Draft Comparative Effectiveness Review

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Comparative Effectiveness and Safety of Analgesics for Osteoarthritis- An Update of the 2006 Report

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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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 State Children's Health Insurance Program (SCHIP).

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://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 are essential to the Effective Health Care Program. Please visit the Web site (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.

Acknowledgements

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Comparative Effectiveness and Safety of Analgesics for Osteoarthritis- An Update of the 2006 Report

Executive Summary

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at
www.effectivehealthcare.ahrq.gov

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. 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. 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.

Common oral medications for osteoarthritis include nonsteroidal antiinflammatory 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. 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. 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.

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

cyclo-oxygenase (COX) enzymes. NSAIDs are thought to exert their effects primarily through blocking different COX isoenzymes, in particular COX-1 and COX-2. COX-1 protects the lining of the stomach from acid. COX-2 is found in joint and muscle, and mediates effects on pain and inflammation. By blocking COX-2, NSAIDs reduce pain compared to placebo in patients with arthritis, low back pain, 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 nonaspirin NSAIDs was estimated at 3,200 annually in the 1990's. 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). 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 "nonaspirin, nonselective NSAIDs" or simply "nonselective NSAIDs" as "all other NSAIDs."

Objectives

The purpose of this comparative effectiveness review (CER) is to update the previous report that assessed the comparative efficacy and safety of nonopioid oral medications (selective and nonselective nonaspirin 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

a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?
b. 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 nonsteroidal antiinflammatory drugs (NSAIDs) includes studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.

Oral Agents include:

- Acetaminophen
- Aspirin
- celecoxib (Celebrex®)
- chondroitin
- diclofenac
- diflunisal
- etodolac
- Ketoprofen
- ketorolac
- meclofenamate sodium
- mefenamic acid
- meloxicam
- nabumetone
- naproxen

- fenoprofen
- flurbiprofen
- glucosamine
- ibuprofen
- indomethacin
- oxaprozin
- piroxicam
- salsalate
- sulindac
- tolmetin

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 co-prescribing H2 receptor antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?

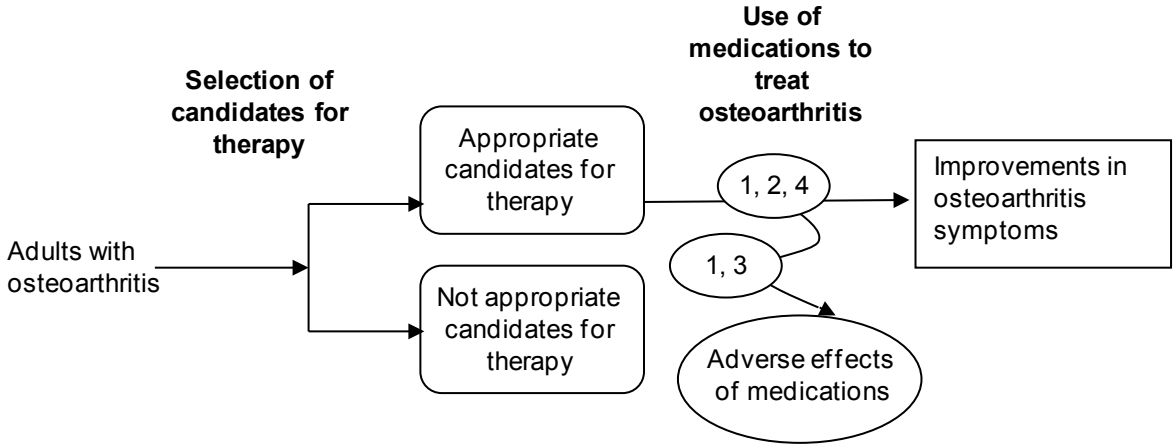
Key Question 4
What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations, or of different topical medications compared with one another?

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 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



Methods

Input from Stakeholders

The topic for the original 2006 report 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). Contacted via teleconference, the TEP served in an advisory capacity for the original report, helping 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 the 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. Prior to participating in official TEP activities for this report, the TEP members disclosed all financial or other potential conflict of interest with the topic and included drugs. These conflicts were reviewed by the authors and AHRQ Task Order Officer and a determination was made 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 2010) the Cochrane Central Register of Controlled Trials (through 1st Quarter 2010) and Ovid ®MEDLINE (2005- March, 2010). 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 SRC 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", salicyclic acid derivatives, and "nonaspirin, nonselective" NSAIDs as described on p. ES-5. We excluded evidence on NSAIDs unavailable in the U.S., 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 [MI], congestive heart failure [CHF], 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.

We included systematic reviews 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 1039 citations from these sources and the original report were imported into an electronic database (EndNote® X2) 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), methods proposed by Downs and Black (observational studies), and methods developed by the US Preventive Services Task Force.[1] The criteria used is similar to the approach recommended by AHRQ in the draft *Methods Reference Guide for Effectiveness and Comparative Effectiveness Review.*

Individual studies were rated as "good," "fair" or "poor". 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.

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. 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 draft Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. We considered the type, number, and quality of studies; the risk of bias; 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; 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: 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. 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 non-selective) appear to be associated with increased risk of serious CV risks.rthermore, 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
1a. 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 worse 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 nonaspirin, 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 versus other NSAIDs.

Key Question	Strength of Evidence	Conclusion
GI and CV harms: Celecoxib	High (multiple systematic reviews and meta-analyses of mostly short-term trials, multiple observational studies; limited long-term data on serious GI harms)	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 the end of followup. There was no difference in rates of ulcer complications or symptomatic ulcers at either 6 month or complete followup. 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 versus ibuprofen or diclofenac in CLASS (0.5% vs. 0.3%). 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 1000 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. Three large observational studies found celecoxib associated with similar 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).
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 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 was associated with a lower risk of ulcer

Key Question	Strength of Evidence	Conclusion
		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: Low 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 (consistent evidence from many trials and observational studies)	GI harms: COX-2 selective NSAIDs as a class were associated with a similar reduction in risk of ulcer complications versus 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: Moderate (almost all evidence from observational studies, few large, long-term controlled trials)	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. 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) versus placebo, but did not employ pre-specified stopping protocols. In most large observational studies, naproxen was associated with a neutral effect on risk of serious CV events.
GI and CV harms: Aspirin	Moderate (many trials, but almost exclusively in patients receiving aspirin for cardiovascular disease prevention, usually at lower prophylactic doses)	GI harms: A systematic review found aspirin associated with a risk of GI bleeding of 2.5%, compared to 1.4% with placebo. Observational studies showed a similar risk of upper GI bleeding with aspirin and nonaspirin, nonselective NSAIDs. CV harms: Aspirin reduced the risk of vascular events by an average of 23% in a collaborative meta-analysis of 65 randomized controlled trials.
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. On 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,	All NSAIDs are associated with deleterious effects on blood pressure, edema, and renal function. No clear evidence of clinically relevant, consistent differences

Key Question	Strength of Evidence	Conclusion
	but analyses limited by incomplete reporting of outcomes)	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, versus 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).
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 0.70-0.80) and withdrawals due to GI adverse events (RR 0.45, 95% CI 0.33-0.56) 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, 955 CI 0.84-0.99), 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 0.54-0.69) 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 NSAID (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). Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies). 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
Glucosamine and chondroitin	High (consistent evidence from recent,	Seven randomized trials showed no clear difference between glucosamine versus oral NSAIDs for pain or

Key Question	Strength of Evidence	Conclusion
	higher-quality trials)	function. One randomized trial showed no difference between chondroitin versus 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 U.S.).
1b. 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 risk of cardiovascular 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.
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) Low for sex and race (most studies included a majority of women,	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.

Key Question	Strength of Evidence	Conclusion
	but studies didn't evaluate whether comparative benefits and harms vary in men and women or in different racial groups)	There is almost no evidence on the comparative benefits and harms of different selective and nonselective NSAIDs in men compared to women, or in different racial groups.
Pre-existing 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 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 versus 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. A large observational study found an increased risk of repeat heart failure admission in patients recently discharged for heart failure prescribed 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 increase 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.
Concomitant use of prophylactic dose aspirin	High for GI safety: Consistent evidence from clinical trials and observational studies Moderate for CV safety: 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 either celecoxib or nonselective NSAIDs. 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

Key Question	Strength of Evidence	Conclusion
		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 didn't clearly demonstrate increased risk.
3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?	High: Consistent evidence from good-quality systematic reviews and numerous clinical trials	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-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. Misoprostol was the only gastroprotective agent to reduce risk of ulcer complications compared to placebo in patients prescribed nonselective NSAIDs, but was also associated with a higher rate of withdrawals due to adverse GI symptoms. 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 combined upper and lower GI events (primarily decreases in hemoglobin or hematocrit 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.
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	Low (no head-to-head trials, 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 higher-quality trials. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events

Key Question	Strength of Evidence	Conclusion
		and withdrawals due to adverse events (13% vs. 3%, RR 4.0, 95% CI 2.3 to 6.8).

Abbreviations: CHF= Congestive Heart Failure; CI= Confidence Interval; CLASS= Celecoxib Long-term Arthritis Safety Study; COX= Cyclo-oxygenase; CV= Cardiovascular; FDA= 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; NSAIDs= Nonsteroidal antiinflammatory drugs; OR= Odds Ratio; PPI= Proton pump inhibitor; PUD= Peptic Ulcer Disease; RR= Relative risk; VAS= Visual analogue scale

Discussion and 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 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 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 nonaspirin 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 U.S. 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 radiolographic 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:

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

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Introduction

Background

Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life.[2] 27 million adults in the United States (U.S.) are thought to have clinical osteoarthritis.[3] In large surveys, 5% to 17% of U.S. adults had symptomatic osteoarthritis of the knee, and 9% had symptomatic osteoarthritis of the hip.[3] 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.[4] The total costs for arthritis, including osteoarthritis, may be greater than 2% of the gross domestic product,[5] with more than half of these costs related to work loss.[4]

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.[6] 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 antiinflammatory 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.[6, 7]

NSAIDs exert analgesic, antiinflammatory, and antipyretic effects by blocking *cyclo-oxygenases (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 three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-2, found in joint and muscle, 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. Less is known about COX-3, which has been found in the cerebral cortex and cardiac tissue and appears to have effects on centrally-mediated pain.[10]

NSAIDs are also associated with important adverse effects. NSAIDs cause gastrointestinal (GI) bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach and intestines from acid. In the 1990's, nonaspirin NSAIDs were estimated to cause 32,000 hospitalizations and 3,200 deaths annually from GI bleeding in the U.S.[11] A risk analysis[12] 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.[13] 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	2100	12,353
45-64	646	3800
65-74	570	3353
≥ 75	110	647

Abbreviations: GI= Gastrointestinal; NSAID= Nonsteroidal antiinflammatory drug
Data are from Blower,[13] recalculated in Moore[12] and in Bandolier[14]

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 stomach and intestinal lining. Appendix B[15] 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.[16-18] 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 1000 mg.[19] Reasons for the increase in thromboembolic 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 pro-thrombotic COX-1 mediated thromboxane A2.[20] However, subsequent in vitro studies have not verified this hypothesis. Blood pressure elevations associated with COX-2 selective NSAIDs may play a role in increasing CV risk,[21] 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.[22] On December 9, 2004, the U.S. Food and Drug Administration (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,[23] leaving celecoxib the only COX-2 selective NSAID available in the U.S.

Aspirin, or acetylsalicylic acid, has long been known to have analgesic, antipyretic, and antiinflammatory effects.[24] It is thought to be the most consumed medicinal drug in the world. Like the nonaspirin NSAIDs, aspirin's effects are due to blockade of cyclo-oxygenases. However, an important distinction between aspirin and nonaspirin NSAIDs is that aspirin also induces irreversible functional defects in platelets (although nonaspirin 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.[25] 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, aspirin is infrequently used at the higher doses more effective for analgesia due to tolerability issues. Salsalate, a nonacetylated salicylate, is a prodrug of salicylic acid, the active metabolite of aspirin. It is considered a relatively weak inhibitor of cyclo-oxygenases.[26]

Acetaminophen (also known as paracetamol) is an antipyretic and analgesic medication that is not thought to have significant antiinflammatory 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.[16, 27] 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.[28]

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.[29] In the European Union countries, glucosamine is available as a prescription drug manufactured by the Rotta Pharmaceutical Company. In the U.S., 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.[30] 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 antiinflammatory effects by direct absorption through the skin, with reduced systemic adverse events compared with oral administration.[31] 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.[32] For a topical NSAID to be effective, it has to reach the inflamed tissue in sufficient concentrations to produce analgesic and antiinflammatory activity. The solubility of specific NSAIDs varies considerably, and is also affected by the carrier or formulation used.[31] Superior *in vivo* permeability characteristics, however, do not necessarily predict clinical effectiveness. At the time of the original CER, no topical NSAID formulations had been approved by the FDA, 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 cyclo-oxygenase, topical rubefacients are thought to relieve pain through counter irritation.[32, 33] 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 cyclo-oxygenase.[32, 34] 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.[35] 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.

Scope and Key Questions

The purpose of this report was to update a previous comparative effectiveness review (CER) funded by the Agency for Healthcare Research and Quality (AHRQ)[36] on the comparative efficacy and safety of nonopioid oral medications (selective and nonselective nonaspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis. The original CER conducted searches 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. The analytic framework and key questions guiding this report are described below.

Key Question 1

a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?
b. 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 nonsteroidal antiinflammatory drugs (NSAIDs) includes studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.

