



# Which NSAID for your patient with osteoarthritis?

Optimal treatment calls for an assessment of cardiovascular and gastrointestinal risk factors.

## PRACTICE RECOMMENDATION

□ *In selecting an NSAID, assess a patient's baseline cardiovascular (CV) and gastrointestinal (GI) risks and the potential for medication-related incremental CV and GI toxicity.* **(C)**

□ *For patients with increased CV risk (taking aspirin for established CV risk) and low GI risk, the preferred agent is naproxen. Consider adding a proton pump inhibitor (PPI) or misoprostol, as dual therapy with aspirin and naproxen may warrant gastroprotection.* **(A)**

□ *For patients with moderate GI risk and low CV risk, use a nonselective NSAID with a PPI or misoprostol; if GI risk is high, use a cyclooxygenase (COX)-2-selective NSAID and gastroprotection.* **(A)**

### Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

**A**lthough clinicians have considerable experience in using analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve the pain of osteoarthritis (OA), emerging data have made the task of weighing benefits and risks of each agent more complex.<sup>1</sup> In this article, we review the latest evidence for NSAIDs and provide a foundation on which you can make more informed decisions for controlling OA pain and—in conjunction with education, physical therapy, exercise, and cognitive and behavioral approaches<sup>2,3</sup>—improve patients' daily function and quality of life.

## Agents for OA pain relief: Benefits and trade-offs

Treatment options for OA pain are the analgesic acetaminophen and the NSAIDs, comprising both nonselective agents and the cyclooxygenase (COX)-2-selective inhibitors.

NSAIDs inhibit COX, a key enzyme in the biosynthesis of prostanooids, including the prostaglandins and leukotrienes, which are important mediators of pain. The COX-1 isoform is constantly expressed in tissue. It regulates protection of the gastric mucosa, platelet activation, and renal function. In contrast, COX-2 is induced primarily in response to inflammatory stimuli.

■ **The nonselective NSAIDs** inhibit both isoforms of COX. The anti-inflammatory and analgesic effects of the NSAIDs result primarily from COX-2 inhibition. Inhibition of COX-1 is largely responsible for the gastrointestinal (GI) ulceration and anti-platelet-promoted bleeding that can occur with these drugs.<sup>4</sup>

■ **The COX-2-selective inhibitors** were developed to spare the normal "housekeeping" functions of COX-1. This benefit, however, has been diminished by the adverse cardiovascular (CV) events occurring with selective inhibition of COX-2, owing to the expression of this isoform in vasculature and the kidneys.<sup>4</sup> Increased risk of CV events may also occur with nonselective NSAIDs.

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With  
nonselective  
NSAIDs,  
patients should  
start therapy  
at the lowest  
effective OTC  
dose and  
increase as  
needed to  
prescription  
doses.

■ **Acetaminophen's** mechanism of action is poorly understood. It is a weak inhibitor of COX-1 and COX-2, but it most likely acts centrally in the hypothalamus and spinal cord, rather than peripherally in joint cartilage where inflammation and damage occur.<sup>5</sup>

#### Revised treatment guidelines in brief

The American College of Rheumatology (ACR) and the Osteoarthritis Research Society International (OARSI) have published treatment recommendations for OA.<sup>1-3</sup>

The recent ACR publication noted that nonselective NSAIDs are more effective than acetaminophen for treating OA pain, but that the differences are small.<sup>1</sup> Because of costs and the risk of adverse events associated with NSAID use, the ACR guidelines recommend that patients with mild to moderate OA pain receive a trial of acetaminophen initially; patients who do not respond could then receive NSAIDs. With moderate to severe OA pain, initial treatment with nonselective NSAIDs is appropriate.<sup>1,3</sup>

The OARSI guidelines<sup>2</sup> state that “acetaminophen (up to 4 g/d) can be an effective initial oral analgesic for treatment of mild to moderate pain in patients with knee or hip OA.” The guidelines warn, however, that recent evidence has questioned both the efficacy and safety of long-term acetaminophen use in doses up to 4 g/d. The OARSI guidelines, like the ACR guidelines, recommend alternative pharmacotherapy when patients do not respond to acetaminophen for mild to moderate OA pain, or when OA pain is more severe. NSAIDs are most appropriately prescribed at the lowest effective dose for the shortest possible time.<sup>2</sup>

■ **Accounting for risk factors.** Current guidelines emphasize the importance of selecting treatments based on a patient's CV and GI risk profiles. For patients with CV risk factors, use nonselective NSAIDs and COX-2-selective inhibitors with caution. For patients with increased GI risk, use either a COX-2-selective inhibitor or a nonselective NSAID with a proton pump inhibitor (PPI) or misoprostol.<sup>2</sup>

#### The evidence underlying guideline revisions

Selecting an agent that optimally balances efficacy and safety requires that we consider

the complexities of 3 competing clinical concerns—relief of arthritis pain, CV toxicity, and GI toxicity.<sup>6</sup> We review here the evidence supporting the revised recommendations.

