Osteoarthritis is one of the most common forms of arthritis seen by primary care physicians. Most patients with osteoarthritis seek medical attention because of pain, the chief complaint associated with this condition. Discomfort can originate from several anatomic sites, including the synovial membrane, joint capsule, periarticular muscles and ligaments, and periosteum and subchondral bone. In addition, although osteoarthritis is traditionally thought of as a noninflammatory type of arthritis, inflammatory mechanisms can be present. Therefore, management of osteoarthritic pain involves both nonpharmacologic and pharmacologic modes of therapy. Nonpharmacologic approaches include osteopathic manipulative treatment, physical therapy, exercise, use of assistive devices, and weight reduction. Pharmacologic options may be topical, intra-articular, or oral in route of administration and include acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids. Patients often benefit from combinations of therapeutic modalities. Although pain relief is a chief motivator for patients with osteoarthritis to seek medical attention, a secondary benefit of successful treatment is slowing the decrease in patients’ quality of life.

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Pharmacologic Options

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**Topical Treatment Modalities**

Topical treatment modalities include capsaicin, topical lidocaine, and topical nonsteroidal anti-inflammatory drugs (NSAIDs).

- **Capsaicin**—Capsaicin is the compound in chili peppers that burns the mouth; repeated use can induce prolonged hypoguesia. When rubbed on the skin, capsaicin can produce initial burning but subsequent reduced sensitivity. Although capsaicin is potentially useful for management of osteoarthritic pain, controlled studies are difficult to conduct because of the burning caused by the active compound.

- **Topical Lidocaine**—Patches containing lidocaine may also offer adjunctive benefit for patients with knee osteoarthritis. In a 2-week open-label trial sponsored by the manufacturer, the lidocaine patch appeared to have a beneficial effect on pain relief in a population of 20 patients with osteoarthritis of the knee. However, the small size of this study and lack of a control group in the study mean that no firm conclusion could be drawn other than the use of topical lidocaine may be adjunctive therapy at best.

- **Topical NSAIDs**—Administration of NSAID creams in treatment of patients with osteoarthritis of the knee is common outside the United States. A prospective double-blind study of the use of 5% ibuprofen cream in 25 patients with osteoarthritis of the knee evaluated pain relief in these patients after 7 days, compared with patients receiving placebo. At the end of the treatment period, 84%...
of patients treated with ibuprofen cream responded favorably to the therapy, whereas only 40% of those in the group receiving placebo had a favorable response. These results were highly significant (P = .0015). Pain relief as measured by several visual analog scales was also clinically significant in the ibuprofen-treated group compared with the group receiving placebo.

Patients (N = 258) with knee osteoarthritis in a pooled analysis of two randomized, double-blind clinical studies received either two daily applications of topical diclofenac or placebo. The mean decrease in pain intensity was 59% in the diclofenac group and 29% in the placebo group. The seemingly high rate of placebo response in this pooled analysis is not dissimilar to the approximately 35% placebo response rate in most oral NSAID studies. Adverse effects of diclofenac were virtually nonexistent in this analysis. However, with long-term use of diclofenac, local skin irritation and gastrointestinal (GI) upset may occur.

In the United States, topical NSAIDs, which are often prepared by local pharmacists, may offer adjunctive benefits to other modes of therapy for patients with osteoarthritis of the knee.

**Intra-Articular Treatment Modalities**

Medications administered via the intraarticular route include corticosteroids and hyaluronans.

- **Intra-Articular Corticosteroids**—Intra-articular corticosteroids have been used for decades as adjunctive therapy, especially in cases when local inflammation is present as indicated by erythema or synovial effusion. Relief of pain with intra-articular corticosteroids lasts for only a few days, typically not longer than 1 week. The presence of an effusion may help predict a better response to intra-articular corticosteroids; age, obesity, and the degree of radiographic change may be of little value in selecting patients who may benefit from these medications.

- **Intra-Articular Hyaluronans**—Intra-articular hyaluronans have been approved by the US Food and Drug Administration (FDA) since 1997 for relief of osteoarthritic knee pain. Hyaluronans are large glycosaminoglycan molecules that allow synovial fluid in normally functioning joints to behave differently depending on the load (ie, with low joint stress, hyaluronans are highly viscous, but when joint stress increases, hyaluronans become more elastic and absorb energy more efficiently). This flexible functioning is beneficial in an osteoarthritic joint.

