

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness and Safety of Analgesics for Osteoarthritis—An Update of the 2006 Report*

Draft review available for public comment from January 10, 2011 to February 8, 2011.

Research Review Citation: Chou R, McDonagh M, Nakamoto E, Griffin J. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis—An Update of the 2006 Report. Comparative Effectiveness Review No. 38 (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHS 290-2007-10057 I). Rockville, MD: Agency for Healthcare Research and Quality. October 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Patrick du Souich	Executive Summary	The disease modifying osteoarthritis drugs (DMOAD) effect of glucosamine and chondroitin might be further evaluated. Addition of PPI to avoid GI adverse effects of NSAIDs may cause other ADEs.	We reviewed the available evidence on glucosamine and chondroitin as well as PPIs + NSAIDs.
Amy Miller	Executive Summary	On behalf of the American College of Rheumatology, thank you for prioritizing osteoarthritis as a topic for evaluation. The ACR is very interested in ongoing evidence reviews in this area because it regularly develops and updates OA clinical practice guidelines. In fact, the ACR is presently completing a new guideline related to pharmacologic and non-pharmacologic treatment of OA of the hip, knee and hand. Upon review of the AHRQ draft document, it appears that the ACR project has reached similar conclusions. The ACR investigators relied on the AHRQ 2006 evidence report on this same topic as well as the AHRQ report that covered the use of dietary supplements, intra-articular hyaluronans and arthroscopy for OA treatment in their work. In the future, the ACR would welcome the opportunity to work more closely with AHRQ in areas of common interest, such as OA, to minimize or eliminate this type of duplicate effort.	Noted.
Kathleen Gans-Brangs, PhD	Executive Summary	AstraZeneca (encompassing AstraZeneca Pharmaceuticals LP and AstraZeneca LP (AstraZeneca)) is pleased to submit comments on the draft report, "Comparative Effectiveness and Safety of Analgesics for Osteoarthritis- An Update of the 2006 Report." AstraZeneca is a leading global healthcare company dedicated to the research and development of new medicines in therapeutic areas including cardiovascular, gastrointestinal, oncology, respiratory and neuroscience. AstraZeneca is committed to the discovery of drugs that will allow patients to lead longer, healthier and more productive lives. Please do not hesitate to contact Kathleen Gans-Brangs (Kathy.gans-brangs@astrazeneca.com, 302-886-2440) with any questions.	Noted.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Executive Summary	<p>p. 10 "COX-1 protects the lining of the stomach from acid." Technically it is not the COX-1 that is protective but the products of the COX-1. Also it is not just protection from acid and not necessarily just the stomach. Might be better to say something like COX-1 mediates mucosal defense of the GI tract, including protection of the stomach from acid.</p> <p>"The number of deaths in the United States due to use of nonaspirin NSAIDs was estimated at 3,200 annually in the 1990's." I wouldn't use this specific number because estimates have been all over and are quite uncertain (and this is on the lower end of the estimates).</p>	<p>We revised to (page 10, starting In 5): "COX-1 mediates the mucosal protection of the gastrointestinal mucosa, including protection from acid and platelet aggregation."</p> <p>We revised the sentence on deaths due to NSAIDs to: "The number of deaths in the United States due to use of nonaspirin NSAIDs is not known with certainty. One study estimated the number at 3,200 annually in the 1990's, though other studies have reported higher estimates."</p>

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Peer Reviewer #4	Executive Summary	<p>p. 18: GI and CV Harms Section (and other subsequent sections). You need to be consistent in this whole section. Currently in some sections you compare to placebo and others you compare to other types of NSAIDs. I believe it makes sense to first compare a drug category to placebo/no Rx and then to other agents. So, coxibs would be compared to placebo and then to non-selective NSAIDs. Similarly, non-selective NSAIDs should first be compared to placebo/no Rx (observational studies are certainly available to provide RR). No need to compare again to coxibs because that was done (or should be done) in the prior coxib section.</p> <p>Aspirin it is inappropriate to lump all aspirin together. Most aspirin is used in low-dose and the GI risk is lower than it is for full dose aspirin used for OA. One could even argue that full dose aspirin may have less CV benefit, because at low doses, aspirin is a weak COX-2 inhibitor while at high doses it is not. So one needs to be sure you are looking at studies of high-dose aspirin or else you cannot make definitive statements about the GI and CV risk or at least have to qualify it. CV benefit is primarily seen in pts with established CV disease (2ndary prevention) where RRR=19% and NNT is very good (67) vs. those with primary prevention where the benefit is much less (RRR=12% but NNT=1429). Most OA pts probably are on primary prevention and again we don't know that aspirin taken in analgesic doses has the same benefit as the RCTs of low dose aspirin indicate.</p>	<p>The results are structured so that direct comparative evidence (e.g., selective vs. non-selective NSAID) is presented first, followed by evidence on NSAIDs versus placebo. This is because the focus of the review is on comparative benefits and harms.</p> <p>Regarding aspirin, the "Strength of Evidence" column (page 18, starting line 41) states "many trials, but almost exclusively in patients receiving aspirin for cardiovascular disease prevention, usually at lower prophylactic doses." The text also makes it clear that most of the trials evaluated low doses (p 27, starting line 43, and p 35, starting line 49). Regarding higher doses of aspirin and CV effects, the Results state (page 35, starting line 54), "The cardioprotective effects of aspirin appeared lower (13%) in three trials evaluating doses of lower than 75 mg daily, but in trials that directly compared higher and lower doses, there were no significant differences."</p>

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Peer Reviewer #4	Executive Summary	<p>p. 19 Tolerability: First need to compare to placebo/no Rx, since this is important issue in deciding to employ an analgesic. Acetaminophen: First need to state if it works at all (e.g., studies vs. placebo/no Rx). Also, need to define GI side effects. This is too broad a term, and the issue is do you mean GI symptoms such as dyspepsia or symptomatic ulcers or? Glucosamine/chondroitin: Start with comparison vs. placebo before comparing to NSAIDs.</p>	<p>The purpose of this review is to understand comparative effectiveness, so comparative data are prioritized accordingly.</p> <p>Regarding the need to describe which GI harms were evaluated, this is described in the Methods section (ES6 and p 11): "For GI toxicity, we focused on serious complications associated with NSAIDs including perforation, bleeding ulcer, and gastric outlet obstruction, though we also evaluated other GI side effects (such as nausea, dyspepsia, and GI tolerability). We only considered rates of endoscopic ulcers when data on clinical ulcer complications were incomplete or not available."</p>
Peer Reviewer #4	Executive Summary	<p>p. 20, Duration of NSAID use: It is misleading to say there is no association between duration of therapy and GI or CV events. Prospective trials clearly show an increase in the cumulative incidence over time, so taking NSAIDs longer results in more patients developing a GI (or CV) event. It is true that the risk probably remains constant over time for GI events—but the important point there is that a pt continues to have a similar risk even if they have taken the NSAID for some time. Age: You make important points about absolute vs. relative risk. However data do show that the RR is increased for older patients (best data perhaps for > 65 and > 75 but data also for > 50). So for NSAIDs there is an increase in baseline absolute risk and in RR. For low-dose aspirin, interestingly, the RR isn't documented to increase with age, but the absolute risk does.</p>	<p>The sentence in question in the Executive Summary is referring to the finding in meta-analysis that the relative risk of CV events does not increase with time (i.e. it appears to be a constant risk, or there is insufficient data to determine if the risk changes). We revised to clarify (page 20, starting line 26): "A meta-analysis of 41 randomized trials found no clear association between longer duration of therapy with COX-2 selective NSAIDs and increase in the relative risk of CV events." Regarding differential risks in older patients, as noted in the Results (page 83, starting line 50): "We found no trial designed to assess whether the relative harms and benefits associated with different NSAIDs for osteoarthritis vary according to age. Large observational studies that have stratified subjects by age have not showed a consistent in relative estimates of risk associated with NSAIDs in older compared to younger age strata for ulcer complications or myocardial infarction."</p>

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Peer Reviewer #4	Executive Summary	<p>p. 21, Low-dose aspirin + coxibs: Best data are from update of Cochrane SR presented in Laine et al. Semin Arthritis Rheum 38:165-187. We found the following: "An updated meta-analysis of over 18,000 patients taking aspirin in these trials revealed no statistically significant difference in the relative risk of upper GI complications between the coxib and nonselective NSAID arms (RR 0.93, 0.68-1.27), but a modest significant benefit with the coxibs in overall upper GI clinical events (RR 0.77, 0.62-0.95). Thus, the difference in aspirin users was driven primarily by a difference in uncomplicated ulcers."</p> <p>You need to include low-dose aspirin with NS-NSAIDS as well. Observational studies have examined low-dose aspirin + NSAIDs and shown a 2-4 fold increase in RR.</p> <p>Also, mention of PPI use in this section doesn't seem to fit here.</p>	<p>The Laine article mentioned by the reviewer was excluded. It did not meet our criteria for a systematic review (no methods provided for synthesizing the evidence); in addition, the meta-analysis described by the reviewer from that article combined different COX-2 selective NSAIDs, including drugs excluded from our report because they are not approved in the U.S. The risk associated with low-dose aspirin and non-selective NSAIDs is discussed (p21, starting lines 47): "Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in patients on celecoxib and those on nonselective NSAIDs in one meta-analysis."</p> <p>We clarified the sentence on PPI's to clarify that this refers to attenuation of risk of GI harms in persons prescribed celecoxib or nonselective NSAIDs and low-dose aspirin (p 21 line 49-51).</p>

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Peer Reviewer #4	Executive Summary	<p>P. 22 Co-therapy: Information on H2RAs is awkwardly stated. You need to state that, compared to placebo, standard dose H2RAs are not effective at significantly decreasing gastric ulcers but that double-dose H2RAs are.</p> <p>Need to state that misoprostol is the only therapy studied in average risk patients taking NSAIDs, although this was RA rather than OA. In addition, need to mention that PPIs not tested in a general population taking NSAIDs but RCTs done in very high-risk patients (recent ulcer bleed) do demonstrate a significant benefit. I would state that celecoxib more effective at decreasing hemoglobin drop > 2 g/dl without overt bleeding than diclofenac + PPI. The CONDOR study had not suggestion of difference in any other endpoint.</p> <p>Also, I'm not sure on what basis you say celecoxib + PPI may reduce ulcers and complications in average risk patients. As mentioned above, you do need to indicate that this does decrease complications in high-risk patients.</p>	<p>The Executive Summary summary table states (page 22, KQ 3), "Co-prescribing 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 NSAIDs compared to placebo, double (full) dose H2-antagonists may be more effective than standard dose for reducing endoscopically detected gastric and duodenal ulcers." The Silverstein systematic review showed a reduction in risk with standard-dose H2-blockers (see page 69, Table 18)</p>
Peer Reviewer #5	Executive Summary	<p>Executive Summary provides good overall outline of the project. The authors have done a good job of summarizing a large body of evidence in the results in Table A. Where possible, especially for harms data in Table A, it would be helpful for the reader to have an idea of the absolute as well as relative results. (e.g as was done on pg 19, line 50 and pg 20, line 30).</p>	<p>Noted. Absolute rates are provided throughout the harms section when available (see GI and CV harms of celecoxib, GI and CV harms of nonselective NSAIDs, GI and CV harms of aspirin).</p>
Peer Reviewer #5	Executive Summary	<p>Pg ES-7 – line 31 'furthermore'</p>	<p>Typo corrected (page 15, line 31).</p>