#### Acetaminophen: A good option, but there are better ones

Acetaminophen relieves OA pain, but not as effectively as nonselective NSAIDs.<sup>1,3,7</sup> A Cochrane meta-analysis showed that although acetaminophen was superior to placebo for reducing OA pain, it was less effective than either nonselective NSAIDs or COX-2-selective NSAIDs for reducing pain and improving functional status, especially in patients with moderate pain.<sup>7</sup>

Acetaminophen at higher doses has been associated with GI toxicity.<sup>8</sup> In a case-control study, acetaminophen at doses  $\geq 2$  g/d increased the risk of upper GI bleeding or perforation.<sup>9</sup> A cohort study showed that doses of acetaminophen  $>3$  g/d led to higher rates of upper GI events (GI hospitalization, ulcer, and dyspepsia) comparable to those seen with NSAIDs.<sup>10</sup> It remains unclear if the acetaminophen in this trial caused GI adverse events among all patients due to the higher doses alone, or if the rates reflected increases in adverse events expected among high-risk GI patients or concomitant NSAID users.<sup>10</sup> Furthermore, healthy adults who ingested 4 g acetaminophen each day for 2 weeks exhibited significant elevations of serum alanine aminotransferase levels, suggestive of liver injury.<sup>11</sup>

Caution is justified with prolonged use of acetaminophen at high doses, particularly in alcohol users. In cohort studies with women and men, acetaminophen has been associated with an increased risk of incident hypertension.<sup>12,13</sup> In case-control studies, long-term use has also been dose-dependently associated with an increased risk of chronic renal failure.<sup>14,15</sup>

#### Nonselective NSAIDs: Keep GI risks in mind

All nonselective NSAIDs, when administered at equivalent therapeutic doses (same degree of COX inhibition), appear to have comparable efficacy in relieving OA pain. Analgesia is dose dependent, which enables patients to start therapy at lower over-the-

counter (OTC) doses and escalate to higher prescription doses as needed.<sup>3</sup> The OTC dose range of ibuprofen is 200 to 400 mg 3 times a day, to a maximum of 1200 mg/d;<sup>16</sup> the maximum prescription dose is 3200 mg/d.<sup>17</sup> Similarly, the maximum dose of OTC naproxen is 660 mg/d,<sup>18</sup> although by prescription it can be given up to 1500 mg/d.<sup>19</sup>

NSAIDs confer a dose-related risk for GI adverse events, including ulcers and bleeding. Patients with a history of ulcers and those at advanced age are at greater risk;<sup>20</sup> those with a history of an ulcer bleed are at the greatest risk for an adverse event. Also at increased risk are those taking high doses of an NSAID, multiple NSAIDs (eg, concomitant low-dose aspirin), or anticoagulant or antiplatelet agents.<sup>21</sup>

Recent data suggest that nonselective NSAIDs, with the exception of naproxen, may increase CV risk on a level seen with COX-2-selective inhibitors.<sup>22,23</sup> In a meta-analysis of 91 randomized active-controlled trials, a comparison of COX-2-selective inhibitors and non-naproxen nonselective NSAIDs showed no significant difference in the risk of myocardial infarction (MI) (relative risk [RR]=1.20; 95% confidence interval [CI], 0.85–1.68); however, COX-2-selective inhibitors had an increased risk compared with naproxen (RR=2.04; 95% CI, 1.41–2.96).<sup>23</sup> In another meta-analysis of 11 observational studies, naproxen reduced the risk of MI compared with COX-2-selective inhibitors and other nonselective NSAIDs (RR=0.86; 95% CI, 0.75–0.99).<sup>22</sup> An increased risk of incident hypertension has been associated with frequent NSAID use in cohort studies in women and men.<sup>12,13</sup>