When intra-articular hyaluronans are used in clinical practice, improvement of pain symptoms can be expected to occur between 3 and 6 months after administration. In a study of 108 patients with knee osteoarthritis treated with an intra-articular hyaluronan, pain relief was documented in 59 (55%) patients for 1 year after a single course of treatment. Repeated treatment with a second course of intra-articular hyaluronan therapy was useful and not associated with any increase in adverse events. Patient selection is difficult in clinical studies of intra-articular hyaluronans, but this therapeutic option may be most useful in earlier disease when radiographic changes are not severe.

Stitik and colleagues recently assessed 60 patients who received either five weekly intra-articular sodium hyaluronate injections, three weekly intra-articular hyaluronate injections, or a combination of three weekly intra-articular hyaluronate injections and a home exercise program. The group receiving three weekly injections along with a home exercise program had the greatest symptomatic improvement and the fastest onset of pain relief.

Adverse effects of intra-articular hyaluronans are usually related to injection site and pseudoseptic reactions, with effusion, erythema, and pain linked especially to the use of hylan G-F 20. Pseudoseptic reaction often occurs when the hyaluronan compound is injected into a bursa rather than intra-articularly, but this reaction can occur even with the proper intra-articular technique. Treatment of patients who have such an adverse effect may require oral NSAIDs or reaspiration of the knee with injection of corticosteroids.

**Oral Analgesic Treatment Modalities**

- **Acetaminophen, NSAIDs, and Cyclooxygenase Type 2 Inhibitors**—Many oral analgesic medications can be used to reduce osteoarthritic knee pain, beginning with acetaminophen in dosages as great as 1000 mg four times daily. Dosages of acetaminophen greater than 400 mg per day may be associated with hepatotoxicity, though even lower dosages can be problematic in patients who have liver disease or who are taking concomitant medications. Acetaminophen may be the most appropriate initial therapy, but intra-articular corticosteroids and even over-the-counter (OTC) NSAIDs can later be added to the patient’s treatment regimen. If pain persists, prescription-strength NSAIDs or a more specific cyclooxygenase type 2 (COX-2) inhibitor may prove useful.

Although published studies have demonstrated the efficacy of COX-2 inhibitors in relieving pain from osteoarthritis of the knee, rofecoxib and valdecoxib are COX-2 inhibitors that were withdrawn from the US market after reports that they were associated with increased incidence of cardiovascular adverse events. The FDA now requires labeling for all selective COX-2 inhibitors and nonselective NSAIDs, both prescription and OTC, to warn of potential related cardiovascular and GI adverse events.

The FDA has also urged both patients and physicians to strictly adhere to daily dose and duration limits for NSAIDs that were noted in a meta-analysis by Bjordal et al. This meta-analysis examined 23 trials with a total of more than 10,000 patients, concluding that NSAIDs provide short-term pain relief in patients with osteoarthritis of the knee. However, GI bleeding, hypertension, congestive heart failure, and renal failure were observed risks with NSAID use, and these risks increased in frequency in elderly patients.

To mitigate the GI adverse effects of NSAIDs—and to not have to rely solely on COX-2 inhibitors in pharmacologic management of knee osteoarthritis—it may be advisable to use a proton pump inhibitor with a nonselective NSAID.
Nutraceuticals—Another pharmacologic treatment option for many patients with osteoarthritis is the use of OTC nutraceuticals (ie, food items, such as fortified food or dietary supplements, that provide certain health benefits). The nutraceutical most frequently used for osteoarthritis of the knee is glucosamine sulfate, either alone or in combination with chondroitin or other agents. Glucosamine, which is obtained from shrimp exoskeletons, is ubiquitous in animal cells and a component of many macromolecules, such as hyaluronic acid (an important substance in collagen formation). The use of glucosamine sulfate is controversial; it is considered an OTC nutritional supplement in the United States, but it is a prescription drug in Europe.23

Although many studies have examined potential mechanisms of action for glucosamine in osteoarthritis, the exact nature of these mechanisms remains unclear. Rubin et al24 conducted a small clinical trial of a glucosamine preparation in 10 patients with osteoarthritis. After 12 weeks, these patients fared substantially better than a cohort receiving placebo, as measured by a physician global assessment and an osteoarthritis severity index.24 Adverse effects observed by Rubin et al24 conformed to previous literature reports indicating that glucosamine treatment is relatively safe.

