Effective Health Care

*Clinician's Guide*

# Choosing Non-Opioid Analgesics for *Osteoarthritis*

## Confidence Scale

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

**High** ● ● ●
There are consistent results from good quality studies.

**Medium** ● ● ○
Findings are supported, but further research could change the conclusions.

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

The source material for this guide is a systematic review of 351 research publications. The review, *Comparative Effectiveness and Safety of Analgesics for Osteoarthritis* (2006), was prepared by the Oregon Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts.

This guide summarizes clinical evidence on the effectiveness and safety of non-opioid analgesics for osteoarthritis. It covers most available over-the-counter (OTC) medications and prescription non-steroidal anti-inflammatory drugs (NSAIDs). The reviewed drugs are listed on the back page. This guide does not address non-pharmacologic therapies such as diet, exercise, acupuncture, or surgical interventions.

### Clinical Issue

Twenty-one million Americans have osteoarthritis. It is a chronic condition associated with pain and substantial disability. Managing pain can assist in maintaining mobility and improving quality of life. Choosing among the available prescription and over-the-counter medications requires careful consideration of benefits, risks, and cost.

The categories of non-opioid drug treatments for osteoarthritis are:

- Acetaminophen.
- NSAIDs, including aspirin and celecoxib.
- Glucosamine and chondroitin.
- Topical medications (including capsaicin, topical salicylates, and topical NSAIDs).

## Clinical Bottom Line

- Acetaminophen relieves mild pain but is inferior to NSAIDs for reducing moderate or severe pain. Acetaminophen has fewer systemic side effects than NSAIDs.
  Level of confidence: ● ● ●
- All non-aspirin NSAIDs work equally well for pain reduction.
  Level of confidence: ● ● ●
- NSAIDs increase the risk of GI bleeding. The risk increases with higher doses and with age. People older than 75 have the highest risk.
  Level of confidence: ● ● ●
- Celecoxib, high dose ibuprofen, and high dose diclofenac increase the risk of myocardial infarction. Naproxen does not increase the risk of myocardial infarction.
  Level of confidence: ● ● ○
- Capsaicin cream relieves chronic osteoarthritic pain, but about half of the people using it will experience local burning sensations. The burning diminishes over time.
  Level of confidence: ● ● ○
- OTC topical creams containing salicylates do not reduce osteoarthritic pain.
  Level of confidence: ● ● ○

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## Assessing Risk of Complications

### GI Bleeding Risk

The most frequent serious complication is gastrointestinal (GI) bleeding due to gastric irritation. Age is one important factor that affects a person's risk, as shown in the box below.

**Risk of NSAID-Associated GI Bleeding Increases With Age**

**For people age 16-44:**
5 of 10,000 people on NSAIDs will have a serious GI bleed
1 of 10,000 people on NSAIDs will die from a GI bleed

**For people age 45-64:**
15 of 10,000 people on NSAIDs will have a serious GI bleed
2 of 10,000 people on NSAIDs will die from a GI bleed

**For people age 65-74:**
17 of 10,000 people on NSAIDs will have a serious GI bleed
3 of 10,000 people on NSAIDs will die from a GI bleed

**For people age 75 or older:**
91 of 10,000 people on NSAIDs will have a serious GI bleed
15 of 10,000 people on NSAIDs will die from a GI bleed

### Strategies to Lower the Risk of GI Bleeding

- **Avoid NSAIDs for people with a history of GI bleeding.**
  LEVEL OF CONFIDENCE: ● ● ●
- **Avoid NSAIDs for people on anticoagulant therapy.**
  LEVEL OF CONFIDENCE: ● ● ○
- **Consider acetaminophen.** It is associated with a lower risk of GI bleeding than NSAIDs.
  LEVEL OF CONFIDENCE: ● ● ●
- **Consider co-prescribing proton pump inhibitors (PPIs) or misoprostol.** These drugs are effective in reducing GI bleeding for people on NSAIDs. Misoprostol is poorly tolerated by many individuals due to its GI side effects.
  LEVEL OF CONFIDENCE: ● ● ●
- **Consider celecoxib.** Results from short-term trials indicate it has a lower risk of GI bleeding than other NSAIDs. Concomitant use of aspirin (even low dose) reduces or negates the benefit of using celecoxib.
  LEVEL OF CONFIDENCE: ● ● ○

### Cardiovascular Risk

The cardiovascular risk of NSAIDs has received considerable attention. In general, the increased risk of myocardial infarction for any of the NSAIDs other than naproxen is about 30 per 10,000 people taking NSAIDs per year.

