



Effective Health Care

Comparative Effectiveness and Safety of Analgesics for Osteoarthritis

Executive Summary

Background

Osteoarthritis is a chronic condition involving degeneration of cartilage within the joints. It is the most common form of arthritis and is associated with pain, substantial disability, and reduced quality of life. About 6 percent of U.S. adults aged 30 years or older have symptomatic osteoarthritis of the knee, and 3 percent have symptomatic osteoarthritis of the hip. Osteoarthritis increases with age: the incidence and prevalence increase two- to tenfold from age 30 to 65 and continue to increase after age 65. 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 over-the-counter supplements not regulated by the U.S. Food and Drug Administration (FDA) as pharmaceuticals, including glucosamine and chondroitin, as well as topical agents. Opioid medications are also used for selected patients with refractory, chronic pain but are not recommended for first-line treatment of osteoarthritis and therefore not included in this review. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition,

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efficacy and safety 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.



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A challenge in treating osteoarthritis is deciding which medications will provide the greatest symptom relief with the fewest serious adverse effects. NSAIDs decrease pain, inflammation, and fever by blocking cyclo-oxygenase (COX) enzymes. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. 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 bleeding. In the United States, there are an estimated 16,500 annual deaths due to NSAID-induced gastrointestinal complications, a higher death rate than that for cervical cancer or malignant melanoma. 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 gastrointestinal bleeding, but they also appear to be associated with increased rates of serious cardiovascular and other adverse effects. Less is known about COX-3, which is found in the cerebral cortex and cardiac tissue and appears to be involved in centrally mediated pain.

For this report, we defined the terms “selective NSAIDs” or “COX-2 selective NSAIDs” as drugs in the “coxib” class (celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib). We defined “partially selective NSAIDs” as 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, and the salicylic acid derivatives (aspirin and salsalate) were considered a separate subgroup. We defined “nonaspirin, nonselective NSAIDs” or simply “nonselective NSAIDs” as “all other NSAIDs.”

This report summarizes the available evidence comparing the benefits and harms of analgesics in the treatment of osteoarthritis.

Oral agents include:

- Acetaminophen
- Aspirin
- Celecoxib
- Choline magnesium trisalicylate
- Chondroitin
- Diclofenac
- Diflunisal
- Etodolac
- Etoricoxib¹
- Fenoprofen
- Flurbiprofen
- Glucosamine
- Ibuprofen
- Indomethacin
- Ketoprofen
- Ketoprofen ER
- Ketorolac
- Lumiracoxib¹
- Meclofenamate sodium
- Mefenamic acid
- Meloxicam
- Nabumetone
- Naproxen
- Oxaprozin
- Piroxicam
- Rofecoxib¹
- Salsalate
- Sulindac
- Tenoxicam¹
- Tiaprofenic acid¹
- Tolmetin
- Valdecoxib¹

¹ These drugs are currently not approved by the FDA for use in the United States (etoricoxib, lumiracoxib, tenoxicam, tiaprofenic acid) or have been withdrawn from the market (rofecoxib and valdecoxib).

Questions addressed in this report are:

1. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, 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? (*Note: The only benefits considered under this question are improvements in osteoarthritis symptoms from long-term use. Evidence of harms associated with NSAID use include long-term studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.*)
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients?
 - Demographic subgroups include age, sex, and race.
 - Coexisting diseases include hypertension, edema, ischemic heart disease, heart failure; peptic ulcer disease; history of previous bleeding due to NSAIDs.
 - Concomitant medication use includes anticoagulants.
3. What are the comparative effects of coprescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?
4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations? Topical preparations include: capsaicin, diclofenac, ibuprofen, ketoprofen, and salicylate.

A summary of the findings is shown in Table A.

Conclusions

Oral NSAIDs

Benefits: improvements in osteoarthritis symptoms

- **Nonselective NSAID vs. another nonselective NSAID**
 - Many trials found no clear differences between various nonaspirin, nonselective NSAIDs or partially selective NSAIDs (meloxicam,

nabumetone, etodolac) in efficacy for pain relief or improvement in function.

- In one short-term trial, salsalate and aspirin did not differ significantly in efficacy for pain relief or symptom improvement.
- No studies evaluated the comparative efficacy of salsalate or aspirin vs. a nonaspirin NSAID.
- **COX-2 selective NSAID vs. nonselective NSAID**
 - COX-2 selective NSAIDs and nonselective NSAIDs did not clearly differ in efficacy for pain relief, based on many good-quality, published trials.
- **COX-2 selective NSAID vs. different COX-2 selective NSAID**
 - Celecoxib and rofecoxib did not differ significantly in efficacy for pain relief at commonly used and comparable doses, based on consistent evidence from six good-quality trials.
 - No studies compared efficacy of COX-2s other than celecoxib and rofecoxib.

