical component (0 to 100): 1.7 (95% CI 1.4 to -1.2) SF-36 mental component (0 to 100): -0.3 (95% CI -3.3 to 2.6)
Glucosamine/Chondroitin Trials			
Messier, 2007[211] Fair	OA of knee 89	Glucosamine hydrochloride 1500 mg and Chondroitin sulfate 1200 mg qd or tid Placebo 1 year; 6 months alone; 6 months treatment plus exercise	Glucosamine hydrochloride + chondroitin sulfate vs. placebo At 12 months: WOMAC pain (0 to 20): 6.0 (0.5) vs. 5.18 (0.5) WOMAC function (0 to 68): 19.4 (1.2) vs. 20.6 (1.2)
Sawitzke, 2008[212] Good	OA of knee 662	Glucosamine sulfate 500 mg tid Chondroitin sulfate 400 mg tid Combination of Glucosamine and Chondroitin Celecoxib 200 mg qd Placebo 24 months	Glucosamine hydrochloride vs. chondroitin sulfate vs. both vs. placebo Mean loss in JSW over 2 years: 0.013 vs. 0.107 vs. 0.194 vs. 0.111 vs. 1.166 Difference from placebo (negative value = less JSW loss): -0.153 (-0.379, 0.074) vs. -0.059 (-0.287, 0.169) vs. 0.028 (-0.214,0.271) vs. -0.055 (-0.279, 0.170) Disease progression over 2 years, % of patients:18.6 vs. 21.4 vs. 24.4 vs. 20.2 vs. 22.4

bid = twice daily; JSM = joint space measurement; JSN = joint space narrowing; JSW = joint space width; NRS LBP = numerical rating scale for low back pain; OA = osteoarthritis; OMERACT-OARSI = Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International; po = orally; RMDQ = Roland Morris Disability Questionnaire; qd = once daily; qid = four time daily; tid = three times daily; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
*Proportion of patients who had a global perceived effect to the intervention

Key Question 1a. How do These Benefits and Harms Change With Dosage and Duration of Treatment, and What is the Evidence That Alternative Dosage Strategies, Such as Intermittent Dosing and Drug Holidays, Affect the Benefits and Harms of Oral Medication use?

Summary of Evidence

- Higher doses of NSAIDs were associated with greater efficacy for some measures of pain relief, and in some trials with greater withdrawals due to adverse events.
- A meta-analysis of 41 randomized trials found no clear association between duration of therapy with COX-2 selective NSAIDs and risk of CV events.
- The meta-analysis found higher doses of celecoxib associated with increased risk of CV events.
- Almost all of the CV events in trials of celecoxib were reported in long-term trials of colon polyp prevention that used higher, twice-daily dosing.
- For nonselective NSAIDs, large observational studies showed no association between higher dose and longer duration of NSAID therapy and increased risk of CV events.
- Many studies found that risk of GI bleeding increases with higher doses of nonselective NSAIDs, but no clear association with duration of therapy.
- One small trial found continuous celecoxib slightly more effective than intermittent use on pain and function, and similar rates of withdrawals due to adverse events. No trial has been designed to assess serious GI or CV harms associated with intermittent dosing strategies.

Detailed Analysis

Eight systematic reviews[10, 95, 99, 101, 114, 121, 186, 226] included in the original CER and one new systematic review[97] evaluated effects of dose and duration on benefits and harms of NSAIDs. We identified one new trial that compared continuous to intermittent use of celecoxib for osteoarthritis.[227]

One good-quality systematic review of eight trials included in the original CER found higher doses of nonselective and partially selective NSAIDs associated with greater efficacy for some measures of pain relief when directly compared to lower doses.[226] Higher doses also were associated with greater withdrawals due to adverse events in two of four trials.

Evidence on the association between dose of NSAID or duration of therapy and risk of CV events is mixed. A meta-analysis of 41 randomized trials included in the original CER found that risk of CV events with COX-2 inhibitors did not vary according to duration of treatment.[121] For celecoxib specifically, evidence of an association with CV events largely comes from long-term trials.[114] The 33-month APC polyp prevention trial was the first to show an increased risk of CV events relative to placebo.[119] The lack of an association in CLASS[54] and other shorter term trials could be due to a duration-dependent effect, or lack of power due to small numbers of events in the shorter trials.

The meta-analysis[121] also found higher doses of celecoxib associated with greater CV risks relative to placebo (p=0.03). Most of the events at the highest dose (800 mg once daily) came from the two long-term polyp prevention trials.[119, 228] Large observational studies showed no association between higher doses of various celecoxib and various nonselective NSAIDs[132, 133, 139, 143, 144, 146] or longer duration of therapy[129, 130, 132, 133, 143, 144, 146] and increased risk of CV

events. However, one new cohort study of patients following an index hospitalization for heart failure found higher doses of celecoxib, ibuprofen, diclofenac, and naproxen associated with increased risk of death compared to lower doses, though there was no dose-dependent effect on risk of subsequent hospitalization due to heart failure of myocardial infarction.[160]

Evidence on the association between dose of NSAID therapy and risk of ulcer complications is more consistent, though the association between duration and risk of ulcer complications is less clear. CLASS found celecoxib more effective than nonselective NSAIDs at reducing GI events at 6 months compared with longer duration of exposure, though interpretation of final results is difficult due to high withdrawal rates.[54, 85] A new systematic review of observational studies found higher doses of selective and nonselective NSAIDs (RR 5.4 compared to nonuse of NSAIDs, 95% CI 4.6 to 6.3) consistently associated with greater risk of upper GI bleeding or perforation compared to lower or medium doses (RR 2.8, 95% CI 2.2 to 3.6).[97] There was no clear association with duration of therapy. Similar findings were reported in older systematic reviews of observational studies included in the original CER.[10, 101, 186] In three studies[98, 102, 104] included in the new systematic review, slow-release formulations of NSAIDs (RR 5.9, 95% CI 4.7 to 7.3) and NSAIDs with a half-life longer than 12 hours (RR 5.7, 95% CI 3.6 to 9.2) were also associated with a greater risk of upper GI bleeding or perforation compared to NSAIDs with a half-life shorter than 12 hours (RR 3.1, 95% CI 2.4 to 4.1).[97]

For aspirin, a systematic review of randomized trials included in the original CER found no association between higher dose and increased risk of upper GI bleeding.[95] Modified release formulations did not attenuate the risk for bleeding. In a fair-quality meta-analysis of 31 randomized trials with more than 190,000 subjects, the risk of major bleeding was 1.6 percent with doses <100 mg once daily, 1.5 percent with 100–200 mg once daily, and 2.3 percent with >200 mg once daily.[229] Although the difference between doses >200 mg once daily and <100 mg once daily was statistically significant, the absolute difference were small. A systematic review of observational studies found that most (but not all) studies found a dose-dependent effect of aspirin on risk of upper GI complications.[99]

The risk of bleeding associated with acetaminophen was not clearly associated with increased dose in a meta-analysis of three case-control studies included in the original CER,[186] though there was a modest dose response in one other case-control[185] and one retrospective cohort study[108] of older adults.

Few studies have evaluated risks associated with lower over-the-counter doses of NSAIDs. Based on data from the ARAMIS database, the risk of GI hospitalizations associated with over-the-counter doses of aspirin, acetaminophen, and ibuprofen were similar to background rates in patients with rheumatoid arthritis or osteoarthritis.[230] A systematic review of observational studies found use of aspirin and nonaspirin NSAIDs at over-the-counter doses associated with an increased risk of GI bleeding, though the risk was lower than observed at prescription doses (approximately twofold greater risk at over-the-counter doses and sixfold or higher increases at heavy prescription levels.[10] One recent analysis of the Nurses' Health Study found that the risk of CV events was dose-related for both NSAIDs and acetaminophen.[187]

Data on effects of intermittent dosing or frequency of dosing is sparse. One new (n=123) randomized trial found continuous celecoxib 200 mg once daily slightly more effective than intermittent use on the WOMAC total score (difference from baseline 38 vs. 25, scale not reported, p<0.05) and associated with a smaller percentage of days using medications for flares (48% vs. 53%, p=0.03) after 24 weeks in patients with osteoarthritis of the knee or hip.[227] Continuous and intermittent dosing were associated with similar rates of withdrawal due to

adverse events, but the trial was not designed to assess serious harms such as ulcer complications or myocardial infarction. One difference between the APC trial (which found an increased risk of CV events with celecoxib) and the PreSAP trial (which reported no association) was twice-daily (APC) versus once-daily (PreSAP) dosing.[120] However, no study has directly compared such dosing strategies. Furthermore, other studies of twice-daily dosing with celecoxib (such as CLASS[54] and ADAPT[122]) reported no increase in CV risk.

Key Question 2. Do the Comparative Benefits and Harms of Oral Treatments for Osteoarthritis Vary for Certain Demographic and Clinical Subgroups?

Summary of Evidence

- Age, sex, and race
  - The absolute risk of serious GI and CV complications increases with age.
  - Large observational studies have not consistently shown increased relative risks of serious GI or CV complications with older age.
  - Because the absolute risk of serious GI and CV complications increases with older age, more complications occur even with similar relative risks.
  - Evidence on effects of sex and race on comparative benefits and harms associated with oral treatments for osteoarthritis is very sparse.
- History of bleeding ulcer
  - Risk of GI bleeding is higher in patients with prior bleeding
  - Two trials found high rates of recurrent ulcer bleeding in patients randomized either to celecoxib (4.9% to 8.9% with 200 mg twice daily) or a nonselective NSAID + PPI (6.3 percent).
  - One trial found the combination of celecoxib with higher dose PPI associated with lower risk of recurrent bleeding compared with celecoxib alone (0% vs. 8.9%; p=0.0004).
- Underlying CV or renal risk
  - A systematic review of randomized trials of celecoxib found risk of CV events doubled in patients at moderate versus low risk (HR 2.0, 95% CI 1.5 to 2.6) and doubled again in patients at high risk (HR 3.9 for high risk vs. low risk, 95% CI 2.3 to 6.7).
  - Most large observational studies found an association between increased CV risk and increased risk of CV events in persons using NSAIDs.
  - Following hospitalization for heart failure, one large observational study found celecoxib and diclofenac associated with a higher risk of death compared to ibuprofen or naproxen, and another large observational study found an increased risk of repeat heart failure admission with indomethacin compared to other nonselective NSAIDs, ibuprofen, acetaminophen, or celecoxib.
- Concomitant use of anticoagulants and analgesics
  - Concomitant use of anticoagulants and nonselective NSAIDs increase the risk of GI bleeding three- to sixfold compared with anticoagulant use without NSAIDs.
  - The risk with concomitant celecoxib is not clear due to conflicting findings among observational studies, but may be increased in older patients.

- o Reliable conclusions about the comparative safety of nonselective, partially selective and selective NSAIDs with concomitant anticoagulants could not be drawn due to small numbers of studies with methodological shortcomings.
  - o Warfarin plus low-dose aspirin increased the risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis.
  - o Acetaminophen can increase International Normalized Ratio (INR) levels, but effects on bleeding rates have not been studied.
- Concomitant use of prophylactic dose aspirin
  - o Concomitant use of aspirin appears to attenuate the GI benefits of COX-2 selective NSAIDs, resulting in risk similar to nonselective NSAIDs.
  - o Addition of a PPI may reduce the risk of GI harms in persons using either celecoxib or nonselective NSAIDs and low-dose aspirin.
  - o Evidence regarding the effects of concomitant aspirin use on CV risk associated with selective or nonselective NSAIDs is limited, though three polyp prevention trials of COX-2 selective NSAIDs found that concomitant aspirin use did not attenuate the observed increased risk of CV events.
  - o Observational studies did not find increased CV risk with the addition of nonselective NSAIDs as a class to low-dose aspirin.
  - o Limited evidence suggests an increased risk of mortality with aspirin and concomitant ibuprofen compared to aspirin alone among high risk patients (HR 1.9, 95% CI 1.3 to 2.9), but studies on effects of ibuprofen added to aspirin on MI risk in average risk patients were inconsistent and did not clearly demonstrate increased risk.

Detailed Analysis

Demographic Subgroups Including Age, Sex, and Race

In general, the risk of CV, cardiorenal, and GI adverse events associated with NSAIDs increase with age.[12] In one United Kingdom population, for example, the risk of adverse GI outcomes in patients taking selective or nonselective NSAIDs was 1.4 per 1,000 patient-years for all patients 25 years or older, but 4.0 per 1,000 patient-years in patients aged 65 or more.[103] Similarly, the risk of myocardial infarction was 1.7 per 100 person-years for all patients 25 years or older, but 4.6 per 100 person-years for those 65 or older.[136] We found no trial designed to assess whether the relative harms and benefits associated with different NSAIDs for osteoarthritis vary according to age. Large observational studies that have stratified subjects by age have not showed a consistent increase in relative estimates of risk associated with NSAIDs in older compared to younger age strata for ulcer complications[107, 133] or myocardial infarction.[130, 132] However, even if the relative benefits and harms associated with different drugs are consistent across age groups, the absolute effects would increase with age because of greater baseline CV and GI risk. In one observational study, the CV event rate in older adults (mean age 80 years) was 12/100 patient-years for ibuprofen overall, and 18/100 patient-years in people 80 years and older.[114]

Studies that evaluated the efficacy and safety of selective and nonselective NSAIDs in average-risk elderly patients have generally reported similar findings compared with studies in populations with younger adults. An individual patient data meta-analysis of three celecoxib trials, for example, found effects of celecoxib 200 mg once daily or 400 mg once daily and

naproxen 1,000 mg once daily similar in elderly patients when evaluating WOMAC and SF-36 scores.[231] For the SF-36, there were no statistically significant differences: naproxen scored better than celecoxib 200 mg on 4 of 10 components of the SF-36, while celecoxib 200 mg scored better on 6, including general health. Celecoxib 200 mg was significantly better than placebo on nine of the 10 components, while naproxen was significantly better than placebo on seven. The study also confirmed that the overall incidence of GI adverse events was lower with celecoxib; the difference was about 1 event in 20 patients for celecoxib 200 mg and 1 in 10 for celecoxib 400 mg. Another meta-analysis found that trials of NSAIDs in patients over the age of 60 reported similar risks for GI complications compared to trials of patients under the age of 60.[91]

Data suggesting differential effects of oral medications for osteoarthritis according to gender, ethnicity, or race remain scant. In most of the published trials, a majority of subjects were women. As noted in the discussion of acetaminophen, results from the Nurses' Health Studies suggest that acetaminophen is associated with modest reductions in renal function in women,[195] but results from the Physicians' Health Study have found no association between acetaminophen use and renal dysfunction in men.[196] The effects of different NSAIDs in specific ethnic minorities have only been evaluated in small studies. In a randomized crossover study of 25 black and Hispanic patients on ACE inhibitors, peak increases in blood pressure were similar in patients on diclofenac compared with celecoxib.[232] We did not find any other publications focusing on the differential efficacy or safety of coxibs in African-Americans, Hispanics, or other ethnic minorities.

Coexisting Diseases Including History of Previous Bleeding Ulcer Due To NSAIDs: Hypertension, Edema, Ischemic Heart Disease, and Heart Failure

Previous Bleeding Ulcer

Two randomized trials included in the original CER[233, 234] and one new trial[235] compared the risk of GI harms in patients with a recent bleeding ulcer randomized to celecoxib versus the combination of celecoxib plus a PPI (Table 16).

In two fair-quality, 24-week trials (total n=529) included in the original CER of patients with a history of a recent bleeding ulcer, rates of recurrent bleeding were similar for celecoxib (200 mg daily 3.7 percent and twice a day 4.9 percent) and the combinations of extended-release diclofenac 75 mg twice a day plus omeprazole 20 mg daily (6.3 percent)[233] or naproxen 250 mg three times a day plus lansoprazole 30 mg a day (6.3 percent)[234] (differences not statistically significant). There were also no differences between celecoxib and either combination therapy in GI, renal, and CV adverse events or in rates of withdrawal due to adverse events. One exception was that celecoxib 200 mg daily was associated with a higher rate of dyspepsia than naproxen 250 mg three times a day plus lansoprazole 30 mg daily in one trial.[236]

A new, fair-quality, 12-month trial (n=273) of patients with recently healed GI bleeding (following cessation of NSAID therapy and treatment with a PPI for 8 weeks) found celecoxib 200 mg twice daily plus esomeprazole 20 mg twice daily associated with significantly fewer ulcer bleeding recurrences compared with celecoxib alone.[235] After a median of 13 months, zero events occurred in the combined treatment group, compared with 12 (8.9 percent) in the celecoxib alone group (p=0.0004). Similar results were found among those taking low-dose

aspirin (0% vs. 19%; p=0.03). Other adverse events and rates of discontinuations were similar between groups.

Table 16. Celecoxib in patients with bleeding ulcer history

Study Sample Size	Treatments	Recurrent Ulcer Bleeding (Difference, 95% CI)	Other Adverse Events	Withdrawals due to Adverse Events
Chan 2002[233] n=287	Celecoxib 200 mg bid Diclofenac 75 mg bid plus omeprazole 20 mg qd	4.9% vs. 6.3% at 6 months (–1.5%, –6.8 to 3.8; NS)	No differences	13% vs. 12%, NS*
Lai 2005[234]† n=242	Celecoxib 200 mg qd Naproxen 250 mg tid plus lansoprazole 30 mg qd	3.7% vs. 6.3% at 6 months (-2.6; –9.1 to 3.7; NS)	No differences for all but dyspepsia: 15% vs. 5.7%, p=0.02	10% vs. 7.4%, NS
Chan 2007[235] n=273	Celecoxib 200 mg bid plus esomeprazole 20mg bid Celecoxib 200 mg bid	0% vs. 19% at median 13 months (p=0.03)	No differences	5.8% vs. 7.4%, NS

bid = twice daily; CI = confidence interval; NS = not significant; qd = three times daily; tid = twice daily
* Includes withdrawals due to lack of efficacy
† Open trial

Underlying Cardiovascular or Renal Risk

We found no randomized trials designed to assess whether the relative harms and benefits associated with different oral treatments for osteoarthritis vary according to underlying CV or renal risk. A new systematic review of long-term celecoxib trials found that risk of CV events doubled between patients at low and moderate baseline CV risk (HR 2.0, 95% CI 1.5 to 2.6) and doubled again in patients at high baseline risk (HR, high risk to low risk, 3.9, 95% CI 2.3 to 6.7).[114] Most[132, 133, 145, 237] but not all[134] large observational studies also found a history of coronary heart disease, coronary heart disease risk factors, or categorization as high CV risk associated with increased risk estimates with NSAIDs as a group. A good-quality, population-based study of a very high-risk group of 58,000 Danish patients with previous myocardial infarction found hazard ratios for death of 2.6 (95% CI 2.2 to 3.1) for celecoxib, 1.5 (95% CI 1.4 to 1.7) for ibuprofen, 2.4 (95% CI 2.1 to 2.8) for diclofenac, and 1.3 (95% CI 1.2 to 1.4) for other NSAIDs compared to nonuse of NSAIDs.[238] Based on the rates of death in this population (95 per 1,000 person-years in those not using NSAIDs), the estimated number of patients needed to treat with an NSAID for one year to cause one additional death was 14 (95% CI 10 to 24) for celecoxib, 45 (95% CI 29 to 102) for ibuprofen, and 24 (95% CI 16 to 45) for diclofenac.

We found no trials evaluating comparative risks of different oral medications in patients with known congestive heart failure. A new cohort study found celecoxib, ibuprofen, diclofenac, and naproxen associated with similar risk of hospitalization due to acute myocardial infarction (HR estimates ranged from 1.3 to 1.5) or hospitalization due to congestive heart failure (HR estimates ranged from 1.2 to 1.4) following an index hospitalization for congestive heart failure, though celecoxib (HR 1.8, 95% CI 1.6 to 1.9) and diclofenac (HR 2.1, 95% C I 2.0 to 2.2) were associated with greater risk of death compared to ibuprofen (HR 1.3, 95% CI 1.2 to 1.4) or naproxen (HR 1.2, 95% CI 1.1 to 1.4).[162] A new nested case-control study found indomethacin associated with increased risk of heart failure compared to celecoxib (OR 2.0, 95% CI 1.2 to 3.6) in patients older than 66 recently hospitalized for heart failure.[158] There was no difference in risk of heart failure between other nonselective NSAIDs (diclofenac [OR 0.82, 95% CI 0.51 to 1.3] and ibuprofen [OR 1.5, 0.66 to 3.2]) or acetaminophen (OR 1.2, 95% CI 0.92 to 1.4) relative to celecoxib. A retrospective cohort study included in the original CER based on the same

Canadian database found nonselective NSAIDs associated with an increased risk of death (HR 1.5, 95% CI 1.2 to 2.0), recurrent heart failure (HR 1.2, 95% CI 0.92 to 1.6), or either (HR 1.3, 95% 1.0 to 1.6) in similarly high risk patients.[161]

One new trial (n=88) compared ibuprofen, acetaminophen, and piroxicam in hypertensive patients on lisinopril/hydrochlorothiazide or amlodipine.[239] Both NSAIDs blunted the effects of the antihypertensive drugs, with the lisinopril/hydrochlorothiazide combination more affected. Acetaminophen had almost no effect on blood pressure.

Concomitant Anticoagulants

Nonselective NSAIDs

Concomitant use of anticoagulants and nonselective NSAIDs increase the risk of GI bleeding three- to sixfold compared to anticoagulants alone.[240, 241] Three observational studies included in the original CER evaluated risk of bleeding in patients on an NSAID plus anticoagulants versus an anticoagulant alone.[242-244] We identified no new studies.

A good-quality nested case-control study of elderly (>66 years old) patients on warfarin in Ontario, Canada, evaluated the association between hospitalization for upper GI bleeding (361 cases) and use of selective or nonselective NSAIDs.[242] It found that after adjustment for potential confounders (antiplatelet agents, hypoglycemic agents, glucocorticoids, gastroprotective agents, history of previous bleed, and comorbidities), recent use of nonselective NSAIDs (OR 1.9, 95% CI 1.4 to 3.7), and celecoxib (OR 1.7, 95% CI 1.2 to 3.6) were associated with increased and overlapping risks for upper GI bleeding, compared with nonuse. Because this study relied on pharmacy databases to identify exposures prior to hospitalization, it could not assess the confounding effects of over-the-counter use of aspirin, other NSAIDs, or acid suppressive medications. It also was unable to control for variations in INR level and the risk for bleeding.

In a fair-quality cohort study of patients enrolled in an anticoagulation clinic, 1,145 patients who were receiving warfarin (INR ≥1.4) but not aspirin, acetaminophen, or other nonselective NSAID were indentified retrospectively. [243] Eleven percent (n=123) were taking celecoxib concurrently with warfarin during the study period. The risk of major bleeding events (requiring hospitalization, transfusion or resulting death) was not significantly elevated in the celecoxib group (RR 1.0, 95% CI 0.14 to 7.8).

A smaller, fair-quality nested retrospective study of patients in the Netherlands evaluated the risk of bleeding in anticoagulated patients receiving partially selective (meloxicam or nabumetone) or nonselective NSAIDs.[244] This study differed from the others in that it included all cases of bleeding, including minor visible bleeding, hematoma, or black tarry stools. Patients were identified as having exposure to anticoagulation by being enrolled in a pharmacy-based anticoagulation program. Bleeding events were identified through the pharmacy clinic records, and discharge diagnosis records (national database). Patient questionnaires were sent out to those identified as having a bleeding event, to assess exposure status and comorbidities. Patients were interviewed over the phone if answers were incomplete or unclear. The response rates were significantly higher in the cases (approximately 70 percent) compared with controls (approximately 31 percent). The study found that nonselective NSAIDs were associated with an increased risk of bleeding compared with partially selective NSAIDs after adjustment for duration of use and INR level (OR 3.1, 95% CI 1.2 to 8.0).

Aspirin and Anticoagulation

In the original CER, we found no studies evaluating risks and benefits of concomitant anticoagulants and aspirin in patients with arthritis. No new studies were identified for this update. Combination therapy has been studied in patients with indications for thromboembolic prophylaxis. However, the results of those studies are not directly applicable to patients with arthritis because of important differences in the populations (particularly with regard to CV risk), and because aspirin was used in lower, prophylactic doses (rather than anti-inflammatory and analgesic doses). One fair-quality meta-analysis (did not evaluate quality of included trials) found major bleeding risk increased with warfarin plus aspirin versus warfarin alone (at the same intensity) in patients with mechanical heart valves (three trials, RR 1.58, 95% CI 1.02 to 2.44).[245] In patients with recent myocardial infarction or atrial fibrillation (one trial each), the increase in risk was not statistically significant (RR 3.07, 95% CI 0.33 to 28.38 and RR 2.13, 95% CI 0.20 to 23.03, respectively). In patients with mechanical heart valves, the increase in bleeding risk was offset by a reduction in thromboembolic events (RR 0.33, 95% CI 0.19 to 0.58), and there was no difference in all-cause mortality (RR 0.78, 95% CI 0.29 to 1.83). Other evidence on the risks and benefits of combination therapy has focused on comparing warfarin plus aspirin to aspirin alone. A good-quality meta-analysis of 10 trials found the combination of warfarin plus aspirin increased the risk of major bleeding compared with aspirin alone following myocardial infarction or the acute coronary syndrome (RR 2.5, 95% CI 1.7 to 3.7).[246] However, the increase in bleeding risk was offset by lower risks for myocardial infarction, ischemic stroke, and revascularization. Mortality did not differ.

Other Analgesics

No study evaluated risk of bleeding in anticoagulated patients on acetaminophen compared with those on NSAIDs. A small, randomized controlled trial found acetaminophen associated with greater increases in INR levels compared with placebo.[247] Several observational studies have also found an association between excess anticoagulation and use of acetaminophen.[248, 249] However, changes in INR are not the only important factor for predicting increased risk of bleeding. NSAIDs, for example, also affect platelet function and disrupt the gastric mucosal lining. Studies evaluating actual bleeding complications are necessary to better assess the comparative risks from acetaminophen and other NSAIDs.

No studies evaluated risk of bleeding in anticoagulated patients on glucosamine, chondroitin, or topical agents.

Concomitant Aspirin: Gastrointestinal Harms

Celecoxib Plus Aspirin Compared With Nonselective NSAID Plus Aspirin

Beneficial effects of COX-2 selective inhibition on GI complication rates could be attenuated or eliminated by the concomitant use of aspirin. The original CER included two large trials (CLASS[54] and SUCCESS-1[55]) and a systematic review[51] that reported rates of ulcer complications associated with celecoxib and nonselective in subgroups of patients also using aspirin. Two new observational studies also compared risks of serious GI harms with celecoxib and nonselective NSAIDs in aspirin users.[250, 251]

In the 20 percent of patients in CLASS who took aspirin in addition to their study drug, there was no difference in rates of ulcer complications (2.0% vs. 2.1%, p=0.92) or ulcer complications

plus symptomatic ulcers (4.7% vs. 6.0%, p=0.49) in patients randomized to celecoxib versus those randomized to diclofenac or ibuprofen.[54, 252] There were also no differences when celecoxib was compared to diclofenac and ibuprofen separately. In SUCCESS-1, among the 7 percent of the study population on aspirin, only four ulcer complications occurred, resulting in imprecise estimates (OR 2.0, 95% CI 0.14 to 27).[55] The systematic review found that use of aspirin increased the rate of endoscopic ulcers by about 6 percent in patients randomized to celecoxib (4.2% without aspirin and 9.9% with aspirin) or those randomized to a nonselective NSAID (18% and 24%, respectively).[51] Celecoxib (any dose) was associated with a lower risk of endoscopic ulcers in aspirin users (RR 0.48, 95% CI 0.28 to 0.83), but ulcer complications were not reported in this subgroup.

The two new, fair-quality retrospective cohort studies were conducted by the same authors and evaluated the same Quebec health services administrative databases (Appendix H).[250, 251] One study found use of celecoxib plus aspirin associated with a lower risk of hospitalizations due to ulcer complications compared with use of a nonselective NSAID plus aspirin (HR 0.62, 95% CI 0.48 to 0.80) among patients 65 years or older.[250] The second study found that in patients 50 years and older, users of celecoxib plus aspirin had a lower risk of hospitalization for GI complications (HR 1.8, 95% CI 1.5 to 2.1) than users of diclofenac plus aspirin (HR 2.8, 95% CI 2.2 to 2.8, 95% CI 2.2 to 3.5), though estimates for ibuprofen plus aspirin (HR 1.4, 95% CI 0.8 to 2.7), naproxen plus aspirin (HR 2.2, 95% CI 1.6 to 3.0), and piroxicam plus aspirin (HR 2.0, 95% CI 0.8 to 5.4) were similar (each compared with users of acetaminophen without aspirin).[251]

Impact of Concomitant PPI use on GI Risk With a Celecoxib or Nonselective NSAID

Subgroup analyses from four randomized controlled trials (reported in three publications) provided evidence on the effects of adding a PPI to celecoxib or nonselective NSAIDs in aspirin users.[235, 253, 254] Only one fair-quality trial reported ulcer complications. [235] In patients (n=273) at very high risk for rebleeding (recently healed GI bleed) enrolled in this study, low-dose aspirin was started during the trial period in 43 patients. The rate of recurrent bleeding in this subgroup was 0 percent with celecoxib 200 mg twice daily plus esomeprazole 20 mg twice daily group compared with 19 percent in the group taking celecoxib alone (p=0.03).[235]

In two similarly designed, fair-quality trials (reported in one publication, total n=861) the pooled rate of endoscopically proven gastric ulcer in the subgroup also taking low-dose aspirin (n= 201) was significantly lower with naproxen plus a PPI (3 percent) compared with enteric coated naproxen alone (28%; p<0.001).[253] A large, fair-quality trial of celecoxib versus naproxen plus lansoprazole in low-dose aspirin users (n = 1,045) found no difference in risk of endoscopically proven gastric or duodenal ulcers (9.9% vs. 8.9%, p=0.65).[254] Post-hoc analyses showed no effect based on aspirin dose (81 mg or 325 mg daily).

Concomitant Aspirin: Cardiovascular Harms

Celecoxib

The original CER included a systematic review, a randomized trial not included in the systematic review, and two large observational studies on effects of aspirin on CV harms associated with celecoxib use. We identified no new studies.

A systematic review of 84 placebo-controlled trials of celecoxib that permitted aspirin use found a very similar risk of vascular events among aspirin users (RR 1.6, 95% CI 0.90 to 2.7)

and aspirin nonusers (RR 1.5, 95% CI 1.1 to 2.0), though the absolute rate of events was higher in aspirin users (1.9 percent/year vs. 1.1 percent/year), perhaps due to higher baseline risk.[121] In a large celecoxib polyp prevention trial not included in the systematic review, use or nonuse of low-dose aspirin did not affect the observed increased risk of thrombotic events.[255] Consistent with these findings, two large observational studies found no significant interaction between concurrent NSAID and aspirin use and risk of myocardial infarction.[134, 136]

Nonselective NSAIDs

It has been suggested that some nonselective NSAIDs may reduce or eliminate the CV benefits associated with low-dose aspirin.[36] In particular, ibuprofen is thought to be associated with unique pharmacokinetic and pharmacologic properties that could interfere with aspirin. Six observational studies[108, 133, 256-259] and one subgroup analysis from a randomized trial[260] evaluated effects of concomitant NSAIDs on CV risk in aspirin users (Table 17, Appendix H). The studies used heterogeneous designs, outcome measures, and methods of analysis, making it difficult to reach firm conclusions about comparative risks.

Three observational studies found no increase in risk of mortality[257] or myocardial infarction[133, 256] in users of a nonselective NSAID plus aspirin versus aspirin alone (Table 17). A subgroup analysis from a randomized trial also found no increased risk with short-term (<60 days) use of a nonselective NSAID plus aspirin compared to aspirin alone.[260] The estimate for longer term use suggested increased risk, but was imprecise and not statistically significant.

For the effect of adding ibuprofen to aspirin, one fair-quality study of patients recently discharged from the hospital for a CV disease diagnosis found an increased risk of overall and CV mortality with the combination of ibuprofen and aspirin compared to aspirin alone (Table 17).[258] The study did not report baseline characteristics of patients, although the analysis did control for potential confounders.

Two other observational studies evaluated risk of acute MI with ibuprofen plus aspirin versus aspirin alone.[256, 259] A fair-quality case-control study found the risk of first nonfatal MI was elevated in those using ibuprofen plus aspirin compared with those using only aspirin, while a retrospective cohort study (also fair quality) found that adding ibuprofen to aspirin resulted in decreased risk of myocardial infarction (Table 17).[256, 259] These studies used different methods, which could account for their discrepant findings. The case-control study identified controls from the community, used telephone interviews to collect exposure and covariate data, and considered the patient to be exposed to ibuprofen or aspirin if they reported using the drug(s) in the week prior to the event.[256] Recall bias is a major concern with this study, and differences between groups suggest potentially important differences in baseline risk. The cohort study used Veterans Affairs prescription and medical records to identify regular users of ibuprofen and aspirin or aspirin alone with matching based on age, race, sex, and cholesterol levels.[259] The study did not measure potential confounders or conduct adjusted analyses, and very limited information was provided about the patients' comparability at baseline.

Two other observational studies found no statistically significant differences in risk between ibuprofen plus aspirin versus ibuprofen alone[108] or use of ibuprofen plus aspirin versus nonuse of NSAIDs (including aspirin),[133] but were not designed to assess risk associated with addition of ibuprofen to aspirin.

Table 17. Observational studies of the cardiovascular risk with concomitant aspirin

Study		Study Design	Number	Outcome Measure	Referent	Effect (95% CI)
Any nonselective NSAID	Ko 2002[255]	Cohort	39,043	Mortality at 1 year	No NSAID, no aspirin	NSAID+ASA OR 0.78 (0.69 to 0.88) ASA alone OR 0.81 (0.77 to 0.86)
	Kurth 2003*[258]	RCT Subgroup analysis	22,071	AMI	No aspirin (placebo)	ASA without NSAID OR 0.56 (0.44 to 0.72) 1-59 days NSAID + ASA OR 0.69 (0.46 to 1.0) $\geq$60 days NSAID + ASA OR 1.57 (0.70 to 6.6)
	Kimmel 2004[254]	Case-control	4,393	First nonfatal MI	Aspirin alone	NSAID+ASA OR 0.92 (0.46 to 1.9)
	Fisher 2005[131]	Case-control	2,989	AMI	No NSAID, no aspirin	NSAID+ASA OR 0.74 (0.57 to 0.97) ASA alone OR 0.87 (0.75 to 1.0)
Ibuprofen	MacDonald 2003[256]	Cohort	7,107	All-cause and cardiovascular mortality	Aspirin alone	Ibuprofen+ASA All-cause mortality HR 1.9 (1.3 to 2.9) Cardiovascular mortality HR 1.7 (1.0 to 2.8)
	Patel 2004[257]	Cohort	14,098	AMI	Aspirin alone	Ibuprofen+ASA OR 0.61 (0.50 to 0.73)
	Kimmel 2004[254]	Case-control	4,393	First nonfatal MI	Aspirin alone	Ibuprofen+ASA OR 2.0 (1.1 to 3.9)
	Rahme 2007[248]	Cohort	76,877	AMI	Acetamin-ophen alone	Ibuprofen+ASA OR 1.4 (0.8 to 2.4) Ibuprofen only OR 1.0 (0.74 to 1.5)
	Fischer 2005[131]	Case-control	2,989	AMI	No NSAID, no aspirin	Ibuprofen+ASA OR 0.69 (0.42 to 1.2)

AMI = acute myocardial infarction; ASA = aspirin; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio

* Composite outcome = CV mortality, nonfatal MI, and stroke at 1 year.

Combined Cardiovascular and Gastrointestinal Harms

A large retrospective cohort study of patients 65 years and older evaluated risk of hospitalizations due to upper GI bleeding or acute myocardial infarction associated with various NSAIDs and acetaminophen in low-dose aspirin users (n=112,141), compared to use of acetaminophen alone.[108] The adjusted odds of GI bleeding or acute myocardial infarction relative to acetaminophen alone were similar for celecoxib, ibuprofen, diclofenac, naproxen, and acetaminophen (RR range 1.3 to 1.7), with overlapping confidence intervals.

Key Question 3. What are the Comparative Effects of Coprescribing of H2-Antagonists, Misoprostol, or Proton Pump Inhibitors (PPIs) on the Gastrointestinal Harms Associated With NSAID use?

Summary of Evidence

- Misoprostol was the only gastroprotective agent to reduce risk of serious ulcer complications (perforation, obstruction, or bleeding) compared with placebo in patients with average risk of GI bleeding prescribed nonselective NSAIDs, but was also associated with a high rate of withdrawals due to adverse GI symptoms.
- Celecoxib alone was associated with fewer decreases in hemoglobin (> 2 g/dl) without overt GI bleeding compared with diclofenac plus a proton pump inhibitor (PPI).
- Coprescribing of PPIs, misoprostol, and H2-antagonists all reduced the risk of endoscopically detected gastric and duodenal ulcers compared to placebo in patients prescribed a nonselective NSAID.
- In direct comparisons, coprescribing of PPIs in patients prescribed a nonselective NSAID was associated with a lower risk of endoscopically detected duodenal ulcers compared to misoprostol or H2-antagonists, a lower risk of endoscopically detected gastric ulcers compared to H2-antagonsits, and a similar risk of endoscopically detected gastric ulcers compared to misoprostol.
- In direct comparisons, coprescribing of misoprostol was associated with a lower risk of endoscopically detected gastric ulcers compared to ranitidine, and a similar reduction in risk of endoscopically detected duodenal ulcers.
- Compared to placebo, double (full) dose H2-antagonists may be more effective than standard dose for reducing endoscopically detected gastric and duodenal ulcers.
- Celecoxib plus a PPI may reduce the risk of endoscopic ulcers and ulcer complications compared to celecoxib alone in average risk persons (see Key Question 2 for high-risk people).

Detailed Analysis

Nonselective NSAIDs Plus Misoprostol, H2 Antagonists, or PPIs Versus NSAIDs Alone

Two good-quality systematic reviews[259,260] and one fair-quality systematic reviews[261] included in the original CER evaluated effects of coprescribing gastroprotective agents (H2-antagonists, misoprostol, and PPIs) with NSAIDs versus placebo or against one another on GI harms. We identified four new fair-quality trials (reported in two publications) of an NSAID plus a PPI versus an NSAID alone.[253, 261]

The three systematic reviews (published in 2002 and 2004)[262-264] included numerous randomized controlled trials[8, 264-293] of patients with osteoarthritis or rheumatoid arthritis prescribed NSAIDs. They found misoprostol, standard- and double-dose H2 blockers and PPIs all effective in reducing risk of endoscopic gastric and duodenal ulcers relative to placebo in patients prescribed nonselective NSAIDs (Table 18).[262-264] Misoprostol (RR 0.36, 95% CI 0.20 to 0.67) and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers, and serious GI complications. None of the coprescribed drugs affected mortality.[262] The

reduction in serious complications with misoprostol was in large part due to one large, good-quality trial (MUCOSA).[290] In this study, misoprostol was associated with a rate of definite ulcer complications of 25/4,404 (0.6 percent) compared with 44/4,439 (0.9 percent) with placebo (p=0.05).[290] However, misoprostol was also the only gastroprotective agent associated with an increased risk of withdrawal due to nausea (RR 1.3, 95% CI 1.1 to 1.6), diarrhea (RR 2.4, 95% CI 2.0 to 2.8), and abdominal pain (RR 1.4, 95% CI 1.2 to 1.6).

The new trials were consistent with the systematic reviews (Appendix H).[253, 261] Two similarly designed, fair-quality trials (total n=861) reported in one publication found naproxen 500 mg plus esomeprazole 20 mg combination tablet associated with better scores on patient-reported ratings of gastric symptoms and fewer endoscopic ulcers compared to enteric coated naproxen alone (RR 0.24, 95% CI 0.15 to 0.39 for endoscopic gastric ulcers and RR 0.14, 95% CI 0.04 to 0.46 for endoscopic duodenal ulcer).[253] The studies reported no serious GI complications in either group over 6 months. Two other similarly designed, fair-quality trials evaluated esomeprazole 20 mg or 40 mg daily added to an NSAID compared to the NSAID alone in 1,378 patients.[261] In one trial, about two-thirds of patients were on a nonselective NSAID, and in the other, about 85 percent. In a pooled analysis stratified by type of NSAID, esomeprazole was associated with decreased risk of endoscopic ulcers in patients on nonselective NSAIDs (6.8% with esomeprazole 20 mg, 4.8% with esomeprazole 40 mg, 17% with placebo, RR 0.29, 95% CI 0.17 to 0.49 for esomeprazole 40 mg versus placebo, RR 0.41, 95% CI 0.26 to 0.64 for esomeprazole 20 mg vs. placebo) after 6 months. Both trials reported more patients in the esomeprazole 20 mg daily group had no sleep disturbance, acid regurgitation, or heartburn after one month of treatment compared with placebo, but results were not stratified by NSAID type. There was no difference in the proportion without nausea or upper abdominal bloating, and the 40 mg daily dose was significantly better than placebo only in the proportion of patients without heartburn in both studies, and acid regurgitation in one study. Rates of withdrawal due to adverse events and overall adverse event were similar across groups. Two patients in the nonselective NSAID alone group (0.4 percent) had GI bleeds during the study, compared with none in the nonselective NSAID plus esomeprazole groups.

Table 18. Summary of results from placebo-controlled trials of gastroprotective agents[262-264]

Treatment	Number of Studies Duration	Prevention of Clinical GI Events*	Prevention of Endoscopic Ulcers	
			Gastric	Duodenal
Misoprostol	8;4-11weeks: 11; ≥ 3 months	OR 0.60, 95% CI 0.36 to 0.98[†]	4–11 weeks: RR 0.17, 95% CI 0.09 to 0.31[‡] 3 months: RR 0.26; 95% CI 0.17 to 0.39[‡]	4–11 weeks: RR 0.28, 95% CI 0.09 to 0.31[‡] 3 months: RR 0.47, 95% CI 0.33 to 0.69[‡]
	Duration NR	RR 0.57, 95% CI 0.36 to 0.91[§]	Either: RR 0.33, 95% CI 0.3 to 0.4[§]	Reported in gastric ulcers column
H2 blockers	Standard dose[¶]: 7; ≥3 months Double dose[¶]: 3; ≥3 months	Not reported	Standard dose: RR 0.73, 95% CI 0.50 to 1.1[‡] Double dose: RR 0.44, 95% CI 0.26 to 0.74[‡]	Standard dose: RR 0.36, 95% CI 0.18 to 0.74[‡] Double dose: RR 0.26, 95% CI 0.11 to 0.65[‡]
	Standard dose Duration NR	RR 0.33, 95% CI 0.01 to 8.14[§]	Gastric or duodenal ulcer: RR 0.55, 95% CI 0.4 to 0.7[§]	Reported in gastric ulcers column
PPIs	4, ≥3 months	Not reported	RR 0.40, 95% CI 0.32 to 0.51[‡]	RR 0.19, 95% CI 0.09 to 0.37[‡]
	Duration NR	RR 0.46, 95% CI 0.07 to 2.9[§]	Gastric or duodenal ulcer: RR 0.37, 95% CI 0.3 to 0.5[§]	Reported in gastric ulcers column

CI = confidence interval; GI = gastrointestinal; NR = not reported; OR = odds ratio; PPI = proton pump inhibitor; RR = relative risk

* Hemorrhage, hemorrhagic erosions, recurrent upper gastrointestinal bleeds, perforation, pyloric obstruction, melena, and death from any of these

[†] Silverstein 1995 (MUCOSA trial)[290]

[‡] Rostom 2002[264]

[§] Hooper 2004[262]

[¶] Standard Doses = 150 mg daily, Double Doses = 300 mg daily.

