Update of ACR Guidelines for Osteoarthritis: Role of the Coxibs

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Abstract
The American College of Rheumatology (ACR) recently provided an update to the guidelines published in 1995 on the management of osteoarthritis (OA) of the knee and hip. Members of the Ad Hoc Committee on OA Guidelines followed an evidence-based medicine approach to revise the guidelines by reviewing an extensive literature search of the Cochrane and Medline databases and published abstracts, and discussing evidence with expert rheumatologists. The goal of the guidelines is to provide recommendations to control patients' OA pain, improve function and health-related quality of life, and avoid therapeutic toxicity. As in the original guidelines, nonpharmacologic interventions involving patient education and physical measures are recommended following initial diagnosis of OA. The pharmacologic algorithm was updated to include currently available therapeutic agents. Acetaminophen remains first-line therapy because of its cost, efficacy, and safety profiles. Cyclooxygenase-2-selective inhibitors (coxibs) have been included as an alternative to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at risk for upper gastrointestinal adverse events. Tramadol is an available alternative for patients who have a contraindication to coxibs or nonselective NSAIDs or for those who have not responded to previous oral therapy. Intra-articular injections or topical therapy may be used as monotherapy, or as an adjunct to oral analgesia. Surgical treatment of OA remains a last resort for patients who have failed to respond to nonpharmacologic and pharmacologic treatment approaches, and have progressive limitation in their activities of daily living. Several therapies for the prevention or treatment of OA are currently under investigation, including nutritional supplements, such as glucosamine and chondroitin, disease-modifying OA drugs, and devices, such as acupuncture and electromagnetic therapy. It is anticipated that the guidelines for the management of OA will continue to evolve as new therapies become available.

Key Words
American College of Rheumatology, treatment guidelines, osteoarthritis, COX-2 inhibitors

Introduction
The treatment of osteoarthritis (OA) continues to evolve as knowledge of the underlying pathophysiology of the condition improves, and as new therapeutic modalities are
developed and tested in the clinic. In 1995, an ad hoc committee of the American College of Rheumatology (ACR) published guidelines for the treatment of patients with OA of the hip or knee. The goals of the treatment of OA of the hip or knee were pain control, limitation of disability, maintenance of joint mobility, and patient education. The guidelines summarized available knowledge and provided an approach to OA management that emphasized the use of safe and effective therapies, particularly highlighting the value and primary position of nonpharmacologic interventions as a base upon which pharmacologic intervention should be built. Because of the chronic nature of OA, safety was a critical factor in distinguishing among various effective pharmacologic therapies. The previous guidelines for OA management recommended that acetaminophen be added to nonpharmacologic modalities in mildly symptomatic patients. A nonsteroidal anti-inflammatory drug (NSAID) was substituted for acetaminophen in patients who had an inadequate response to therapy, unless contraindicated. NSAIDs were not recommended as first-line therapy because of toxicity concerns, primarily involving the gastrointestinal (GI) tract, but also the kidneys and other organs. For example, studies demonstrated that 20% to 30% of hospitalizations and deaths from peptic ulcer disease in patients older than 65 years of age were caused by NSAIDs. Patients with severe symptoms who failed to respond to nonpharmacologic and pharmacologic treatment approaches, and had progressive limitation in their activities of daily living, were evaluated for surgical intervention. Intra-articular corticosteroid injections were not routinely recommended, but were reserved for early treatment of patients with OA of the knee who had effusion or local inflammation. Topical analgesics (e.g., capsaicin) were shown to be effective, and joint lavage and arthroscopic debridement were recommended for use only in patients with OA of the knee. Opioid analgesics were reserved for acute exacerbations of pain.

The purpose of this article is to review all aspects of the updated guidelines published in 2000 for the management of OA of the hip or knee, with emphasis on the role of the cyclooxygenase-2 inhibitors (coxibs).

