Implementing AHRQ Effective Health Care Reviews

Helping Clinicians Make Better Treatment Choices

Analgesics for Osteoarthritis

Practice Pointers by COREY D. FOGLEMAN, MD, Lancaster General Hospital Residency Program, Lancaster, Pennsylvania

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 H₂ 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.¹² This Agency for Healthcare Research and Quality (AHRQ) review examined the effectiveness and adverse effects of nonopioid oral and topical analgesics for osteoarthritis 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 Six 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 H₂ antagonists, proton pump inhibitors, or misoprostol (Cytotec) decreases the risk of endoscopically detected ulcers.³
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.

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.

Three meta-analyses reviewed by the AHRQ concluded that acetaminophen is modestly inferior to NSAIDs for relieving osteoarthritic pain. 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. 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.

In summary, all oral and topical NSAIDs have similar effectiveness for osteoarthritic pain.
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 osteoarthritis pain. ♂♂♂
• Poses less risk of GI adverse effects than NSAIDs ( mocker), but may cause elevations of liver enzymes at therapeutic doses in healthy persons ( MOCK to ♂♂♂).
Glucosamine* and chondroitin:
• No clear difference in effect on pain or function was found between oral NSAIDs and glucosamine ( mocker) or chondroitin ( MOCK).
• 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. MOCK
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.) MOCK
Topical salicylates are not effective for osteoarthritis in placebo comparisons, and are associated with increased local adverse effects. MOCK

Strength of evidence scale
High: ♂♂♂ There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.
Moderate: ♂ _mock Findings are supported, but further research could change the conclusions.
Low: ♂ Mock There are very few studies, or existing studies are flawed.
Insufficient: MOCK Research is either unavailable or does not permit estimation of a treatment effect.

*p—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.


pain and, overall, provide better relief than acetaminophen. 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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REFERENCES