# Managing Osteoarthritic Knee Pain

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**Osteoarthritis is one of the most common forms of arthritis seen in primary care practice. Pain associated with this condition is the chief complaint of most patients, prompting them to seek medical attention. Pain can originate from the synovial membrane, joint capsule, periarticular muscles and ligaments, and periosteum and subchondral bone, among other sources. 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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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 of pain can be present in this condition. Therefore, management of osteoarthritic pain involves a variety of options. Patients may benefit from a combination of different nonpharmacologic and pharmacologic modes of therapy. A secondary benefit of treatment is slowing the decline in quality of life resulting from osteoarthritic pain.

The present article describes mechanisms by which pain may occur in osteoarthritis, an approach that forms the basis for understanding nonsurgical treatment options available to patients. Because osteoarthritis is such a broad topic, the present article is limited to osteoarthritis of the knee. Although recommended modes of therapy are focused on the knee joint, some treatment recommendations may also apply to osteoarthritis in other regions of the body.

## Mechanisms of Pain in Osteoarthritis

In patients with osteoarthritis, pain is usually localized to joints without associated findings of inflammation, such as fever, fatigue, or other systemic complaints. In osteoarthritis of the knee, however, actual causes of pain are not clear. Because joint cartilage has no nerve supply, surrounding tissues probably contribute to pain. When local anesthetics are injected into the knee, pain is reduced, indicating that nerve endings in the joint capsule and other surrounding tissues are affected.

Although one possible cause of pain in osteoarthritis of the knee could be growth of osteophytes and stretching of adjacent periosteum, other factors potentially contributing to pain include microfractures, synovitis, and increased intraosseous pressure.[1] Another clinical feature often found in osteoarthritis of the knee is that pain is poorly correlated with radiographic findings. Based on personal observations, findings on radiographic films appear to correlate with the patient's age rather than the patient's symptoms.

## Nonpharmacologic Management of Osteoarthritic Knee Pain

Several nonpharmacologic modalities may be used to treat patients with knee osteoarthritis, including osteopathic manipulative treatment (OMT), physical therapy, exercise, and use of braces,

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canes, and crutches. The strengthening of quadriceps muscles improves joint stability and can lessen pain.[2] For patients with varus malalignment, use of neoprene sleeves or valgus braces may reduce pain.[3] Weight loss can also play an important role in relieving discomfort from osteoarthritis. A recent study of 316 patients showed that a combination of exercise and weight loss (mean weight loss, 4.6 kg) in obese individuals with knee osteoarthritis improved physical function and lessened pain more than weight loss alone.[4]

Because of the nebulous nature of knee pain in osteoarthritis and varying success rates with pharmacologic therapy, nontraditional treatment modalities for this condition frequently appear in the medical literature. Baird and Sands[5] conducted a pilot investigation using guided imagery with progressive muscle relaxation in a group of women with osteoarthritis. This guided-image approach has been useful in reducing muscle tension and decreasing pain in other conditions, including fibromyalgia[6] and cancer.[7]

In the small study by Baird and Sands,[5] 18 patients were assigned to active treatment and 10 to control. The active treatment group received guided imagery consisting of verbal discussions to focus patient thoughts on imagined sensations that lead to relaxation. Participants were allowed to select images that they thought were the most relaxing, and they were guided to visualize moving without stiffness or pain in their affected joints.[5] After 12 weeks of intervention, pain was significantly reduced in the patients receiving active treatment ($P<.001$).[5] Advantages to this progressive muscle relaxation approach are that it is safe and can be self-administered. Difficulties with the approach, however, are that it is time-consuming and requires motivated, intelligent patients who will comply with instructions.

Vas et al[8] examined acupuncture as adjunctive therapy for pain relief in 97 patients with osteoarthritis of the knee. Patients received either acupuncture plus diclofenac sodium or sham acupuncture plus diclofenac for 12 weeks. The diclofenac sodium dose for both groups was 50 mg, to be taken every 8 hours; the dose was reduced if symptoms improved. There was a significant ($P<.001$) reduction in pain as measured by several different pain scales after 12 weeks of treatment with acupuncture plus diclofenac, versus diclofenac alone.[8]

Two intriguing investigations evaluated the use of magnetic bracelets[9] and leeches[10] for relieving osteoarthritic knee pain. The ideas behind such studies are that magnets generate magnetic fields that may have therapeutic potential,[9] while leeches produce saliva that may have anti-inflammatory properties.[10] These studies demonstrated, respectively, that magnetic bracelets and leech therapy provided greater symptom relief than placebo.[9,10] However, because it would be easy for patients to tell if strong magnets or leeches were being used, the studies may have had inherent self-fulfilling prophecies.