- Celecoxib, ibuprofen at high doses (800 mg three times a day), and diclofenac at high doses (75 mg twice a day) have a higher risk of myocardial infarction compared to not taking these medications.
  LEVEL OF CONFIDENCE: ● ● ○
- Naproxen, even at high doses (500 mg twice a day), does not increase the risk of myocardial infarction.
  LEVEL OF CONFIDENCE: ● ● ○
- For other oral NSAIDs, we do not have enough data on cardiovascular risks to make reliable judgments.

### Hepatotoxicity Risk

- Clinically significant hepatotoxicity is rare for all the NSAIDs in this guide.
  LEVEL OF CONFIDENCE: ● ● ●
- Diclofenac is associated with higher rates of aminotransferase elevations (compared to other NSAIDs) but not with a higher incidence of serious liver disease.
  LEVEL OF CONFIDENCE: ● ● ○

### Renal Risk

- All NSAIDs, including COX-2 inhibitors, can cause or aggravate hypertension, congestive heart failure, edema, and kidney problems.
  LEVEL OF CONFIDENCE: ● ● ○
- 5 mm Hg is the average increase in mean blood pressure for nonselective NSAIDs.
  LEVEL OF CONFIDENCE: ● ● ○
- 2 out of 1,000 people stop taking an NSAID because of renal problems.
  LEVEL OF CONFIDENCE: ● ● ○
- Long-term, regular acetaminophen use is associated with a small decrease in renal function in women but not in men. In people without underlying renal disease, this decrease is unlikely to progress to clinically significant renal failure.
  LEVEL OF CONFIDENCE: ● ● ○

## Resource for Patients

*Choosing Pain Medicine for Osteoarthritis: A Guide for Consumers* is a companion to this Clinician's Guide. It can help people talk with their health care professional about pain relief options. It provides information about:

- Types of over-the-counter and prescription pain relievers.
- Benefits, risks, and price of pain relievers.

## For More Information

For electronic copies of the consumer's guide, this clinician's guide, and the full systematic review, visit this Web site:
www.effectivehealthcare.ahrq.gov

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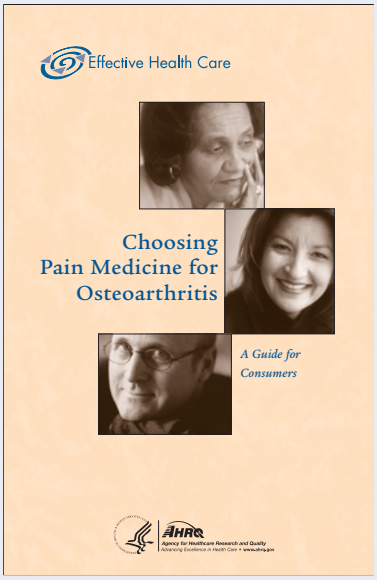


AHRQ created the John M. Eisenberg Center at Oregon Health & Science University to make research useful for clinicians. This guide was prepared by David Hickam, M.D., Roger Chou, M.D., Valerie King, M.D., Theresa Bianco, Pharm.D., Sandra Robinson, M.S.P.H., and Martha Schechtel, R.N., of the Eisenberg Center.

## Alternatives to Oral NSAIDs

- **Consider glucosamine and chondroitin.** Pharmaceutical grade glucosamine hydrochloride (1500 mg a day) plus chondroitin sulfate (1200 mg a day) reduces moderate to severe pain without serious side effects, but this combination has no effect on mild pain. The Food and Drug Administration (FDA) does not regulate these supplements as drugs, so the purity may vary.
  LEVEL OF CONFIDENCE: ● ● ○
- **Consider acetaminophen.** For mild pain, it is an effective alternative to NSAIDs.
  LEVEL OF CONFIDENCE: ● ● ●
- **Consider capsaicin cream.** It relieves chronic osteoarthritic pain, but about half of the people using it will experience local burning sensations. The burning diminishes over time.
  LEVEL OF CONFIDENCE: ● ● ○
- **Consider topical creams containing prescription NSAIDs.** They work as well as oral NSAIDs for osteoarthritic pain relief and have fewer systemic side effects. Topical diclofenac and topical ibuprofen are the best studied topicals. The FDA has not approved any topical NSAID formulations, but compounding is widely available.
  LEVEL OF CONFIDENCE: ● ● ●

