Implementing AHRQ Effective Health Care Reviews

Helping Clinicians Make Better Treatment Choices

Analgesics for Osteoarthritis

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EB CME

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The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. A key clinical question based on the AHRQ Effective Health Care Program review is presented, followed by an evidence-based answer and an interpretation that will help guide clinicians in making treatment decisions. For the full review, clinician summary, and consumer summary, go to http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=951.

Key Clinical Issue

What are the comparative effectiveness, benefits, and adverse effects of oral and topical analgesics for osteoarthritis?

Evidence-Based Answer

No differences in efficacy for pain and other symptoms of osteoarthritis have been found in direct comparisons of nonselective, selective, and partially selective nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen is modestly inferior to NSAIDs for pain relief. Among topical formulations, diclofenac is comparable to oral NSAIDs for treating localized osteoarthritis symptoms. Limited evidence from placebo comparisons shows benefits with topical capsaicin, but not with topical salicylates. Pharmaceutical-grade glucosamine also has demonstrated some efficacy against osteoarthritic pain compared with placebo and NSAIDs; however, these findings may not apply to the unregulated products available in the United States, and the evidence is still unresolved.

All NSAIDs have deleterious effects on blood pressure, edema, and kidney function. Risk of cardiovascular adverse effects is increased by nonselective and selective NSAIDs. Gastrointestinal (GI) adverse effects encountered with nonselective NSAIDs are further aggravated by low-dose aspirin and anticoagulants. Selective NSAIDs pose lower risks of GI complications than nonselective NSAIDs, but concomitant use of low-dose aspirin eliminates this benefit. GI adverse effects may be ameliorated with proton pump inhibitors or histamine H_2 antagonists.

None of the analgesics examined have shown greater benefits relative to adverse effects. Trade-offs between benefits and adverse effects differ across analgesics, increasing the need to consider individual patient priorities, age, comorbidities (e.g., preexisting GI bleeding, cardiovascular disease), and concomitant medications (e.g., low-dose aspirin and anticoagulants, prednisone) when choosing among these medications. (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Symptoms of osteoarthritis include pain, stiffness, loss of function, and joint swelling.[1,2] This Agency for Healthcare Research and Quality (AHRQ) review examined the effectiveness and adverse effects of nonopioid oral and topical analgesics for osteoarthritic pain.[3] Selective (e.g., celecoxib [Celebrex]) and nonselective (e.g., ibuprofen) cyclooxygenase-2 inhibitors provide similar pain relief, as do topical NSAIDs. All oral NSAIDS increase the risk of myocardial infarction (relative risk versus placebo ranging from 1.5 for ibuprofen to 1.7 for celecoxib), with the exception of naproxen (Naprosyn).[3] Cardiac risks are greater in older patients, persons with a history of cardiac events, and persons taking higher doses.[3]

One study suggested that NSAIDs cause as many as 3,200 deaths from GI bleeding in the United States per year.[4] Selective NSAIDs decrease the risk of endoscopically detected GI ulcers compared with nonselective NSAIDs (relative risk = 0.23); however, some of these data are taken from manufacturer-sponsored systematic reviews that included unpublished trial data.[5,6] Naproxen causes more GI bleeds than ibuprofen, and all NSAIDs cause more GI adverse effects at higher doses.[3] Simultaneous use of aspirin attenuates the GI benefit of using a selective NSAID.[3] Prescribing NSAIDs with H_2 antagonists, proton pump inhibitors, or misoprostol (Cytotec) decreases the risk of endoscopically detected ulcers.[3]

Clinical Bottom Line: Analgesics for Osteoarthritis

Comparative benefits of NSAIDs

Comparisons among the selective NSAID celecoxib, partially selective NSAIDs (etodolac, meloxicam), and nonselective NSAIDs revealed no differences in efficacy. ●●●

Comparisons among various nonselective NSAIDs exhibit no differences in efficacy for the relief of osteoarthritic symptoms. ●●●

For NSAIDs in general, higher doses increase efficacy for some measures of pain relief. ●●●

Topical diclofenac is similar to oral NSAIDs in efficacy for treating localized osteoarthritis. The risk of GI adverse events is lower with topical diclofenac than with oral NSAIDs, but dermatologic adverse effects (dry skin, rash, itching) are more likely with diclofenac. ●●○

GI adverse effects of NSAIDs

Higher doses of nonselective NSAIDs increase the risk of GI bleeding, but there is no clear association between duration of therapy and the risk of GI bleeding. ●●●

The risk of GI bleeding is higher in persons who had previous bleeding. ●●○

The risk of serious GI adverse effects is higher with naproxen than with ibuprofen. ●●●

The partially selective NSAIDs meloxicam and etodolac are associated with lower risk of ulcer-related complications and symptomatic ulcers than nonselective NSAIDs. ●●○

Concomitant use of nonselective NSAIDs and anticoagulants increases the risk of GI bleeding three- to sixfold over the risk with anticoagulants only. ●●○

Selective NSAIDs as a class are associated with a lower risk of ulcer complications than the nonselective NSAIDs naproxen, ibuprofen, and diclofenac. However, concomitant use of low-dose aspirin eliminates these GI benefits, resulting in risks similar to those of nonselective NSAIDs. ●●●

Concomitant use of low-dose aspirin and nonselective or selective NSAIDs increases the rate of endoscopically detected ulcers by about 6 percent. ●●●

