Drug Class Review

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Final Update 4 Report
Executive Summary

November 2010

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Nonsteroidal Antiinflammatory Drugs", dated November 2010. The full report can be accessed at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Readers are advised to review the full report. The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 3: November 2006
Update 2: May 2004
Update 1: September 2003
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The literature on this topic is scanned periodically

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INTRODUCTION

Compared with placebo, nonsteroidal antiinflammatory drugs (commonly called NSAIDs) reduce pain significantly in patients with arthritis, low back pain, and soft tissue pain. However, NSAIDs have important adverse effects, including gastrointestinal bleeding, peptic ulcer disease, hypertension, edema, and renal disease. More recently, some NSAIDs have also been associated with an increased risk of myocardial infarction. NSAIDs reduce pain and inflammation by blocking cyclo-oxygenases (COX), enzymes that are needed to produce prostaglandins. Most NSAIDs block 2 different cyclo-oxygenases, COX-1 and COX-2. COX-2, found in joints and muscle, contributes to pain and inflammation. NSAIDs cause bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. In the United States, complications from NSAIDs are estimated to cause about 6 deaths per 100 000, a higher death rate than that for cervical cancer or malignant melanoma. A risk analysis based on a retrospective case-control survey of emergency admissions for upper gastrointestinal disease in 2 United Kingdom general hospitals provided useful estimates of the frequency of serious gastrointestinal complications from NSAIDs. In people taking NSAIDs, the 1-year risk of serious gastrointestinal bleeding ranges from 1 in 2100 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.

Scope and Key Questions

The goal of this report is to compare the effectiveness and harms of nonsteroidal antiinflammatory drugs (NSAIDs) in the treatment of chronic pain from osteoarthritis, rheumatoid arthritis, soft tissue pain, back pain, and ankylosing spondylitis. Included drugs are shown in Table 1.

Table 1. Included NSAIDs

Generic name	Trade name(s)	Dosage forms
Oral drugs		
Celecoxib	Celebrex®	Capsule
Diclofenac sodium	Voltaren [a]	Tablet, suppository
	Voltaren SR [a]	Tablet, ER
	Voltaren® XR [b]	Tablet, ER
Diclofenac potassium	Cataflam® [b]	Tablet
	Voltaren Rapide® [a]	Tablet
	Zipsor® [b]	Capsule
Diflunisal	*Generic only*	Tablet
Etodolac	Ultradol [a]	
Fenoprofen [b]	Nalfon® [b]	Capsule
Flurbiprofen	Ansaid®	Tablet
Ibuprofen	Advil® [c]	Tablet, caplet, gel caplet
	Motrin® IB [c]	Tablet, caplet
Indomethacin	Indocin® [b]	Suspension
	Indocin® SR [b]	Capsule, ER
	Generic only [a]	Capsule; suppository
Ketoprofen	Nexcede® [b, c]	Film
	Generic only [a]	Capsule, EC tablet, suppository
Ketoprofen SR [a]	*Generic only*	
Ketorolac tromethamine	Toradol® [a]	Tablet
Meclofenamate [b]	*Generic only* [b]	Capsule
Mefenamic acid	Ponstel® [b]	Capsule
	Ponstan® [a]	Capsule
Meloxicam	Mobic® [b]	Tablet, suspension
	Mobicox® [a]	Tablet
Nabumetone	*Generic only*	Tablet
Naproxen	Aleve® [c]	Tablet
	Naprosyn® [b]	Tablet, suspension
	EC-Naprosyn® [b]	EC Tablet, DR
	Naprosyn E [a]	EC Tablet
Naproxen SR [a]	Naprosyn® SR [a]	Tablet
Naproxen sodium	Anaprox®, Anaprox® DS	Tablet
	Naprelan®	Tablet, ER
Oxaprozin	Daypro®	Tablet
Piroxicam	Feldene® [b]	Capsule
	Generic only [a]	Capsule, suppository
Sulindac	Clinoril® [b]	Tablet
	Generic only [a]	Tablet
Tenoxicam [a]	*Generic only* [a]	Tablet
Tiaprofenic Acid [a]	*Generic only* [a]	Tablet
Tolmetin [b]	Tolectin® [b], Tolectin® 600 [b]	Tablet
	Tolectin® DS [b]	Capsule
Topical drugs		
Diclofenac epolamine [b]	Flector®	Topical patch 1.3%
Diclofenac sodium	Voltaren® [b]	Topical gel 1%
	Pennsaid®	Topical solution 1.5%
	Solaraze®	Topical gel 3%
Diclofenac diethylamine [a]	Voltaren® Emulgen™ [a]	Topical gel 1.16%

