Analgesics for Osteoarthritis

Focus of Research for Clinicians

As an update to a 2006 report, a systematic review of 273 clinical studies published between January 2005 and January 2011 examined the comparative effectiveness, benefits, and adverse effects of analgesics and the supplements glucosamine and chondroitin for osteoarthritis. The review did not include studies on opioid medications or nonpharmacological interventions for osteoarthritis. The full report, listing all studies, is available at www.effectivehealthcare.ahrq.gov/analgesicsupdate.cfm. This summary, based on the full report of research evidence, is provided to inform discussions with patients of options and to assist in decisionmaking along with a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Osteoarthritis is a chronic condition involving degradation of cartilage within the joints. It is the most common form of arthritis and is more common in older people. It is associated with pain, substantial disability, and reduced quality of life.

Common oral medications for osteoarthritis studied in this review were nonopioid medications, including selective and nonselective nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, salsalate, acetaminophen, over-the-counter dietary supplements (glucosamine and chondroitin), and topical agents (NSAIDs and rubefacients, including capsaicin). The over-the-counter supplements glucosamine and chondroitin have grown in popularity; however, these are not regulated by the United States Food and Drug Administration (FDA).

NSAIDs block cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2. An important role of COX-1 is to mediate the mucosal protection of the gastrointestinal (GI) mucosa, and COX-2 mediates effects on pain and inflammation.

By blocking COX-2 enzymes, NSAIDs decrease pain and inflammation. Nonselective NSAIDs block both COX-1 and COX-2. NSAIDs that block COX-1 can cause GI adverse effects, including bleeding. Selective or partially selective (in vitro) NSAIDs block mostly COX-2 and thus should be safer with regard to GI adverse effects. However, it is unclear if partially selective NSAIDs are truly different from nonselective NSAIDs because COX-2 selectivity may be lost at higher doses. The effects of in vitro COX-2 selectivity on clinical outcomes are uncertain.

Conclusion

When analgesics are compared to each other, none appears to offer greater benefits relative to adverse effects at this time. Trade-offs between benefits and adverse effects appear to differ across analgesics, increasing the need to consider individual patient priorities when choosing among these medications. No significant analgesic differences were found in the benefits offered by NSAIDs; however, differences in GI adverse effects must be balanced with associated cardiovascular (CV) risks. Evidence suggests that age, comorbid conditions, and concomitant medication are key considerations affecting decisionmaking.

The evidence concerning the use of glucosamine and chondroitin appears unresolved and may not directly apply to unregulated products available in the United States. There is evidence that the topical NSAID diclofenac works as effectively as the oral agent.

Clinical Bottom Line

Comparative Effectiveness of Oral Agents
NSAIDs versus NSAIDs
No difference in efficacy in relieving osteoarthritic pain was found between celecoxib, the partially selective NSAIDs meloxicam and etodolac, and nonselective NSAIDs. ●●●
No difference in efficacy was found among various nonselective NSAIDs for the relief of osteoarthritic symptoms. ●●●
NSAIDs versus other agents
Acetaminophen was modestly inferior to NSAIDs in reducing osteoarthritic pain but was associated with less risk of GI adverse effects than were NSAIDs. ●●●
No clear difference was found between glucosamine* and oral NSAIDs for pain or function. Evidence from a systematic review of higher quality trials suggests that glucosamine had some small benefits for pain over placebo. ●●●
No clear difference was found between chondroitin and oral NSAIDs for pain or function. ●○○
Aspirin and salsalate
Salsalate and full-dose aspirin were not compared to NSAIDs but had similar efficacy when compared with each other. ●○○
Comparative Adverse Effects of Oral Agents
GI Effects
Acetaminophen could cause elevations of liver enzymes at therapeutic doses in healthy people. ●●○ to ●○○
Selective NSAIDs as a class were associated with less risk of ulcer complications than were the nonselective NSAIDs naproxen, ibuprofen, and diclofenac. ●●●
The partially selective NSAIDs meloxicam and etodolac were associated with less risk of ulcer-related complications and symptomatic ulcers than were various nonselective NSAIDs. ●●○
A higher risk of serious GI adverse effects was found with naproxen than with ibuprofen. ●●●

*Note: Most trials showing therapeutic benefits from 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 preparations.

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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.