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Peer Reviewer #5	Executive Summary	Pg ES-8, line 16 “but a systematic review that included trials of patients with osteoarthritis or rheumatoid arthritis found worse effects on pain compared to nonselective NSAIDs (difference 1.7 points on a 10 point VAS pain scale). Suggest changing “worse effects on pain” to “pain was reduced less with meloxicam compared to nonselective NSAIDs...” or something along those lines to make the meaning clearer.	Revised to “...lesser effects on pain...” (page 16, line 17).
Peer Reviewer #5	Executive Summary	p. ES-9 –line 7-14 “The systematic review included the pivotal, large, long-term CLASS study, in which celecoxib was superior to diclofenac or ibuprofen for ulcer complications or symptomatic ulcers at 6 month followup (2.1% vs. 3.5%, p=0.02), but not at the end of followup. There was no difference in rates of ulcer complications or symptomatic ulcers at either 6 month or complete followup.” Found the second sentence seems to contradict the first – does it refer to the results of the overall SR, not the CLASS study? If so, needs to be clearer.	The second sentence should have referred only to ulcer complications (i.e. without symptomatic ulcers). We revised to state (page 17, line 14): “The systematic review included the pivotal, large, long-term CLASS study, in which celecoxib was superior to diclofenac or ibuprofen for ulcer complications or symptomatic ulcers at 6 month followup (2.1% vs. 3.5%, p=0.02), but not at the end of followup. However, CLASS found no difference in rates of ulcer complications alone at either 6 month or complete followup.”
Peer Reviewer #5	Executive Summary	Pg ES-9, line 12 and pg 19, line 40 – please state what was the timing of the ‘end of follow-up’ or ‘complete follow-up’ for the CLASS study in which “celecoxib was superior to diclofenac or ibuprofen for ulcer complications or symptomatic ulcers at 6 month followup (2.1% vs. 3.5%, p=0.02), but not at the end of followup (12 months).	Revised to clarify that “end of followup” results were through 12 months (page 17, line 15).
Peer Reviewer #5	Executive Summary	Some copyediting needed in Table A	We reviewed and revised Table A for copyediting errors.
Patrick du Souich	Introduction	The update of the 2006 report "Comparative effectiveness and safety of analgesics for osteoarthritis" represents an excellent summary of the drugs available to reduce pain in pain in patients with OA. However the DMOAD effect of glucosamine and chondroitin as well as the ADEs of PPIs should be further discussed.	See response to similar comment by reviewer above.

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Peer Reviewer #1	Introduction	As a consumer reading the introduction, I was able to clearly understand the questions, process of selecting research studies and observational studies. I appreciated the overview of the pharmaceuticals reviewed including both the risk and benefits of each. It increased my knowledge of approaches of selecting analgesics for osteoarthritis.	Noted.
Peer Reviewer #2	Introduction	The reviewer respectfully notes that there is NO evidence of 3 isoforms of cyclooxygenase in humans. COX-3 has been reported in canines and it is unclear whether this has been reproduced by other groups. In humans, there are only 2 functional isoforms of the COX enzyme. COX-1 is located not only in the gastric mucosa but also in platelets. While one of the reasons for GI bleeding in patients who take NSAIDs that inhibit COX-1 is gastric ulcers, there are also ulcers that occur in the small bowel (not visible on routine upper endoscopy) and these drugs inhibit platelet aggregation contributing to bleeding from surface lesions. COX-2 is ubiquitous and not just in joints and muscles. Indeed, the effects of NSAIDs on fluid retention and blood pressure elevation are mediated by inhibition of COX-2 in the kidney. On page 2, line 46, please change "black box" to "boxed"	We revised the Introduction to remove the reference to COX-3 (we had included this in the original report because several peer reviewers pointed out some emerging evidence about its potential presence in humans). We also revised to make the effects and location of COX-1 and COX-2 clearer (page 25, starting line 38) to: "Understanding of the pharmacology of NSAIDs continues to evolve, but it is thought that most NSAIDs block the COX-1 and COX-2 isoenzymes. COX-2 is found throughout the body, including joint and muscle, where it contributes to pain and inflammation. Because they block COX-2, NSAIDs reduce pain compared to placebo in patients with arthritis, low back pain, minor injuries, and soft tissue rheumatism. NSAIDs are also associated with important adverse effects. NSAIDs cause gastrointestinal (GI) bleeding because they also block the COX-1 enzyme, which mediates mucosal defense of the gastrointestinal tract, including protection from acid and platelet aggregation." We also revised the Executive Summary introduction accordingly (top of page 10).
Peer Reviewer #3	Introduction	The Introduction is clear and describes many of the important clinical issues. However, I would suggest that the comparative benefits aspect of the key questions is not well motivated by the data presented in the Introduction.	Noted. Comparative benefits of NSAIDs were included as a Key Question.

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Peer Reviewer #4	Introduction	<p>P. 25, Is it now well-accepted that COX-3 clearly exists?</p> <p>Again I wouldn't use the estimate of hospitalizations and deaths you have here. The reference for this you list by the way is a basic science article. There were other much higher estimates, but all are problematic and divert from the message that NSAIDS increase the risk of GI complications such as bleeding by several fold and therefore increase the risk of hospitalizations and deaths.</p>	<p>We removed the reference to COX-3, see response to similar comment by another review.</p> <p>Regarding estimates of hospitalizations and deaths, see response to similar previous comment from this review; we revised the Introduction as noted previously (page 25, starting line 50).</p>
Peer Reviewer #4	Introduction	<p>p. 26 I wouldn't think it really appropriate to suggest the prostacyclin hypothesis is not correct. I agree it is not verified to be the etiology but I don't believe it is verified not to be the cause, as the wording seems to suggest.</p>	<p>We revised to state (page 26, line 39-41), "have not definitely confirmed this hypothesis."</p>
Peer Reviewer #4	Introduction	<p>p. 27 I don't believe it is correct to say aspirin is rarely used in higher doses for analgesia. Survey data show a high proportion of the general population takes aspirin regularly for analgesia (although they don't tell us the specific doses being used).</p>	<p>We revised to state (page 27, lines 5-6) , "It is not known with certainty how frequently aspirin is used at the higher doses more effective for analgesia, where tolerability may be an issue"</p>
Peer Reviewer #5	Introduction	<p>Introduction is appropriate. However, reference number 2 (pg.1. line 9) at the beginning of the introduction incorrect. The authors in this reference is incorrect (I've worked with Drs Towheed and Anastassiades on systematic reviews, but this is not one of our papers together) 2. Towheed TE, Maxwell L, Anastassiades TP, et al. Impact of musculoskeletal disorders in Canada. Annals of the Royal College of Physicians and Surgeons of Canada 1998;31: 229-32. "Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life.2"</p>	<p>This is an older reference and we deleted it; other references describe the current impact of osteoarthritis in the U.S.</p>

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Peer Reviewer #6	Introduction	<p>The background is succinct and well written. Personally i find the inclusion of the category of "partial cox 2 inhibitors" inappropriate. This is not an fda accepted class, and largely was created for marketing purposes. The data is correct when the class is discussed, but it fails to recognize that the in vitro properties are irrelevant, as selectivity is lost with increasing doses. And the dose issue here, as well as throughout the paper is missed or under emphasized for nonselective nsaid, particularly when observational studies are mentioned. These drugs have very dose dependent toxicity, and that issue is completely unexplored. On p 10 it is mention cox-1 protects the stomach--eicosanoids regulated by that isoform are important in mucosal defense is the correct concept.</p> <p>p 15 line 31 f missing in furthermore</p>	<p>See response to previous similar comment by another reviewer. Typo corrected (page 15, line 31).</p>
Peer Reviewer #1	Methods	<p>It appears that the inclusion/exclusion criteria took into account the factors that would provide information to assess the study into the three categories used. I am not an expert, so I am not aware of the available databases that should be included. Saying that, it appears that there was a thorough search including asking pharmaceutical manufactures to submit information providing the most current studies.</p> <p>The appendixes were helpful in understanding some of the methods and measures used to rate studies. Observational studies are important, even if not high quality, and glad to see they were considered.</p> <p>Based on my knowledge it appears that the statistical methods were appropriate. They took into account a number of variables when rating each study.</p>	Noted.