### COX-2-selective NSAIDs: Good on gut, but increase MI risk

COX-2-selective NSAIDs lower the incidence of upper GI tract complications compared with nonselective agents, while maintaining comparable efficacy in pain relief, both when used alone (without concomitant aspirin therapy)<sup>20,24,25</sup> and in combination with PPIs.<sup>26,27</sup>

But despite their GI safety profile, the COX-2-selective NSAIDs increased the risk of MI and ischemic cerebrovascular events in trials where they were being studied for ar-

thritis pain and for GI polyp prevention.<sup>22,28,29</sup> Among the proposed mechanisms for this effect is that selective COX-2 inhibition reduces the level of the antithrombotic prostanoid, prostacyclin, relative to the level of the prothrombotic prostanoid, thromboxane, thereby leading to a prothrombotic tendency.<sup>30</sup>

Rofecoxib and valdecoxib were withdrawn from the market in the United States by the manufacturers after the drugs were linked to serious CV adverse effects—and in the case of valdecoxib, to a serious skin reaction.<sup>30</sup> Celecoxib remains commercially available in the United States.<sup>30</sup> The CV risks associated with celecoxib are dose related, with once-daily dosing (400 mg/d) associated with a much lower risk than twice-daily dosing (200 or 400 mg twice a day).<sup>31</sup> The recommended dose is 200 mg/d.<sup>32</sup>

### The deleterious impact of combining low-dose aspirin with NSAIDs

Many patients who take NSAIDs also require aspirin for cardioprotection. Catella-Lawson and colleagues<sup>33</sup> investigated the potential interactions between aspirin and several NSAIDs used in managing OA. They found that ibuprofen, when taken before aspirin, reduced aspirin's inhibition of platelet aggregation, demonstrating potential impairment of aspirin's cardioprotective effect.<sup>33</sup> Subsequent observational studies have supported these *in vitro* findings.<sup>34</sup>

The US Food and Drug Administration (FDA) states that “healthcare professionals should be aware of an interaction between low-dose aspirin (81 mg/d) and ibuprofen, which might render aspirin less effective when used for its antiplatelet cardioprotective effect.” To minimize the interaction, the FDA recommends taking ibuprofen 8 hours before or 30 minutes after the ingestion of immediate-release (not enteric-coated) aspirin.<sup>35</sup> It is not clear if this strategy can circumvent the interaction. For those who depend on aspirin's lifesaving antiplatelet activity, it would seem more prudent to avoid medications known to interact with it.

This interaction, thought to be due to the competitive binding of ibuprofen and aspirin to the COX-1 molecule, has not been clinically demonstrated with other NSAIDs,



**COX-2-selective NSAIDs lower the incidence of upper GI tract complications compared with nonselective agents, while maintaining comparable efficacy in pain relief.**

TABLE

## Choose NSAID options according to CV and GI risks

	None or low risk	Moderate to high NSAID GI risk*
No CV risk (without aspirin)	Any nonselective NSAID (cost consideration)	COX-2-selective inhibitor or any nonselective NSAID + PPI†  COX-2-selective inhibitor + PPI for patients with prior ulcer GI bleeding
CV risk (with aspirin)	Naproxen‡  Add PPI if GI risk of aspirin/NSAID combination warrants gastro-protection	Add PPI regardless of NSAID  COX-2-selective inhibitor + PPI for patients with previous ulcer GI bleeding

COX, cyclooxygenase; CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

\*Age ≥70 years or receiving concomitant corticosteroids or anticoagulants; highest GI risk is a prior ulcer bleed.<sup>45</sup>

†Misoprostol at full dose (200 mcg, 4 times a day) may be substituted for a PPI.

‡If naproxen is ineffective, use a nonselective or COX-2-selective (low-dose) inhibitor without established aspirin interaction—eg, diclofenac or sulindac.

Adapted from: Scheiman JM, et al. *Lancet*. 2007.<sup>41</sup>

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**PPIs are the preferred gastroprotective agent with NSAID use.**

such as diclofenac<sup>33</sup> and naproxen, or with acetaminophen.<sup>36,37</sup>

A small, open-label, crossover study in healthy volunteers showed that both low-dose aspirin and naproxen (500 mg, twice daily) produced persistent and nearly complete suppression of platelet thromboxane production when naproxen was given 2 hours before aspirin or 2 hours after aspirin, suggesting no interference with aspirin's effect.