Harms: gastrointestinal (GI) and cardiovascular (CV)

- **Rofecoxib vs. nonselective NSAID**
 - In the only large, long-term trial (VIGOR), rofecoxib 50 mg daily caused fewer serious ulcer complications than naproxen 1,000 mg daily in patients with rheumatoid arthritis but also significantly increased the risk of myocardial infarction. The overall rate of serious adverse events was higher with rofecoxib than with naproxen.
 - There were about 16 fewer symptomatic ulcers, including 5.2 fewer serious GI complications, for every 1,000 patients treated with rofecoxib vs. naproxen after a median of 9 months of treatment.
 - There were 3.0 additional myocardial infarctions for every 1,000 patients treated with rofecoxib compared to naproxen in VIGOR.
 - Rofecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of randomized controlled trials (RCTs).

- About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with rofecoxib compared to placebo in the systematic review.
- Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks.
- **Celecoxib vs. nonselective NSAID or placebo**
 - It is not clear whether celecoxib has fewer potential harms than nonselective NSAIDs when used longer than 3-6 months. In the only large, published trial (CLASS), celecoxib at 800 mg daily did not decrease predefined serious ulcer complications overall compared with diclofenac and ibuprofen; the risk of serious GI events was lower than with ibuprofen, but not diclofenac, at 6 months in patients who did not use aspirin; and there was no reduction in serious GI events at the end of followup. The overall rate of serious adverse events with celecoxib was similar to the rate with ibuprofen and diclofenac.
 - In fair-quality meta-analyses of arthritis trials, most of which evaluated short-term use, celecoxib caused fewer ulcer complications than nonselective NSAIDs and did not increase the risk of myocardial infarction.
 - Celecoxib 400 mg twice daily was associated with an increased risk of serious CV events (CV death or myocardial infarction) relative to placebo in a long-term trial of polyp prevention.
 - Celecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of 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.
 - About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with celecoxib compared to placebo.
- **Valdecoxib vs. nonselective NSAID or placebo**
 - Valdecoxib was associated with a lower risk of upper GI complications compared with diclofenac, ibuprofen, or naproxen in two fair-quality meta-analyses of published and unpublished trials.
 - There have been too few events reported in RCTs of patients with chronic conditions to accurately assess CV risk associated with valdecoxib.
 - Two short-term trials in a high-risk post-coronary-artery-surgery setting found that valdecoxib was associated with a two- to threefold higher risk of CV events compared with placebo.
 - Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk.
- **Etoricoxib vs. nonselective NSAID**
 - Etoricoxib was associated with fewer GI adverse events (perforations, symptomatic ulcers, and bleeds) than nonselective NSAIDs in a fair-quality meta-analysis of 10 trials.
 - In primarily short-term trials, systematic reviews of RCTs suggest that etoricoxib has a similar CV safety profile compared to other NSAIDs, with the possible exception of naproxen. Definitive conclusions are not possible because of small numbers of CV events.
- **Lumiracoxib vs. nonselective NSAID**
 - Results from one large trial (TARGET) found fewer adverse GI events with lumiracoxib than with naproxen and ibuprofen.
 - There was no statistically significant difference in rates of serious CV events between lumiracoxib relative to naproxen or ibuprofen in TARGET.
 - Too few events have been reported in RCTs to accurately assess CV risk associated with lumiracoxib.
- **Partially selective NSAID vs. nonselective NSAID**
 - Meloxicam: There were no significant differences in risks of serious GI events in several meta-analyses of up to 28 primarily short-term clinical trials, and no difference in CV risk in three observational studies.

- Nabumetone or etodolac: There was insufficient evidence to make reliable judgments about relative GI safety and no evidence on CV safety.
- **Nonselective NSAID vs. nonselective NSAID or any COX-2 selective NSAID**
 - No clear difference in GI safety was found among nonselective NSAIDs at commonly used doses.
 - The CV safety of naproxen was moderately superior to that of any COX-2 selective NSAID in a large systematic review of RCTs.
 - There were 3.3 additional myocardial infarctions for every 1,000 patients treated with any COX-2 inhibitor instead of naproxen for 1 year.
 - 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, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo.
- **Aspirin**
 - Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds compared to placebo or nonuse when given in 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. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs.
 - Almost no data are available on CV safety.