Oral agents include:

- Acetaminophen
- aspirin
- celecoxib (Celebrex®)
- chondroitin
- diclofenac
- diflunisal
- etodolac
- fenoprofen
- flurbiprofen
- glucosamine
- ibuprofen
- indomethacin
- ketoprofen
- ketorolac
- meclofenamate sodium
- mefenamic acid
- meloxicam
- nabumetone
- naproxen
- oxaprozin
- piroxicam
- salsalate
- sulindac
- tolmetin

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 co-prescribing 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 as compared with topical preparations, or of different topical medications compared with one another?

For the update of this comparative effectiveness review, changeshave 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: 650–1000 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;	OA: delayed	Renal impairment: initiate

Drug	Labeled indications	Dosing	Dose adjustments for special populations
	extraction of cataract; inflammatory disorder of eye; light intolerance; pain in eye; refractive keratoplasty; osteoarthritis; pain; rheumatoid arthritis	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	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, 1500 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, 600–1000 mg/day 2–4x/day with a maximum dose of 1200 mg/day; extended release, 400–1000 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,1000 mg 1x/day
Fenoprofen	Migraine; osteoarthritis; pain, mild to moderate; rheumatoid arthritis	OA and RA: 300–600 mg, 3 to 4x/day; maximum daily dose, 3200 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,	OA and RA: 1200–3200 mg/day in 3 to 4	Renal impairment: initiate with lowest recommended dose, then monitor

Drug	Labeled indications	Dosing	Dose adjustments for special populations
	minor; pain, mild to moderate; primary dysmenorrhea; rheumatoid arthritis	divided doses	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 (creatinine clearance [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

Drug	Labeled indications	Dosing	Dose adjustments for special populations
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, 1000 mg/day in a single dose; maintenance, 1000–2000 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, 1500 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: 1200 mg 1x/day; maximum, 1800 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: 1200 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: 3000 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	Renal impairment: initiate with lowest recommended dose, then monitor closely and reduce dose if necessary; juvenile rheumatoid arthritis, ≥2

	Drug	Labeled indications	Dosing	Dose adjustments for special populations
			3x/day; maximum, 1800 mg/day	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
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

Abbreviations: JRA= Juvenile rheumatoid arthritis; OA= Osteoarthritis ; RA= Rheumatoid arthritis.

Methods

Topic Development

The topic for the original 2006 report[36] was nominated in a public process. The key questions for that report were developed by investigators from the EPC with input from a Technical Expert Panel (TEP). Contacted via teleconference, the TEP served in an advisory capacity for the original report, helping 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 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 CER for studies published in the years 2005- present. We searched the Cochrane Database of Systematic Reviews (through January 2010) the Cochrane Central Register of Controlled Trials (through 1st Quarter 2010) and Ovid ®MEDLINE (2005- March, 2010.) 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 SRC 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 1039 citations from these sources and the original report were imported into an electronic database (EndNote® X2) 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 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:

- Acetaminophen
- aspirin
- celecoxib (Celebrex®)
- chondroitin
- diclofenac
- diflunisal
- etodolac
- fenoprofen
- flurbiprofen
- glucosamine
- ibuprofen
- indomethacin
- ketoprofen
- ketorolac
- meclofenamate sodium
- mefenamic acid
- meloxicam
- nabumetone
- naproxen
- oxaprozin
- piroxicam
- salsalate
- sulindac
- tolmetin

For this report, we defined the terms "selective NSAID" or "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. The salicylic acid derivatives aspirin and salsalate were also considered a separate subgroup. We defined "nonaspirin, nonselective NSAIDs" or simply "nonselective NSAIDs" as all other NSAIDs. We excluded evidence on NSAIDs unavailable in the U.S., 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
    - CV: stroke, MI, CHF, hypertension, and angina
    - 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.[37]

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 to 40%.[38]

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.[39] 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%.[38]
- 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.[40]
- *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.[38]
- *American College of Rheumatology (ACR) criteria* measure disease activity and response to treatment. ACR 20, ACR 50, or ACR 70 reflects an improvement to the 20%, 50%, or 70% level in the parameters outlined.

Another method for measuring outcomes is classifying patients dichotomously as "responders" or "nonresponders." Responders are often defined as patients with at least a 50% 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 pre-defined 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).[41]

"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 establish a minimum threshold for duration of intervention. However, study duration was considered when assessing applicability of studies.

Setting

Studies conducted in primary care and specialty settings were included.

Types of studies

We included systematic reviews[42] 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.

Figure 1. Analytic framework

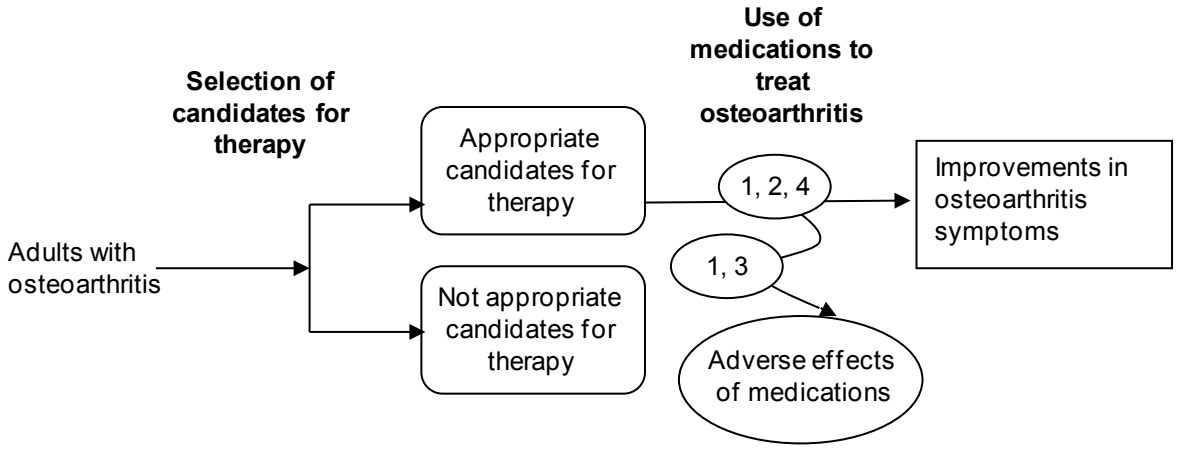


Figure 1 depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how the nonopioid oral medications, over- the-counter supplements, and topical agents may result in outcomes such as improvements in osteoarthritis symptoms. Also, 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, 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),[43] methods proposed by Downs and Black (observational studies),[44] and methods developed by the US Preventive Services Task Force.[1] The criteria used is similar to the approach recommended by AHRQ in the draft *Methods Reference Guide for Effectiveness and Comparative Effectiveness Review*.[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.[1]

Included systematic reviews were also rated for quality based on pre-defined criteria assessing whether they had a clear statement of the questions(s), reported inclusion criteria, used an 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.[43] 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.[42]

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.[44] 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.[44] 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:[1]

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.

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.

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 draft Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[45] We considered the type, number and quality of studies; the risk of bias; 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; 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:[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

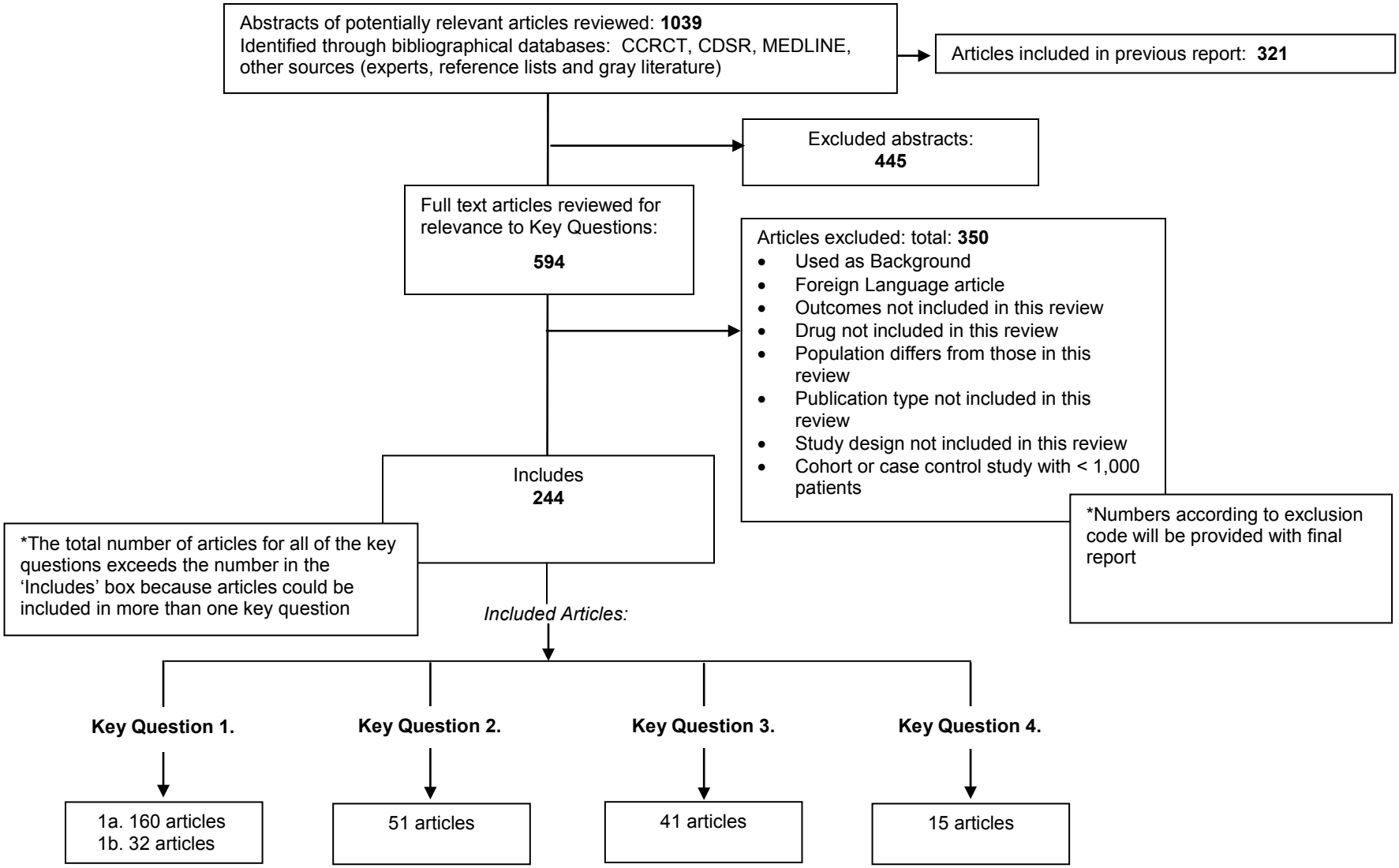
Overview

For the original CER, searches identified 2,789 publications: 1,522 from the Cochrane Central Register of Controlled Trials, 68 from the Cochrane Database of Systematic Reviews, 1015 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 75 citations from the Cochrane Central Register of Controlled Trials, 44 from the Cochrane Database of Systematic Reviews, 497 from MEDLINE and 102 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 theEndNote® library. A total of 594 full text articles were reviewed for inclusion in this update, with 244 publications determined to be eligible. There were 160 articles included in Key Question 1a, 32 articles for Key Question 1b, 51 articles for Key Question 2, 41 articles for Key Question 3, and 15 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



Key Question 1a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?

Summary of Evidence

Benefits

- Celecoxib versus nonselective 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 nonaspirin, 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 the end of followup; 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 the end of followup. 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 (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.
- Partially selective NSAIDs
  - Meloxicam (RR 0.53, 95% C I 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 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 was moderately superior to that of any COX-2 selective NSAID in a large systematic review of RCTs.
        - One additional myocardial infarction occurred for about every 300 patients treated for one 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.
    - In indirect analyses from a systematic review, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo (RR 0.92, 95% CI 0.67 to 1.3).
- Aspirin
    - Aspirin is associated with a lower risk of thromboembolic events (average 23% reduction) and a higher risk of GI bleeds (2.5%, compared to 1.4% with placebo) compared to placebo when given at long-term 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-percent confidence interval [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 (78/1000 patient-years with diclofenac versus 16 to 28/1000 for other NSAIDs in one systematic review; 3.6% versus <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 one fair-quality head-to-head trial of celecoxib versus diclofenac (n=925) published since the original CER (Appendix H).[52]

A good-quality systematic review (published in 2002) funded by the makers of celecoxib found similar effects on 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 OA or 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)[53] and the Successive Celecoxib Efficacy and Safety Study-1 (SUCCESS-1).[54] 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.[53] The nonselective NSAIDs were associated with a slightly higher (but statistically significant) likelihood of withdrawal due to lack of efficacy compared to celecoxib (15% versus 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.[54] Withdrawals due to lack of efficacy were not reported.

The 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 with osteoarthritis.[52] Withdrawals due to adverse events were slightly less frequent with celecoxib compared to diclofenac, but the difference was not statistically significant (27% versus 31%, RR 0.87, 95% CI 0.71-1.1).