A systematic review included in the original CER included five trials[279, 281, 286, 291, 293] that directly compared one gastroprotective agent with another when coprescribed with a nonselective NSAID.[263] The systematic review found both misoprostol and omeprazole superior to ranitidine for prevention of endoscopic gastric ulcers, and omeprazole and lansoprazole superior to misoprostol and ranitidine for prevention of duodenal ulcers. Other outcomes were not reported. We identified no new head-to-head trials (Table 19).

Table 19. Head-to-head trials of gastroprotective agents[263]

Comparison	Reductions in Ulcer Risk	
	Gastric	Duodenal
Misoprostol vs. ranitidine* (2 trials; n=600)	RR 0.12 95% CI 0.03 to 0.89	No differences
Omeprazole* vs. ranitidine* (1 trial, n=425)	RR 0.32 95% CI 0.17 to 0.62	RR 0.11 95% CI 0.01 to 0.89
PPI[†] vs. misoprostol[‡] (2 trials; n=838)	No differences	RR 0.29 95% CI 0.15 to 0.56

CI = confidence interval; PPI = Proton pump inhibitor; RR = relative risk

*Standard dose

[†]Omeprazole or lansoprazole standard doses

[‡]Secondary prophylaxis trials – misoprostol doses 400 mcg daily in one trial and 800 mcg daily in another trial

COX-2 Inhibitors Alone Compared With Nonselective NSAIDs Plus a PPI

The original CER included a good-quality systematic review of 26 trials that compared coprescribing of a PPI with a nonselective NSAID versus a COX-2 selective NSAID on GI harms.[294] We identified two new trials[254, 295] and two new observational studies.[296, 297]

The systematic review found coadministration of a PPI with a nonselective NSAID associated with a lower risk of dyspepsia, epigastric pain, and nausea compared with a selective COX-2 inhibitor alone, when each was compared to a nonselective NSAID alone (relative risk reduction 66 percent and absolute risk reduction 9 percent for the PPI + nonselective NSAID vs. RRR 12 percent and ARR 3.7 percent with COX-2 inhibitor).[294] The systematic review did not assess endoscopic ulcers, symptomatic ulcers, or ulcer complications.

One large (n=4,484), new, good-quality trial was designed to assess ulcer complications.[295] It found diclofenac slow release 75 mg twice a day plus omeprazole 20 mg once a day associated with a higher risk of clinically significant upper and lower GI events (bleeding, obstruction or perforation in the upper and lower GI tract, decrease in hemoglobin ≥ 2 g/dL and/or hematocrit $\geq$ 10%) compared with celecoxib 200 mg twice daily after 6 months in patients with osteoarthritis or rheumatoid arthritis (3.8% vs. 0.9%, HR 4.3, 95% CI 2.6 to 7.0). An independent, blinded expert panel adjudicated adverse events and categorized anemia as of GI origin or presumed occult GI origin. Most of the GI events were decreases in hemoglobin or hematocrit without overt bleeding. Five patients in the celecoxib group and four in the diclofenac plus omeprazole group experienced GI hemorrhage; no cases of perforation or obstruction were reported in either group. Of those allocated to celecoxib, 114 (6 percent) patients withdrew early because of GI adverse events versus 167 (8 percent) allocated diclofenac SR plus omeprazole (p=0.0006). Another new, fair-quality trial (n=1,045) found no difference in risk of endoscopic gastric or duodenal ulcers in patients with osteoarthritis using low-dose aspirin after 12 weeks between celecoxib alone compared with naproxen plus lansoprazole.[254] Only one GI complication (0.1 percent) was reported.

Two new, large observational studies found the risk of GI complications similar with a nonselective NSAID plus a PPI compared with celecoxib alone.[296, 297] A fair-quality retrospective cohort study found similar reduction in risk of a hospitalization due to a GI adverse event (peptic ulcer, gastritis with hemorrhage, or any GI hemorrhage) for a COX-2 selective NSAID alone (RR 0.60, 95% CI 0.46 to 0.77) and a nonselective NSAID plus PPI (RR 0.46, 95% CI 0.28 to 0.73), when each was compared to a nonselective NSAID alone.[297] A fair-quality retrospective cohort study found a similar risk of hospitalization due to perforated or bleeding ulcer in older patients using an NSAID plus a PPI versus celecoxib alone (HR 0.98, 95% CI 0.67 to 1.4).[296]

COX-2 Inhibitors Alone Compared With COX-2 Inhibitors Plus a PPI

The original CER found no studies on GI harms associated with use of a COX-2 selective NSAID plus a PPI versus a COX-2 selective NSAID alone. Two new, similarly designed fair-quality trials (reported in one publication) reported GI harms associated with an NSAID plus esomeprazole versus an NSAID alone.[261] Although most patients in this trial used nonselective NSAIDs, some results were stratified according to the type of NSAID (nonselective or celecoxib, see section on nonselective NSAIDs plus a PPI versus a nonselective NSAID alone for details).

Another new, fair-quality trial evaluated patients at very high risk due to recent GI bleeding and is discussed in Key Question 2.[235] The two new observational studies that evaluated GI harms with a nonselective NSAID plus a PPI versus celecoxib alone also evaluated risks associated with celecoxib plus a PPI versus celecoxib alone.[296, 297]

A pooled analysis of 400 patients from two fair-quality trials found celecoxib plus esomeprazole associated with fewer endoscopic ulcers compared to celecoxib plus placebo (0.9 percent for esomeprazole 20 mg once daily [p<0.001 vs. placebo], 4.1 percent for esomeprazole 40 mg once daily [p=0.002 vs. placebo], 16 percent for placebo). [261] Two upper GI bleeds were reported, both in the placebo groups. Other GI harms were not reported in the subgroup of patients on celecoxib.

The two large observational studies also found some benefit from adding a PPI to celecoxib.[296, 297] A fair-quality retrospective cohort study found celecoxib plus a PPI associated with a lower risk of hospitalizations related to perforated or bleeding ulcer of the stomach compared to celecoxib alone (HR 0.69, 95% CI 0.52 to 0.93) among older (age greater than 65 years) adults.[296] In stratified analyses, the benefit was observed in patients 75 years and older, with no benefit in those 66 to 74 years old. A good-quality retrospective cohort study found celecoxib plus a PPI (RR 0.18, 95% CI 0.09 to 0.37) associated with a lower risk of hospitalization due to GI bleeding compared to celecoxib alone (RR 0.34, 95% CI 0.24 to 0.49) when each was compared to naproxen alone, though confidence intervals overlapped.[297]

Key Question 4. What are the Comparative Benefits and Harms of Treating Osteoarthritis With Oral Medications as Compared With Topical Preparations?

Summary of Evidence

- The only FDA-approved topical NSAIDs are formulations with diclofenac.
- Three head-to-head trials found topical diclofenac similar to oral NSAIDs for efficacy in patients with localized osteoarthritis.
- Topical NSAIDs were associated with a lower risk of GI adverse events and higher risk of dermatologic adverse events compared to oral NSAIDs.
- There was insufficient evidence to evaluate comparative risks of GI bleeding or CV events.
- No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs for osteoarthritis.
- Topical salicylates were no better than placebo in two trials of patients with osteoarthritis, and associated with increased risk of local adverse events.
- Topical capsaicin was superior to placebo for pain relief (NNT 8.1) in a systematic review of trials and subsequent randomized trial, but associated with increased local adverse events and withdrawals due to adverse events (13% vs. 3%, RR 4.0, 95% CI 2.3 to 6.8).

Detailed Analysis

Topical Compared With Oral NSAIDs: Benefits

Eight trials directly compared topical and oral NSAIDs for osteoarthritis (Table 20 and Appendix J).[49, 298-304] Four trials published since the original CER evaluated topical diclofenac,[301] topical ketoprofen,[299] or topical ibuprofen [302] versus an oral NSAID (one trial each), or advice to use topical ibuprofen versus advice to use oral ibuprofen (one trial).[49] The original CER included four other trials of topical diclofenac (two trials), topical eltenac (one trial), and topical piroxicam (one trial), each versus an oral NSAID.[298, 300, 303, 304] Of the eight trials, we rated three good quality[299, 301, 303] and four fair quality.[49, 298, 300, 302] We could not rate the eighth trial[304] because it was not published in English, though a systematic review[305] gave it the maximum 5 points on the Jadad scale. The original CER included two systematic reviews[305, 306] that would now be considered outdated since they included only three of the eight currently available trials. We identified no new systematic reviews that met inclusion criteria.

The only topical NSAIDs approved by the FDA as of late 2010 are diclofenac-based formulations. Three trials of topical versus oral diclofenac found no differences in efficacy for localized osteoarthritis.[301, 303, 304] Two good-quality trials (n=622[303] and n=305[301]) the latter new for this update) found no clinically or statistically significant differences at 12 weeks in WOMAC Pain or Stiffness scores or patient global assessment scores (Table 20 and Appendix J). Both trials evaluated topical diclofenac in a DMSO-based carrier. In one of the trials, topical diclofenac was slightly inferior to oral diclofenac on the WOMAC Physical Function score, but the difference was not clinically significant (difference of 90 mm on a 1,700 mm scale, with 255 mm thought to be clinically significant).[303] This trial also reported a similar proportion of responders (as defined by the Outcomes Measures in Arthritis Clinical Trials and the Osteoarthritis Research Society VI recommendations) with topical or oral diclofenac (66 percent vs. 70 percent, p=0.37). A third, non-English language trial (n=321) found no difference between diclofenac 1 percent gel versus oral ibuprofen at 3 weeks in the proportion of patients with hand osteoarthritis with a ≥40 percent improvement in pain on a 100 mm VAS (40% vs. 34%, RR 1.20, 95% CI 0.88 to 1.60; data as reported in a systematic review).[304,305]

The other trials evaluated topical NSAIDs not approved by the FDA. None found any differences between a topical and oral NSAID in efficacy. One new, fair-quality trial (n=282) found no differences in WOMAC Pain, Stiffness, Physical Function, or Global scores through 12 months between advice to use topical or oral ibuprofen in patients with knee osteoarthritis (Table 20).[49] A new, small (n=20) trial of topical versus oral ibuprofen found no differences in WOMAC or SF-36 scores.[302] Another new, fair-quality (n=270) trial of topical ketoprofen 110 mg in 4.8 g transferone carrier versus oral celecoxib found no difference in WOMAC Pain or Stiffness scores; patient global assessment scores; or the proportion of OMERACT-OARSI responders (69 percent vs. 64 percent).[299] One fair-quality trial included in the original CER found no difference between piroxicam 0.5% and oral ibuprofen in the proportion of patients reporting a "good" or "excellent" response.[298]

A fair-quality trial of eltenac 1 percent gel was included in the original CER but is of limited relevance since it is no longer being investigated for use in humans.[300]

Table 20. Efficacy, head-to-head trials of topical compared with oral NSAID for osteoarthritis

Author, Year Quality	Condition Number Enrolled	Comparison	Duration of Study	Main Results
Dickson, 1991[298] Fair	OA of knee 235	Piroxicam 0.5% gel tid Ibuprofen 400 mg po tid	4 weeks	Patient global assessment 'good' or 'excellent': 64% vs. 60% Pain during day (0-9): 3.0 vs. 3.0, p=0.56 Pain at night (0-9): 2.0 vs. 2.0, p=0.54
Sandelin, 1997[300] Fair	OA of knee 208	Eltenac 1% gel tid Diclofenac 50 mg po bid	4 weeks	Lequesne Index (0-24): 6.3 vs. 6.9 Pain (0-100 VAS): 28 vs. 30
Zacher, 2001[304] Not rated*	OA of fingers 321	Diclofenac 1% gel Ibuprofen 400 mg po tid	3 weeks	>=40% improvement in pain on 100 mm VAS: 40% vs. 34%, RR 1.2 (95% CI 0.88-1.6)
Tugwell, 2004[303] Good	OA of knee 622	Diclofenac 1.5% in 45.5% DMSO tid Diclofenac 50 mg po tid	12 weeks	Clinical responder (OMERACT VI criteria[38]): 66% vs. 70% WOMAC Pain (0-500, mean change): -118 vs. -134, p=0.10 WOMAC Physical Function (0-1700, mean change): -348 vs. -438, p=0.008 WOMAC Stiffness (0-200, mean change): -45 vs. -52, p=0.14 Patient global assessment (0-100, mean change): -27 vs. -32, p=0.08
Rother, 2007[299] Good	OA of knee 270	Ketoprofen 110 mg in 4.8 g transferone every 12 hours Celecoxib 100 mg every 12 hours	6 weeks	Clinical responder (OMERACT criteria): 69% vs. 64% Patient global assessment of response "good" or "excellent": 46% vs. 39% WOMAC Pain (0 to 100, mean change): -19 vs. -21 WOMAC Physical Function (0 to 100, mean change): -16 vs. -18 WOMAC Stiffness (0 to 100, mean change): -15 vs. -17 Use of rescue medication (capsules/day): 0.24 vs. 0.16
Underwood, 2008[49] Fair	OA of knee 282	Advice to use a topical NSAID, preferably ibuprofen Advice to use an oral NSAID	1 year	Mean differences in change WOMAC Pain (0 to 100): 1 (95% CI -4 to 6) WOMAC Stiffness (0 to 100): 0 (95% CI -6 to 5) WOMAC Physical Function (0 to 100): 3 (95% CI -2 to 7) WOMAC Global (0 to 100): 2 (95% CI -2 to 6) SF-36: No differences at 1 year in mental or physical component summary scores

Table 20. Efficacy, head-to-head trials of topical compared with oral NSAID for osteoarthritis (continued)

Author, Year Quality	Condition Number Enrolled	Comparison	Duration of Study	Main Results
Simon, 2009[301] Good	OA of knee 305	Diclofenac 1.5% in 45.5% DMSO qid Diclofenac 100 mg po qd	12 weeks	WOMAC Pain (0 to 20, mean change): -6.0 vs. -6.4, p=0.43 WOMAC Physical Function (0 to 68, mean change): -16 vs. -18, p=0.32 WOMAC Stiffness (0 to 8, mean change): -1.9 vs. -2.1, p=0.60 Patient global assessment (0 to 4, mean change): -1.4 vs. -1.4, p=0.44
Tiso, 2010[302] Fair	Chronic knee pain (presumed OA of knee) 20	Ibuprofen 4% gel qid Ibuprofen 800 mg po tid	2 weeks	WOMAC Pain (0 to 500, mean change): -83 vs. -84, NS WOMAC Physical Function (0 to 1700, mean change): -312 vs. -323, NS WOMAC, Stiffness (0 to 200, mean change): -48 vs. -26, NS SF-36: No differences on mental component score, physical component score, or subscales

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OMERACT = Outcomes Measures in Arthritis Clinical Trials; po = orally; tid = three times daily; qd = once daily; qid = four times daily; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
*Non-English language study, data as reported in Mason et al[305].

Topical Compared With Oral NSAIDs: Harms

Eight head-to-head trials reported adverse events associated with topical versus oral NSAIDs. Three trials evaluated topical versus oral diclofenac.[301, 303, 304] In two good-quality trials (one published since the original CER[301]), rates of withdrawal due to adverse events were similar (21 percent vs. 25 percent[303] and 10 percent vs. 13 percent,[301] respectively). Topical diclofenac was associated with fewer GI, systemic, and laboratory adverse events but more dermatologic adverse events compared to oral diclofenac (Table 21, Appendix J). The risk of GI events with topical and oral NSAIDS was 35 percent versus 48 percent[303] and 6.5 percent versus 24 percent,[301] respectively. One trial that categorized adverse event severity also found topical diclofenac associated with a lower risk of serious GI events (7.4 percent vs. 21 percent).[303] A similar pattern was observed for specific GI adverse events (dyspepsia, nausea, diarrhea, abdominal pain, abnormal liver function tests). Topical NSAIDs were also associated with smaller increases in serum creatinine and smaller decreases in hemoglobin compared with oral NSAIDs. Topical NSAIDs were associated with an increased risk of dry skin, rash, and pruritus. A third, non-English language trial[304] found topical diclofenac associated with a lower risk of withdrawal due to adverse events compared to oral ibuprofen (data as reported in Mason et al.[305]).

Other trials evaluated topical NSAIDs not approved by the FDA. A new, good-quality trial found topical ketoprofen associated with similar withdrawal due to adverse events compared to oral celecoxib, fewer GI adverse events, and more skin adverse events.[299] A new, fair-quality trial on advice to use topical ibuprofen versus advice to use oral ibuprofen found few differences

in GI adverse events, perhaps because the dosing regimen was not fixed and may have resulted in less consistent or lower doses.[49] The exception was for respiratory events, which favored topical NSAIDs, due to a greater risk of a decrease in peak expiratory flow in the oral NSAIDs group. A third, fair-quality trial was too small to draw reliable conclusions about comparative harms.[302]

A fair-quality trial included in the previous systematic review found no clear differences in adverse events between topical piroxicam and oral ibuprofen.[298] Another trial evaluated topical eltenac, a drug no longer being investigated for use in humans.[300]

Table 21. Adverse events: Head-to-head trials of topical compared with oral NSAID for osteoarthritis

Author, Year Quality	Condition Number Enrolled Comparison	Withdrawal due to Adverse Events Any Adverse Events	Gastrointestinal Adverse Events	Skin Adverse Events	Other Adverse Events
Dickson, 1991[298] Fair	OA of knee 235 Topical piroxicam 0.5% vs. ibuprofen 400 mg po tid	Withdrawal due to adverse events: 7.7% (9/117) vs. 5.9% (7/118) Any adverse event: 26% (31/117) vs. 23% (27/118)	Upper GI: 10% vs. 8.5% Other GI: 2.6% vs. 0.8%	Rash: 0.8% vs. 0.8%	CNS: 6.0% vs. 6.8%
Sandelin, 1997[300] Fair	OA of knee 208 Eltenac 1% gel vs. diclofenac 50 mg po bid	Withdrawal due to adverse events: 3.2% (4/126) vs. 1.2% (1/82) Any adverse event: 27% (34/126) vs. 24% (20/82)	GI: 4.8% vs. 13%	Local skin reaction: 13% vs. 1.2%	CNS: 9.5% vs. 7.3%
Zacher, 2001[304] Not rated*	OA of fingers 321 Diclofenac 1% gel vs. ibuprofen 400 mg po tid	Withdrawal due to adverse events: 3.0% (5/165) vs. 10% (16/156)	Data not available	Data not available	Data not available

Table 21. Adverse events: Head-to-head trials of topical compared with oral NSAID for osteoarthritis (continued)

Author, Year Quality	Condition Number Enrolled Comparison	Withdrawal due to Adverse Events Any Adverse Events	Gastrointestinal Adverse Events	Skin Adverse Events	Other Adverse Events
Tugwell, 2004[303] Good	OA of knee 622 Diclofenac 1.5% in 45.5% DMSO vs. diclofenac 50 mg po tid	Withdrawal due to adverse events: 21% (64/311) vs. 25% (79/311)	Any GI adverse event: 35% vs. 48% (p=0.0006); severe 7.4% vs. 21% (p=0.002) Abdominal pain: 12% vs. 22% (p=0.0008); severe 5.6% vs. 19% Diarrhea: 9% vs. 17% (p=0.001), severe 3.7% vs. 17% Dyspepsia: 15% vs. 26% (p=0.001), severe 4.2% vs. 14% Melena: 1% vs. 2% (p=0.36) Nausea: 8% vs. 13% (p=0.36) Vomiting: 2% vs. 2% (p=0.56) AST normal to abnormal: 2% vs. 10% (p=0.0001) Hemoglobin (g/l): normal to abnormal 2% vs. 10% (p<0.0001), mean change from baseline 0.9 vs. -2.2 (p<0.0001)	Dry skin: 27% vs. 1% (p<0.0001 Rash: 12% vs. 2% (p<0.0001 Pruritus: 6% vs. 0.6% (p<0.0001) Vesiculobullous rash: 5% vs. 0% (p<0.0001)	Asthma: 0.6% vs. 3% (p=0.002) Dizziness: 0.6% vs. 4% (p=0.002) Dyspnea; 0% vs. 2% (p=0.01) Mean blood pressure increased 5 mm Hg or greater: 24% vs. 28% (p=0.30) Creatinine: normal to abnormal 1% vs. 3% (p=0.08), mean change from baseline 0.3 vs. 3.3 (p=0.003)
Rother, 2007[299] Good	OA of knee 270 Ketoprofen 110 mg in 4.8 g transferone q 12 h vs. celecoxib 100 mg every 12 hours	Withdrawal due to adverse events: 17% (23/138) vs. 14% (18/132), p=0.15 Any adverse event: 54% vs. 50%	GI adverse event: 9.4% vs. 14% Abdominal pain, upper: 1.4% vs. 3.0% Diarrhea: 0.7% vs. 1.5% Dyspepsia: 0.7% vs. 3.0% Gastritis: 2.2% vs. 0% Nausea: 1.4% vs. 2.3%	Any skin: 28% vs. 20% Dermatitis allergic: 1.4% vs. 0.8% Erythema: 21% vs. 14% Exanthema: 2.2% vs. 1.5% Pruritus: 0% vs. 3.8% Skin irritation: 1.4% vs. 0% Urticaria: 1.4% vs. 0.8%	Any respiratory, thoracic, and mediastinal disorders: 12% vs. 11%

Table 21. Adverse events: Head-to-head trials of topical compared with oral NSAID for osteoarthritis (continued)

Author, Year Quality	Condition Number Enrolled Comparison	Withdrawal due to Adverse Events Any Adverse Events	Gastrointestinal Adverse Events	Skin Adverse Events	Other Adverse Events
Underwood, 2008[49] Fair	OA of knee 282 Advice to use topical NSAID (preferably ibuprofen) vs. advice to use an oral NSAID (preferably ibuprofen)	Any defined minor adverse event: 53% vs. 57% (mean difference 0%, 95% CI -11% to 12%)	GI minor event: 42% vs. 40% (mean difference 2%, 95% CI -9% to 14%) Liver enzymes >upper limit of normal: 2.7% vs. 2.2 (mean difference 0.4%, 95% CI -3.4% to 4.3%) Change in hemoglobin (g/l): 0.2 vs. 0.7, difference 0.5 (95% CI -1.3 to 2.3)	Not reported	Unplanned hospitalization through 1 year (rate per 100 per year): 4.5 vs. 1.4 (mean difference 3.1, 95% CI -1.0 to 7.2) Renovascular minor adverse event: 16% vs. 15% (mean difference 1%, 95% CI -8% to 9%) Respiratory: 7% vs. 17% (mean difference -9%, 95% CI -17% to -2%) Change in systolic blood pressure (mm Hg): 2.5 vs. 4.4, difference 1.9 (95% CI -1.7 to 5.5) Change in serum creatinine (micromol/l): 2.4 vs. -1.3, difference -3.7 (-6.5 to -0.9)
Simon, 2009[301] Good	OA of knee 305 Diclofenac 1.5% in 45.5% DMSO qid vs. diclofenac 100 mg po qd	Withdrawal due to adverse events: 10% (16/154) vs. 13% (19/151) Any adverse event: 62% vs. 62% Serious adverse event: 0% vs. 0.7%	Any GI adverse event: 6.5% vs. 24% Abdominal pain: 3.2% vs. 7.3% Dyspepsia: 2.6% vs. 4.0% Diarrhea; 1.3% vs. 4.6% Liver function tests abnormal: 1.9% vs. 7.9%; AST normal to abnormal 6.9% vs. 20% Rectal hemorrhage: 0.6% vs. 0% Nausea: 0% vs. 2.0% Hemoglobin normal to abnormal: 2.1% vs. 5.8%; mean change (g/l): -1.0 vs. -3.8	Any skin/appendages event: 27% vs. 7.3% Dry skin: 18% vs. 2.6% Contact dermatitis: 2.6% vs. 0.7% Rash: 2.6% vs. 0% Contact dermatitis with vesicles: 1.9% vs. 0.7%	Respiratory disorder: 3.2% vs. 5.3% Creatinine normal to abnormal: 2.8% vs. 7.2%; mean change (micromol/l): -0.4 vs. 3.1

Table 21. Adverse events: Head-to-head trials of topical compared with oral NSAID for osteoarthritis (continued)

Author, Year Quality	Condition Number Enrolled Comparison	Withdrawal due to Adverse Events Any Adverse Events	Gastrointestinal Adverse Events	Skin Adverse Events	Other Adverse Events
Tiso, 2010[302] Fair	Chronic knee pain (presumed OA of knee) 20 Ibuprofen 4% gel qid vs. ibuprofen 800 mg po tid	Not reported	Stomachache: 0% vs. 10% Constipation: 0% vs. 10% Diarrhea: 0% vs. 10%	Rash: 11% vs. 0%	Dizziness: 11% vs. 20% Headache: 0% vs. 20%

AST = alanine aminotransferase; CI = confidence interval; CNS = central nervous system; DMSO = Dimethyl sulphoxide; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; po = orally; qid = four times daily; tid = three times daily
*Non-English language study, data as reported in Mason et al[305].

No RCT was adequately designed to assess risks for serious but uncommon adverse events such as myocardial infarction, renal failure, or GI bleeding. In one new trial, only one serious adverse event (postpolypectomy lower GI bleed) was observed with either topical or oral diclofenac.[301]

Two case-control studies included in the original CER evaluated the risk of GI bleeding with topical and oral NSAIDs. A nested case-control study of the General Practice Research Database found topical NSAID use was not associated with symptomatic peptic ulcer (RR=1.0 vs. nonuse, 95% CI 0.6 to 1.7), though oral NSAID use was associated with increased risk (RR=4.0, 95% CI 3.2 to 5.1).[184] Similarly, a study (1,103 cases) found no association between exposure to topical NSAIDs within 45 days and risk of hospital admission for upper GI bleeding and perforation after adjusting for the confounding effects of exposure to oral NSAIDs and ulcer healing drugs (OR 1.45, 95% CI 0.84 to 2.50 with community controls and OR 1.06, 95% CI 0.60 to 1.88 with hospital controls).[307] By contrast, oral NSAIDs were associated with increased risk (OR 2.59, 95% CI 2.12 to 3.16 for community controls and 2.00, 95% CI 1.60 to 2.50 for hospital controls).

One case-control study of similar design included in the original CER found exposure to topical NSAIDs not associated with acute renal failure (adjusted OR 1.33, 95% CI 0.79 to 2.24 using community controls and 1.04, 95% CI 0.60 to 1.83 using hospital controls).[308] Recent exposure to oral NSAIDs was associated with increased risk of renal failure using either community (adjusted OR 2.20, 95% CI 1.49 to 3.25) or hospital (adjusted OR 1.84, 95% CI 1.15 to 2.93) controls.

We identified no studies comparing the risk of CV events in persons on topical versus oral NSAIDs.

Topical Salicylates and Capsaicin

We identified no trials comparing topical salicylates to oral or topical NSAIDs for osteoarthritis. We also identified no new trials comparing topical salicylates to placebo. A systematic review[30] included in the original CER has been updated.[309] It included only two trials

of topical salicylates versus placebo for osteoarthritis.[310, 311] Both trials found topical salicylates associated with no greater likelihood of clinical success (50 percent reduction in chronic pain) compared with placebo (RR 1.2, 95% CI 0.59 to 2.7[310] and RR 1.0, 95% CI 0.63 to 1.6).[311] The systematic review also found topical salicylates associated with increased risk of local adverse events compared to placebo, when used for any acute or chronic pain condition (RR 2.2, 95% CI 1.1 to 4.1).

We identified no trials comparing topical capsaicin to oral or topical NSAIDs for osteoarthritis. We also identified one new trial comparing topical capsaicin to placebo.[312] A systematic review included in the original CER found that for chronic musculoskeletal pain, capsaicin was superior to placebo for achieving clinical success (defined as approximately a 50 percent reduction in pain), with a relative benefit of 1.5 (three trials, 95% CI 1.1 to 2.0) and number needed to treat of 8.1 (4.6 to 34).[313] About 54 percent of patients had local adverse events with capsaicin, compared with 15 percent with placebo (relative risk 3.6, 95% CI 2.6 to 5.0). Withdrawals due to adverse events were also significantly more likely with capsaicin (13% vs. 3%, relative risk 4.0, 95% CI 2.3 to 6.8). A new, fair-quality crossover trial (n=100) not included in the systematic review found capsaicin 0.125 percent gel associated with greater changes from baseline compared to placebo in VAS pain score (0 to 100 scale, mean difference 0.72, 95% CI 0.17 to 1.27), WOMAC pain (0 to 20 scale, mean difference 3.4, 95% CI 2.3 to 4.5), WOMAC stiffness (0 to 8 scale, mean difference 0.82, 955 CI 0.19 to 1.5), and WOMAC function (0 to 68 scale, mean difference 9.0, 95% CI 5.5 to 12).[312]

Summary and Discussion

Table 22 summarizes the strength of evidence and results for each key question based on the evidence included in the original comparative effectiveness review (CER) and new evidence identified in the update.

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis

Key Question	Strength of Evidence	Conclusion
1. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?		
Benefits: Celecoxib vs. nonselective NSAIDs	High (consistent evidence from many randomized trials)	No clear difference in efficacy for pain relief, or withdrawals due to lack of efficacy.
Benefits: Partially selective NSAIDs vs. nonselective NSAIDs	High for meloxicam and etodolac (many randomized trials) , low for nabumetone (2 short-term randomized trials)	Meloxicam was associated with no clear difference in efficacy compared to nonselective NSAIDs in eleven head-to-head trials of patients with osteoarthritis, but a systematic review that included trials of patients with osteoarthritis or rheumatoid arthritis found lesser effects on pain compared to nonselective NSAIDs (difference 1.7 points on a 10 point VAS pain scale) and withdrawals due to lack of efficacy (RR 1.5, 95% CI 1.2 to 1.7). Etodolac and nonselective NSAIDs were associated with no statistically significant differences on various efficacy outcomes in several systematic reviews of patients with osteoarthritis, with consistent results reported in 7 trials not included in the systematic reviews. Nabumetone was similar in efficacy to nonselective NSAIDs in two trials.
Benefits: Nonselective NSAID vs. nonselective NSAID	High (consistent evidence from many randomized trials)	No difference in efficacy between various non-aspirin, nonselective NSAIDs.
Benefits: Aspirin or salsalate vs. other NSAIDs	Low (one randomized trial)	No difference in efficacy between aspirin and salsalate in one head-to-head trial. No trial compared aspirin or salsalate vs. other NSAIDs.

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
GI and CV harms: Celecoxib	High for GI harms vs. nonselective NSAIDs (multiple systematic reviews and meta-analyses of mostly short-term trials, multiple observational studies; limited long-term data on serious GI harms) Moderate for CV harms vs. nonselective NSAIDs (multiple systematic review and meta-analyses of longer-term trials; some inconsistency between randomized trials and observational studies) Moderate for CV harms vs. placebo (multiple systematic reviews and meta-analyses; mostly from trials of colon polyp prevention)	GI harms: Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) and ulcer complications or symptomatic ulcers (RR 0.39, 95% CI 0.21-0.73) compared to nonselective NSAIDs in a systematic review of randomized trials. The systematic review included the pivotal, large, long-term CLASS study, in which celecoxib was superior to diclofenac or ibuprofen for ulcer complications or symptomatic ulcers at 6-month followup (2.1% vs. 3.5%, p=0.02), but not at 12-month followup. However, CLASS found difference in rates of ulcer complications alone at either 6 or 12 months. Other long-term followup data from randomized trials is lacking. A systematic review found celecoxib associated with a lower risk of upper GI bleeding or perforation compared to various nonselective NSAIDs based on 8 observational studies, though confidence interval estimates overlapped in some cases. CV harms: There was no increase in the rate of cardiovascular events with celecoxib vs. ibuprofen or diclofenac in CLASS (0.5% vs. 0.3%). In three systematic reviews of randomized trials, celecoxib was associated with increased risk of cardiovascular events compared to placebo (risk estimates ranged from 1.4 to 1.9). A systematic review of placebo-controlled trials with at least 3 years of planned followup found celecoxib associated with an increased risk of cardiovascular events (CV death, myocardial infarction, stroke, heart failure, or thromboembolic event) compared to placebo (OR 1.6, 95% CI 1.1 to 2.3). About 3.7 additional cardiovascular events occurred for every 1,000 patients treated for one year with celecoxib instead of placebo, or 1 additional cardiovascular event for every 270 patients treated for 1 year with celecoxib instead of placebo. The risk was highest in patients prescribed celecoxib 400 mg twice daily compared to celecoxib 200 mg twice daily or 400 mg once daily. Much of the evidence for increased risks comes from two large colon polyp prevention trials. A network analysis of randomized trials and three large observational studies found celecoxib associated with no clear difference in risk of myocardial infarction compared to naproxen, ibuprofen, or diclofenac; a fourth observational study found celecoxib associated with lower risk than ibuprofen or naproxen. 11 of 13 large observational studies found celecoxib associated with no increased risk of myocardial infarction compared to nonuse of NSAIDs. An analysis of all serious adverse events in CLASS based on FDA data found no difference between celecoxib (12/100 patient-years), diclofenac (10/100 patient-years), and ibuprofen (11/100 patient-years). A retrospective cohort study found celecoxib and ibuprofen associated with neutral risk of hospitalization for acute myocardial infarction or GI bleeding compared to use of acetaminophen, but naproxen was associated with increased risk (HR 1.6, 95% CI 1.3 to 1.9).

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
GI and CV harms: Partially selective NSAIDs	GI harms: Moderate for meloxicam and etodolac (fewer trials with methodological shortcomings), low for nabumetone (sparse data)	GI harms: Meloxicam (primarily at a dose of 7.5 mg/day) was associated with a lower risk of ulcer complications or symptomatic ulcers compared to various nonselective NSAIDs in 6 trials included in a systematic review (RR 0.53, 95% CI 0.29 to 0.97), but the difference in risk of ulcer complications alone did not reach statistical significance (RR 0.56, 95% CI 0.27 to 1.2). Etodolac (primarily at a dose of 600 mg/day) was associated with a lower risk of ulcer complications or symptomatic ulcer compared to various nonselective NSAIDs in 9 trials included in a systematic review (RR 0.32, 95% CI 0.15 to 0.71), but the difference in risk of ulcer complications alone did not reach statistical significance (RR 0.39, 95% CI 0.12 to 1.2) and the number of events was very small. Evidence was insufficient to make reliable judgments about GI safety of nabumetone.
	CV harms: Insufficient for all (no trials, few large observational studies)	CV harms: Three observational studies found meloxicam associated with no increased risk of serious CV events relative to nonuse. One observational study evaluated etodolac and nabumetone, but estimates were imprecise.
GI and CV harms: Nonselective NSAIDs	GI harms: High for naproxen, ibuprofen, and diclofenac (consistent evidence from many trials and observational studies); insufficient for other nonselective NSAIDs (very little evidence) CV harms vs. placebo: Moderate for ibuprofen, diclofenac, and naproxen (almost all evidence from observational studies, few large, long-term controlled trials, indirect evidence); insufficient for other nonselective NSAIDs (very little evidence) CV harms vs. selective NSAIDs: Moderate for ibuprofen, diclofenac, and naproxen (few large, long-term controlled trials, indirect evidence); insufficient for other nonselective NSAIDs (very little evidence)	GI harms: COX-2 selective NSAIDs as a class were associated with a similar reduction in risk of ulcer complications vs. naproxen (RR 0.34, 95% CI 0.24 to 0.48), ibuprofen (RR 0.46, 95% CI 0.30 to 0.71), and diclofenac (RR 0.31, 95% CI 0.06 to 1.6) in a systematic review of randomized trials. Evidence from randomized trials on comparative risk of serious GI harms associated with other nonselective NSAIDs is sparse. In large observational studies, naproxen was associated with a higher risk of serious GI harms than ibuprofen in 7 studies. Comparative data on GI harms with other nonselective NSAIDs was less consistent. CV harms: An indirect analysis of randomized trials found ibuprofen (RR 1.5, 95% CI 0.96 to 2.4) and diclofenac (RR 1.6, 95% CI 1.1 to 2.4), but not naproxen (RR 0.92, 95% CI 0.67 to 1.3) associated with an increased risk of myocardial infarction relative to placebo. 1 additional myocardial infarction occurred for about every 300 patients treated for 1 year with celecoxib instead of naproxen. A network analysis of randomized trials reported consistent results with regard to CV events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; ibuprofen: RR 2.3, 95% CI 1.1 to 4.9; diclofenac: RR 1.6, 95% CI 0.85 to 3.0 and naproxen: RR 1.2, 955 CI 0.78 to 1.9). An Alzheimer's disease prevention trial was stopped early due to a trend towards increased risk of myocardial infarction (HR 1.5, 95% CI 0.69 to 3.2) vs. placebo, but did not employ prespecified stopping protocols. In most large observational studies, naproxen was associated with a neutral effect on risk of serious CV events.

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
GI and CV harms: Aspirin	Moderate for GI and CV harms (many trials, but almost exclusively in patients receiving aspirin for cardiovascular disease prevention, usually at lower prophylactic doses)	GI harms: A systematic review of individual patient trial data found aspirin associated with increased risk of major GI and other extracranial bleeding when given for primary prevention of vascular events (RR 1.5, 95% CI 1.3 to 1.8, absolute risk 0.10% vs. 0.07%). Observational studies showed a similar risk of upper GI bleeding with aspirin and non-aspirin, nonselective NSAIDs. CV harms: Aspirin reduced the risk of vascular events in a collaborative meta-analysis of individual patient data from18 randomized controlled trials (0.51% aspirin vs. 0.57% control per year, p=0.0001 for primary prevention and 6.7% vs. 8.2% per year, p<0.0001 for secondary prevention).
GI and CV safety: Salsalate	Insufficient	No randomized trial or observational study evaluated risk of serious GI or CV harms with salsalate.
Mortality	Moderate (randomized trials with few events, and observational studies)	Large randomized trials and a meta-analysis of trials showed no difference between celecoxib and nonselective NSAIDs, but there were few events. One fair-quality cohort study found nabumetone associated with lower all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
HTN, CHF, and impaired renal function	Moderate (randomized trials and observational studies, but analyses limited by incomplete reporting of outcomes)	All NSAIDs are associated with deleterious effects on blood pressure, edema, and renal function. No clear evidence of clinically relevant, consistent differences between celecoxib, partially selective, and nonselective NSAIDs in risk of hypertension, heart failure, or impaired renal function.
Hepatotoxicity	High (many trials and large epidemiologic studies)	Several NSAIDs associated with high rates of hepatotoxicity have been removed from the market. A systematic review found clinically significant hepatotoxicity rare with currently available NSAIDs. A systematic review of randomized trials found no difference between celecoxib, diclofenac, ibuprofen, and naproxen in clinical hepatobiliary adverse events, though diclofenac was associated with the highest rate of hepatic laboratory abnormalities (78/1,000 patient-years, vs. 16 to 28/1,000 patient-years for the other NSAIDs). Another systematic review found diclofenac associated with the highest rate of aminotransferase elevations compared to placebo (3.6% vs. 0.29%, compared to <0.43% with other NSAIDs).

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
Tolerability	High for celecoxib and nonselective NSAIDs, moderate for partially selective NSAIDs (fewer trials with some methodological shortcomings)	The most recent systematic review of randomized trials found celecoxib associated with a lower risk of GI-related adverse events (RR 0.75, 95% CI 0.70 to 0.80) and withdrawals due to GI adverse events (RR 0.45, 95% CI 0.33 to 0.56) compared to nonselective NSAIDs, but the difference in risk of any adverse event or withdrawal due to any adverse event did not reach statistical significance). Meloxicam was also associated with decreased risk of any adverse event (RR 0.91, 95% CI 0.84 to 0.99), any GI adverse events (RR 0.31, 95% CI 0.24 to 0.39), and withdrawals due to GI adverse events (RR 0.61, 95% CI 0.54 to 0.69) compared to nonselective NSAIDs, though there was no difference in risk of withdrawal due to any adverse event. Etodolac was associated with lower risk of any adverse event compared to nonselective NSAIDs (RR 0.83, 95% CI 0.70 to 0.99), but there was no difference in risk of GI adverse events, withdrawal due to adverse events, or withdrawal due to GI adverse events. A meta-analysis found nabumetone associated with similar GI adverse events (25% vs. 28%, p=0.007) compared to nonselective NSAIDs. In a systematic review of randomized trials, the only relatively consistent finding regarding the tolerability of different nonselective NSAIDs was that indomethacin was associated with higher rates of toxicity than other NSAIDs (statistical significant unclear).
Acetaminophen	High for benefits, moderate to low for harms (few trials, limited number of observational studies)	Acetaminophen is consistently modestly inferior to NSAIDs for reducing pain and improving function in randomized trials included in multiple systematic reviews. Acetaminophen is superior to NSAIDs for GI side effects (clinical trials data) and GI complications (observational studies). Some observational studies found acetaminophen associated with modest increases in blood pressure or higher risk of renal dysfunction compared to NSAIDs, but results may be susceptible to confounding by indication. One observational study found risk of acute myocardial infarction similar in users of acetaminophen compared to users of NSAIDs. Acetaminophen may cause elevations of liver enzymes at therapeutic doses in healthy persons; comparative hepatic safety has not been evaluated

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
Glucosamine and chondroitin	High for glucosamine vs. oral NSAIDs (consistent evidence from multiple trials) Low for chondroitin vs. oral NSAIDs (one trial) High for glucosamine or chondroitin vs. placebo (consistent evidence from recent, higher-quality trials)	Seven randomized trials showed no clear difference between glucosamine vs. oral NSAIDs for pain or function. One randomized trial showed no difference between chondroitin vs. an oral NSAID. A systematic review including recent, higher-quality trials found glucosamine associated with statistically significant but clinically insignificant beneficial effects on pain (-0.4 cm on a 10 cm scale, 95% CI -0.7 to -0.1) and joint space narrowing (-0.2 mm, 95% CI -0.3 to 0.0) compared to placebo. The systematic review reported similar results for chondroitin. A recent large, good-quality NIH-funded trial found the combination of pharmaceutical grade glucosamine hydrochloride and chondroitin sulfate modestly superior to placebo only in an analysis of a small subset of patients with at least moderate baseline pain. Older trials showed a greater benefit with glucosamine or chondroitin, but were characterized by lower quality. For glucosamine, the best results have been reported in trials sponsored by the manufacturer of a European, pharmaceutical grade product (no pharmaceutical grade glucosamine available in the United States).
1a. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?	High for effects of dose and duration (many trials and observational studies with some inconsistency); low for alternative dosage strategies (1 randomized trial)	Higher doses of NSAIDs were associated with greater efficacy for some measures of pain relief, and in some trials with greater withdrawals due to adverse events A meta-analysis of 41 randomized trials found no clear association between longer duration of therapy with COX-2 selective NSAIDs and increase in the relative risk of CV events. The meta-analysis found higher doses of celecoxib associated with increased risk of cardiovascular events, but most events occurred in the long-term polyp prevention trials. Almost all of the cardiovascular events in trials of celecoxib were reported in long-term trials of colon polyp prevention. Large observational studies showed no association between higher dose and longer duration of nonselective NSAID therapy and increased risk of cardiovascular events. Many observational studies found that risk of GI bleeding increased with higher doses of nonselective NSAIDs, but no clear association with duration of therapy. One small trial found continuous celecoxib slightly more effective than intermittent use on pain and function, and similar rates of withdrawals due to adverse events. No trial was designed to assess serious GI or CV harms associated with intermittent dosing strategies.