Harms: mortality

- Individual trials were not large enough to detect differences in mortality between the included drugs.

- One meta-analysis of celecoxib found no difference between celecoxib and nonselective NSAIDs, but there were few events.
- 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), edema, and impaired renal function

- All NSAIDs and COX-2 inhibitors can cause or aggravate these conditions.
- There is good evidence from short-term trials that, on average, nonselective NSAIDs raise mean blood pressure by about 5.0 mm Hg (95-percent confidence interval [CI] 1.2 to 8.7). However, similar average blood pressure changes may not necessarily correspond with similar likelihoods of an event requiring withdrawal, medication change, or other clinical consequences.
- Evidence from good-quality observational studies suggests that rofecoxib is associated with greater risks of hypertension, CHF, and edema than celecoxib. Indirect evidence from various meta-analyses of either rofecoxib or celecoxib vs. nonselective NSAIDs are consistent with these findings. Direct randomized trial evidence, however, is limited in quantity and difficult to interpret because of possible non-equivalent dosing of drugs. Evidence regarding the comparative risk of renal dysfunction for celecoxib and rofecoxib is sparse.
- There was weak evidence that aspirin and sulindac have less hypertensive effect than other nonselective NSAIDs.
- There were no clear differences among other selective or nonselective NSAIDs for these adverse events.

Harms: hepatotoxicity

- Clinically significant hepatotoxicity was rare.
- Among currently marketed NSAIDs, only diclofenac was associated with a significantly higher rate of liver-related discontinuations compared with placebo (1 additional case for every 53 patients treated with diclofenac).

Tolerability

- Relative to nonselective NSAIDs, COX-2 selective and partially selective NSAIDs were better or

similarly tolerated and aspirin was less well tolerated.

- There were no clear differences in tolerability among COX-2 selective or nonselective NSAIDs.
- Uncertainty remains regarding the comparative tolerability of salsalate and nonselective NSAIDs. Available evidence is somewhat sparse and mixed, with two of three short-term trials suggesting salsalate is less well tolerated than nonselective NSAIDs and older, flawed observational studies suggesting that salsalate is less toxic 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 analog 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 at therapeutic doses does not appear to be associated with an increased risk of hepatotoxicity compared to nonuse in patients without underlying liver disease.

Glucosamine and chondroitin

- In one large, good-quality trial the combination of pharmaceutical-grade glucosamine hydrochloride plus chondroitin (not currently available in the United States) was not superior to placebo among all patients studied. Neither glucosamine nor chondroitin alone was superior to placebo. In an analysis of a small subgroup of patients with at least moderate

baseline pain, there was a modest benefit for pain relief, but this did not appear to be a preplanned analysis.

- Systematic reviews of older trials found glucosamine modestly superior to oral NSAIDs and placebo in most trials, but there was some inconsistency between trials, most trials had some flaws and results may not be directly applicable to the United States because the positive trials primarily evaluated pharmaceutical-grade glucosamine available in Europe.
- Only 2 of 20 placebo-controlled trials assessed effects of glucosamine on radiologic disease progression. One fair- and one good-quality trial found pharmaceutical-grade glucosamine superior to placebo for progression of knee joint space narrowing over 3 years.
- Glucosamine and chondroitin were generally well tolerated and no serious adverse events were reported in clinical trials.

Effect of dosage and duration of treatment on the benefits and harms of oral medication use

- We found no studies evaluating the GI or CV safety of alternative dosing strategies (such as alternate day dosing, once daily versus twice daily dosing, or periodic drug holidays).
- The risk of GI bleeding increases with higher doses of nonselective NSAIDs.
- The most comprehensive systematic review of RCTs found no clear association between duration of exposure and CV risk of COX-2 inhibitors. However, estimates of CV risk with shorter duration of exposure are imprecise due to low numbers of events.
- The most comprehensive systematic review of RCTs found higher doses of celecoxib associated with increased CV risk, but could not determine the effects of dose on CV risk associated with rofecoxib due to low numbers of events at lower doses. Most trials of nonselective NSAIDs involved high doses.

Differences in demographic and clinical subgroups

- GI and CV complication rates are higher among older patients and those with predisposing comorbid conditions, but there is no evidence that

the relative safety of different NSAIDs varies according to baseline risk.