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, 55, 56] One new, good-quality systematic review evaluated comparative efficacy of the partially selective NSAIDs for osteoarthritis or rheumatoid arthritis (Appendix H).[57] 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.[58-68] In two of the

trials, meloxicam was associated with a greater likelihood of withdrawal due to lack of efficacy than nonselective NSAIDs.[62, 67] 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).[57]

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),[69] back (through 1998),[9] or knee (through 1997).[56] In seven trials published after or not included in the Cochrane reviews, there were also no differences between sustained-release etodolac and diclofenac[70] or tenoxicam[71]; or between standard-formulation etodolac and piroxicam (2 trials[72, 73]), naproxen (2 trials[74, 75]) or nimesulide[76] 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.[57]

The Cochrane review of NSAIDs for knee osteoarthritis found nabumetone similar in efficacy to the nonselective NSAIDs diclofenac SR[77] and etodolac[78] in two 4-week trials.[56]

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), [69] back (through 1998),[9] or knee (through 1997).[56] These reviews found no clear differences in efficacy between nonaspirin, primarily nonselective NSAIDs. We identified no new head-to-head trials comparing efficacy of one nonaspirin, 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.[54]

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 two weeks of treatment.[79]

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 identified one good-quality systematic review that only had preliminary results available at the time of the original CER (Appendix H).[80] We identified one new head-to-head trial of celecoxib versus diclofenac, but it reported too few events (2 GI ulcers in nearly 1000 patients) to affect the conclusions of the systematic reviews.[52]

The systematic reviews both included the pivotal CLASS trials (n=7968),[53] 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 pre-specified primary outcome was ulcer-related complications, defined as gastric or duodenal perforation, gastric outlet obstruction, or upper GI bleeding (POBs).[81] Another pre-specified 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.[82] The pre-specified 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 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.[53] Additional details of the study were subsequently made public on the FDA web site.[82]

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 (32/3987 versus 51/3981, annualized incidence rates 2.1% versus 3.5%, p=0.02),[53] while the rates of POBs (the primary outcome) were not significantly different (13/3987 versus 22/3981, annualized incidence rates 0.76% versus 1.4%, p=0.09). By 12 months, according to FDA documents (see Table 13, FDA Medical Officer Review)[82] there was no longer a trend favoring celecoxib for POBs (17/3987 [0.43%] events with celecoxib versus 21/3981 [0.53%] with the nonselective NSAIDs,[82] relative risk 1.1, 95% CI 0.47 to 2.6[83, 84], also see Figure 4, Scheiman review[85]). 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.[83] For the secondary outcome of PUBs, celecoxib was superior to ibuprofen, but not to diclofenac at 6 months and the end of followup.[83] Celecoxib was also associated with a lower risk of hemoglobin (>2 g/dL) and/or hematocrit drops (≥0.10), among all patients (2.4% versus 4.4% and 5.7% for celecoxib, diclofenac, and ibuprofen, respectively.[82]

Twenty 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).[82, 83] However, serious ulcer complications were equivalent for celecoxib and diclofenac after exclusions of patients taking aspirin.

The new, good-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).[80] 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 RCTs of celecoxib (not including CLASS) versus placebo or nonselective NSAIDs (usually naproxen).[86] 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 two 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 0.22-0.80) and PUBs (RR 0.34, 95% CI 0.22-0.80) compared to nonselective NSAIDs.[80]

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,[86] 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 eight-item validity scale.[51] Only two 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.[54] SUCCESS-1 found celecoxib associated with a lower risk of POBs than naproxen or diclofenac after 12 weeks in patients with osteoarthritis (0.1% versus 0.8%, 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 1.4-100).[54]

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.[53] 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,[53] compared to 0.1/100 patient-years and 0.8/100 patient-years, respectively, in SUCCESS-1.[54] 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% of patients randomized to celecoxib were on aspirin and 31% on corticosteroids,[53] whereas in SUCCESS-1 7% were on aspirin and corticosteroid use was not permitted.[54] In addition, antiulcer medications (except for occasional antacids) were prohibited in CLASS, but used in 16% of celecoxib patients in the Goldstein et al combined analysis.[86] 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.[87-91] We identified one new systematic review (Appendix H).[57] 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.[57, 89-91] 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 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).[57] 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 0.28-0.96) compared to nonselective NSAIDs.[90] The third meta-analysis was funded by the manufacturer of meloxicam and used manufacturer-held documents from 28 trials.[91] 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, 1.6), and a similar risk compared to nonselective NSAIDs.[89] Estimates for GI hospitalizations or GI-related deaths alone were not reported.

The new systematic review found etodolac 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).[57] 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 six short-term (3 to 6 months) studies (five published and one abstract) found one PUB event among 4,098 patients taking nabumetone versus 17 events among 1,874 nonselective NSAID patients; this difference was highly statistically significant.[87] 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.[88] 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.[89, 92] One was included in the original CER[89]. We also included final results from a fair-quality systematic review which only had preliminary results[92] at the time of the original CER (Appendix H).[80] 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, 0.48), ibuprofen (RR 0.46; 95% CI 0.30, 0.71), and diclofenac (RR 0.31; 95% CI 0.06, 1.6).[80] 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.[54]

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, 5.1), naproxen (RR 1.8; 95% CI 1.2, 2.7), diclofenac (RR 1.7; 95% CI 1.2, 2.5), piroxicam (RR 1.7; 95% CI 1.1, 2.4), tenoxicam (RR 1.4; 95% CI 0.40, 5.1), and ibuprofen (RR 1.2; 95% CI 0.93, 1.5).[89]

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 (50 mg to 1500 mg daily) than the doses considered effective for analgesia and antiinflammatory 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% with aspirin compared with 1.4% with placebo (OR 1.7, 95% CI 1.5 to 1.9), based on an average of 28 months therapy.[93]

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

Observational studies
One new systematic review[94] and five systematic reviews[11, 95-98] 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 0.85-2.4), but the risk was lower than for nonselective NSAIDs as a group (eight studies, RR 4.5, 95% CI 3.8-5.3) as well as for individual nonselective NSAIDs, though confidence interval estimates overlapped in some cases (Table 3, Appendix H).[94]

Table 3. Risk of upper gastrointestinal bleeding or perforation with use of an NSAID compared with nonuse of NSAIDs, systematic review of observational studies[94]

	Number of studies	Pooled estimate (95% CI)
Celecoxib	4	1.4 (0.85-2.4)
Meloxicam	4	4.2 (2.6-6.6
Naproxen	6	5.6 (3.8-8.3)
Ibuprofen	5	2.7 (2.2-3.3)
Diclofenac	6	4.0 (3.4-4.7)
Indomethacin	5	5.4 (4.2-7.0)
Ketoprofen	5	5.6 (3.9-7.9)
Piroxicam	5	9.9 (6.0-16)
Ketorolac	2	15 (5.9-36)
Aceclofenac	3	1.4 (0.65-3.2)

Abbreviations: GI= Gastrointestinal; NSAID= Nonsteroidal antiinflammatory 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.[97] As in the Masso Gonzalez et al review, ibuprofen was associated with the lowest risk of peptic ulcer complication-related hospitalizations compared to other nonselective NSAIDs.[97] 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 nonaspirin, nonselective NSAID when results were stratified by low to medium (RR 2.1 versus nonuse, 95% CI 1.6, 2.7) or high dose (RR 5.5 versus nonuse, 95% CI 3.0, 10) (Table 4).[95, 98] 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.[11]

Eight large case-control (>1000 cases) or cohort (n>100,000) studies reported risks of serious upper GI complications associated with various NSAIDs (Table 4, Appendix H).[95, 99-105] Two of the studies were published after the original CER,[99, 105] and all but two were included in the new systematic review.[100, 105] Three studies used a cohort design[103-105] and the remainder used a case-

control (or nested case-control) design. Two case-control studies were rated good-quality[99, 101] 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[100, 101, 103] or acetaminophen use.[105] 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.[99]

Table 4. Serious gastrointestinal events in observational studies

Author, Year Study design Sample size	Mean age (yrs) Country	Outcome	Main findings
Garcia Rodriguez, 2007[99] 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[95] Nested case-control Cases: 2105	NR UK (GPRD)	Upper GI perforation or bleeding	*NSAID use vs. nonuse of NSAIDs* Ibuprofen: RR 2.5 (1.9-3.4) Etodolac: RR 2.2 (0.4-11) Fenbufen: RR 1.1 (0.2-5.1) Mefenamic acid: RR 2.7 (0.8-9.4) Ketoprofen: RR 3.3 (1.9-5.9) Nabumetone: RR 3.4 (1.1-11) Tenoxicam: RR 3.4 (0.9-13) Meloxicam: RR 3.8 (0.8-17) Naproxen: RR 4.0 (2.8-5.8) Diclofenac: RR 4.6 (3.6-5.8) Flurbiprofen: RR 4.6 (2.0-11) Indomethacin: RR 5.2 (3.2-8.3) Piroxicam: RR 6.2 (3.7-10)
Hippisley-Cox 2005[100] Nested case-control Cases: 9407	NR; ≥ 25 UK	Complicated GI Event	*NSAID use within 90 days versus no prescription for 3 years* Celecoxib: OR 1.2 (95% CI 0.91, 1.7) Ibuprofen: OR 1.6 (95% CI 1.4, 1.8) Diclofenac: OR 2.1 (95% CI 1.8, 2.4) Naproxen: OR 2.0 (95% CI 1.5, 2.6) Aspirin: OR 1.8 (95% CI 1.6, 1.9)
Lanas, 2006[101] 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, 2.1) *NSAID use vs. nonuse of nonselective NSAID* Ibuprofen: RR 4.1 (95% CI 3.1, 5.3) Diclofenac: RR 3.1 (95% CI 2.3, 4.2) Aceclofenac: RR 2.6 (95% CI 1.5, 4.6)

Author, Year Study design Sample size	Mean age (yrs) Country	Outcome	Main findings
			Naproxen: RR 7.3 (95%CI 4.7, 11) Piroxicam: RR 13 (95% CI 7.8, -20) Indomethacin: RR 9.0 (95% CI 3.9, 21) Meloxicam: RR 9.8 (95% CI 4.0, 24) Ketorolac: RR 14 (95% CI 5.2, 50) Lornoxicam: RR 7.7 (95% CI 2.4, 24) Ketoprofen: RR 8.6 (95% CI 2.5, 29)
Laporte 2004[102] Case-control Cases=2,813	NR; ≥ 18 Spain and Italy	Upper GI bleeding	*NSAID use vs. nonuse of NSAIDs* Aspirin: OR 8.0 (6.7-9.6) Dexketoprofen: OR 4.9 (1.7-14) Diclofenac: OR 3.7 (2.6-5.4) Ibuprofen: OR 3.1 (2.0-4.9) Indomethacin: OR 10 (4.4-23) Ketoprofen: OR 10 (3.9-26) Ketorolac: OR 25 (8.0-77) Meloxicam: OR 5.7 (2.2-15) Naproxen: OR 10 (5.7-18) Nimesulide: OR 3.2 (1.9-5.6) Piroxicam: OR 16 (10-24)
Mamdani 2002[103] 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, 1.6) Diclofenac + misoprostol: HR 3.0 (95% CI 1.7, 5.5) Nonselective NSAIDs: HR 4.0 (95% CI 2.3, 6.9) *NSAID use vs. celecoxib* Dicofenac + misoprostol: HR 3.2 (95% CI 1.6, 6.5) Nonselective NSAIDs: HR 4.4 (95% CI 2.3, 8.5)
Mellemkjaer, 2002[104] Cohort n=156,138 NSAID users	NR Denmark	Hospitalization for GI bleeding	*NSAID use vs. no use of NSAIDs* 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 (RR 2.1-4.2) Piroxicam: RR 5.0 (3.3-7.2)
Rahme, 2007[105] 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, 1.0) Ibuprofen: HR 1.1 (95% CI 0.56, 2.2) Diclofenac: HR 1.2 (95% CI 0.86, 1.6) Naproxen: HR 2.8 (95% CI 2.0, 3.7)

Abbreviations: CI= Confidence Interval; GI= Gastrointestinal; HR= Hazard ratio; NR= Not reported; NSAID= Nonsteroidal antiinflammatory drug; OR= Odds ratio; RR= Relative risk; UK GPRD= United Kingdom General Practice Research Database

The partially selective NSAID meloxicam was evaluated in 4 of the large observational studies.[95, 99, 101, 102] Meloxicam was associated with a risk of upper GI bleeding relative to nonuse of NSAIDs that was generally in the mid-range of risks reported for various nonselective NSAIDs. Only one study reported risks associated with other partially selective NSAIDs, and estimates were imprecise.[95]

For various nonselective NSAIDs, the observational studies generally showed increased risk of GI bleeding relative to nonuse.[95, 99, 100, 102-104] Naproxen was associated with a higher risk than ibuprofen in 7 studies,[95, 99-102, 104, 105] though the risk estimates were relatively close in two of them.[100, 104] Comparative data for other nonselective NSAIDs was less consistent. For example, diclofenac was associated with similar or lower risk compared to ibuprofen in 3 studies, [100, 101, 105], but higher in 4 others.[95, 99, 102, 104]

The risk of upper GI bleeding was similar with aspirin compared to nonaspirin, nonselective NSAIDs in one large nested case-control study.[100] 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.[96, 97]

Serious GI event rates (bleeding, perforation, obstruction) associated with salsalate were reported in one smaller cohort study (n=1198) of long-term care residents in Indiana.[106] The number of cases of GI-related hospitalizations associated with salsalate (1, 5.9%) after 14 months was similar to that of other selective and nonselective NSAIDs.

CV 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[107]) evaluated risk of serious CV events in randomized controlled trials of celecoxib (Table 5, Appendix H).[51, 108-110] One new systematic review was identified for this update (Table 5, Appendix H).[111] We identified one new placebo-controlled Chinese trial of celecoxib for prevention of gastric cancer that reported serious CV events,[112] and one head-to-head trial of celecoxib versus diclofenac for osteoarthritis.[52]

The systematic reviews all included CLASS.[53] 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]).[53] 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.[113] 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.