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?		
Demographic subgroups including age, sex, and race	Moderate for age (consistent evidence from observational studies) Insufficient for sex and race (most studies included a majority of women, but studies didn't evaluate whether comparative benefits and harms vary in men and women or in different racial groups)	The absolute risks of serious GI and CV complications increase with age. Large observational studies that stratified patients by age found no clear evidence of different risk estimates for different age groups. However, because the event rates increases in older patients, even if the relative risk estimates are the same, the absolute event rates are higher. There is insufficient evidence on the comparative benefits and harms of different selective and nonselective NSAIDs in men compared to women, or in different racial groups.
Preexisting disease including history of previous bleeding due to NSAIDs or peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure	Moderate for previous bleeding Moderate for hypertension, edema, ischemic heart disease, heart failure (observational studies and few randomized trials)	The risk of GI bleeding is higher in patients with prior bleeding. Two trials found high rates of recurrent ulcer bleeding in patients randomized to either celecoxib (4.9% to 8.9% with 200 mg twice daily) or a nonselective NSAID + PPI (6.3%). One trial found celecoxib plus high dose PPI associated with lower risk of bleeding compared with celecoxib alone (0% vs. 8.9%, p=0.0004). A systematic review of randomized trials of celecoxib found risk of CV events doubled in patients at moderate vs. low risk (HR 2.0, 95% CI 1.5 to 2.6) and doubled again in patients at high risk (HR 3.9 for high risk vs. low risk, 95% CI 2.3 to 6.7). Most large observational studies found an association between increased cardiovascular risk and increased risk of cardiovascular events in persons using NSAIDs. Following hospitalization for heart failure, one large observational study found celecoxib and diclofenac associated with a higher risk of death compared to ibuprofen or naproxen, and another large observational study found an increased risk of repeat heart failure admission with indomethacin compared to other nonselective NSAIDs, ibuprofen, acetaminophen, or celecoxib.
Concomitant anticoagulant use	Moderate overall: Primarily observational studies	Concomitant use of anticoagulants and nonselective NSAIDs increases the risk of GI bleeding three- to sixfold compared with anticoagulant use without NSAIDs. The risk with concomitant celecoxib is not clear due to conflicting findings among observational studies, but may be increased in older patients. Reliable conclusions about the comparative safety of nonselective, partially selective, and COX-2 selective NSAIDs with concomitant anticoagulants could not be drawn due to small numbers of studies with methodological shortcomings. Warfarin plus low-dose aspirin increased the risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis. Acetaminophen can increase INR levels, but effects on bleeding rates have not been studied.

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
Concomitant use of prophylactic dose aspirin	High for GI harms: Consistent evidence from clinical trials and observational studies Moderate for CV harms: Subgroup analyses from few trials, few observational studies	Concomitant use of aspirin appears to attenuate or eliminate the GI benefits of selective NSAIDs, resulting in risks similar to nonselective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6 percent in patients on celecoxib and those on nonselective NSAIDs in one meta-analysis. Addition of a PPI may reduce the risk of GI harms associated with use of either celecoxib or nonselective NSAIDs plus low-dose aspirin. Evidence regarding the effects of concomitant aspirin use on CV risk associated with selective or nonselective NSAIDs is limited, though three polyp prevention trials of COX-2 selective NSAIDS found that concomitant aspirin use did not attenuate the observed increased risk of CV events. Observational studies did not find increased CV risk with the addition of nonselective NSAIDs as a class to low-dose aspirin. Limited evidence suggests an increased risk of mortality with aspirin and concomitant ibuprofen compared to aspirin alone among high risk patients (HR 1.9, 95% CI 1.3 to 2.9), but studies on effects of ibuprofen added to aspirin on MI risk in average risk patients were inconsistent and did not clearly demonstrate increased risk.
3. What are the comparative effects of coprescribing of H2-antagonists, misoprostol, or PPIs on the gastrointestinal harms associated with NSAID use?	High: Consistent evidence from good-quality systematic reviews and numerous clinical trials	Misoprostol was the only gastroprotective agent to reduce risk of ulcer complications compared to placebo in patients with average risk of GI bleeding prescribed nonselective NSAIDs, but was also associated with a higher rate of withdrawals due to adverse GI symptoms. Coprescribing of PPIs, misoprostol, and H2-antagonists all reduced the risk of endoscopically detected gastric and duodenal ulcers compared to placebo in patients prescribed a nonselective NSAID. In direct comparisons, coprescribing of PPIs in patients with increased risk of GI bleeding who were prescribed a nonselective NSAID was associated with a lower risk of endoscopically detected duodenal ulcers compared to misoprostol or H2-antagonists, a lower risk of endoscopically detected gastric ulcers compared to H2-antagonists, and a similar risk of endoscopically detected gastric ulcers compared to misoprostol. Coprescribing of misoprostol was associated with a lower risk of endoscopically detected gastric ulcers compared to ranitidine, and a similar reduction in risk of endoscopically detected duodenal ulcers. Compared to placebo, double (full) dose H2-antagonists may be more effective than standard dose for reducing endoscopically detected gastric and duodenal ulcers. Celecoxib alone was associated with fewer decreases in hemoglobin (> 2 g/dl) without overt GI bleeding compared with diclofenac plus a PPI. Celecoxib plus a PPI may reduce the risk of endoscopic ulcers and ulcer complications compared to celecoxib alone in average risk persons.

Table 22. Summary of evidence on comparative benefits and harms of analgesics for osteoarthritis (continued)

Key Question	Strength of Evidence	Conclusion
4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations?		
Topical NSAIDs: efficacy	Moderate (consistent evidence for topical diclofenac from three trials)	Three head-to-head trials found topical diclofenac similar to oral NSAIDs for efficacy in patients with localized osteoarthritis.
Topical NSAIDs: safety	Moderate (consistent evidence for topical diclofenac from three trials)	Topical NSAIDs were associated with a lower risk of GI adverse events and higher risk of dermatologic adverse compared to oral NSAIDs. There was insufficient evidence to evaluate comparative risks of GI bleeding or CV events. Other topical NSAIDs evaluated in head-to-head trials have not been FDA-approved.
Topical salicylates and capsaicin	Insufficient for topical salicylates or capsaicin versus oral NSAIDs (no head-to-head trials)	No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs for osteoarthritis.
	Low (some placebo-controlled trials)	Topical salicylates were no better than placebo in two trials of patients with osteoarthritis included in a systematic review, and associated with increased risk of local adverse events when used for any acute or chronic pain condition. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events (13% vs. 3%, RR 4.0, 95% CI 2.3 to 6.8).

CHF = congestive heart failure; CI = confidence interval; CLASS = Celecoxib Long-term Arthritis Safety Study; COX = cyclooxygenase; CV = cardiovascular; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; H2 = Histamine 2; HR = hazard ratio; HTN = hypertension; INR = International Normalized Ratio; NIH = National Institutes of Health; NNT = number needed to treat; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PPI = proton pump inhibitor; PUD = peptic ulcer disease; RR = relative risk; VAS = visual analogue scale

Discussion

This report provides a summary of the evidence on the comparative benefits and harms of oral nonsteroidal anti-inflammatory drugs (NSAIDs) (celecoxib, partially selective, nonselective, aspirin, and salsalate), acetaminophen, certain over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs, salicylates, and capsaicin) that are commonly used for pain control and improvement of functional status in patients with osteoarthritis. At this time, no drug or supplement is known to modify the course of disease, though some data suggest potential effects of glucosamine or chondroitin on slowing progression of joint space narrowing.

Major new evidence included in this update include a large trial of celecoxib versus a proton pump inhibitor plus naproxen and risk of gastrointestinal (GI) bleeding, new placebo-controlled trials of glucosamine and chondroitin, and a new head-to-head trial of topical versus oral diclofenac. Other new evidence in this update includes large observational studies on serious GI and cardiovascular (CV) harms associated with NSAIDs, and a number of systematic reviews. Like the original CER, a limitation of this update is that studies have not used standardized methods for defining and assessing harms.

As in the original CER, evidence indicates that each of the analgesics evaluated in this report is associated with a unique set of risks and benefits. The role of selective, partially selective, and nonselective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence varies, no currently available analgesic reviewed in this report offers a clear overall advantage compared with the others, which is not surprising given the complex tradeoffs between many benefits (pain relief, improved function, improved tolerability, and others) and harms (CV, renal, GI, and others). In addition, individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of a small increase in CV risk, for example, could be an acceptable tradeoff for many patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and CV events), comorbid conditions, and concomitant medication use (such as aspirin and anticoagulation). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant tradeoffs.

Future Research

- Nearly all of the clinical trials reviewed in this report were "efficacy" trials conducted in ideal settings and selected populations. "Pragmatic" trials that allow flexible dosing or medication switches and other clinical trials of effectiveness would be very valuable for learning the outcomes of different analgesic interventions in real-world settings.
- The cardiovascular (CV) safety of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) has not been adequately assessed in large, long-term clinical trials. Naproxen in particular might have a different CV safety profile than other NSAIDs and should be investigated in long-term, appropriately powered trials.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms, but have generally had a narrow focus on single adverse events. More observational studies that take a broader view of all serious adverse events would be more helpful for assessing the overall tradeoffs between benefits and harms.
- The CV risks and gastrointestinal (GI) benefits associated with different cyclooxygenase (COX)-2 selective NSAIDs might vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.
- Meta-analyses of the risks associated with selective COX-2 inhibitors need to better assess for the effects of dose and duration, as most of the CV harms have only occurred with prolonged use and at higher doses.
- Large, long-term trials of GI and CV safety associated with full-dose aspirin, salsalate, or acetaminophen compared with non-aspirin NSAIDs or placebo are lacking.
- Trials and observational studies evaluating comparative safety or efficacy should be sufficiently inclusive to evaluate whether effects differ by race or gender.
- Genetic testing could theoretically help predict patients who are at higher risk of CV complications from selective COX-2 inhibitors because of differences in the COX-2 gene promoter or other genes. This remains a promising area of future research.

- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been well studied. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once-daily versus twice-daily dosing of certain COX-2 inhibitors could affect CV risk, this hypothesis has not yet been tested in a clinical trial.
- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical grade glucosamine not available in the United States and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations to oral NSAIDs are needed, as these are likely to remain available even if the U.S. Food and Drug Administration approves a pharmaceutical grade glucosamine. Additional long-term trials are also required to further evaluate effects of glucosamine on progression of joint space narrowing and to determine the clinical effects of any beneficial effects on radiographic outcomes.
- Head-to-head trials of topical versus oral NSAIDs have not been large enough to evaluate the risks of serious CV and GI harms. Additional head-to-head trials and large cohort studies may be required to adequately assess serious harms.

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Acronyms and Abbreviations

ACR	American College of Rheumatology
ADAPT	Alzheimer's Disease Anti-Inflammatory Prevention Trial
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AMSTAR	Assessment of Multiple Systematic Reviews
APC	Adenoma Prevention with Celecoxib trial
ARAMIS	Arthritis, Rheumatism, and Aging Medical Information System
ARR	Adjusted relative risk
AST	Aspartate aminotransferase
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CDME	Central Diabetic Macular Edema trial
CER	Comparative effectiveness review
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CLASS	Celecoxib Long-term Arthritis Safety Study
CNS	Central nervous system
COX	Cyclooxygenase
CV	Cardiovascular
DMSO	Dimethyl sulphoxide
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GI	Gastrointestinal
GAIT	Glucosamine/chondroitin Arthritis Intervention Trial
H2	Histamine 2
HR	Hazard ratio
HTN	Hypertension
INR	Immediate release
JAMA	Journal of the American Medical Association
JSM	Joint space measurement
JSN	Joint space narrowing
JSW	Joint space width
MeSH	Medical Subject Headings
MI	Myocardial infarction
MUCOSA	Misoprostol Ulcer Complications Outcomes Safety Assessment Trial
NIH	National Institutes of Health
NNT	Number needed to treat
NR	Not reported
NRS LBP	Numerical rating scale for low back pain
NS	Not significant
NSAID	Nonsteroidal anti-inflammatory drug

OA	Osteoarthritis
OR	Odds ratio
OMERACT-OARSI	Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International
PCT	Placebo-controlled trial
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing and Setting
POBs	Gastric or duodenal perforation, gastric outlet obstruction, or upper gastrointestinal bleeding
PPI	Proton pump inhibitor
PreSAP	Prevention of colorectal sporadic adenomatous polyps
PUBs	Perforations, symptomatic gastroduodenal ulcers, and upper GI bleeding
PUD	Peptic ulcer disease
qd	Once a day (quaque die)
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RMDQ	Roland Morris Disability Questionnaire
RR	Relative risk
RRR	Relative risk reduction
SCHIP	State Children's Health Insurance
SF-36	Medical Outcomes Short Form-36
SMD	Standardized mean difference
SR	Sustained release
SR	Rystematic review
SUCCESS-1	Successive Celecoxib Efficacy and Safety Study-1
TARGET	Therapeutic Arthritis Research and Gastrointestinal Event Trial
TEP	Technical Expert Panel
tid	Three times a day (ter in die)
UGIB	Upper gastrointestinal bleeding
UK GPRD	United Kingdom General Practice Research Database
VAS	Visual analog scale
VIGOR	Vioxx Gastrointestinal Outcomes Research
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Glossary

For this report, we have defined the terms as follows:

- **All other NSAIDs:** Non-aspirin, nonselective NSAIDs, or simply nonselective NSAIDs.
- **Aspirin:** Differs from other NSAIDs, because it irreversibly inhibits platelet aggregation; salicylic acid derivatives (aspirin and salsalate) are considered a separate subgroup.
- **Partially selective NSAIDs:** Other drugs shown to have partial in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam).
- **Selective NSAIDs or COX-2 selective NSAIDs:** Drugs in the "coxib" class (celecoxib).

Appendix A. Comparable NSAID Dose Levels*

Nonselective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Diclofenac potassium	50mg bid	50mg tid	50mg qid (in OA/RA only)
Diclofenac sodium	50mg bid	75mg bid	50mg qid or 100mg SR bid (in RA only)
Fenoprofen	200-300mg qid	600mg tid-qid	800mg qid
Flurbiprofen	50mg bid	50mg tid-qid	100mg tid
Ibuprofen	400mg tid	600mg tid-qid	800mg qid
Ketoprofen	25–50mg tid	75mg tid	IR =300mg/day (divide), SR =200mg/day
Naproxen	250mg tid	500mg bid	1250mg/day (divided)
Naproxen sodium	275mg tid	550mg bid	1375mg/day (divided)
Oxaprozin	600mg qd	1,200mg qd	1,200mg qd
Sulindac	150mg bid	200mg bid	200g bid
Piroxicam	10mg qd	20mg qd	40mg per day (not indicated for OA or RA)
Partially-selective NSAIDs	**Low Dose**	**Medium Dose**	**High or Max Dose**
Etodolac	200mg tid	400mg bid	1,200mg max (IR or SR divided doses)
Meloxicam/Mobic	7.5mg qd	7.5mg qd	15mg qd
Nabumetone	1,000mg qd	1,000mg bid	2,000mg/day (qd or divided bid)
Cox-2 inhibitors	**Low Dose**	**Medium Dose**	**High or Max Dose**
Celecoxib/Celebrex	200mg qd	200mg bid	200mg bid

COX = cyclo-oxygenase; IR = immediate release; NSAID = nonsteroidal antiinflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; SR = sustained release

*This table does not represent exact or equivalent dosing conversions. It is based on U.S. Food and Drug Administration approved dosing ranges and comparative doses from clinical trials.

Source: www.ashp.org/emplibrary/NSAIDsConversiontools.pdf

Appendix B. Cyclooxygenase Selectivity of NSAIDs

NSAID	Ratio*
Flurbiprofen	10.27
Ketoprofen	8.16
Fenoprofen	5.14
Tolmetin	3.93
Aspirin	3.12
Oxaprozin	2.52
Naproxen	1.79
Indomethacin	1.78
Ibuprofen	1.69
Ketorolac	1.64
Piroxicam	0.79
Nabumetone	0.64
Etodolac	0.11
Celecoxib	0.11
Meloxicam	0.09
Mefenamic acid	0.08
Diclofenac	0.05

NSAID = nonsteroidal antiinflammatory drug

*Expressed as the ratio of the 50 percent inhibitory concentration of cycloogenase-2 to the 50 percent inhibitory concentration of cyclooxygenase-1 in whole blood. NSAIDs with a ratio of <1 indicate selectivity for cyclooxygenase-2.

Adapted 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 C. Exact Search Strings

Original Report

Ovid MEDLINE Searches (1966 to July Week 3 2005)

I. Search Strategy: NSAIDs, focus on efficacy (OA)
1   exp OSTEOARTHRITIS/ (26153)
2   limit 1 to (humans and english language) (18162)
3   celecoxib.mp. (1545)
4   choline magnesium trisalicylate.mp. (38)
5   DICLOFENAC/ (3399)
6   DIFLUNISAL/ (380)
7   ETODOLAC/ (284)
8   FENOPROFEN/ (257)
9   FLURBIPROFEN/ (1184)
10   IBUPROFEN/ (4177)
11   INDOMETHACIN/ (23527)
12   KETOPROFEN/ (1443)
13   KETOROLAC/ (723)
14   meclofenamate sodium.mp. (51)
15   Mefenamic Acid/ (764)
16   meloxicam.mp. (522)
17   nabumetone.mp. (350)
18   NAPROXEN/ (2378)
19   oxaprozin.mp. (121)
20   PIROXICAM/ (1920)
21   salsalate.mp. (74)
22   SULINDAC/ (923)
23   TOLMETIN/ (1255)
24   valdecoxib.mp. (183)
25   3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (40472)
26   limit 25 to (humans and english language) (17770)
27   2 and 26 (1094)
28   Comparative Study/ (1202473)
29   Cohort Studies/ (57012)
30   Randomized Controlled Trials/ (38090)
31   27 and (28 or 29 or 30) (532)
32   from 31 keep 1-532 (532)

II. Search Strategy: NSAIDs, focus on adverse events (OA & RA)
1   Arthritis, Rheumatoid/ (53548)
2   limit 1 to (humans and english language) (37493)
3   celecoxib.mp. (1545)

4   choline magnesium trisalicylate.mp. (38)
5   *DICLOFENAC/ae [Adverse Effects] (374)
6   *DIFLUNISAL/ae [Adverse Effects] (27)
7   *ETODOLAC/ae [Adverse Effects] (19)
8   *FENOPROFEN/ae [Adverse Effects] (41)
9   *FLURBIPROFEN/ae [Adverse Effects] (41)
10   *IBUPROFEN/ae [Adverse Effects] (356)
11   *INDOMETHACIN/ae [Adverse Effects] (678)
12   *KETOPROFEN/ae [Adverse Effects] (109)
13   *KETOROLAC/ae [Adverse Effects] (16)
14   meclofenamate sodium.mp. (51)
15   *Mefenamic Acid/ae [Adverse Effects] (67)
16   meloxicam.mp. (522)
17   nabumetone.mp. (350)
18   *NAPROXEN/ae [Adverse Effects] (269)
19   oxaprozin.mp. (121)
20   *PIROXICAM/ae [Adverse Effects] (130)
21   salsalate.mp. (74)
22   *SULINDAC/ae [Adverse Effects] (116)
23   *TOLMETIN/ae [Adverse Effects] (74)
24   valdecoxib.mp. (183)
25   3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
or 20 or 21 or 22 or 23 or 24 (4875)
26   limit 25 to (humans and english language) (3433)
27   2 and 26 (357)
28   Cohort Studies/ (57012)
29   Comparative Study/ (1202473)
30   Randomized Controlled Trials/ (38090)
31   27 and (28 or 29 or 30) (128)
32   from 31 keep 1-128 (128)

III. Search Strategy: Aspirin/acetaminophen
1   exp OSTEOARTHRITIS/ (26153)
2   limit 1 to (humans and english language) (18162)
3   ASPIRIN/ (26642)
4   ACETAMINOPHEN/ (8992)
5   2 and (3 or 4) (323)
6   exp Arthritis, Rheumatoid/ (71858)
7   limit 6 to (humans and english language) (50057)
8   *ASPIRIN/ae [Adverse Effects] (2386)
9   *ACETAMINOPHEN/ae [Adverse Effects] (719)
10   7 and (8 or 9) (81)
11   5 or 10 (400)
12   Cohort Studies/ (57012)
13   Comparative Study/ (1202473)
14   Randomized Controlled Trials/ (38090)

15   11 and (12 or 13 or 14) (158)
16   from 15 keep 1-158 (158)

IV. Search Strategy: Topical analgesics
    1   exp OSTEOARTHRITIS/ (26153)
    2   limit 1 to (humans and english language) (18162)
    3   (topical and capsaicin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (614)
    4   (topical and diclofenac).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (356)
    5   (topical and ibuprofen).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (137)
    6   (topical and ketoprofen).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (114)
    7   (topical and salicylate).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (160)
    8   2 and (3 or 4 or 5 or 6 or 7) (40)
    9   exp Arthritis, Rheumatoid/ (71858)
    10   9 and (3 or 4 or 5 or 6 or 7) (11)
    11   8 or 10 (49)
    12   from 11 keep 1-49 (49)

CDSR/CRCT Searches (Through Third Quarter 2005)

I. Search Strategy: NSAIDs, focus on efficacy (OA)
    1   exp OSTEOARTHRITIS/ (1546)
    2   limit 1 to (humans and english language) (1546)
    3   celecoxib.mp. (219)
    4   choline magnesium trisalicylate.mp. (29)
    5   DICLOFENAC/ (878)
    6   DIFLUNISAL/ (90)
    7   ETODOLAC/ (70)
    8   FENOPROFEN/ (35)
    9   FLURBIPROFEN/ (272)
    10   IBUPROFEN/ (776)
    11   INDOMETHACIN/ (1224)
    12   KETOPROFEN/ (299)
    13   KETOROLAC/ (279)
    14   meclofenamate sodium.mp. (37)
    15   Mefenamic Acid/ (92)
    16   meloxicam.mp. (133)
    17   nabumetone.mp. (141)
    18   NAPROXEN/ (645)
    19   oxaprozin.mp. (47)
    20   PIROXICAM/ (447)
    21   salsalate.mp. (31)

22   SULINDAC/ (119)
23   TOLMETIN/ (360)
24   valdecoxib.mp. (56)
25   3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
or 20 or 21 or 22 or 23 or 24 (5040)
26   limit 25 to (humans and english language)(5040)
27   2 and 26 (555)
28   Comparative Study/ (96540)
29   Cohort Studies/ (2139)
30   Randomized Controlled Trials/ (4538)
31   27 and (28 or 29 or 30) (402)

II. Search Strategy: NSAIDs, focus on adverse events (OA & RA)
1   Arthritis, Rheumatoid/ (2385)
2   limit 1 to (humans and english language) (2385)
3   celecoxib.mp. (219)
4   choline magnesium trisalicylate.mp. (29)
5   *DICLOFENAC/ae [Adverse Effects] (39)
6   *DIFLUNISAL/ae [Adverse Effects] (6)
7   *ETODOLAC/ae [Adverse Effects] (3)
8   *FENOPROFEN/ae [Adverse Effects] (2)
9   *FLURBIPROFEN/ae [Adverse Effects] (5)
10   *IBUPROFEN/ae [Adverse Effects] (40)
11   *INDOMETHACIN/ae [Adverse Effects] (61)
12   *KETOPROFEN/ae [Adverse Effects] (9)
13   *KETOROLAC/ae [Adverse Effects] (6)
14   meclofenamate sodium.mp. (37)
15   *Mefenamic Acid/ae [Adverse Effects] (0)
16   meloxicam.mp. (133)
17   nabumetone.mp. (141)
18   *NAPROXEN/ae [Adverse Effects] (62)
19   oxaprozin.mp. (47)
20   *PIROXICAM/ae [Adverse Effects] (19)
21   salsalate.mp. (31)
22   *SULINDAC/ae [Adverse Effects] (11)
23   *TOLMETIN/ae [Adverse Effects] (0)
24   valdecoxib.mp. (56)
25   3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
or 20 or 21 or 22 or 23 or 24 (846)
26   limit 25 to (humans and english language) [Limit not valid in: CDSR,ACP Journal
Club,DARE,CCTR; records were retained] (846)
27   2 and 26 (98)
28   Cohort Studies/ (2139)
29   Comparative Study/ (96540)
30   Randomized Controlled Trials/ (4538)
31   27 and (28 or 29 or 30) (73)

III. Search Strategy: Aspirin/acetaminophen
1   exp OSTEOARTHRITIS/ (1546)
2   limit 1 to (humans and english language) (1546)
3   ASPIRIN/ (3028)
4   ACETAMINOPHEN/ (1128)
5   2 and (3 or 4) (115)
6   exp Arthritis, Rheumatoid/ (2730)
7   limit 6 to (humans and english language) (2730)
8   *ASPIRIN/ae [Adverse Effects] (271)
9   *ACETAMINOPHEN/ae [Adverse Effects] (32)
10   7 and (8 or 9) (10)
11   5 or 10 (124)
12   Cohort Studies/ (2139)
13   Comparative Study/ (96540)
14   Randomized Controlled Trials/ (4538)
15   11 and (12 or 13 or 14) (90)

IV. Search Strategy: Topicals
1   exp OSTEOARTHRITIS/ (1546)
2   limit 1 to (humans and english language) (1546)
3   (topical and capsaicin).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (123)
4   (topical and diclofenac).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (199)
5   (topical and ibuprofen).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (69)
6   (topical and ketoprofen).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (46)
7   (topical and salicylate).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (44)
8   2 and (3 or 4 or 5 or 6 or 7) (18)
9   exp Arthritis, Rheumatoid/ (2730)
10   9 and (3 or 4 or 5 or 6 or 7) (6)
11   8 or 10 (22)

Current CER Update Search Strings

Database: Ovid MEDLINE 1996 to January week 2 2011
RCTs
1   exp OSTEOARTHRITIS/ (18286)
2   osteoarthriti$.mp. (23317)
3   1 or 2 (23317)
4   Aspirin/ or aspirin.mp. (20844)
5   acetaminophen.mp. or Acetaminophen/ (7386)
6   Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7518)
7   capsaicin.mp. or Capsaicin/ (6135)
8   Chondroitin/ or chondroitin.mp. (5835)
9   diclofenac.mp. or Diclofenac/ (4611)
10   diflunisal.mp. or Diflunisal/ (162)

11   etodolac.mp. or Etodolac/ (295)
12   fenoprofen.mp. or Fenoprofen/ (106)
13   flurbiprofen.mp. or Flurbiprofen/ (813)
14   Glucosamine/ or glucosamine.mp. (4146)
15   ibuprofen.mp. or Ibuprofen/ (4484)
16   indomethacin.mp. or Indomethacin/ (11590)
17   ketoprofen.mp. or Ketoprofen/ (1574)
18   Ketorolac/ or ketorolac.mp. (1209)
19   meclofenamate.mp. (157)
20   mefenamic acid.mp. or Mefenamic Acid/ (362)
21   meloxicam.mp. (881)
22   nabumetone.mp. (218)
23   naproxen.mp. or Naproxen/ (2158)
24   oxaprozin.mp. (59)
25   piroxicam.mp. or Piroxicam/ (1288)
26   salsalate.mp. (27)
27   sulindac.mp. or Sulindac/ (878)
28   tolmetin.mp. or Tolmetin/ (410)
29   or/4-28 (71421)
30   randomized controlled trial.mp. or exp Randomized Controlled Trial/ (189494)
31   randomized controlled trial.pt. (186325)
32   controlled clinical trial.mp. or exp Controlled Clinical Trial/ (38495)
33   controlled clinical trial.pt. (34791)
34   clinical trial.mp. or exp Clinical Trial/ (404159)
35   clinical trial.pt. (252913)
36   or/30-35 (406908)
37   limit 36 to humans (397588)
38   3 and 29 and 37 (542)
39   38 and (200507$ or 200508$ or 200509$ or 20051$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ed. (211)
40   limit 39 to english language (189)
41   limit 39 to abstracts (202)
42   40 or 41 (210)

Systematic Reviews
1   exp OSTEOARTHRITIS/ (18286)
2   osteoarthriti$.mp. (23317)
3   1 or 2 (23317)
4   Aspirin/ or aspirin.mp. (20844)
5   acetaminophen.mp. or Acetaminophen/ (7386)
6   Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7518)
7   capsaicin.mp. or Capsaicin/ (6135)
8   Chondroitin/ or chondroitin.mp. (5835)
9   diclofenac.mp. or Diclofenac/ (4611)
10   diflunisal.mp. or Diflunisal/ (162)

11   etodolac.mp. or Etodolac/ (295)
12   fenoprofen.mp. or Fenoprofen/ (106)
13   flurbiprofen.mp. or Flurbiprofen/ (813)
14   Glucosamine/ or glucosamine.mp. (4146)
15   ibuprofen.mp. or Ibuprofen/ (4484)
16   indomethacin.mp. or Indomethacin/ (11590)
17   ketoprofen.mp. or Ketoprofen/ (1574)
18   Ketorolac/ or ketorolac.mp. (1209)
19   meclofenamate.mp. (157)
20   mefenamic acid.mp. or Mefenamic Acid/ (362)
21   meloxicam.mp. (881)
22   nabumetone.mp. (218)
23   naproxen.mp. or Naproxen/ (2158)
24   oxaprozin.mp. (59)
25   piroxicam.mp. or Piroxicam/ (1288)
26   salsalate.mp. (27)
27   sulindac.mp. or Sulindac/ (878)
28   tolmetin.mp. or Tolmetin/ (410)
29   or/4-28 (71421)
30   meta-analysis.mp. or exp Meta-Analysis/ (33804)
31   (cochrane or medline).tw. (33065)
32   search$.tw. (112106)
33   30 or 31 or 32 (139975)
34   "Review Literature as Topic"/ or systematic review.mp. (19084)
35   33 or 34 (146484)
36   3 and 29 and 35 (163)
37   36 and (200507$ or 200508$ or 200509$ or 20051$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ed. (77)
38   limit 37 to humans (75)
39   limit 38 to english language (72)
40   limit 38 to abstracts (66)

Harms

1   Aspirin/ or aspirin.mp. (20844)
2   acetaminophen.mp. or Acetaminophen/ (7386)
3   Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7518)
4   capsaicin.mp. or Capsaicin/ (6135)
5   Chondroitin/ or chondroitin.mp. (5835)
6   diclofenac.mp. or Diclofenac/ (4611)
7   diflunisal.mp. or Diflunisal/ (162)
8   etodolac.mp. or Etodolac/ (295)
9   fenoprofen.mp. or Fenoprofen/ (106)
10   flurbiprofen.mp. or Flurbiprofen/ (813)
11   Glucosamine/ or glucosamine.mp. (4146)
12   ibuprofen.mp. or Ibuprofen/ (4484)
13   indomethacin.mp. or Indomethacin/ (11590)

14   ketoprofen.mp. or Ketoprofen/ (1574)
15   Ketorolac/ or ketorolac.mp. (1209)
16   meclofenamate.mp. (157)
17   mefenamic acid.mp. or Mefenamic Acid/ (362)
18   meloxicam.mp. (881)
19   nabumetone.mp. (218)
20   naproxen.mp. or Naproxen/ (2158)
21   oxaprozin.mp. (59)
22   piroxicam.mp. or Piroxicam/ (1288)
23   salsalate.mp. (27)
24   sulindac.mp. or Sulindac/ (878)
25   tolmetin.mp. or Tolmetin/ (410)
26   or/1-25 (71421)
27   (ae or co or de).fs. (1917797)
28   (adverse effect$ or adverse event$ or harm$).mp. (125151)
29   27 or 28 (1980478)
30   rheumatoid arthritis.mp. or Arthritis, Rheumatoid/ (34754)
31   Alzheimer Disease/pc [Prevention & Control] (1442)
32   (alzheimer$ adj2 prevent$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (267)
33   31 or 32 (1566)
34   Neoplasms/pc [Prevention & Control] (6517)
35   (cancer adj1 prevent$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (6643)
36   34 or 35 (11729)
37   30 or 33 or 36 (47989)
38   26 and 29 and 37 (1011)
39   38 and (200507$ or 200508$ or 200509$ or 20051$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ed. (332)
40   limit 39 to humans (290)
41   limit 40 to english language (264)
42   limit 40 to abstracts (252)
43   41 or 42 (278)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials (fourth quarter 2010)
1   exp OSTEOARTHRITIS/ (2149)
2   osteoarthriti$.mp. (3327)
3   1 or 2 (3327)
4   Aspirin/ or aspirin.mp. (6044)
5   acetaminophen.mp. or Acetaminophen/ (2083)
6   Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (639)
7   capsaicin.mp. or Capsaicin/ (427)
8   Chondroitin/ or chondroitin.mp. (212)
9   diclofenac.mp. or Diclofenac/ (2245)

10   diflunisal.mp. or Diflunisal/ (207)
11   etodolac.mp. or Etodolac/ (154)
12   fenoprofen.mp. or Fenoprofen/ (83)
13   flurbiprofen.mp. or Flurbiprofen/ (499)
14   Glucosamine/ or glucosamine.mp. (171)
15   ibuprofen.mp. or Ibuprofen/ (1769)
16   indomethacin.mp. or Indomethacin/ (2174)
17   ketoprofen.mp. or Ketoprofen/ (687)
18   Ketorolac/ or ketorolac.mp. (909)
19   meclofenamate.mp. (69)
20   mefenamic acid.mp. or Mefenamic Acid/ (196)
21   meloxicam.mp. (160)
22   nabumetone.mp. (137)
23   naproxen.mp. or Naproxen/ (1268)
24   oxaprozin.mp. (48)
25   piroxicam.mp. or Piroxicam/ (900)
26   salsalate.mp. (31)
27   sulindac.mp. or Sulindac/ (249)
28   tolmetin.mp. or Tolmetin/ (421)
29   or/4-28 (17609)
30   3 and 29 (1357)
31   limit 30 to yr="2005 -Current" (192)

Database: EBM Reviews - Cochrane Database of Systematic Reviews (2005 to January 2011)
1   osteoarthriti$.mp. (203)
2   Aspirin/ or aspirin.mp. (303)
3   acetaminophen.mp. or Acetaminophen/ (86)
4   Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, abstract, full text, keywords, caption text] (58)
5   capsaicin.mp. or Capsaicin/ (37)
6   Chondroitin/ or chondroitin.mp. (10)
7   diclofenac.mp. or Diclofenac/ (99)
8   diflunisal.mp. or Diflunisal/ (17)
9   etodolac.mp. or Etodolac/ (17)
10   fenoprofen.mp. or Fenoprofen/ (14)
11   flurbiprofen.mp. or Flurbiprofen/ (24)
12   Glucosamine/ or glucosamine.mp. (17)
13   ibuprofen.mp. or Ibuprofen/ (126)
14   indomethacin.mp. or Indomethacin/ (92)
15   ketoprofen.mp. or Ketoprofen/ (40)
16   Ketorolac/ or ketorolac.mp. (43)
17   meclofenamate.mp. (8)
18   mefenamic acid.mp. or Mefenamic Acid/ (27)
19   meloxicam.mp. (14)
20   nabumetone.mp. (9)

21   naproxen.mp. or Naproxen/ (90)
22   oxaprozin.mp. (5)
23   piroxicam.mp. or Piroxicam/ (33)
24   salsalate.mp. (2)
25   sulindac.mp. or Sulindac/ (21)
26   tolmetin.mp. or Tolmetin/ (8)
27   or/2-26 (536)
28   1 and 27 (60)
29   limit 28 to full systematic reviews (49)

Appendix D. Inclusion and Exclusion Criteria

Abstract-Level Eligibility Criteria

Study Characteristic	Inclusion/Exclusion
Population	Include: all ages >18; patients with osteoarthritis (for studies reporting benefits or harms); patients with rheumatoid arthritis, Alzheimer's or enrolled in cancer prevention trials (for studies reporting harms) Exclude: Juvenile populations; Post-surgical pain patients
Interventions	Include: acetaminophen, aspirin, celecoxib, chondroitin, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, glucosamine, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin Exclude: all other medications, including COX-2 and other drugs included in previous report but no longer FDA approved for use in the United States
Comparators	Include: any above medication, placebo Exclude: drugs not included in this review
Outcomes	Include: Improvements in osteoarthritis symptoms; Adverse events: any cardiovascular, gastrointestinal, renal toxicity, hepatic toxicity; quality of life; sudden death
Timing/Duration	Include any study duration (no minimum exposure)
Setting	Include primary care or specialty setting
Study Design	Include: RCT, cohort, case control, systematic review, meta-analysis

Full-Text Eligibility Criteria

Study Characteristic	Inclusion/Exclusion
Population	Include: all ages >18; patients with osteoarthritis (for studies reporting benefits or harms); patients with rheumatoid arthritis, Alzheimer's or enrolled in cancer prevention trials (for studies reporting harms) Exclude: Juvenile populations; post-surgical pain patients
Interventions	Include: acetaminophen, aspirin, celecoxib, chondroitin, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, glucosamine, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin Exclude: all other medications, including COX-2 and other drugs included in previous report but no longer FDA approved for use in the United States; combination therapies of multiple NSAIDs
Comparators	Include: any above medication, placebo Exclude: drugs not included in this review
Outcomes	Include: Improvements in osteoarthritis symptoms; Adverse events: any cardiovascular, gastrointestinal, renal toxicity, hepatic toxicity; quality of life; sudden death
Timing/Duration	Include any study duration (no minimum exposure)
Setting	Include primary care or specialty setting
Study Design	Include: RCT, cohort, case control, systematic review, meta-analysis Exclude: cohort or case control study with <1000 patients, dose-ranging study, pharmacokinetics, single-dose study, drug interaction, case report, nonsystematic review

Appendix E. Excluded Studies

1. Diclofenac gel for osteoarthritis. Med Lett Drugs Ther 2008;50(1284):31–2. **Publication type not included in this review**

2. Ahmed M, Khanna D, Furst DE. Meloxicam in rheumatoid arthritis. Expert Opin Drug Metab Toxicol 2005;1(4):739–51. **Population differs from those in this review**

3. Aisen PS, Thal LJ, Ferris SH, et al. Rofecoxib in patients with mild cognitive impairment: further analyses of data from a randomized, double-blind, trial. Curr Alzheimer Res 2008;5(1):73–82. **Outcomes not included in this review**

4. Alekseeva LI. [Comparative evaluation of the safety and efficacy of etoricoxib and diclofenac on the upper gastrointestinal tract in patients with osteoarthrosis and rheumatoid arthritis (the multinational etoricoxib and diclofenac arthritis long-term (MEDAL) study program)]. Terapevticheskii Arkhiv. 82(8):57–62. **Foreign Language article**

5. Allegrini A, Nuzzo L, Pavone D, et al. Efficacy and safety of piroxicam patch versus piroxicam cream in patients with lumbar osteoarthritis. A randomized, placebo-controlled study. Arzneimittel-Forschung 2009;59(8):403–9. **Foreign Language article**

6. Altman RD. Pharmacological therapies for osteoarthritis of the hand: a review of the evidence. Drugs Aging 2010;27(9):729–45. **Publication type not included in this review**

7. Balthazar-Letawe D. Voltaren Emulgel en pratique rhumatologique. Essai comparatif avec Indocid gel. [Voltaren Emugel in clinical rheumatology. Comparative trial with Indocid gel]. Acta Belg Med Phys 1987;10:109–10. **Foreign Language article**

8. Bannwarth B. Safety of the nonselective NSAID nabumetone : focus on gastrointestinal tolerability. Drug Safety 2008;31(6):485–503. **Population differs from those in this review**

9. Bannwarth B, Berenbaum F. Clinical pharmacology of lumiracoxib, a second-generation cyclooxygenase 2 selective inhibitor. Expert Opin Investig Drugs 2005;14(4):521–33. **Population differs from those in this review**

10. Bansal SS, Joshi A, Bansal AK. New dosage formulations for targeted delivery of cyclo-oxygenase-2 inhibitors: focus on use in the elderly. Drugs Aging 2007;24(6):441–51. **Outcomes not included in this review**

11. Baraf HS, Fuentealba C, Greenwald M, et al. Gastrointestinal side effects of etoricoxib in patients with osteoarthritis: results of the Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) trial. J Rheumatol 2007;34(2):408–20. **Outcomes not included in this review**

12. Barthel HR, Peniston JH, Clark MB, et al. Correlation of pain relief with physical function in hand osteoarthritis: randomized controlled trial post hoc analysis. Arthritis Res Ther 2010;12(1):R7. **Outcomes not included in this review**

13. Beaulieu AD, Peloso PM, Haraoui B, et al. Once-daily, controlled-release tramadol and sustained-release diclofenac relieve chronic pain due to osteoarthritis: a randomized controlled trial. Pain Res Manag 2008;13(2):103–10. **Outcomes not included in this review**

14. Benito-Garcia E, Michaud K, Wolfe F. The effect of low-dose aspirin on the decreased risk of development of dyspepsia and gastrointestinal ulcers associated to cyclooxygenase-2 selective inhibitors. J Rheumatol 2007;34(8):1765–9. **Drug not included in this review**

15. Berge HM, Gjelstad S, Furu K, et al. [Use of glucosamine does not reduce the need for other pain-relieving drugs]. Tidsskrift for Den Norske Laegeforening 130(15):1463–6. **Foreign Language article**

16. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. Rheumatology (Oxford) 2005;44(5):677–80. **Outcomes not included in this review**

17. Bertagnolli MM. Chemoprevention of colorectal cancer with cyclooxygenase-2 inhibitors: two steps forward, one step back. Lancet Oncol 2007;8(5):439–43. **Population differs from those in this review**

18. Bertagnolli MM, Zauber AG, Solomon S. Prostaglandin inhibition and cardiovascular risk: maybe timing really is everything. Cancer Prev Res (Phila) 2009;2(3):195–6. **Population differs from those in this review**

19. Bessette L, Risebrough N, Mittmann N, et al. Cost-utility of celecoxib use in different treatment strategies for osteoarthritis and rheumatoid arthritis from the Quebec healthcare system perspective. J Med Econ 2009;12(3):246–58. **Outcomes not included in this review**