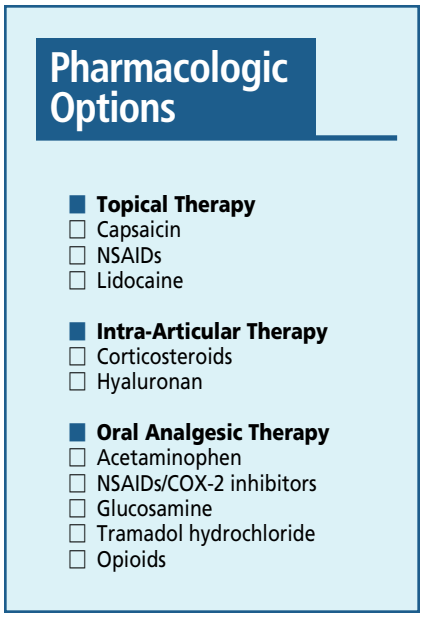


**Figure 1.** *Pharmacolgic agents for osteoarthritic knee pain. NSAIDs indicates nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase type 2.*

## Pharmacologic Management of Osteoarthritic Knee Pain

Pharmacologic treatment options available for pain relief in patients with osteoarthritis of the knee can be categorized into three main groups: topical therapy, intra-articular therapy, and oral analgesic therapy (*Figure 1*).

### *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 hypogeusia. 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.

Mason et al[11] reviewed placebo-controlled trials involving use of capsaicin cream (0.025%) in treatment of patients with musculoskeletal pain. They concluded that capsaicin was statistically more efficacious than placebo, with the relative benefit from topical capsaicin compared with placebo being 1.5 (95% confidence interval [CI], 1.1-2.0; CI lower limit >1.0).[11] However, capsaicin was less efficacious than topical NSAIDs.[11] In general, the role of capsaicin can best be described as adjunctive to more traditional modes of therapy.

**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.[12] However, the small size of this study and lack of a control group in the study[12] 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.[13] 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[13] 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 ($P=.0015$).[13] 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.[14] 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.[14] However, with long-term use of diclofenac, local skin irritation and gastrointestinal (GI) upset may occur.[14]

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 intra-articular 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.[15] Relief of pain with intra-articular corticosteroids lasts for only a few days, typically not longer than 1 week.[15] 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.[16] 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).[17] This flexible functioning is beneficial in an osteoarthritic joint.[17]

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.[18,19] 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.[18] Repeated treatment with a second course of intra-articular hyaluronan therapy was useful and not associated with any increase in adverse events.[18] 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[19] 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.[19]

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 4000 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.[20] 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.[20]

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.[21] 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.[21] 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.[21]

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.[22]

**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 al[24] 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 al[24] conformed to previous literature reports indicating that glucosamine treatment is relatively safe.

Herrero-Beaumont and colleagues[25] 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