Two systematic reviews provided the best information on CV risks associated with long-term use of celecoxib. Both included preliminary or published results from trials of celecoxib for prevention of colon polyps or Alzheimer's disease (APC, ADAPT, PreSAP).[108, 111] Both meta-analyses were rated fair-quality due to failure to adequately assess trial quality[108, 111] or report statistical heterogeneity.[111] In addition, both meta-analyses excluded a number of short-term trials[108, 111] and one of the meta-analyses[108] 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.[111] It included 6 trials (3664 persons 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 (HR 1.6, 95% CI 1.1-2.3). 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 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.[108] It found the risk of myocardial infarction increased in 3 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 5 trials (APC, CLASS, ADAPT, PreSAP, VACT; the latter 2 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).[54]

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 0.19-2.35),[52] or a new, fair-quality Chinese trial (n=1024) which 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 0.23-3.2).[112] 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[109] Search dates not reported	15 (18,942)	No	Antiplatelet Trialists' Collaboration composite CV events (cardiovascular, hemorrhagic, and unknown deaths; nonfatal MI; or nonfatal stroke) All patients Celecoxib vs. placebo: RR 0.85 (95% CI 0.23, 3.15) Celecoxib vs. NSAIDs: RR 1.06 (95% CI 0.70, 1.61) Celecoxib vs. naproxen: RR 0.85 (95% CI 0.29, 2.46)	Poor

			Aspirin nonusers Celecoxib vs. placebo: RR 0.60 (95% CI 0.11, 3.29) Celecoxib vs. NSAIDs: RR 0.86 (95% CI 0.48, 1.56) Celecoxib vs. naproxen: RR 0.82 (95% CI 0.18, 2.46)	
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, 4.1) Celecoxib any dose vs. NSAID to maximum daily dose: RR 1.6 (0.93, 2.6)	Fair
Caldwell, 2006[108] Searches through April 2005	6 (6,859)	Yes	Celecoxib vs. placebo Myocardial infarction: RR 2.3 (1.0, 5.1) Cerebrovascular event: RR 1.0 (0.51, 1.8) Cardiovascular death: RR 1.1 (0.38, 3.0) Composite cardiovascular events: RR 1.38 (0.91, 2.1) Celecoxib vs. placebo, diclofenac, ibuprofen, or paracetamol Myocardial infarction: RR 1.9 (1.2, 3.1) Cerebrovascular event: RR 0.73 (0.42, 1.3) Cardiovascular death: RR 1.0 (0.52, 2.0) Composite cardiovascular events: RR 1.2 (0.92, 1.6)	Fair
White, 2007[110] Trials completed by October 2004	41 (23,030)	No	Celecoxib 200-800 mg vs. placebo Antiplatelet Trialists' Collaboration composite CV events: RR 1.1 (0.47, 2.7) CV deaths: RR 1.3 (0.33, 4.8) Nonfatal MI: RR 1.6 (0.21, 12) Nonfatal stroke: RR 0.80 (0.19, 3.3) Celecoxib 200-800 mg vs. nonselective NSAIDs Antiplatelet Trialists' Collaboration composite CV events: RR 0.90 (0.60, 1.3) CV deaths: RR 0.57 (0.28, 1.1) Nonfatal MI: RR 1.8 (0.93, 3.4) Nonfatal stroke: RR 0.51 (0.23, 1.1)	Poor
Solomon, 2008[111] Search dates not reported	6 (3664)	Yes	Cardiovascular death, MI, stroke, heart failure, or thromboembolism Celecoxib any dose vs. placebo: HR 1.6 (1.1, 2.3) Celecoxib 400 mg qd vs. placebo: HR 1.1 (0.6, 2.0) Celecoxib 200 mg bid vs. placebo: HR 1.8 (1.1, 3.1) Celecoxib 400 mg bid vs. placebo: HR 3.1 (1.6, 6.1)	Fair

Abbreviations: bid= twice daily; CI= Confidence Interval; CV= Cardiovascular; HR= Hazard Ratio; MI= Myocardial Infarction; NSAID= Nonsteroidal antiinflammatory drug; qd= once daily; RR= Relative Risk
* Colon polyp prevention trials: PreSAP, APC; Alheimer's prevention: ADAPT

Three meta-analyses included in the original CER found no increased risk of serious CV events with celecoxib versus placebo.[51, 109, 110] However, these meta-analyses did not include trials completed after 2004, including two large, long-term trials of colon polyp prevention (APC and PreSAP).[114, 115] These two trials account for a high proportion of the myocardial infarctions in the celecoxib trials (70 events in persons randomized to celecoxib, compared to 31 in one of the meta-analyses[110]). 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.[116] Rates of fatal or nonfatal myocardial infarction were 1.6% (22/1356) versus 0.4% (3/679) in the APC trial and 9/933 (1.0%) vs. 4/628 (0.6%) 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% to 94%.[51, 109, 110] 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,[109, 110]

resulting in loss of randomization effects, and making it impossible to evaluate heterogeneity across studies.

A meta-analysis[117] 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% (44/8976 person-years) compared to 0.2% (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.[117] Two trials included in the original CER and not included in the systematic review also reported serious CV events in patients prescribed naproxen.[54, 118]

A fair-quality systematic review 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).[117] 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 two-fold greater for COX-2 inhibitors compared to 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 one additional myocardial infarction for every 300 patients treated for one 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[117]

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)

Abbreviations: CI= Confidence Interval; COX= Cyclo-oxygenase; NSAID= Nonsteroidal antiinflammatory drug
*Rate ratios below one favor COX 2 inhibitors and rate ratios above one favor NSAIDs

Kearney and colleagues 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 versus 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.[119]

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).[54] 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."[120] Results from ADAPT showed a nonsignificant increased in risk of CV deaths (HR 1.5, 95% CI 0.30-7.3), myocardial infarction (HR 1.5, 95% CI 0.69-3.2), or stroke (HR 2.1, 95 5cI 0.81-5.6).[118] 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 1.0-2.6). 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.[121]

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 65 randomized controlled trials of aspirin for prophylaxis against thrombotic events included in the original CER, any dose of aspirin reduced the risk of vascular events by an average of 23% (standard error 2).[122] The cardioprotective effects of aspirin appeared lower (13%) in three trials evaluating doses of lower than 75 mg once daily, but in trials that directly compared higher and lower doses, there were no

significant differences. 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.[123-125] Two were included in the original CER and focused on risks associated with naproxen.[123, 124] 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).[125] We also identified four large observational studies not included in the original CER.[105, 126-128]

The new systematic review included a total of 23 observational studies (16 case-control and 7 cohort studies).[125] 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[125]

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

Abbreviations: CI= Confidence Interval; NSAID= Nonsteroidal antiinflammatory 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).[105, 126-143] All of these studies except for four[105, 126-128] were included in the original CER. Seven studies[105, 126-129, 138, 143] not included in the systematic review of observational studies.[125] Six studies used a cohort design[105, 127, 128, 137, 143, 144] and the remainder a case-control (or nested case-control) design. Three studies evaluated the UK General Practice Research Database[130, 131, 140] and three evaluated the same Canadian (Quebec) database.[105, 127, 138] Only one study was rated good-quality,[136] 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.

Fourteen observational studies evaluated risk of serious CV events (primarily myocardial infarction) associated with celecoxib.[105, 126-129, 132-137, 142-144] Three studies found celecoxib associated with similar risk of CV events compared to naproxen, ibuprofen, or diclofenac.[127, 142, 143] A fourth study found ibuprofen (OR 1.3, 95% CI 1.0-1.6) and naproxen (OR 1.4, 95% CI 1.1-1.8) associated with a higher risk of acute MI requiring admission or sudden cardiac death than celecoxib.[132] Eleven studies found no increased risk of serious CV events with celecoxib relative to nonuse of NSAIDs.[105, 126, 128, 132, 133, 135-137, 142-144] Two studies found current (RR 1.6, 95% CI 1.2-2.0)[129] or new (RR 2.1, 95% CI 1.4-3.1)[134] use of celecoxib associated with increased risk compared to nonuse of NSAIDs. In these studies, the increased MI risk was either time-[134] or dose-dependent.[129]

Table 8. Cardiovascular events in observational studies

Author, Year Data source Sample size	Mean age Country	Rate of aspirin use	Main findings
Andersohn 2006[129] 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* Celecoxib: RR 1.6 (1.2-2.0) Diclofenac: RR 1.4 (1.2-1.6) Ibuprofen: RR 1.0 (0.86-1.2) Naproxen: RR 1.2 (0.84-1.6) Other nonselective NSAIDs: RR 1.1 (0.98-1.2)
Fischer, 2005[130] Nested case-control Cases=8688	NR UK (GPRD)	NR	***Acute MI*** *Current NSAID use vs. nonuse of NSAIDs* Diclofenac: OR 1.2 (1.0-1.5) Ibuprofen: OR 1.2 (0.92-1.5) Naproxen: OR 0.96 (0.66-1.4) Indomethacin: OR 1.4 (0.82-2.2) Piroxicam: OR 0.95 (0.53-1.7) Ketoprofen: OR 0.86 (0.44-1.7) Fenbufen: OR 3.1 (1.2-8.1) Nabumetone: OR 0.62 (0.25-1.5) Mefenamic acid: OR 2.3 (0.79-6.7) Etodolac: OR 1.1 (0.40-3.2) Tiaprofenic acid: OR 0.65 (0.17-2.5)
Garcia Rodriguez, 2004[131] Nested case-control Cases: 4,975	NR UK (GPRD)	NR	***MI*** *NSAID use vs. nonuse of NSAIDs* Naproxen: OR 0.89 (0.64-1.2) Ibuprofen: OR 1.1 (0.87-1.3.) Diclofenac: OR 1.2 (0.99-1.4) Ketoprofen: OR 1.1 (0.59-2.0) Meloxicam: OR 0.97 (0.60-1.6) Piroxicam: OR 1.2 (0.69-2.2) Indomethacin: OR 0.86 (0.56-1.3)
Graham 2005[132] 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* Celecoxib: OR 0.84 (0.67-1.0) Ibuprofen: OR 1.1 (0.96-1.2) Naproxen: OR 1.1 (1.0-1.3) *Current NSAID use vs. celecoxib use* Ibuprofen: OR 1.3 (1.0-1.6) Naproxen: OR1.4 (1.1-1.8)

Author, Year Data source Sample size	Mean age Country	Rate of aspirin use	Main findings
Helin-Salmivaara, 2006[126] Case-control Cases=33,309	NR Finland	NR	***First time MI*** *Current NSAID use vs. nonuse of NSAIDs* Indomethacin: OR 1.6 (1.2-2.0) Ibuprofen: OR 1.4 (1.3-1.6) Diclofenac: OR 1.4 (1.2-1.5) Naproxen: OR 1.2 (1.0-1.4) Piroxicam: OR 1.4 (0.92-2.0) Ketoprofen: OR 1.1 (0.94-1.3) Tolfenamic acid: OR 1.4 (0.90-2.2) Nimesulide: OR 1.7 (1.4-2.0) Etodolac: OR 1.4 (0.44-4.2) Nabumetone: OR 1.3 (0.59-2.7) Meloxicam: OR 1.2 (0.99-1.6) Celecoxib: OR 1.1 (0.83-1.3) *Recent (within 30 days) NSAID use vs. nonuse of NSAIDs* Indomethacin: OR 1.5 (1.0-2.1) Ibuprofen: OR 1.1 (0.94-1.3) Diclofenac: OR 0.93 (0.77-1.1) Naproxen: OR 1.3 (1.0-1.7) Piroxicam: OR 0.89 (0.49-1.6) Ketoprofen: OR 1.3 (1.0-1.7) Tolfenamic acid: OR 1.3 (0.74-2.3) Nimesulide: OR 1.1 (0.91-1.4) Etodolac: OR 0.95 (0.23-4.0) Nabumetone: OR 3.0 (0.96-9.4) Meloxicam: OR 1.0 (0.77-1.4) Celecoxib: OR 0.95 (0.65-1.4)
Hippisley-Cox 2005[133] Nested case-control Cases: 9218	NR; aged 25-100 UK	NR	***First ever MI*** *NSAID use within 3 months vs. no prescription for 3 years* Celecoxib: OR 1.2 (0.96-1.5) Ibuprofen: OR 1.2 (1.1-1.4) Diclofenac: OR 1.6 (1.4-1.7) Naproxen: OR 1.3 (1.0-1.6) Other nonselective NSAIDs: OR 1.2 (1.0-1.4)
Johnsen 2005[134] Case-control Cases=10,280	70 Denmark	7% high-dose	***Acute MI*** *Current NSAID use vs. nonuse of NSAIDs* Celecoxib: RR 1.2 (0.97-1.6) Naproxen: RR 1.5 (0.99-2.3) Other nonaspirin NSAID: RR 1.7 (1.5-1.8) *New NSAID use vs. nonuse of NSAIDs* Celecoxib: RR 2.1 (1.4-3.1) Naproxen: RR 1.6 (0.57-4.8) Other nonaspirin NSAID: RR 2.6 (2.0-3.5)
Kimmel 2005[135] Case-control Cases: 1718	NR; aged 40 to 75 USA	34%	***Nonfatal MI*** *NSAID use vs. nonuse of NSAIDs* Celecoxib: OR 0.43 (0.23-0.79) Nonselective NSAID: OR 0.61 (0.52-0.71)
Levesque 2005[136] Nested case-control Cases: 2844	NR; ≥ 66 Canada	22%	***Acute MI, fatal or nonfatal*** *NSAID current use vs. nonuse of NSAIDs* Celecoxib: RR 0.99 (0.85-1.2) Naproxen: RR 1.2 (0.75-1.8) Meloxicam: RR 1.1 (0.49-2.3)