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Peer Reviewer #2	Methods	<p>This reviewer has a strong disagreement with the grouping of meloxicam, etodolac and nabumetome as a group of NSAIDs separate from nonselective NSAIDs. The WHO identifies a class of coxibs (COX-2 selective inhibitors) that don't inhibit the COX-1 enzyme using "ex vivo" assays at pharmacologic doses. This group includes celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib. Only celecoxib is available in the U.S. The remaining NSAIDs are all nonselective; they differ mainly in their ability to inhibit platelet aggregation throughout the dosing interval. Only naproxen is capable of doing this (having an aspirin-like effect) when taken at doses of 500 mg twice daily.</p> <p>Pitiful little data are available on salsalate and one should consider dropping this from the report. Finally, on page 12 lines 39-41, the ACR criteria were developed for RA and are not used for OA; they do not belong in the report at all.</p>	<p>We believe that there remains some uncertainty about whether "partially selective" NSAIDs have any advantages relative to nonselective NSAIDs. The purpose of the CER, in fact, is to examine the evidence behind such claims. Others have also categorized NSAIDs in this way. For example, a recent systematic review commissioned by CCOHTA (Canadian Coordinating Office for Health Technology Assessment) classified etodolac and meloxicam as COX-2 selective NSAIDs. Our classification was based on in vitro differences in COX-2 selectivity for these NSAIDs that are intermediate between the COX-2 selective and non-selective NSAIDs. We revised the Intro (Executive Summary, p 10 line 21 and Main report, p 35 line 29): "However, whether partially selective NSAIDs are truly different from nonselective NSAIDs is unclear because COX-2 selectivity may be lost at higher doses and effects on clinical outcomes are uncertain." In addition, the Introduction states (p 26, line 20): "The table gives an idea of how widely NSAIDs vary in their selectivity, but should be interpreted with caution. Different assay methods give different results and assay method may not reliably predict what will happen when the drug is given to patients. Clinical studies, rather than these assay studies, are the best way to determine whether patients actually benefit from using more selective NSAIDs." Our results support some potential differences for the partially selective NSAIDs meloxicam and etodolac versus nonselective NSAIDs for symptomatic ulcers or ulcer complications (see Table A, KQ 1A, GI and CV harms: Partially selective NSAIDs, page 17).</p> <p>Salsalate was selected as an included drug for this review. We also think it is clinically relevant as it has been proposed as being safer than non-selective NSAIDs. The purpose of the review is to identify and synthesize the available evidence, even if it is determined that the evidence is lacking. We removed the bullet on the ACR criteria from page 36 (lines 39-41).</p>
Peer Reviewer #3	Methods	The process for selecting articles, extracting information, and synthesizing data is thorough.	Noted.
Peer Reviewer #3	Methods	However, the Technical Expert Panel does not include many whom I consider expert in OA or NSAIDs. I wonder how they were selected. The relevance of the questions may have been greater if a different Technical Expert Panel were chosen.	The Technical Expert Panel was selected through a process with AHRQ and included stakeholders with difference backgrounds and expertise with regard to NSAIDs.

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Peer Reviewer #3	Methods	It is not clear why opioids were not included as part of this review. This class of agents has been used increasingly and is part of recommendations from the AGS, APS, and ACR. They are controversial. Thus, a systematic review of their comparative benefits and harms would be very useful.	Opioids were outside the scope of this review.
Peer Reviewer #3	Methods	The first key question pertains to comparative benefits and harms of NSAIDs and acetaminophen. The comparative benefit aspect of this question yielded little important information. A more expert Technical Panel would have quickly been able to suggest that this would not yield useful information.	Noted. Acetaminophen and NSAIDs were included drugs for this review and the purpose of the review was to identify any available evidence for this comparison, not presume whether or not it was present.
Peer Reviewer #5	Methods	Yes, basic inclusion criteria clear and acceptable. However, could specify that all grades of OA and any definition of OA used by trialists were included. Was there a reason only English-language studies were included?	We revised to state, "...any grade of osteoarthritis" (page 34, line 53). English-language studies were excluded because we did not have the resources to translate foreign language studies.
Peer Reviewer #5	Methods	Pg.12, line 39 – ACR 20, 50,70 response is defined for RA so unclear how this fits here. Earlier section explains that RA trials included for assessment of harms only.	See response to a similar comment by another review (we deleted the bullet referring to the ACR criteria).
Peer Reviewer #5	Methods	Pg 13. Line 10: Re Timing, as part of the PICOTS statement, "However, study duration was considered when assessing applicability of studies." Would appreciate if this statement could be clarified. Also, in Table A it would be helpful for readers to know the range or median of study duration upon which the summaries of the results are based.	We revised (page 13, lines 9-11) to eliminate the second sentence, which is not necessary for describing the inclusion criteria. Assessment of applicability is discussed on page 15 (bottom). Regarding the study duration, these are described when important (see page 17, GI and CV harms of celecoxib; page 18, GI and CV harms of nonselective NSAIDs, KQ 1b (page 20), effects of duration of therapy).
Peer Reviewer #5	Methods	Pg 13, line 20 re Figure 1 – the second bubble with 1, 3 is somewhat confusing as key questions 1,2,4 all focus on both benefit and harm, while 3 is focused on solely on harm. Please clarify.	We revised Figure 1 so that KQ's 1, 2, 3, and 4 are all included in the harm "bubble" in Figure 1 (page 13).
Peer Reviewer #5	Methods	Pg F1, line 33 – I think this line is duplicated with line 44. Line 34 refers to generation of randomization sequence	There was a typo so that "allocation concealment" appeared twice (Appendix F). We revised to clarify those criterion 1 addresses the generation of the randomization sequence and criterion 2 addresses treatment allocation. Uses of alternate days, birth date, etc are both inadequate sequence generation and inadequate allocation concealment.

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Peer Reviewer #5	Methods	I don't see a methods section detailing any statistical methods and whether any additional meta-analysis was carried out (ie use of random or fixed effects; how heterogeneity was handled, etc.). If no additional MA was conducted by the authors and only the results of existing individual studies or systematic reviews were used, it would be helpful to clarify this.	We re-named the "Rating the Body of Evidence" to "Evidence Synthesis and Rating the Body of Evidence" (page 16, line 7). We added a sentence stating (page 16, starting line 14): "We did not perform original meta-analyses. Rather, we relied on the results of existing individual studies and systematic reviews (including meta-analyses)."
Peer Reviewer #5	Methods	While the search strategies in Appendix C appear appropriate, I am not an expert in electronic searching. I would assume that these would have been checked by an information specialist with expertise in this area.	The searches were conducted by a member of the review team (Tracy Dana, MLS) with expertise in research library and search methods.
Peer Reviewer #5	Methods	Re Inclusion criteria outlined in Appendix D and that stated on page 10, line 55: In appendix D, line 8 reads like RA was included for both benefit and harm, while Alzheimer's and cancer prevention was included for just harm. However, page 10 makes it clear that RA was only included for adverse event assessment; perhaps this could be clarified in Appendix D	We revised Appendix D (Eligibility criteria for population) to be clear that studies of osteoarthritis were included for benefits or harms; studies of rheumatoid arthritis, Alzheimer's and cancer prevention were included only for harms.
Peer Reviewer #6	Methods	The methods are detailed and standard.	Noted.
Patrick du Souich	Results	In page 52, based on the meta-analysis of Wandel et al.(1) it is stated that: "a statistically significant but clinically nonsignificant beneficial effect of glucosamine on pain (-0.4 cm on a 10 cm scale, 95% credible interval -0.7 to -0.1) and joint space narrowing (-0.2 mm, 95% CI -0.3 to 0.0) compared to placebo." The results and conclusions reported by Wandel et al.(1) are questionable due to the following reasons.	The absolute pooled effect from the Wandel study (0.10 mm) is very similar to the effect from the Hochberg meta-analysis (-0.13 mm) (the difference is not statistically significant in Wandel et al but statistically significant in Hochberg et al). As stated in the report, we believe that the clinical significance of this degree of effect on joint space narrowing (an intermediate outcome) is uncertain.

Commentator & Affiliation	Section	Comment	Response
Patrick du Souich	Results	Another meta-analysis (2) evaluating the DMOAD effect of chondroitin sulphate including the same three trials (3,4,5) considered in the meta-analysis of Wandel et al.(1), reached the conclusion that the difference between placebo and chondroitin sulfate in joint space width over 2 years was 0.13 mm (95% CI 0.06, 0.19) (P =0.0002), corresponding to an effect size of 0.23 (95% CI 0.11, 0.35) (P=0.0001), effect size that differs significantly from those shown in the manuscript of Wandel et al.(1) Taking into account that baseline values of joint space width were 2.41 mm (3), 3.81 mm (4) and 3.86 mm (5), a difference with placebo of 0.13 mm represents 3.4-5.4% of baseline over two or three years, value that is clinically meaningful for osteoarticular diseases. On the other hand, Wandel et al.(1) report an effect size for glucosamine as DMOAD of 0.16 (0.25, 0.00).	See above. The Hochberg systematic review referred to by the reviewer has been added to the report (p 77, line 20); as noted above its estimate was similar to the estimate from the Wandel systematic review and the review was rated fair-quality (in contrast to the good-quality Wandel review).
Patrick du Souich	Results	According the criteria of Wandel et al.(1) the effect size reported for chondroitin sulfate and glucosamine sulfate as DMOADs are not clinically meaningful. However, the follow-up for 5 and more years of the patients included in the Reginster et al.(6) trial shows that the incidence of knee replacement in patients who received glucosamine was 6.3%, less than half the incidence observed in the patients on placebo, e.g. 14.5% (7), clearly demonstrating that an effect size lower than 0.40 is clinically meaningful when considering the DMOAD effect of chondroitin sulfate and glucosamine sulfate. However, ES <0.4 are considered clinically meaningful: paracetamol is recommended by EULAR and OARSI, yet its ES is <0.20.	The issue is not what effect size (SMD) is clinically meaningful; it is whether a 0.20 mm difference in joint space narrowing is clinically meaningful. As we state above, we considered joint space narrowing an intermediate outcome with uncertain clinical significance. Parenthetically, an effect size of 0.2-0.5 is classified categorized as "small" according to Cohen.

Commentator & Affiliation	Section	Comment	Response
Patrick du Souich	Results	In pages 67- 70, it should also be mentioned that PPI have numerous adverse effects, among them: - Increase the potential of drug-drug interactions at the levels of CYP2C19 and CYP3A4 - Increase of osteoporosis and bone fractures (8) - Increased incidence of infectious processes (9) - Increased incidence of cardiovascular adverse events (10), effect that may potentiate the CV adverse events of NSAIDs.	Reviewing general harms associated with PPIs was outside the scope of this review; we reported harms associated with co-prescribing of PPIs + NSAIDs vs. NSAIDs without a PPI (see KQ 3).
Kathleen Gans-Brangs, PhD	Results	Key Question3, Page 68, paragraph 2, lines 203: The draft report states: “naproxen plus esomeprazole.” To provide clarity that this is a combination tablet that contains a different formulation of esomeprazole (an immediate release esomeprazole), we recommend rewording to: “naproxen 500 mg plus immediate release esomeprazole 20 mg combination tablet.”	Revised as suggested, page 92, lines 14-15.
Kathleen Gans-Brangs, PhD	Results	Key Question 3 and Appendix H, Pages 68, G-1, G-2 and H-2 of Appendices: Rating of Goldstein et al 2010 (studies 301 and 302 - reference #240) as fair quality: Please consider changing the quality rating from fair to good based on the following supplemental information on studies 301 and 302: 1. and 2. Was the assignment to the treatment groups really random? – Yes. Was the treatment allocation concealed? Yes. – Patients were randomized via the Interactive Voice Response System to receive either VIMOVO or EC naproxen 500 mg alone, supplied as tablets of identical appearance in identical packaging to maintain blinding. The randomization schedule was provided by a third-party statistician. Patients, investigators and study staff remained blinded to treatment throughout the study.	The Goldstein et al 2010 study already received “yes” ratings for the criteria mentioned by the reviewer; it was primarily rated fair-quality due to high lost to follow-up (28% at 6 months). In addition, at the outset of the review, each manufacturer with a product being reviewed was requested to submit a Scientific Information Packet, where information like this can be provided to the reviewers. The Scientific Information Packet submitted by AstraZeneca did not include supplemental information on the conduct of the trial. We cannot accept additional unpublished supplemental information submitted through the public comment process because of the non-systematic nature of the process.