Herrero-Beaumont and colleagues25 conducted a clinical trial involving 318 patients who received a 6-month treatment course of glucosamine (1500 mg/d), acetaminophen (3 g/d), or placebo. Substantial improvement in symptoms of knee osteoarthritis was demonstrated in patients receiving glucosamine, compared with patients given placebo.25 Acetaminophen also resulted in a more beneficial response than placebo, though this difference was not statistically significant.25 In patients with moderate to severe knee osteoarthritic pain, research indicates that glucosamine sulfate may be more beneficial than glucosamine hydrochloride, and that chondroitin sulfate may produce an additive beneficial effect.26

In contrast to these favorable reports about glucosamine, other studies have suggested that glucosamine alone,27 or in combination with chondroitin,28 is no more effective than placebo in managing the symptoms of knee osteoarthritis. Although more data are needed, it may be reasonable to pursue a trial course of glucosamine in treatment, especially for patients who are intolerant of other medications. In such cases, glucosamine should be discontinued if no improvement is achieved after 3 months.26

Opioid Analgesics—For patients with chronic osteoarthritis of the knee who have not responded to any of the preceding therapeutic options (or who have had adverse effects that reduce efficacy), opioids may be useful. These powerful analgesic drugs can be used as adjunctive therapy in addition to acetaminophen or NSAIDs. They may also be used as sole analgesics for patients as appropriate (eg, when NSAIDs have caused adverse effects, are poorly tolerated, or are contraindicated).

For patients with chronic pain (ie, pain persisting more than 6 months), long-term use of opioids may not only be effective, but may also actually improve overall quality of life. The World Health Organization and the Joint Commission on Accreditation of Healthcare Organizations classify “pain” as a vital sign for physicians and other healthcare providers to assess when evaluating patients with osteoarthritis and other chronic debilitating conditions.29 Yet, many physicians have concerns about using opioids to manage pain because of the potential for patient abuse of these drugs and the possibility of increased scrutiny by physician licensing boards. Despite such concerns, there clearly are patients with chronic osteoarthritic pain who would benefit from opioid analgesics. Therefore, it is imperative that physicians have a basic understanding of which patients can benefit from opioids, how to match opioid therapy with comparable pain severity, what routes of administration are appropriate, and which opioid-related adverse effects may occur. Physicians also need to understand how addiction (ie, psychological dependence, which is rare with opioid use) differs from physical dependence (which can occur in any patient who takes opioids for more than 1 week).30

The proper dosage and route of administration of opioids varies from case to case. Because physicians tend to look for reproducible tests, scans, or laboratory results to quantitate a patient’s disease burden and to evaluate treatment outcomes, most physicians will be disconcerted by the fact that a patient’s self-report of pain is the most accurate measure for determining the amount of opioid analgesic needed. For most patients, the oral route of opioid administration is easiest and least expensive. However, in many patients with osteoarthritis who take numerous other medications or have esophageal irritation, a transdermal opioid is preferable. Around-the-clock opioid administration is the preferred method for obtaining maximal benefit. Therefore, long-acting opioid oral formulations (eg, morphine or oxycodone controlled-release tablets) or opioid transdermal units are useful.

For short-acting opioid agents to provide continuous pain relief, they must be taken every 4 hours. If these agents are combined with acetaminophen, hepatic toxicity becomes a concern. The preferred alternative may be to use long-acting opioid agents either once or twice daily, or to apply a transdermal opioid system every 3 days.

Sustained-release oxycodone and morphine, and even once-daily morphine, can be effective in osteoarthritis pain relief. These medications improve quality of life for patients with osteoarthritis by providing long-term pain relief. Consequently, patients do not have to worry about scheduling their activities around limited intervals that must be timed to coincide with their need to take short-term opioids.