20. Bin SI, Wu SS, Zeng X, et al. Efficacy of lumiracoxib in relieving pain associated with knee osteoarthritis: A 6-week, randomized, double-blind, parallel-group study. APLAR Journal of Rheumatology 2007;10(3):190–7. **Outcomes not included in this review**

21. Block JA, Oegema TR, Sandy JD, et al. The effects of oral glucosamine on joint health: is a change in research approach needed? Osteoarthritis Cartilage 2010;18(1):5–11. **Publication type not included in this review**

22. Bombardier C, Laine L, Burgos-Vargas R, et al. Response to expression of concern regarding VIGOR study. N Engl J Med 2006;354(11):1196–9. **Outcomes not included in this review**

23. Boswell DJ, Ostergaard K, Philipson RS, et al. Evaluation of GW406381 for treatment of osteoarthritis of the knee: two randomized, controlled studies. MedGenMed 2008;10(11):259. **Outcomes not included in this review**

24. Bourgeois P, Dehais J, Delcambre B, et al. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3x 400 mg/day vs placebo. Osteoarthritis Cartilage 1998;6(A):25–30. **Study results included through another publication**

25. Bruyere O, Burlet N, Delmas PD, et al. Evaluation of symptomatic slow-acting drugs in osteoarthritis using the GRADE system. BMC Musculoskelet Disord 2008;9:165. **Publication type not included in this review**

26. Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage 2008;16(2):254–60. **Outcomes not included in this review**

27. Cannon CP, Curtis SP, Bolognese JA, et al. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program: Cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. American Heart Journal 2006;152(2):237. **Outcomes not included in this review**

28. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006;368(9549). **Outcomes not included in this review**

29. Castelnuovo E, Cross P, Mt-Isa S, et al. Cost-effectiveness of advising the use of topical or oral ibuprofen for knee pain;the TOIB study [ISRCTN: 79353052]. Rheumatology (Oxford) 2008;47(7):1077–81. **Publication type not included in this review**

30. Champion P. Re: Beaulieu AD, Peloso PM, Haraoui B, et al. Once-daily, controlled-release tramadol and sustained-release diclofenac relieve chronic pain to osteoarthritis: a randomized controlled trial. Pain Res Manage 2008;13:103–10, and Thorne C, Beaulieu AD, Callaghan DJ, et. al. A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. Pain Res Manage 2008;13:93–102. Pain Res Manag 2008;13(4):342. **Outcomes not included in this review**

31. Chan FKL, Cryer B, Goldstein JL, et al. A novel composite endpoint to evaluate the gastrointestinal (GI) effects of nonsteroidal antiinflammatory drugs through the entire GI tract. J Rheumatol 2010;37(1):167–74. **Publication type not included in this review**

32. Chang ST, Chen LC, Chang CC, et al. Efficacy and safety of piroxicam beta-cyclodextrin sachets for treating chronic low back pain: a randomized, parallel, active-controlled trial. J Med Sci 2008;28(3):111–9. **Drug not included in this review**

33. Chang ST, Chen LC, Chang CC, et al. Effects of piroxicam-beta-cyclodextrin sachets on abnormal postural sway in patients with chronic low back pain. J Clin Pharm Ther 2008;33(5):495–506. **Drug not included in this review**

34. Charlot M, Ahlehoff O, Norgaard ML, et al. Proton-Pump Inhibitors Are Associated With Increased Cardiovascular Risk Independent of Clopidogrel Use. Ann Intern Med 2010;153(6):378–86. **Publication type not included in this review**

35. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289(19):2560–71. **Publication type not included in this review**

36. Cibere J, Kopec JA, Thorne A, et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. Arthritis Rheum 2004;51(5):738–45. **Study results included through another publication**

37. Cibere J, Thorne A, Kopec JA, et al. Glucosamine sulfate and cartilage type II collagen degradation in patients with knee osteoarthritis: randomized discontinuation trial results employing biomarkers. J Rheumatol 2005;32(5):896–902. **Outcomes not included in this review**

38. Combe B, Swergold G, McLay J, et al. Cardiovascular safety and gastrointestinal tolerability of etoricoxib vs diclofenac in a randomized controlled clinical trial (The MEDAL study). Rheumatology (Oxford) 2009;48(4):425–32. **Outcomes not included in this review**

39. Crofford LJ, Breyer MD, Strand CV, et al. Cardiovascular effects of selective COX-2 inhibition: is there a class effect? The International COX-2 Study Group. J Rheumatol 2006;33(7):1403–8. **Population differs from those in this review**

40. Cross PL, Ashby D, Harding G, et al. TOIB Study. Are topical or oral ibuprofen equally effective for the treatment of chronic knee pain presenting in primary care: a randomised controlled trial with patient preference study. BMC Musculoskelet Disord 2005;6:55. **Study design not included in this review**

41. Curfman GD, Morrissey S, Drazen JM. Expression of concern reaffirmed. N Engl J Med 2006;354(11):1193. **Population differs from those in this review**

42. Curtis SP, Bockow B, Fisher C, et al. Etoricoxib in the treatment of osteoarthritis over 52-weeks: a double-blind, active-comparator controlled trial. BMC Musculoskelet Disord 2005;6:58. **Outcomes not included in this review**

43. Curtis SP, Ko AT, Bolognese JA, et al. Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective Inhibitor etoricoxib. Curr Med Res Opin 2006;22(12):2365–74. **Outcomes not included in this review**

44. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 2009;10(5):501–7. **Population differs from those in this review**

45. D'Ambrosio E, Casa B, Bompani R, et al. Glucosamine sulphate: a controlled clinical investigation in arthrosis. Pharmatherapeutica 1981;(2):504–8. **Study results included through another publication**

46. Dhillon S. Tramadol/paracetamol fixed-dose combination: a review of its use in the management of moderate to severe pain. Clin Drug Invest 2010;30(10):711–38. **Publication type not included in this review**

47. Elwood PC, Gallagher AM, Duthie GG, et al. Aspirin, salicylates, and cancer. Lancet 2009;373(9671):1301–9. **Population differs from those in this review**

48. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet 1999;354(9196):2106–11. **Study results included through another publication**

49. Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? Ann Intern Med 2000;132(2):134–43. **Study results included through another publication**

50. Felson DT. Glucosamine and chondroitin sulfate in knee osteoarthritis: where now? Nat Clin Pract Rheumatol 2006;2(7):356–7. **Population differs from those in this review**

51. Fleischmann R, Sheldon E, Maldonado-Cocco J, et al. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. Clin Rheumatol 2006;25(1):42–53. **Drug not included in this review**

52. Fleischmann R, Tannenbaum H, Patel NP, et al. Long-term retention on treatment with lumiracoxib 100 mg once or twice daily compared with celecoxib 200 mg once daily: a randomised controlled trial in patients with osteoarthritis. BMC Musculoskelet Disord 2008;9:32. **Outcomes not included in this review**

53. Florentinus SR, Heerdink ER, de Boer A, et al. The trade-off between cardiovascular and gastrointestinal effects of rofecoxib. Pharmacoepidemiol Drug Saf 2005;14(7):437–41. **Outcomes not included in this review**

54. Garner SE, Fidan D, Frankish RR, et al. Rofecoxib for rheumatoid arthritis Cochrane Database Syst Rev 2009. **Outcomes not included in this review**

55. Geba G, Weaver, AL, Polis, AB, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee. JAMA 2002;287(1):64–71. **Study results included through another publication**

56. Ghosh S, Paul S, Das N, et al. A study on the effects of diclofenac sodium and etoricoxib in the treatment of osteoarthritis. J Indian Med Assoc 2007;105(5):260–2. **Outcomes not included in this review**

57. Giacovelli G, Rovati LC. Glucosamine and osteoarthritis. Conclusions not supported by methods and results. BMJ 2010;341:c6338. **Publication type not included in this review**

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177. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16(2):137–62. **Population differs from those in this review**

178. Zhang YX, Dong W, Liu H, et al. Effects of chondroitin sulfate and glucosamine in adult patients with Kaschin-Beck disease. Clin Rheumatol 2010;29(4):357–62. **Population differs from those in this review**

Appendix F. Quality Assessment Methods

Individual studies were rated as "good," "fair" or "poor" as defined below*:

Studies rated "good" have the least risk of bias and results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; appropriate measurement of outcomes, and reporting results.

Studies rated "fair" are susceptible to some bias, but it is not sufficient to invalidate the results. These studies do not meet all the criteria for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The "fair" quality category is broad, and 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.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:
Each criterion was give an assessment of yes, no, or unclear.
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
>   Randomization reported, but method not stated
>   Not clear or not reported
>   Not randomized
2. Was the treatment allocation concealed?
Adequate approaches to concealment of randomization:
- Centralized or pharmacy-controlled randomization (randomization performed without knowledge of patient characteristics).
- Serially-numbered identical containers
- On-site computer based system with a randomization sequence that is not readable until allocation
- Sealed opaque envelopes

Inferior approaches to concealment of randomization:
- Use of alternation, case record numbers, birth dates or week days
- Open random numbers lists
- Serially numbered non-opaque envelopes

- Not clear or not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors and/or data analysts 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?

For Cohort Studies:

Each criterion was give an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?
2. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
3. Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?
4. Were outcome assessors and/or data analysts blinded to treatment?
5. Did the article report attrition?
6. Did the study perform appropriate statistical analyses on potential confounders?
7. Is there important differential loss to followup or overall high loss to followup?
8. Were outcomes prespecified and defined, and ascertained using accurate methods?

For Case-Control Studies:

Each criterion was given an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) cases using predefined criteria?
2. Were the controls derived from the same population as the cases, and would they have been selected as cases if the outcome was present?
3. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
4. Did the study report the proportion of cases and controls who met inclusion criteria that were analyzed?
5. Did the study use accurate methods for identifying outcomes?
6. Did the study use accurate methods for ascertaining exposures and potential confounders?
7. Did the study perform appropriate statistical analyses on potential confounders?

Systematic Reviews:
Each criterion was given an assessment of yes, no, unclear, or not applicable.
1. Was an "a priori" design provided?
    The research question and inclusion criteria should be established before the conduct of the review.
2. Was there duplicate study selection and data extraction?
    There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
3. Was a comprehensive literature search performed?
    At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, Embase, and MEDLINE). Key words and/or MeSH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
4. Was the status of publication (i.e., gray literature) used as an inclusion criterion?
    The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.
5. Was a list of studies (included and excluded) provided?
    A list of included and excluded studies should be provided.
6. Were the characteristics of the included studies provided?
    In an aggregated from such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
7. Was the scientific quality of the included studies assessed and documented?
    'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
8. Was the scientific quality of the include studies used appropriately in formulating conclusions?
    The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating the recommendations.
9. Were the methods used to combine the findings of studies appropriate?
    Reviews should not combine or pool dissimilar studies. If studies are pooled using a fixed effects model, there should be a clear rationale for doing so. A test should be done to assess for statistical heterogeneity (i.e., Chi-squared test for homogeneity, I^2).
10. Was the likelihood of publication bias assessed?
    An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test). If assessment of publication bias is not possible, the review should provide justification (e.g., small numbers of studies, too much heterogeneity, poor quality, etc.)

11. Was the conflict of interest stated?
    Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

*Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21–35.

Appendix G. Quality Assessment of Trials, Systematic Reviews, and Observational Studies*

Trials

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Chan, 2007[235]	Yes	Yes	Yes	Yes	Yes	Unclear
Chan, 2010[295]	Yes	Yes	Yes	Yes	No	Yes
Cheung, 2010[82]	Yes	Unclear	Yes	Yes	Unclear	Yes
Dahlberg, 2009[52]	Yes	Unclear	Yes	Yes	Yes	Yes
Dequeker, 1998[60]	Unclear	Unclear	Yes	No	Unclear	Unclear
Dickson, 1991[298]	Unclear	Unclear	Yes	Yes	Unclear	Yes
Emery, 2008[53]	Yes	No	No	Yes	Unclear	Yes
Feng, 2008[116]	Unclear	Unclear	Yes	Yes	Yes	Yes
Furst, 2001[61]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Goldstein, 2000[88]	Yes	Unclear	Yes	Yes	Unclear	Unclear
Goldstein, 2007[254]	Yes	Yes	No	Yes	Yes	Yes
Goldstein, 2010[253]	Yes	Yes	Yes	Yes	Yes	Yes
Hawkey, 1996[63]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Herrero-Beaumont, 2007[206]	Yes	Yes	Yes	Yes	Unclear	Yes
Hosie, 1996[64]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kahan, 2009[209]	Yes	Unclear	Yes	Yes	Yes for radiographs, Unclear for other outcome assessment	Yes
Kosuwon 2010[312]	Yes	Unclear	Yes	Yes	Yes	Yes
Linden, 1996[66]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Mazieres, 2007[210]	Yes	Unclear	Yes	Yes	Unclear	Yes
McKenna, 1998[284]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Messier, 2007[213]	Unclear	Unclear	No	Yes	Unclear	Yes

*Quality ratings for the original 2006 CER available at: Chou R, Helfand M, Peterson K, Dana T, Roberts C. Comparative effectiveness and safety of analgesics for osteoarthritis. Comparative Effectiveness Review No.6 (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-02-0024.). Rockville, MD: Agency for Healthcare Research and Quality, 2006. AHRQ Publication No. 06-EHC009.

Author, Year	Patient Masked?	Reporting of Attrition, Crossovers, Adherence, and Contamination?	Loss to Followup and Attrition: Differential/High?	Intention-to-Treat Analysis?	Quality Rating	Funding
Chan, 2007[235]	Unclear	Yes; Unclear; Yes; Yes	Yes; No	Yes	Fair	Research grant
Chan, 2010[295]	Yes	Yes; No; Yes; No	Yes; Yes	Yes	Fair	Pfizer
Cheung 2010[82]	Yes	Yes; No; No; No	No; No	Yes, >95% included in ITT	Fair	Pfizer
Dahlberg, 2009[52]	Yes	No; No; Yes; No	No; Yes	Yes	Fair	Pfizer
Dequeker, 1998[60]	Yes	No; No; No; No	No; No	No	Fair	Boehringer Ingelheim
Dickson, 1991[298]	Yes	Yes; No; No; No	No; Yes	No	Fair	Pfizer Ltd.
Emery 2008[53]	Yes	Yes; No; Yes; No	Yes; Yes	No	Fair	Pfizer
Feng, 2008[116]	Yes	No; No; Yes; No	Unclear; Unclear	No	Fair	Chinese Government
Furst, 2001[61]	Unclear	No; No; No; No	No; No	No	Fair	Boehringer Ingelheim
Goldstein, 2000[88]	Unclear	No; No; No; No	No; No	Yes	Fair	GD Searle; Pfizer
Goldstein, 2007[254]	Yes	Yes, No, No, No	Yes, No	No	Fair	TAP pharmaceuticals
Goldstein, 2010[253]	Yes	Yes; No; Yes; No	No, Yes	Yes	Fair	AstraZeneca
Hawkey, 1996[63]	Unclear	No; No; No; No	No; No	Unclear	Fair	NR
Herrero-Beaumont, 2007[206]	Yes	Yes; No; Yes; No	No; Yes	Yes	Fair	Rottapharm
Hosie, 1996[64]	Unclear	No; No; No; No	No; No	Yes	Fair	NR
Kahan, 2009[209]	Yes	Yes; No; Yes; No	No; Yes (32% at 2 years)	Yes	Fair	IBSA and Genevrier Laboratories
Kosuwon 2010[312]	Yes	Yes; NA; Yes; No	No; No	Yes, >95% included in ITT	Fair	Faculty of Medicine, Khon Kaen University and Bangkok Drug Company
Linden, 1996[66]	Unclear	No; No; No; No	No; No	No	Fair	NR
Mazieres, 2007[210]	Yes	Yes; No; Yes; No	No; No	Yes	Fair	Pierre Fabre Company
McKenna, 1998[284]	Unclear	No; No; No; No	No; No	Yes	Fair	NR (Pharmacia)
Messier, 2007[213]	Yes	Yes; No; Yes; No	No; No	Yes	Fair	Rexall Sundown

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Michel, 2005[211]	Yes	Unclear	Yes	Yes	Yes for reading radiographs, Unclear for other outcome assessment	Yes
Moller, 2010[212]	Yes	Unclear	Yes	Yes	Unclear	Yes
Rother, 2007[299]	Yes	Yes	Yes	Yes	Unclear	Yes
Rozendaal, 2008[207]	Yes	Yes	Yes	Yes	Yes	Yes
Sandelin, 1997[300]	Unclear	Unclear	Yes	Yes	Unclear	Yes
Sawitzke, 2008[214] Sawitzke, 2010[215]	Yes	Yes	Yes	Yes	Yes	Yes
Scheiman, 2006[261]	Yes	Yes	No	Yes	Yes	Yes
Silverstein, 2000[54]	Yes	Yes	Yes	Yes	Yes	Unclear
Simon, 2009[301]	Yes	Yes	Yes	Yes	Yes	Yes
Temple, 2006[183]	Yes	No	Yes	Yes	No	Yes
Tiso, 2010[302]	Yes	Yes	Yes	Yes	No	No
Tugwell, 2004[303]	Yes	Yes	Yes	Yes	Yes	Yes
Underwood, 2007[49]	Yes	Yes	Yes	Yes	No	No
Valat, 2001[67]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Wilkens, 2010[208]	Yes	Yes	Yes	Yes	Unclear	Yes
Wojtulewski, 1996[68]	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Reporting of Attrition, Crossovers, Adherence, and Contamination?	Loss to Followup and Attrition: Differential/High?	Intention-to-Treat Analysis?	Quality Rating	Funding
Michel, 2005[211]	Yes	Yes; No; Yes; No	No; Yes	Yes	Fair	NR
Moller, 2010[212]	Yes	Chondroitin: 9.4% Placebo: 20%	Yes; No	No	Fair	Bioiberica
Rother, 2007[299]	Yes	Yes; Yes; Yes; No	No; No	Yes	Good	IDEA AG and McNeall Consumer and Specialty Pharmaceuticals
Rozendaal, 2008[207]	Yes	Yes; No; Yes; No	No; No	Yes	Good	Erasmus Medical Center
Sandelin, 1997[300]	Yes	Unclear; No; No; No	Unclear; Unclear	Yes	Fair	NR
Sawitzke, 2008[214] Sawitzke, 2010[215]	Yes	Yes; No; Yes; No	No; No	Yes	Good	NIH
Scheiman, 2006[261]	Yes	Yes, No, No, No	Yes, No	Yes	Fair	AstraZeneca
Silverstein, 2000[54]	Yes	No; No; No; No	No; No	No	Good	Pharmacia
Simon, 2009[301]	Yes	Yes; No; No; No	No; No	Yes	Good	Nuvo Research Inc
Temple, 2006[183]	Yes	Yes; No; Yes; No	Yes; Yes	Yes	Fair	McNeil Consumer & Specialty Pharmaceuticals
Tiso, 2010[302]	No	Yes; No; No; No	No; No	Yes	Fair	Helm Pharmaceuticals
Tugwell, 2004[303]	Yes	Yes; No; Yes; No	No; No	Yes	Good	Dimethaid Healthcare Ltd.
Underwood, 2007[49]	No	Yes; Yes; Yes; Yes	No; Yes	No	Fair	NHS Health Technology Programme
Valat, 2001[67]	Unclear	No; No; No; No	No; No	Yes	Fair	NR
Wilkens, 2010[208]	Yes	Yes; No; Yes; No	No; No	Yes	Good	Norwegian Foundation for Health and Rehabilitation
Wojtulewski, 1996[68]	Unclear	No; No; No; No	No; No	Yes	Fair	NR

NA = not applicable; NR = not reported; NSAID = nonsteroidal antiinflammatory drug; QR = quality result; RA = rheumatoid arthritis

Systematic Reviews

Author, Year	A Priori Design Provided?	Duplicate Study Selection and Data Extraction? a. Study Selection b. Data Extraction	Comprehensive Literature Search Performed?	Status of Publication Used as an Inclusion Criteria?	List of Studies (Included and Excluded) Provided?	Characteristics of the Included Studies Provided?
Bjordal, 2007[197]	Yes	Unclear; Unclear	Yes	Yes	Yes; No	Yes
Caldwell, 2006[111]	Yes	Yes; Yes	Yes	Yes	Yes; No	Yes
Chen et al., 2008[58]	Yes	Yes; Yes	Yes	Yes	Yes;Yes	Yes
Hochberg, 2010[199]	Yes	Unclear; Yes	No	Unclear	No	Yes
Juni, 2004[127]	Yes	Unclear; Yes	Yes	Yes	Yes; No	Yes
Kearney et al., 2006[121]	Yes	Unclear; Unclear	Yes	Yes	Yes; No	Yes
Lee, 2004[179]	Yes	Unclear; Unclear	Yes	Yes	Yes; Yes	Yes
Lee, 2010[200]	Unclear	Unclear; Unclear	Yes	No	No	Yes
Masso Gonzalez, 2010[97]	Yes	Unclear; Yes	No	No	Yes; No	Yes
Moore, 2005[51]	Yes	Unclear; Unclear	Yes	Yes	Yes; No	No
Niculescu, 2009[170]	Yes	No; No	No	Yes	No	Yes
Rostom, 2007[81]	Yes	Yes; Yes	Yes	Yes	Yes; No	Yes
Rostom, 2002[264]	Yes	Yes; Yes	Yes	Yes	Yes; No	No
Rubenstein, 2004[166]	Yes	Yes; Yes	Yes	Yes	Yes; Yes	Yes
Solomon, 2008[114]	Yes	Unclear; Yes	Unclear	Yes	Yes; No	Yes
Soni, 2009[165]	Unclear	No; Unclear	No	No	Yes; No	Yes
Towheed, 2006[180]	Yes	Yes; Yes	Yes	Yes	Yes; Yes	Yes
Towheed, 2006[70]	Yes	Yes; Yes	Yes	Yes	Yes; No	Yes
Trelle 2011[115]	Yes	Yes; Yes	Yes	Yes	Yes; No	Yes
Vlad, 2007[201]	Yes	Unclear; Unclear	Yes	Yes	No	No
Watson, 2006[57]	Yes	Unclear; Unclear	No	Yes	Yes; No	Yes
Wegman, 2004[181]	Yes	Unclear; Unclear	Yes	Yes	Yes; Yes	Yes
White, 2003[112]	Yes	Unclear; Unclear	No	Yes	Yes; No	No
White, 2007[113]	Yes	Unclear; Yes	No	Yes	Yes; No	No
Zhang, 2004[182]	Yes	Unclear; Yes	Yes	Yes	Yes; Yes	No
Zhang, 2006[157]	Unclear	Unclear; Yes	Yes	Unclear	Yes; No	Yes

Author, Year	Scientific Quality of Included Studies Assessed and Documented?	Scientific Quality of the Included Studies Used Appropriately in Formulating Conclusions?	Methods Used to Combine the Findings of Studies Appropriate?	Likelihood of Publication Bias Assessed?	Conflict of Interest Stated? a. Systematic Review b. Individual Studies	Quality Rating
Bjordal, 2007[197]		Yes	Yes	No	Yes; No	Fair
Caldwell, 2006[111]	No	No	Yes	Yes	Yes; No	Fair
Chen et al., 2008[58]	Yes	Yes	Yes	No	Yes; No	Good
Hochberg, 2010[199]	Yes	Yes	Yes	No	Yes; No	Fair
Juni, 2004[127]	Yes	Yes	Yes	Yes	Yes; Yes	Good
Kearney et al., 2006[121]	No	No	Yes	Yes	Yes; No	Fair
Lee, 2004[179]	Yes	Yes	Yes	Yes	Yes; Yes	Good
Lee, 2010[200]	Yes	Unclear	Yes	Yes	No; No	Fair
Masso Gonzalez, 2010[97]	No	No	Yes	No	Yes; No	Fair
Moore, 2005[51]	Yes	No	No	Yes	Yes; Yes	Fair
Niculescu 2009[170]	Yes	No	Unclear	No	Yes; No	Poor
Rostom, 2007[81]	Yes	Yes	Yes	No	No; No	Fair
Rostom, 2002[264]	Yes	Yes	No	Yes	Yes; No	Fair
Rubenstein, 2004[166]	Yes	Yes	NA	No	Yes; No	Good
Solomon, 2008[114]	No	No	No	Yes	Yes; Yes	Fair
Soni, 2009[165]	No	No	Yes	No	Yes; No	Fair
Towheed, 2006[180]	Yes	Yes	Yes	Yes	Yes; Yes	Good
Towheed, 2006[70]	Yes	Yes	Yes	No	Yes; No	Fair
Trelle 2011[115]	Yes	Yes	Yes	Yes	Yes; No	Good
Vlad, 2007[201]	Yes	Yes	Yes	Yes	Yes; Yes	Good
Watson, 2006[57]	No	No	No	No	Yes; No	Poor
Wegman, 2004[181]	Yes	Yes	Yes	No	Yes; No	Fair
White, 2003[112]	No	No	No	No	Yes; Yes	Poor
White, 2007[113]	No	No	No	No	No; No	Poor
Zhang, 2004[182]	Yes	Yes	Yes	Yes	Yes; No	Good
Zhang, 2006[157]	No	Unclear	Yes	Yes	Yes; No	Fair

RA = rheumatoid arthritis

Cohort Studies

Author, Year	Did the Study Attempt to Enroll all (or a Random Sample of) Patients Meeting Inclusion Criteria, or a Random Sample (Inception Cohort)?	Were the Groups Comparable at Baseline on key Prognostic Factors (e.g., by Restriction or Matching)?	Did the Study use Accurate Methods for Ascertaining Exposures, Potential Confounders, and Outcomes?	Were Outcome Assessors and/or Data Analysts Blinded to Treatment?	Did the Article Report Attrition?	Did the Study Perform Appropriate Statistical Analyses on Potential Confounders?	Is There Important Differential Loss to Followup or Overall High Loss to Followup?	Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods?	Quality Rating
Cunnington, 2008[148]	Yes	No	Yes	Unclear	Unclear	Yes	Unclear	Yes	Fair
Fosbol, 2009[149]	Yes	No	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair
Gislason, 2009[160]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Hudson, 2005[161]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Ko, 2002[257]	Yes	No	Yes	Yes	No	Yes	Unclear	Yes	Fair
Kurth, 2003[260]	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Fair
Mamdani, 2002[106]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Mamdani, 2003[140]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Mamdani, 2004[162]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Mann, 2004[109]	No	N/A	Yes	Unclear	No	No	Unclear	Yes	Fair
Mellemkjar, 2002[107]	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Yes	Fair
Patel, 2004[259]	No	No	Yes	Yes	No	Yes	Unclear	Yes	Fair
Rahme & Nedjar, 2007[108] *Rheumatology*	Yes	No	Yes	Unclear	No	Unclear	Unclear	Yes	Fair
Rahme, 2007 *Arthritis and Rheumatism*[130]	Yes	No	Yes	Yes	No	Yes	Unclear	Yes	Fair
Rahme, 2007[130] *Pharmacoepidemiology and Drug Safety*	Yes	No	Yes	Unclear	No	Unclear	Unclear	Yes	Fair
Ray, 2007[297]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Ray, 2002[142]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Solomon, 2008[114]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Solomon 2010[114]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Velentgas, 2006[146]	Yes	Yes	Yes	Yes	No	No	Unclear	Yes	Fair

Case-Control Studies

Author, Year	Did the Study Attempt to Enroll all or Random Sample of Cases Using Predefined Criteria?	Were the Controls Derived From the Same Population as the Cases? Would They Have Been Selected as Cases if the Outcome was Present?	Were the Groups Comparable at Baseline on key Prognostic Factors (e.g., by Restriction or Matching)?	Did the Study Report the Proportion of Cases and Controls who met Inclusion Criteria That Were Analyzed?	Did the Study use Accurate Methods for Identifying Outcomes?
Andersohn, 2006[132]	Yes	Yes; Yes	Yes	No	Yes
Fischer, 2005[133]	Yes	Yes; Yes	No	No	Yes
Garcia-Rodriguez, 2004[134]	Yes	Yes; Unclear	Yes	Yes	Yes
Garcia-Rodriguez, 2000[237]	Yes	Yes; Yes	No	No	Yes
Garcia-Rodriguez, 2001[98]	Yes	Yes; Yes	Yes	No	Yes
Garcia-Rodriguez, 2007[102]	Yes	Yes; Yes	Yes	Yes	Yes
Graham, 2005[135]	Yes	Yes; Yes	Yes	No	Yes
Helin-Salmivaara, 2006[129]	Yes	Yes; Yes	No	No	Yes
Hippisley-Cox, 2005[136]	Yes	Yes; Yes	Yes	No	Yes
Johnsen, 2005[137]	Yes	Yes; Yes	Yes	No	Yes
Kimmel, 2005[138]	Yes	Yes; Yes	No	No	Yes
Lanas, 2006[104]	Yes	Yes; Yes	No	Yes	Yes
Laporte, 2004[105]	Yes	Yes; Yes	Yes	Unclear	Unclear
Levesque, 2005[139]	Yes	Yes; Yes	Yes	Yes	Yes
Mamdani, 2002[140]	Yes	No; No	Yes	Unclear	No
Mann, 2004[109]	No	N/A	Yes	Unclear	No
Mellemkjar, 2002[107]	Yes	Unclear	Yes	Unclear	Yes
Patel, 2004[259]	Yes	Yes; Yes	Yes	No	Yes
Rahme&Nedjar, 2007[108]	Yes	No; No	Yes	Unclear	No
Rahme, 2002[141]	Yes	Yes; Yes	Yes	Yes	Yes
Ray, 2007[297]	Yes	No; No	Yes	Unclear	No
Schlienger, 2002[143]	Yes	Yes; Yes	Yes	No	Yes
Solomon, 2002[144]	Yes	Yes; Yes	Yes	No	Yes
Solomon, 2004a[145]	Yes	Yes; Yes	Unclear	No	Yes

Author, Year	Did the Study use Accurate Methods for Ascertaining Exposures and Potential Confounders?	Did the Study Perform Appropriate Statistical Analyses on Potential Confounders?	Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods?	Quality Rating
Andersohn, 2006[132]	Yes	Yes	Yes	Fair
Fischer, 2005[133]	Yes	Yes	Yes	Fair
Garcia-Rodriguez, 2004[134]	Yes	Yes	Yes	Fair
Garcia-Rodriguez, 2000[237]	Yes	Yes	Yes	Fair
Garcia-Rodriguez, 2001[98]	No	Unclear	Yes	Fair
Garcia-Rodriguez, 2007[102]	Yes	Yes	Yes	Good
Graham, 2005[135]	Yes	Yes	Yes	Fair
Helin-Salmivaara, 2006[129]	Yes	Yes	Yes	Fair
Hippisley-Cox, 2005[136]	Yes	Yes	Yes	Fair
Johnsen, 2005[137]	Yes	Yes	Yes	Fair
Kimmel, 2005[138]	Yes	Yes	Yes	Fair
Lanas, 2006[104]	Yes	Yes	Yes	Good
Laporte, 2004[105]	Yes	Yes	Yes	Fair
Levesque, 2005[139]	Yes	Yes	Yes	Good
Mamdani, 2002[140]	Yes	Unclear	Yes	Fair
Mann, 2004[109]	No	Unclear	Yes	Fair
Mellemkjar, 2002[107]	Unclear	Unclear	Yes	Fair
Patel, 2004[259]	Yes	Yes	Yes	Fair
Rahme&Nedjar, 2007[108]	Unclear	Unclear	Yes	Fair
Rahme, 2002[141]	Yes	Yes	Yes	Fair
Ray, 2007[297]	Yes	Unclear	Yes	Fair
Schlienger, 2002[143]	Yes	No	Yes	Fair
Solomon, 2002[144]	Yes	Yes	Yes	Fair
Solomon, 2004a[145]	Yes	Yes	Yes	Fair

Appendix H. Evidence Tables: Oral NSAIDs

Oral NSAID Trials

Author Year	Subjects	Demographics (age, Gender, Race)	Comparison (mg)		Number of Subjects	Duration (Weeks)	Aspirin Permitted?
Chan, 2007[235]	Arthritis (OA, RA and others)	Mean age: 71 years 52% female	Celecoxib 200	Esomeprazole 20	273	52	No
Cheung, 2010[82]	OA or RA	Age range:18-88 years Mean age= 51 years 83% Female Race: 100% Asian	Celecoxib 100	Diclofenac 50	759	12	Yes
Dahlberg, 2009[52]	Knee or hip osteoarthritis	Mean age: 71 years Female: 69% Race: NR	Celecoxib 200	Diclofenac 50	925	52	Unclear
Emery, 2008[53,]	OA hip	Mean age: 64 years 46% Female Race: 99% White	Celecoxib 200	Diclofenac 50 mg	249	12	Unclear
Goei The, 1997[62]	OA knee	Mean age: 71 years Female: 81.9% Race: NR	Meloxicam 7.5	Diclofenac 100	258	6	Yes
Goldstein, 2000[88]	OA and RA with no ulcer on EGD	Mean age: 57 years Female: 57% White: 84% Black: 13% Hispanic: 4%	Celecoxib 200	Naproxen 500	537	12	Yes (included in study)
Goldstein, 2007[254]	OA without history of ulcer taking low-dose ASA	Mean age: 56.7 years Female: 66% White: 72% Black: 13% Hispanic: 11% Asian: 2% Other: 2%	Celecoxib 200	Naproxen 500 + Lansoprazole 30	1045	12	Yes (included in study)
Goldstein 2010[253], included two Phase III studies	H pylori negative patients with OA, RA, ankylosing spondylitis or other condition requiring daily NSAID therapy	Mean age: 60 years Female: 67% White: 86% Black: 12% Other: 2%	enteric-coated naproxen 500 mg and immediate-release esomeprazole 20 mg	Enteric-coated naproxen 500	438; 423	26	Yes

Author Year	Efficacy Measures	Withdrawals due to Adverse Events		Other Outcomes	Run-in/ Washout	Class Naïve Patients Only
Chan, 2007[235]	PGA, pain	NR	NR	Combination therapy with PPI was more effective in preventing ulcers	NR/NR	No
Cheung 2010[82]	Incidence of GI ulcers	3%	6%	Incidence of GI ulcer celecoxib vs. diclofenac 2.8% vs. 5.1%; p =0.083	NR/NR	No
Dahlberg, 2009[52]	Pain, Physician and patient PGA and adverse events	27%	31%	No difference	Unclear/NR	No
Emery, 2008[53]	Patient and Physician GA	10%	15%	Improvement in GA with Celecoxib vs. Diclofenac	NR/10 days-2 weeks	No
Goei The, 1997[62]	Pain during active movement, PGA, acetaminophen use	3.9%	2.3%	No difference, trend favored meloxicam	NR/7 day minimum	No
Goldstein, 2000[88]	PGA, withdrawals	7.0%	9.0%	No difference in adverse event severity.	NR/NR	No
Goldstein, 2007[254]	Joint pain, GI complications and GDU incidence at final visit	6.3%	6.6%	No difference	Unclear/NR	No
Goldstein 2010[253], included two Phase III studies	Ulcer incidence, other harm related outcomes	9.3%; 9.4%	15.7%14.2%	Enterica coded with PPI protective	Unclear/14 days	No

Author Year	Subjects	Demographics (age, Gender, Race)	Comparison (mg)		Number of Subjects	Duration (Weeks)	Aspirin Permitted?
Hawkey, 1998[281] (MELISSA)	OA hip, knee, hand, or spine	Mean age: 61 years Female: 67% Race: NR	Meloxicam 7.5	Diclofenac 100	9323	4	Unclear
Hosie, 1996[64]	OA hip or knee	Mean age: 64 years Female: 68% Race: NR	Meloxicam 7.5	Diclofenac 100	336	24	Unclear
Hosie, 1997[65]	OA hip or knee	Mean age: 65 years Female: 55% Race: NR	Meloxicam 15	Piroxicam 20	455	24	Unclear
Linden, 1996[66]	OA hip	Mean age: 67 years Female: 63% Race: NR	Meloxicam 15	Piroxicam 20	255	6	Unclear

Author Year	Efficacy Measures	Withdrawals due to Adverse Events		Other Outcomes	Run-in/ Washout	Class Naïve Patients Only
Hawkey, 1998[281] (MELISSA)	Pain, PGA, withdrawals	1.7%	1.0%	No difference, trend slightly favored meloxicam	NR/washout 3 days	No
Hosie, 1996[64]	Pain, quality of life	4.0%	4.2%	No difference	NR/washout 3 days	No
Hosie, 1997[65]	Overall pain, pain on movement, joint stiffness, global efficacy and quality of life	57.0%	15.0%	No difference	NR/ 7 day minimum	No
Linden, 1996[66]	Pain, pain on active movement, global efficacy, withdrawals	9.3%	7.9%	No difference	NR/washout 3-7 days	No

Author Year	Subjects	Demographics (age, Gender, Race)	Comparison (mg)		Number of Subjects	Duration (Weeks)	Aspirin Permitted?
Scheiman, 2006;[262] Includes two similar RCT	At risk of ulcer (age 60 or greater or history of ulcer within past 5 yr) and taking NSAID for OA or RA	Mean age: 64 years Female: 72% Race: NR	COX-2 + esomeprazole 20 or 40	COX-2 + placebo	844; 585	26	Yes
Silverstein, 2000[52] (CLASS)	OA and RA	Mean age: 60 years Female: 69% White: 88.2%; Black: 7.7%; Hispanic: 2.8%; Asian: 0.8%	Celecoxib 400	Ibuprofen 800 or diclofenac 75	7968	24	Yes
Valat, 2001[65]	OA lumbar spine	Mean age: 58 years Female: 82% Race: NR	Meloxicam 7.5	Diclofenac 100	229	2	Unclear
Wojtulewski, 1996[66]	RA	Aged 18-75 years Gender and race: NR	Meloxicam 7.5	Naproxen 750	379	24	No

Author Year	Efficacy Measures	Withdrawals due to Adverse Events		Other Outcomes	Run-in/ Washout	Class Naïve Patients Only
Scheiman, 2006;[261] Includes two similar RCT	Related to ulcer development including pain and other symptoms	4.2% 20 mg 8.3% 40 mg	11% 20 mg 18% 40 mg	PPI reduced risk compared to placebo. COX-2 users: 16.5% placebo vs. 0.9% 20 mg esomeprazole (P < 0.001) non-selective NSAID: 17.1% placebo vs. 6.8% 20 mg esomeprazole (P <0.001).	NR/NR	No
Silverstein, 2000[54] (CLASS)	No efficacy measures reported except withdrawals	18.4%	20.6%	No difference	NR/NR	No
Valat, 2001[67]	Pain on motion	0.0%	0.0%	No difference	NR/washout 3-7 days	No
Wojtulewski, 1996[68]	PGA, several others	23.6%	14.4%	No difference, trend favored naproxen	NR/washout 3-11 days	No

ASA = aspirin; CLASS = Celecoxib Long-term Arthritis Safety Study; COX = cyclo-oxygenase; EGD = esophagogastroduodenoscopy; GDU = gastroduodenal ulcer; GI = gastrointestinal; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PPI = proton pump inhibitor; RA = rheumatoid arthritis RCT = randomized controlled trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Oral NSAID Systematic Reviews

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Caldwell, 2006[111]	To examine whether the increased risk ofcardiovascular events with rofecoxib represents a class effect of COX-2 specific inhibitors (celecoxib).	Searches through April 2005MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ACP Journal Club, Database of Abstracts of Review of Effects, EMBASE, FDA website, requested additional data from Pfizer (none provided)	RCTs of celecoxib of at least 6 weeks duration and reported serious cardiovascular thromboembolic events	12,780 (6,859 randomized to celecoxib)	6 RCTs: 3 celecoxib vs. placebo, 1 celecoxib vs. another NSAID, 1 celecoxib vs. another NSAID vs. placebo, 1 celecoxib vs. paracetamol	Osteoarthritis (2 trials) Mixed osteoarthritis or rheumatoid arthritis (1 trial) Prevention of colorectal carcinoma recurrence (2 trials) Prevention of Alzheimer's disease (1 trial)

Author Year	Characteristis of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events
Caldwell, 2006[111]	2 trials 6 weeks in duration, 2 trials 52 weeks in duration, 1 trial 156 weeks in duration, 1 trial 145-161 weeks in duration	--	--	Celecoxib vs. placebo: Myocardial infarction (n=2574 vs. n=1247): RR 2.3 (1.0, 5.1); Cerebrovascular event (n=2775 vs. n=1447): RR 1.0 (0.51, 1.8); Cardiovascular death (n=2574 vs. n=1247): RR 1.06 (0.38, 3.0); Composite cardiovascular events (n=2775 vs. n=1447): RR 1.4 (0.91, 2.1); Celecoxib vs. placebo, diclofenac, ibuprofen, or paracetamolMyocardial infarction (n=6658 vs. n=5522): RR 1.9 (1.2, 3.1); Cerebrovascular event (n=6859 vs. n=5921): RR 0.73 (0.42, 1.3); Cardiovascular death (n=6561 vs. n=5428): RR 1.0 (0.52, 2.0); Composite cardiovascular events (n=6859 vs. n=5921): RR 1.2 (0.92, 1.6)

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Chen, et al 2008[58]	To review the clinical and cost effectiveness of COX-2s for OA and rheumatoid arthritis RA	Cochrane Library through Issue 4, 2003; Ovid MEDLINE 1966-October 2003; Ovid MEDLINE In-Process and Other Non-Indexed Citations November 4 and 11, 2003; EMBASE 1980-October 2003; EMEA and FDA websites	RCTs with duration of treatment ≥2 weeks; OA or RA population; COX-2 vs. placebo, nonselective NSAID or other COX-2	Etodolac n=5,775 Meloxicam n=22,886 Celecoxib n=NR	Etodolac: 29 RCTs; etodolac vs. naproxen, piroxicam, diclofenac , indomethacin, tenoxicam, ibuprofen, nabumetone, nimesulide, placebo Meloxicam: 16 RCTs; meloxicam vs. diclofenac, piroxicam, nabumetone, naproxen nabumetone, placebo; 11 abstracts reporting adverse event outcomes also included in meta-analysis but not quality-rated Celecoxib: 40 RCT; celecoxib vs. naproxen, diclofenac, dexibuprofen, acetaminophen, ibuprofen, rofecoxib, lumiracoxib, placebo	OA (63 trials), RA (15 trials) or both (7 trials)

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events
Chen, et al 2008[58]	Etodolac 300-1000 mg/day vs. naproxen 750-1000 mg/day (10 studies), piroxicam 20 mg/day (7 studies), diclofenac 100-150 mg/day (4 studies), indomethacin 100-150 mg/day (2 studies); tenoxicam 20 mg/day (2 studies), nimesulide 200 mg/day (1 study), nabumetone 1500 mg/day (1 study), ibuprofen 2400 mg/day (1 study) Meloxicam 3.75-15 mg/day vs. diclofenac 100-150 mg/day (6 studies), piroxicam 20 mg/day (5 studies), nabumetone 1000 mg/day (2 studies), naproxen 750 mg/day (1 study) Celecoxib 80-800 mg/day vs. naproxen 1000 mg/day, diclofenac 100-150 mg/day, acetaminophen 4000 mg/day, ibuprofen 1000 mg/day (not all interventions and doses could be listed and number of studies for each intervention could not be accurately determined; information from some studies not reported)	Etodolac vs. NSAIDs Mean difference, pain score: 2.06 (CI -2.09 to 6.22) Mean difference, global efficacy: -0.08 (CI -0.25 to 0.09) Withdrawals due to lack of efficacy RR 1.00 (CI 0.85 to 1.19) Meloxicam vs. NSAIDs Mean difference, pain score: 1.7 (CI 0.8 to 2.7) Mean difference, global efficacy: -0.05 (CI -0.25 to 0.15) Withdrawals due to lack of efficacy RR 1.47 (CI 1.24 to 1.73) Celecoxib vs. NSAIDs Mean difference, pain score: -0.42 (CI -2.4 to 1.6) Mean difference, global efficacy: 0 (-0.05 to 0.03) ACR-20 RR 1.00 (CI 0.89 to 1.14) Withdrawals due to lack of efficacy RR 0.94 (CI 0.77 to 1.14)	Etodolac vs. NSAIDs No analysis; 1 trial reported higher AE incidence in patients >65 yrs in etodolac and placebo groups Meloxicam vs. NSAIDs No analysis; two studies reported lower AE rates in patients >65 yrs in meloxicam arms relative to piroxicam and diclofenac Celecoxib vs. NSAIDs Risk of POBs, concomitant low-dose aspirin use: comparative RR 2.82; p=0.138 Risk of PUBs, concomitant low-dose aspirin use: comparative RR 0.67; p=0.04 Risk of MI, concomitant low-dose aspirin use: comparative RR 2.24; p=0.121	Etodolac vs. NSAIDs All-cause withdrawals RR 0.97 (CI 0.90 to 1.05) Withdrawals due to AEs RR 0.93 (CI 0.77 to 1.12) Withdrawals due to GI AEs RR 0.95 (CI 0.54 to 1.65) Any AE incidence RR 0.83 (CI 0.70 to 0.99) GI AE incidence RR 0.77 (CI 0.55 to 1.08) PUBs RR 0.32 (CI 0.15 to 0.71) POBs RR 0.39 (CI 0.12 to 1.24) Meloxicam vs. NSAIDs All-cause withdrawals RR 0.86 (CI 0.77 to 0.96) Withdrawals due to AEs RR 0.92 (CI 0.66 to 1.28) Withdrawals due to GI AEs RR 0.61 (CI 0.54 to 0.69) Any AE incidence RR 0.91 (CI 0.84 to 0.99) GI AE incidence RR 0.31 (CI 0.24 to 0.39) PUBs RR 0.53 (CI 0.29 to 0.97) POBs RR 0.56 (CI 0.27 to 1.15) MI RR 0.33 (CI 0.01 to 8.03) Serious CV events 0.99 (CI 0.06 to 15.9) Celecoxib vs. NSAIDs All-cause withdrawals RR 0.93 (CI 0.84 to 1.05) Withdrawals due to AEs RR 0.86 (CI 0.73 to 1.00) Withdrawals due to GI AEs RR 0.45 (CI 0.35 to 0.56) Any AE incidence RR 0.96 (CI 0.91 to 1.01) GI AE incidence RR 0.90 (CI 0.78 to 1.04) PUBs RR 0.55 (CI 0.40 to 0.76) POBs RR 0.57 (CI 0.35 to 0.95) MI RR 1.77 (CI 1.00 to 3.11) Serious CV events RR 0.99 (CI 0.54 to 1.79)

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Kearney, 2006[121]	To assess the effects of selective COX-2 inhibitors and traditional NSAIDs on the risk of vascular events	January 1966-April 2005 (MEDLINE and Embase)	RCTs at least 4 wks "scheduled treatment" of COX-2 vs. placebo or NSAID that reported serious CV events	145,373	only described as RCTs (n=138); either placebo (n=121) or active	Numerous indications, including: RA, OA, low back pain, ankylosing spondylitis, polyps and Alzheimer's Disease.