Abbreviations: DR, delayed release; EC, Enteric coated; ER, extended release; SR, sustained release; XR, extended release.
[a] Available in Canada, *not* available in the United States (generic products may be available in the United States).
[b] Not available in Canada, available in the United States.
[c] Miscellaneous over-the-counter brand names; prescription-only products available as generic products.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
2. Are there clinically important differences in short-term harms (< 6 months) between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
3. Are there clinically important differences in long-term harms (≥ 6 months) between NSAIDs, with or without antiulcer medication, when used chronically in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one medication is more effective or associated with fewer harms?

METHODS

We searched Ovid MEDLINE® (1996 to June week 2, 2010), the Cochrane Database of Systematic Reviews® (2005 to May 2010), the Cochrane Central Register of Controlled Trials® (2nd Quarter 2010), and Database of Abstracts of Reviews of Effects (2nd Quarter 2010) using included drugs, indications, and study designs as search terms. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review.

We assessed the internal validity (quality) of included studies as *good, fair, or poor* based on predefined criteria. We graded the overall strength of a body of evidence pertaining to a particular key question or outcome based on the approach proposed in the Evidence-based Practice Center Methods Guide. This approach considers the risk of bias of the studies (based on quality and study designs), consistency of results, directness of evidence, and precision of pooled estimates resulting from the set of studies relevant to the question. Strength of evidence was graded as High, Moderate, Low, and Insufficient.

RESULTS

Overview

A total of 2941 (1139 from update 4) records were identified from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comments. By applying the eligibility and exclusion criteria, we ultimately included 159 publications (33 for Update 4). Of these, 68 were trials (23 for Update 4), 47 were observational studies (4 for Update 4), 32 were systematic reviews (4 for Update 4), and 12 were pooled analyses and post-hoc analyses (2 for Update 4).

Key Question 1

Among oral drugs, celecoxib 200 mg daily to 800 mg daily and nonselective NSAIDs have been associated with similar pain reduction effects in primarily short-term randomized controlled trials of patients with osteoarthritis, rheumatoid arthritis, soft tissue pain, and ankylosing spondylitis. Compared with nonselective NSAIDS, partially selective NSAIDs (meloxicam, nabumetone, and etodolac) were associated with similar pain reduction effects in short-term randomized controlled trials. Good-quality Cochrane reviews and more recent trials found no clear differences among nonselective NSAIDs in efficacy for treating osteoarthritis of the knee or hip or for low-back pain. Evidence on the comparative efficacy of salsalate was limited to 2 randomized controlled trials that found no significant difference as compared with indomethacin. Based on findings from a good-quality systematic review of 18 randomized controlled trials, improvement in pain with tenoxicam was significantly greater as compared with piroxicam, but was similar to that of diclofenac and indomethacin. Randomized controlled trials have also found the pain reduction effects of tiaprofenic acid to be comparable to those of diclofenac, ibuprofen, indomethacin, naproxen, piroxicam, and sulindac in the treatment of rheumatoid arthritis and osteoarthritis.

We found no trials that directly compared the effectiveness or efficacy between different topical NSAIDs. Both diclofenac 1.5% topical solution and 1.0% topical gel had significantly greater mean changes in pain subscale scores than the placebo groups.

Comparison between diclofenac 1.5% topical solution and oral diclofenac found no significant differences on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function variables in 2 head-to-head trials.

Key Questions 2 and 3

Celecoxib

Among oral drugs, celecoxib may offer a short-term advantage over nonselective NSAIDs with regard to upper gastrointestinal adverse events, but this has not been conclusively demonstrated in longer-term (>6 months) studies. In high-risk patients, 3 short-term randomized controlled trials found rates of ulcer complications to be similar with celecoxib and nonselective NSAIDs when a proton pump inhibitor is given concomitantly with the nonselective NSAID. In contrast, the short-term risk of clinically significant upper and lower gastrointestinal events (combined) was lower with celecoxib than diclofenac slow release plus omeprazole in a good-quality trial of

4484 patients (CONDOR). However, the findings from the CONDOR trial should be interpreted with caution as celecoxib's advantage on the primary composite outcome was mostly due to its advantage on the individual outcome of anemia, which was only presumed to be of lower gastrointestinal tract origin.

The strategy of adding esomeprazole 20 mg to celecoxib 200 mg in patients at very high risk, with a recent upper gastrointestinal bleed, resulted in lower risk of 13-month cumulative incidence of recurrent ulcer bleeding compared with celecoxib 200 mg alone in a good-quality randomized controlled trial.

Based on findings from 3 meta-analyses of randomized controlled trials that were primarily 12 weeks in duration, as well as in 1 large case-control study, risk of myocardial infarction for celecoxib was not significantly different compared with NSAIDs and no significant increase in risk of other cardiovascular events or cerebrovascular events was found for celecoxib as compared with nonselective NSAIDs in 6 meta-analyses of randomized controlled trials and 5 observational studies. With regard to cardiorenal harms, results from the longest-term CLASS trial and meta-analyses of shorter-term trials found no increased risk of hypertension or heart failure with celecoxib compared with nonselective NSAIDs. Celecoxib was also not associated with an increased fracture risk in a fair-quality, large-scale, Danish population-based cohort study.

Partially selective NSAIDs

Among oral partially selective NSAIDs, meloxicam has not been conclusively demonstrated to offer an advantage over nonselective NSAIDs with regard to gastrointestinal adverse events and limited evidence from observational studies has not suggested any increased risk for meloxicam in myocardial infarction, hepatotoxicity, or fracture. Compared with nonselective NSAIDs, nabumetone had a lower short-term risk of gastrointestinal perforation, symptomatic ulcer, or bleeding events, but long-term comparative risks are unknown, and nabumetone was not associated with an increased fracture risk in a fair-quality, large-scale, Danish population-based cohort study. Comparative short-term and long-term gastrointestinal risk for etodolac relative to nonselective NSAIDs has not been evaluated. But, a small increase in risk of fracture was found to be associated with recent use of etodolac (within 1 year) in a fair-quality, large-scale, Danish population-based study (adjusted relative risk, 1.14; 95% CI, 1.06 to 1.22).

Nonselective NSAIDs

There was strong evidence from numerous randomized controlled trials and observational studies that all oral nonselective NSAIDs are associated with relatively similar risks of serious gastrointestinal events relative to nonuse. All nonselective NSAIDs except naproxen were associated with similar risks of clinically important cardiovascular events (primarily myocardial infarction) compared with COX-2 inhibitors (data primarily on high-dose ibuprofen and diclofenac), whereas naproxen was associated with a lower risk of myocardial infarction compared with COX-2 inhibitors (relative risk, 2.04; 95% CI, 1.41 to 2.96; P=0.0002). In a systematic review of published and unpublished short-term randomized controlled trials, diclofenac was associated with the highest rates of aminotransferase elevations >3 times the upper limit of normal (3.55%; 95% CI, 3.12 to 4.03) compared with ibuprofen (0.43%; 95% CI, 0.26 to 0.70), and the only evidence available for diclofenac regarding longer-term risk of

hepatotoxicity was noncomparative, but similar rates of aminotransferase elevations >3 times the upper limit of normal (3.1%) were found. In a large, fair-quality population-based study, the nonselective NSAID that had the highest overall risk of fracture was ibuprofen (adjusted relative risk, 1.76; 95% CI, 1.72 to 1.81) and an observed inverse dose-response relationship did not clearly suggest a direct correlation with the COX system.

Evidence on serious gastrointestinal and cardiovascular harms was limited for salsalate, tenoxicam and tiaprofenic acid. For salsalate, the best evidence comes from a single observational study that found the rates of gastrointestinal-related hospitalizations after 14 months similar for salsalate and other NSAIDs. Whereas, for tenoxicam or tiaprofenic acid, no specific data was found on the comparative risks of serious cardiovascular or serious gastrointestinal effects. However, 3 observational studies reported cases of potentially serious cystitis in patients using tiaprofenic acid, particularly in patients >70 years old.