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CV Effects
Celecoxib and the nonselective NSAIDs ibuprofen and diclofenac were associated with an increased risk of CV adverse effects when compared with placebo. ●●○
The nonselective NSAIDs ibuprofen and diclofenac, but not naproxen, were associated with an increased risk of heart attack when compared with placebo. ●●○
All NSAIDs had deleterious effects on blood pressure, edema, and kidney function. There were no consistent clinically relevant differences between celecoxib, partially selective NSAIDs, and nonselective NSAIDs in the risk of hypertension, heart failure, or impaired kidney function. ●●○
Comparing Dosage and Duration of Treatment
Higher doses of NSAIDs were associated with greater efficacy for some measures of pain relief but also with more adverse effects in some cases. ●●●
Higher doses of celecoxib increased the risk of CV adverse effects; however, there was no clear association between the duration of therapy and the risk of CV adverse effects. ●●●
Higher doses of nonselective NSAIDs increased the risk of GI bleeding; however, there was no clear association between the duration of therapy and the risk of GI bleeding. ●●●
Factors Affecting Outcomes
Demographic Subgroups
The absolute risk of serious GI and CV complications increased with age. ●●○
Evidence was insufficient to determine the comparative benefits and adverse effects of different selective and nonselective NSAIDs in men and women or in different racial groups. ○○○
Pre-existing Disease
The risk of GI bleeding with NSAID use was higher for individuals who had previous bleeding than for those who had not. ●●○
Concomitant Medication Use
Concomitant use of low-dose aspirin with celecoxib or a nonselective NSAID increased the rate of endoscopic ulcers by about 6 percent. ●●●
Concomitant use of low-dose aspirin eliminated the GI benefits of selective NSAIDs, resulting in risks similar to those for nonselective NSAIDs. However, adding a PPI could reduce the risk of GI adverse effects associated with the use of either celecoxib or nonselective NSAIDs plus low-dose aspirin. ●●●
Concomitant use of anticoagulants and nonselective NSAIDs increased the risk of GI bleeding three-fold to six-fold when compared with anticoagulant use without NSAIDs. ●●○
Adding an H-2 Antagonist, Misoprostol, or a PPI on GI Adverse Effects Associated With NSAIDs
Adding an H-2 antagonist, misoprostol, or a PPI reduced the risk of endoscopically detected gastric and duodenal ulcers in patients prescribed a nonselective NSAID. ●●●
Misoprostol was the only gastroprotective agent to reduce the risk of ulcer-related complications versus placebo in individuals with average risk of GI bleeding who were prescribed nonselective NSAIDs. However, individuals could experience other adverse GI symptoms while taking misoprostol. ●●●
In individuals with increased risk of GI bleeding who were prescribed a nonselective NSAID, adding a PPI resulted in a reduced risk of endoscopically detected duodenal ulcers when compared with misoprostol or H-2 antagonists, a lower risk of endoscopically detected gastric ulcers when compared with H-2 antagonists, and a similar risk of endoscopically detected gastric ulcers when compared with misoprostol. ●●●
Celecoxib plus a PPI could reduce the risk of endoscopic ulcers and ulcer-related complications when compared to celecoxib alone in individuals at average risk. ●●● Celecoxib plus a high-dose PPI lowered the risk of GI bleeding when compared to celecoxib alone. ●●○
When compared with placebo, double-dose H-2 antagonists could be more effective than standard-dose H-2 antagonists for reducing endoscopically detected gastric and duodenal ulcers. ●●●
Topical Analgesics
Topical diclofenac was similar in efficacy to oral NSAIDs for treating localized osteoarthritis. ●●○
Topical NSAIDs were associated with a lower risk of GI adverse effects but a higher risk of dermatologic adverse effects (dry skin, rash, and itching) when compared to oral NSAIDs. ●●○
Topical salicylates were not effective for patients with osteoarthritis and were associated with increased risk of local adverse effects. Topical salicylates were not compared to NSAIDs. ●○○
Topical capsaicin was effective for treating osteoarthritis but was associated with an increase in local adverse effects. Topical capsaicin was not compared to NSAIDs. ●○○

COX = cyclooxygenase; CV = cardiovascular; GI = gastrointestinal; H-2 antagonist = histamine-2 receptor antagonist; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

Gaps in Knowledge

- Most of the clinical trials reviewed were "efficacy" trials conducted in ideal settings and among selected populations. "Pragmatic" trials that allow flexible dosing or medication switches and other clinical trials of effectiveness would be valuable for learning the outcomes of different analgesic interventions in real-world settings.
- More evidence is needed to assess the comparative CV risks and GI benefits associated with different COX-2 selective NSAIDs.
- The risks associated with selective COX-2 inhibitors need better assessment for the effects of dose and duration.
- More evidence is needed to determine the CV safety of nonselective NSAIDs.
- Evidence is lacking to determine the GI and CV safety of full-dose aspirin, salsalate, or acetaminophen when compared with nonaspirin NSAIDs or placebo.
- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been well studied.
- Most trials showing therapeutic benefits from glucosamine were conducted with pharmaceutical-grade glucosamine not available in the United States. Therefore, the results of these trials may not be applicable to currently available over-the-counter preparations. More evidence is needed comparing currently available over-the-counter preparations with oral NSAIDs, as these over-the-counter preparations are likely to remain available even if the FDA approves a pharmaceutical-grade glucosamine.
- More evidence is needed to evaluate the comparative risks of serious CV and GI adverse effects for oral NSAIDs versus topical NSAIDs.

What To Discuss With Your Patients

- The importance of managing osteoarthritis-related pain and inflammation for improving quality of life and function.
- The potential benefits and adverse effects associated with different types of analgesics based on the characteristics of the individual patient.
- Individual patient values and preferences when considering the trade-offs between benefits and adverse effects of each treatment option.
- Information on symptoms that indicate GI and/or CV adverse effects, and directions for when these symptoms should be reported.

Resource for Patients

Managing Osteoarthritis Pain With Medicines, A Review of the Research for Adults is a free companion to this clinician research summary. It can help patients talk with their health care professionals about the options for treating their osteoarthritis with analgesics. It provides:

- Information about the symptoms of osteoarthritis.
- Descriptions of the different analgesics.
- Simplified summaries of the research on benefits and adverse effects for each analgesic.
- Questions for patients to ask their doctor.

Ordering Information

For electronic copies of *Managing Osteoarthritis Pain With Medicines, A Review of the Research for Adults* (AHRQ Pub. No. 11(12)-EHC076-A), this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/analgesicsupdate.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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