An additional analysis in the same study examined thromboxane production in ex vivo platelets and showed that naproxen, like aspirin, inhibited thromboxane production in a concentration-dependent fashion, but reversibly, whereas aspirin's effect was irreversible.<sup>38</sup> Lower, nonprescription doses of naproxen 220 mg 2 and 3 times a day resulted in antiplatelet effects similar to the 550 mg twice-daily prescription dose used in a study of healthy volunteers whose blood was tested for inhibition of serum thromboxane as a measure of platelet COX-1 activity and inhibition of platelet aggregation.<sup>39</sup>

The propensity of aspirin cotherapy to increase the risk of NSAID-related GI adverse events is an underappreciated concern. A recent review of low-dose aspirin use em-

phasizes that concomitant NSAID use exacerbates GI bleeding, and low-dose aspirin may significantly offset the reduced GI toxicity of COX-2-selective NSAIDs.<sup>40</sup>

### New recommendations in detail

In choosing an NSAID for a patient with OA, consider the patient's baseline health risks, the potential for incremental medication-related GI and CV risks, and known hypersensitivity reactions or drug intolerance.<sup>41</sup> The following recommendations also take into account the impact of aspirin cotherapy.

The presence of GI risk may necessitate using a PPI or misoprostol with the selected NSAID. Both PPIs and misoprostol decrease the rate of gastroduodenal ulceration in NSAID users. Additionally, misoprostol reduces ulcer complications, and PPIs reduce recurrent ulcer bleeding.<sup>42-44</sup> One drawback with misoprostol is that it is not well tolerated. Thus PPIs, given their once-daily administration and superiority to histamine-2 (H<sub>2</sub>) blockers, are the preferred gastroprotective agent.<sup>42</sup> The TABLE summarizes the following recommendations.<sup>7,41</sup>

■ **Patients with no CV risk (not receiving aspirin) and little or no GI risk.** Any nonselective NSAID would be reasonable initial

therapy for patients with uncomplicated, mild to moderate OA pain.<sup>7,41,45</sup> Acetaminophen at doses of up to 4 g/d is an acceptable alternative, but does not relieve pain as effectively as a nonselective NSAID.<sup>1,3,8</sup> The risk of GI adverse events is very low with short-term use of OTC NSAID doses.<sup>46</sup>

**Patients with no CV risk (not receiving aspirin) but moderate to high GI risk.** For patients with moderate GI risk (eg, age  $\geq 70$  years, receiving concomitant corticosteroids or anticoagulants), a COX-2-selective NSAID or any nonselective NSAID with a gastroprotective agent (PPI) is appropriate. If all else is equal in your clinical assessment, cost favors low OTC dosing with nonselective NSAIDs over more costly COX-2-selective agents.<sup>7,41,45,47</sup> However, for patients with very high GI risk (eg, prior complicated upper GI event or multiple GI risk factors), choose a COX-2-selective NSAID in combination with a PPI for gastroprotection.<sup>7,41,45</sup>

**Patients with no GI risk and increased CV risk (receiving aspirin).** For patients who have an increased CV risk (10-year risk  $\geq 10\%$  according to the Framingham equation for primary prevention; or a history of ischemic heart disease, or cerebrovascular or peripheral vascular disease [secondary prevention]), avoid NSAIDs, with the exception of naproxen.<sup>7,45</sup> Large meta-analyses have shown that naprox-

en is associated with a lower risk of adverse CV events compared with other nonselective NSAIDs and COX-2-selective agents.<sup>22,23</sup> Concomitant treatment with a PPI may be appropriate for patients taking naproxen and aspirin, because the risk of gastric ulcers may be increased with cotherapy.<sup>7,41,45</sup>

**Patients with both CV risk (receiving aspirin) and GI risk.** Gastroprotection is essential for the aspirin-related risk of bleeding, and PPIs reduce this risk.<sup>7,21,41</sup> If an NSAID is required, naproxen in combination with a PPI may be the best choice.<sup>45</sup> If naproxen is ineffective, you may consider another NSAID, but limit your selection to those agents without proven aspirin antagonism, such as the nonselective agents diclofenac and sulindac or low-dose celecoxib.<sup>33,48</sup> Patients with elevated CV risk commonly take aspirin, potentially reducing the gastroprotective benefits of COX-2-selective NSAIDs; prescribe a concomitant PPI.<sup>20</sup>

A low-dose COX-2-selective NSAID with a PPI is an evidence-based recommendation for patients who have both CV and GI risks and who have had a previous GI ulcer bleed. Use the lowest possible dose of a COX-2-selective agent, because lower doses are associated with fewer CV adverse events.<sup>30,31</sup> **JFP**

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