- Compared to nonuse of NSAIDs, one additional death per 1 year of use occurred for every 13 patients treated with rofecoxib, 14 with celecoxib, 45 with ibuprofen, and 24 with diclofenac in one large, population-based observational study of high-risk patients with acute myocardial infarction.
- There is no evidence that the comparative safety or efficacy of specific selective or nonselective NSAIDs varies depending on age, gender, or racial group, although data are sparse.
- Among patients who had a recent episode of upper GI bleeding, there is good evidence that rates of recurrent ulcer bleeding are high (around 5 percent after 6 months) in patients prescribed celecoxib or a nonselective NSAID plus a PPI.

Concomitant anticoagulant use

- Concomitant use of anticoagulants (e.g., warfarin) and any nonselective NSAID increases the risk of GI bleeding three- to sixfold compared to anticoagulants alone.
- Reliable conclusions about the safety of selective NSAIDs used with anticoagulants are not possible due to flaws in existing observational studies, although there are case reports of serious bleeding events, primarily in the elderly.

Concomitant aspirin use

- In the CLASS studies, there was no difference in rates of ulcer complications between celecoxib and nonselective NSAIDs in the subgroup of patients who took aspirin.
- Concomitant low-dose aspirin use increased the rate of endoscopic ulcers by about 6 percent in both patients on celecoxib and those on nonselective NSAIDs in one meta-analysis.
- Rofecoxib plus low-dose aspirin or ibuprofen alone were associated with similar risks of endoscopic ulcers (16-17 percent), which were significantly higher than those for placebo (6 percent) or aspirin alone (7 percent).
- The most comprehensive systematic review of RCTs found that compared to nonuse of aspirin, concomitant aspirin use did not ameliorate the increased risk of vascular events associated with COX-2 selective NSAIDs.

Effects of coprescribing H2-antagonists, misoprostol, or PPIs

- Consistent evidence from good-quality systematic reviews and numerous clinical trials found coprescribing of PPIs to be associated with the lowest rates of endoscopically detected duodenal ulcers relative to gastroprotective agents.
- Coprescribing of misoprostol is associated with similar rates of endoscopically detected gastric ulcers as coprescribing of PPIs.
- While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of perforation, obstruction, or bleeding, there is a high rate of withdrawals due to adverse GI symptoms.
- The risk of endoscopic duodenal ulcers for *standard*-dose H2 blockers was lower than placebo, similar to misoprostol, and higher than omeprazole. Standard dosages of H2 blockers were associated with no reduction of risk for gastric ulcers relative to placebo.
- *Double (full)* dose H2 blockers were associated with a lower risk of endoscopic gastric and duodenal ulcers relative to placebo. It is unknown how full-dose H2 blockers compare to other antiulcer medications because head-to-head trials are lacking.

Comparison of oral medications with topical preparations

- **Topical NSAIDs: efficacy**
 - Studies of topical NSAIDs typically evaluated proprietary formulations not approved by the FDA.
 - Topical NSAIDs were similar to oral NSAIDs for pain relief in trials primarily of patients with osteoarthritis of the knee, with topical diclofenac (often with dimethyl sulphoxide [DMSO], a drug not approved for use in humans in the United States) best studied.
 - Topical ibuprofen was superior to placebo in several trials.
- **Topical NSAIDs: safety**
 - Consistent evidence from good-quality trials, systematic reviews, and observational studies found topical NSAIDs to be associated with increased local adverse events compared with oral NSAIDs.

- Total adverse events and withdrawal due to adverse events were similar.
- Data from one good-quality trial found topical NSAIDs superior to oral NSAIDs for GI events, including severe events, and changes in hemoglobin.
- **Topical salicylates and capsaicin**
 - Topical salicylates were no better than placebo in higher quality placebo-controlled trials.
 - Compared to placebo, one additional patient achieved pain relief for every eight that used topical capsaicin in a good-quality meta-analysis, but capsaicin was associated with increased local adverse events and withdrawals due to adverse events.

Balance of evidence and harms

Each of the analgesics evaluated in this report was associated with a unique set of benefits and risks. Each was also associated with gaps in the evidence necessary to determine the true balance of benefits vs. harms. The role of 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 vary, no currently available analgesic reviewed in this report was identified as offering a clear overall advantage compared with the others. This is not surprising, given the complex tradeoffs between the many benefits (pain relief, improved function, improved tolerability, and others) and harms (CV, renal, GI, and others) involved.

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.