Commentator & Affiliation	Section	Comment	Response
Kathleen Gans-Brangs, PhD	Results	3. Were groups similar at baseline in terms of prognostic factors? Yes – pg. 404, Table 1. of the Goldstein 2010 publication shows that the patient demographics and baseline characteristics were similar between treatment groups. Additionally, patients were stratified at baseline for presence on concomitant LDA, a known risk factor for gastric ulcer. Similar to what is seen in real world, approximately a quarter of the patients in studies 301 and 302 (trials in the Goldstein 2010 publication) were taking concurrent low-dose aspirin.	See above.
Kathleen Gans-Brangs, PhD	Results	4. Were eligibility criteria specified? Yes – information found on pg. 402 of the Goldstein 2010 publication.	See above.
Kathleen Gans-Brangs, PhD	Results	5. Were outcome assessors blinded to treatment allocation? Yes – pg. 403 of the Goldstein 2010 publication includes this information (as noted for criteria question 1 and 2 above).	See above.
Kathleen Gans-Brangs, PhD	Results	6. Was the care provider blinded? Yes – pg. 403 of the Goldstein 2010 publication includes this information (as noted for criteria question 1 and 2 above).	See above.
Kathleen Gans-Brangs, PhD	Results	7. Was the patient blinded? Yes – pg. 403 of the Goldstein 2010 publication includes this information (as noted for criteria question 1 and 2 above).	See above.
Kathleen Gans-Brangs, PhD	Results	8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subject who finished in each group and their results)? Yes – pg. 403 of the Goldstein 2010 publication states that all efficacy analyses were performed on the intent-to treat (ITT) populations (all randomized patients who received >1 dose of study drug and had no ulcer as detected by endoscopy at screening). – pg. 405 of the publication lists the ITT population and pg. 407 (figures 2 and 3) show the ITT population results.	See above.
Kathleen Gans-Brangs, PhD	Results	9. Did the study maintain comparable groups: Yes, the study defined completers as those completing 6 months as well as though who developed the primary outcome of ulcer which, as per protocol, lead to discontinuation.	See above. 28% of the study population did not complete the study, thus not meeting the criteria for low loss to follow-up.

Source: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=494&pageaction=displayproduct>

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Commentator & Affiliation	Section	Comment	Response
Kathleen Gans-Brangs, PhD	Results	10. Levels of crossovers, adherence and contamination: below specified cut-offs or no information provided about protocol violations? Reporting of attrition - Yes – as per comment for #11 below Reporting of crossovers - No – Please consider the following additional information relevant to the original evidence rating – There were no crossovers in treatment (see additional details below). Reporting adherence – Yes – In the Goldstein publication page 403, Planned supportive analyses were performed on the per-protocol population (patients in the ITT population with no major protocol violation and treatment compliance >70%). Reporting of contamination? - - No – Please consider the following supplemental information relevant to the evidence rating. There were no reports of contamination with study treatments (see additional details below).	See above.
Kathleen Gans-Brangs, PhD	Results	The following information is provided to support the lack of crossover or contamination issues identified in these PN400 (Vimovo) studies. The violations that were identified are also not likely to contribute to study bias. Major protocol violations were identified for 9 (4%) of the randomized subjects in Study 301. The majority of these pertained to subjects with no post-baseline endoscopy (15 subjects). The PP population excluded 15 subjects from each treatment group of the ITT population. Subjects with study drug compliance <70% or unknown applied to 13 PN 400 (Vimovo) subjects and 11 EC naproxen subjects.	See above.

Commentator & Affiliation	Section	Comment	Response
Kathleen Gans-Brangs, PhD	Results	In Study 302, major protocol violations were identified for 28 (7%) of randomized subjects; all of the major violations pertained to subjects with no post-baseline endoscopy. The PP population excluded 30 subjects from each treatment group of the ITT population. Subjects with study drug compliance <70% or unknown applied to 26 PN 400 (Vimovo) subjects and 22 EC naproxen subjects. 11. Was the rate of overall attrition and the difference between groups in attrition with acceptable levels? Please consider the following supplemental information relevant to the evidence rating.	See above.
Kathleen Gans-Brangs, PhD	Results	- In Study 301 the difference in premature discontinuation rate was greater than 10% between the two treatment groups but in Study 302 there was a < 10% difference between the 2 treatment groups in premature discontinuation rates. The primary and secondary endpoint results for both studies 301 and 302 are presented independently and are consistent in both studies. Therefore, there is no evidence that the difference in premature discontinuation rate between the treatment groups in study 301 in any way biased the results or the participants in the study.	See above.

Commentator & Affiliation	Section	Comment	Response
Kathleen Gans-Brangs, PhD	Results	<p>Key Question 3, Page 69, Section Cox-2 Inhibitors alone compared to nonselective NSAIDs plus a PPI. In the section under Cox-2 Inhibitors alone compared to nonselective NSAIDs plus a PPI, we recommend adding GI tolerability data from the following study: Hochberg MC, Cryer B, Fort JG, et al. A fixed-dose combination of naproxen and esomeprazole magnesium (VIMOVO™) has comparable efficacy and tolerability to celecoxib in patients with osteoarthritis (OA) of the knee: results from two randomized, controlled trials (poster). Presented at: American College of Rheumatology Annual Meeting, November 6- 10, 2010; Atlanta, GA. Supplemental Methodology Details (Hochberg et al, Studies 307/309):</p> <p>Randomization methods: Subjects who met entry criteria including the clinical diagnosis of OA of the knee were randomized in a 2:2:1 ratio to receive VIMOVO 500 mg/20 mg twice daily, celecoxib 200 mg once daily, or placebo. At randomization, study site staff logged into the interactive web response system to identify the study drug to dispense to the subject. Blinding methods: The randomization schedule was provided by a third-party statistician. The identities of the treatments were concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, and appearance. Patients, investigators, and study staff remained blinded to the identity of the treatment throughout the study. In the event of an emergency, an unblinding procedure was implemented.</p>	Because this study has not been fully published, we are unable to include these results.