**Updating Guidelines for the Treatment of Osteoarthritis**

**Rationale**

During the past 5 years, much additional literature relating to all aspects of OA has been published. Many of the basic mechanisms involved in OA are being targeted for pharmacologic intervention, providing the first real hope for development of agents that will directly affect the disease process. In addition, several new therapies shown to reduce the signs and symptoms of OA (i.e., hyaluronan preparations, tramadol, coxibs) have been approved by the United States Food and Drug Administration (FDA). Furthermore, other studies provided additional support for the benefits of nonpharmacologic interventions. In light of these new data, an updated approach to the management of patients with OA was deemed desirable.

**Approach**

Based on these observations, the ACR reconvened some of the members of the original ad hoc committee to review and update the original guidelines for the treatment of OA of the hip or knee. The committee used an evidence-based medicine approach to revise the guidelines by assembling and evaluating existing data from an extensive review of the Cochrane and Medline databases and published meeting abstracts, and by applying clinical judgment and values of expert rheumatologists. The goal of the revised guidelines is to provide physicians with an approach for controlling patient pain, improving function and health-related quality of life, and avoiding therapeutic toxicity. The committee’s philosophy was not to generate fixed rules for practitioners to follow, but rather to generate a range of choices for clinicians, with the most appropriate choice dictated by patient type and preference, and sound clinical judgment.

**Treatment Approach**

**Nonpharmacologic Treatment**

As in the original guidelines, nonpharmacologic therapy (Table 1) retains its primacy and position as a base upon which other modalities (Table 2) may be added. Considerable new
data have bolstered this approach and have confirmed both efficacy and cost-effectiveness when used appropriately. However, many, if not most, patients with OA will find that nonpharmacologic interventions alone often do not provide sufficient control of symptoms, and do not allow them to function adequately. Hence, pharmacologic treatment is usually an important and essential next step.

**Pharmacologic Treatment**

Acetaminophen has long been considered the drug of first choice in patients with OA who require pharmacologic intervention. The current guidelines continue to support this position, based on the fact that acetaminophen provides effective relief of pain for many patients with OA, and has been demonstrated to be safe in a wide range of populations. However, the guidelines also recognize that several prospective, randomized trials have now convincingly demonstrated that NSAIDs and coxibs provide superior efficacy compared with acetaminophen in patients with OA. In addition, surveys have reported that a greater percentage of patients perceive NSAIDs to be more effective and preferable to acetaminophen. Some available data suggest that patients with more severe pain respond better to NSAIDs than to acetaminophen, and there is a commonly held belief that patients with inflammatory OA (clinically defined by the presence of detectable effusion) may respond better to an anti-inflammatory drug. These latter two groups make up a distinct minority of individuals with OA, but are ones in which consideration of an NSAID or coxib may be warranted as initial pharmacologic therapy.

Coxibs may be utilized in at least three different clinical circumstances for pain relief in patients with OA. First, these agents can be used in patients who have had an inadequate response to nonpharmacologic modalities and to maximum doses of acetaminophen. Second, they can be used as initial therapy in the relatively small group of patients with more severe pain who require a greater magnitude of pain relief than commonly obtained with acetaminophen, or in individuals with pain and signs of inflammation (effusion). Finally, coxibs can be utilized as adjunctive therapy for patients who wish to continue acetaminophen, with the hope that there will be a need for lower doses of the coxib because of the underlying analgesic activity of acetaminophen. Although the efficacy of coxibs in the treatment of OA in individuals who have not received adequate pain relief with either NSAIDs or acetaminophen has been demonstrated, no specific studies have tested the other uses, and additional confirmatory data would be helpful.