Remaining Issues

- The CV safety of nonselective NSAIDs has not been well studied in large, long-term clinical trials. Naproxen, in particular, may be associated with fewer CV risks 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. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall tradeoffs between benefits and harms.
- The CV risks and GI benefits associated with different COX-2 selective NSAIDs may 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 continue to assess the effects of dose and duration as more data become available; current estimates of risks at lower doses and with shorter duration of exposure are less precise than estimates at higher doses and longer duration of exposure because of small numbers of events.
- 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. Recent observational data suggesting an increased CV risk with heavy use of acetaminophen highlight the need for long-term, appropriately powered clinical trials.
- Given the large number of patients who meet criteria for aspirin prophylaxis for CV events, more trials evaluating the dose-related effects of aspirin 50-1500 mg on GI benefits and CV safety are needed.
- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. 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 reduce CV risk, this hypothesis has not yet been tested in a clinical trial.

- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical-grade glucosamine not available in the United States and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations of glucosamine and chondroitin with oral NSAIDs are needed, as these are likely to remain available even if the FDA approves pharmaceutical-grade formulations.
- No topical NSAIDs are FDA approved in the United States, yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO, which is not approved in the United States for use in humans. Cohort studies using large observational databases may be required to adequately assess CV risk.

Addendum

As this report was going to press, two relevant meta-analyses on risks associated with NSAIDs were published. We were unable to fully incorporate these studies into this report, but found their results generally consistent with our conclusions:

- A fair-quality meta-analysis of arrhythmia and renal event (peripheral edema, hypertension, or renal dysfunction) risk from 114 randomized trials of COX-2 selective NSAIDs found rofecoxib associated with increased risks of arrhythmia (primarily ventricular fibrillation, cardiac arrest, or sudden cardiac death) and renal dysfunction (peripheral edema, hypertension, or renal dysfunction) relative to control treatments (placebo, other NSAIDs, or mixed/other). The increased risk was equivalent to approximately 1.1 additional arrhythmia events per 1,000 patients treated with rofecoxib. Celecoxib was associated with lower risks of renal dysfunction and hypertension than control treatments, although

there was no difference for the prepecified, primary composite renal outcome of peripheral edema, hypertension, renal dysfunction, or arrhythmia. There was no clear association between other COX-2 inhibitors (valdecoxib/parecoxib, etoricoxib, or lumiracoxib) and either arrhythmia or renal events (no arrhythmia events reported with lumiracoxib).

- A good-quality meta-analysis of cardiovascular risk (primarily myocardial infarction) from 23 observational studies was largely consistent with our qualitative assessment of the observational literature. It found rofecoxib associated with a dose-dependent, increased risk of cardiovascular events that was detectable during the first month of treatment. Of the other NSAIDs, diclofenac was associated with the highest risk, followed by indomethacin and meloxicam. Celecoxib, naproxen, piroxicam, and ibuprofen were not associated with increased risks. Assessments of increased risk were modest (relative risks all <2.0), and all of the main analyses were associated with substantial between-study heterogeneity.

Full Report

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Table A. Summary of Findings on Comparative Effectiveness and Safety of Analgesics for Osteoarthritis, with Strength of Evidence

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
<p>COX-2 selective NSAIDs</p>	<ul style="list-style-type: none"> • Good evidence COX-2 selective NSAIDs are comparable in efficacy (pain relief) to nonselective NSAIDs. • Good evidence COX-2 selective NSAIDs are comparable in efficacy to each other. 	<ul style="list-style-type: none"> • GI: Fair to good evidence of fewer serious GI events with COX-2 selective NSAIDs compared to nonselective NSAIDs, at least in the first 6 months of treatment. • CV: Comparative data on CV risks of COX-2 selective vs. nonselective and partially selective NSAIDs are sparse, with a few exceptions (see below). Fair evidence that COX-2 selective NSAIDs are associated with increased risks of serious CV events (primarily myocardial infarction) compared to placebo. CV risks may increase with greater dosages and durations of treatment, but estimates of risks at lower doses and with shorter durations of treatment are imprecise due to small numbers of events. • Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks. • Cautions about CV risk apply primarily to rofecoxib and celecoxib, as CV safety data are less precise (due to small numbers of events) for valdecoxib, etoricoxib, and lumiracoxib. • Other <ul style="list-style-type: none"> • Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk. • Fair evidence suggests that rofecoxib is associated with greater risk of hypertension, CHF, edema, and cardiorenal events than celecoxib. 	<ul style="list-style-type: none"> • Good evidence that risk of GI bleeding and CV events increases with age. • Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. • Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities.
<p>NSAIDs : nonselective (including naproxen), partially selective</p>	<ul style="list-style-type: none"> • Good evidence nonselective and partially selective NSAIDs are comparable in efficacy to each other. 	<ul style="list-style-type: none"> • GI: Good evidence that all nonselective NSAIDs are associated with comparable, dose-dependent increases in risk of serious GI events compared to nonuse. Good evidence that coprescription of misoprostol or PPIs can attenuate this risk, but misoprostol is less well tolerated. • No clear evidence (fair for meloxicam and poor for etodolac and nabumetone) that partially selective NSAIDs are associated with decreased risk relative to nonselective NSAIDs. • CV: Data on CV risks of nonselective and partially selective NSAIDs are sparse, with a few exceptions: <ul style="list-style-type: none"> • Fair evidence that high doses of ibuprofen and diclofenac carry similar risks of serious CV events compared to COX-2 selective NSAIDs. 	<ul style="list-style-type: none"> • Good evidence that risk of GI bleeding and CV events increases with age. • Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. • Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities.