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
Kearney, 2006[121]	Randomized trials that included a comparison of a selective COX-2 inhibitor versus placebo or a selective COX-2 inhibitor versus a traditional NSAID, of at least four weeks' duration, with information on serious vascular events. 41 Celecoxib trials, 17 Etoricoxib trials, 12 Lumiracoxib trials, 14 Valdecoxib trials.	NA	No subgroup analysis	COX-2 vs. placebo short- and long-term studies: COX-2s associated with increase in rate of MI - 0.6%/yr vs. 0.3%/yr (RR 1.86 CI 95% 1.33 to 2.59, p=0.0003) RR or all vascular events increases to 1.45 (95% CI 1.12 to 1.80, p=0.0003) when only long-term (>1 yr) were analyzed.

COX-2 vs. NSAID: Overall RR of any vascular event among heterogeneous studies 1.0%/yr vs. 0.9%/yr was 1.16 (CI 95% 0.97 to 1.38, p=0.1) | Quality of included studies not considered

Of 121 placebo trials, nine were long-term. 2/3 of CV events occurred in long-term trials. |

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Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Lee, 2004[179]	To compare efficacy and safety of recommended doses of NSAIDs, including Cox 2 inhibitors, vs. acetaminophen in the treatment of symptomatic hip and knee osteoarthritis	1966 through February 2003 MEDLINE 1991 to 1st quarter 2003 EMBASE Drugs and Pharmacy database	Original clinical trials with direct comparisons of an NSAID with acetaminophen or paracetamol without combination with a nonnarcotic analgesic or narcotic agent. Duration of NSAID exposure $\geq$ 7 days. Sufficient analyzable data	1252	7 clinical trials: 2 randomized active comparator trials without placebo arms, 2 randomized parallel-group double-blinded trials, 2 randomized crossover trials, and 1 randomized placebo-controlled double-blinded trial.	All trials included patients with knee OA, and 2 also included patients with hip OA. 71% were women.

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
Lee, 2004[179]	1 study compared acetaminophen to placebo, and 5 compared acetaminophen to NSAIDs. Acetaminophen dose ranged from 2600 mg/d (1 study) to 4000 mg/d (5 studies). Mean duration of trials was 22 weeks, with a range from 6 days to 2 years. If outlier study (104 weeks) removed, mean duration was 5.8 weeks.	Acetaminophen vs. placebo Based on 1 cross-over, double-blind RCT Improvement in rest pain: 16/22 (73%) vs. 2/22 (9%) Improvement in pain on motion:15/22 (68%) vs. 4/22 (18%) Physician global assessment: 20/21 (95%) vs. 1/21 (5%) Patient global assessment:10/10 (100%) vs. 1/10 (10%) Acetaminophen vs. NSAIDS : absolute values not available except for global assessment Rest pain and HAQ pain: NSAIDs superior to acetaminophen. Rest pain effect sizes measured by SMD: 0.32(95% CI, 0.08 to 0.56) and 0.34 (95% CI, 0.10 to 0.58). HAQ pain: 0.27 (95% CI, 0.05 to 0.48) and 0.24 (95% CI, 0.03 to 0.45). Pain on motion: SMDs not significant. Physical function: Neither 50 foot walk time nor HAQ showed significant differences between NSAIDs and acetaminophen. Group 1 (ibuprofen 2400 mg, Arthrotec, celecoxib, naproxen) Physician global assessment: 23/61 (38%) vs. 23/61 (38%) Patient global assessment: 37/94(39%) vs. 45/97(46%) Group 2 (ibuprofen 1200 mg, Arthrotec, rofecoxib 25 mg, naproxen) Physician global assessment: 23/61(38%) vs. 27/62 (44%) Patient global assessment: 37/94 (39%) vs. 57/95 (60%) Group 3 (ibuprofen 1200 mg, Arthrotec, rofecoxib 12.5 mg, naproxen) Physician global assessment: not reported Patient global assessment: 37/94 (39%) vs. 54/96 (56%)	Not reported	Acetaminophen vs. Placebo No participant removed from study due to side effects. Withdrawals/total number of AEs: 10/25 (40%) acetaminophen vs. 8/25 (32%) placebo. Acetaminophen vs. NSAIDS Group 1: Total number of AEs: 164/360 (46%) vs. 179/353 (51%). Withdrawals due to toxicity: 35/448 (8%) vs. 38/443 (8%). Group 2: Total number of AEs: 164/360 (46%) vs. 170/352 (48%). Withdrawals due to toxicity: 35/448 (8%) vs. 38/442 (9%). Group 3: Total number of AEs: 164/360 (46%) vs. 180/353 (51%). Withdrawals due to toxicity: 35/448 (8%) vs. 39/443 (9%). GI events, acetaminophen vs. traditional NSAIDs 10/148 (7%) vs. 38/212 (18%) GI events, acetaminophen vs. Coxib NSAIDs 16/94 (17%) vs. 47/288 (16%) GI withdrawals, acetaminophen vs. traditional NSAIDS 9/151 (6%) vs. 24/213 (11%)	Results do not account for differences in baseline pain Most trials had short follow-up periods. 1 included trial was an abstract only (Altman 1999)

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Moore, 2005[51]	The objective was to improve understanding of adverse events occurring with celecoxib in the treatment of osteoarthritis and rheumatoid arthritis.	Trials completed by December 2003 Pfizer supplied company clinical trial reports	RCTs, 2 weeks or longer in duration, any dose of celecoxib and any comparator, in osteoarthritis or rheumatoid arthritis	38,746 (22,192 randomized to celecoxib)	31 RCTs: 12 celecoxib vs. another NSAID, 5 celecoxib vs. placebo, 14 celecoxib vs. another NSAID vs. placebo	Osteoarthritis (21 trials) Rheumatoid arthritis (4 trials) Mixed osteoarthritis or rheumatoid arthritis (6 trials)	All trials 2-12 weeks in duration, with the exception of 1 trial 24 weeks (n=655), 1 trial 52 weeks (n=7968)
Niculescu 2009[170]	To compare the (GI) tolerability of celecoxib and NSAIDs at approved doses in patients with common musculoskeletal conditions.	Pfizer Corporate Clinical Trials Registry available to October 31 2004.	RCTs parallel-group studies; with at least one treatment group receiving celecoxib at a total daily dose of ≥ 200mg or higher; at least one placebo or active comparator (e.g., NSAIDs) group; planned duration ≥2 weeks.	21 studies involving 26,574 patients	21 RCTs. Duration ranged from 6 wks to 1 year. 6 had duration of 6 wks, 13 lasted for 12 wks, 1 lasted for 24 wks and 1 for 52 wks.	Patients had a mean age of 60.7 years, 72.6% were female, (72.7%) were white. 85.9% of patients in these RCTs had OA.	OA/RA: 6993/667 patients received celecoxib total daily dose 200 mg; 5542/950 patients received celecoxib total daily dose 400 mg; 2280/516 patients received naproxen; 408/91 patients who received ibuprofen, and 5010/633 patients who received diclofenac.

Author Year	Main Results	Subgroups	Adverse Events
Moore, 2005[51]	--	--	Myocardial infarction Celecoxib vs. placebo: 0.12% vs. 0.07%, RR not reported (10 events, n=9315) Celecoxib vs. paracetamol: RR not reported (0 events, n=1056) Celecoxib 200-400 mg vs. NSAID to maximum daily dose: 0.15% vs. 0.04%, RR 1.9 (95% CI 0.87 to 4.1) (23 events, n=21,818) Celecoxib any dose vs. NSAID to maximum daily dose: 0.22% vs. 0.14%, RR 1.6 (95% CI 0.93 to 2.6) (56 events, n=30,220) Celecoxib any dose vs. any active comparator: 0.19% vs. 0.13%, RR 1.4 (95% CI 0.88 to 2.2) (57 events, n=34,174) Celecoxib any dose vs. any comparator: 0.18% vs. 0.12%, RR 1.4 (95% CI 0.88 to 2.2) (59 events, n=38,499) Celecoxib any dose vs. any noncoxib: 0.19% vs. 0.12%, RR 1.4 (95% CI 0.88 to 2.2) (57 events, n=36,316)
Niculescu 2009[170]	Safety of Celecoxib vs. drug; RR (95% CI) 1) Naproxen Abdominal pain: 1.42 (1.23–1.63) Dyspepsia: 1.72 (1.51–1.95) Flatulence: 2.06 (1.64–2.60) Nausea: 2.00 (1.68–2.39) 2) Ibuprofen Abdominal pain: 1.19 (1.04–1.36) Dyspepsia: 1.71 (1.30–2.24) Flatulence: 1.48 (0.83–2.62) Nausea: 2.23 (1.58–3.16) 3) Diclofenac Abdominal pain: 1.38 (1.00–1.89) Dyspepsia: 1.07 (0.95–1.21) Flatulence: 1.36 (1.10–1.69) Nausea: 1.17 (0.98–1.38) 4) Pooled NSAIDs Abdominal pain: 1.72 (1.51–1.95) Dyspepsia: 1.07 (0.95–1.21) Flatulence: 1.17 (0.98–1.38)	--	Significant greater proportion of patients treated with naproxen (24.3%), ibuprofen (24.2%), or diclofenac (19.9%) experienced a tolerability-related GI AE (combined incidence of abdominal pain, dyspepsia, nausea and flatulence)

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Rostom, 2002[263]	To determine the frequency of lab and clinical hepatic side effects associated with NSAID use.	MEDLINE, EMBASE and Cochrane through January 2004.	RCTs (>4 wks, >40 pts) in duration of adults with OA or RA including one of the following drugs: celecoxib, rofecoxib, valdecoxib, meloxicam, diclofenac, naproxen or ibuprofen.	Total NR	64 RCTs: designs not specified	Patients age >18 with a diagnosis of OA or RA	18 NSAID vs. placebo; 33 diclofenac studies; 12 ibuprofen studies; 14 naproxen studies; 5 meloxicam studies; 8 rofecoxib studies; 5 celecoxib studies; 1 valdecoxib study.
Rostom, 2007[81]	To assess upper GI harms of long-term COX-2 use	CCRCT through 2005; Cochrane Collaboration library through 2005; MEDLINE 1966-2006; EMBASE 1980-2005	RCTs of COX-2s reporting upper GI toxicity relative to nonselective NSAID or placebo; study participants age ≥18 yrs with osteoarthritis, rheumatoid arthritis or other arthritic condition; NSAID exposure ≥4 wks	31,106 celecoxib vs. nonselective NSAID; other interventions not abstracted (outside scope of report)	4 RCTs celecoxib vs. nonselective NSAID (clinical outcomes)	Not described; all had OA, RA or other arthritic condition per inclusion criteria	Celecoxib doses not specified

Author Year	Main Results	Subgroups	Adverse Events
Rostom, 2002[263]	See Adverse Events	Use of high dose of diclofenac (>100mg/day) was associated with a higher proportion of patients having aminotransferase elevation >3x ULN. No SS differences for other subgroups (high dose rofecoxib; longer duration for all comparators including placebo)	Among all comparisons, no NSAID had higher rates of renal serious adverse events, hospitalizations or death. Diclofenac and rofecoxib both showed higher rates of aminotransferase elevations (>3x ULN) when compared to all other NSAIDs (3.55% [95% CI 3.12 to 4.03] and 1.80% [95% CI 1.52 to 2.13] respectively, vs. <0.43%)
Rostom, 2007[81]	Clinical GI events - celecoxib vs. NSAIDS: PODs (perforation, obstruction or bleeding) RR 0.23 (CI 0.07 to 0.76) PUDs (perforation, obstruction, bleeding or symptomatic ulcer) RR 0.39 (CI 0.21 to 0.73) Sensitivity analysis removing combined analysis study eliminated heterogeneity and results still favored celecoxib	Not reported	Not stratified according to intervention; for all COX-2s vs. NSAIDs: Withdrawals due to GI tolerability RR 0.65 (CI 0.57 to 0.73) Withdrawals due to dyspepsia RR 0.37 (CI 0.18 to 0.74) Withdrawals due to abdominal pain RR 0.25 (CI 0.13 to 0.49) GI symptoms (low-dose COX-2s) RR 0.78 (CI 0.74 to 0.82) Dyspepsia RR 0.83 (CI 0.75 to 0.90) Nausea RR 0.72 (CI 0.64 to 0.82) Abdominal pain RR 0.25 (CI 0.58 to 0.70)

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Rubenstein, 2004[166]	To systematically review the published literature of population-based epidemiological studies reporting the incidence or comparative risk of NSAIDs for liver injury resulting in clinically significant events (defined as hospitalization or death)	MEDLINE, Pre-MEDLINE and EMBASE through 2004.	Case-control, controlled cohort, single cohort population-based studies.	Total NR; 396,392 patient years included in analysis	1 case-control; 1 nested case-control; 2 retrospective single-cohort w/ nested case-control studies; 3 retrospective single-cohort w/out nested case-control.	Patients taking NSAIDs for any indication
Solomon, 2008[114]	inhibitor celecoxib affects CV risk,	Time period covered not specified (publication date 2008) Electronic databases not specified, "asked" NIH and Pfizer for unpublished trials	RCTs that were double-blind and placebo-controlled, planned follow-up at least 3 years	7950 (3664 randomized to celecoxib)	6 RCTs of celecoxib vs. placebo	Prevention of colorectal adenoma recurrence (3 trials) Prevention of recurrent breast cancer in postmenopausal women receiving aromatase inhibitors (1 trial) Prevention of Alzheimer's disease and age-related cognitive decline (1 trial) Treatment of diabetic retinopathy with photocoagulation (1 trial)
Towheed, 2006[180]	To determine which NSAID is most effective and which is most toxic in the treatment of hip OA	1966 - August, 1994 MEDLINE Cochrane Musculoskeletal Group trials register and CCTR through August 1994	RCTs published in English; placebo-controlled comparative treatment w/analgesics or NSAIDs; single and double-blinded trials	Total number of patients not specified, however mean number of randomized patients per trial was 95, with a range from 9 to 455. Mean number of patients completing trial was 81, range of 9 to 397.	43 RCTs: 21 crossover study design and 22 parallel group design.	Eligible participants were any adult (>18) with a diagnosis of primary or secondary OA. 53% of trial participants were women, mean age 63.

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
Rubenstein, 2004[166]	6 studies: unspecified NSAIDs (including any of the following: diclofenac, diflunisal, fenbufen, fenoprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, nimesulide, sulindac, tenoxicam); 2 of these 6 included aspirin. 1 study: diclofenac, naproxen and piroxicam only.	--	Not reported	No SS difference between current NSAID user and past NSAID users in hospitalization rates for liver injury (range 1.2-1.7) Incidence of liver injury resulting in hospitalization ranged from 3.1-23.4/100,000 patient years for current NSAID users, compared to 4.8-8.6/100,000 patient years for past NSAID users.	Assessed adverse events only
Solomon, 2008[114]	Planned followup >=3 years in all trials	--	--	Cardiovascular death, MI, stroke, heart failure, or thromboembolism Celecoxib any dose (101/4286) vs. placebo (52/3664): HR 1.6 (1.1, 2.3) Celecoxib 400 mg QD (30/1347) vs. placebo (20/1038): HR 1.1 (0.6, 2.0) Celecoxib 200 mg bid (38/1450) vs. placebo (29/1809): HR 1.8 (1.1, 3.1) Celecoxib 400 mg bid (33/1489) vs. placebo (11/1496): HR 3.1 (1.5, 6.1)	Risk increased from low to moderate CV risk groups (HR 2.0 [1.5, 2.6]) and from low-risk to high-risk groups (HR 3.9 [2.3, 6.7]). Celecoxib associated with increased risk regardless of baseline aspirin use
Towheed, 2006[180]	Placebo: etodolac, tenoxicam, ketoprofen, diacerhein\n\nHead to head: flurbiprofen vs. sulindac diclofenac vs. naproxen proquazone vs. naproxen piroxicam vs. naproxen diclofenac vs. ibuprofen sulindac vs. ibuprofen carprofen vs. diclofenac piroxicam vs. indomethacin naproxen vs. indomethacin tenoxicam vs. diacerhein	Efficacy When compared to placebo, all NSAIDs except diacerhein resulted in pain decrease and improvement of global assessment (no RR provided) In head to head trials, no SS difference amongst any of the compared interventions (no RR provided) Low-dose ibuprofen (<1600 mg/day) and low-dose naproxen (<750 mg/day) less efficacious than other NSAIDs An alternative, more sensitive technique of results analysis (Heller, et al) found that indomethacin was more effective than its comparators in 5 of 7 cases.	Not reported	Out of 29 NSAID combinations, 9 revealed clinically relevant differences in toxicity. Indomethacin was found to be more toxic in 7 of these 9 combinations. However, only 6 of the 29 comparisons were tested for SS differences.	SR limited by lack of standardization of OA diagnosis and OA outcomes\n\nResults suggest that best NSAID varies widely depending on a particular patient

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Towheed, 2006[68]	1) To assess the efficacy and safety of acetaminophen vs.placebo for treating participants with OA. 2) To assess the efficacy and safety of acetaminophen vs. other NSAIDs (e.g., ibuprofen, diclofena) for treating participants with OA.	MEDLINE (up to July 2005), EMBASE (2002-July 2005), Cochrane Central Register of Controlled Trials, ACP Journal Club, DARE, CDSR (all from 1994 to July 2005)	Published RCTs evaluating the efficacy and safety of acetaminophen alone in patients with OA.	5986	15 RCTs, 7 of acetaminophen vs. placebo and 10 of acetaminophen vs. NSAIDs. Mean duration of the RCTs=13.1 weeks (duration ranged from 1-104 weeks, median of 6 weeks).	Mean age= 62.2 years (69% female and 31% male). In 3 RCTs included participants with primary OA, 1 RCT enrolled both primary and secondary OA participants and in other 11 RCTs did not specify. In 15 RCTs patients had OA of the knee and in 5, had OA of hip.

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
Towheed, 2006[70]	Dosage of acetaminophen for 12 of the RCTs was 1000 mg four times daily. One trial used 650 mg four times daily	Pooled RR (95% CI): A) SMD: -0.13 (-0.22 to -0.04) B) GI Safety: 1.47 (1.08 to 2.00), patients taking NSAIDs at higher risk	NR	A) Any AE: 1.02 (0.89 to 1.17) in acetaminophen vs. placebo trials B) Withdrawals due to AE: 1.24 (0.87 to 1.77) in acetaminophen vs. placebo.	Update to 2006 review

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Trelle, 2011[115]	To analyze the current evidence availble on CV safety of NSAIDs.	Bibliographica databases, conference proceedings, study registers, FDA website and used the Science Citation Index through July 2009.	RCTs comparing any NSAIDs with other non-NSAIDs, paracetamol (acetaminophen), or placebo for any medical condition. Trials required at least two arms h arms with at least 100 patient years of follow-up.	116429 patients indeified from 31 trials and included 115000 patient years of follow-up.	31 RCTs included: 1) 29 reporting MI with 554 events 2) 26 reporting stroke with 337 events 3) 26 trials with 312 events related to CV death 4) 28 trials with all cause mortality with 676 events	Not specified

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
Trelle, 2011[115]	All NSAIDs vs. placebo	Compared with placebo (rate ratios) A) Risk of MI: Lumiracoxib: 2.00, 95% CI 0.71 to 6.21 B) Risk of stroke: Ibuprofen 3.36, 1.00 to 11.6 Diclofenac 2.86, 1.09 to 8.36 C) Risk of CV Death Etoricoxib: 4.07, 1.23 to 15.7 Diclofenac 3.98, 1.48 to 12.7	--	--	--

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Watson, 2005[57]	To determine difference in efficacy of NSAIDs in treatment of knee OA.	1966 - November, 1996 MEDLINE 1980- December, 1995 EMBASE	Double-blind RCTs published in English evaluating two NSAIDs	not stated	16 RCTs: All double-blind although most failed to report method used to achieve double-blind conditions	Patients age >16 with a confirmed diagnosis of OA of the knee.
Wegman, 2004[181]	To systematically evaluate RCT evidence on short and long term efficacy of NSAID compared to acetaminophen for OA of the hip or knee. To critically appraise the quality of guidelines for management of OA, and compare content of recommendations in these guidelines on treatment of OA with NSAID or acetaminophen.	To December 2001	For evidence review: RCTs published as full reports comparing NSAIDs with acetaminophen for patients with pain and/or disability related to OA of the hip or knee. At least one of the following outcomes included: overall change, pain or disability. Random allocation of interventions. For guidelines: Guidelines developed by a professional working group of experts. Recommendations on pharmacological management of hip or knee OA.	655	7 publications describing 5 RCTs, two of which were of cross-over design 9 guidelines	All trials included patients with knee OA, and two included those with hip or knee OA.

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
Watson, 2005[57]	Etodolac (600 mg and 800 mg) vs. diclofenac (100-150 mg), naproxen (1000 mg), piroxicam (20 mg), indomethacin (150 mg), nabumetone (1500 mg) Nabumetone (1000 mg) vs. diclofenac (100 mg) Tenoxicam (20 mg) vs. piroxicam (20 mg) Tenoxicam (20 mg) vs. diclofenac (150 mg) Flurbiprofen (150 mg) vs. diclofenac (150 mg) Naproxen (750 mg) vs. diclofenac (150 mg)	Efficacy Withdrawal due to lack of efficacy: Meta-analysis of nine trials showed no SS differences between etodolac, diclofenac or naproxen. Patient Global Assessment: Favored etodolac in two trials however results are questionable due to nonequivalent dose comparisons. Pain: Only 2 of 14 trials assessed pain measurement with adequate power (70%) to detect minimum clinical difference between treatments. Both trials favored etodolac over the comparator drug. Again, nonequivalent dose comparisons resulted in questionable validity of results. Physical function: Only one trial showed a SS difference in favor of tenoxicam vs. diclofenac (OR 3.93 95% CI 1.07 to 14.44)	Not reported	--	Poor methodology resulted in little SS evidence favoring one NSAID over another Only 5 of 16 trials compared equivalent dosing of trial and comparators
Wegman, 2004[181]	7 different types of NSAIDs, including 3 coxibs within recommended dose ranges were compared to acetaminophen with daily doses ranging from 2600 mg to 4000 mg. Mean duration of trail period from which data were drawn was 49 ± 25 days, with a range of 24 - 84 days.	Rest pain (Based on 5 trials with 1208 subjects) Overall improvement using pooled data: inverse-variance-weighted mean difference (WMD) = -6.33 (95% CI -9.24 to -3.41) and an average ES of 0.23 favoring NSAID-treated groups. In 3/6 studies, there was a reduction in rest pain favoring NSAIDs (p<0.05) Walking pain (Based on 6 trials with 1051 subjects) Pooled data demonstrated a WMD of -5.76 (95% CI -8.99 to -2.52) and an average ES of 0.23 favoring NSAID-treated groups.	Not reported	Dropouts due to adverse events All NSAID groups: 63/752 (8.4%) High dose NSAID groups only: 48/497 (9.7%) Acetaminophen: 32/500 (6.4%) The overall safety measure derived from pooled data for dropouts due to AEs showed no statistically significant difference between NSAID vs. acetaminophen (OR 1.45; 95% CI 0.93 to 2.27). Specific types of AEs resulting in withdrawal were not discernable due to lack of data in primary studies.	No data on specific AEs

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
White, 2003[112]	To determine whether the celecoxib affects cardiovascular thrombotic risk.	Time period covered not specified (publication date 2003) Databases not described, possibly Pfizer database of trials.	Completed RCTs of celecoxib for arthritis with planned duration of >=4 weeks	31,879 (18,942 randomized to celecoxib)	15 RCTs: 9 celecoxib vs. another NSAID, 4 celecoxib vs. placebo, 2 celecoxib vs. another NSAID vs. placebo	Osteoarthritis (8 trials) Rheumatoid arthritis (4 trials) Mixed osteoarthritis or rheumatoid arthritis (3 trials)
White, 2007[113]	To determine whether the celecoxib affects CV risk.	Trials completed through October 31, 2004 Pfizer's celecoxib drug safety database	RCTs with a parallel group design; 1 treatment arm given celecoxib at doses of >=200 mg/day; 1 treatment arm given a placebo comparator or a NSAID comparator; planned double-blind treatment period >=2 weeks; final study report completed by October 31, 2004	41,077 (23,030 randomized to celecoxib)	41 RCTs: 12 celecoxib vs. another NSAID, 16 celecoxib vs. placebo, 13 celecoxib vs. another NSAID vs. placebo	Osteoarthritis (21 trials) Rheumatoid arthritis (4 trials) Mixed osteoarthritis or rheumatoid arthritis (6 trials) Ankylosing spondylitis (2 trials) Low back pain (4 trials) Alzheimer's disease (2 trials)

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
White, 2003[112]	All trials 4-12 weeks in duration with the exception of 1 trial 24 weeks (n=655), 1 trial 26 weeks (n=7968)	--	--	Antiplatelet Trialists' Collaboration composite CV events All patients Celecoxib (n=4849) vs. placebo (n=1794): 9/700 vs. 3/200 patient-years, RR 0.85 (95% CI 0.23 to 3.15) Celecoxib (n=17,473) vs. NSAIDs (n=11,143): 54/4969 vs. 38/3613 patient-years, RR 1.06 (95% CI 0.70 to 1.61) Celecoxib (n=12,449) vs. naproxen (2,271): 4/606 vs. 2/171 patient-years, RR 0.85 (95% CI 0.29 to 2.46) Aspirin nonusers Celecoxib (n=4192) vs. placebo (n=1,553): 4/606 vs. 2/171 person-years, RR 0.60 (95% CI 0.11 to 3.29) Celecoxib (n=15,353) vs. NSAIDs (n=9649): 24/4224 vs. 20/3012 person-years, RR 0.86 (95% CI 0.48 to 1.56) Celecoxib (n=11,289) vs. naproxen (n=1975): 11/2204 vs. 3/343 person-years, RR 0.82 (95% CI 0.18 to 2.46)	Pooled CV across all trials (instead of pooling RR's from individual trials)
White, 2007[113]	All trials 4-12 weeks in duration, with the exception of 1 trial 24 weeks (n=655), 2 trials 52 weeks (n=1341), 1 trial 52-65 weeks (n=7968), 1 trial 104 weeks (n=36)	--	--	Celecoxib 200-800 mg (n=7462) vs. placebo (n=4057) (adjudicated events, nonadjudicated events) Antiplatelet Trialists' Collaboration composite CV events (18 vs. 7, 23 vs. 8): RR 1.1 (95% CI 0.47 to 2.7), RR 1.3 (95% CI 0.57 to 2.8) CV deaths (8 vs. 3, 11 vs. 3): RR 1.3 (95% CI 0.33 to 4.8), RR 1.7 (95% CI 0.49 to 6.2) Nonfatal MI (5 vs. 1, 7 vs. 2): RR 1.6 (95% CI 0.21 to 12), RR 1.2 (95% CI 0.27 to 5.8) Nonfatal stroke (5 vs. 3, 5 vs. 3): RR 0.80 (95% CI 0.19 to 3.3), RR 0.80 (95% CI 0.19 to 3.3) Celecoxib 200-800 mg (n=19,773) vs. nonselective NSAIDs (n=13,990): (adjudicated events, nonadjudicated events) Antiplatelet Trialists' Collaboration composite CV events (54 vs. 49, 57 vs. 54): RR 0.90 (95% CI 0.60 to 1.3), RR 0.86 (95% CI 0.59 to 1.3) CV deaths (12 vs. 19, 15 vs. 19): RR 0.57 (95% CI 0.28 to 1.1), RR 0.72 (95% CI 0.37 to 1.4) Nonfatal MI (32 vs. 15, 35 vs. 19): RR 1.8 (95% CI 0.93 to 3.4), RR 1.5 (95% CI 0.82 to 2.7) Nonfatal stroke (10 vs. 15, 7 vs. 16): RR 0.51 (95% CI 0.23 to 1.1), RR 0.33 (95% CI 0.14 to 0.78)	Appeared to simply pool CV events across all trials (instead of pooling RR's from individual trials), did not include Pre SAP, ADAPT, or APC trials

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Zhang, 2004[182]	To assess the best available evidence for efficacy of paracetamol (acetaminophen) in the treatment of OA.	1966 through July, 2003	RCTs comparing paracetamol with placebo or NSAIDs for treatment of OA (radiographic evidence or ACR clinical criteria) or OA pain.	1712	10 RCTs: 5 double blind parallel, 3 double blind crossover, one "n of 1" and one undefined RCT (abstract only) design	Patients with either symptomatic OA of the knee (6 trials) or hip/knee (3 trials) or multiple joints (1 trial).

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Adverse Events	Comments
Zhang, 2004[182]	5 types of NSAIDs were compared to acetaminophen with daily doses ranging from 2600 mg/d to 6000 mg/d. Trial periods ranged from 7 days to 2 years.	General pain/rest pain (Based on 3 trials, OA of hip or knee, 4 - 6 weeks follow-up) Pooled standardized mean difference of 0.33 (95% CI 0.15 to 0.51), indicating a small effect in favor of NSAIDs. Pain on motion, comparison with high dose ibuprofen: 0.24 (95% CI 0.00 to 0.48); with low dose: 0.18 (95% CI -0.06 to 0.42) Functional disability, comparison with high dose ibuprofen: 0.19 (95% CI 0.01 to 0.37); with low dose: 0.18 (95% CI 0.00 to 0.35) Overall change (physician assessment): 0.22 (95% CI 0.02 to 0.43) 3/9 guidelines satisfied more AGREE criteria than others, especially rigor of development. Most guidelines had poor descriptions of stakeholder involvement, applicability and editorial independence were poorly described in most guidelines. The recommendations on use of NSAIDs or acetaminophen were fairly consistent.	Not reported	Not reported	Main results based on 3 trials with a total n of 589 Baseline pain levels not accounted for in analysis

ACP = American College of Physicians; ACR = American College of Rheumatology; ADAPT = Alzheimer's Disease Anti-Inflammatory Prevention Trial; AE = adverse event; APC = the Adenoma Prevention with Celecoxib trial; AGREE = Appraisal of Guidelines for Research & Evaluation trial; COX = Cyclo-oxygenase; CI = confidence interval; bid = twice daily; CLASS = Celecoxib Long-term Arthritis Safety Study; CV = cardiovascular; ES = effect size; EULAR = the European League Against Rheumatism; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; HAQ = Health Assessment Questionnaire; HR = hazard ratio; MI = myocardial infarction; NNT = number needed to treat; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OMERACT = Outcomes Measures in Arthritis Clinical Trials; OR = odds ratio; PreSAP = Prevention of Colorectal Sporadic Adenomatous Polyps; POB = Gastric or duodenal perforation, gastric outlet obstruction, or upper gastrointestinal bleeding; PUB = Perforations, symptomatic gastroduodenal ulcers, and upper GI bleeding; qd = once daily; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SR = systematic review; SS = statistically significant; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WMD = weighted mean difference; ULN = upper limit of normal; VIGOR = Vioxx Gastrointestinal Outcomes Research; wk = week, yr = year

Cardiovascular Safety in Observational Studies

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Andersohn, 2006[132] UK General Practice Research Database (GPRD) (6/1/00-10/31/04) Cases=3,643	Age ≥ 40 years; ≥ 1 NSAID prescription between June 1, 2000 and October 31, 2004; from a practice with ensured quality standards of data recording for ≥ 1 year	Recent use: within 15 to 183 days before index date Past use: 184 days to 1 year Nonuse: no use during 1 year before index date	Age: Mean 69 years Female: 41% Race: Not reported	Nested case-control study	CHD, hypertension, diabetes mellitus, cerebrovascular disease, hyperlipidemia, rheumatoid arthritis, body mass index, smoking status. Controls matched on age, sex, practice, year of cohort entry.
Cunnington, 2008[148] Medical and pharmacy claims from Life-link database (1/1/94-12/31/98) N=71, 026	Patients diagnosed with osteoarthritis before 1999	Chronic user: At least 90 days continuous use with at least two prescriptions Non-user: No recorded exposure to NSAIDs	Chronic user vs. non-user Age: 52% vs. 46% >=65 years Female: 64% vs. 54% Race: Not reported	Retrospective cohort study	Diabetes, smoking-related illness, anticoagulant use, use of lipid lowering drugs, antihypertensive medication, estrogen hormone replacement therapy, intermittent COX-2 inhibitor use or chronic non-selective NSAID use, prior acute myocardial infarction, ischemic stroke, revascularizations, time since osteoarthritis diagnosis
Cunnington, 2008[148] Life-link US claims database (1/1/1994-12/31/1998) N=80,826	A cohort of subjects with osteoarthritis diagnosed before 1999 introduced to COX-2s.	User: chronic medication exposure defined as at least 90 days continuous use with at least two prescriptions. A non chronic/non-user category was no recorded exposure to NSAIDs or COX-2s or short-term use of NSAIDs and COX-2s.	Age: 52% <65 years, 48% >65 years Female: 58% Race: NR	Cohort	Age and sex

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Andersohn, 2006[132] UK GPRD (6/1/00-10/31/04) Cases=3,643	(A) Celecoxib (B) Diclofenac (C) Ibuprofen (D) Naproxen (E) Other nonselective NSAIDs	NR	AMI, death from AMI, or sudden death from CHD: 3.7 per 1000 person-years	Current use vs. nonuse: adjusted RR (95% CI) (A) 1.56 (1.23 to 1.98) (B) 1.36 (1.17 to 1.58) (C) 1.00 (0.83 to 1.21) (D) 1.16 (0.86 to 1.58) (E) 1.19 (1.02 to 1.39)	Risk increased with dose for celecoxib. No significant interaction with age, gender, or presence of risk factors
Cunnington, 2008[148] Medical and pharmacy claims from Life-link database (1/1/94-12/31/98) N=71, 026	(A) Celecoxib (B) Naproxen	NR	Hospitalization for acute myocardial infarction or ischemic stroke: 8.6/1000 person-years for acute myocardial infarction and 4.2 per 1000 person-year for ischemic stroke	Chronic use vs. non-use: adjusted HR (95% CI) (A) 1.05 (0.91 to 1.22) (B) 0.99 (0.64 to 1.54)	No effect on estimates in stratified analysis by age or history of ischemic stroke
Cunnington, 2008[148] Life-link US claims database (1/1/1994-12/31/1998) N=71,026	A) Celecoxib B) Naproxen	NR	CV events per 1000 patient yrs of chronic users A) a) 65 years of age + history of ischemic stroke: 55.4 b) 65 years of age: 29.2 c) Hx of ischemic stroke: 49.4 B) a) 65 years of age + history of ischemic stroke: 65.0 b) 65 years of age: 32.2 c) Hx of ischemic stroke: 49.6	Adjusted HR (95% CI) of chonic vs. non-users A) 1.05 (0.99 to 1.22) B) 0.99 (0.64 to 1.54)	The strongest predictors of AMI/ ischemic stroke risk were history of ischemic stroke and age 65 years or greater. Dose, duration of use and time since OA diagnosis did not meet statistical signficance.

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Fischer, 2005[133] UK GPRD database January 1995 - April 2001 Cases= 8688	Residents of the England and Wales who see a GP registered with the General Practice Research Database (GPRD)	Current users: supply of the last prescription for an NSAID before the index date ended or after the index date Non-users: without exposure before index date	Age: $\leq$89 years Female: 37.1% Race: NR	Case-control	Age, sex, smoking status, aspirin use, body mass index, and diagnosed CV or metabolic diseases (hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, arrhythmias of heart failure, arterial thrombosis, kidney disease, rheumatoid arthritis, lupus), acute chest infections and NSAID drug use
Fosbol 2009[149] Danish Cohort (as of 1/1/1997) Population A: N=1,028,437 Population B: N=153,456	A cohort of Danish citizens with no hospital admissions 10 years before their first claimed NSAID prescription and no claimed prescription for concomitant medication (e.g., ACE inhibitors)	Any use (one or more claimed prescription) and by dose.	Median age: 43 (IQR: 26-56) Age: 33% 31-50 years; 27% 51-70 years, 8% >70 years 28% Female Race NR	Cohort: Population B	Age, sex, and calendar year

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Fischer, 2005[133] UK GPRD database January 1995 - April 2001Cases= 8688	(A) Current use (B) Diclofenac (C) Ibuprofen (D) Naproxen (E) Indomethacin (F) Piroxicam (G) Ketoprofen (H) Fenbufen (I) Nabumetone (J) Etodolac (K)Flurbiprofen	4.4% of cases (and never NSAIDs use)	First-time acute myocardial infarction	Current use vs. no use: adjusted OR (95% CI) (1)1.07 (0.96-1.19) (A) 1.23 (1.00-1.51) (B) 1.16 (0.92-1.46) (C) 0.96 (0.66-1.38) (D) 1.36 (0.82 to 2.25) (E) 0.95 (0.53-1.69) (F) 0.86 (1.44-1.70) (G) 3.08 (1.18-8.06) (H) 0.62 (0.25-1.53) (I) 1.13 (0.40-3.22) (J) 0.68 (0.22-2.12)	Concomitant use of aspirin with NSAIDs was associated with a decreased risk of MI 0.74 (0.57-0.97)
Fosbol 2009[149] Danish Cohort (as of 1/1/1997) Population A: N=1,028,437 Population B: N=153,456	A) Ibuprofen B) Diclofenac C) Naproxen D) Celecoxib	NR	Death rate per 1,000 person years (95% CI); NNH (95% CI) A) 16 (13-19); 432 (184-1251) B) 18 (17-19); 77 (51-158) C) 12 (5-19); -165 (-76 to -941) D) 68 (41-95); 20 (13-43)	Adjusted HR (95% CI) of death; MI for no use vs. any use or by dose of NSAID A) Any use: 0.78 (0.64–0.94); 0.88 (0.74–1.06) ≤ 1,200: 0.68 (0.54–0.85); 0.76 (0.62–0.94) >1,200: 1.49 (0.99–2.24); 1.75 (1.21–2.53) B) Any use: 1.40 (1.13–1.75); 1.58 (1.29–1.93) <100 mg: 0.51 (0.28–0.92); 0.71 (0.44–1.16) ≥ 100 mg1.93 (1.53–2.44); 2.09 (1.68–2.61) C) Any use: 0.76 (0.42–1.36); 0.85 (0.49–1.46) ≤ 500 mg : 0.73 (0.38–1.41); 0.85 (0.47–1.53) >500 mg: 0.87 (0.22–3.47); 0.83 (0.21–3.30) D) Any use: 1.56 (1.04–1.75); 1.49 (0.99–2.25) ≤200 mg: 1.02 (0.58–1.79); 1.05 (0.61–1.81) >200 mg: 3.60 (1.99–6.51); 3.12 (1.68–5.81)	A dose-dependent increase in risk of death and MI was seen for selective COX-2 inhibitors and diclofenac. Particularly high doses should be avoided of both these should be avoided. Risk also increased with age.

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Garcia-Rodriguez, 2000[237] (1/1/1991-12/31/1995) N=164,769 Cases= 1,013	Residents of the England and Wales who see a GP registered with the GPRD	Current user: prescribed aspirin/NSAIDs during the month before the index date Past user: No prescribed NSAID before index date	Age: 50-74 years (60% < 65 years) Female only Race: NR	Case-control (authors state within a cohort)	Age, HRT use, smoking, hypertension, diabetes, obesity, surgical menopause, family history of CHD, and aspirin use (if applies)
Garcia-Rodriguez, 2004[134] UK GPRD (1/1997-12/2000) Controls= 20,000 Cases= 4975	Residents of the U.K. who see a GP registered with the GPRD	Current user: supply of the most recent prescription lasted until index date or ended in the 30 days before the index date Recent user: ended between 31 and 180 days before the index date Past user: ended between 6 months and 2 years before the index date Nonusers: no recorded use in the 2 years before the index date	Age: 50-84 years Men and women Race: NR	Case-control (authors state within a cohort)	Age, sex, calendar year, cancer diagnosis, smoking, diabetes, hypertension, hyperlipidemia, BMI, RA, osteoarthritis, anemia, CHD, cerebrovascular disease, alcohol intake, use of steroids, aspirin, anticoagulants, paracetamol, and NSAIDS
Gislason 2009[160] Danish National Patient Registry (1/1/1995 to 12/31/2004) N=107,092	Patients aged 30 years or older who survived their first hospitalization from heart failure.	Claims for prescription of NSAIDs categorized by low and high doses.	Mean age: 74.8 years Female: 48% Race: Not reported	Cohort	Age, sex, year of first hospitalization due to heart failure, comorbidity, severity, and concomitant medical treatment.

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Garcia-Rodriguez, 2000[237] (1/1/1991-12/31/1995) N=164,769 Cases= 1,013	(A) Aspirin (B) NSAIDs	NA Aspirin evaluated as drug	First recorded date of MI	Current user vs. non user: adjusted OR (95% CI) (A) 0.80 (0.41-1.53) (B) 1.45 (1.18-1.79) Past user vs. non user: adjusted OR (95% CI) (A) 0.86 (0.46 to 1.58) (B) 0.89 (0.76-1.05)	Beneficial effects of aspirin use seen in women using ≤150 mg
Garcia-Rodriguez, 2004[134] UK GPRD (1/1997-12/2000) Controls= 20,000 Cases= 4975	(A) Naproxen (B) Ibuprofen (C) Diclofenac (D) Ketoprofen (E) Meloxicam (F) Piroxicam (G) Indomethacin	27% of cases 14% of controls	MI association with current use of individual NSAIDS	NSAID use vs. non-use of NSAIDs OR (95% CI) (A) 0.89 (0.64-1.2) (B) 1.1 (0.87-1.3) (C) 1.2 (0.99-1.4) (D) 1.1 (0.59-2.0) (E) 0.97 (0.60-1.6) (F) 1.2 (0.69-2.2) (G) 0.86 (0.56-1.3)	Duration or daily dose did not change the results
Gislason 2009[160] Danish National Patient Registry (1/1/1995 to 12/31/2004) N=107,092	A) Celecoxib B) Ibuprofen C) Diclofenac D) Naproxen E) Other NSAIDs	NR	Death, hospitalization due to HF and hospitalization due to AMI.	Adjusted HR (95% CI) of death, HF hospitalization, and AMI hospitaltion for any use of drug vs. no NSAID A) 1.75 (1.63-1.88), p<.001 1.40 (1.26-1.55) .001 1.30 (1.07-1.59) .01 B) 1.31 (1.25-1.37), p<.001 1.24 (1.12-1.39) .001 1.38 (1.13-1.69) .001 C) 2.08 (1.95-2.21), p<.001 1.16 (1.10-1.23) .001 1.33 (1.19-1.50) .001 D) 1.22 (1.07-1.39), p=.004 1.35 (1.24-1.48) 1.36 (1.12-1.64) .002 E) 1.22 (1.07-1.39) p=.004 1.18 (1.00-1.40) .05 1.52 (1.11-2.06) .01	Dose dependent increase of mortailty and cardiovascular morbidity with NSAIDs.

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Graham 2005[135] State of California Kaiser Permanente health care database (1/1/99-12/31/09) Cases=8,143	Age 18-84 years, filled ≥ 1 prescription for celecoxib, rofecoxib or any other non-selective NSAID; ≥ 12 months of health plan coverage before index prescription date	Current use: overlap with index date Remote use: ended >60 days before index date Recent use: ended 1-60 days before index date	Age: Mean 67 years Female: 38% Race: Not reported	Nested case-control study	Age, sex, health plan region, cardiovascular risk score, admission for non-cardiac-related disorders and same-day procedures, emergency room visits for non-cardiac reasons, hormone replacement therapy, and high-dose prednisone. Controls matched on index date, age, sex, health plan region.

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Graham 2005[135] State of California Kaiser Permanente health care database (1/1/99-12/31/09) Cases=8,143	(A) Celecoxib (B) Ibuprofen (C) Naproxen (D) Other NSAIDs	Random sample of n=817 cases participated in phone interview and 23% reported using aspirin	Acute MI requiring admission or sudden cardiac death: 3.5/1000 person-years	Current use vs. remote use: adjusted OR (95% CI) (A) 0.84 (0.67, 1.04) (B) 1.06 (0.96, 1.17) (C) 1.14 (1.00, 1.30) (D) 1.13 (1.01, 1.27) Current use vs. celecoxib use (A) 1 (reference) (B): 1.26 (1.00, 1.60) (C): 1.36 (1.06, 1.75) (D): 1.35 (1.06, 1.72)	3.8% taking anticoagulants

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Hippisley-Cox 2005[136] Case-control QRESEARCH database (8/1/00-7/31/04) Cases=9218	Age 25 to 100 years, registered for at least 1 year prior to index date	No use in past 3 years Use >3 months before index date Use within 3 months of index date	Age: 20% 55-64 years, 28% 65-74 Male: 63% Race: Not reported	Nested case-control study	Other NSAIDs, use of aspirin, statin, tricyclic antidepressant, SSRI, ischemic heart disease, diabetes, hypertension, osteoarthritis, rheumatoid arthritis, smoking obesity, deprivation. Controls matched on age, calendar time, sex, and practice.
Hudson 2005[161] Database of hospital discharge summaries (4/1/00-3/31/02) N=997	Aged > 66 with admission for CHF from 4/00-3/02	Prescription following hospitalization for CHF	Celecoxib vs. NSAIDs Age: Median 79 vs. 76 years Female: 60% vs. 44% Race: Not reported	Retrospective cohort study	Age, sex, comorbidities, other drugs prescribed, characteristics of the treating doctor or hospital, length of stay, year of exposure, acute myocardial infarction in the previous 3 years, time to first prescription, episodes of CHF after the index admission but before the first prescription
Johnsen 2005[137] Denmark National Health Service registries (1/100-12/31-03) Cases=10,280	Persons living in 3 counties in Denmark, using a hospital registry	Nonuser: No recorded prescription Current user: Filled prescription within 0-30 days New users: Current users who filled first prescription within 0-30 days Recent users: Filled prescription within 31-90 days Former users: Filled prescription >90 days before index date	Age: Mean 70 years Female: 40% Race: Not reported	Case-control study	Discharge diagnosis of cardiovascular disease, various comorbid conditions, various prescription drugs. Controls matched on age and sex.

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Hippisley-Cox 2005[136] Case-control QRESEARCH database (8/1/00-7/31/04) Cases=9218	(A) Celecoxib (B) Ibuprofen (C) Diclofenac (D) Naproxen (E) Other non-selective NSAIDs	Yes, but proportion NR	First ever MI: 1.7/1000 person-years	Use within 3 months vs. no use in past three years: adjusted OR (95% CI) (A) 1.21 (0.96, 1.54) (B) 1.24 (1.11, 1.39) (C) 1.55 (1.39, 1.72) (D) 1.27 (1.01, 1.60) (E) 1.21 (1.02, 1.44)	No interactions between any NSAID and aspirin use or coronary heart disease; smoking and BMI interacted only with naproxen; age 65 and over only interacted with other non-selective NSAIDs
Hudson 2005[161] Database of hospital discharge summaries (4/1/00-3/31/02) N=997	(A) Celecoxib (B) Any nonselective NSAID	Yes, in 1006 (53.9%)	Celecoxib vs. nonselective NSAIDs Recurrent CHF: 28 vs. 34/100 person-years Death: 19 vs. 29/100 person-years Death OR recurrent HF: 42 vs. 53/100 person-years (Primary outcome)	Nonselective NSAID use vs. celecoxib use: adjusted hazard ratio, (95% CI) Recurrent CHF: 1.21 (0.92, 1.60) Death: 1.54 (1.17, 2.04) Death or recurrent CHF: 1.26 (1.00, 1.57)	NR
Johnsen 2005[137] Denmark National Health Service registries (1/100-12/31-03) Cases=10,280	(A) Celecoxib (B) Naproxen (C) Other nonselective NSAID	6.9% high dose	Acute MI: Incidence not reported	Current user vs. non-user: adjusted HR (95% CI) (A) 1.25 (0.97, 1.62); (B) 1.50 (0.99, 2.29) (C) 1.68 (1.52, 1.85) New user vs. nonuser: (A) 2.13 (1.45, 3.13) (B) 1.65 (0.57, 4.83) (C) 2.65 (2.00, 3.50)	13.7% CV disease; 2.2% cc anticoagulant use; rofecoxib was associated with increased risk regardless of baseline risk status

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Kimmel 2005[138] Hospitals in 5-county region (5/98-12/02) Cases: 1718	Persons aged 40 to 75 years in a 5-country region	Use within 1 week before the index date	Cases vs. controls Age: Mean 58 vs. 53 years Female: 37% vs. 59% Non-white: 28% vs. 19%	Case-control study	Age, sex, race, smoking, insurance, number of physician visits in the previous year, family history of coronary disease, body mass index, activity score, year, previous angina or coronary disease, history of diabetes, hypertension, heart failure, and hypercholesterolemia, use of statins, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and diuretics. Controls randomly selected from study population.
Levesque 2005[139] Computerized health insurance and vital statistics databases of Quebec, Canada (1/1/99-6/30/02) Cases=2844	≥ 66 years of age prescribed an NSAID or COX-2 who've never had an MI	Current user: Duration of the last prescription dispensed overlapped with the index date Past user: Filled at least 1 NSAID prescription in the year prior to the index date but not currently exposed Ever user: Current or past user Nonuser: No NSAIDs in the last year	Age: Mean 78 years Female: 54% (cases) vs. 68% (controls) Race: Not reported	Nested case-control study	Age, sex, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, use of lipid-lowering drugs, anticoagulant, and aspirin; co-morbid conditions or use of oral corticosteroids; measures of health utilization, measures of comorbidity. Controls matched on month and year of cohort entry and age.
Mamdani 2003[140] Ontario healthcare administrative database (4/1/98-3/31/01) N=154,808	NSAID-naïve patients aged ≥ 66 years of age prescribed an NSAID or COX-2	New user: Received prescription for a drug of interest, no prior prescription within the last year Control: Not prescribed a drug of interest in the 1 year prior to the index date, or during the observation period	Age: Mean 75 years Female: 64% Race: Not reported	Retrospective cohort study	Age, sex, long-term care, low-income status, hospitalizations, cancer, cardiovascular hospitalizations, cardiovascular procedures, concomitant drugs
Mamdani 2004[162] Ontario healthcare administrative database (4/17/00-3/31/01) N=130,514	NSAID-naïve patients aged ≥ 66 years of age prescribed an NSAID or COX-2	New user: Prescribed drug of interest (at least two successive prescriptions), no drug of interest in the year prior to the index prescription	Age: Mean 76 years Female: 58% Race: Not reported	Retrospective cohort study	Age, sex, long-term care, low-income status, hospitalizations, cancer, cardiovascular hospitalizations, cardiovascular procedures, concomitant drugs

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Kimmel 2005[138] Hospitals in 5-county region (5/98-12/02) Cases: 1718	(A) Celecoxib (B) Any nonselective NSAID (C) Ibuprofen or diclofenac (D) Naproxen	33.60%	Nonfatal MI: Incidence not reported	NSAID use within 1 week vs. no use within 1 week: adjusted OR (95% CI) overall, among aspirin nonusers, and among aspirin users (A) 0.43 (0.23, 0.79), 0.35 (0.16, 0.76), 0.67 (0.25, 1.80) (B) 0.61 (0.52, 0.71), 0.55 (0.46, 0.66), 0.77 (0.59, 1.00) (C) 0.53 (0.43, 0.66) overall (D) 0.48 (0.32, 0.73) Celecoxib vs. ibuprofen or diclofenac use within 1 week: 0.77 (0.40, 1.48) overall Celecoxib vs. naproxen use within 1 week: 0.81 (0.37, 1.77)	Some results stratified by aspirin use
Levesque 2005[139] Computerized health insurance and vital statistics databases of Quebec, Canada (1/1/99-6/30/02) Cases=2844	(A) Celecoxib (B) Naproxen (C) Meloxicam (D) Non-naproxen nonselective NSAIDs	22.50%	Acute MI, fatal or nonfatal: 10.4/1000 person-years	Current use vs. no use: adjusted RR (95% CI) (A) 0.99 (0.85, 1.16) overall, 0.98 (0.83, 1.17) low-dose, 1.00 (0.78, 1.29) high dose, 1.07 (0.89, 1.30) no aspirin, 0.88 (0.70, 1.10) taking aspirin (B) 1.17 (0.75, 1.84) overall, 1.59 (0.95, 2.65 no aspirin), 0.60 (0.24-1.50) taking aspirin (C) 1.06 (0.49, 2.30) overall, 0.59 (0.14, 2.41) no aspirin, 1.59 (0.61, 4.14) on aspirin (D) 1.00 (0.73, 1.37) overall, 1.04 (0.71, 1.54) no aspirin, 0.94 (0.57, 1.54) taking aspirin	--
Mamdani 2003[140] Ontario healthcare administrative database (4/1/98-3/31/01) N=154,808	(A) Celecoxib (B) Naproxen (C) Non-naproxen nonselective NSAIDs	14.70%	Hospitalization for acute MI: 9/1000 person-years	New user vs. nonuser: adjusted RR (95% CI) (A) 0.9 (0.7-1.2) (B) 1.0 (0.6-1.7) (C) 1.2 (0.9, 1.4)	--
Mamdani 2004[162] Ontario healthcare administrative database (4/17/00-3/31/01) N=130,514	(A) Celecoxib (B) Nonselective NSAIDs	NR	Admission for CHF: 10/1000 person-years	New user vs. nonuser: adjusted RR (95% CI) (A) 1.0 (0.8, 1.3) (B) 1.4 (1.0, 1.9) Non-selective NSAIDs vs. celecoxib: 1.4 (1.0, 1.9)	History of heart failure admission within past 3 years increased risk

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Patel, 2004[259] Durham VA 1/1/1990-12/31/2000 Cases=3850 aspirin + ibuprofen; 10239 aspirin only (Controls matched by patient month, not patient)	Patients in clinical database of the Durham VA Medical Center	Outpatient prescription of aspirin or ibuprofen; aspirin alone, aspirin + ibuprofen and combined	Average birth year, 1933 97% Male Race: 29% black	Case control	Controls matched to cases by sex, race, age and LDL cholesterol level
Rahme 2002[141] Quebec, Canada RAMQ and Med-Echo databases (1/1/1988-12/31/1994) Controls= 14,160 Cases= 4163	Residents of Quebec (all persons ≥65 years are eligible) registered for health coverage, maintained by RAMQ and Med-Echo databases	Current user: prescriptions with a duration that covered or overlapped with the index date Chronic user: filled at least twice and with 60+ consecutive days of prescription duration Current-chronic user: subject of primary analysis Interrupted-chronic user: chronic user without use at the index date	Age: ≥65 years Men: 52.8% cases; 52.8% controls	Case-control (population-based)	Age, sex, use of anticoagulants, nitrates, lipid-lowering agents, antidiabetic agents, or antihypertensive agents, prior AMI, cardiovascular diseases, presence of comorbidity factors
Rahme, 2007 *Arthritis and Rheumatism*[130] Health care records and hospital records of patients in Quebec Canada including those with OA (1997 to 12/2002)	Patients of 65 years of age or older who filled a prescription for acetaminophen or a NSAIDs.	The number of days of supply for each NSAID or acetaminophen prescription with a grace period of 25%.	Age ≥65 years Male: 45%	Retrospective cohort	Age, gender, alcohol/drug use, co-morbidities (e.g., COPD) and other drugs
Rahme 2007[108] Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183	Patients of 65-80 years of age or older who filled a prescription for NSAIDs	The number of days of supply for each NSAID or acetaminophen prescription. Exposure was designated to be 1.25 x number of days supplied).	Age 65-80 years of age Male: 40%	Retrospective cohort	Concomitant drugs and baseline characteristics

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Ray 2002[142] Tennessee Medicaid program database (1/1/99-6/30/01) N=354,644	Aged 50-84 (mean=61.5); eligible for TennCare benefits for past 365 days; not in a nursing home; no history of non-CV life-threatening illness; new users	User: Taking an NSAID at enrollment, or during the time they were eligible for the study New user: Began an NSAID during follow-up Non-users: No NSAID within 1 year	Age: Mean 61 years Female: 66% Non-white: 27%	Retrospective cohort study	Age, sex, summary cardiovascular disease risk score, ethnic origin, calendar year, basis for inclusion in TennCare, use of estrogen, hospital admission for non-cardiovascular illness, visits to emergency department, rheumatoid arthritis, visits to family doctor, current aspirin use
Schlienger 2002[143] UK GPRD (1/1/92-10/31/97) Cases=3,315	≤ 75 years of age; free of metabolic or cardiovascular diseases predisposing to AMI; registered on the database for at least 3 years before the index date	Current user: Last prescription for an NSAID ended on or after the index date Recent user: Supply ended between 1 and 29 days prior to index date Past user: Supply ended 30 or more days prior to index date Nonuser: No NSAID prescription prior to index date	Age: 25% 50-59 years, 37% 60-69 Female: 26% Race: Not reported	Case-control study	Smoking status, body mass index, hormone replacement therapy, aspirin use. Controls matched on age, sex, index date, practice attended.
Solomon 2002[144] New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs (1/1/91-12/31/95) Cases=4425	Participants in a state Medicaid program or a program for older adults with moderate incomes, who were continuous participants in the program	Cumulative duration in the prior 6 months 1 to 30 days, 31 to 90 days, or 91 to 180 days	Age: 15% <=64 years, 30% 65-74 years Female: 69% (cases) vs. 79% (controls) Non-white: 28% (cases) vs. 31% (controls)	Case-control study	Age, sex, ethnicity, Medicaid enrollment, nursing home use, diabetes mellitus, hypertension, congestive heart failure, Charlson Comorbidity Index, number of different drug prescriptions, number of hospitalizations. Controls matched on age.

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Ray 2002[142] Tennessee Medicaid program database (1/1/99-6/30/01) N=354,644	(A) Celecoxib (B) Ibuprofen (C) Naproxen	NR	Serious CHD (hospital admission for AMI or death from CHD): 12/1000 person-years	Current user vs. nonuser (A) 0.96 (0.76, 1.21) (B) 0.91 (0.78, 1.06) (C) 0.93 (0.82, 1.06) New user vs. nonuser (A) 0.88 (0.67, 1.16) (B) 1.01 (0.77, 1.33) (C) 0.92 (0.73, 1.16)	NR
Schlienger 2002[143] UK GPRD (1/1/92-10/31/97) Cases=3,315	(A) Ibuprofen (B) Diclofenac (C) Piroxicam (D) Ketoprofen (E) Indomethacin (G) Naproxen	Yes	First-time acute MI: Proportion not reported	Current use vs. nonuse: adjusted OR (95% CI) (A) 1.17 (0.87, 1.58) (B) 1.38 (1.08, 1.77) (C) 1.65 (0.78, 3.49) (D) 2.06 (0.80, 5.30) (E) 1.39 (0.77, 2.51) (F) 1.03 (0.58, 1.85) (G) 2.26 (0.93, 5.46) (H) 0.68 (0.42, 1.13)	Current use of aspirin at the index date and longer term use of HRT in women interacted with AMI risk; exposure duration, age, and gender did not.
Solomon 2002[144] New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs (1/1/91-12/31/95) Cases=4425	(A) Any nonselective NSAID (B) Naproxen (C) Ibuprofen (D) Etodolac (E) Fenoprofen	Excluded	Acute MI: Incidence not reported	NSAID user vs. non-user: adjusted OR (95% CI) (A) 1.00 (0.92, 1.08) (B) 0.84 (0.72-0.98) (C) 1.02 (0.88, 1.18) (D) 1.28 (1.00, 1.64) (E) 1.95 (1.16, 3.30) Naproxen user vs. ibuprofen user: 0.82 (0.67-1.01)	No dose- or duration-response relationship

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Solomon 2004a[145] Chart review of prescription drug benefit program participants (1998-2000) Cases=10,895	Low-income, elderly, Medicare beneficiaries who had at least 1 healthcare visit in each 6-month period	Cumulative duration of exposure during the 1-30 days 31-90 days > 90 days	Mean age: 82 years Female: 78% Non-white: 9%	Case-control study	Race, number of physician visits, hospitalized in previous year, comorbid conditions, diabetes, hypertension, number of prescription drugs, history of cardiovascular conditions, use of statin, hormone replacement therapy, an anticoagulant, rheumatoid arthritis, osteoarthritis, prior nonselective NSAID use. Controls matched on age, sex, and month of index date.
Solomon 2004b[131] Medicare Prescription Drug Benefit Program databases through Pennsylvania PACE or the New Jersey PAAD (1998-2000) Cases=3,915	Active users of prescription drug benefit program for 2 consecutive years out of the 3-year period with no prior diagnosis of hypertension and no use of antihypertensive medications	NSAID use: Active prescription on the day before the index date Short duration of use: 1-30 days Long duration of use: 31-90 days	Mean age: 79 years Female: 81% Non-white: 5%	Case-control study	Age >=75 years, sex, race, hospitalization in prior year, nursing home resident in prior year, diabetes, coronary artery disease, osteoarthritis, physician visits in prior year, number of different medications, and comorbid illnesses. Controls randomly selected from eligible pool of patients

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Solomon 2004a[145] Chart review of prescription drug benefit program participants (1998-2000) Cases=10,895	(A) Celecoxib (B) Naproxen (C) Ibuprofen (D) Other nonselective NSAID	NR	Acute MI: Incidence not reported	Adjusted OR (95% CI) Celecoxib use vs. no current NSAID use: 0.93 (0.84, 1.02) Celecoxib use vs. naproxen use: 0.95 (0.74, 1.21) Celecoxib use vs. ibuprofen use: 0.98 (0.76, 1.26) Celecoxib use vs. other nonselective NSAID use: 0.95 (0.82, 1.10)	Dose had an effect for rofecoxib but not celecoxib; couldn't adjust for aspirin use
Solomon 2004b[131] Medicare Prescription Drug Benefit Program databases through Pennsylvania PACE or the New Jersey PAAD (1998-2000) Cases=3,915	(A) Celecoxib (B) Nonspecific NSAID	NR	New onset hypertension and the filling of at least 1 antihypertensive medication prescription: Incidence not reported	Adjusted OR (95% CI) Celecoxib use vs. no NSAID use: 1.0 (0.9, 1.2) Celecoxib use vs. nonspecific NSAID use: 0.9 (0.7, 1.1) Celecoxib use <=200 mg vs. no NSAID use: 1.0 (0.8, 1.2) Celecoxib use >200 mg vs. no NSAID use: 1.2 (0.8, 1.7) Celecoxib use <=200 mg vs. nonspecific NSAID use: 0.9 (0.6, 1.1) Celecoxib use >200 mg vs. nonspecific NSAID use: 1.1 (0.6, 1.7) Celecoxib use 1-30 days vs. no NSAID use: 1.4 (1.0, 1.9) Celecoxib use >30 days vs. no NSAID use: 0.9 (0.7, 1.1) Celecoxib use 1-30 days vs. nonspecific NSAID use: 0.8 (0.5, 1.3) Celecoxib use >30 days vs. nonspecific NSAID use: 0.9 (0.7, 1.2)	Dose, duration had no effect; but presence of renal disease, liver disease, or congestive heart failure appeared in increase risk for rofecoxib users

Author, Year Data Source Sample Size	Population	Categorization of Exposure	Demographics (Age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Solomon, 2008[114] Medicare database (1999-2004) N=140, 437	Medicare beneficiaries also eligible for a drug benefits program for older adults and enrolled for at least 12 continuous months during 1999 to 2003	New user: No use in 180 days prior to the study, initiated drug during study Continuous user: No gap longer than 15 days between successive prescription periods	Age: Mean 80 years Female: 86% Non-white race: 7%	Retrospective cohort study	Age, sex, race, hospitalized, nursing home resident, physician visits, number of different medications, myocardial infarction, CHF, coronary revascularization, angina, diabetes, hypertension, hyperlipidemia, statin use, clopidogrel use, peripheral vascular disease, stroke, carotid revascularization, chronic renal disease, rheumatoid arthritis, osteoarthritis, malignancy, number of comorbid conditions
Velentgas 2005[146] Insurance claims/administrative records of United Healthcare (1/1/99 to 6/30/01) N=424,584	Patients aged 40-64 who received at least one dispensing of rofecoxib, celecoxib, naproxen, ibuprofen, or diclofenac in oral tablet or capsule from 1/1/99 to 6/30/01	Current use: Use began on day of new medication dispensing and continued through the number of days supplied Recent use: Began the day following the last day of current use and continued for 60 days	Age: range 21% to 24% for 50-54 years, 14% to 21% for 55-59 years Female: 57% Race: Not reported	Retrospective cohort study	Age, sex, and prior history of vascular event

Author, Year Data Source Sample Size	NSAIDs Evaluated	Aspirin use (%)	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Solomon, 2008[114] Medicare database (1999-2004) N=140, 437	(A) Celecoxib (B) Diclofenac (C) Ibuprofen (D) Naproxen (E) Other nonspecific NSAID	NR	Hospitalization for myocardial infarction, stroke, or congestive heart failure; or out-of-hospital death attributable to cardiovascular disease: 8.5 to 15/1000 person-years	New user vs. nonuser: adjusted HR (95% CI) (A) 0.89 (0.83, 0.94) (B) 0.91 (0.74, 1.13) (C) 0.96 (0.83, 1.10) (D) 0.79 (0.67, 0.93) (E) 0.87 (0.79, 0.96)	Ibuprofen associated with additional 3.4 CVD events/1000 person-years in patients >80 years old, and additional 11.4 CVD events/1000 person-years in persons with prior myocardial infarction
Velentgas 2005[146] Insurance claims/administrative records of United Healthcare (1/1/99 to 6/30/01) N=424,584	(A) Celecoxib (B) Naproxen (C) Ibuprofen or diclofenac	NR	Acute coronary syndrome or myocardial infarction: 8.0 to 10/1000 person-years	Current NSAID use vs. current ibuprofen or diclofenac use: adjusted RR (95% CI) (A) 1.03 (0.83, 1.27) (B) 1.14 (0.93, 1.39) Recent NSAID use vs. current ibuprofen or diclofenac use: adjusted RR (95% CI) (A) 0.91 (0.70, 1.17) (B) 0.86 (0.70, 1.04) (C) 1.00 (0.83, 1.20)	No dose-relationship; increased risk for males and for individuals with a cardiac history, peripheral arterial disease, diabetes, beta blocker use, nitrate use

AMI = acute myocardial infarction; ASA = aspirin; BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COX = cyclo-oxygenase; CV = cardiovascular; CVD = cardiovascular disease; GP = general practitioner; GPRD = General Practice Research Database; HF = heart failure; HRT = hormone replacement therapy; LDL = low-density lipoprotein (cholesterol); MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; NA = not applicable; NR = not reported; OR = odds ratio; PACE = Pharmaceutical Assistance Contract for the Elderly; PAAD = Pharmaceutical Assistance Program for the Aged and Disabled, RR = relative risk; SSRI = selective serotonin reuptake inhibitor; TARGET = Therapeutic Arthritis Research and Gastrointestinal Event Trial; UK = United Kingdom

Gastrointestinal Safety in Observational Studies

Author, Year Data Dource Sample Size	Population	Categorization of Exposure	Demographics (age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)	NSAIDs Evaluated
Garcia-Rodriguez, 2001[98] UK General Practice Research Database (4/2003-10/2008); Cases=2,105 Controls=11,500	Age 40-79 years; enrolled with the General Practitioner free of cancer, esophageal varices, Mallory-Weiss disease, liver disease, coagulopathies, and alcohol-related disorders at start date	Current use: prescription lasted until the index date or ended in the 30 days before the index date Recent use: prescription ended 31-90 days before index date Past use: 91-180 days before the index date Non-use: no recorded use in the 6 months before index date Duration evaluated by adding periods of an interval of < 2 months between 2 prescriptions ("consecutive" prescriptions) Dose-response for Acetaminophen: 1) ≤1,000g 2) 1,001-1,999 3) 2,000 4) 2,001-3,999 5) ≥ 4,000g	Age= 40-79 years Male and Female Race not reported	Nested, case-control	Age, sex, calendar year, smoking, antecedents to of upper GI disorders and use of possible meds with interactions Controls frequency matched by age and sex (randomly selected index-date)	A) Etodolac B) Ibuprofen C) Ketoprofen D) Nabumetone E) Tenoxicam F) Meloxicam G) Naproxen H) Diclofenac I) Flurbiprofen J) Indomethacin K) Piroxicam

Author, Year Data Source Sample Size	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration	Notes
Garcia-Rodriguez, 2001[98] UK General Practice Research Database (4/2003-10/2008); Cases=2,105 Controls=11,500	Codes for UGIC: 1) Bleed/perforation in stomach or duodenum 2) Clinical diagnosis of peptic ulcer with referral to consultant or admitted to a hospital a) Uncomplicated ulcer NSAID use: 16.0/1,000 person-years b) Complicated ulcer NSAID use: 24.6/1000 person-years *Case status validated by a random sample of 100 patients; 99% had confirmed UGIC)	Adjusted RR (95% CI) Acetaminophen vs. nonuse: 1.3 (1.1-1.5) NSAIDs vs. nonuse A) Etodolac: 2.2 (0.4-11.3) B) Ibuprofen: 2.5 (1.9, 3.4) C) Ketoprofen: 3.3 (1.9, 5.9) D) Nabumetone: 3.4 (1.1, 10.6) E) Tenoxicam: 3.4 (0.9, 13.1) F) Meloxicam: 3.8 (0.8, 17.2) G) Naproxen: 4.0 (2.8, 5.8) H) Diclofenac: 4.6 (3.6, 5.8) I) Flurbiprofen: 4.6 (2.0, 10.9) J) Indomethacin: 5.2 (3.2, 8.3) K) Piroxicam: 6.2 (3.7, 10.1)	Dose: Acetaminophen $\geq$2g had greater risk of UGIC compared to lower doses and risk of dose-response increase was independent of duration Dose NSAIDs: Medium or lower daily dose, 2.5 (CI 1.9-3.1) High daily dose, 4.9 (CI 4.1-5.8) Substantial interaction when taking NSAIDs and $\geq$2 g or more of acetaminophen	Etodolac, nabumetone, meloxicam: risk estimates compatible with average NSAID; small sample size per NSAID resulted in wide CI's

Author, Year Data Dource Sample Size	Population	Categorization of Exposure	Demographics (age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)	NSAIDs Evaluated
Garcia-Rodriguez, 2007[102] UK Health Improvement Network database (1/2000-2005) Cases=1,561 Controls=10,000	Age 40-85 years enrolled at least 2 years with GP and 1 year since first recorded prescription without cancer, esophageal varices, Mallory-Weiss syndrome, coagulopathies, alcohol-related disorders and liver disease	Prescription records; duration determined by consecutive prescriptions (less than 2 months between prescriptions)	Mean age, gender, race not reported	Nested, case-control	Age, sex, calendar year, GP visits, smoking, alcohol consumption, history of peptic ulcer disease, use of aspirin, anticoagulants and steroids Controls random date matched (based on case length follow-up)	A) Aceclofenac B) Acemetacin C) Apazone D) Azapropazone, Celecoxib E) Diclofenac F) Diflunisal G) Etodolac, Etoricoxib H) Fenbufen I) Fenoprofen J) Flurbiprofen K) Ibuprofen L) Indomethacin M) Ketoprofen N) Ketorolac O) Mefenamic acid P) Meloxicam Q) Nabumetone R) Naproxen S) PiroxicamRofecoxib T) Sulindac U) Tenoxicam V) Tiaprofenic acid W) Valdecoxib
Hippisley-Cox, 2005[136] 367 general practices in the UK contributing to the QRESEARCH database (8/1/00-7/31/04)Cases: 9407Controls: 88,867	Age ≥ 25 with first ever upper GI event and ≥ 3 yrs of recorded medical data	Grouped by usage and type (COX-2 inhibitor), other NSAIDS, and aspirin Non-use: no prescription in past 3 years Past use: prescribed > 90 days of index date Current use: prescribed < 90 days of index date	Age at index date, Median (IQR): Cases: 68 years, (53-79) Controls: 67 years, (52-78) Gender (% Female): Cases: 47.2 Controls: 52.8 Race not reported	Nested, case-control	Smoking, obesity, Townsend score (comparable to SES), ulcer healing drugs, antidepressants, statins, and comorbidities (i.e., diabetes) Controls matched up to 10 per case by age, calendar time, sex and general practice	A) Celecoxib B) Other selective NSAIDs C) Ibuprofen D) Diclofenac E) Naproxen F) Other non-selective NSAIDs

Author, Year Data Source Sample Size	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Garcia-Rodriguez, 2007[102] UK Health Improvement Network database (1/2000-2005)Cases=1,561 Controls=10,000	Upper GI complications, bleeding or perforations	Adjusted RR of upper GI complications – Celecoxib 2.7 (CI 1.5 to 4.1*) Ibuprofen 2.0 (CI 1.4 to 2.9) Meloxicam 2.7 (CI 1.4 to 4.3*) Diclofenac 3.7 (CI 2.4 to 4.2*) Ketoprofen 5.4 (CI 1.5 to 16.1*) Indomethacin 7.2 (CI 3.8 to 13.8*) Naproxen 8.1 (CI 4.9 to 12.2*) *CIs estimated based on graph	Non-use vs. current steroid use RR 1.4 (CI 1.0 to 1.9) Non-use vs. past steroid use RR 1.1 (CI 0.8 to 1.5) Non-use vs. current aspirin use RR 1.1 (CI 1.5 to 2.0) Non-use vs. recent aspirin use RR 1.7 (CI 1.3 to 2.2) Non-use vs. current warfarin use RR 2.0 (CI 1.5 to 2.6) Non-use vs. past warfarin use RR 1.6 (CI 0.9 to 2.8)
Hippisley-Cox, 2005[136] 367 general practices in the UK contributing to the QRESEARCH database (8/1/00-7/31/04)Cases: 9407Controls: 88,867	Complicated GI event (those involving hemorrhage, perforation, or surgery) Overall incidence: 1.36 per 1000 p-years (95% CI 1.34 to 1.39)	Adjusted Odds Ratio (95% CI): Past use vs. non-use A) 1.00 (0.77 to 1.29) B) 0.87 (0.69 to 1.10) C) 1.05 (0.96 to 1.15) D) 1.09 (0.99 to 1.19) E) 1.06 (0.89 to 1.26) F) 1.08 (0.94 to 1.24) Current Use vs. non-use A) 1.25 (0.91 to 1.72) B) 1.72 (1.29-2.29) C) 1.58 (1.37-1.83) D) 2.07 (1.82-2.35) E) 1.97 (1.48-2.61) F) 1.59 (1.29 to 1.96) **Aspirin:** Past use vs. non-use 1.64 (1.49, 1.81) Current Use vs. non-use 1.60 (1.49, 1.72)	Increase incidence of peptic ulcer or gastrointestinal hemorrhage Reduction in GI adverse events in NSAIDs with concurrent use of ulcer healing drugs

Author, Year Data Dource Sample Size	Population	Categorization of Exposure	Demographics (age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)	NSAIDs Evaluated
Lanas 2006[104] Hospitals in the Spanish Association of Gastroenterology (2001-2005) Cases=2,777 Controls=5,532	Age 20-85 years free of liver disease, coagulation disorders or malignancies, excluding GI varices, vascular lesions, tumors, Mallory-Weiss syndrome, coagulopathy and esophagitis	Current use: drug taken up to 7 days prior to index date Past use: drug taken more than 7 days prior to index date	Mean age 61 years Gender, race not reported	Case-control	Age, sex, calendar semester, ulcer history, nitrate use, oral anticoagulants, antiplatelets, acid-suppressing drugs, NSAIDs, coxibs and aspirin Controls age-matched based on hospital admission of outpatient visit for reasons considered to be unrelated to NSAIDs	(A) Aceclofenac (B) Diclofenac (C) Ibuprofen (D) Indomethacin (E) Ketoprofen (F) Ketorolac (G) Lornoxicam (H) Meloxicam (I) Naproxen (J) Piroxicam
Laporte 2004[105] 18 hospitals in Spain and Italy (9/1998-12/2001) Cases=2,813 Controls=7193	Patients aged > 18 years admitted with primary diagnosis of acute upper GI bleeding, acute lesions of gastric mucosa, erosive duodenitis, or mixed lesions	Any use in the 7 days before the index day	> 18 years of age Male and female Race not reported	Case-control	History of peptic ulcer, diabetes, heart failure, smoking, alcohol consumption, SSRIs and other medications with possible interactions Controls: randomly selected and matched according to center, date of admission (within 2 months), sex and age (+/- 5 years)	(A) Diclofenac (B) Ibuprofen (C) Indomethacin (D) Ketoprofen (E) Ketorolac (F) Meloxicam (G) Naproxen (H) Nimesulide (I) Piroxicam (J) Other NSAIDs

Author, Year Data Source Sample Size	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration	Notes
Lanas 2006[104] Hospitals in the Spanish Association of Gastroenterology (2001-2005) Cases=2,777 Controls=5,532	Clinically confirmed hospitalization due to GI bleeding	Adjusted RR, upper GI bleeding - Non-use vs. current use RR 5.3 (CI 4.5 to 6.2) Non-use vs. past use RR 0.9 (CI 0.7 to 1.2) Non-use vs. low/medium dose RR 4.0 (CI 3.2 to 5.0) Non-use vs. high dose RR 6.8 (CI 5.3 to 8.8) Non-use vs. use 1-30 days RR 7.6 (CI 6.0 to 9.5) Non-use vs. use 90 days RR 7.3 (CI 4.0 to 13.2) Non-use vs. use 91-365 days RR 2.6 (CI 1.6 to 4.1) Non-use vs. use >365 days RR 2.5 (CI 1.8 to 3.4)	--	--
Laporte 2004[105] 18 hospitals in Spain and Italy (9/1998-12/2001) Cases=2,813 Controls=7193	Upper GI bleeding	Adjusted Odds Ratio (95%): Exposed vs. non-exposed Acetaminophen: 1.2 (1.0, 1.5) NSAIDs (A) 3.7 (2.6, 5.4) (B) 3.1 (2.0, 4.9) (C) 10.0 (4.4, 22.6) (D) 10.0 (3.9, 25.8) (E) 24.7 (8.0, 77.0) (F) 5.7 (2.2, 15.0) (G) 10.0 (5.7, 17.6) (H) 3.2 (1.9, 5.6) (I) 15.5 (10.0, 24.2) (J) 3.6 (2.0, 6.8)	Risk increased with dose, history of peptic ulcer and/or upper GI bleeding, and use of antiplatelet drugs	Excluded patients on anticoagulants

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Author, Year Data Dource Sample Size	Population	Categorization of Exposure	Demographics (age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)
Mellemkjaer 2002[107] Pharmaco-Epidemiologic Database of North Jutland (1991-1995) n=156,138	Age range not reported, but <16 year or >105 years excluded; other exclusions due to alcoholism, esophageal varices, Mallory-Weiss syndrome, liver cirrhosis; cancer	Dispensed prescriptions based on database information	Mean age not reported; 70% (110,062/156,138) <60 years; 12% (19,307/156,138) 60-69 years; 17% (26,768/156,138) >70 years 55% female Race not reported	Retrospective cohort	Sex, five-year age group, 1 -year calendar period
Rahme, 2007 *Arthritis and Rheumatism*[130] Health care records and hospital records of patients in Quebec Canada including those with OA (1997 to 12/2002)	Patients of 65 years of age or older who filled a prescription for acetaminophen or a NSAIDs.	The number of days of supply for each NSAID or acetaminophen prescription with a grace period of 25%.	Age >65 years Male: 45%	Retrospective cohort	Age, gender, alcohol/drug use, co-morbidities (e.g., COPD) and other drugs

Author, Year Data Source Sample Size	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Mellemkjaer 2002[107] Pharmaco-Epidemiologic Database of North Jutland (1991-1995) n=156,138	Hospitalization for upper GI bleeding	Relative risk, hospitalization due to UGIC, non-use vs.: Diclofenac RR 4.9 (3.5-6.6) Ibuprofen RR 2.4 (2.0-2.9) Indomethacin RR 4.3 (2.9-6.0) Ketoprofen RR 6.3 (4.5-8.5) Naproxen RR 3.0 (2.1-4.2) Piroxicam RR 5.0 (3.3-7.2)	Women 4.2 (CI 3.7 to 4.8) Men 2.9 (CI 2.4 to 3.4)
Rahme, 2007 *Arthritis and Rheumatism*[130] Health care records and hospital records of patients in Quebec Canada including those with OA (1997 to 12/2002)	First hospitalization for AMI or GI bleed	Adjusted HR (95% CI) for GI bleed with acetaminophen as a reference A) 0.82 (0.66-1.01) B) 1.11 (0.56-2.16) C) 1.18 (0.86-1.62) D) 2.75 (2.05-3.69) Adjusted HR (95% CI) in patients with OA of AMI or GI bleed A) 1.13 (0.92-1.40) B) 0.61 (0.19-1.91) C) 1.54 (1.12-2.11) D) 1.86 (1.23-2.80)	Aspirin use with a NSAID increased risk of GI bleed

Author, Year Data Dource Sample Size	Population	Categorization of Exposure	Demographics (age, Gender, Race)	Study Design/Type	Adjusted Variables, Selection of Controls (for Case-Control Studies)	NSAIDs Evaluated
Rahme 2007[130] Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183	Patients 65 years old or older who filled a prescription for acetaminophen or a NSAIDs with or w/o PPI versus those taking acetaminophen alone.	The number of days of supply for each NSAID or acetaminophen prescription. Exposure was designated to be 1.25 times number of days supplied). Doses of ≤3 g/day of acetaminophen and/or NSAIDs.	Age ≥65 years Male: 39%	Retrospective cohort	Aspirin, anticoagulants, clopidogrel and other baseline characteristics	(A) Acetaminophen ≤3 g/day (B) Acetaminophen > 3 g/day (C) Acetaminophen and NSAIDs (D) NSAIDs
Rahme 2007[130] Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183	Patients of 65 years of age or older who filled a prescription for acetaminophen or a NSAIDs with or w/o PPI versus those taking acetaminophen alone.	The number of days of supply for each NSAID or acetaminophen prescription. Exposure was designated to be 1.25 times number of days supplied). Doses of ≤3 g/day of acetaminophen and/or NSAIDs.	Age ≥65 years Male: 39%	Retrospective cohort	Aspirin, anticoagulants, clopidogrel and other baseline characteristics	(A) Celecoxib (B) Ibuprofen (C) Diclofenac (D) Naproxen

Author, Year Data Source Sample Size	Outcome: Incidence	Results	Effects of Confounders, Dose, Duration
Rahme 2007[130] Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183	Number of GI hospitalizations (crude rate/1,000 patient-years) A) 640 (4.3) B) 234 (4.9) C) 68 (8.6)	Adjusted HR (95% CI): with acetaminophen $\leq$3g/day (Upper and Lower GI hospitalizations) (A) Reference (B)1.20 (1.03-1.40) (C) 2.55 (1.98-3.28) (D) 1.63 (1.44-1.85) Users of PPI: (A) 0.95 (0.81-1.11) (B)1.16 (0.94-1.43) (C) 2.15 (1.35-3.40) (D) 1.07 (0.82-1.39)	NSAIDs and acetaminophen increase GI risk, PPIs were not protective
Rahme 2007[130] Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183	Hospitalization for GI bleeding or acute MI	Celecoxib: HR 0.82 (CI 0.66 to1.0) Ibuprofen: HR 1.1 (CI 0.56 to 2.2) Diclofenac: HR 1.2 (CI 0.86 to 1.6) Naproxen: HR 2.8 (CI 2.0 to 3.7)	Celecoxib + aspirin: HR 1.85 (CI 1.48 to 2.31) Ibuprofen + aspirin: HR 1.81 (CI 0.75 to 4.40) Diclofenac + aspirin: HR 3.06 (CI 2.16 to 4.35) Naproxen + aspirin: HR 2.37 (CI 1.40 to 3.99)

AMI = acute myocardial infarction; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COX = cyclo-oxygenase; GI = gastrointestinal; GP = general practitioner; HR = hazard ratio; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PPI = proton pump inhibitor; RR = relative risk; SES = socioeconomic status; SSRI = selective serotonin reuptake inhibitor; UGIC = upper gastrointestinal complecations; U.K. = United Kingdom; VA = Veterans Affairs

Appendix I. Evidence Tables: Glucosamine and Chondroitin Studies

Trials

Author Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period	Allowed Other Medications/ Interventions
Herrero-Beaumont, 2007[206] (GUIDE)	Male and female outpatients, diagnosed with primary symptomatic knee OA in 1 or both knees according to the American College of Rheumatology criteria. Grade II or III on the Kellgren/Lawrence radiographic system. Discouraged enrollment of obese patients. Excluded patients with inflammatory joint disease.	Age: Mean age NR overall Placebo: 64.5 +/- 7.2 Acetaminophen: 63.8 +/- 6.9 Glucosamine sulfate: 63.4 +/- 6.9 Female: 278/318 (87.4%) Placebo: 89/104 (86%) Acetaminophen: 93/108 (86%) Glucosamine: 96/106 (91%) Race/Ethnicity NR	RCT	A: Glucosamine: 1500 mg glucosamine sulfate, oral solution, once daily. Rottapharm. B: Acetaminophen side comparator: 1 gram tablets 3 times per day C: Placebo 6 month treatment duration	Narcotic, non-narcotic analgesics or anti-inflammatory symptomatic medications including topical agents were discontinued for the duration of at least 5 half-lives or 72 hours, whichever was longer. Recommended washout for corticosteroids was 3 months and was 6 months for glucosamine or other drugs considered specific for OA.	Ibuprofen 400mg tablets as rescue medication. Physical and/or occupational therapy were allowed if the regimen had been stable for at least 3 months prior to randomization.

Author Year	Other Population Characteristics (Diagnosis, etc)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Herrero-Beaumont, 2007[206] (GUIDE)	Duration of knee OA: 7.4+/-6.0 vs. 6.5 +/-5.3 vs. 7.2+/-5.8 Baseline Lequesne index: 11.0+/-3.1 vs. 11.1+/-2.7 vs. 10.8+/-2.6 Baseline Kellgren/Lawrence grade: Grade 2: 50% vs. 56% vs. 52% Grade 3: 41% vs. 31% vs. 36% Grade 2/3 unspecified: 9% vs. 12% vs. 11% Baseline WOMAC: Total: 38.3+/-15.2 vs. 40.4+/-14.8 vs. 37.9+/-14.3 Pain: 7.8+/-3.0 vs. 8.0+/-2.9 vs. 7.9+/-3.0 Function: 27.8+/-11.4 vs. 29.4+/-11.0 vs. 27.2+/-10.9	334 screened 325 randomized 7 excluded with no efficacy data 318 ITT population	A: 4 adverse events; 7 Lack of efficacy; 5 loss to followup;12 Protocol violations Analyzed 78 protocol completers. 106 ITT population. B: 12 adverse events; 5 Lack of efficacy; 3 loss to fu; 8 protocol violations Analyzed 80 protocol completers. 108 ITT population C: 9 adverse events; 8 Lack of efficacy; 5 Loss to fu; 12 Protocol violations Analyzed 70 protocol completers 104 ITT population	Comparisons to Placebo. No head-to-head. 6 month change in Lequesne Index from baseline A: -3.1 (-3.8, -2.3); p=0.032 B: NS: -2.7 (-3.3,-2.1); p=0.18 C: -1.9 (-2.6, -1.2) 6 month change in WOMAC from baseline Total: A: -12.9 (-15.6, -10.1); p=0.039 B: NS: -12.3 (-14.9, -9.7); p=0.08 C: -8.2 (-11.3,-5.1) Pain: A: NS: -2.7 (-3.3, -2.1); p=0.12 B: NS: -2.4 (-3.0, -1.8); p=0.41 C: -1.8 (-2.6, -1.1) Function: A: -9.2 (-11.2, -7.2); p=0.022 B: -8.7 (-10.6, -6.8); p=0.049 C: -5.5 (-7.7, -3.3) OARSI-A responders: A: 39.6 (p=0.004) B: 33.3 (p=0.047) C: 21.2 OARSI-B, Pain MCII, Function MCII, Pain PASS, Function PASS also reported as secondary outcomes Per-protocol Completers- For all 3 treatments, the degree of improvement in per-protocol completers was higher than that in the ITT population.

Author Year	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Adverse Effects Reported	Total Withdrawals; Withdrawals due to Adverse Events
Herrero-Beaumont, 2007[206] (GUIDE)	Pre-specified: For non- lab AEs: No (general question): For lab AEs: Yes, laboratory tests including measurement of serum glucose and liver function tests were preformed at enrollment, 3 months and 6 months of treatment. Active or passive ascertainment: Active- asked a non leading question during clinic visits and drew labs Assessment of severity: Yes, MedDRA	A vs. B vs. C Total AEs: 95 vs. 96 vs. 89 Symptoms occurring in at least 3 patients during treatment: Dyspepsia: 5 vs. 2 vs. 4 Abdominal pain: 3 vs. 4 vs. 4 Diarrhea: 3 vs. 4 vs. 4 Respiratory tract infections: 8 vs. 4 vs. 9 Gastroenteritis: 4 vs. 0 vs. 2 Coughing and associated symptoms: 1 vs. 4 vs. 0 Headache: 2 vs. 6 vs. 4 Dizziness: 1 vs. 4 vs. 1 Back pain: 7 vs. 4 vs. 5 Neck pain: 3 vs. 2 vs. 0 Fall: 5 vs. 3 vs. 2 Injury: 2 vs. 4 vs. 0 Laboratory: Liver function (transaminases and/or GGT) : 2 vs. 21 vs. 6 Glucose: no change	Withdrawal due to AEs: 4 vs. 12 vs. 9

Author Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period	Allowed Other Medications/ Interventions
Kahan, 2009[209]	Male and female outpatients 45-80 years, primary knee OA of the medial tibiofemoral compartment diagnosed according to ACR.	Chondroitin Sulfate: Age: 62.9 ± 0.5; Female: 70%; Race: NR Placebo: Age: 61.8 ± 0.5; Female: 67%; Race: NR	RCT	A: Chondroitin Sulfates 4&6 800 mg sachet daily, every evening with glass of water B: Placebo sachet daily, every evening with glass of water 2 years	24 hours for acetaminophen, 5 days for NSAIDs prior to symptom assessments	Acetaminophen in 500 mg tablets (max dosage 4 gm/day) NSAIDs in cases of acute pain

Author Year	Other Population Characteristics (Diagnosis, etc)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Kahan, 2009[209]	Duration of knee OA: Left knee: 6.1 ± 0.3 vs. 6.5 ± 0.4; Right knee: 6.6 ± 0.4 vs. 6.3 ± 0.4 KL grade 1: 17.4% vs. 19.7%; KL grade 2: 26.2% vs. 21.6%; KL grade 3: 56.4 vs. 58.7% Minimum JSW, mm: 3.73 ± 0.08 vs. 3.81 ± 0.07 Pain score, 100 mm VAS: 57.2 ± 0.9 vs. 57.3 ± 1.0 WOMAC score, normalized 100mm scales: Total: 40.5 ±1.2 vs. 41.6 ± 1.2; Pain: 40.0±1.2 vs. 40.5±1.2; Function: 39.2±1.3 vs. 39.0±1.2; Stiffness: 42.3±1.5 vs. 43.5±1.5	1052/ NR/ 622	103 vs. 96 withdrawals/ 18 vs. 18 lost to followup/ ITT analysis 622	Interaction between time and treatment effect, indicating that the effect of treatment significantly increased over time ($p<0.01$) Decrease in minimum JSW loss: -0.07 ± 0.03 vs. -0.31 ±0.04, median effect of treatment 0.14mm (0.06-0.21mm), $p<0.0001$ Percentage of patient with radiographic progression: 28% vs. 41%, $p<0.0005$. Relative risk reduction: 33% (16%, 46%) Reduction in minimum JSW loss at 2 years: -0.11 ± 0.04mm vs. -0.39±0.04 mm. treatment effect= 0.20mm (0.11,0.30 mm), $p<0.0001$ Percentage of responder patients at 6 months: reduction in VAS pain score of at least 40%: 53% vs. 45%, $p=0.04$ reduction in VAS pain score of at least 60%: 41% vs. 32%, $p=0.03$ reduction in VAS pain score of at least 40mm: 28% vs. 19%, $p=0.01$ reduction in VAS pain score of at least 60mm: 9% vs. 4%, $p<0.01$ decreased WOMAC of at least 40%: 41% vs. 34%, $p=0.05$ patient assessed VAS at 6 months: 42.2 ± 1.8mm vs. 36.6 ± 1.7mm, $p<0.02$ doctor assessed VAS at 6 months: 39.6 ± 1.6mm vs. 34.8±1.7mm, $p<0.04$

Author Year	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Adverse Effects Reported	Total Withdrawals; Withdrawals due to Adverse Events
Kahan, 2009[209]	Pre-specified: NR Active or passive ascertainment: NR Severity: NR	Gastrointestinal side effects were the most frequently reported, 6% vs. 5.9% No significant laboratory abnormalities	103 vs. 96 withdrawals. 16 vs. 17 withdrawals due to AE

Author Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period	Allowed Other Medications/ Interventions
Mazieres, 2007[210]	Male and female outpatients 50-80 years with medial OA, defined according to ACR criteria. Patients with symptomatic knee OA that had lasted for >6 months, with pain during daily activity ≥ 40 mm on a 0-100 mm visual analogue scale, a Lequesne's Index Score of between 6 and 12, and Kellgren/Lawrence grade 2 or 3 on an anterior-posterior view in an extended standing position taken within the previous 6 months. Exclusions: secondary knee OA, isolated patella-femoral OA and those requiring knee surgery in the coming year, know hypersensitivities to CS or paracetamol, NSAID use for >50% of the time during the previous 2 months, NSAID use within 48 hours before inclusion or SYSADOA, steroid by any route, intra-articular hyaluronic acid or arthroscopic debridement within 6 months before inclusion	CS: Age: 66 (8.8) Female 71% Race: NR Placebo: Age: 66 (7.7) Female: 69% Race: NR	RCT	A: Chondroitin Sulfate 500mg, twice daily by oral route B: Placebo, twice daily by oral route 24 weeks	NR	Start with paracetamol (up to 4 gm/day). NSAIDS allowed if paracetamol was not effective. NSAIDs not allowed 2 days and paracetamol not allowed 12 hours prior to evaluation visits.
Michel, 2005[211]	Male and female patients 40-85 years with clinically symptomatic knee OA (knee pain while standing, walking, and/or on motion for at least 25 of the 30 days prior to study entry) diagnosed according to the ACR clinical and radiographic criteria for OA of the knee. Exclusion criteria: Kellgren/Lawrence grade 4, any causes of secondary OA, traumatic knee lesions, severe comorbidity (severe renal, heart, lung, or neurologic disease), previous joint surgery, intraarticular medications, including corticosteroids into he last month, and the foreseeable prospect of major surgery during the 2- year study period.	Chondroitin Group: Mean age: 62.5 ± 9.1 Female: 51% Race: NR Placebo Group: Mean age: 63.1 ± 10.7 Female: 52% Race: NR	RCT	A: Chondroitin Sulfates 4 & 6, 800mg tablet daily B: Placebo 2 years	3 month washout required for potentially longer acting substances such as Chondroitin Sulfate and Glucosamine	Acetaminophen in 500-mg tablets at a maximum dose of 3 gm/day. Secondary rescue with NSAIDs were allowed up to a maximum 5 consecutive days if the primary rescue analgesia with acetaminophen was insufficient. Physical therapy was limited to application of warmth and strengthening exercises No other interventions allowed

Author Year	Other Population Characteristics (Diagnosis, etc)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Mazieres, 2007[210]	Duration of disease:6.2 (6.8) vs. 6.6 (7.6) VAS pain during activity: 62 (13) vs. 61 (12) VAS pain at rest: 40 (20) vs. 40 (22) Lequesne's Index: 9.5 (2) vs. 9.4 (2) KL stages 2-3: 69% vs. 59%	322/NR/307 (153 CS, 154 Placebo)	14 vs. 14 withdrawals during treatment period, 12 vs. 11 withdrawals during washout period.307 ITT population	Pain During Activity: VAS, mm; Mean (SD)Week 0: 61 (13) vs. 61 (13)Week 4: 48 (21) vs. 51 (20)Week 12: 40 (23) vs. 42 (21)Week 24: 36 (24) vs. 41 (23)Week 32: 33 (23) vs. 40 (24)Change from baseline to week 24: -26.2 (24.9) mm vs. -19.9 (23.5) mm, p= 0.029Lequesne's Index: Mean (SD):Week 0: 9.5 (2.1) vs. 9.4 (1.8)Week 4: 8.3 (2.8) vs. 8.4 (2.4)Week 12: 7.8 (3.6) vs. 7.9 (3.1)Week 24: 7.2 (3.7) vs. 7.7 (3.3)Week 32: 6.8 (3.9) vs. 7.5 (3.6)Change from baseline to week 24: -2.4 (3.4) vs. -1.7 (3.3), p=0.109.OMERACT-OARSI responders: 68% vs. 56% (p=0.03)Change in pain at rest (VAS; mm): -18.8 (23.8) vs. -16.6 (24.2), NSPatient's global assessment: 3.1 (3.0) vs. 2.5 (3.1), NS Investigator's global assessment: 3.1 (2.7) vs. 2.5 (3.0), p=0.044Consumption of analgesics (days): 28 (29) vs. 28 (32), NSConsumption of NSAIDs (days): 6.9 (20.2) vs. 9.2 (24.6), NS QOL, mental: 1.2 (10.4) vs. 0.3 (11.3), NS QOL, physical: 5.8 (9.0) vs. 3.8 (10.2), p=0.021Carry over effect: changes at the end of the follow-up (week 32) compared to the end of the treatment period (week 24):Change in pain on activity -1.9 (20.9) vs. -0.4 (18.7), NS Change in Lequesne's index: -0.4 (2.3) vs. -0.2(2.6), NS
Michel, 2005[211]	ITT Group: Minimum JSW, mm: 2.41 ± 0.14 vs. 2.35 ± 0.14 Mean JSW, mm: 3.04 ± 0.14 vs. 3.00 ± 0.15 WOMAC score, range 0-10: Total: 2.3 ± 1.6 vs. 2.6 ± 1.7 Pain: 2.5 ± 1.6 vs. 2.7 ± 1.8 Function: 2.1 ± 1.6 vs. 2.5 ±1.8 Stiffness: 3.0 ± 2.3 vs. 3.5 ± 2.5	341/300/300	40 vs. 41 withdrawals during treatment 300 ITT analysis	A vs. B, at 2 years JSN Minimum: 0.045 ± 0.48 vs. -0.07 ± 0.56, difference: 0.12 (95% CI 0.00 to 0.24), p=0.05 JSN Mean: 0.00 ± 0.53 vs. -0.14 ± 0.61, difference 0.14 (95% CI 0.01 to 0.27), p =0.04 NS changes in WOMAC: Total: -3.9% vs. 2.1% Pain: -11.0% vs. -6.2% Stiffness: -7.8% vs. -4.6% Function: -0.8% vs. 5.9%

Author Year	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Adverse Effects Reported	Total Withdrawals; Withdrawals due to Adverse Events
Mazieres, 2007[210]	Pre-specified: No Active ascertainment: requested at visits Severity: NR	Total Number of AEs: 141 vs. 155, majority were gastro-intestinal troubles including dyspepsia, nausea, vomiting, abdominal pain and diarrhea. Patients with at least one AE: 49% vs. 49% Patients with at least on SAE: 6.5% vs. 5.2%, one in each group was considered related to treatment, eczema and urticaria	Total withdrawals: 26 vs. 25 due to AE: 13 vs. 8
Michel, 2005[211]	Pre-specified: No Active ascertainment Assessment of severity: No	AEs with frequencies of at least 5% in one of the two study groups: Upper respiratory tract infection: 29% vs. 31% Headache: 7% vs. 9% Abdominal pain: 4% vs. 11% Allergic episode: 6% vs. 6% Cardiac problem: 6% vs. 5% Urinary tract infection: 5% vs. 5%	9 vs. 9 withdrawals due to AE 2 events judged to be related to Chondroitin: abdominal pain and nausea in 1 patient each.

Author Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period	Allowed Other Medications/ Interventions
Messier, 2007[213]	Males and females ≥ 50 years with radiographic evidence of mild to moderate knee OA, Kellgren-Lawrence grade II-III; radiographic classification criteria or confirmation of mild to moderate radiographic evidence of knee OA from a personal physician; not participating in any other intervention study.	Mean Age Overall NR GH/CS: 70.0 ± 1.28 Placebo: 74.1 ± 1.32, p0.03 Female: GH/CS: 75.6% Placebo: 65.9% Race, GH/CS vs. Placebo: Caucasian: 68.9% vs. 77.3% African American: 20% vs. 11.4% Asian/Pacific Islander: 6.7% vs. 2.3% Native American: 4.4% vs. 6.8%	RCT with run-in/washout period, Phase 1 treatment. Phase 2 treatment plus exercise.	A: Glucosamine hydrochloride 1500mg/ day and Chondroitin sulfate 1200mg/day taken either once or three times per day B: Placebo taken either once or three times per day 1 year treatment period	2-week discontinuation of all over-the-counter or prescription medications. Rescue medication with acetaminophen up to 4g per day and any other necessary medications unrelated to OA were permitted.	Rescue medication of acetaminophen up to 4g/day

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Total Withdrawals; Withdrawals due to Adverse Events	Notes
Messier, 2007[213]	--	865 screened/ 435 not interested/ 341 ineligible 89 randomized	17 withdrawn/ 89 analyzed using ITT last observation carried forward	Function (WOMAC physical function 0-68) Mean(SE): Baseline: 25.9 (1.7) vs. 21.1 (1.5), p=0.04 6 months: 21.9 (1.1) vs. 22.9 (1.1), NS 12 months: 19.4 (1.2) vs. 20.6 (1.2), NS Pain (WOMAC pain 0-20): Baseline: 7.1 (0.5) vs. 5.9 (0.5), NS 6 months: 6.2 (0.4) vs. 6.2 (0.4), NS 12 months: 6.0 (0.5) vs. 5.18 (0.5), NS 6 minute walk (meters): Baseline: 384.7 (17.6) vs. 398.7 (17.3), NS 6 months: 393.6 (8.0) vs. 396.5 (7.9), NS 12 months: 409.2 (8.7) vs. 410.5(8.6), NS Knee concentric extension strength (N): Baseline: 209.4 (31.2) vs. 163.9 (20.6), NS 6 months: 176.9 (16.3) vs. 202.7 (17.5), NS 12 months: 207.6 (14.1) vs. 209.7 (15.0), NS Knee concentric flexion strength (N): Baseline: 106.0 (16.1) vs. 83.0 (10.9), NS 6 months: 106.1 (7.3) vs. 106.7 (7.8), NS 12 months: 102.9 (7.7) vs. 124.8 (8.3), p=0.05 Balance (foot length): Baseline: 0.52 (0.04) vs. 0.53 (0.03) 6 months: 0.523 (0.014) vs. 0.583 (0.017), p=0.01 12 months: 0.538 (0.017) vs. 0.591 (0.020), p=0.05 During Phase II: Pill compliant GH/CS group had less pain than the non-compliant group (p=0.02) and a nonsignificant trend in function (p=0.06)	Pre-specified: NR Active or passive: NR Severity: NR	17 withdrawals, 0 due to adverse events 1 AE reported: Hair loss	Groups differ at baseline on age, BMI, gender, annual household income and WOMAC function

Author Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period	Allowed Other Medications/ Interventions
Moller, 2010[212]	Males and females ≥ 40 years of age, with OA of the knee as defined by criteria of the American College of Rheumatology, with pain in the affected knee scoring ≥ 30 on Huskisson's VAS, and a confirmatory knee X-ray diagnosis, Kellgren-Lawrence grades I-III, associated to cutaneous plaque- type psoriasis with a Psoriasis Area and Severity Index score of >5. Exclusion criteria were Kellgren-Lawrence grade IV, VAS ≥ 30 due to pain of any cause in other sites, non- plaque type psoriasis forms, concurrent arthritic conditions that could confound evaluation of the index joint, presence of any clinically significant cutaneous disease that may interfere with the assessment of lesions during the study and presence of any medical condition judged by the investigator to preclude the patient's inclusion in the study.	Age (mean ± SD): Overall: 59.8±10.8 CS: 58.6±11.4 Placebo: 61.0±10.4 Gender (% female): Overall: 52.6% CS: 48.3% Placebo: 57.1% Race: NR	Randomized controlled trial	A: Chondroitin Sulfate 800mg daily B: Placebo 3 months duration	Washout periods: 6 months for intra-articular hyaluronic acid; 3 months for intra-articular corticosteroids and SYSADOAs; 1 month for oral corticosteroids, 1 week for oral NSAIDs; 1 month for high- potency topical corticosteroids, psoralen photochemotherapy and systemic treatment for psoriasis; 2 weeks for ultraviolet and topical treatment for psoriasis.	Acetaminophen allowed for osteoarthritic symptoms. Syndet soap and moisturizing body milk for daily skin care were provided by the study.

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Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Total Withdrawals; Withdrawals due to Adverse Events
Moller, 2010[212]	Kellgren-Lawrence grade I: A: 6.7%, B: 7.1% Kellgren-Lawrence grade II: A: 78.3%, B: 75.0% Kellgren-Lawrence grade III: A: 15.0%, B: 21.4%

Pain intensity, VAS score, mm, mean ± SD: A: 58.1 ± 16.7, B: 56.8 ± 16.0 | 181 screened, 129 randomized | A: 4- No data for at least one follow-up 2- Non compliance 60- ITT population analyzed 58- Per protocol population analyzed

B: 5- No data for at least one follow-up 3- No fulfillment of inclusion criteria 3- Non-compliance 2- Use of medication other than study drug or paracetamol 56- ITT population analyzed 51- Per protocol population analyzed | Pain intensity, VAS, mm, mean ± SD: Baseline: A: 58.8 ± 1.7, B: 56.8 ± 15.3 1 month: A: 43.5 ± 2.8, B: 50.3 ± 2.4; Mean difference: -6.8; 95% CI -13.3 to -0.3; p = 0.041 2 months: A: 36.5 ± 2.7, B: 42.0 ± 2.8; Mean difference: -5.5; 95% CI -13.3 to 2.3; p = 0.165 3 months: A: 31.3 ± 2.8, B: 43.2 ± 2.9; Mean difference: -11.8; 95% CI -19.9 to -3.7; p = 0.0004

Lequesne index, mean ± SD: Baseline: A: 9.0 ± 3.5, B: 9.9 ± 3.5 1 month: A: 7.5 ± 0.3, B: 7.3 ± 0.3; Mean difference: 0.19, 95% CI -0.8 to 1.1, p = 0.700 2 months: A: 5.4 ± 0.4, B: 6.3 ± 0.4; Mean difference: -0.93, 95% CI -2.1 to 0.2, p = 0.109 3 months: A: 4.5 ± 0.5, B: 6.1 ± 0.5; Mean difference: -1.7, 95% CI -3.0 to -0.4, p = 0.013

Acetaminophen, number pills/month, mean ± SD: 1 months: A: 29.5 ± 31.4, B: 29.5 ± 29.6; Mean difference: 3.4, 95% CI 22.7 to 36.3, p = 0.991 2 months: A: 32.3 ± 33.9, B: 28.8 ± 28.2; Mean difference: 3.9, 95% CI 22.6 to 38.7, p = 0.668 3 months: A: 38.2 ± 42.6, B: 30.2 ± 33.8; Mean difference: 5.1, 95% CI 23.1 to 43.7, p = 0.453 | Prespecified: Yes for laboratory blood tests, NR for others

Active ascertainment for blood tests, NR for other

Severity NR | A: 2 withdrawals, 0 for adverse events

B: 13 withdrawals, 0 for adverse events |

Author Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period	Allowed Other Medications/ Interventions
Rozendaal, 2008[207]	Patients met the American College of Rheumatology clinical criteria for hip osteoarthritis and were able to complete questionnaires in Dutch. Excluded patients who had undergone or were awaiting hip replacement surgery, Kellgren and Lawrence score of 4, renal disease, liver disease, diabetes mellitus, or a disabling comorbid condition that would make visits to the research center impossible, patients receiving glucosamine.	Age: Mean age NR overall Placebo: 63.7 (8.5) Glucosamine sulfate: 63.1 (9.5) Female: Placebo: 70.3% Glucosamine: 68.5% Race/Ethnicity NR	RCT	1500mg oral glucosamine sulfate, administered once daily or as two 750 mg tablets Placebo 24 months treatment duration	NR	Baseline Pain Med use: Placebo overall: Daily 18.9% Sometimes: 27.9% None: 53.2% Glucosamine overall: Daily: 28.8% Sometimes: 25.2% None: 46.0% Interventions NR, except Total Hip Arthroplasty was collected and used in analyses.
Rozendaal, 2009[207]	See Rozendall, 2008	See Rozendall, 2008	RCT, subgroup analysis of Rozendall, 2008 data Predefined subgroups: KL=1, KL ≥ 2, localized OA, generalized OA Exploratory subgroups: VAS ≤ 30, VAS > 30, No pain medication, pain medication, no knee OA, knee OA, JSN ≥ 2.5mm, <2.5 mm	See Rozendall, 2008	See Rozendall, 2008	See Rozendall, 2008

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Rozendaal, 2008[207]	Kellgren and Lawrence Score (%): 1: 49.5 vs. 53.2 ≥2: 50.5 vs. 46.8 Mean minimum JSW (SD), *mm*: 2.13 (1.00) vs. 2.33 (0.90) Mean WOMAC score (SD): Pain: 35.9 (23.0) vs. 32.4 (23.2) Function: 36.0 (24.1) vs. 34.1 (21.7) Stiffness: 44.2 (27.2) Mean pain in past week (SD), *mm:* 34.3 (26.5) vs. 30.5 (25.2)	Screened: 387 Eligible & Randomized: 222	Withdrawals during treatment period: NR Lost to follow-up: 7 vs. 8 ITT analysis: 111 vs. 111	Primary Outcomes: WOMAC (negative difference favors glucosamine): Pain overall (SE): -1.90 ± 1.6 vs. -0.30 ± 1.6; Unadjusted difference: -1.60 (-5.60, 2.40); Adjusted difference: -1.54 (-5.43, 2.36) Function overall (SE): -1.69 ± 1.3 vs. 0.38 ± 1.3; Unadjusted difference: -2.07 (-5.53, 1.39); Adjusted difference: -2.01 (-5.38, 1.36) JSN, *mm* (positive difference favors glucosamine sulfate): Minimal: -0.094 (0.32) vs. -0.057 (0.32); Unadjusted difference: -0.038 (-0.130, 0.055); Adjusted difference: -0.029 (-0.122, 0.064) Lateral: -0.180 (0.34) vs. -0.159 (0.36); Unadjusted difference: -0.020 (-0.124, 0.083); Adjusted difference: -0.017 (-0.121, 0.088) Superior: -0.123 (0.36) vs. -0.129 (0.30); Unadjusted difference: 0.006 (-0.090, 0.101); Adjusted difference: 0.016 (-0.079, 0.111) Axial: -0.070 (0.48) vs. -0.079 (0.30); Unadjusted difference: 0.009 (-0.108, 0.124); Adjusted difference: -0.005 (-0.118, 0.108) Secondary Outcomes: WOMAC (Negative difference favors glucosamine): *Pain, 3mos.* -2.50 (19.2) vs. -1.79 (16.2); Unadjusted difference: -0.71 (-5.47, 4.05); Adjusted difference: 0.06 (-4.11, 4.22). *12 mos.* -0.54 (19.9) vs. -0.89 (23.3); Unadjusted difference: 0.35 (-5.66, 6.36); Adjusted difference: 1.42 (-3.82, 6.67). *24 mos.* -1.47 (20.7) vs.0.88 (26.4); Unadjusted difference: -2.34 (-9.16, 4.48); Adjusted difference: -0.77 (-6.53, 4.98). *Function, 3 mos.* -3.29 (14.9) vs. -1.08 (12.7); Unadjusted difference: -2.22 (-5.97, 4.05); Adjusted difference: -2.04 (-5.48, 1.40). *12 mos.* -0.98 (14.9) vs. -0.88 (17.6); Unadjusted difference: -0.11 (-4.63, 4.42); Adjusted difference: 0.11 (-4.14, 4.35). *24 mos.* -0.84 (19.1) vs. 1.92 (19.7); Unadjusted difference: -2.76 (-8.35, 2.84); Adjusted difference: -1.63 (-6.73, 3.47). *Stiffness, 3 mos.*-4.59 (22.6) vs. -3.39 (17.7). Unadjusted difference: -1.20 (-6.66, 4.26); Adjusted difference: -0.12 (-4.94, 4.71). *12 mos.* -1.38 (22.1) vs. -3.43 (21.6); Unadjusted difference: 2.06 (-4.00, 8.12); Adjusted difference: 3.11 (-2.07, 8.28). *24 mos.* -3.43 (26.2) vs. -2.19 (24.1); Adjusted difference: -1.24 (-8.47, 5.98); Unadjusted difference: 0.66 (-5.27, 6.59). VAS pain also reported.

Rozendaal, 2009[207]	See Rozendall, 2008	See Rozendall, 2008	See Rozendall, 2008	The predefined subgroup analyses based on radiographic severity of OA and type of OA did not yield differences between GS and placebo in WOMAC pain, function and JSN. The exploratory analyses showed no difference in WOMAC pain, function and JSN. WOMAC Pain (Negative value favors glucosamine): No Knee OA: 0.3 (21.5) vs. 0.1 (26.2); Unadjusted difference: 0.3 (-7.9, 8.5); Adjusted difference: -0.1 (-4.9, 4.7). WOMAC pain: Concomitant Knee OA: -5.8 (18.1) vs. 2.9 (27.1); Unadjusted difference: -8.7 (-21.2, 3.8); Adjusted difference: -5.68 (-12.62, 1.26).

Author Year	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Adverse Effects Reported		Total Withdrawals; Withdrawals due to Adverse Events
Rozendaal, 2008[207]	Prespecified: yes, used a checklist Active ascertainment; used a checklist at baseline and every 3 months Severity measured: NR	Serious Adverse Events: 4 vs. 2 AE resulting in treatment termination: 4 vs. 6 Abdominal pain: 14 vs. 10 Stomach symptoms: 25 vs. 19 Intestinal symptoms: 19 vs. 17 Increased blood pressure: 11 vs. 19 Decreased blood pressure: 4 vs. 3 Fatigue: 24 vs. 18 Headache: 16 vs. 26 Vertigo: 16 vs. 18 Cardiac problems: 6 vs. 9 Depressive mood: 10 vs. 6 Allergic episode: 7 vs. 5		Lost to follow up: 7 vs. 8, withdrawal during treatment NR. Withdrawal of treatment due to AE: 4 vs. 6
Rozendaal, 2009[207]	See Rozendall, 2008	See Rozendall, 2008		See Rozendall, 2008

Author Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period	Allowed Other Medications/ Interventions

Sawitzke, 2008[214] (GAIT)	Males and females ≥ 40 years of age, had knee pain for at least 6 months occurring on the majority of days in the month preceding their enrollment in GAIT, and had Kellgren/Lawrence gade 2 or 3 knee OA determined on a screening AP radiograph of the knee in a weight bearing position. Exclusion: Minimum baseline medial tibiofemoral JSW of <2mm, predominant lateral compartment OA on any film of the MTP joints, history of significant trauma or surgery to the knee	Age (mean ± SD years): Glucosamine: 56.7± 10.4 CS: 56.4± 9.2 Glucosamine + CS: 56.5± 9.9 Celecoxib: 58.3± 10.7 Placebo: 56.6± 8.4 Female (%): Glucosamine: 61.0CS: 71.8 Glucosamine + CS: 55.9 Celecoxib: 63.8 Placebo: 64.3 Race: NR	Prospective observational study of GAIT enrollees; ancillary study to assess structural changes in knee OA	A: Glucosamine 500 mg 3 times daily B: Chondroitin sulfate (400mg 3 times daily) C:Combination of Glucosamine and Chondroitin D: Celecoxib 200mg daily E: Placebo24 months	NR-check other GAIT pubs	NR- check other GAIT pubs
Sawitzke, 2010[215]	Males and females ≥ 40 years of age, had knee pain for at least 6 months occuring on the majority of days in the month preceding their enrollment in GAIT, and had Kellgren/Lawrence gade 2 or 3 knee OA determined on a screening AP radiograph of the knee in a weight bearing position. Exclusion: Minimum baseline medial tibifemoral JSW of <2mm, predominant lateral compartment OA on any film of the MTP joints, history of signicant trauma or surgery to the knee	Age (mean ± SD years): Glucosamine: 56.7± 10.5 CS: 56.3± 8.8 Glucosamine + CS: 56.7± 10.7 Celecoxib: 57.6± 10.6 Placebo:56.9± 9.8 Female (%): Glucosamine: 68.7 CS: 73.0 Glucosamine + CS: 65.1 Celecoxib: 65.5 Placebo: 65.7 Race: NR	Prospective observational study of GAIT enrollees; ancillary study to assess structural changes in knee OA	A: Glucosamine 500mg 3 times daily B: Chondroitin sulfate (400mg 3 times daily) C:Combination of Glucosamine and Chondroitin D: Celecoxib 200mg daily E: Placebo 24 months	NR	NR

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Total Withdrawals; Withdrawals due to Adverse Events
Sawitzke, 2008[214] (GAIT)	Kellgren/Lawrence Grade 2, %:80.5 vs. 81.0 vs. 69.2 vs. 72.6 vs. 80.5

Kellgren/Lawrence Grade 3, %:19.5 vs. 19.0 vs. 30.9 vs. 27.4 vs. 19.5 | 662 GAIT participants consented to this study | A (177 initial): 33/NR/77 B (123 initial): 30/NR/71 C (128 initial): 40/NR/59 D (143 initial): 32/NR/80 E (134 initial): 36/NR/70 | Mean loss in JSW over 2 years: All NS 0.013 vs. 0.107 vs. 0.194 vs. 0.111 vs. 1.166 Difference from placebo (negative value = less JSW loss): -0.153 (-0.379, 0.074) vs. -0.059 (-0.287, 0.169) vs. 0.028 (-0.214,0.271) vs. -0.055 (-0.279, 0.170) Disease progression over 2 years, % of patients: All NS 18.6 vs. 21.4 vs. 24.4 vs. 20.2 vs. 22.4 OR vs. placebo for disease progression: 0.79 (0.48,1.3) vs. 0.94 (0.57,1.55) vs. 1.12 (0.67,1.88) vs. 0.87 (0.53,1.43) | NR- check earlier GAIT pub | Withdrawals: 33 vs. 30 vs. 40 vs. 32 vs. 36 Technical Loss: 9 vs. 6 vs. 11 vs. 10 vs. 8 Withdrawals due to AE: see earlier GAIT report |
| Sawitzke, 2010[215] | Kellgren/Lawrence Grade 2, %: 59.7 vs. 66.7 vs. 51.9 vs. 62.0 vs. 61.1, p=0.19

Duration of OA symptoms, mean years (SD): 9.7 (10.3) vs. 9.0 (9.0) vs. 10.0 (9.4) vs. 10.2 (9.2) vs. 10.1 (9.4) | 662 GAIT participants consented to this study | See Sawitzke, 2008 | Odds of pain response over 24 months versus placebo by WOMAC, OR (95% CI): A: 1.16 (0.65 to 2.04) B: 0.69 (0.40 to 1.21) C: 0.83 (0.51 to 1.34) D: 1.21 (0.71 to 2.07) E: reference

Odds of a pain response over 24 months versus placebo by OMERACT/OARSI, OR (95% CI): A: 1.16 (0.74 to 1.83) B: 0.89 (0.53 to 1.50) C: 0.85 (0.55 to 1.31) D: 1.45 (0.86 to 2.42) E: reference

Change in WOMAC pain and function score over 24 months | NR in ancillary study | NR in ancillary study |

Author, Year	Eligibility Criteria	Demographics (Age, Gender, Race)	Study Design/ Type	Interventions (Drug, Dose, Duration)	Run-in/ Washout Period
Wilkens, 2010[208]	INCLUSION: Nonspecific chronic LBP (defined as the area below the 12th rib and above the gluteal folds); LBP for at least 6 months with summed score of at least 3 out of 24 points on the Roland Morris Disability Questionnaire, older than 25 years of age. Patients with concomitant leg pain were included as long as the LBP pain rating was higher than the leg pain rating. MRI scans no older than 1 year prior to inclusion consisting of at least 1 axial view and 2 sagittal views were required. MRI confirmed degenerative process. At least one of the following MRI criteria: disk signal intensity changes, reduced disk height compared with adjacent superior disk, facet joint changes, modic changes, or high-intensity zone. EXCLUSION: symptomatic intervertebral disk herniation or spinal stenosis, previous lumbar fracture or surgery, pregnancy or breastfeeding, seafood allergy, ongoing psychiatric or somatic disease potentially influencing a patient's pain and use of any type of glucosamine 1 year prior to enrollment.	Age; mean (SD): Total: 48.5 (11.24) Glucosamine: 47.5 (11.5) Placebo: 49.4 (11.0) Female: Total: 121/250 (48.4%) Glucosamine: 54/125 (43.2%) Placebo: 67/125 (53.6%) Race: NR	RCT	A: Glucosamine sulfate 1500mg or placebo administered as three 500-mg capsules per day. Could be taken as one pill 3 times per day or all at once. B: Placebo 6 month treatment period	NR

Author, Year	Allowed Other Medications/ Interventions	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed
Wilkens, 2010[208]	Rescue medication: Pain killers or NSAIDs, existing analgesics, or usual LBP therapy (e.g., manipulation, physiotherapy, massage)	Mean (SD) Roland Morris Disability Questionnaire (RMDQ) (0-24): 9.2 (3.9) vs. 9.7 (4.5) Numeric Rating Scale (NRS) (0-10): LBP at rest: 3.7 (2.6) vs. 3.9 (2.4) Leg pain at rest: 1.8 (2.2) vs. 2.0 (2.3) LBP when active: 4.9 (2.5) vs. 5.1 (2.3)Leg pain when active: 2.4 (2.6) vs. 2.7 (2.6) EuroQol-5 Dimensions (EQ-5D) (-0.59 to 1.0): 0.57 (0.3) vs. 0.63 (0.2) EuroQol- Visual analog scale (EQ-VAS) (0-100): 5.8 (2.2) vs. 6.4 (2.0)	473 screened/ 250 randomized and enrolled	Withdrawals during treatment period: 7 vs. 10 Loss to followup: 4 vs. 4 Primary analysis is ITT and includes all 250 randomized patients

Author, Year	Results
Wilkens, 2010[208]	Mean SD (95% CI); All results NS: RMDQ (0-24): 6 weeks: 7.0 (6.1, 7.8) vs. 7.1 (6.3, 7.9); 3 months: 5.8 (5.0, 6.6) vs. 6.5 (5.7, 7.3); 6 months: 5.0 (4.2, 5.8) vs. 5.0 (4.2,5.8); 1 year: 4.8 (3.9, 5.6) vs. 5.5 (4.7, 6.4) NRS LBP at rest (0-10): 6 weeks: 2.9 (2.5, 3.3) vs. 2.9 (2.5, 3.3); 3 months: 2.7 (2.4, 3.1) vs. 2.9 (2.5, 3.3); 6 months: 2.5 (2.1, 2.9) vs. 2.4 (2.0, 2.8); 1 year: 2.5 (2.1, 2.9) vs. 2.8 (2.4, 3.1) NRS Leg pain at rest (0-10): 6 weeks: 1.3 (1.0, 1.7) vs. 1.5 (1.2, 1.9); 3 months: 1.4 (1.0, 1.8) vs. 1.7 (1.4, 2.1); 6 months: 1.4 (1.0, 1.7) vs. 1.5 (1.1, 1.8); 1 year: 1.5 (1.1, 1.8) vs. 1.6 (1.3, 2.0) NRS LBP when active (0-10): 6 weeks: 3.7 (3.2, 4.1) vs. 3.6 (3.2, 4.0); 3 months: 3.3 (2.9, 3.7) vs. 3.2 (2.8, 3.6); 6 months: 3.1 (2.7, 3.5) vs. 2.9 (2.5, 3.3); 1 year: 3.0 (2.5, 3.4) vs. 2.9 (2.5, 3.3) NRS Leg pain when active (0-10): 6 weeks: 1.8 (1.4, 2.2) vs. 1.9 (1.5, 2.3); 3 months: 1.7 (1.2, 2.1) vs. 1.9 (1.5, 2.3); 6 months: 1.6 (1.2, 2.0) vs. 1.9 (1.5, 2.3); 1 year: 1.7 (1.3, 2.1) vs. 2.0 (1.5, 2.4) EQ-5D (-0.59 to 1.0): 6 weeks: 0.68 (0.64, 0.72) vs. 0.69 (0.65, 0.72); 3 months: 0.73 (0.70, 0.78) vs. 0.69 (0.65, 0.73); 6 months: 0.74 (0.70, 0.78) vs. 0.76 (0.65, 0.74); 1 year: 0.74 (0.70, 0.78) vs. 0.70 (0.65, 0.74) EQ-VAS (0-100): 6 weeks: 6.8 (6.2, 7.3) vs. 6.7 (6.1, 7.2); 3 months: 7.2 (6.7, 7.8) vs. 6.8 (6.2, 7.3); 6 months: 7.2 (6.6, 7.8) vs. 7.1 (6.7, 7.4); 1 year: 7.4 (7.0, 7.7) vs. 6.6 (6.3, 7.0) Global perceived effect: No. (%): 6 weeks: 22 (18.6) vs. 27 (22.0); 3 months: 26 (21.5) vs. 26 (22.2); 6 months: 39 (33.1) vs. 42 (36.2); 1 year: 14 (30.9) vs. 32 (29.4)