Commentator & Affiliation	Section	Comment	Response
Rosa L. Hong, Pharm.D., M.B.A.	Results	<p>In section Key Question 1a, What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements? On pg. 20, under the section "Nonselective NSAID versus nonselective NSAID or any COX-2-selective NSAID", bullet 4 reads, "Most observational studies showed similar estimates for CV risk for naproxen, COX-2 selective NSAIDs, and other nonselective NSAIDs." We request that you please provide supporting references for the above statement. This critical statement is not consistent and is contradictory to bullet 5 and 6 right below (as noted in the 2006 version and 2010 draft).</p>	<p>The studies supporting this statement are shown in Table 8 (starting p 61), including ref's 129, 130, 131, 132, 126, 133, 134, 135, 136, 137, 105, 144, 142, 128, and 143.</p>
Rosa L. Hong, Pharm.D., M.B.A.	Results	<p>Bayer HealthCare is requesting clarification on the following new statement noted in the updated 2010 draft. This additional statement added to the 2010 draft is contradictory to other statements regarding CV safety profiles of non-selective NSAIDs.</p> <p>Bullets 5 and 6 read, "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" and "In indirect analyses from a systematic review, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo". Bullet 5 states that naproxen differs in its CV safety profile from other NSAIDs while bullet 6 states that naproxen appears to be the only NSAID associated with neutral risk relative to placebo in indirect analyses. These statements are in contrast to bullet 4. There doesn't appear to be many additional references regarding CV safety profiles for the 2010 draft, particularly with regards to naproxen compared to the references evaluated in the 2006 version. Therefore, Bayer HealthCare requests clarification on the scope and number of studies that formed the basis for this statement.</p>	<p>Bullets 5 and 6 are in reference to systematic reviews of randomized trials, which reported different results compared to the observational studies described in bullet 4. We revised bullets 5 and 6 (p 44 lines 21-27) to be clear that the systematic reviews included RCTs.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	<p>As a consumer I found that overall the studies were clearly described for the most part. It depended on study design and results as to how much information was available. I do not think that the lack of information in several of the studies was due to those who prepared this report, but in the study itself.</p> <p>I found the charts captured details of studies examined making it easy to summarize the information. The appendices were very helpful as reference reading through the materials. Because I am not familiar with all the current research, I can't say if they left anything out. I do know that the FDA is taking a closer look at the risk and benefits of Acetaminophen in prescription medication and has recently made some recommendations. Liver damage was the impetus for this investigation.</p> <p>One thing that I found confusing was the contradiction of facts reported from one study to the next. It appeared that while one saw low risk another would state high risk. While some studies were "graded" on their quality, it would have been helpful to have additional comments on quality of each study to help understand the findings.</p>	<p>Noted. Regarding the contradictory results between some studies, the quality ratings for all studies are discussed in the text and included in the appendices. The text also describes potential reasons for contradictory results. For example, on page 49, starting on line 49, the text describes why the Moore and Rostom systematic reviews of GI complications came to different conclusions (i.e., differential access to individual trials, no inclusion of a recent large trial in one of the reviews).</p>
Peer Reviewer #3	Results	<p>The Results are clearly presented and in enough detail to understand the rationale for the bulleted conclusions. I did not notice any studies that were missed. The figures and tables are very useful.</p>	<p>Noted.</p>
Peer Reviewer #4	Results	<p>p. 43, Benefits: Again you don't provide data showing that these drugs work better than placebo or no Rx. It would be important to document that they work and give the reader some idea of the degree of benefit.</p>	<p>The purpose of the review was to focus on comparative benefits and harms.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	<p>p. 44 Aspirin: I'm not sure you're using the most up-to-date systematic reviews for low-dose aspirin. The Lancet study of 2009 from Oxford gave lower RRR for CV—and again you should differentiate between primary and secondary CV prevention.</p> <p>The GI numbers you're using may include some studies in which aspirin was given at doses greater than the upper bound of the accepted definition of "low-dose" which is 325 mg daily. Thus it is not really correct to say these results are indicative of long-term prophylactic doses. If you want to give data regarding long-term prophylactic doses, you should use another meta-analysis that is restricted to low-dose aspirin.</p>	<p>As described in the results for aspirin (page 51, starting line 50): "In these studies, the dose of aspirin varied widely and was generally lower (50 mg to 1500 mg daily) than the doses considered effective for analgesia and anti-inflammatory effects, and patients typically received aspirin for prolonged periods." We did not identify a meta-analysis restricted to low-dose aspirin.</p>
Peer Reviewer #4	Results	<p>p. 48 You say 20% of patients in CLASS took aspirin, but I believe you'll find it was 22%.</p>	<p>We revised to say (page 24, line 46): "About twenty percent" (the precise estimate is not critical here).</p>
Peer Reviewer #4	Results	<p>p. 50 I would think you'd include the CONDOR study here to show that coxibs clearly decrease the risk of an occult hemoglobin drop with NSAID therapy.</p>	<p>CONDOR compared a selective NSAID vs. a selective NSAID + PPI and is therefore included in Key Question 3 (COX-2 Inhibitors alone compared to nonselective NSAIDs plus a PPI, page 93, starting line 41).</p>
Peer Reviewer #4	Results	<p>p. 51 I think it is fine to use the meta-analysis of Derry & Loke for this review since it includes trials with low-dose aspirin and higher doses of aspirin up to 1500 mg daily. However, this is not as useful a meta-analysis if one wants to look at the effect of only low-dose aspirin as taken for CV prophylaxis. You clearly indicate that we don't have data for analgesic doses of aspirin, but I probably would make the point that this meta-analysis includes all the doses you refer to up to 1500 mg and thus is not strictly low-dose aspirin.</p>	<p>P 51 starting line 50 states: "In these studies, the dose of aspirin varied widely and was generally lower (50 mg to 1500 mg daily) than the doses considered effective for analgesia and anti-inflammatory effects."</p>
Peer Reviewer #4	Results	<p>p. 59 Again you don't appear to be using the most recent meta-analysis from the Oxford group published in Lancet in 2009.</p> <p>And again, it will be important to indicate that we don't know that these CV benefits of low-dose aspirin can be extrapolated to high doses used for analgesia (again, the greater COX-2 inhibition of high dose theoretically could mitigate some of the benefit of the anti-platelet effect).</p>	<p>This study was excluded; see response to similar previous comment from this reviewer. We did not speculate about effects of high-dose aspirin since all of the evidence is on low-dose aspirin + NSAIDs (the section clearly indicates that it addresses concomitant use of prophylactic dose aspirin, p 59 line 20).</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	p. 69-70 Tolerability: Again it would be good to provide data on the risk of symptoms (e.g., dyspepsia) with these drugs (e.g., NS-NSAIDs) vs. placebo/no Rx.	Given the focus of this review, we focused on comparative tolerability, not tolerability versus placebo.
Peer Reviewer #4	Results	p. 71 Acetaminophen. Again, you should first establish that acetaminophen works (e.g., is better than placebo/no Rx). Similarly, best to mention harms vs. placebo/no Rx first and then vs. other agents.	Given the focus of this review, we focused on comparative efficacy and safety of acetaminophen versus NSAIDs.
Peer Reviewer #4	Results	p. 81 Comparing >200 mg and < 100 mg aspirin is not really clinically relevant if the > 200 includes patients taking > 325. One issue is whether there is a difference among different doses of low-dose aspirin (50-325) and the other is whether there is increased GI risk with high-dose aspirin (which is what you should be focused on for a review of analgesia, since low-dose aspirin holds no relevance related to analgesia)	We reported results as provided in the meta-analysis, which compared <100 mg, 100-200 mg, and >200 mg daily. We do think there is some clinical relevance since some patients take 75 mg for prophylaxis. As noted elsewhere in the review (and in responses to comments by this reviewer), there is little data on harms and benefits or high-dose aspirin.
Peer Reviewer #4	Results	p. 91 Say that only misoprostol reduces complications. This is true in a general population and perhaps also true in terms of placebo-controlled for traditional NSAIDs. But Hong Kong studies in very high-risk patients (recent ulcer bleed) do show decrease with PPI (in traditional NSAID users as compared to control of HP treatment; and as compared to placebo in low-dose aspirin users).	Effectiveness of PPIs in high-risk patients (celecoxib vs. celecoxib + PPI) are covered in KQ 2 (high-risk patients) (page 84, starting line 40)
Peer Reviewer #5	Results	Tables summarize results well.	Noted.
Peer Reviewer #5	Results	Pg 19, line 56 add word 'trials' after 'randomized'.	Typo corrected ("randomized trials", page 43, line 56-57).
Peer Reviewer #5	Results	Table 11: re Towheed reference; note that SMDs should be negative as there was a reduction in pain in the NSAID vs acetaminophen groups.	Table 11 states that NSAIDs were "superior" and reports the SMD (which is not directional); also other results are reported similarly in this Table (see Zhang, Wegman), so no changes made. However we did revise the Lee entry to be consistent with the others (WMD 6.33, 95% CI 3.41 to 9.24).
Peer Reviewer #5	Results	Pg 74, line 28, add word 'trial' after 'fair-quality'	Typo corrected ("fair-quality trial", page 98, line 28).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results/ Executive Summary	<p>The executive summary is the focus of my comments, as it is the results of the detailed analysis in each section.</p> <p>I do take issue with what was selected for reporting in the summary, as it seems random. For example p 17 line 40--why is naproxen in one study singled out? Line 52 same page--need to always mention dosing particularly when discussing the so called partially selective agent. On p 18 lines 17 and 32--why is naproxen singled out here and trend reported for the adapt study? ADAPT is a very poor quality study. The dose issue for comparing naproxen with ibuprofen is essential for line 17--implies there is a GI toxicity difference that may not be real.</p>	<p>The line raised by the reviewer does not single out one study of naproxen, in fact it summarizes all of the large observational studies comparing celecoxib versus naproxen (p 17 line 40): "Three large observational studies found celecoxib associated with similar risk of MI compared to naproxen, ibuprofen, or diclofenac; a fourth observational study found celecoxib associated with lower risk than ibuprofen or naproxen." Re: doses of meloxicam and etodolac, we revised to state (p 17 line 52 and 58): "Meloxicam (primarily at a dose of 7.5 mg/day)" and "etodolac (primarily at a dose of 600 mg/day)..." ADAPT is not referred to on p 18 line 17 (which refers to a systematic review). Regarding p 18 line 32, we believe it is important to discuss results of ADAPT since it was one of the key trials showing an increased CV risk associated with celecoxib; in fact, one of the reasons we discuss it is to highlight the methodological issues that complicate interpretation, in particular the decision to terminate the trial early without using rigorous stopping protocols, as well as the fact that events were not adjudicated, the number of events was small, and most CV outcomes didn't reach statistical significance (see p 18 line 32 and p 59 lines 43-47).</p>
Peer Reviewer #6	Results/ Executive Summary	<p>p19 line 43--why put something with unclear statistical significance in the summary--can we reach any clinically relevant conclusion?</p>	<p>The result is discussed because indomethacin was the only nonselective NSAID in which there was a trend towards higher rates of toxicity (p 19 line 40-43): "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 significance unclear).</p>
Peer Reviewer #6	Results/ Executive Summary	<p>The summary and detailed section on question 3 does not adequately use observational studies to support the RCT information as they do in the other question sections. The summary suggests PPIs may not even be as effective as misoprostol, yet oral prostaglandins have no supportive observational data and are not used due to poor tolerability.</p> <p>There is strong observational data to demonstrate PPIs are superior to all other gastroprotective agents and this is reflected in other guidelines.</p>	<p>We only included observational studies when RCTs did not provide enough evidence to answer the KQs. For KQ3, given the potential for confounding by indication we only included RCTs, which we rated high-quality. We found that (p 22 lines 23-29) "In direct comparisons, coprescribing of PPIs in patients prescribed a nonselective NSAID was associated with a lower risk of endoscopically detected duodenal ulcers compared to misoprostol or H2-antagonists, a lower risk of endoscopically detected gastric ulcers compared to H2-antagonists, and a similar risk of endoscopically detected gastric ulcers compared to misoprostol" (i.e. PPIs are superior to misoprostol for duodenal ulcers and equivalent for gastric ulcers). We also state that misoprostol is associated with a higher rate of withdrawals due to adverse GI symptoms.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	In the section on acetaminophen, p 73 the observational data on GI bleeding is almost certainly heavily confounded by channeling bias. This may be true for the other putative toxicities as well.	This comment appears to be asking us to downplay the observational studies here, whereas the previous comment from this reviewer asks us to weigh observational studies more highly than RCTs. We believe that all observational studies are susceptible to confounding by indication and this is reflected in the grade of evidence for harms associated with acetaminophen (low to moderate, see p 19 lines 46-48).
Peer Reviewer #6	Results	P88--there are many observational studies supporting PPI with nsaids including coxibs, why weren't they included?	See response to previous similar comment from this reviewer.
Patrick du Souich	Summary and Discussion	There is evidence that the DMOAD effect of glucosamine is clinically relevant since it reduces knee arthroplasty by 50% in the next 5-8 years. PPIs have many ignored ADEs that may have clinical relevancy in the elderly (infections), in patients with osteoporosis and in patients with cardiovascular diseases, effect that may potentiate the cardiovascular ADEs of NSAIDs.	Rates of knee arthroplasty were not reported in the RCTs included in the systematic reviews. See response to similar comments from this reviewer regarding general harms of PPIs.
Joseph Vassalotti	Summary and Discussion	It is the position of the National Kidney Foundation that acetaminophen remains the non-narcotic analgesic of choice for patients with underlying chronic kidney disease. [Please see: William L. Henrich, et al., "Analgesics and the Kidney: Summary and Recommendations to the Scientific Advisory Board of the National Kidney Foundation From an Ad Hoc Committee of the National Kidney Foundation," American Journal of Kidney Diseases, Vol 27, No 1 (January) 1996: pp 162-165. The observational data that suggest an association between acetaminophen and chronic kidney disease may be confounded by physicians deliberately recommending acetaminophen use as an alternative for individuals at risk for chronic kidney disease to reduce the impact of COX-2 inhibitors and non-selective NSAIDs on increasing blood pressure, exacerbating edema and volume overload and reducing kidney function.	Noted. The section on acetaminophen (p 73 starting line 40) notes that case-control studies had many important flaws. We revised to emphasize that residual confounding may still be present even in well-designed observational studies (p 73, line 47): "The largest (926 cases) case-control study was designed to try to avoid many of these flaws, though results remain susceptible to confounding by indication." We also revised the Summary Table (p 19, acetaminophen entry) accordingly: "Some observational studies found acetaminophen associated with modest increases in blood pressure or higher risk of renal dysfunction compared to NSAIDs, but results may be susceptible to confounding by indication."

Commentator & Affiliation	Section	Comment	Response
Joseph Vassalotti	Summary and Discussion	In addition, the European data on the association between acetaminophen and chronic kidney disease is confounded by the use of combination analgesic products in Europe. NSAIDs and COX-2 inhibitors also cause resistant hypertension; and drug resistance to Angiotensin Converting Enzyme(ACE) Inhibitors, Angiotensin Receptor Blockers (ARBs) as well as diuretics. See: AV Chobanian, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 Report. JAMA 289:2560-2572, 2003. Hypertension is the second leading cause of kidney failure or End Stage Renal Disease in the United States.	See above regarding possibility of confounding, which are described as methodological flaws in a number of case-control studies. Effects of NSAIDs on HTN and renal function are reviewed starting on page 66, line 7.
Rosa L. Hong, Pharm.D., M.B.A.	Summary and Discussion	Due to these discrepancies in the summary conclusions, Bayer HealthCare respectfully requests the references that support the statement " Most observational studies showed similar estimates for CV risk for naproxen, COX-2 selective NSAIDs, and other nonselective NSAIDs. "	See above.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/ Conclusion	<p>While the implications for the major findings in the trials reviewed were clearly stated, I believe it is the findings themselves that reinforces the need for more high quality trials. It is in the review of all the findings that points out the difficulty in indentifying the quality of trials that would help form strong conclusions and recommendations. The summary of evidence was stated clearly and tied together all the reviews of studies in the report. In addition, I do not believe it demonstrated results that were conclusive on demographic subgroups.</p> <p>Overall, my sense is that more research is needed to form clear guidelines for these medications when treating OA to determine safety and comparative effectiveness in different demographics.</p> <p>It seems the bottom line in choosing the most effective medication is determined by which of the side effects/adverse events one wants to risk. As with all medication it seems there are risk and benefits associated with each choice. That is exactly what the discussion section pointed out.</p>	<p>We agree that more research is needed to address some of the issues brought up by the reviewer (such as differential effects in subgroups) and limited high-quality evidence to answer some key questions. These and other areas are discussed in the Future Research section on pages 111-112 (e.g., starting line 32, "Trials and observational studies evaluating safety or effect should be sufficiently inclusive to evaluate whether effects differ by race or gender)."</p>
Peer Reviewer #3	Discussion/ Conclusions	<p>The implications of the findings are not clear and neither are they clearly stated. The future research section is adequate, but I think it reflects a lack of OA expertise.</p>	<p>This comment does not provide specific issues in the report to address. Other comments from this review focus on the lack of key questions regarding non-included interventions, which were outside the scope of the review.</p>
Peer Reviewer #4	Discussion/ Conclusion	<p>The written Discussion (other than the 1st paragraph) was really of little if any value. It should try to pull out and focus on a few of the major points and put them in clinically relevant terms. You don't do that at all now.</p>	<p>The results of the review are summarized in Table 22. The Discussion section describes what the review covers, major new evidence covered in the review, and the unique trade-offs between risks and benefits for the different drugs covered in the review.</p>
Peer Reviewer #5	Discussion/ Conclusions	<p>Implications of the major findings clearly laid out in Table A and after each key question. Limitations of the studies/reviews included in the CER not really addressed in the discussion section. Authors could mention limitations specific to addressing harms; e.g difficulty in standardization of how AE are defined and assessed in different studies.</p>	<p>We added a sentence to the discussion stating that a limitation of the review is that studies didn't use standardized methods to define and assess harms (p 109, line 56): "Like the original CER, a limitation of this update is that studies have not used standardized methods for defining and assessing harms."</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Discussion/Conclusions	Future research section addresses important, broad future research agendas. Not sure how specific AHRQ would like this section to be; could consider structuring future research questions around a PICOT statement for future trialists.	We did not adopt a PICOTs format for the future research section of this CER update, though such a format is being considered by AHRQ for future CER's. We highlighted key gaps to highlight in the Future Research section.
Peer Reviewer #6	Discussion/Conclusion	I believe a much stronger emphasis on dose needs to be added throughout the paper, as it clouds interpretation of differences in toxicity when comparing agents, particularly the data so called partially selective NSAIDs. See my comments above on relevant omissions. This can help clinicians do the CV/GI tradeoff a bit better which can be improved. The NNH data is of value, but trying to balance them given the heterogeneous nature of the studies they were derived from is problematic. No discussion of cost-effectiveness in the paper is provided.	See previous to similar comment from this reviewer regarding dosing of the partially-selective NSAIDs. We reported NNH as requested by AHRQ staff for the original report. We believe it provides a clinically useful estimate of the magnitude of the risk. Cost-effectiveness is outside of the scope of the AHRQ Effective Health Care Program.
Peer Reviewer #6	Discussion/Conclusion	The future research section is fine, but many of the proposed studies can/ will never be done due to regulatory, funding, and human protection issues --such as dose effects on CV outcomes.	Noted. We do not see why a study on dose effects on CV outcomes associated with NSAIDs could not be designed and conducted, as it is an important clinical question.
Joseph Vassalotti	Future Research	The role of topical nonselective NSAIDs versus acetaminophen should be studied in patients with Chronic Kidney Disease.	We identified no studies comparing topical NSAIDs versus acetaminophen, in patients with or without chronic kidney disease.
Patrick du Souich	References	1. Wandel S, Jüni P, Tendal B, Nuesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. <i>BMJ</i> . 2010 Sep 16;341:c4675. doi: 10.1136/bmj.c4675. 2. Hochberg MC. Structure-modifying effects of chondroitin sulfate in knee osteoarthritis: an updated meta-analysis of randomized placebo-controlled trials of 2-year duration. <i>Osteoarthritis Cartilage</i> . 2010 Jun;18 Suppl 1:S28-31. 3. Michel BA, Stucki G, Frey D, De Vathaire F, Vignon E, Bruhlmann P, Uebelhart D. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. <i>Arthritis Rheum</i> . 2005 Mar;52(3):779-86. 4. Kahan A, Uebelhart D, De Vathaire F, Delmas PD, Reginster JY. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized,	1. Wandel et al. (2010) article: Already included. 2. Hochberg (2010) article: Identified in update search and added to the report. 3. Michel et al. (2005) article: Already included. 4. Kahan et al. (2009) article: Already included. 5. Sawitzke et al. (2008) article: Already included. 6. Reginster et al. (2001) article: Included in Wandel et al systematic review. 7. Bruyere et al. (2008) article: Excluded, it was an unblinded observational follow-up study of patients originally enrolled in RCTs. 8. Mazziotti et al. Excluded, no original data; also addresses general harms of PPIs (i.e. not in patients also prescribed NSAIDs). 9. Lodato et al. Excluded, no original data; also addresses general harms of PPIs (i.e. not in patients also prescribed NSAIDs). 10. Charlot et al. Excluded, does not address AEs associated with PPI use in persons prescribed NSAIDs.

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		<p>double-blind, placebo-controlled trial. Arthritis Rheum. 2009 Feb;60(2):524-33. 5. Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham CO 3rd, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE, Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. Arthritis Rheum. 2008 Oct;58(10):3183-91. 6. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet. 2001 Jan 27;357(9252):251-6. 7. Bruyere O, Pavelka K, Rovati LC, Gatterová J, Giacovelli G, Olejarová M, Deroisy R, Reginster JY. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage. 2008 Feb;16(2):254-60. 8. Mazziotti G, Canalis E, Giustina A. Drug-induced osteoporosis: mechanisms and clinical implications. Am J Med. 2010 Oct;123(10):877-84. 9. Lodato F, Azzaroli F, Turco L, Mazzella N, Buonfiglioli F, Zoli M, Mazzella G. Adverse effects of proton pump inhibitors. Best Pract Res Clin Gastroenterol. 2010 Apr;24(2):193-201. 10. Charlot M, Ahlehoff O, Norgaard ML, Jørgensen CH, Sørensen R, Abildstrøm SZ, Hansen PR, Madsen JK, Køber L, Torp-Pedersen C, Gislason G. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. Ann Intern Med. 2010 Sep 21;153(6):378-86.</p>	

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Kathleen Gans-Brangs, PhD	Appendixes	Key Question 3 and Appendix H, Pages 68, G-1, G-2 and H-2 of Appendixes: Rating of Goldstein et al 2010 (studies 301 and 302 - reference #240) as fair quality: Please consider changing the quality rating from fair to good based on the following supplemental information on studies 301 and 302: 1. and 2. Was the assignment to the treatment groups really random? – Yes. Was the treatment allocation concealed? Yes. – Patients were randomized via the Interactive Voice Response System to receive either VIMOVO or EC naproxen 500 mg alone, supplied as tablets of identical appearance in identical packaging to maintain blinding. The randomization schedule was provided by a third-party statistician. Patients, investigators and study staff remained blinded to treatment throughout the study.	See responses to identical previous comments by this reviewer.
Kathleen Gans-Brangs, PhD	Appendixes	3. Were groups similar at baseline in terms of prognostic factors? Yes – pg. 404, Table 1. of the Goldstein 2010 publication shows that the patient demographics and baseline characteristics were similar between treatment groups. Additionally, patients were stratified at baseline for presence on concomitant LDA, a known risk factor for gastric ulcer. Similar to what is seen in real world, approximately a quarter of the patients in studies 301 and 302 (trials in the Goldstein 2010 publication) were taking concurrent low-dose aspirin.	See above.
Kathleen Gans-Brangs, PhD	Appendixes	4. Were eligibility criteria specified? Yes – information found on pg. 402 of the Goldstein 2010 publication.	See above.
Kathleen Gans-Brangs, PhD	Appendixes	5. Were outcome assessors blinded to treatment allocation? Yes – pg. 403 of the Goldstein 2010 publication includes this information (as noted for criteria question 1 and 2 above).	See above.
Kathleen Gans-Brangs, PhD	Appendixes	6. Was the care provider blinded? Yes – pg. 403 of the Goldstein 2010 publication includes this information (as noted for criteria question 1 and 2 above).	See above.
Kathleen Gans-Brangs, PhD	Appendixes	7. Was the patient blinded? Yes – pg. 403 of the Goldstein 2010 publication includes this information (as noted for criteria question 1 and 2 above).	See above.

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Kathleen Gans-Brangs, PhD	Appendixes	8. Did the article include an intention-to –treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subject who finished in each group and their results)? Yes – pg. 403 of the Goldstein 2010 publication states that all efficacy analyses were performed on the intent-to treat (ITT) populations (all randomized patients who received >1 dose of study drug and had no ulcer as detected by endoscopy at screening). – pg. 405 of the publication lists the ITT population and pg. 407 (figures 2 and 3) show the ITT population results.	See above.
Kathleen Gans-Brangs, PhD	Appendixes	9. Did the study maintain comparable groups: Yes, the study defined completers as those completing 6 months as well as though who developed the primary outcome of ulcer which, as per protocol, lead to discontinuation.	See above.

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Kathleen Gans-Brangs, PhD	Appendixes	<p>10. Levels of crossovers, adherence and contamination: below specified cut-offs or no information provided about protocol violations? Reporting of attrition - Yes – as per comment for #11 below Reporting of crossovers - No – Please consider the following additional information relevant to the original evidence rating – There were no crossovers in treatment (see additional details below). Reporting adherence – Yes – In the Goldstein publication page 403, Planned supportive analyses were performed on the per-protocol population (patients in the ITT population with no major protocol violation and treatment compliance >70%). Reporting of contamination? - - No – Please consider the following supplemental information relevant to the evidence rating. There were no reports of contamination with study treatments (see additional details below). The following information is provided to support the lack of crossover or contamination issues identified in these PN400 (Vimovo) studies. The violations that were identified are also not likely to contribute to study bias. Major protocol violations were identified for 9 (4%) of the randomized subjects in Study 301. The majority of these pertained to subjects with no post-baseline endoscopy (15 subjects). The PP population excluded 15 subjects from each treatment group of the ITT population. Subjects with study drug compliance <70% or unknown applied to 13 PN 400 (Vimovo) subjects and 11 EC naproxen subjects. In Study 302, major protocol violations were identified for 28 (7%) of randomized subjects; all of the major violations pertained to subjects with no post-baseline endoscopy. The PP population excluded 30 subjects from each treatment group of the ITT population. Subjects with study drug compliance <70% or unknown applied to 26 PN 400 (Vimovo) subjects and 22 EC naproxen subjects.</p>	See above.

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Kathleen Gans-Brangs, PhD	Appendixes	11. Was the rate of overall attrition and the difference between groups in attrition with acceptable levels? Please consider the following supplemental information relevant to the evidence rating. - In Study 301 the difference in premature discontinuation rate was greater than 10% between the two treatment groups but in Study 302 there was a < 10% difference between the 2 treatment groups in premature discontinuation rates. The primary and secondary endpoint results for both studies 301 and 302 are presented independently and are consistent in both studies. Therefore, there is no evidence that the difference in premature discontinuation rate between the treatment groups in study 301 in any way biased the results or the participants in the study.	See above.
Peer Reviewer #5	Appendixes	Appendix H provides adequate detail on the included trials and systematic reviews. Note that on page H-22, line 8 states that the Towheed 2005 systematic review covers to 2002; however, this search date of this review was updated to July 2005 and includes 15 RCTs with 5986 participants, not the 6 RCTs as stated in the table.	We revised Appendix H with the updated results from the Cochrane review and also updated the Results accordingly (Table 11, page 47, Table 12, p 48).
Kathleen Gans-Brangs, PhD	General		Prescribing information for Vimovo was provided
Ingrid Moller	General	Dear Sirs/Madams Regarding the draft report <i>Comparative Effectiveness and Safety of Analgesics for Osteoarthritis- An Update of the 2006 Report</i> , you have issued for public comment; I would like to provide you with a study we performed with chondroitin sulphate which interesting results I believe would help you in this review (1). The study was conducted in Spain and our first aim was to investigate the efficacy of chondroitin sulphate on symptomatic knee osteoarthritis associated to psoriasis, to corroborate the results obtained in a previous clinical series of 11 patients with knee osteoarthritis and concomitant psoriasis. In these previous studies the use of chondroitin sulphate as a symptomatic treatment for knee osteoarthritis resulted in a marked	This RCT (n=129) of chondroitin vs. placebo in patients with knee osteoarthritis and psoriasis was added to the report. It did not change overall conclusions.

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		<p>clinical and histological improvement of the psoriatic lesions after two months of treatment (2,3).</p> <p>The study was published on the peer reviewed Osteoarthritis and Cartilage supplement journal, the official journal of the <i>Osteoarthritis Research Society International</i>.</p> <p>The trial we performed was designed as a randomized, double-blind, placebo controlled clinical trial and included 129 patients with symptomatic knee osteoarthritis and concomitant psoriasis. Patients were randomized into two groups receiving 800 mg daily of chondroitin sulphate or placebo for 3 months.</p> <p>The primary efficacy outcome for knee osteoarthritis was the Huskisson's VAS and for psoriasis was the Psoriasis Area and Severity Index (PASI) score at the end of treatment as compared with baseline. Secondary efficacy parameters for osteoarthritis included pain relief and function improvement in the knee using the Lequesne ISK, acetaminophen consumption, assessment of efficacy by patients and investigators and quality of life measured by the SF-36.</p> <p>Regarding the primary efficacy variable for osteoarthritis, treatment with chondroitin sulphate was superior to placebo in reducing the intensity of pain throughout the study period. Absolute differences in VAS scores were statistically significant after 1 month of treatment (chondroitin sulphate -14.6 ± 19.5 mm vs placebo -7.2 ± 17.1mm, $P < 0.05$) and after the 3 months (chondroitin sulphate -26.9 ± 24.8 mm vs placebo -14.23 ± 20.8mm, $P < 0.01$).</p> <p>Moreover, the administration of chondroitin sulphate was associated with a steady improvement in Lequesne ISK scores over the 3-month study period. At the end of the treatment period, absolute differences were statistically significant as compared with the placebo group (chondroitin sulphate -4.8 ± 3.4 vs placebo -3.3 ± 3.5, $P < 0.05$). Acetaminophen consumption was scarce and very similar in both treatment groups.</p>	

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		<p>At the end of the treatment period, no statistically significant differences were detected among treatment groups (chondroitin sulphate 38.2 ±42.6 vs placebo 30.2± 33.8, P >0.05). However, at the final visit, a significantly higher percentage of placebo-treated patients than chondroitin sulphate-treated patients consumed acetaminophen (chondroitin sulphate 43% vs placebo 64%, P< 0.05).</p> <p>Although chondroitin sulphate did not reach statistically significant results in the outcomes studied for psoriasis, chondroitin sulphate at dose of 800 mg/day demonstrated a statistically significant improvement of plantar psoriasis (chondroitin sulphate 87% vs placebo 27%, P<0.05).</p> <p>Quality of life improved significantly in chondroitin sulphate-treated patients according to the SF-36 health survey.</p> <p>The data available on the beneficial effect of chondroitin sulphate in psoriasis and the results observed in this clinical trial suggest that chondroitin sulphate could represent a therapeutic alternative for patients suffering concomitantly from osteoarthritis and psoriasis, a situation that it is expected to increase according to the demographic change in age distribution, which will lead to more elderly people with psoriasis. Moreover, it should be born in mind the fact that some anti-inflammatory medications commonly used in the management of osteoarthritis are considered potential risk factors for psoriasis, as it has been described that NSAIDs may induce psoriasis flares or aggravate pre-existing lesions (4,5). The incidence</p> <p>This study confirms the efficacy and safety of chondroitin sulphate as a symptomatic slow-acting drug in osteoarthritis and shows that chondroitin sulphate improves plantar psoriasis. I hope you find this study of your interest and could help you in the review you are performing, please find enclosed the pdf of the study for your information.</p> <p>(1) Möller I, Pérez M, Monfort J, Benito P,</p>	

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		<p>Cuevas J, Perna C, Doménech G, Herrero M, Montell E, Vergés J. Effectiveness of chondroitin sulfate in patients with concomitant knee osteoarthritis and psoriasis: a randomized, double-blind, placebo-controlled study. <i>Osteoarthritis Cartilage</i>. 2010; Suppl 1: S32-40.</p> <p>(1) Vergés J, Montell E, Herrero M, Perna C, Cuevas J, Pérez M, et al. Clinical and histopathological improvement of psoriasis in patients with osteoarthritis treated with chondroitin sulfate: report of 3 cases. <i>Med Clin (Barc)</i> 2004;123:739e42.</p> <p>(2) Vergés J, Montell E, Herrero M, Perna C, Cuevas J, Dalmau J, et al. Clinical and histopathological improvement of psoriasis with oral chondroitin sulfate: a serendipitous finding. <i>Dermatol Online J</i> 2005;11:31.</p> <p>(3) Abel EA. Diagnosis of drug-induced psoriasis. <i>Semin Dermatol</i>. 1992;11:269e74.</p> <p>Ben-Chetrit E, Rubinow A. Exacerbation of psoriasis by ibuprofen. <i>Cutis</i> 1986;38:45.</p>	
Anonymous	General	<p>We are aware that the AHRQ issued a draft publication for public comment on the Comparative Effectiveness and Safety of Analgesics for Osteoarthritis – An update of the 2006 Report.</p> <p>Our research team has recently performed a new clinical trial which we believe provides new interesting data on the use of chondroitin sulphate and its effectiveness in the treatment of knee osteoarthritis (OA). The study has just been accepted for publication in the Annals of the Rheumatic Diseases, the EULAR (European League Against Rheumatism organisation) peer-reviewed journal (1).</p> <p>We performed a pilot, multicentre, randomized, double-blind, controlled trial in knee OA patients with the aim to determine the effect of chondroitin sulphate on the progression of OA structural</p>	<p>The new trial described in this comment is not yet published and therefore does not meet inclusion criteria. Regarding the Wandel et al systematic review, a detailed post publication review by the editors of BMJ found “The criticisms raised in the rapid responses mainly address the selection and inclusion of studies and the assumptions made by the authors in their modeling analyses. We concluded that these criticisms continue the debate but do not negate the findings of the study. This article and its accompanying web extras on bmj.com gave an accurate and suitably cautious account of this study’s findings, strengths, and limitations. The authors were particularly thorough and transparent in reporting their methods and justifying their assumptions. We noted, too, that the authors had posted an “authors’ reply” Rapid Response addressing the criticisms directly (and since the review meeting they have posted another)” (see http://www.bmj.com/content/341/bmj.c4675.full%20/reply#bmj_el_247719). The editors did request that Wandel et al revise</p>