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
Aspirin/salsalate	<ul style="list-style-type: none"> No evidence comparing efficacy of aspirin or salsalate to COX-2s or NSAIDs 	<ul style="list-style-type: none"> Fair evidence that naproxen is associated with a lower risk of CV events than COX-2 selective NSAIDs and no excess risk compared to placebo. Other: Fair evidence that diclofenac is associated with higher rates of aminotransferase elevations than other NSAIDs. Good evidence that aspirin 50-1500 mg (for thrombotic event prophylaxis) is associated with greater risks of serious GI events compared to placebo or when added to warfarin. Good evidence that low-dose aspirin is effective for preventing CV events. Insufficient evidence to assess GI and CV risks associated with higher doses of aspirin for pain control or with salsalate. 	<ul style="list-style-type: none"> Fair evidence that using NSAIDs concomitantly with anticoagulants increases GI bleeding risk three- to sixfold. Good evidence that concomitant use of aspirin attenuates or eliminates the GI benefits of COX-2 selective NSAIDs. Fair evidence that concomitant use of low-dose aspirin does not eliminate CV risks when added to NSAIDs.
Acetaminophen	<ul style="list-style-type: none"> Good evidence that acetaminophen is modestly inferior in efficacy compared to NSAIDs. 	<ul style="list-style-type: none"> Good evidence of lower risk of GI complications with acetaminophen compared to NSAIDs. Fair evidence of increased risk of blood pressure and renal dysfunction with acetaminophen compared to nonuse. Poor evidence (a single observational study) that heavy use of acetaminophen carries a similar CV risk compared to heavy use of NSAIDs. 	None
Glucosamine (pharmaceutical grade)/	<ul style="list-style-type: none"> Fair evidence (some inconsistency between clinical trials) clinical that pharmaceutical-grade glucosamine and chondroitin are not more effective than placebo in unselected patients, including one recent, large, good-quality trial finding no beneficial effects from glucosamine or chondroitin alone or in combination. 	<ul style="list-style-type: none"> Good evidence that glucosamine and chondroitin are well tolerated and do not appear to be associated with serious adverse events. 	None

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
	<p>In an analysis of a small subgroup of patients with at least moderately severe baseline pain in the latter trial, there appeared to be a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis.</p> <ul style="list-style-type: none"> • Fair evidence of no clear difference in efficacy between pharmaceutical-grade glucosamine or chondroitin and NSAIDs. • No studies compared glucosamine or chondroitin to acetaminophen. 	<p>Harms: gastrointestinal, cardiovascular, and other</p>	
Topical NSAIDs	<ul style="list-style-type: none"> • Good evidence they are comparable to oral NSAIDs for pain relief in trials primarily of patients with knee osteoarthritis. • Most trials of topical NSAIDs evaluate proprietary formulations not available in the United States. 	<ul style="list-style-type: none"> • Good evidence that topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. • Good evidence that topical and oral NSAIDs are comparable in rates of total adverse events and withdrawals due to adverse events. • Good evidence that topical NSAIDs are associated with fewer GI events, including severe events, and changes in hemoglobin compared to oral NSAIDs. 	
Topical salicylates and capsaicin	<ul style="list-style-type: none"> • Fair evidence that capsaicin, but not topical salicylates are superior for pain relief compared to placebo. 	<ul style="list-style-type: none"> • Good evidence that topical capsaicin is associated with increased local adverse events and withdrawals due to adverse events compared to placebo. 	None

Abbreviations: CHF = congestive heart failure; COX = cyclo oxygenase; CV = cardiovascular; GI = gastrointestinal; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor.