Table A-3. Comparative effectiveness and safety of analgesics for osteoarthritis

| Original Key Questions/Conclusions | Updated Key Questions/Conclusions (2011-2012) | 2009 Prediction | Concordance |
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| Comparative Effectiveness and Safety of Analgesics for Osteoarthritis (Original report date - Sep 2006[5](#_ENREF_5) and Update report date - Oct 2011[6](#_ENREF_6)) |
| Key Question 1 - What are the comparative benefits and harms of treating osteoarthritis 20 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: This question addresses the therapeutic benefits of long-term use for the condition osteoarthritis. However, the question does address all harms associated with NSAID use, including | Key Question 1 - What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment? The only benefits considered here are improvements in osteoarthritis symptoms. Evidence of harms associated with the use of NSAIDs includes studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention. Oral agents include: COX-2 selective NSAIDs: o Celecoxib Partially selective NSAIDs: o Etodolac, Meloxicam, Nabumetone Non-aspirin, nonselective NSAIDs: Diclofenac, Diflunisal, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Meclofenamate sodium, Mefenamic acid, Naproxen, Oxaprozin, Piroxicam, Sulindaco, Tolmetin Aspirin and salsalate: Aspirin, SalsalateAcetaminophen and supplements: Acetaminophen, Chondroitin, Glucosamine |   |   |
| There are no clear differences between various nonaspirin, nonselective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac) in efficacy for pain relief or improvement in function. | No clear difference in efficacy for pain relief, or withdrawals due to lack of efficacy. Meloxicam was associated with no clear difference in efficacycompared to nonselective NSAIDs in eleven head-to-head trials of patients with osteoarthritis, but a systematic review that included trials of patients with osteoarthritis or rheumatoid arthritis found lesser effects on pain compared to nonselective NSAIDs (difference 1.7 points on a 10 point VAS pain scale) and withdrawals due to lack of efficacy (RR 1.5,95% CI 1.2 to 1.7). Etodolac and nonselective NSAIDs were associated with no statistically significant differences on various efficacy outcomes in several systematic reviews of patients with osteoarthritis, with consistent results reported in 7 trials not included in the systematic reviews. Nabumetone was similar in efficacy to nonselective NSAIDs in two trials. No difference in efficacy between various non-aspirin, nonselective NSAIDs.No difference in efficacy between aspirin and salsalate in one head-to-head trial. No trial compared aspirin or salsalate vs. other NSAIDs. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| It is not clear whether celecoxib has fewer potential harms than nonselective NSAIDs when used longer than 3-6 months. | GI harms: Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) and ulcer complications or symptomatic ulcers (RR 0.39, 95% CI 0.21-0.73) compared to nonselective NSAIDs in a systematic review of randomized trials. The systematic review included the pivotal, large, long-term CLASS study, in which celecoxib was superior to diclofenac or ibuprofen for ulcer complications or symptomatic ulcers at 6-month followup (2.1% vs. 3.5%, p=0.02), but not at 12-month followup. However, CLASS found difference in rates of ulcer complications alone at either 6 or 12 months. Other long-term followup data from randomized trials is lacking. A systematic review found celecoxib associated with a lower risk of upper GI bleeding or perforation compared to various nonselective NSAIDs based on 8 observational studies, though confidence interval estimates overlapped in some cases. CV harms: There was no increase in the rate of cardiovascular events with celecoxib vs. ibuprofen or diclofenac in CLASS (0.5% vs. 0.3%). In three systematic reviews of randomized trials, celecoxib was associated with increased risk of cardiovascular events compared to placebo (risk estimates ranged from 1.4 to 1.9).A systematic review of placebo-controlled trials with at least 3 years of planned followup found celecoxib associated with an increased risk of cardiovascular events (CV death, myocardial infarction, stroke, heart failure, or thromboembolic event) compared to placebo (OR 1.6, 95% CI 1.1 to 2.3). | Conclusion is probably out of date and this portion of the CER may need updating based on new data and expert opinion. | Good - updated CER reports that celcoxib is superior at 6 months to diclofenac or ibuprofen |
| Celecoxib is associated with an increased risk of myocardial infarction. Most of the CV events with celecoxib were reported in two large polyp-prevention trials. | About 3.7 additional cardiovascular events occurred for every 1,000 patients treated for one year with celecoxib instead of placebo, or 1 additional cardiovascular event for every 270 patients treated for 1 year with celecoxib instead of placebo. The risk was highest in patients prescribed celecoxib 400 mg twice daily compared to celecoxib 200 mg twice daily or 400 mg once daily. Much of the evidence for increased risks comes from two large colon polyp prevention trials. A network analysis of randomized trials and three large observational studies found celecoxib associated with no clear difference in risk of myocardial infarction compared to naproxen, ibuprofen, ordiclofenac; a fourth observational study found celecoxib associated with lower risk than ibuprofen or naproxen. 11 of13 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.) | Conclusion is still valid and this portion of the CER does not need updating.  | Good |
| Etoricoxib is associated with fewer GI adverse events (perforations, symptomatic ulcers, and bleeds) than nonselective NSAIDs. 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. | No comparable conclusion in the update as etoricoxib was not given FDA approval. | Conclusion is possibly out of date and this portion of the CER may need updating based on diversity of expert opinion. | Good - Etoricoxib is not included in the updated review, as it was rejected by FDA for approval. |
| Results from one large trial found fewer adverse GI events with lumiracoxib than with naproxen and ibuprofen. Too few events have been reported in RCTs to accurately assess CV risk associated with lumiracoxib. | No comparable conclusion since lumiracoxib was not included in the update. | Conclusion is out of date and this portion of the CER needs updating since lumiracoxib is not FDA approved and has been withdrawn from the market of several countries.  | Good |
| Meloxicam - There were no significant differences in risks of serious GI events or CV risk. | GI harms: Meloxicam (primarily at a dose of 7.5 mg/day) was associated with a lower risk of ulcer complications or symptomatic ulcers compared to various nonselective NSAIDs in 6 trials included in a systematic review (RR 0.53,95% CI 0.29 to 0.97), but the difference in risk of ulcer complications alone did not reach statistical significance (RR0.56, 95% CI 0.27 to 1.2).  | Conclusion is still valid and this portion of the CER does not need updating.  | Good |
| Nabumetone or etodolac - There was insufficient evidence to make reliable judgments about relative GI safety and no evidence on CV safety. | Etodolac (primarily at a dose of 600 mg/day) was associated with a lower risk of ulcer complications or symptomatic ulcer compared to various nonselective NSAIDs in 9 trials included in a systematic review (RR 0.32, 95% CI 0.15 to 0.71), but the difference in risk of ulcer complications alone did not reach statistical significance (RR 0.39, 95% CI 0.12 to 1.2) and the number of events was very small. Evidence was insufficient to make reliable judgments about GI safety of nabumetone.CV harms: One observational study evaluated etodolac and nabumetone, but estimates were imprecise. | Conclusion is out of date and this portion of the CER needs updating to reflect change in labeling due to addition of FDA boxed warning label.  | Good. The following box warning on etidolac. The box warning was: Etodolac 1/18/2006 - Revised label to add a boxed warning to address possible CV risks as well as known GI risks |
| No clear difference in GI safety was found among nonselective NSAIDs at commonly used doses. | GI harms: COX-2 selective NSAIDs as a class were associated w/ a similar reduction in risk of ulcer complications vs. naproxen (RR 0.34, 95% CI 0.24 to 0.48), ibuprofen (RR 0.46, 95% CI 0.30 to 0.71), and diclofenac (RR 0.31, 95% CI 0.06 to 1.6) in a syst. 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. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| The CV safety of naproxen is moderately superior to that of any COX-2 selective NSAID. The CV safety of nonselective NSAIDs other than naproxen (data primarily on ibuprofen and diclofenac) was similar to that of COX-2 selective NSAIDs. | CV harms: An indirect analysis of randomized trials found ibuprofen (RR 1.5, 95% CI 0.96 to 2.4) and diclofenac (RR 1.6, 95% CI 1.1 to 2.4), but not naproxen (RR 0.92, 95% CI 0.67 to 1.3) associated with an increased risk of myocardial infarction relative to placebo. 1 additional myocardial infarction occurred for about every 300 patients treated for 1 year with celecoxib instead of naproxen. A network analysis of randomized trials reported consistent results with regard to CV events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; ibuprofen: RR 2.3, 95% CI 1.1 to 4.9; diclofenac: RR 1.6, 95% CI 0.85 to 3.0 and naproxen: RR 1.2, 955 CI 0.78 to 1.9). An Alzheimer‘s disease prevention trial was stopped early due to a trend towards increased risk of myocardial infarction (HR 1.5, 95% CI 0.69 to 3.2) vs. placebo, but did not employ pre specified stopping protocols. In most large observational studies, naproxen was associated with a neutral effect on risk of serious CV events. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| 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. | GI harms: A systematic review of individual patient trial data found aspirin associated with increased risk of major GI and other extra cranial bleeding when given for primary prevention of vascular events (RR 1.5, 95% CI 1.3 to 1.8, absolute risk 0.10% vs. 0.07%). Observational studies showed a similar risk of upper GI bleeding with aspirin and non-aspirin, nonselective NSAIDs. CV harms: Aspirin reduced the risk of vascular events in a collaborative meta-analysis of individual patient data from18 randomized controlled trials (0.51% aspirin vs. 0.57% control per year, p=0.0001 for primary prevention and 6.7% vs. 8.2% per year, p<0.0001 for secondary prevention). | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Almost no data are available on CV safety for salsalate. | No randomized trial or observational study evaluated risk of serious GI or CV harms with salsalate. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| All NSAIDs and COX-2 inhibitors can cause or aggravate hypertension, congestive heart failure (CHF), edema, and impaired renal function | 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. | Conclusion is possibly out of date and this portion of the CER may need updating based on upcoming publication of new evidence (article by Winkelmayer, 2008) | Fair - the article identified in the surveillance was: Winkelmayer WC, Waikar SS, Mogun H, Solomon DH. Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. Am J Med. Dec 2008;121(12):1092-1098. However, the update report included observational studies of adverse events with sample size greater than 1,000 only if the adverse event was CV or GI, not renal |
| Among currently marketed NSAIDs, only diclofenac was associated with a significantly higher rate of liver-related discontinuations compared with placebo. | 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 hepaticlaboratory abnormalities (78/1,000 patient-years, vs. 16 to28/1,000 patient-years for the other NSAIDs). Another systematic review found diclofenac associated with the highest rate of aminotransferase elevations compared to placebo (3.6% vs. 0.29%, compared to <0.43% with other NSAIDs). | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Uncertainty remains regarding the comparative tolerability of salsalate and nonselective NSAIDs. | In a systematic review of randomized trials, the only relatively consistent finding regarding the tolerability of different nonselective NSAIDs was that indomethacin was associated with higher rates of toxicity than other NSAIDs (statistical significant unclear). | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Acetaminophen is modestly inferior to NSAIDs for pain and function. Compared with NSAIDs, acetaminophen had fewer GI side effects and serious GI complications. Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction. | Acetaminophen is consistently modestly inferior to NSAIDs for reducing pain and improving function in randomized trials included in multiple systematic reviews. Acetaminophen is superior to NSAIDs for GI side effects (clinical trials data) and GI complications (observational studies). Some observational studies found acetaminophen associated with modest increases in blood pressure or higher risk of renal dysfunction compared to NSAIDs, but results may besusceptible to confounding by indication. One observational study found risk of acute myocardial infarction similar in users of acetaminophen compared to users of NSAIDs Acetaminophen may cause elevations of liver enzymes at therapeutic doses in healthy persons; comparative hepatic safety has not been evaluated. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| 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. |  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). 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. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Glucosamine and chondroitin were generally well tolerated and no serious adverse events were reported in clinical trials.  | Seven randomized trials showed no clear difference between glucosamine vs. oral NSAIDs for pain or function. One randomized trial showed no difference between chondroitin vs. an oral NSAID.A systematic review including recent, higher-quality trials found glucosamine associated with statistically significant but clinically insignificant beneficial effects on pain (-0.4 cm on a10 cm scale, 95% CI -0.7 to -0.1) and joint space narrowing(-0.2 mm, 95% CI -0.3 to 0.0) compared to placebo. The systematic review reported similar results for chondroitin. A recent large, good-quality NIH-funded trial found the combination of pharmaceutical grade glucosamine hydrochloride and chondroitin sulfate modestly superior to placebo only in an analysis of a small subset of patients with at least moderate baseline pain. Older trials showed a greater benefit with glucosamine or chondroitin, but were characterized by lower quality. For glucosamine, the best results have been reported in trials sponsored by the manufacturer of a European, pharmaceutical grade product (no pharmaceutical grade glucosamine available in the United States). | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| 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. | 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. | Conclusion is possibly out of date and this portion of the CER may need updating based on new data. | Good - there is now the one celecoxib alternative dosing study, so the conclusion that there were no studies was out of date |
| Higher doses of celecoxib were 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. | Higher doses of NSAIDs were associated with greaterefficacy for some measures of pain relief, and in some trials with greater withdrawals due to adverse eventsA meta-analysis of 41 randomized trials found no clear association between longer duration of therapy with COX-2selective NSAIDs and increase in the relative risk of CV events. The meta-analysis found higher doses of celecoxib associated with increased risk of cardiovascular events, but most events occurred in the long-term polyp prevention trials. Almost all of the cardiovascular events in trials of celecoxib were reported in long-term trials of colon polyp prevention. Large observational studies showed no association between higher dose and longer duration of nonselective NSAID therapy and increased risk of cardiovascular events. Many observational studies found that risk of GI bleeding increased with higher doses of nonselective NSAIDs, but no clear association with duration of therapy. One small trial found continuous celecoxib slightly more effective than intermittent use on pain and function, and similar rates of withdrawals due to adverse events. No trial was designed to assess serious GI or CV harms associated with intermittent dosing strategies. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| 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 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. | 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) |   |   |
| 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. | The absolute risks of serious GI and CV complicationsincrease with age. Large observational studies that stratified patients by age found no clear evidence of different risk estimates for different age groups. However, because the event rates increases in older patients, even if the relative risk estimates are the same, the absolute event rates are higher. There is insufficient evidence on the comparative benefits and harms of different selective and nonselective NSAIDs in men compared to women, or in different racial groups. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| 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. | 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% to8.9% with 200 mg twice daily) or a nonselective NSAID + PPI(6.3%).  | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Concomitant use of anticoagulants (e.g., warfarin) and any nonselective NSAID increases the risk of GI bleeding three- to six fold 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 use of anticoagulants and nonselective NSAIDs increases the risk of GI bleeding three- to six fold compared with anticoagulant use without NSAIDs. The risk with concomitant celecoxib is not clear due to conflicting findings among observational studies, but may be increased in older patients. Reliable conclusions about the comparative safety of nonselective, partially selective, and COX-2 selective NSAIDs with concomitant anticoagulants could not be drawn due to small numbers of studies with methodological shortcomings.  | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| 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 in both patients on celecoxib and those on nonselective NSAIDs. Rofecoxib plus low-dose aspirin or ibuprofen alone were associated with similar risks of endoscopic ulcers which were significantly higher than those for placebo (6 percent) or aspirin alone. Compared to nonuse of aspirin, concomitant aspirin use did not ameliorate the increased risk of vascular events associated with COX-2 selective NSAIDs. | Concomitant use of aspirin appears to attenuate or eliminate the GI benefits of selective NSAIDs, resulting in risks similar to nonselective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6 percent inpatients on celecoxib and those on nonselective NSAIDs in one meta-analysis. 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-2selective 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 to2.9), but studies on effects of ibuprofen added to aspirin on MI risk in average risk patients were inconsistent and did not clearly demonstrate increased risk. | Conclusion is possibly out of date and this portion of the CER may need updating based on expert opinion. | Fair. The studies suggested by the experts ended up being either ineligible for inclusion in the update or were already included in the original CER. |
| Key Question 3 - What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors? | Key Question 3 - What are the comparative effects of coprescribing H2 receptor antagonists, misoprostol, or proton pump inhibitors on the gastrointestinal harms associated with NSAID use? |   |   |
| Consistent evidence 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. | Misoprostol was the only gastroprotective agent to reduce risk of ulcer complications compared to placebo in patients with average risk of GI bleeding prescribed nonselective NSAIDs, but was also associated with a higher rate of withdrawals due to adverse GI symptoms. Coprescribing of PPIs, misoprostol, and H2-antagonists all reduced the risk of endoscopically detected gastric and duodenal ulcers compared to placebo in patients prescribed a nonselective NSAID. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| 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. | In direct comparisons, coprescribing of PPIs in patients with increased risk of GI bleeding who were prescribed a nonselective NSAID was associated with a lower risk of endoscopically detected duodenal ulcers compared tomisoprostol or H2-antagonists, a lower risk of endoscopically detected gastric ulcers compared to H2-antagonists, and a similar risk of endoscopically detected gastric ulcers compared to misoprostol. Coprescribing of misoprostol was associated with a lower risk of endoscopically detected gastric ulcers compared to ranitidine, and a similar reduction in risk of endoscopically detected duodenal ulcers. Compared to placebo, double (full) dose H2-antagonists maybe more effective than standard dose for reducing endoscopically detected gastric and duodenal ulcers. Celecoxib alone was associated with fewer decreases in hemoglobin (> 2 g/dl) without overt GI bleeding compared with diclofenac plus a PPI. Celecoxib plus a PPI may reduce the risk of endoscopic ulcers and ulcer complications compared to celecoxib alone in average risk persons. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Key Question 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. | Key Question 4 - What are the comparative benefits and harms of treating osteoarthritis with oral medications compared with topical preparations, or of different topical medications compared with one another? |   |   |
| 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). Topical ibuprofen was superior to placebo in several trials. 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 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.  | 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 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. No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs for osteoarthritis. Topical salicylates were no better than placebo in two trials of patients with osteoarthritis included in a systematic review, and associated with increased risk of local adverse events when used for any acute or chronic pain condition. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events (13% vs. 3%, RR 4.0, 95% CI 2.3 to 6.8). | Conclusion is still valid and this portion of the CER does not need updating. | Good |

**References**

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