Although NSAIDs could also be utilized in these settings, coxibs are the drug of choice in patients at high risk for developing GI toxicity or bleeding. Factors associated with increased risk of GI adverse events (Table 3) have

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**Table 1**

Nonpharmacologic Therapy for Patients with Osteoarthritis (reprinted from Ref. 5, by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient education</td>
<td>Self-management programs (e.g., Arthritis Foundation Self-Management Program)</td>
</tr>
<tr>
<td>Personalized social support through telephone contact</td>
<td></td>
</tr>
<tr>
<td>Aerobic exercise programs</td>
<td></td>
</tr>
<tr>
<td>Physical therapy range-of-motion exercises</td>
<td></td>
</tr>
<tr>
<td>Muscle-strengthening exercises</td>
<td></td>
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<tr>
<td>Assistive devices for ambulation</td>
<td></td>
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<tr>
<td>Patellar taping</td>
<td></td>
</tr>
<tr>
<td>Appropriate footwear</td>
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<tr>
<td>Lateral-wedge insoles (for genu varum)</td>
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</tr>
<tr>
<td>Bracing</td>
<td></td>
</tr>
<tr>
<td>Occupational therapy</td>
<td></td>
</tr>
<tr>
<td>Joint protection and energy conservation</td>
<td></td>
</tr>
<tr>
<td>Assistive devices for activities of daily living</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2**

Pharmacologic Therapy for Patients with Osteoarthritis (Reprinted from Ref. 5, by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

<table>
<thead>
<tr>
<th>Route</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Acetaminophin, Coxibs, Nonselective nonsteroidal anti-inflammatory + nonacetylated salicylate, Other pure analgesics (Tramadol, Opioids)</td>
</tr>
<tr>
<td>Intra-articular</td>
<td>Glucocorticoids, Hyaluronan</td>
</tr>
<tr>
<td>Topical</td>
<td>Capsaicin, Methylsalicylate</td>
</tr>
</tbody>
</table>

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Factors associated with increased risk of GI adverse events (Table 3) have...
been repeatedly identified in epidemiologic, as well as prospective, outcome studies.\(^3,29–31\) Additionally, in several studies, fewer patients experienced GI adverse events with coxibs than with traditional NSAIDs.\(^23–25,27–28\) After lack of efficacy, GI side effects are the primary reason individuals discontinue or switch NSAID medications. Thus, fewer GI side effects should result in better compliance, less switching, and a reduced need for GI comedication or GI procedures. The latter two expectations have been documented in the course of clinical efficacy studies, and ultimately can support a pharmaecoconomic basis for the use of coxibs in a wider range of patients than simply those at very high risk of developing GI bleeds. There are special patient populations in whom standard NSAIDs should not be used, and for whom coxibs represent a potential alternative, such as patients on anticoagulation therapy or during the perioperative period.\(^32–39\) However, additional studies are warranted to evaluate coxibs in these situations.

**Alternatives to Coxibs**

Alternatives to coxibs for the treatment of patients with OA do exist, and the ultimate choice of agent must depend on an overall analysis of benefit, risk, convenience, price, and patient satisfaction. The use of a gastroprotective agent (misoprostol) in combination with an NSAID has been shown to be effective in reducing the rate of serious clinical GI events.\(^40–42\) Proton pump inhibitors or high-dose H\(_2\)-receptor antagonists in combination with an NSAID have been shown to be effective in reducing the formation of endoscopic ulceration.\(^42–45\) Although providing greater safety than with an NSAID alone, the addition of a gastroprotective agent means additional pills, additional costs (which are substantial in the case of proton pump inhibitors), and the potential for additional side effects, particularly with misoprostol. However, the use of a traditional NSAID results in platelet inhibition, limiting the use of these combinations in patients with bleeding diatheses, on anticoagulants, or in the perioperative period. Alternatively, for patients with OA who are already taking gastroprotective agents, perhaps for symptomatic relief of gastroesophageal reflux disease, the addition of a traditional NSAID may be both logical and cost-effective.