Managing GI adverse effects of NSAIDs

Adding a histamine H_2 antagonist, misoprostol, or PPI reduces the risk of endoscopically detected gastric and duodenal ulcers in patients prescribed a nonselective NSAID. ●●●

- Indirect comparisons suggest that double-dose H_2 antagonists could be more effective than standard dose. ●●●

Adding a high-dose PPI lowers the risk of GI bleeding associated with celecoxib. ●●○

Adding a PPI could reduce the risk of GI adverse effects associated with the use of low-dose aspirin and celecoxib or nonselective NSAIDs. ●●●

In persons with average risk of GI bleeding:

- Misoprostol reduces the risk of ulcer complications associated with nonselective NSAIDs. However, persons could experience other adverse GI symptoms while taking misoprostol. ●●●
- Adding a PPI reduces the risk of endoscopically detected ulcers and ulcer complications associated with celecoxib. ●●●

In persons with increased risk of GI bleeding who were prescribed a nonselective NSAID, PPIs:

- Reduce the risk of endoscopically detected gastric or duodenal ulcers more than H_2 antagonists. ●●●
- Lower the risk of endoscopically detected duodenal ulcers more than misoprostol. Gastric ulcer risks were comparable between these agents. ●●●

continued

NOTE: *This table has been modified from the table that appeared in the original clinician summary.*

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

In the AHRQ review, three trials with a total of 1,248 patients comparing topical diclofenac with oral diclofenac or ibuprofen found no difference between the groups in pain, stiffness, or physical function. The topical diclofenac group experienced significantly fewer GI adverse effects.[3] The AHRQ review also showed that, in two case-control trials and one retrospective study, topical NSAIDs were not associated with an increased risk of bleeding compared with placebo.[3]

Three meta-analyses reviewed by the AHRQ concluded that acetaminophen is modestly inferior to NSAIDs for relieving osteoarthritic pain.[3] Although acetaminophen was associated with fewer GI adverse effects than were nonselective NSAIDs, the risk of any adverse GI event was similar between celecoxib and acetaminophen in two systematic reviews.[3] Large observational studies in the AHRQ review found that patients who reported heavy acetaminophen use (in one study, more than 22 days per month) had a risk of cardiovascular events similar to that of patients taking NSAIDs.[3]

In summary, all oral and topical NSAIDs have similar effectiveness for osteoarthritic

Clinical Bottom Line: Analgesics for Osteoarthritis *(continued)*

Cardiovascular adverse effects of NSAIDs

All NSAIDs have deleterious effects on blood pressure, edema, and kidney function, but no consistent, clinically relevant differences have been found in risks of hypertension, heart failure, or impaired kidney function. ●●○

Celecoxib is associated with an increased risk of cardiovascular adverse effects compared with placebo. ●●○ Higher doses increase the risk, but there is no clear association between the duration of therapy and cardiovascular adverse effect risks. ●●●

Ibuprofen and diclofenac are associated with an increased risk of cardiovascular adverse effects and myocardial infarction, compared with placebo. Naproxen has not been associated with an increased risk of myocardial infarction. ●●○

Other findings on adverse effects of NSAIDs

Higher doses increase the risk of adverse effects in some cases. ●●●

The absolute risk of serious GI and cardiovascular complications increases with age. ●●○

Comparative benefits of NSAIDs and other agents

Acetaminophen:

- Is modestly inferior to NSAIDs in reducing osteoarthritic pain. ●●●
- Poses less risk of GI adverse effects than NSAIDs (●●●), but may cause elevations of liver enzymes at therapeutic doses in healthy persons (●○○ to ●●○).

Glucosamine* and chondroitin:

- No clear difference in effect on pain or function was found between oral NSAIDs and glucosamine (●●●) or chondroitin (●○○).
- A systematic review of higher quality, placebo controlled trials shows that glucosamine has some small benefits for pain. ●●●

Other analgesics

Salsalate and full-dose aspirin have similar efficacy. Comparisons to NSAIDs were unavailable in the included studies. ●○○

Topical capsaicin is effective for treating osteoarthritis compared with placebo, but is associated with increased local adverse effects. (Topical capsaicin has not been compared with NSAIDs.) ●○○

Topical salicylates are not effective for osteoarthritis in placebo comparisons, and are associated with increased local adverse effects. ●○○

Strength of evidence scale

High: ●●● There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.

Moderate: ●●○ Findings are supported, but further research could change the conclusions.

Low: ●○○ There are very few studies, or existing studies are flawed.

Insufficient: ○○○ Research is either unavailable or does not permit estimation of a treatment effect.

**—Most trials showing therapeutic benefits of glucosamine were conducted with pharmaceutical-grade glucosamine not available in the United States; therefore, the findings of these trials may not be applicable to currently available over-the-counter formulations.*

Adapted from the Agency for Healthcare Research and Quality, Effective Health Care Program. Analgesics for osteoarthritis. Clinician summary. http://effectivehealthcare.ahrq.gov/ehc/products/180/951/anal_osteo_clin_fin_to_post.pdf. Accessed October 5, 2012.

pain and, overall, provide better relief than acetaminophen.[3] Family physicians treating patients with osteoarthritis should begin with nonpharmacologic options and take into account drug risks and patient goals before prescribing medication. They should also prescribe the lowest dose and shortest duration of treatment whenever possible.

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