Topical NSAIDs

Evaluation of comparative harms among topical NSAIDs was limited to indirect evidence based on 1 placebo-controlled trial of diclofenac 1.5% topical solution and 2 of diclofenac 1.0% topical gel. Compared with placebo, withdrawals due to adverse events were significantly greater with diclofenac 1.5% topical solution, but not for diclofenac 1% topical gel. Dry skin at the application site was significantly greater for diclofenac 1.5% topical solution compared with placebo solution, but rates of overall application site reactions were not significantly different for diclofenac 1.0% topical gel compared with placebo gel. There was no significant difference between diclofenac 1.5% topical solution and placebo solution or between 1.0% topical gel and placebo gel in gastrointestinal adverse events.

Comparative harms between topical and oral NSAIDs were evaluated in 2 trials that directly compared diclofenac 1.5% topical solution to oral diclofenac. Incidence of dry skin at the application site was significantly greater for topical diclofenac and incidence of gastrointestinal adverse events was significantly greater for oral diclofenac. However, withdrawals due to adverse events were similar in the topical and oral diclofenac treatment groups.

Key Question 4

Concerning differential effects in specific patient subgroups of interest, the strongest evidence was available for comparison among oral drugs specifically in high-risk patients with a history of ulcer bleeding and for patients using low-dose aspirin concomitantly.

In patients with a history of ulcer bleeding, the 13-month cumulative incidence of recurrent ulcer bleeding was significantly lower for celecoxib plus esomeprazole compared with celecoxib alone in a good-quality trial and two shorter-term trials found no statistically significant differences in recurrent ulcer bleeding between celecoxib and treatment with a nonselective NSAID plus a proton pump inhibitor.

For patients taking an NSAID and low-dose aspirin (325 mg or less), similar rates of endoscopically confirmed gastroduodenal ulcers were found with celecoxib alone compared with treatment with naproxen plus lansoprazole based on a single randomized controlled trial. Findings were consistent in prior subgroup analyses according to the use of low-dose aspirin,

which also indicated no significant differences between celecoxib and nonselective NSAIDs in endoscopic ulcer rates.

Evidence remains unclear as to whether concomitant NSAID use could interfere with the cardioprotective effects of aspirin in patients with preexisting cardiovascular disease. While limited evidence from 1 case-control study suggested that concomitant NSAID use could interfere with the cardioprotective effects of aspirin in patients with preexisting cardiovascular disease, 2 other observational studies in more broadly defined populations found no increased risk of myocardial infarction.

Regarding subgroups of patients based on demographics, although evidence from randomized controlled trials of elderly populations consistently found no significant differences in efficacy outcomes between celecoxib and either naproxen or diclofenac, results from primarily retrospective cohort studies suggested that celecoxib may be associated with fewer selected serious adverse events than some nonselective NSAIDs when used in elderly populations. There were significantly fewer gastrointestinal hospitalizations when a proton pump inhibitor was added to celecoxib compared with celecoxib alone when age was above 75 years, but not when age was 66 to 74 years. Additionally, in high-risk elderly patients with a recent admission for heart failure, compared with nonselective NSAIDs, rates of death and recurrent congestive heart failure were lower for celecoxib. One randomized controlled trial found no significant differences between celecoxib and diclofenac on pain when used concomitantly with angiotensin-converting enzyme inhibitors in a small study of all black or Hispanic patients.

Regarding subgroups of patients taking other concomitant medications, a single, small crossover trial examining the effects of using NSAIDs in patients taking anticoagulants found no significant changes in the mean international normalized ratio values after 5 weeks of either celecoxib or codeine. Comparative evidence of the safety of celecoxib relative to NSAIDs when used concomitantly with anticoagulants was limited to 2 small observational studies and was inconclusive due to flaws in design.

No evidence was found regarding the comparative effectiveness and harms of topical diclofenac products or between oral and topical NSAIDs in patient subgroups.