Although coxibs have clearly been shown to reduce GI morbidity compared with NSAIDs, it should be kept in mind that these drugs act in a similar manner at the level of the kidney.\(^46–48\) NSAIDs have been known to demonstrate a dose-dependent effect on blood pressure, and are associated with a small, but measurable, increase in the incidence of edema.\(^49–54\) Similar mechanism-based effects have been reported with the use of rofecoxib and celecoxib.\(^46,48\) Because of the known association between use of NSAIDs and exacerbation of congestive heart failure (CHF), use of NSAIDs or coxibs in patients at high risk for developing CHF, or in those with compromised renal function, should be undertaken with caution.\(^55,56\) Tramadol is an alternative for patients with a contraindication (e.g., impaired renal function) to NSAIDs or coxibs, or those who have not received adequate pain relief with previous oral therapy.\(^5\) Patients who experience severe pain despite treatment with tramadol or those who cannot tolerate the side effects may be candidates for traditional opioid therapy.\(^57\) Topical agents and/or intra-articular injection of involved joints may be used as an adjunct to oral analgesia, as monotherapy in patients with a contraindication to NSAIDs or coxibs, or in patients who have experienced adverse events or a lack of clinical efficacy with oral therapy.\(^5\) As in the original guidelines, surgical treatment of OA is reserved for patients with severe OA who have failed to respond to nonpharmacologic and pharmacologic regimens and have progressive limitations in their activities of daily living.

**Table 3**

<table>
<thead>
<tr>
<th>Risk Factors for NSAID-Induced Upper Gastrointestinal Adverse Events (reprinted from Ref. 5, by permission of Wiley-Liss, Inc., a subsidiary of John Wiley &amp; Sons, Inc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
</tr>
<tr>
<td>Comorbid medical conditions</td>
</tr>
<tr>
<td>Concomitant use of anticoagulants or oral glucocorticoids</td>
</tr>
<tr>
<td>History of peptic ulcer disease or upper gastrointestinal bleeding</td>
</tr>
</tbody>
</table>

**NSAID** = nonsteroidal anti-inflammatory drug.

**Investigational Treatments**

As previously mentioned, our understanding of the treatment of OA evolves as knowledge of the underlying pathophysiology of the condition improves and as new therapeutic agents are developed. Many of the basic mechanisms
involved in OA are being targeted for pharmacologic intervention, resulting in the development of treatment modalities that directly affect the disease process. Several therapies currently under investigation for their role in the prevention or treatment of OA include nutritional supplements, such as glucosamine and chondroitin, disease-modifying OA drugs, and devices, such as acupuncture and electromagnetic therapy (Table 4).

**Conclusion**

Coxibs offer an important new alternative to NSAIDs for the treatment of osteoarthritis. In patients in whom acetaminophen and nonpharmacologic interventions do not adequately control pain, coxibs provide a safe and effective therapy that should be considered based on the patient’s medical background, tolerance of both serious and nuisance side effects, and availability of this form of therapy. Data from large outcome studies demonstrate that even in patients at low risk of developing serious gastrointestinal events, coxibs cause fewer ulcers than NSAIDs. There is little doubt that rapid acceptance and widespread use of coxibs will lead to fewer serious GI events, and wider use of effective analgesia, not only in patients with OA but in patients with other pain states as well. It is anticipated that the guidelines for the treatment of OA will continue to evolve as new therapies become available.

### Table 4

**Therapies Under Investigation for Use in Patients with Osteoarthritis**

<table>
<thead>
<tr>
<th>Pharmacologic agents</th>
<th>Devices</th>
<th>Lasers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nutritional supplements</td>
<td>• Acupuncture</td>
<td>• Pulsed electromagnetic fields</td>
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<tr>
<td>—Glucosamine</td>
<td>• Magnets</td>
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<tr>
<td>—Chondroitin sulfate</td>
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<td></td>
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<tr>
<td>—Antioxidants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Disease-modifying osteoarthritis drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>—Matrix metalloproteinase inhibitors</td>
<td></td>
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<tr>
<td>—Growth factors</td>
<td></td>
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<tr>
<td>• Matrix metalloproteinase inhibitors</td>
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</tbody>
</table>

**References**


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