Author, Year Data source Sample size	Mean age Country	Rate of aspirin use	Main findings
Mamdani 2003[137] Cohort n=166,964	NR; ≥ 66 Canada	15%	***Hospitalization for acute MI*** *NSAID user vs. nonuser control* Celecoxib: RR 0.9 (0.7-1.2) Naproxen: 1.0 (0.7-1.7) Nonnaproxen nonselective NSAIDs: 1.2 (0.9-1.4)
Rahme, 2002[138] Case-control Cases=4163	NR (older than 65 years) Canada	NR	***Hospitalization for acute MI*** Exposure to naproxen versus exposure to other NSAIDs: OR 0.79 (95% CI 0.63-0.99)
Rahme, 2007[127] Retrospective cohort N=283,799	NR (>65 years) Canada	24%	***Acute myocardial infarction hospitalization*** Celecoxib vs. diclofenac/ibuprofen: 0.90 (0.76-1.1)
Rahme, 2007[105] Retrospective cohort N=510,871	NR; ≥65 Canada	22%	***Acute myocardial infarction*** *NSAID use vs. acetaminophen use* Celecoxib: HR 0.97 (0.86-1.1) Ibuprofen: HR 1.0 (0.68-1.6) Diclofenac: HR 1.2 (0.96-1.4) Naproxen: HR 1.2 (0.89-1.5)
Ray 2002[144] Cohort n=378,776	61.5 USA	NR	***Serious CHD (hospital admission for AMI or death from CHD)*** *Current NSAID use vs. nonuse of NSAIDs* Celecoxib: RR 0.96 (0.76-1.2) Naproxen: RR 0.93 (0.82-1.1) Ibuprofen: RR 0.91 (0.78-1.1) *New NSAID use vs. nonuse of NSAIDs* Celecoxib: RR 0.88 (0.67-1.2) Naproxen: RR 0.92 (0.73-1.2) Ibuprofen: RR 1.0 (0.77-1.3)
Schlienger, 2002[140] Nested case-control Cases=3319	NR UK (GPRD)	NR	***First acute MI*** *NSAID use vs. nonuse of NSAIDs* Ibuprofen: OR 1.2 (0.87-1.6) Diclofenac: OR 1.4 (1.1-1.8) Piroxicam: OR 1.6 (0.78-3.5) Fenbufen: OR 2.1 (0.80-5.3) Ketoprofen: OR 1.4 (0.77-2.5) Indomethacin: OR 1.0 (0.58-1.8) Flurbiprofen: OR 2.3 (0.93-5.5) Naproxen: OR 0.68 (0.42-1.1)
Solomon, 2002[141] Case-control Cases=4425	NR USA	NR	***Hospitalization for MI*** *NSAID use vs. nonuse of NSAIDs* Naproxen: RR 0.84 (0.72-0.98) Ibuprofen: RR 1.0 (0.88-1.2) *NSAID use vs. ibuprofen use* Naproxen: RR 0.82 (0.67-1.0)
Solomon 2004[142] Case-control Cases=10,895	NR; > 80 USA	NR	***Acute MI*** Celecoxib use vs. no celecoxib use: OR 0.93 (0.84-1.0) Celecoxib use vs. naproxen use: OR 0.95 (0.74-1.2) Celecoxib use vs. ibuprofen use: OR 0.98 (0.76-1.3) Celecoxib use vs. other NSAID use: OR 0.95 (0.82-1.1)

Author, Year Data source Sample size	Mean age Country	Rate of aspirin use	Main findings
Solomon, 2008[128] Cohort n=175,654	80 years USA	NR	***MI, stroke, CHF, and out-of-hospital death attributable to cardiovascular disease*** *NSAID use versus nonuse of NSAIDs* Celecoxib: HR 0.89 (0.83-0.94) Diclofenac: HR 1.2 (1.1-1.3) Ibuprofen: HR 0.96 (0.83-1.1) Naproxen: HR 0.79 (0.67-0.93) Other nonselective NSAIDs: HR 0.87 (0.79-0.96)
Velentgas 2005[143] Cohort n=424,584	NR (40-64 years) USA	NR	***Acute coronary syndrome or MI*** *Current NSAID use vs. current ibuprofen use* Celecoxib: RR 1.0 (0.83-1.3) Naproxen: RR 1.1 (0.93-1.4

Abbreviations: AMI= Acute Myocardial Infarction; CHD= Coronary Heart Disease; HR= Hazard Ratio; MI= Myocardial Infarction; NR= Not reported; NSAID= Nonsteroidal antiinflammatory 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[19] 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[117] 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),[125] two systematic reviews included in the original CER specifically focused on CV risks associated with naproxen.[123, 124] 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.[124] Seven observational studies published after this systematic review showed no cardioprotective effect associated with naproxen,[105, 126, 129, 132-134, 136] though one other study showed a modest protective effect (HR 0.79, 95% 0.67-0.93).[128] An FDA review included in the original CER concluded no cardioprotective effect of naproxen after taking into account various methodological issues.[123]

Large observational studies found no other nonselective NSAID consistently associated with increased risk of CV events compared to nonuse of NSAIDs.[126, 128-134, 136, 137, 139-141] For example, ibuprofen was associated with a modest increased risk (OR 1.4, 95% CI 1.3-1.6 and OR 1.2, 95% CI 1.1-1.4) of serious CV events compared to nonuse of NSAIDs in two[126, 133] studies, but no increased risk in 8 others.[128-132, 140, 141, 144]

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.[126, 131, 136] One study found no increased risk of acute myocardial infarction with use of etodolac or nabumetone versus nonuse of NSAIDs, but estimates were imprecise.[130]

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."[145] 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 trade-offs 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[82] to analyze serious adverse events, defined as death, hospitalization, or "any life-threatening event, or event leading to severe disability.[146] It found similar rates of all serious adverse events between celecoxib and ibuprofen or diclofenac (6.8% vs. 5.8%). 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.[82]

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.[105] For the combined outcome, naproxen use was associated with the largest risk compared to acetaminophen use (HR 1.6, 95% CI 1.3-1.9). Celecoxib (HR 0.93, 95% CI 0.83-1.0) and ibuprofen (HR 1.0, 95% CI 0.74-1.5) were associated with neutral risk, and diclofenac with an intermediate but nonstatistically significant increased risk (HR 1.2, 95% CI 0.99-1.4)

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.[53, 147] In CLASS, mortality rates were 0.47%, 0.37%, and 0.45% for celecoxib, diclofenac, and ibuprofen, respectively.[82] In SUCCESS-1, 5 deaths (0.06%) were observed after 12 weeks in the celecoxib group and 5 (0.11%) in the nonselective NSAIDs group.[54] 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 versus 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, 3.1) and

naproxen (OR 3.0, 95% CI 1.9, 4.6).[148] 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.[21, 51, 107, 149-151] A seventh systematic review was published too late to be fully included in the original CER, but described in an appendix.[152] It was rated fair-quality because it did not assess the quality of included studies. One new observational study evaluated risk of congestive heart failure in high risk patients.[153]

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, 95% CI 1.2 to 8.7).[149] 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 (one trial), diclofenac and sulindac (one trial), ibuprofen and sulindac (one trial), and naproxen and sulindac (three 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.[150] 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.[150]

Several meta-analyses of celecoxib included in the original CER found no increased risk of hypertension compared to nonselective NSAIDs.[21, 51, 107] 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).[21] 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).[107] 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 to control treatments (placebo, other NSAID, or mixed/other).[152] 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 pre-existing) compared with diclofenac (2.7% vs. 2.6%), and a lower rate compared to ibuprofen (2.7% vs. 4.2%).[113] In the shorter-term (12 weeks) SUCCESS-I trial (N=13,274), rates of hypertension were similar with celecoxib 100 or 200 mg bid compared to either diclofenac or naproxen (RR 0.86, 95% CI 0.62 to 1.20).[54] 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).[116] 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.[116]

With regards 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.[151] 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 to 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%), diclofenac (0.1%), or ibuprofen (0.2%), though the nonselective NSAIDs were associated with slightly greater increases in serum creatinine, particularly in patients with prerenal azotemia at baseline.[154] 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).[152]

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 versus one of 4,057, p=0.05), though not compared with nonselective NSAIDs (0.1% vs. 0.2%, p=0.06).[107] 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% vs. 0.3%).[113], and withdrawals due to heart failure rare with all three NSAIDs (0.1% vs. <0.1% vs. 0.3%).[154] 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).[115]

The risks of hypertension and heart failure with celecoxib and nonselective NSAIDs were evaluated in several observational studies. 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.[153] There was no difference in risk of heart failure between other nonselective NSAIDs (diclofenac [OR 0.82, 95% CI 0.51-1.3] and ibuprofen [OR 1.5, 0.66-3.2]) or acetaminophen (OR 1.2, 955 CI 0.92-1.4) 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, 1.0 to 1.6) in similarly high risk patients.[155] 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.[156] 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).[157]

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.[152]

Hepatotoxicity

One systematic review[158] included in the original CER and one new meta-analysis[159] evaluated randomized controlled trials reporting hepatotoxicity associated with various NSAIDs. Another systematic review included in the original CER evaluated observational studies.[160] We identified one new randomized controlled trial that reported rates of hepatic adverse events.[52]

The new meta-analysis included 41 randomized trials involving celecoxib.[159] It found risk of hepatobiliary abnormalities (clinical or laboratory) similar for celecoxib (276/24933 or 1.1%), 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 Hy'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 ALT abnormalities was higher with diclofenac (78/1000 patient-years) compared to 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.[158] 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 >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%), 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.

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% vs. 2.2%), serum AST (0.5 % vs. 1.8%), and withdrawals due to hepatic enzyme elevations (<0.1% vs. 1.2%) compared to diclofenac or ibuprofen.[53] In SUCCESS-1, rates of increase in ALT levels were 0.5% with celecoxib vs. 1.3% with diclofenac or naproxen (p<0.001).[54] 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% vs. 3.5%).[52]

A systematic review of seven population-based epidemiological studies found a similarly low risk of serious hepatic toxicity associated with NSAIDs.[160] 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 over 396,392 patient-years of exposure. A recent cohort study from Italy found that nimesulide, an NSAID not available in the U.S., was associated with a higher incidence of serious liver injury compared with other NSAIDs.[161] 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 5-10 fold higher incidence of hepatic injury compared with other NSAIDs.[162] 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[57] evaluated the relative tolerability of celecoxib compared to nonselective NSAIDs (Table 9). We also identified one new randomized trial not included in the original CER.[52]

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 0.78-1.0), or withdrawals due to adverse events (RR 0.86, 95% CI 0.73-1.0).[57] However, celecoxib was associated with a lower likelihood of withdrawals due to GI adverse events (RR 0.45, 95% CI 0.35-0.56). 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 0.81-0.91), withdrawal due to GI adverse events (RR 0.75, 95% CI 0.70-0.80), or any GI adverse event (RR 0.85, 95% CI 0.82-0.88).[51] The risk of serious adverse events (RR 1.0, 95% CI 0.91-1.2) and any adverse event (RR 0.96, 95% CI 0.94-0.98) 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% vs. 21%) and withdrawal due to GI adverse events (8.7% vs. 11%) with celecoxib compared to diclofenac or ibuprofen.[53]

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

Review	AE incidence		Withdrawals	
	Overall	***GI-related***	***Any AE***	***GI-related***
Celecoxib vs. NSAIDs for OA/RA				
Deeks 2002[50]	-	-	RR 0.86 (0.72, 1.04)	**RR 0.54 (0.42, 0.71)**
Moore 2005[51]	**RR 0.96 (0.94, 0.98)**	**RR 0.84 (0.81, 0.87)**	**RR 0.86 (0.81, 0.91)**	**RR 0.75 (0.7, 0.8)**
Chen, 2008[57]	RR 0.96 (0.91, 1.0)	**RR 0.75 (0.70, 0.80)**	RR 0.86 (0.73, 1.0)	**RR 0.45 (0.35, 0.56)**

Abbreviations: AE= Adverse event; COX= Cyclo-oxygenase; GI= Gastrointestinal; NSAID= Nonsteroidal antiinflammatory drug; OA= Osteoarthritis; RA= Rheumatoid Arthritis; RR= Relative Risk

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% vs. 14%).[52]

Partially selective NSAIDs
Two systematic reviews[87, 90] of randomized trials included in the original CER and one new systematic review[57] 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 0.84-0.99), any GI adverse event (RR 0.31, 95% CI 0.24-0.39), and withdrawals due to GI adverse events (RR 0.61, 95% CI 0.54-0.69), though there was no difference in the risk of withdrawal for any adverse event (RR 0.92, 95% CI 0.66-1.3).[57] The median Jadad quality score for the trials included in the systematic review was 3 (maximum 5), 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, 0.69) and withdrawals due to GI events (OR 0.59; 95% CI 0.52, 0.67) with meloxicam compared with nonselective NSAIDs.[90]

The new systematic review also evaluated tolerability of etodolac.[57] 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% 0.55-1.1), withdrawal due to adverse events (RR 0.93, 95% CI 0.77-1.1), or withdrawal due to GI adverse events (RR 0.95, 95% CI 0.54-1.6). 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.[87]

Nonselective NSAIDs
A Cochrane review included in the original CER evaluated the tolerability of different NSAIDs.[55] 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.[79, 163-166] All were short-term (≤ 12 weeks) and involved a total of 471 patients; of the subjects enrolled, only four 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%, $p<0.05$)[79] and diclofenac (61% vs. 46%; $p<0.05$);[165] 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[163, 166] 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.[167-170] 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[169]	1.19	1.94	1.28	2.17 (Naproxen) to 3.99 (Indomethacin)
Fries 1993[168]	1.33	1.89	NR	1.90 (Naproxen) to 2.86 (Tolmetin)
Fries 1996[167]	1.77	2.68	2.00	1.63 (Sulindac) to 3.09 (Ketoprofen)
Singh 1997[170]	2.25	1.95	1.79	3.29 (Naproxen) to 5.14 (Meclofenamate)

Abbreviation: ARAMIS= Arthritis, Rheumatism, and Aging Medical Information System

Acetaminophen

Four systematic reviews included in the original CER evaluated the efficacy and safety of acetaminophen compared with NSAIDs (selective or nonselective) for osteoarthritis.[171-174] We identified no new systematic reviews. One new randomized trial compared acetaminophen versus naproxen for osteoarthritis.[175] One new observational study evaluated risk of acute myocardial infarction associated with various NSAIDs compared to acetaminophen.[105]

The systematic reviews generally met all criteria for good-quality systematic reviews, except that three[172-174] 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.[172, 173].\ Only two reviews assessed functional disability; neither found clear differences.[172, 173]

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[172]	Through 8/02	5 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (SMD 0.20, 95% CI 0.03 to 0.36), overall pain (SMD 0.25, 95% CI 0.17 to 0.33), WOMAC pain (SMD 0.24, 95 5CI 0.09 to 0.38), WOMAC stiffness (SMD 0.20, 95% CI 0.05 to 0.34), WOMAC function (SMD 0.25, 95% CI 0.11 to 0.40), and global assessment of efficacy (RR 1.2, 955 CI 1.1 to 1.43)
Zhang, 2004[174]	Through 7/03	8 (3 trials evaluated coxibs)	NSAIDS superior using WOMAC scale (pooled ES 0.3, 95% CI 0.17 to 0.44) and clinical response rate (RR 1.24, 95% CI 1.08 to 1.41)

Systematic review	Date of last search	Number of head-to-head trials included	Main results for outcome of general or rest pain
Lee, 2004[171]	Through 2/03	6 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (weighted mean difference –6.33, 95% CI –9.24 to –3.41)
Wegman, 2004[173]	Through 12/01	3 (no trials evaluated coxibs)	NSAIDs superior for general/rest pain (standardized mean difference 0.33, 95% CI 0.15 to 0.51)

Abbreviations: CI= Confidence Interval; NSAID= Nonsteroidal antiinflammatory 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).[171, 172, 174] In two reviews, there were no differences in withdrawal due to any adverse event.[171, 172] Acetaminophen was associated with fewer GI adverse events compared with nonselective NSAIDs in two systematic reviews (though not compared with coxibs)[172, 174] and fewer withdrawals due to GI adverse events in one systematic review.[172]

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

Systematic review	Withdrawal due to adverse events	GI adverse events
Towheed, 2006[172]	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[174]	Not reported	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[171]	NSAID vs. acetaminophen: OR 1.4, 95% CI 0.93 to 2.3)	Not reported

Abbreviations: CI= Confidence Interval; COX= Cyclo-oxygenase; GI= Gastrointestinal; NSAID= Nonsteroidal antiinflammatory 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).[175] Acetaminophen and naproxen were also associated with similar rates of withdrawal due to adverse events (25% vs. 22%, NS), serious adverse events (3.5% vs. 2.5%), any adverse event (72% vs. 74%), renal adverse events (3 total), or hepatic enzyme increases (3 in acetaminophen group vs. 0 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 persons 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.[176] 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.[95] 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).[177] 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.[178] 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).[179] 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).[105]

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 insure 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.[180] The largest (926 cases) case-control study was designed to try to avoid many of these flaws.[181] 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 ($p=0.88$).[182] 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.[183, 184]

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).[157]

The risk of hypertension has been evaluated using data from the Nurses' Health Studies[185-187] and the Physicians' Health Study.[188] 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 versus nonuse: odds ratio	NSAID use versus nonuse: odds ratio
Nurses' Health Study I (women 51 to 77 years old)[187]	1.9 (1.3 to 2.9)	1.8 (1.2 to 2.6)
Nurses' Health Study II (women 34 to 53 years old)[187]	2.0 (1.4 to 2.8)	1.6 (1.1 to 2.3)
Physicians' Health Study[188]	1.1 (0.87 to 1.3)	1.0 (0.89 to 1.2)

Abbreviation: NSAID= Nonsteroidal antiinflammatory drug

Glucosamine and chondroitin

Two new systematic reviews (Appendix I)[189, 190] and four systematic reviews [191-194] 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,[195] two trials of glucosamine versus placebo,[196, 197] three trials of chondroitin versus placebo,[198-200] and one trial of the combination of glucosamine and chondroitin versus placebo (Table 14, Appendix I).[201] We also identified a new analysis from the previously included Glucosamine/chondroitin Arthritis Intervention Trial (GAIT).[202]

Glucosamine. The most promising results for glucosamine have been reported in trials evaluating a pharmaceutical grade glucosamine not available in the U.S., 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.[203]

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).[194] 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[204] was also conducted in Europe, but funding information was not reported. One of the trials has only been published as an abstract,[205] with analyses based on data from an unpublished manuscript. Two of the four trials found glucosamine superior to oral NSAIDs for efficacy,[204, 205] and two found no difference.[206, 207] 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, 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[208-210] 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, chondoitin, and the combination of glucosamine plus chondroitin (Tables 14 and 15, Appendix I).[208] GAIT evaluated pharmaceutical grade glucosamine hydrochloride (over-the-counter supplements commonly available in U.S. are typically glucosamine sulfate) and chondroitin 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% decrease in WOMAC pain score (70% vs. 64%, RR 0.91 [95% CI 0.82-1.02]), or as defined using OMERACT-OARSI criteria (67% vs. 61%,, RR 0.90 [95% CI 0.80-1.01]). 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% vs. 2.2%), 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[209] or tempomandibular joint osteoarthritis.[210] 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)[211]

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)

Abbreviations: 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 [-3.3 to -2.1] vs. -2.4 [-3.0 vs. -1.8]), the WOMAC function score (-9.2 [-11 vs. -7.2] vs. -8.7 [-11 vs. -6.8]).[195] There was also no difference in the proportion of responders based on OARSI-A criteria (40% vs. 33%). Adverse events were similar.

Two systematic reviews not included in the original CER focused on evaluations of glucosamine versus placebo (Appendix I).[189, 190] 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).[189] 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, 1939 patients randomized to glucosamine versus placebo), included more recently published trials, and conducted network analysis to incorporate indirect evidence.[190] 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. There was no difference between glucosamine and placebo in withdrawals due to adverse events.

Other systematic reviews[191, 193, 194] 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.[194] Other older systematic reviews also found important methodological flaws in the glucosamine trials that could have exaggerated estimates of effect.[191, 193]

The previously described, good-quality GAIT trial is the largest trial of glucosamine.[211] 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 0.94-1.2]), or various WOMAC, SF-36, and Health Assessment Questionnaire scores. There was also no difference in joint space width narrowing after 24 months.[202]

Three trials of glucosamine versus placebo have been published since the original CER.[195-197] All except one,[197] were included in the Wandel et al systematic review.[190] Of the three new trials, two were rated good quality.[196, 197] Both found no differences on outcomes related to pain, function, or (in one trial) radiographic narrowing between glucosamine and placebo for hip osteoarthritis[196] or low back pain with degenerative osteoarthritis.[197] 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.[196] 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]).[195] 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.[211] It found no difference between chondroitin and celecoxib in the proportion of patients with a 20% decrease in WOMAC pain score (65% vs. 70%, RR 0.93 [95% CI 0.84-1.0]), response based on OMERACT-OARSI criteria, or mean changes in WOMAC, SF-36, or Health Assessment Questionnaire Scores.

For chondroitin versus placebo, the 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).[190] 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.

Systematic reviews[191, 193, 212] included in the original CER are now outdated as they don't include several recently published, larger trials.[191, 193, 212] In addition, two of the systematic reviews did not evaluate effects of trial quality,[193, 212] and one did not evaluate effects of chondroitin separately from glucosamine.[193] One of the systematic reviews found that lower-quality and smaller trials reported larger effects compared to higher-quality and larger trials.[191]

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.[211] 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 1.0-1.2) or various WOMAC, SF-36, and Health Assessment Questionnaire scores. There was also no difference in joint space width narrowing after 24 months.[202] Adverse events with chondroitin and placebo were similar.

Three new fair-quality trials (unclear allocation concealment methods in all 3 trials,[198-200] and high attrition in 2[198, 200] of the 3 trials) 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[198, 200] that evaluated radiographic outcomes found chondroitin associated with less joint space narrowing. All three trials were included in the Wandel et al systematic review.[190] 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 1.0-1.5])[199]. In all three trials, adverse events with chondroitin and placebo were similar.[198-200]

Glucosamine plus chondroitin. The GAIT trial also evaluated the combination of glucosamine plus chondroitin.[211] It found no differences between the combination and placebo in the likelihood of achieving a clinical response after 24 weeks. In a post-hoc analysis, the combination was superior to placebo for achieving a clinical response in an analysis of a small (20% of enrollees) subgroup of patients with moderate to severe (WOMAC 301 to 400 mm) baseline pain (79% vs. 54.3%, RR 1.5 [95% 1.1-1.9]). 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.[201] 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 Fair	OA of knee 318	Glucosamine sulfate 1500mg powder for oral solution qd Acetaminophen 1 gm po tid Placebo 6 months	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 Rozendaal, 2009 Good	OA of hip 222	Glucosamine sulfate 1500 mg po qd or bid Placebo 24 months	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 (-5.38 to 1.36) JSN, mm adjusted difference: Minimal: -0.029 (-0.122 to 0.064) Lateral: -0.017 (-0.121 to 0.088) Superior: 0.016 (-0.079 to 0.111) Axial: -0.005 (-0.118 to 0.108)
Wilkens, 2010 Good	Degenerative lumbar OA 250	Glucosamine sulfate 1500 mg po qd or tid Placebo 6 months	Treatment Effect at 1 year (negative values favor glucosamine): RMDQ (0 to 24): -0.8 (-2.0 to 0.4), p=.50 NRS LBP (0 to 10): -0.3 (-0.8 to 0.3). p=.85 Global perceived effect, No. (%):* 34 (30.9%) vs. 32 (29.4%), p=.30
Chondroitin Trials			
Kahan, 2009 Fair	OA of knee 622	Chondroitin sulfates 4 & 6 800 mg q evening Placebo 2 years	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

Author, year Quality	Condition Number Enrolled	Comparison Duration of Study	Main results
			Hodges-Lehmann estimator of median effect of treatment: -0.14 (95% CI 0.06 – 0.21 mm, p<0.0001)
Mazieres, 2010 Fair	OA of knee 307	Chondroitin sulfate 500 mg po bid Placebo 24 weeks	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	OA of knee	Chondroitin sulfates 4 & 6 800 mg po qd Placebo 2 years	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
Glucosamine/ Chondroitin Trials			
Messier, 2007 Fair	OA of knee	Glucosamine hydrochloride 1500 mg and Chondroitin sulfate 1200 mg qd or tid Placebo 1 year; 6 months alone; 6 months treatment plus exercise	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 Good	OA of knee	Glucosamine 500 mg tid Chondroitin sulfate 400 mg tid Combination of Glucosamine and Chondroitin Celecoxib 200 mg qd Placebo 24 months	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

Abbreviations: 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; RMDQ= Roland Morris Disability Questionnaire; 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 1b. 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[11, 93, 96, 98, 111, 117, 178, 213] included in the original CER and one new systematic review[94] 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.[214]

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.[213] Higher doses were also 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.[117] For celecoxib specifically, evidence of an association with CV events largely comes from long-term trials.[111] The 33 month APC polyp prevention trial was the first to show an increased risk of CV events relative to placebo.[115] The lack of an association in CLASS[53] 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[117] 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.[115, 215] Large observational studies consistently showed no association between higher doses of various celecoxib and various nonselective NSAIDs[129, 130, 136, 140, 141, 143] or longer duration of therapy[126, 127, 129, 130, 140, 141, 143] and increased risk of CV events.