Fentanyl is a transdermal opioid patch that can be useful for patients with osteoarthritis, though its adhesive may irritate the skin of some patients.31 In July 2005, the FDA issued a public health advisory after reports of patient deaths from overdoses of improperly used fentanyl.31 The FDA advised that fentanyl skin patches should be reserved for patients with severe, chronic pain.31 In fact, these patches are contraindicated for patients with acute pain and for those...
Figure 2. Algorithm for managing osteoarthritic knee pain. COX-2 indicates cyclooxygenase type 2; NSAIDs, nonsteroidal anti-inflammatory drugs. Readers are advised to keep current with US Food and Drug Administration advisories and alerts regarding COX-2 inhibitors and non-selective NSAIDs via documents posted to the FDA Web page at: http://www.fda.gov/cder/drug/infopage/COX2.
All patients placed on long-term opioid therapy should sign a “pain contract” that is placed in their medical record. Many variations of these contracts are in use, but most of them involve patients acknowledging that they will follow these four basic principles:

- receive analgesics from only one office
- keep regular physician appointments
- obtain the appropriate physician-approved quantity of analgesics at every regularly scheduled visit
- understand that their healthcare provider will not tolerate any excuses for “lost” prescriptions

If it is discovered that a patient is obtaining opioids from another physician’s office, the contracting office should refuse to prescribe further opioids to that patient. Such a policy allows office staff to have a nonconfrontational framework from which to deal with difficult patients who may be “doctor shopping”—yet remain responsive to the need for compassionate care of patients who need to manage their osteoarthritis. Thus, physicians need to assess patients’ pain systematically, educate patients and staff to ensure appropriate prescribing, educate patients and families about their responsibilities regarding pain control, and monitor the entire process to ensure that the goal of adequate relief of chronic nonmalignant pain is achieved.

Emkey et al. studied the efficacy of tramadol combined with acetaminophen as additional therapy for 153 patients already receiving a COX-2 inhibitor. They found that daily addition of four tramadol (37.5 mg)-acetaminophen (325 mg) combination tablets decreased reported pain as determined by various self-reported qualitative measures. In addition, the reported incidence of adverse effects with tramadol-acetaminophen tablets was lower than that seen with codeine-acetaminophen compounds.

Figure 2 provides an algorithm for the nonpharmacologic and pharmacologic management of osteoarthritis of the knee.

**Case Presentation**

George, an overweight 68-year-old man, reports gradually worsening bilateral knee pain. The pain is worse after prolonged walking or stair climbing, and rarely, it awakens him at night. He notes that rainy weather exacerbates his symptoms. Rarely, when walking through the mall, he uses a cane. He denies knee swelling, morning stiffness, prior knee injuries, or pain in other joints. He occasionally takes 1000 mg of acetaminophen every 6 to 8 hours, which provides some relief. X-ray films show joint space narrowing and osteophyte formation. He is interested in other treatment options and schedules an appointment to discuss them.

George would like to try a topical agent but was unsure of what options were available, if any. His physician discusses the risks and benefits and tells George that certain patients with osteoarthritis of the knee obtain some relief with capsaicin cream, topical lidocaine, and topical NSAIDs.

George has read on the Internet about the benefit from glucosamine and chondroitin and is interested in trying the supplement; however, he does not know how long to take it to see if it will help his pain. His physician suggests a 3-month trial of the supplement, based on his experience that these supplements are slow in onset when they do offer symptomatic relief of osteoarthritis pain.

George wants to know what other non-surgical options are available in the future if his knee osteoarthritis symptoms worsen. His physician tells George that possible options for treatment include acetaminophen, NSAIDs, opioids, physical therapy, corticosteroid injections, hyaluronate injections, and knee braces. His physician emphasizes that George must also try to lose weight and prescribes quadriiceps strengthening exercises while George weighs his options.

George will likely have periods of short-term improvement with these options, but eventually when the pain is so severe and persistent that it keeps him awake at night, he may require referral to a rheumatologist prior to his ultimate need to see an orthopedic surgeon for possible total knee replacements.

**Comment**

Although nonpharmacologic measures are important in management of osteoarthritis of the knee, most patients require various oral pharmacologic agents either alone or in combination, including acetaminophen, COX-2 inhibitors, NSAIDs, nutraceuticals, and opioids. In addition, transdermal NSAIDs and opioids and intra-articular injections of corticosteroids and hyaluronans are indicated in certain patients with
osteoarthritis of the knee. Physicians must individualize therapy and focus on pain relief for each patient, because data about disease retardation or modification in patients with osteoarthritis are scant and preliminary.

For celecoxib and all nonselective NSAIDs, including OTC NSAIDs, the FDA requires labeling that emphasizes increased patient awareness of potential cardiovascular and GI risks. Physicians should remind patients that it is also essential, as noted on the required labeling, that patients strictly adhere to instructions regarding drug dosage and duration of treatment.

References


Editor’s Note
Physicians are advised to check the full prescribing information for all the medications discussed in this article and keep current with all FDA advisories and warnings.