Author Year	Adverse Effects Assessment: Pre-Specified, Active or Passive Ascertainment, Measured the Severity of Adverse Effect?	Adverse Effects Reported	Total Withdrawals; Withdrawals due to Adverse Events
Wilkens, 2010[208]	Pre-specified: NR Ascertainment: NR Severity: NR	OR (95% CI) All NS differences AEs resulting in treatment discontinuation: 0.66 (0.48-1.36) All AEs: 0.83 (0.49-1.40) Skin problems: 0.79 (0.35-1.76) Neurological: 0.65 (0.31-1.38) Heartburn: 0.99 (0.06-15.9) Flatulence: 0.55 (0.21-1.44) Abdominal pain: 1.32 (0.29-6.04) Nausea/vomiting: 1.77 (0.50-6.21) Constipation: 4.03 (0.44-36.69) Diarrhea: 0.55 (0.16-1.92) Headache/vertigo: 0.98 (0.28-3.49) Musculoskeletal concerns: 0.42 (0.14-1.25) 10 AEs resolved with treatment discontinuation; 7 resolved with continuation of study drug; 2 Serious AEs (death and surgery) were considered unrelated to study drug. Fasting blood glucose, cholesterol, and blood pressure levels did not deviate from normal fluctuations during the trial	Total during treatment period: 7 vs. 10 Withdrawals due to AE: Glucosamine: 6 vs. 6

ACR = American College of Rheumatology; AE = adverse event; BMI = body mass index ; CI = confidence interval; CS = chondroitin sulfate; EQ-VAS = EuroQol visual analogue scale; GAIT = Glucosamine/chondroitin Arthritis Intervention Trial; GH = glucosamine hydrochloride; GS = glucosamine sulfate; GUIDE = Glucosamine Unum-in-Die (Once a Day) Efficacy trial; ITT = intention to treat; JSN = joint space narrowing; JSW = joint space width; KL = Kellgren-Lawrence scale; LBP = low back pain; MCII = minimal clinically important improvement; MRI = magnetic resonance imaging; MTP = metatarsophalangeal; NR = not reported; NRS = nonrandomized study; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OARSI = Osteoarthritis Research Society International; OMERACT-OARSI = Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International; PASS = Patient Acceptable Symptom Scale; QOL = quality of life; RCT = randomized controlled trial; RMDQ = Roland Morris Disability Questionnaire; SD = standard deviation; SE = standard error; SYSADOA = Symptomatic Slow Acting Drugs in Osteoarthritis; UTI = urinary tract infection; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Systematic Reviews

Author, Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients
Bjordal, 2007[197]	To determine the short-term pain-relieving effects of seven pharmacological agents for OA knee pain	MEDLINE, Embase, PedRo, Cochrane Controlled Trials Register 1996 through November 2005	Diagnosis: Knee OA verified by clinical exam and/or by x ray. If less than 4 trials available for an intervention, trials also including hip OA were considered, if more than 2/3 of their patients had knee OA; Symptom duration: 3 months; Trial designs: Blinded, placebo-controlled parallel groups RCTs; Outcome measures: Pain intensity within 4 weeks of treatment start on WOMAC or on a 100mm VAS for global or walking pain. Pain intensity at 8-12 weeks follow-up; Intervention groups: Identical placebo drug and adequate daily defined drug dosage equal to or exceeding set dosages per drug: paracetamol 4g, diclofenac 100mg, etodolac 400mg, ibuprofen 2400 mg, nabumetone 1500mg, naproxen 1000mg, oxaprozin 1200mg, tiaprofenic acid 600mg, valdecoxib 10mg, celecoxib 200mg, meloxicam 7.5mg, etoricoxib 30mg, lumiracoxib 200mg, rofecoxib 12.5mg, topical diclofenac, piroxicam or meloxicam 1%, ibuprofen gel 3%, triamcinolone 20mg, methylprednisolone 40mg, cortivazol 3.75mg, glucosamine sulfate 1500mg, chondroitin sulfate 800mg, codeine 50mg, oxymorphone 20mg, oxycodone 20mg, morphine sulfate 30mg, tramadol 100mg	14,060 patients for all included drugs. 9964 patients received Oral NSAIDs including coxibs, 749 received topical NSAIDs, 401 received glucosamine sulfate, 362 received chondroitin sulfate
Hochberg, 2010[199]	To update the 2008 systematic review and meta-analysis with results of an updated meta-analysis that includes data from two recently published studies and limits the pooling to studies of 2- year duration	1996–October 2007	RCTs of 2-year duration that compared orally administered chondroitin sulfate to placebo and reported structural outcomes in the form of change in minimum joint space. No language restriction was applied.	1179

Author Year	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions	Main Results	Subgroups
Bjordal, 2007[197]	64 RCTs total. 25 RCTs of oral NSAIDs (including coxibs), 9 topical NSAIDs, 7 glucosamine sulfate, 6 chondroitin sulfate	Mean Age: Oral NSAIDs: 62.6 years Topical NSAIDs: 64.2 years Glucosamine sulfate: 58.6 years Chondroitin sulfate: 63.0 years Mean baseline pain on 100mm VAS: Oral NSAIDs: 64.3 Topical NSAIDs: 54.7 Glucosamine sulfate: 57.8 Chondroitin sulfate: 50.7	Trials of included Oral NSAIDs:* 6 celecoxib studies; 2 naproxen studies; 2 diclofenac studies; 3 etodolac studies; 1 diflunisal study; 1 meloxicam study; 2 nabumetone studies; 1 oxaprozin study Trials of included Topical NSAIDs: 7 diclofenac, 2 eltenac, 1 ibuprofen Trials of glucosamine: 7 Trials of chondroitin: 6	Best mean difference of change over placebo (100mm VAS): Glucosamine: 4.7 (95% CI 0.3 to 9.1) Chondroitin: 3.7 (95% CI 0.3 to 7.0) Glucosamine and chondroitin did not have effect size or 95% CI exceeding the mean threshold for minimal clinical important improvement, slight improvement, or minimal perceptible improvement	NR
Hochberg, 2010[199]	Randomized controlled trials	Michel et al., 2005: mean age 63, 52% women Sawitzke et al., 2008: mean age 57, 68% women Kahan et al., 2009: mean age 62, 68% women	Michel et al., 2005: 800 mg chondroitin sulfate once daily, 24 month duration Sawitzke et al., 2008: 400 mg chondroitin sulfate three times daily, 24 month duration Kahan et al., 2009: 800 mg chondroitin sulfate once daily, 24 month duration	Joint space narrowing (mm ± SD): Michel et al., 2005: CS: -0.045 ± 0.48, PBO: 0.07 ± 0.56; Mean difference (mm (95% CI)): 0.12 (0.00 to 0.23); Effect size (95 % CI): 0.22 (0.01 to 0.45) Sawitzke et al., 2008: CS: 0.107 ± 0.68, PBO: 0.166 ± 0.68; Mean difference (mm (95% CI)): 0.06 (-0.17 to 0.28); Effect size (95% CI): 0.09 (-0.24 to 0.42) Kahan et al., 2009: CS: 0.07 ± 0.03, PBO: 0.31 ± 0.04; Mean difference (mm (95% CI)): 0.14 (0.06 to 0.21); Effect size (95% CI): 0.26 (0.11 to 0.42) Pooled analysis: Mean difference (mm (95% CI)): 0.13 (0.06 to 0.19); Effect size (95% CI): 0.23 (0.11 to 0.35)	NR

Author, Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients
Lee, 2010[200]	To assess the structural efficacies of daily glucosamine sulfate and chondroitin sulfate in patients with knee OA	Through July 2008	English language RCTs that compared glucosamine sulfate or chondroitin sulfate with a placebo in patients with OA, and utilized JSN as an outcome variable after treatment commencement. Studies were excluded if they did not contain a placebo group, if the OA site was not the knee joint, they did not contain adequate data, or if they were cross-sectional.	749

Author Year	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions	Main Results	Subgroups
Lee, 2010[200]	Randomized controlled trials	Pavelka et al, 2002: mean age patients: 61.2, controls: 63.5; 79% female patients, 76% female controls Reginster et al, 2001: mean age patients: 66.0, controls: 65.5; 75% female patients, 78% female controls Kahan et al, 2006: mean age not available; 68% female patients, 68% female controls Michel et al, 2005: mean age patients: 62.5, controls: 63.1; 51% female patients, 52% female controls Uebelhart et al, 2004: mean age patients: 63.2, controls: 63.7; 79.6% female patients, 82.1% female controls Uebelhart et al, 1998: mean age patients: 60.13, controls: 57.11; 47.8% female patients, 56.5% female controls	Pavelka et al, 2002: GS 1,500 mg qd Reginster et al, 2001: GS 1,500 mg qd Kahan et al, 2006: CS 800 mg qd Michel et al, 2005: CS 800 mg qd Uebelhart et al, 2004: CS 800 mg 2 periods of 3 months during 1 year Uebelhart et al, 1998: CS 400 bid	Glucosamine Sulfate: std diff in means (95% CI): Follow-up for 1 year (2 studies): 0.078 (-0.116 to 0.273), p=0.429 Follow- up for 3 years (2 studies): 0.432 (0.235 to 0.628), p=0.000 JSN > 0.5 mm (2 studies): OR 0.361 (0.204-0.640), p=0.000 Chondroitin Sulfate: std diff in means (95% CI): Minimum JSW (3 studies): 0.317 (0.136-0.497), p=0.001 Mean JSW (4 studies): 0.236 (0.148-0.386), p=0.000 Follow- up for 1 year (2 studies): 0.295 (0.000-0.590), p=0.050 Follow- up for 2 years (2 studies): 0.261 (0.131-0.392), p=0.000	NR

I-22

Author, Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients
Vlad, 2007[201]	To identify factors that explain heterogeneity in trials of glucosamine	1966-2006	Randomized, double-lind, placebo- controlled trials of parenteral or oral glucosmine for pain from OA of the knee or hip, and subjects were followed for >4 weeks.	2613

Author Year	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions	Main Results	Subgroups
Vlad, 2007[201]	Randomized controlled trials	Mean age, % female NR	Glucosamine preparation: Clegg et al, 2006: Hydrochloride Herrero- Beaumont et al, 2005: GS Usha and Naidu, 2004: GS McAlindon et al 2004: Hydrochloride and GS Cibere et al, 2004: GS Pevelka et al, 2002: GS Hughes and Carr, 2002: GS Reginster et al, 2001: GS Rindone et al, 2000: GS Houpt et al, 1999: Hydrochloride Reichelt et al, 1994: GS Noack et al, 1994: GS Vajaradul, 1981: GS Pujalte et al, 1980: GS Rovati et al, 1999: GS	Pooled estimates of heterogeneity and pooled effect estimates (95% CI), P for difference: All studies (15 studies): 0.35 (0.14, 0.56) Glucosamine hydrochloride (3 studies): 0.06 (-0.08, 0.20) Glucosamine sulfate (12 studies): 0.44 (0.18, 0.70) Industry funding absent (4 studies): 0.05 (-0.32, 0.41) Industry funding present (11 studies): 0.47 (0.24, 0.70), $p=0.05$ Industry participation absent (7 studies): 0.11 (-0.16, 0.38) Industry participation present (8 studies): 0.55 (0.27, 0.84), $p=0.02$ Industry-affiliated author absent (8 studies): 0.16 (-0.11, 0.42) Industry-affiliated author present (7 studies): 0.55 (0.27, 0.84), $p=0.04$ Rottapharm product absent (7 studies): 0.11 (-0.16, 0.38) Rottapharm product present (8 studies): 0.55 (0.29, 0.82), $p=0.01$ Allocation concealment adequate (5 studies): 0.09 (-0.24,0.42) intermediate (6 studiess): 0.47 (0.14, 0.80) inadequate (4 studies): 0.54 (0.14, 0.94), $p=0.09$ No ITT analysis (5 studies): 0.44 (0.03, 0.84) ITT analysis (10 studies): 0.31 (0.05, 0.58), $p=0.62$ Jadad score 1-3 (4 studies): 0.30 (-0.14, 0.73) Jadad score 4-5 (11 studies): 0.37 (0.11, 0.63) No rescue medication (3 studies): 0.55 (0.01, 1.10) Rescue medication use (12 studies): 0.31 (0.07, 0.55), $p=0.42$	NR

I-23

Author, Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients
Wandel, 2010[198]	To determine the clinical effect of glucosamine, chondroitin, or the two in combination on joint pain and on radiological progression of disease in OA of the hip or knee	MEDLINE, EMBASE, CINAHL, and Cochrane Controlled Trials Register through June 2010.	Randomized trials with an average of at least 100 patients with knee or hip osteoarthritis per arm. Comparisons included chondroitin sulphate, glucosamine sulphate, glucosamine hydrochloride, or the combination of any two with placebo or head to head. Excluded trial arms with sub-therapeutic doses (<800mg/day of chondroitin, <1500mg/day glucosamine.	3803 to the interventions or placebo. Glucosamine sulphate vs. Placebo: 5 trials, 1104 randomized patients; Glucosamine sulphate or hydrochloride vs. Placebo: 1 trial, 205 patients; Chondroitin sulphate vs. Placebo: 3 trials 1229 patients; Glucosamine hydrochloride, chondroitin sulphate, and their combination vs. placebo: 1 trial, 1265 patients

Author Year	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions	Main Results	Subgroups
Wandel 2010[198]	10 RCTs: designs not specified	8 trials with knee OA only, one trial with hip or knee OA, one trial with hip OA only. Mean age: 58-66 years % Female: 27-86 (median = 68%) Average duration of symptoms: 6 months-10 years	6 glucosamine vs. placebo 3 chondroitin vs. placebo 1 glucosamine, chondroitin, combination vs. placebo	Pain Intensity (10cm VAS): Glucosamine vs. Placebo: -0.4 cm (-0.7 to -0.1) Chondroitin vs. Placebo: -0.3 cm (-0.7 to 0.0) Glucosamine and Chondroitin vs. Placebo: -0.5 cm (-0.9 to 0.0) Radiological joint space difference (negative number favors intervention): Glucosamine vs. Placebo: -0.2 mm (-0.3 to 0.0) Chondroitin vs. Placebo: -0.1mm (-0.3 to 0.1) Glucosamine and Chondroitin vs. Placebo: 0.00 mm (-0.2 to 0.2) Adverse Events, OR (95% CI): Glucosamine vs. Placebo: 0.94 (0.59 to 1.47) Chondroitin vs. Placebo: 0.99 (0.49 to 2.00) Glucosamine and Chondroitin vs. Placebo: no data Withdrawals due to AE, OR (95% CI) Glucosamine vs. Placebo: 0.99 (0.61 to 1.50) Chondroitin vs. Placebo: 0.92 (0.56 to 1.51) Glucosamine and Chondroitin vs. Placebo: 0.90 (0.43 to 1.85)	Estimated differences in pain intensity between supplements and placebo were on average 0.5 cm (0.1 to 0.9) higher in industry sponsored trials (p=0.02 for interaction)

AE = adverse event; CI = confidence interval; CS = chondroitin sulfate; ITT = intention to treat; GS = glucosamine sulfate; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OR = odds ratio; RCT = randomized controlled trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
* Characteristics of oral NSAID trials of included drugs for the current systematic review.

Appendix J. Evidence Tables: Topical NSAIDs

Trials of Topical Compared With Oral

Author Year	Eligibility Criteria	Demographics (age, Gender, Race)	Study Design/ Type	Interventions (Drug, Dose, Duration)	Allowed Other Medications/ Interventions
Dickson, 1991[298]	Male and female patients between 18 and 86 years old with well-documented, mild osteoarthritis of the knee	Mean age: 63 years (range 21-86 years) Female: 66% Race: NR	RCT	A: Topical piroxicam (0.5%) tid + placebo tablet B: Ibuprofen 400 mg po + placebo gel tid 4 weeks	Paracetamol up to 4 mg allowed during washout and throughout trial; no significant difference between groups
Kosuwon, 2010[312]	Ambulatory males, or non-pregnant females, between 40 and 80 years of age diagnosed with OA ≥ 6 months prior to screening according to ACR and confirmed by radiolographic evidence (grade 2 or 3 on Kellgren ascale). Pain in the knee < 80 mm (100 mm VAS scale) and a baseline minimum joint space width in the medial and lateral compartments of the index knee of > 1.5 and > 2.5 mm, respectively.	Age Range: 44-82 (Mean= 61 years) 100% Female Race: NR	RCT, cross-over design	Capsicum tincture 45.50 g (equivalent to capsaicin 0.0125%) per 100 g of Capsika gel®. Subjects applied 2 inches of gel topically 3 times per day for 12 weeks.	Acetaminophen for pain—500 mg three times a day (or every 4-6 hours).

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Dickson, 1991[298]	Baseline overall pain during day: 5.0 vs. 5.0	NR/NR/235 (117 topical piroxicam, 118 oral ibuprofen)	39/3/196 (101 topical piroxicam, 95 oral ibuprofen)	Topical gel piroxicam vs. oral ibuprofen, at 4 weeks Overall pain during day (median, 1-9 scale): 3.0 vs. 2.0, p=0.56 Overall pain during night (median, 1-9 scale): 3.0 vs.3.0, p=0.54 Ability to perform specified activity (median, 1-9 scale): 5.0 vs. 5.0, p=0.33 Rescue analgesic use: 69% vs. 62%
Kosuwon, 2010[312]	Baseline (Mean +/-) VAS: 6.40 +/- 1.64 WOMAC : 51.65 +/- 13.30	NR/NR/100	1/0/99	A) VAS mean difference in capsaicin-placebo (95% CI) Visit 1: 0.16 +/ 0.24 (-0.31, 0.63) Visit 2: 0.56 + 0.23 (0.10, 1.02) Visit 3: 0.43 + 0.25 (0.06, 0.93) Visit 4: 0.72 + 0.27 (0.17, 1.27) B) WOMAC mean difference in capsaicin-placebo (95% CI) Visit 1: 2.86 +/- 0.53 (1.81, 3.92) Visit 2: 3.16 +/- 0.54 (2.09, 4.23) Visit 3: 3.15 +/- 0.53 (2.09, 4.21) Visit 4: 3.42 +/- 0.55 (2.34, 4.51)

Author Year	Adverse Events Assessment: Pre-Specified, Active or Passive Ascertainment, Assessed the Severity of Adverse Events?	Adverse Events Reported	Total Withdrawals; Withdrawals due to Adverse Events	Run-in/ Washout	Class Naïve Patients Only
Dickson, 1991[298]	Prespecified: No (general question) Active or passive ascertaination: Active Assessment of severity: Yes	Topical gel piroxicam (n=117) vs. oral ibuprofen (n=118) Any adverse event judged to be definitely or possibly related to study treatment: 26% vs. 23% Upper GI events: 10% vs. 8.5% Other GI events: 2.6% vs. 0.8% CNS events: 6.0% vs. 6.8% Rash events: 0.8% vs. 0.8% Dependent edema: 0% vs. 6.8% Local effects: 1.7% vs. 0.8%	Topical gel piroxicam vs. oral ibuprofen Total withdrawals: 14% vs. 19% Withdrawal due to adverse events: 7.7% vs. 9.9% Withdrawal due to upper GI events: 5.1% vs. 3.4% Withdrawal due to other GI events: 0.9% vs. 0% Withdrawal due to CNS events: 1.7% vs. 2.5% Withdrawal due to rash: 0% vs. 0.8%	7-day washout free of anti-inflammatory medication	No
Kosuwon, 2010[312]	Unclear if active or passive ascertaination and did not assess severity.	Burning sensation: 66 episodes (17%) in placebo group vs. 272 episodes (67%) in the capsaicin group during 4 week study period. 34 patients (34%) in placebo vs. 57 patients (57.58%) had a burning sensation during the capsaicin period (p < 0.05).	0/1	Washout was 4 weeks (middle of placebo or treatement weeks)	No

Author Year	Eligibility Criteria	Demographics (age, Gender, Race)	Study Design/ Type	Interventions (Drug, Dose, Duration)	Allowed Other Medications/ Interventions
Rother, 2007[299]	Minimum of 6 months' history of osteoarthritis with 2 of 3 criteria: 1) morning stiffness < 30 minutes/duration, crepitus on motion and age $\geq$ 40 years; 2) pain rating as $\geq$3 on a 5 point Likert scale; 3) oral NASIDs at least 3 days per week in the past 3 months or >25 of the past 30 days AND meeting of three osteoarthritis flare criteria	Mean age: 63 years (range NR) Female: 79% Race: NR	RCT	A: 100 mg topical ketoprofen in 4.8 g IDEA-033 (Transfersome) + oral placebo bid B: Celecoxib 100 mg po + placebo gel bid 6 weeks	2,000 mg paracetamol per day for 3 days any week except 48 hours before study visit
Sandelin, 1997[300]	Male and female outpatient patients with radiologically confirmed OA including osteophytes of one or both knees and with pain symptoms for most days of the prior month where analgesics was needed	Mean age: 61 years (range NR) Female: 66% Race: NR	RCT	A: Topical eltenac 1% 3 g tid + placebo 1 T po bid B: Diclofenac 50 mg po bid + placebo gel 3 g tid	NR

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Rother, 2007[299]	Baseline WOMAC pain score (mean, 0 to 100): 55 vs. 56 Baseline WOMAC stiffness score (mean, 0 to 100): 49 vs. 51 Baseline WOMAC physical function score (mean, 0 to 100): 54 vs. 55 Baseline patient global assessment of osteoarthritis (mean, 0 to 4): 3.9 vs. 3.9	499/NR/397 (138 topical ketoprofen, 132 oral celecoxib)	Topical ketoprofen and oral celecoxib arms only 48/1/270 (138 topical ketoprofen, 132 oral celecoxib)	Topical ketoprofen + IDEA-033 vs. oral celecoxib, at 6 weeks WOMAC pain score (mean change from baseline, 0 to 100 scale): -19 vs. -21, p not reported WOMAC physical function score (mean change from baseline, 0 to 100 scale): -16 vs. -18, p not reported Patient global assessment excellent (poor, fair, good, or excellent): 12% vs. 11% Patient global assessment good or excellent: 46% vs. 39% Withdrawal due to lack of efficacy: 0.7% vs. 2.3%
Sandelin, 1997[300]	Bilateral OA: 53% vs. 51% Baseline pain (mean, 0 to 100 VAS): 48 vs. 52 Baseline Lequesne index score (mean, 0 to 24): 9.5 vs. 10	NR/NR/290 (number randomized in each group unclear)	9/0/281 (124 topical eltenac, 89 oral diclofenac)	Topical eltenac vs. oral diclofenac, average at 2-4 weeks Overall pain (mean, 0-100 VAS): 31 vs. 30 Lequesne Index (mean, 0-24 scale): 6.9 vs. 7.3 Physician rated effect "good" (none, slight, moderate, or good): 18% vs. 30%

Author Year	Adverse Events Assessment: Pre-Specified, Active or Passive Ascertainment, Assessed the Severity of Adverse Events?	Adverse Events Reported	Total Withdrawals; Withdrawals due to Adverse Events	Run-in/ Washout	Class Naïve Patients Only
Rother, 2007[299]	Prespecified: Unclear Active or passive ascertainment: Active Assessment of severity: No	Topical ketoprofen + IDEA-033 (n=138) vs. oral celecoxib (n=132) Any GI event: 9.4% vs. 14% Upper abdominal pain: 1.4% vs. 3.0% Dyspepsia: 0.7% vs. 3.0% Nausea: 1.4% vs. 2.3% Musculoskeletal and connective tissue disorders: 8.7% vs. 14% Respiratory, thoracic and mediastinal: 12% vs. 11% Allergic dermatitis: 1.4% vs. 0.8% Erythema: 21% vs. 14%	Topical ketoprofen + IDEA-033 vs. oral celecoxib Total withdrawals: 18% vs. 17% Withdrawal due to adverse events: 17% vs. 14%	NR/NR	No
Sandelin, 1997[300]	Prespecified: Unclear Active or passive ascertainment: Unclear Assessment of severity: No	Topical eltenac (n=126) vs. oral diclofenac (n=82) Any adverse events: 27% vs. 24% Any GI event: 4.8% vs. 13% CNS events: 9.5% vs. 7.3% Local skin reactions: 13% vs. 1.2% Other: 5.6% vs. 4.9%	Topical eltenac vs. oral diclofenac Total withdrawals: Not reported Withdrawal due to adverse events: 5% vs. 1.2%	NR/NR	No

Author Year	Eligibility Criteria	Demographics (age, Gender, Race)	Study Design/ Type	Interventions (Drug, Dose, Duration)	Allowed Other Medications/ Interventions
Simon, 2009[301]	Male and non-pregnant women aged 40-85 with primary OA of the knee based on a) standard radiological criteria from a recent examination within 3 months; b) pain with regular use of pain meds; c) a flare of pain and a minimum Likert pain score of 8 at baseline	Mean age: 62 years (range NR) Female: 65% Non-white: 22%	RCT	A: Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium in 45.5% DMSO) 40 drops qid + oral placebo B: Oral diclofenac slow release 100 mg + placebo solution qid 12 weeks	Acetaminophen (up to four, 325 mg per day), except 3 days before efficacy assessment Glucosamine, chondroitin, anti-depressants or proton pump inhibitor, or low dose ($\leq$325 mg/day) aspirin allowed
Tugwell, 2004[303]	Men and nonpregnant women 40 to 85 years old, with symptomatic primary OA of the knee and recent (<3 months) x ray showing osteoarthritis (confirmed by radiologist)	Mean age: 64 years (range NR) Female: 57% Non-white: 6%	RCT	A: Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium in 45.5% DMSO) 50 drops + oral placebo tid B: Diclofenac 50 mg po + topical placebo tid 12 weeks	Aspirin up to 325 mg/day for cardiovascular prophylaxis (use comparable in groups 14% topical and 15% oral)

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Simon, 2009[301]	Bilateral OA: 99% vs. 99% Baseline WOMAC pain score (mean, 0 to 20): 13 vs. 13 Baseline WOMAC physical function score (mean, 0 to 68): 42 vs. 42 Baseline WOMAC stiffness score (mean, 0 to 8): 5.1 vs. 5.2	1396 (overall)/NR/775 (154 to topical diclofenac, 151 to oral diclofenac)	Topical and oral diclofenac arms only 95/4/305 (154 topical diclofenac, 151 oral diclofenac)	Topical diclofenac vs. oral dicofenac, at 12 weeks WOMAC pain score (mean change from baseline, 0-20): -6.0 vs. -6.4, p=0.43 WOMAC physical function score (mean change from baseline, 0 to 68): -16 vs. -18, p=0.32 WOMAC stiffness score (mean change from baseline, 0 to 8): -1.9 vs. -2.1, p=0.60 Patient overall health assessment score (mean change from baseline, 0 to 4): -0.95 vs. -0.88, p=0.96 Patient global assessment of the study knee (mean change from baseline, 0 to 4): -1.4 vs. -1.4, p=0.44 Withdrawal due to lack of efficacy: 10% vs. 3.3%
Tugwell, 2004[303]	Mean OA duration: NR Total x-ray score (mean, maximum 27): 6.4 vs. 6.2 Baseline WOMAC pain score (mean, 0 to 500): 288 vs. 289 Baseline WOMAC physical function score (mean, 0 to 1700): 979 vs. 983 WOMAC stiffness score (mean, 0 to 200): 123 vs. 124	1057/NR/622 (311 topical diclofenac, 311 oral diclofenac)	145/10/604 (303 topical diclofenac, 301 oral diclofenac)	Topical vs. oral diclofenac, at 12 weeks WOMAC pain score (mean change from baseline, 0-500 scale): -118 vs. -134; difference 16 (-3.4 to 36.1), p=0.10 WOMAC physical function score (mean change from baseline, 0-1700 scale): -348 vs. -438; difference 90 (24 to 156), p=0.008 WOMAC stiffness score (mean change from baseline, 0-200 scale): -45 vs. -52; p=0.14 Pain on walking (mean change from baseline, 0 to 100 scale [based on 1st item of the WOMAC pain subscale): -25 vs. -24; difference 1.7 (-2.9 to 6.4), p NS Patient global assessment (mean change from baseline, 0-100 scale): -27 vs. -32; difference 4.5 (-0.5 to 9.6), p=0.08 Number of responders (OMERACT criteria, >=50% improvement in pain or function that was >=20 mm on a 100 mm VAS, or >=20% improvement in at least two of pain, function, or patient global assessment that was >=10 mm on a 100 mm VAS): 66% vs. 70%, p=0.37 Withdrawal due to lack of efficacy: 9.0% vs. 3.2%

Author Year	Adverse Events Assessment: Pre-Specified, Active or Passive Ascertainment, Assessed the Severity of Adverse Events?	Adverse Events Reported	Total Withdrawals; Withdrawals due to Adverse Events	Run-in/ Washout	Class Naïve Patients Only	Notes
Simon, 2009[301]	Pre-specified: Unclear Active or passive ascertainment: Active Assessment of severity: No	Topical diclofenac (n=154) vs. oral diclofenac (n=151) Any adverse event: 62% vs. 62% Any GI event: 6.5% vs. 24% Abdominal pain: 3.2% vs. 7.3% Dyspepsia: 2.6% vs. 4.0% Nausea: 0% vs. 2.0% Dry skin at application site: 18% vs. 2.6% Contact dermatitis at application site: 2.6% vs. 0.7% Rash: 2.6% vs. 0% Headache: 18% vs. 17% Back pain: 10% vs. 7.3% Arthralgia: 9.1% vs. 7.9%	Topical diclofenac vs. oral diclofenac Total withdrawals: 33% vs. 29% Withdrawal due to adverse events: 10% vs. 13%	NR/NR	No	Has topical diclofenac + oral diclofenac group
Tugwell, 2004[303]	Prespecified: Unclear Active or passive ascertainment: Unclear Assessment of severity: Yes	Topical diclofenac (n=311) vs. oral diclofenac (n=311) Any GI events: 35% vs. 48%, p=0.0006 Abdominal pain: 12% vs. 22%, p=0.0008 Diarrhea: 9% vs. 17%, p=0.001 Dyspepsia: 15% vs. 26%, p=0.001 Flatulence: 10% vs. 17%, p=0.009 Melena: 1% vs. 2%, NS Nausea: 25% vs. 41%, p=0.4 Dry skin: 27% vs. 1%; p<0.0001 Rash: 12% vs. 2%, p<0.0001 Vesiculobullous rash: 5% vs. 0%, p<0.0001 Asthma: 0.6% vs. 3%, p=0.02 Dizziness: 0.6% vs. 4%, p=0.002 Dyspnea: 0% vs. 2%, p=0.01	Topical diclofenac vs. oral diclofenac Total withdrawals: 41% vs. 37% Withdrawal due to adverse events: 21% vs. 25%	NR/wash out 3-10 days	No	

Author Year	Eligibility Criteria	Demographics (age, Gender, Race)	Study Design/ Type	Interventions (Drug, Dose, Duration)	Allowed Other Medications/ Interventions
Underwood, 2007[49] (TOIB study)	Literate men and women ≥ 50 years of age with troublesome pain around the knee most days for at least 1 month with knee pain more than three months out of preceding year; consultation with or treatment prescribed by GP for knee pain in the last 3 years.	Mean age: 64 years (range 50-89 years) Female: 56% Non-white: 1%	RCT	A: Advice to use a topical NSAID (over-the-counter or prescription), preferably ibuprofen, as needed for knee pain B: Advice to use an oral NSAID, preferably ibuprofen (up to 1.2 g/day), as needed for knee pain 24 months or longer	Not specified
Tiso, 2010[302]	Subjects from a pain management practice who were ≥ 50 years old and ≥ 3 months of knee pain	Mean age 58 years Female: 89%	RCT	A: 800 mg ibuprofen 3 times daily B: 2 ml of 4% topical ibuprofen applied 4 times per day (320 mg total)	Not specified

Author Year	Other Population Characteristics (Diagnosis, etc.)	Number Screened/ Eligible/ Enrolled	Number Withdrawn/ Lost to fu/ Analyzed	Results
Underwood, 2007[49] (TOIB study)	Met ACR criteria for OA: 97% vs. 98% Baseline WOMAC pain score (mean, 0 to 100): 19 vs. 22 Baseline WOMAC stiffness score (mean, 0 to 100): 25 vs. 26 Baseline WOMAC physical function score (mean, 0 to 100): 23 vs. 18 Baseline WOMAC global assessment (mean, 0 to 100): 18 vs. 22	Number assessed and eligible for RCT unclear/282 randomized (138 to advice for topical NSAID, 144 to advice for oral NSAID)	18 at 3 months, 34 at 1 year/NR/264 at 3 months, 248 at 1 year	Advice to use a topical NSAID vs. advice to use an oral NSAID, at 3 months, 1 year, 2 years, and end of study (last value carried forward or 2 years); positive scores favor oral WOMAC pain score (difference in change from baseline, 0 to 100): -2 (-6 to 2), 1 (-4 to 6), 6 (0 to 12), 5 (0 to 9) WOMAC stiffness score (difference in change from baseline, 0 to 100): -3 (-8 to 2), 0 (-6 to 5), -1 (-8 to 6), -2 (-7 to 4) WOMAC physical function score (difference in change from baseline, 0 to 100): -2 (-5 to 2), 3 (-2 to 7), 5 (-1 to 10), 3 (-2 to 7) WOMAC global assessment (mean difference in change from baseline, 0 to 100: -2 (-5 to 2), 2 (-2 to 6), 4 (-1 to 10), 3 (-1 to 7)
Tiso, 2010[302]	Pain duration >12 months: 95% Chronic Grade Pain: I: 5% II: 16% III: 37% IV: 42%	30/22/20	0/1/19	--

Author Year	Adverse Events Assessment: Pre-Specified, Active or Passive Ascertainment, Assessed the Severity of Adverse Events?	Adverse Events Reported	Total Withdrawals; Withdrawals due to Adverse Events	Run-in/ Washout	Class Naïve Patients Only	Notes
Underwood, 2007[49] (TOIB study)	Prespecified: Yes Active of passive ascertainment: Unclear Assessment of severity: Yes	Advice to use topical NSAID (n=136) vs. advice to use oral NSAID (n=140) Deaths by 24 months: 0% vs. 0% Gastric bleeding by 24 months: 0% vs. 0% Emergency hospital admission (any reason) by 24 months: 7% vs. 4% (difference 3.1%, -2.5 to 8.6%) Cardiovascular hospital admission by 24 months: 2.9% vs. 3.5% Defined GI adverse event (dyspepsia, laboratory evidence of anemia) by or at 12 months: 42% vs. 40% (difference 2.5%, -9 to 14%) New diagnosis of heart failure at 12 months: 1% vs. 0% Increase in systolic blood pressure >=20 mm Hg at 12 months: 13% vs. 11% Peak expiratory flow reduced by 15% or more at 12 months: 8% vs. 18%; difference -10% (-19 to -1%) Minor GI events: 42% vs. 40% Minor renovascular events: 16% vs. 15% Minor respiratory events: 7% vs. 17% Any minor adverse event: 56% vs. 56%	Advice to use topical NSAID vs. advice to use oral NSAID Missing follow-up data: 12% vs. 12% at 12 months; 42% vs. 36% at 24 months Withdrawal due to adverse events: Not reported	NR/NR	No	Comprehensive data available, also has patient preference data of oral vs. topical as well as cost-effectiveness analyses
Tiso, 2010[302]	Prespecified: Yes Active of passive ascertainment: Unclear Assessment of severity: Yes	NR	NR	NR/2 days	No	

ACR = American College of Rheumatology; bid = twice daily; CNS = central nervous system; DMSO = dimethyl sulfoxide; GI = gastrointestinal; GP = general practitioner; IDEA = drug name for epicutaneous ketoprofen in transfersome; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OMERACT = Outcomes Measures in Arthritis Clinical Trials; QR = quality result; RCT = randomized controlled trial; tid = three times daily; TOIB = Topical or Oral Ibuprofen study; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Systematic Reviews

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Lin 2004[306]	To access the efficacy of topical NSAIDS in the treatment of osteoarthritis	MEDLINE, Embase, CINAHL, Scientific Search Index and Cochrane Library, and conference abstracts 1966 to 10/31/2003	RCTs comparing topical NSAIDs with placebo OR oral NSAIDs Studies included those with clinical or radiographical (cross checked by 2 radiologists) evidence of osteoarthritis	n=1983	13 RCTs: double blinded crossovers, double blinded parallel	Patients with diagnosis of radiographical evidence of osteoarthritis
Mason 2004[305]	To access the efficacy of topical NSAIDS in relieving pain	MEDLINE, Embase, Pre Medline, Cochrane Library and references supplied by pharmaceutical companies 1966 to April 2003	Double blinded RCTs in which treatments were given to adult patients with moderate to severe chronic pain resulting from musculoskeletal or other painful disorders	n=1,502 (efficacy) n=2,302 (trials with adverse events)	14 efficacy trials 18 placebo controlled trials	Generally, patients were over 40 years of age with predominantly musculoskeletal disorder and with baseline pain of moderate to severe intensity
Mason 2004[313] (capsaicin)	To determine the efficacy and safety for topically applied capsaicin for chronic pain from neuropathic or musculoskeletal disorder	MEDLINE, Cochrane Library, Embase, and PubMed up to April 2003	16 trials	n=1556	RCT	Patients aged 20 to 95 years with 11 trials of a baseline pain of moderate to severe and 7 allowed concomitant drugs

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Comments
Lin 2004[306]	(A) Topical NSAIDs vs. placebo= 9 trials (B) Topical NSAIDs vs. oral NSAIDS or placebo=2 trials (C) Topical NSAIDS vs. oral NSAIDs=2 trials	(A) Superior in pain reduction in the first two weeks of treatment: effect sizes for weeks 1 AND 2 were 0.41 [95% CI 0.16 to 0.66] and 0.40 [95% CI 0.15 to 0.65] respectively; no benefit observed in weeks 3 and 4 (B) Topical NSAIDs vs. oral NSAIDS; Week 1 Pooled effect size -0.38 [95% CI -0.66 to -0.10] AND Week 2 -0.19 [-0.47 to 0.09]	Efficacy: pain reduction, topical NSAIDs were superior to placebo in the first two weeks of treatment; topical NSAIDs were less effective than oral NSAIDs numerically at any week and statistically in the first week	Adverse events (A) Rate Ratio: 1.02 (0.62 to 1.68); (C) Rate ratio: 0.99 (.77 to 1.27) Topical NSAIDs had no more side effects than placebo. Compared with oral NSAIDs, fewer patient taking topical NSAIDs had any adverse events, withdrawals due to side effects and GI side effects, but significantly more patients had local side effects such as rash, itch and burning.
Mason 2004[305]	Pennsaid vs. Placebo (3 trials) WOMAC (1) Pain (2) Stiffness (3) Physical function scale	(A) Topical vs. oral 1.1 (95% CI, 0.9 to 1.3) (B) Local adverse events occurred in 8% in topical vs. oral NSAID, 3%	Efficacy: for 4 or 5 patients with chronic pain treated with topical NSAID, one would benefit who would not have with placebo 95% CI Osteoarthritis of the knee with topical NSAIDs: 2.02 (1.57, 2.60) Topical NSAIDs vs. placebo for chronic pain 1.87 (1.61, 2.17)	RR (95% CI) Local adverse events: 1.0 (0.7 to 1.5) Systematic events: 1.7 (0.96 to 2/85) Withdrawal due to adverse events 0.9 (0.4 to 2.1)
Mason 2004[313] (capsaicin)	Capsaicin vs. placebo (A) Pain in neuropathic conditions (B) Pain in musculoskeletal conditions	Relative benefit (95% CI) (A) 4 weeks: 1.5 (1.1 to 2.0) (B) 4 weeks: 1.4 (1.1 to 1.7); 8 weeks: 1.4 (1.2 to 1.7)	Topical capsaicin is better than placebo for the treatment of chronic pain. Local adverse events are common.	Local 3.6 (2.6 to 5.0) Withdrawals 4.0 (2.3 to 6.8)

Author Year	Aims	Time Period Covered	Eligibility Criteria	Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Mason 2004[30] (rubefacients)	To determine the efficacy and safety of topical rubefacients containing salicylates in acute and chronic pain	MEDLINE, Cochrane Library, Embase, and PubMed up to March 2003	3 trials, acute conditions 5 trials, chronic conditions	n=862	Randomized placebo controlled	Patients age ranged from 14 to 86 years and treatments contained salicylate as the primary ingredient
Towheed 2006[180]	To access the efficacy of topical diclofenac in patients with osteoarthritis of the knee	MEDLINE (1966 to February 2nd, 2005), Embase, CSDR, ACP Journal Club, DARE, CCTR	4 trials, Pennsaid vs. VCP vs. placebo; 2 trials Pennsaid vs. VCP; Pennsaid vs. oral diclofenac	n=1412 (randomized subjects) n=666 (Pennsaid) n=746 randomized to comparator groups n= 970 completed trials	4 RCTs	Mean trial duration was 8.5 weeks, all patients had osteoarthritis of the knee and in 3 trials specified radiographic criteria used by investigators to establish OA diagnosis

Author Year	Characteristics of Identified Articles: Interventions	Main Results	Subgroups	Comments
Mason 2004[30] (rubefacients)	Topical vs. placebo (A) Pooled relative benefit for acute conditions (B) Pooled relative benefit for chronic conditions	Relative benefit (95% CI) (A) 3.6 (2.4 to 5.6) (B) 1.5 (1.3 to 1.9)	Efficacious in acute pain and moderately to poorly effective in chronic arthritic and rheumatic pain. Longest trial lasted 28 days most lasted 14 days	Acute pain local: 1.1 (0.4 to 3.5)
Towheed 2006[180]	Pennsaid vs. VCP (3 trials) (A)WOMAC (1) Pain (2) Stiffness (3) Physical function scale (B) Patient Global Assessment (PGA)	RR 95% CI (A) WOMAC (1) -0.33 (-0.40 to -0.18) (2) -0.30 (-0.45 to -0.15) (3) -0.35 (-0.50 to -0.20) (B) -0.39 (-0.50 to -0.20) (C) Safety	Pennsaid was of equivalent efficacy as oral dicofenac in WOMAC outcomes and was significantly better tolerated than oral diclofenac	(A) Safety, adverse events, localized (1) Skin dryness: 1.74 (1.37 to 2.22) (2) Paresthesias: 0.60 (0.33 to 1.10 (3) Rash: 1.69 (0.96 to 2.95) (B) Systemic (Absolute Risk) (1) GI events: 1.11 (0.74 to 1.68) (B) Any adverse event (1) 1.11 (0.74 to 1.68) (2) 1.11 (1.0 to 1.24)

ACP = American College of Physicians; CI = confidence interval; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; VCP = vehicle control placebo; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.