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		<p>changes including cartilage volume loss, subchondral bone marrow lesions, synovitis as well as disease symptoms.</p> <p>A total of 69 patients with knee OA and with clinical signs of synovitis were included and were randomized to receive either 800 mg chondroitin sulfate or placebo once daily for 6 months followed by an open-label phase of another 6 months in which patients of both groups received 800 mg of chondroitin sulphate once a day. Cartilage volume and bone marrow lesions were assessed by MRI at baseline, 6, and 12 months and synovial membrane thickness was assessed at baseline and 6 months.</p> <p>The results from this study revealed that patients in the chondroitin sulphate group compared to those in the placebo group experienced a significant reduction in cartilage volume loss in the global knee at 6 months ($p=0.030$,) which persisted at 12 months ($p=0.021$). A similar significant reduction was seen at both 6 and 12 months in the lateral compartment ($p=0.015$, $p=0.004$, respectively) and the tibial plateaus ($p=0.002$, $p=0.017$, respectively). Significantly lower bone marrow lesions scores were found for the chondroitin sulphate group at 12 months in the lateral compartment ($p=0.035$) and the lateral femoral condyle ($p=0.044$). Disease symptom effects were similar between the two groups and side effects were evenly distributed between both treatment groups.</p> <p>This pilot study provides, for the first time using MRI, evidence of the structure protective effect of chondroitin sulphate in patients with knee OA as early as 6 months into treatment and on cartilage lesions combined with a protective effect on subchondral bone lesions.</p> <p>This study brings an interesting introspect on the conclusion of the recent network meta-analysis performed by Wandel and colleagues on the symptomatic and disease modifying effects of chondroitin sulphate, glucosamine and the combination of both compounds (2). The actual findings contrast with the negative conclusion of</p>	<p>statements in the study recommending against coverage of glucosamine and chondroitin; however, these statements in themselves are not relevant for our review.</p>

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		<p>that analysis.</p> <p>From our point of view, Wandel and collaborators should have noted the limitations to the methodology and approach used in their network meta-analysis and how these limitations affect the ability to make conclusions based on their results, as I and other colleagues noted in a the Letter to the Editor published in the British Medical Journal (3). We found several points of the meta-analysis to be questionable, for example, they only considered a limited number of trials from the wide range of available studies. The justification for such an approach remains obscure. In doing so, no consideration was given to the fact that the effect of these products is delayed as it is stated in the European Medicines Agency guidelines, which recommends evaluation of analgesia in OA clinical trials for at least 6 to 12 months.</p> <p>In a post-publication report by the editors of BMJ (4), a number of issues were raised including the selection and inclusion of studies and the assumptions made by the authors in their meta-analysis. The editors found that although it was a well reported piece of work, the authors' conclusions about funding or prescribing these preparations seemed only indirectly based on their findings and did not add usefully to the article.</p> <p>Finally, it seems appropriate at this time to bring to the attention of the reader, that the meta-analyses conducted by Professor Hochberg (2008 and 2009) (4,5) to assess the efficacy of chondroitin sulphate as a structure-modifying drug for knee OA, the results of which strongly support that chondroitin sulphate is effective for reducing the rate of decline in minimum joint space width in patients with OA of the knee. These results are in accordance with the results obtained by Lee et al (2009) (6) who examined the controlled studies that assessed the effects of long term use of glucosamine sulfate and chondroitin sulphate on joint space narrowing in patients with knee OA. Results showed that daily administration of chondroitin sulphate may delay,</p>	

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		<p>for over 2 years, the radiological progression of knee OA.</p> <p>We hope that the above information is useful in your Update of the 2006 Report on Comparative Effectiveness and Safety of Analgesics for Osteoarthritis. Below you will find the mentioned references, for your information.</p> <p>References</p> <p>(1) Wildi LM; Raynauld JP, Martel-Pelletier J, Beaulieu A, Bessette L, Morin F, Abram F, Dorais M, Pelletier JP. Chondroitin sulfate reduces both cartilage volume loss and bone marrow lesions in knee OA patients starting as early as 6 months after initiation of therapy: a randomized, double-blind, placebo controlled pilot study using MRI. Accepted for publication Annals of the Rheumatic Diseases 2011.</p> <p>(2) Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis BMJ. 2010;341:c4675. doi: 10.1136/bmj.c4675.</p> <p>(3) Pelletier JP, Hochberg MC, du Souich P, Kahan A, Michel BA. Glucosamine and osteoarthritis. Effect size is encouraging. BMJ. 2010 Nov 9;341:c6328. doi: 10.1136/bmj.c6328.</p> <p>(4) Groves T. Report from BMJ post publication review meeting. BMJ (Published 10 January 2011) http://www.bmj.com/content/341/bmj.c4675.long/reply#bmj_el_247719.</p> <p>(5) Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate. Curr Med Res Opin. 2008; 24(11):3029-35.</p> <p>(6) Hochberg MC. Structure-modifying effects of chondroitin sulfate in knee osteoarthritis: an updated meta-analysis of randomized placebo-controlled trials of 2-year duration. Osteoarthritis Cartilage. 2010; Suppl 1:S28-31.</p> <p>(7) Lee YH, Woo JH, Choi SJ, Ji JD, Song GG.</p>	

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		Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. <i>Rheumatol Int.</i> 2010;30 (3):357-63.	
Peer Reviewer #1	General	I believe that the report, while comprehensive, leaves many unknown factors when selecting the right analgesic for the right person. This is not a fault of the review, but the current research to explore each question. The report can only be as comprehensive as the research available. Some of the studies are clearly targeted toward a specific population. The one that stood out as most decisive was the serious GI and CV complications will increase with age. The key questions were focused on the areas that clinicians face every day in making choices for treating OA. They also looked at how to reduce risk of side effects with the NSAIDS. The end results of question four reinforced the need for each patient to be treated based on their medical needs and history.	Noted.
Peer Reviewer #2	General	Overall this is an excellent report. The authors have successfully updated their prior work with literature that includes references to works published in 2010. The questions are clinically relevant and the population to which these results apply is well described. This report will provide useful information to groups that are developing clinical practice recommendations for the management of patients with osteoarthritis.	Noted.

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Peer Reviewer #3	General	<p>I did not find the report that useful. It is a carefully conducted report, but the questions were not that provocative and many of the answers should have been self-evident to experts in the field. I am not sure that this exhaustive piece of work has moved the field forward. However, it is a very nice compendium with an excellent bibliography.</p> <p>My main problems surround the formulation of the key questions. While they are explicitly defined and not inappropriate, they did not ask controversial questions, i.e., the role of opioids, the role of hyaluronic acid and/or steroid injections, the role of weight loss and physical therapy. The comparative benefit questions would have been most interesting if there were data comparing different modes of therapy, i.e., injection vs. oral. The comparative safety questions are the most relevant aspect of this review.</p> <p>One final general comment is that since the last report there has not been a lot of new data about the controversial areas. While updating a report is always useful, this update was of relative minor incremental value.</p>	The interventions discussed by the reviewer are outside the scope of this review.
Peer Reviewer #4	General	<p>Although this was an exhaustive (and exhausting) review, I felt that within the individual sections, the studies and data were not presented in a well-organized and smoothly flowing fashion. Rather it read like a data dump of one study after another without good organization.</p> <p>For example, throughout the document, it would be useful to present data for benefit or harm in ordered manner: e.g., agent vs. placebo/no Rx followed by agent vs. other agents.</p>	See responses to previous comments by this reviewer. The main purpose of this review was to evaluate comparative effectiveness, thus head-to-head comparisons were prioritized.
Peer Reviewer #5	General	<p>Authors should be congratulated on undertaking a comprehensive review that is well-written. Yes, this report addresses important questions. Key questions are clearly stated. Pg.4 line 26: re “osteoarthritis symptoms” – may be helpful to clarify here for the reader what outcomes are being considered ie. Pain and functional status?</p>	The outcomes of interest are described in detail in the Methods (page 35 starting line 36).

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Peer Reviewer #6	General	<p>The report is encyclopedic so realistically a clinician would only examine the summary of evidence, and my comments will focus on that section. It is difficult to avoid bias here, but clearly I don't agree with everything that was chosen to include or not include.</p> <p>The document itself is so long and detailed and heavy on methodology and having read the prior document as well as the constant referral to existing prior syntheses (systematic reviews) its hard to tell how much old vs. new was reevaluated or not. The target population and audience well defined.</p> <p>The key questions are appropriate and explicitly stated.</p>	Noted. Throughout the review, we describe new evidence and highlight its results. E.g., page 46, lines 9-10 and lines 39-42; p 46 lines 51-52 and p 47, lines 5-8.
Peer Reviewer #1	General: Clarity and Usability	<p>I found it very easy to navigate through the report and find the information I needed as I prepared my comments. Each category of analgesics provided a detailed analysis. I liked the way the key questions were laid out on page 80-110. The body of research examined was well organized and provided insight to each study. But I found myself concerned with the conflicting results based on study designs. The new ACTION (Analgesic Clinical Trial Innovations, Opportunities, and Networks Initiative) formed by the FDA might help in providing standardized methods so that all trials can be analyzed equally in the future.</p> <p>I am not certain that the conclusion can be used in policy due to some of the conflicting information. The observational studies (where the general population would fit) are not crystal clear as to outcomes. One example can be found on page 82 line 30-31.</p> <p>The definitions are out of line on page 132-133</p>	Noted. See response to previous comment from this reviewer regarding conflicting studies.
Peer Reviewer #3	General: Clarity and Usability	Yes. It is well structured and clear. I find it easy to navigate through the report.	Noted.
Peer Reviewer #4	General: Clarity and Usability	Not really well structured and organized. Summary of main questions OK, but I'm not sure conclusions readily can be used to inform policy and/or inform practice decisions as the document is written now.	The results of the review are summarized in Table 22 and in the Summary of Evidence for each Key Question.

Source: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=494&pageaction=displayproduct>
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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General: Clarity and Usability	The report is well-structured; laying out the summary of the evidence after each key question with the details of the evidence provided afterwards is helpful for the reader. Table A provides a good overall summary of the evidence; however, as mentioned above, it would be helpful to know the range or median duration of studies on which the evidence is based to better inform clinical decisions.	See response to previous comment by this reviewer regarding the duration of studies.
Peer Reviewer #5	General: Clarity and Usability	The summary of evidence sections after each key question provide information for those needing to make practice decisions. And as the authors point out, knowing the evidence-base is only one factor in the decision-making process as the values that patients and practitioners use on weighing the trade-off between benefit and harm can differ widely.	Noted.
Peer Reviewer #6	General: Clarity and Usability	I think I have answered this above. The summary needs a lot of tightening, as the very dense literature review is unlikely to be used on a regular basis. It does summarize the literature for those trying to sort out policy and reimbursement however.	Noted. Unfortunately, the scope of the review was quite large and we had to summarize evidence for many comparisons and key questions.