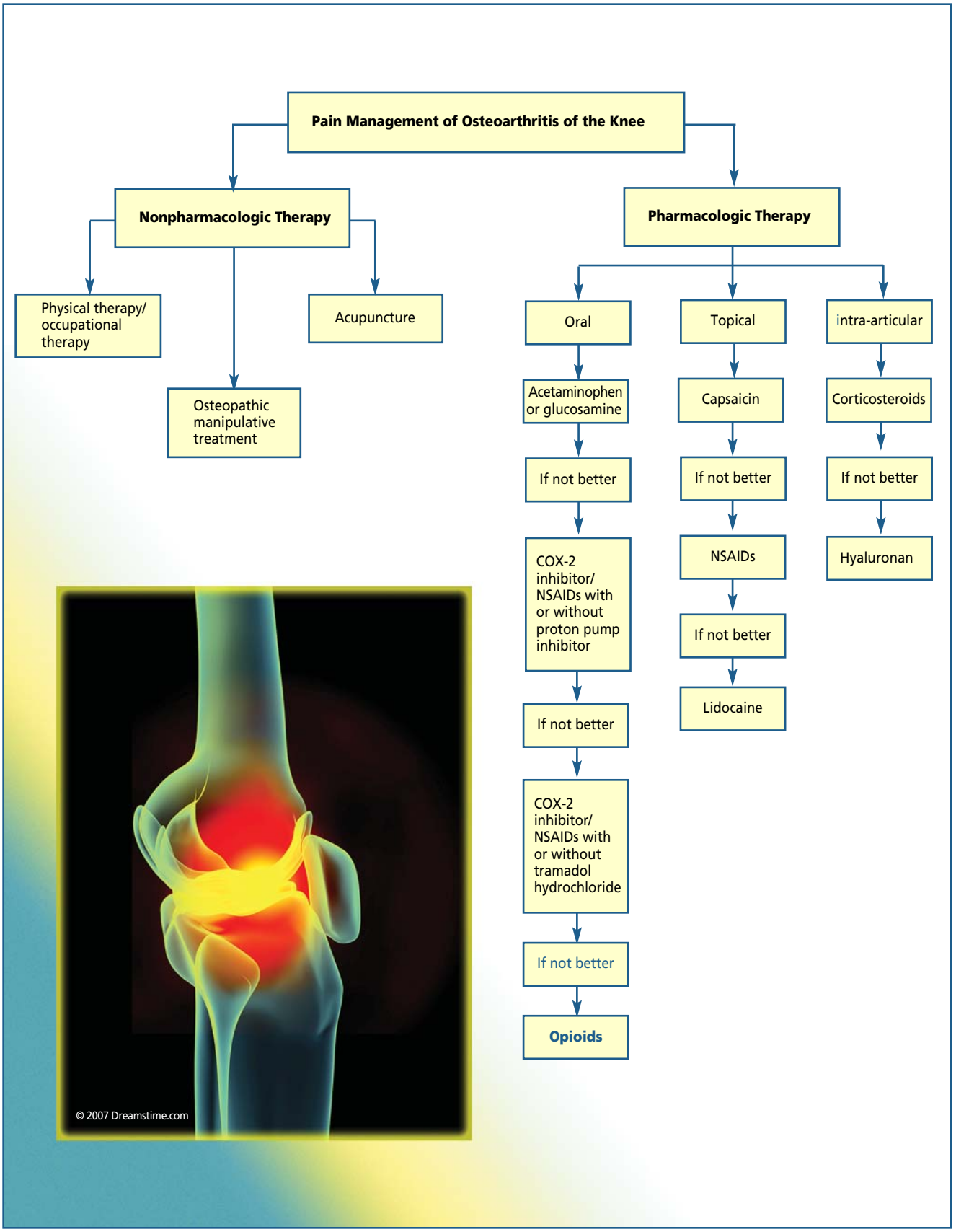


**Figure 2.** *Algorithm for managing osteoarthritic knee pain. COX-2 indicates cyclooxygenase type 2; NSAIDs, nonsteroidal anti-inflammatory drugs. Readers are advised to keep current with US Food and Drug Administration advisories and alerts regarding COX-2 inhibitors and non-selective NSAIDs via documents posted to the FDA Web page at: http://www.fda.gov/cder/drug/infopage/COX2.*

naïve to opioid therapy.[31] Fentanyl patches should not be cut, and patients should avoid simultaneous use of other medications or substances (eg, alcohol) that could affect brain function. In addition, because elevated skin temperatures can increase dermal absorption, heating pads should not be used with fentanyl skin patches.[31]

Breakthrough pain can be easily controlled with short-acting opioids. Because cost is usually a consideration, acetaminophen with codeine and hydrocodone with acetaminophen may be appropriate treatment choices in many cases.

Methadone hydrochloride is highly effective, and its low cost and long half-life have allowed it to become a common alternative opioid for the treatment of patients with osteoarthritis.[32] This powerful opioid is usually prescribed to be taken every 8 to 12 hours.[32] An initial dosage of methadone hydrochloride may be 5 mg twice daily with slow upward titration.[32] One may increase the dose to 10 mg in the morning and 5 mg in the evening for about 30 days and then go to 10 mg twice a day for another 30 days. The titration should be very slow with careful monitoring of pain levels.

It is important to be aware of potential adverse effects, as well as potential drug-drug interactions, for all opioid medications. Adverse effects of opioids include constipation, nausea and vomiting, respiratory depression, sedation, tolerance, and physical dependence. Constipation is so common that physicians should anticipate it and routinely prescribe laxatives to patients. Nausea and vomiting usually occur early in opioid treatment and spontaneously subside after development of tolerance.

The most serious adverse effect of opioids is respiratory depression. Methadone, in particular, is associated with central apnea, typically when the dosage is increased too quickly or when the drug is given too frequently. Concomitant use of ethanol, benzodiazepines, or both has been associated with increased respiratory depression. In addition, impaired cognition may occur early in opioid treatment or when the drug dosage is increased. Less common adverse effects of opioids include weight gain and sexual dysfunction, though the etiology of these effects is unclear.

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 analgesic 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[33] 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.[33]

*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 osteoarthritic pain.*

*George wants to know what other nonsurgical 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 quadriceps 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.

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### 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.