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.[53, 83] 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 4.6-6.3) consistently associated with greater risk of upper GI bleeding or perforation compared to lower or medium doses (RR 2.8, 95% CI 2.2-3.6).[94] 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.[11, 98, 178] In three studies[95, 99, 101] included in the new systematic review, slow-release formulations of NSAIDs (RR 5.9, 95% CI 4.7-7.3) and NSAIDs with a half-life longer than 12 hours (RR 5.7, 95% CI 3.6-9.2) 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 2.4-4.1).[94]

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.[93] Modified release formulations did not attenuate the risk for bleeding. In a fair-quality meta-analysis of 31 randomized trials with over 190,000 subjects, the risk of major bleeding was 1.6% with doses <100 mg once daily, 1.5% with 100-200 mg once daily, and 2.3% with >200 mg once daily.[216] 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.[96]

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,[178] though there was a modest dose response in one other case-control[177] and one retrospective cohort study[105] 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.[217] 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.[11] One recent analysis of the Nurses' Health Study found that the risk of CV events was dose-related for both NSAIDs and acetaminophen.[179]

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.[214] 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.[116] However, no study has directly compared such dosing strategies. Furthermore, other studies of twice-daily dosing with celecoxib (such as CLASS[53] and ADAPT[118]) 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 200mg twice daily) or a nonselective NSAID + PPI (6.3%).
  - One trial found the combination of celecoxib with higher dose PPI associated with lower risk of recurrent bleeding compared with celecoxib alone (0% versus 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 versus 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.
  - A large observational study found an increased risk of repeat heart failure admission in patients recently discharged for heart failure prescribed

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 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 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.
- Concomitant use of prophylactic dose aspirin
  - Concomitant use of aspirin appears to attenuate the GI benefits of COX-2 selective NSAIDs, resulting in risk similar to nonselective NSAIDs.
  - Addition of a PPI may reduce the risk of GI harms associated with either celecoxib or nonselective NSAIDs.
  - 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 didn't 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.[13] In one UK 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.[100] 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.[133] 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[104, 130] or myocardial infarction.[127, 129] 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 persons 80 years and older.[111]

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.[218] For the SF-36, there were no statistically significant differences: naproxen scored better than celecoxib 200 mg on four of 10 components of the SF-36, while celecoxib 200 mg scored better on six, 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 one event in 20 patients for celecoxib 200 mg and one 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.[89]

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,[187] but results from the Physicians' Health Study have found no association between acetaminophen use and renal dysfunction in men.[188] 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.[219] We did not find any other publications focusing on the differential efficacy or safety of coxibs in African-Americans, Hispanics, or other ethnic minorities.

Co-existing 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[220, 221] and one new trial[222] compared the risk of GI harms in patients with a recent bleeding ulcer randomized to celecoxib versus the combination of celecoxib plus a PPI.

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% and twice a day 4.9%) and the combinations of extended-release diclofenac 75 mg twice a day plus omeprazole 20 mg daily (6.3%)[220] or naproxen 250 mg three time a day plus lansoprazole 30 mg a day (6.3%)[221] (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 time a day plus lansoprazole 30 mg daily in one trial.[223]

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.[222] After a median of 13 months, zero events occurred in the combined treatment group, compared with 12 (8.9%) 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[220] 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%, CI –6.8, 3.8%; NS)	No differences	13% vs. 12%, NS*
Lai 2005[221] † 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; CI –9.1, 3.7; NS)	No differences for all but dyspepsia: 15% vs. 5.7%, p=0.02	10% vs. 7.4%, NS
Chan 2007[222] 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

Abbreviations: 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).[111] Most[129, 130, 142, 224] but not all[131] 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.[225] Based on the rates of death in this population (95 per 1000 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 10-24) for celecoxib, 45 (95% CI 29-102) for ibuprofen, and 24 (95% CI 16-45) for diclofenac.

We found no trials evaluating comparative risks of different oral medications in patients with known congestive heart failure. 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.[153] There was no difference in risk of

heart failure between other nonselective NSAIDs (diclofenac [OR 0.82, 95% CI 0.51-1.3] and ibuprofen [OR 1.5, 0.66-3.2]) or acetaminophen (OR 1.2, 955 CI 0.92-1.4) 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, 1.0 to 1.6) in similarly high risk patients.[155]

One new trial (n=88) compared ibuprofen, acetaminophen, and piroxicam in hypertensive patients on lisinopril/hydrochlorothiazide or amlodipine.[226] 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 six-fold compared to anticoagulants alone.[227, 228] Three observational studies included in the original CER evaluated risk of bleeding in patients on an NSAID plus anticoagulants versus an anticoagulant alone.[229-231] 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.[229] 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, 1145 patients who were receiving warfarin (INR ≥1.4) but not aspirin, acetaminophen or other nonselective NSAID were indentified retrospectively. [230] 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.[231] 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%) compared with controls (approximately 31%). 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 antiinflammatory 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 (3 trials, RR 1.58, 95% CI 1.02 to 2.44).[232] 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).[233] 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.[234] Several observational studies have also found an association between excess anticoagulation and use of acetaminophen.[235, 236] 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 versus 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[53] and SUCCESS-1[54]) 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.[237, 238]

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.[53, 239] There were also no differences when celecoxib was compared to diclofenac and ibuprofen separately. In SUCCESS-1, among the 7% of the study population on aspirin, only 4 ulcer complications occurred, resulting in imprecise estimates (OR 2.0, 95% CI 0.14 to 27).[54] The systematic review found that use of aspirin increased the rate of endoscopic ulcers by about 6% 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 0.28-0.83), 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).[237, 238] One study found use of celecoxib plus aspirin associated with a lower risk of hospitalizations due to ulcer complications compared to use of a nonselective NSAID plus aspirin (HR 0.62, 95% CI 0.48 to 0.80) among patients 65 years or older.[237] 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 to users of acetaminophen without aspirin).[238]

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 proton pump inhibitor (PPI) to celecoxib or nonselective NSAIDs in aspirin users.[222, 240, 241] Only one fair-quality trial reported ulcer complications. [222] 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% with celecoxib 200 mg twice daily plus esomeprazole 20 mg twice daily group compared with 19% in the group taking celecoxib alone (p=0.03).[222]

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%) compared with enteric coated naproxen alone (28%; p<0.001).[240] A large, fair-quality trial of celecoxib versus naproxen plus lansoprazole in low-dose aspirin users (n = 1045) found no difference in risk of endoscopically proven gastric or duodenal ulcers (9.9% versus 8.9%, p=0.65).[241] 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%/year versus 1.1%/year), perhaps due to higher baseline risk.[117] In a large celecoxib polyp prevention trial of not included in the systematic review, use or nonuse of low-dose aspirin did not affect the observed increased risk of thrombotic events.[242] Consistent with these findings, two large observational studies found no significant interaction between concurrent NSAID and aspirin use and risk of myocardial infarction.[131, 133]

Nonselective NSAIDs

It has been suggested that some nonselective NSAIDs may reduce or eliminate the CV benefits associated with low-dose aspirin.[37] In particular, ibuprofen is thought to be associated with unique pharmacokinetic and pharmacologic properties that could interfere with aspirin. Six observational studies[105, 130, 243-246] and one subgroup analysis from a randomized trial[247] 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[244] or myocardial infarction[130, 243] 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.[247] 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).[245] 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.[243, 246] 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).[243, 246] 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.[243] Recall bias is a major concern with this study, and differences between groups suggest potentially important differences in baseline risk. The cohort study used

VA 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.[246] 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[105] or use of ibuprofen plus aspirin versus nonuse of NSAIDs (including aspirin),[130] 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	N	Outcome measure	Referent	Effect (95% CI)
Any nonselective NSAID	Ko 2002	Cohort	39,043	Mortality at 1 year	No NSAID, no aspirin	NSAID+ASA OR 0.78 (0.69–0.88) ASA alone OR 0.81 (0.77-0.86)
	Kurth 2003*	RCT Subgroup analysis	22,071	AMI	No aspirin	1-59 days NSAID OR 0.69 (0.46–1.0) ≥60 days NSAID OR 1.57 (0.70–6.6)
	Kimmel 2004	Case-control	4,393	First nonfatal MI	Aspirin alone	NSAID+ASA vs ASA OR 0.92 (0.46–1.9)
	Fisher 2005	Case-control	2,989	AMI	No NSAID, no aspirin	NSAID+ASA OR 0.74 (0.57–0.97) ASA alone OR 0.87 (0.75–1.0)
Ibuprofen	MacDonald 2003	Cohort	7107	All-cause and cardiovascular mortality	Aspirin alone	Ibuprofen+ASA All-cause mortality HR 1.9 (1.3-2.9) Cardiovascular mortality HR 1.7 (1.0-2.8)
	Patel 2004	Cohort	14,098	AMI	Aspirin alone	Ibuprofen+ASA OR 0.61 (0.50–0.73)
	Kimmel 2004	Case-control	4,393	First nonfatal MI	Aspirin alone	Ibuprofen+ASA OR 2.0 (1.1-3.9)
	Rahme 2007	Cohort	76,877	AMI	Acetamin-ophen alone	Ibuprofen+ASA OR 1.4 (0.8-2.4) Ibuprofen only OR 1.0 (0.74–1.5)
	Fischer 2005	Case-control	2,989	AMI	No NSAID, no aspirin	Ibuprofen+ASA OR 0.69 (0.42–1.2)

Abbreviations: AMI= Acute myocardial infarction; ASA= Aspirin; HR= hazard ratio; MI= Myocardial infarction; NSAID= nonsteroidal antiinflammatory 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.[105] 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 co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?

Summary of Evidence

- 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.
- Misoprostol was the only gastroprotective agent to reduce risk of ulcer complications (perforation, obstruction, or bleeding) compared to placebo in patients prescribed nonselective NSAIDs, but was also associated with a high rate of withdrawals due to adverse GI symptoms.
- 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 resulted was associated with fewer combined upper and lower GI events (primarily lower rates of hemoglobin or hematocrit declines 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 (see Key Question 2 for high-risk persons)

Detailed Analysis

Nonselective NSAIDs plus misoprostol, H2 antagonists, or PPIs versus NSAIDs alone

Three good-quality systematic reviews included in the original CER evaluated effects of co-prescribing gastroprotective agents (H2-antagonists, misoprostol, and proton pump inhibitors [PPIs]) with NSAIDs versus placebo or against one another on GI harms.[248-250] We identified four new fair-quality trials (reported in two publications) of an NSAID plus a PPI versus an NSAID alone.[240, 251]

The three systematic reviews (published in 2004 and 2005)[248-250] included numerous randomized controlled trials[8, 250, 252-280] 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).[248-250] 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 co-prescribed drugs affected mortality.[248] The reduction in serious complications with misoprostol was in large part due to one large, good-quality trial (MUCOSA).[277] In this study, misoprostol was associated with a rate of definite ulcer complications of 25/4404 (0.6%) compared to 44/4439 (0.9%) with placebo (p=0.05).[277] 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).[240, 251] Two similarly designed, fair-quality trials (total n = 861) reported in one publication found naproxen plus esomeprazole 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).[240] 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 1378 patients.[251] In one trial, about two-thirds of patients were on a nonselective NSAID, and in the other, about 85%. 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 versus 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%) had GI bleeds during the study, compared with none in the nonselective NSAID plus esomeprazole groups.

Table 18. Summary of results from systematic reviews of placebo-controlled trials of gastroprotective agents[248-250]

Treatment	# studies Duration	Prevention of clinical GI events	Prevention of endoscopic ulcers	
			Gastric	Duodenal
Misoprostol	8 1-1.5 months: ≥ 3 months: 11	Silverstein 1995* (MUCOSA trial): OR 0.60; 95% CI 0.36 to 0.98	1-1.5 months: RR=0.17, 95% CI: 0.09 to 0.31 3 months: RR=0.26; 95% CI 0.17 to 0.39	1-1.5 months: RR=0.28; 95% CI 0.09 to 0.31 3 months: RR=0.47, 95% CI 0.33 to 0.69
	Duration NR	Hooper 2004[†] RR=0.57, 95% CI 0.36 to 0.91	Either: RR=0.33, 95% CI: .3 to 0.4	
H2 blockers	Standard dose[‡]: 7; 3 months Double dose[‡]: 3; 1-3 months		Standard dose: nonsignificant effect Double dose: RR=0.44, 95% CI: 0.026 to 0.74	Standard dose: RR=0.36, 95% CI: 0.18 to 0.74 Double dose: 0.26, 95% CI 0.11 to 0.65

Treatment	# studies Duration	Prevention of clinical GI events	Prevention of endoscopic ulcers	
			Gastric	Duodenal
	Standard dose Duration NR	Hooper 2004† RR= 0.33, 95% CI 0.01 to 8.14	Either: RR=0.55, 95% CI 0.4 to 0.7	
PPIs	4, Duration NR		RR=0.40, 95% CI 0.32 to 0.51	RR 0.19, 95% CI 0.09 to 0.37
	Duration NR	Hooper 2004† RR= 0.46, 95% CI 0.07 to 2.9	Either: RR=0.37, 95% CI 0.3 to 0.5	

Abbreviations: PPI= Proton pump inhibitor; NR= Not reported; OR= odds ratio; RR= relative risk
* Upper GI hemorrhage, perforation, pyloric obstruction, death
†Hemorrhage, hemorrhagic erosions, recurrent upper gastrointestinal bleeds, perforation, pyloric obstruction, melena, and death from any of these
‡Standard Doses = 150 mg daily, Double Doses = 300 mg daily

A systematic review included in the original CER included five trials[266, 268, 273, 278, 280] that directly compared one gastroprotective agent with another when co-prescribed with a nonselective NSAID.[249] 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. Head-to-head trials of gastroprotective agents[249]

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

Abbreviations: 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 to nonselective NSAIDs plus a PPI

The original CER included a good-quality systematic review of 26 trials that compared co-prescribing of a PPI with a nonselective NSAID versus a COX-2 selective NSAID on GI harms.[281] We identified two new trials[241, 282] and two new observational studies.[283, 284]

The systematic review found co-administration of a PPI with a nonselective NSAID associated with a lower risk of dyspepsia, epigastric pain and nausea compared to a selective COX-2 inhibitor alone, when each was compared to a nonselective NSAID alone (relative risk reduction 66% and absolute risk reduction 9% for the PPI + nonselective NSAID versus RRR 12% and ARR 3.7% with COX-2 inhibitor).[281] The systematic review did not assess endoscopic ulcers, symptomatic ulcers, or ulcer complications.