SUMMARY

The main findings of this review are summarized in Table 2. Little evidence on the comparative effectiveness of NSAIDs was truly effectiveness or "real world" – while some trials evaluated longer-term (>6-12 months) and real life (symptoms, clinical ulcers, functional status, myocardial infarctions, pain relief) outcomes, none were conducted in primary care or office-based setting or used broad enrollment criteria.

Table 2. Summary of the evidence by key question

Key Question	Strength of evidence	Conclusion
1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?		
1a. How do oral drugs compare to one another?		
Celecoxib	High. Evidence is available from many published trials.	No clear differences in pain reduction.
Meloxicam	High. Consistent evidence from many published trials	No consistent differences.
Nabumetone	Moderate. Fewer	No consistent differences.

Key Question	Strength of evidence	Conclusion
	RCTs/systematic review	
Etodolac	High. Consistent evidence from many published trials	No consistent differences.
Nonselectives	High. Consistent evidence from many published trials and several good-quality systematic reviews	No consistent differences.
Salsalate	Moderate. Limited evidence from few RCTs	No consistent differences.
Tenoxicam	High. Many published RCTs, meta-analysis	No consistent differences.
Tiaprofenic acid	High. Several RCTs and 1 fair-quality review	No consistent differences.
1b. How do topical drugs compare to one another?		
Diclofenac 1.5% topical solution and 1.0% topical gel	Low. Indirect evidence from placebo-controlled trials.	Both topical drugs had significantly greater mean changes in pain subscale scores than placebo.
Other topical drugs	Insufficient	No trials met inclusion criteria.
1c. How do oral drugs compare to topical drugs?		
Diclofenac 1.5% topical solution	High. 2 head-to-head trials	Compared with oral diclofenac, diclofenac 1.5% topical solution produced similar improvement in WOMAC pain and physical function variables.
2 and 3. Are there clinically important differences in short-term (< 6 months) or long-term (≥ 6 months) harms between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?		
2a and 3a. How do oral drugs compare to one another?		
Celecoxib	High. Evidence from many published trials and systematic reviews	*GI Harms:* Lower risk for celecoxib than nonselective NSAIDs in the short-term, but longer-term evidence is inconclusive. *CV Harms:* No significant difference in risk of MI for celecoxib compared with nonselective NSAIDs, but evidence is primarily from short-term studies. *Other serious adverse events:* No consistent differences.
Meloxicam	Moderate for GI harms; low for others	*Short-term and long-term GI harms:* No consistent differences. *Long-term CV harms:* No conclusive evidence of increased risk relative to nonselectives. *Hepatotoxicity:* No evidence of increased risk relative to placebo. *Other serious adverse events:* No evidence.
Nabumetone	Moderate for short-term GI safety; low for others	*Short-term GI harms:* Decreased risk relative to nonselectives. *Other serious adverse events:* No evidence.
Etodolac	Low for perforation, symptomatic ulcer, or bleeding, insufficient for others	*Perforation, symptomatic ulcer, or bleeding rates (duration unknown):* No increased risk relative to nonuse. *Other serious adverse events:* No evidence.
Nonselectives	High for GI safety; moderate for CV safety; low for other serious adverse events	*Short-term/long-term GI safety:* All nonselectives are associated with similar increased risks relative to nonuse.

Key Question	Strength of evidence	Conclusion
		Short-term/long-term CV safety: Nonselective NSAIDs other than naproxen are associated with increased risks of CV events similar to that seen with COX-2 inhibitors (most data on high-dose ibuprofen and diclofenac). Naproxen appears to be risk-neutral with regard to cardiovascular events. *Hepatotoxicity:* In short-term trials, diclofenac associated with highest rates of aminotransferase elevations >3 times upper limits of normal. Noncomparative evidence suggests similar rates in the longer term. *Fracture risk:* Preliminary evidence from 1 case-control study suggestive of higher risk with ibuprofen compared with other nonselective NSAIDs. *All-cause mortality/blood pressure/ CHF/edema/renal function/hepatotoxicity:* No consistent difference.
Nonselective+antiulcer medications	Low for GI events; moderate for endoscopic ulcers	*Clinical GI events:* Misoprostol only antiulcer medication proven to reduce rates, but at expense of reduced GI tolerability. *Endoscopic ulcers:* All proven to reduce rates.
Salsalate	Low for short-term overall toxicity and long-term GI harms, insufficient for others	*Short-term overall toxicity:* Significantly lower rates. *Long-term GI harms:* No differences. *Other serious adverse events:* No evidence.
Tenoxicam	Insufficient	No evidence found for specific GI and CV adverse events; reporting of AEs and dropouts slightly lower with tenoxicam compared with indomethacin and piroxicam respectively.
Tiaprofenic acid	Moderate for cystitis, insufficient for others	Observational studies report serious cases of cystitis.
2b and 3b. How do topical drugs compare to one another?		
Diclofenac 1.5% topical solution and 1.0% topical gel	Low. Indirect evidence from placebo-controlled trials.	Withdrawals due to adverse events: Significantly greater for diclofenac 1.5% topical solution, but not for 1.0% topical gel. Short-term GI harms: Compared with placebo, neither topical product resulted in significant increased incidence. Application site reactions: Only diclofenac 1.5% topical solution resulted in significantly greater skin dryness.
2c and 3c. How do oral drugs compare to topical drugs?		
Diclofenac 1.5% topical solution	High. 2 head-to-head trials	Topical diclofenac resulted in significantly lower incidence of GI adverse events, but higher incidence of application site skin dryness. Withdrawals due to adverse events were similar for oral and topical diclofenac.
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one medication is more effective or associated with fewer harms?		

Key Question	Strength of evidence	Conclusion
4a. How do oral drugs compare to one another?		
All	Moderate for concomitant use of low-dose aspirin and for NSAID use in high-risk patients with recent GI bleed. Low for others.	*Demographics*: No differences in efficacy, but risk of certain serious harms may be lower for celecoxib than some NSAIDs in elderly patients. *History of ulcer bleeding:* Recurrent ulcer bleeding significant lower for celecoxib plus esomeprazole compared with celecoxib alone. No significant difference for celecoxib alone compared with a nonselective NSAID plus a PPI. *Cardiac/renal comorbidities:* Celecoxib possibly associated with decreased risk of death and recurrent heart failure compared with nonselective NSAIDs in elderly patients with a recent admission for heart failure. *Concomitant use of anticoagulants*: Comparative evidence from observational studies was inconclusive. Noncomparative evidence suggested no significant increase in INR after 5 weeks of celecoxib. *Concomitant use of low-dose aspirin:* Similar rates of endoscopic ulcers for celecoxib compared with naproxen plus lansoprazole in prospective RCT. Subgroup analyses also found similar endoscopic ulcer rates for celecoxib and nonselective NSAIDs.
4b. How do topical drugs compare to one another?		
All	Insufficient	No evidence
4c. How do oral drugs compare to topical drugs?		
All	Insufficient	No evidence

Abbreviations: AE, adverse event; COX, cyclo-oxygenase; CV, cardiovascular; GI, gastrointestinal; INR, international normalized ratio; MI, myocardial infarction; NSAID, nonsteroidal antiinflammatory drug; OARSI, Osteoarthritis Research Society International; PPI, proton pump inhibitor; RCT, randomized controlled trial; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

CONCLUSION

For pain relief, no significant short-term (< 6 months) differences were found among oral NSAIDs, topical NSAIDs, or between oral and topical NSAIDs. For serious harms, celecoxib did not appear to be associated with higher risk of cardiovascular events and is gastroprotective in the short term compared with nonselective NSAIDs. These findings vary by subgroup, depending on age, recent history of gastrointestinal bleeding, and concomitant use of antiulcer medication. Nonselective NSAIDs were associated with similar increased risks of serious gastrointestinal events, and all but naproxen were associated with similar increased risk of serious cardiovascular events, but the partially selective NSAID nabumetone was gastroprotective compared with nonselective NSAIDs. Compared with oral NSAIDs, topical diclofenac was gastroprotective but had higher risk of application site dryness. Compared with placebo, application site reactions and withdrawals due to adverse events were higher with diclofenac 1.5% topical solution, but not with diclofenac 1.0% topical gel.