## Still Unknown

- There have been few studies comparing aspirin or salsalate to other NSAIDs for the treatment of osteoarthritis.
- We do not have enough data to make reliable judgments about the cardiovascular risks of many oral NSAIDs. The drugs most studied are celecoxib, ibuprofen, diclofenac, and naproxen.
- There is insufficient evidence to assess whether therapeutic doses (up to 4 grams a day) of acetaminophen lead to liver abnormalities in people without underlying liver disease.
- Results from recent observational studies suggest an increased cardiovascular risk with heavy use of acetaminophen, but large, long-term trials of acetaminophen and associated cardiovascular safety are lacking.
- It is not known whether using celecoxib is a better strategy than adding a PPI or misoprostol to a conventional NSAID for lowering the risk of GI bleeding.

## NON-PRESCRIPTION ANALGESICS

| DRUG NAME[1] | BRAND NAMES[2] | STRENGTH | PRICE FOR 100 TABLETS/1 TUBE[3] GENERIC | BRAND |
|---|---|---|---|---|
| Acetaminophen | Tylenol® | 325 mg | $2 | $7 |
| | | 500 mg | $3 | $8 |
| **ORAL NSAIDs** | | | | |
| Aspirin | Bayer®, Ecotrin® | 325 mg | $2 | NA |
| | | 325 mg EC | $2 | $5 |
| Ibuprofen | Advil®, Motrin® | 200 mg | $4 | $10 |
| Naproxen | Aleve® | 220 mg | $7 | $8 |
| **TOPICAL PAIN RELIEVERS** | | | | |
| Capsaicin | Theragen®, Zostrix® | 60-gram tube (.025%) | $8 | $12 |
| | | 60-gram tube (.075%) | NA | $17 |
| **SUPPLEMENTS** | | | | |
| Glucosamine hydrochloride plus chondroitin sulfate | | 500 mg/400 mg tid | $55 | NA |

## PRESCRIPTION NSAIDs

| DRUG NAME[1] | BRAND NAMES | DOSE | PRICE FOR 1-MONTH SUPPLY[3] GENERIC | BRAND |
|---|---|---|---|---|
| **TRADITIONAL NSAIDs** | | | | |
| Diclofenac | Cataflam®, Voltaren® | 75 mg bid | $70 | $160 |
| | | 50 mg tid | $85 | $175 |
| | | 100 mg XR daily | $85 | $160 |
| Etodolac | Lodine® | 400 mg bid | $90 | $110 |
| | | 400 mg tid | $130 | $170 |
| Ibuprofen | Motrin® | 400 mg tid | $20 | $30 |
| | | 800 mg tid | $35 | $45 |
| Indomethacin | Indocin® | 50 mg tid | $65 | NA |
| | | 75 mg SR bid | $130 | $140 |
| Ketoprofen | Oruvail® | 75 mg tid | $95 | $115 |
| | | 200 mg ER daily | $85 | $100 |
| Meloxicam | Mobic® | 7.5 mg daily | NA | $100 |
| | | 15 mg daily | NA | $155 |
| Nabumetone | Relafen® | 1000 mg daily | $85 | $125 |
| | | 1500 mg daily | $100 | $150 |
| Naproxen | Anaprox®, Naprelan®, Naprosyn® | 250 mg tid | $70 | $105 |
| | | 500 mg bid | $80 | $110 |
| | | 500 mg tid | $120 | $165 |
| Piroxicam | Feldene® | 20 mg daily | $75 | $115 |
| **COX-2 INHIBITOR** | | | | |
| Celecoxib | Celebrex® | 100 mg bid | NA | $125 |
| | | 200 mg bid | NA | $200 |
| | | 400 mg bid | NA | $300 |
| **SALICYLATES** | | | | |
| Salsalate | Amigesic®, Salflex® | 750 mg bid | $20 | $30 |

[1]These drugs were evaluated in the systematic review.

[2]OTC brand names were selected based on OTC sales in 2005.

[3] Average Wholesale Price from *Drug Topics Redbook*, 2006.

EC = enteric coated, XR/ER = extended release, SR = sustained release, bid = twice a day, tid = three times a day, NA = not available.

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