One large (n=4484), new, good-quality trial was designed to assess ulcer complications.[282] 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 ≥ 10%) compared to 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 2.6-7.0). 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%) patients withdrew early because of GI adverse events versus 167 (8%) allocated diclofenac SR plus omeprazole (p=0.0006). Another new, fair-quality trial (n=1045) 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.[241] Only 1 GI complication (0.1%) 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.[283, 284] A good-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.[284] 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).[283]

COX-2 inhibitors alone compared to 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.[251] 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.[222] 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.[283, 284]

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% for esomeprazole 20 mg once daily [p<0.001 vs. placebo], 4.1% for esomeprazole 40 mg once daily [p=0.002 vs. placebo], 16% for placebo). [251] 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.[283, 284] 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.[283] In stratified analyses, the benefit was observed in patients 75 years and older, with no benefit in those 66 to 74 years of age. A good-quality retrospective cohort study found celecoxib plus a PPI (RR 0.18, 95% CI 0.09-0.37) associated with a lower risk of hospitalization due to GI bleeding compared to celecoxib alone (RR 0.34, 95% CI 0.24-0.49) when each was compared to naproxen alone, though confidence intervals overlapped.[284]

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 higher-quality trials.
- Topical capsaicin was superior to placebo for pain relief (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).

Detailed Analysis

Topical versus oral NSAIDs: Benefits

Eight trials directly compared topical and oral NSAIDs for osteoarthritis (Table 20 and Appendix J).[49, 285-291] Four trials published since the original CER evaluated topical diclofenac,[288] topical ketoprofen,[286] or topical ibuprofen [289] vs. an oral NSAID (1 trial each), or advice to use topical ibuprofen versus advice to use oral ibuprofen (1 trial [49]. The original CER included 4 other trials of topical diclofenac (2 trials), topical eltenac (1 trial), and topical piroxicam (1 trial), each versus an oral NSAID.[285, 287, 290, 291] Of the eight trials, we rated three good-quality[286, 288, 290] and four fair-quality.[49, 285, 287, 289] We could not rate the eighth trial[291] because it was not published in English, though a systematic review[292] gave it the maximum 5 points on the Jadad scale. The original CER included two systematic reviews[292, 293] 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.[288, 290, 291] Two good-quality trials (n=622[290] and n=305[288]) 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 1700 mm scale, with 255 mm thought to be clinically significant).[290] 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% vs. 70%, p=0.37). A third, non-English language trial (n=321) found no difference between diclofenac 1% gel versus oral ibuprofen at 3 weeks in the proportion of patients with hand osteoarthritis with a ≥40% improvement in pain on a 100 mm VAS (40% vs. 34%, RR 1.20, 95% CI 0.88-1.60; data as reported in a systematic review).[291,292]

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.[289] 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% vs. 64%).[286] 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.[285]

A fair-quality trial of eltenac 1% gel was included in the original CER but is of limited relevance since it is no longer being investigated for use in humans.[287]

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[285] 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[287] 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[291] 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[290] 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

Author, year Quality	Condition Number enrolled	Comparison	Duration of study	Main results
				change): -45 vs. -52, p=0.14 Patient global assessment (0-100, mean change): -27 vs. -32, p=0.08
Rother, 2007[286] Good	OA of knee 270	Ketoprofen 110 mg in 4.8 g Transferone q 12 h Celecoxib 100 mg q 12 h	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
Simon, 2009[288] 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[289] 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

Abbreviations: CI= Confidence Interval; NSAID= Nonsteroidal antiinflammatory drug; OA= Osteoarthritis; OMERACT= Outcomes Measures in Arthritis Clinical Trials; VAS= Visual analogue scale; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index
*Non-English language study, data as reported in Mason et al[292]

Topical versus oral NSAIDs: Harms

Eight head-to-head trials reported adverse events associated with topical versus oral NSAIDs. Three trials evaluated topical versus oral diclofenac.[288, 290, 291] In two good-quality trials (one

published since the original CER[288]), rates of withdrawal due to adverse events were similar (21% vs. 25%[290] and 10% vs. 13%,[288] 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% versus 48%[290] and 6.5% versus 24%,[288] respectively. One trial that categorized adverse event severity also found topical diclofenac associated with a lower risk of serious GI events (7.4% vs. 21%).[290] 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 to oral NSAIDs. Topical NSAIDs were associated with an increased risk of dry skin, rash, and pruritus. A third, non-English language trial[291] 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[292]).

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.[286] 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, was too small to draw reliable conclusions about comparative harms.[289] A fair-quality trial included in the previous systematic review found no clear differences in adverse events between topical piroxicam and oral ibuprofen.[285] Another trial evaluated topical eltenac, a drug no longer being investigated for use in humans.[287]

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[285] 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[287] 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	GI: 4.8% vs. 13%	Local skin reaction: 13% vs. 1.2%	CNS: 9.5% vs. 7.3%

Author, year Quality	Condition Number enrolled Comparison	Withdrawal due to adverse events Any adverse events	Gastrointestinal adverse events	Skin adverse events	Other adverse events
		event: 27% (34/126) vs. 24% (20/82)			
Zacher, 2001[291] 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
Tugwell, 2004[290] 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[286] Good	OA of knee 270 Ketoprofen 110 mg in 4.8 g Transferone q 12 h vs. celecoxib 100 mg q 12h	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%	Any respiratory, thoracic, and mediastinal disorders: 12% vs. 11%

Author, year Quality	Condition Number enrolled Comparison	Withdrawal due to adverse events Any adverse events	Gastrointestinal adverse events	Skin adverse events	Other adverse events
				Urticaria: 1.4% vs. 0.8%	
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[288] 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
Tiso, 2010[289]	Chronic knee pain (presumed OA of knee)	Not reported	Stomachache: 0% vs. 10% Constipation: 0% vs. 10%	Rash: 11% vs. 0%	Dizziness: 11% vs. 20% Headache: 0% vs. 20%

Author, year Quality	Condition Number enrolled Comparison	Withdrawal due to adverse events Any adverse events	Gastrointestinal adverse events	Skin adverse events	Other adverse events
	20 Ibuprofen 4% gel qid vs. ibuprofen 800 mg po tid		Diarrhea: 0% vs. 10%		

Abbreviations: CNS= Central nervous system; GI= Gastrointestinal; NSAID= Nonsteroidal antiinflammatory drug; OA= Osteoarthritis
*Non-English language study, data as reported in Mason et al[292]

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 1 serious adverse event (post-polypectomy lower GI bleed) was observed with either topical or oral diclofenac.[288]

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 versus 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).[176] 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).[294] 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).[295] 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 included in the original CER found topical salicylates superior to placebo for pain relief when data from six trials were pooled (relative benefit 1.5, 95% CI 1.3 to 1.9; NNT 5.3, 95% CI 3.6 to 10.2).[33] However, the three higher quality trials found no significant benefit (relative benefit 1.3, 95% CI 0.98 to 1.6). Local adverse events were rare, but the quality of adverse-event reporting was poor.

We identified no trials comparing topical capsaicin to oral or topical NSAIDs for osteoarthritis. We also identified no new trials comparing topical capsaicin to placebo. 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% 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).[296] About 54% of patients had local adverse events with capsaicin, compared with 15% 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).

Summary and Discussion

Table 22 summarizes the strength of evidence and results for each key question.

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

Key Question	Strength of Evidence	Conclusion
1a. 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 worse 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 nonaspirin, 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 versus other NSAIDs.
GI and CV harms: Celecoxib	High (multiple systematic reviews and meta-analyses of mostly short-term trials, multiple observational studies; limited long-term data on serious GI harms)	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 the end of followup. There was no difference in rates of ulcer complications or symptomatic ulcers at either 6 month or complete followup. Other long-term followup data from randomized trials is lacking. A systematic review found celecoxib associated with a lower risk of upper gastrointestinal 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

Key Question	Strength of Evidence	Conclusion
		cardiovascular events with celecoxib versus ibuprofen or diclofenac in CLASS (0.5% vs. 0.3%). 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 1000 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. Three large observational studies found celecoxib associated with similar 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).
GI and CV harms: Partially selective NSAIDs	GI harms: Moderate for meloxicam and etodolac (fewer trials with methodological shortcomings), low for nabumetone (sparse data) CV safety: Low for all (no trials, few large observational studies)	GI harms: Meloxicam 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 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: 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 (consistent evidence from many trials and observational studies) CV harms: Moderate	GI harms: COX-2 selective NSAIDs as a class were associated with a similar reduction in risk of ulcer complications versus 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

Key Question	Strength of Evidence	Conclusion
	(almost all evidence from observational studies, few large, long-term controlled trials)	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. 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) versus placebo, but did not employ pre-specified stopping protocols. In most large observational studies, naproxen was associated with a neutral effect on risk of serious CV events.
GI and CV harms: Aspirin	Moderate (many trials, but almost exclusively in patients receiving aspirin for cardiovascular disease prevention, usually at lower prophylactic doses)	GI harms: A systematic review found aspirin associated with a risk of GI bleeding of 2.5%, compared to 1.4% with placebo. Observational studies showed a similar risk of upper GI bleeding with aspirin and nonaspirin, nonselective NSAIDs. CV harms: Aspirin reduced the risk of vascular events by an average of 23% in a collaborative meta-analysis of 65 randomized controlled trials.
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. On 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, versus 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).
Tolerability	High for celecoxib and nonselective NSAIDs, moderate for partially	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 0.70-0.80)

Key Question	Strength of Evidence	Conclusion
	selective NSAIDs (fewer trials with some methodological shortcomings)	and withdrawals due to GI adverse events (RR 0.45, 95% CI 0.33-0.56) 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, 955 CI 0.84-0.99), 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 0.54-0.69) 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 NSAID (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). Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies). 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
Glucosamine and chondroitin	High (consistent evidence from recent, higher-quality trials)	Seven randomized trials showed no clear difference between glucosamine and oral NSAIDs for pain or function. One randomized trial showed no difference between chondroitin and 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

Key Question	Strength of Evidence	Conclusion
		available in the U.S.).
1b. 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)	A meta-analysis of 41 randomized trials found no clear association between duration of therapy with NSAIDs and risk of cardiovascular events. However, almost all of the cardiovascular events in trials of celecoxib have been reported in long-term trials of colon polyp prevention. The meta-analysis found higher doses of celecoxib associated with increased risk of cardiovascular events, but most of the events occurred in the long-term polyp prevention trials. For NSAIDs other than celecoxib, large observational studies showed no association between higher dose and longer duration of NSAID therapy and increased risk of cardiovascular events. Many observational studies found that risk of GI bleeding increases with higher doses of nonselective NSAIDs, but no clear association with duration of therapy.
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) Low 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 almost no evidence on the comparative benefits and harms of different selective and nonselective NSAIDs in men compared to women, or in different racial groups.
Pre-existing 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 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 versus 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. A large observational study found an increased risk of repeat heart failure admission in patients recently discharged for heart failure prescribed indomethacin compared to other nonselective NSAIDs, ibuprofen, acetaminophen, or celecoxib.
Concomitant anticoagulant use	Fair overall: Primarily	Concomitant use of anticoagulants and nonselective

Key Question	Strength of Evidence	Conclusion
	observational studies	NSAIDs increase 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.
Concomitant use of prophylactic dose aspirin	Good for GI safety: Consistent evidence from clinical trials and observational studies Fair for CV safety: 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 either celecoxib or nonselective NSAIDs. 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 didn't clearly demonstrate increased risk.
3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?	Good: Consistent evidence from good-quality systematic reviews and numerous clinical trials	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-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. Misoprostol was the only gastroprotective agent to reduce risk of ulcer complications compared to placebo in patients prescribed nonselective NSAIDs, but was also associated with a higher rate of withdrawals due to adverse GI symptoms.

Key Question	Strength of Evidence	Conclusion
		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 combined upper and lower GI events (primarily decreases in hemoglobin or hematocrit 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.
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	Low (no head-to-head trials, 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 higher-quality trials. 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).

Abbreviations: CHF= Congestive Heart Failure; CI= Confidence Interval; CLASS= Celecoxib Long-term Arthritis Safety Study; COX= Cyclo-oxygenase; CV= Cardiovascular; FDA= 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; NSAIDs= Nonsteroidal antiinflammatory drugs; 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 antiinflammatory 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 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.

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 trade-off 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), co-morbid 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 trade-offs.

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 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 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 nonaspirin 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 U.S. 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.

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Abbreviations

Acronym/ Abbreviation	Definition
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	The 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	Cyclo-oxygenase
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	International Normalized Ratio
IR	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 antiinflammatory 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	

PreSAP	Proton Pump Inhibitor
PUBs	Prevention of Colorectal Sporadic Adenomatous Polyps
PUD	Perforations, symptomatic gastroduodenal ulcers, and upper GI bleeding
qd	Peptic Ulcer Disease
RA	Once a day (quaque die)
RCT	Rheumatoid Arthritis
RMDQ	Randomized controlled trial
RR	Roland Morris Disability Questionnaire
RRR	Relative Risk
SCHIP	Relative Risk Reduction
SF-36	State Children's Health Insurance
SMD	Medical Outcomes Short Form-36
SR	Standardized mean difference
SR	Sustained Release
SRC	Systematic Review
SUCCESS-1	Scientific Resource Center
TARGET	Successive Celecoxib Efficacy and Safety Study-1
TEP	Therapeutic Arthritis Research and Gastrointestinal Event Trial
tid	Technical Expert Panel
UGIB	Three times a day (ter in die)
UK GPRD	Upper gastrointestinal bleeding
VAS	United Kingdom General Practice Research Database
VIGOR	Visual analogue scale
WOMAC	Vioxx Gastrointestinal Outcomes Research
	Western Ontario and McMaster Universities Osteoarthritis Index