



## Management of Osteoarthritic Knee Pain

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Osteoarthritis (OA) is one of the most common forms of arthritis seen in primary care practice. The 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. Osteoarthritis is traditionally thought of as a noninflammatory type of arthritis; however, inflammatory mechanisms can be present. Therefore, the management of osteoarthritic pain involves nonpharmacologic modes of therapy as well as pharmacologic agents. Nonpharmacologic therapeutic modalities include osteopathic manipulative treatment, physical therapy, exercise, use of assistive devices, and weight reduction. Pharmacologic options, categorized as topical, intra-articular, or oral, include acetaminophen, nonsteroidal anti-inflammatory agents, and cyclooxygenase type 2 inhibitors. Patients often benefit from use of a combination of these therapeutic modalities.

Although pain relief is a chief motivator for patients with OA to seek medical attention, a secondary benefit of successful treatment is to delay the decreased quality of life associated with osteoarthritic pain.

Osteoarthritis (OA) is one of the most common forms of arthritis seen by primary care physicians. Most patients seek medical attention because of the chief complaint of the pain associated with this condition. Discomfort

can originate from several anatomic sites, including the synovial membrane, joint capsule, periarticular muscles and ligaments, and finally the periosteum and subchondral bone. In addition, although OA is traditionally thought of as a noninflammatory type of arthritis, inflammatory mechanisms of pain can be present. Therefore, management of osteoarthritic pain involves a variety of options. Patients may benefit from a combination of various pharmacologic and nonpharmacologic modes of

therapy. A secondary benefit of treatment is to delay the decrease in quality of life that can result from OA pain.

This article describes mechanisms by which pain may occur in OA, an approach that forms the basis for understanding nonsurgical treatment options available to help manage this pain. Because OA is such a broad topic, this article is limited to OA of the knee; though modes of therapy discussed are focused on this joint, some treatment recommendations may apply to OA of other regions of the body, as well.

### Mechanisms of Pain in Osteoarthritis

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

Although one possible cause of pain could be growth of osteophytes and stretching of adjacent periosteum, other possible factors include microfractures, synovitis, and increased intra-osseous pressure.<sup>1</sup> Another clinical feature found in OA of the knee is that pain is often poorly correlated with radiographic findings. Based on personal observations, findings on x-ray 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 OA, including exercise, use of canes and crutches, physical therapy, osteopathic manipulative treatment, and braces. Weight loss can play a role in relieving pain. Every step taken places approximately three times the body weight on each knee; therefore, even a small weight

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reduction can lead to less pain. Because of the nebulous nature of pain in OA of the knee and the imperfect nature of pharmacologic therapy, nontraditional treatment modalities are always appearing in the medical literature.

Baird and Sands<sup>2</sup> conducted a pilot study using guided imagery with progressive muscle relaxation in a group of women with OA. Although guided imagery and relaxation techniques have been useful in decreasing pain in other conditions, including fibromyalgia<sup>3</sup> and cancer,<sup>4</sup> this study (one of a series) used these techniques in patients with OA. In this small investigation, 18 patients were assigned to the treatment group and 10 to the control group. The active treatment group received guided imagery that consisted of verbal discussions to create thoughts to focus patients' attention on imagined sensations that lead to relaxation. Progressive muscle relaxation is often used with guided imagery to help reduce muscle tension. Participants are verbally guided to visualize moving without stiffness or pain in specifically affected joints. Subjects were able to select images that they themselves thought were relaxing. After 12 weeks of intervention, pain was significantly reduced ( $P < .001$ ). The beauty of this technique is that it is safe and can be self-administered. The difficulties are that it is time-consuming and requires motivated, intelligent patients who will comply with instructions.

Vas et al<sup>5</sup> examined acupuncture as adjunctive therapy for pain relief of OA of the knee. Patients received acupuncture plus diclofenac or sham acupuncture plus diclofenac for 12 weeks. The diclofenac 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 drug versus drug alone.

Two even more intriguing investigations looked at use of magnetic bracelets<sup>6</sup> and leeches<sup>7</sup> for relieving osteoarthritic knee pain.

In the first study, the magnetic bracelets were commercially available in the United Kingdom, where the study was conducted. Patients were randomly assigned to one of three groups who used



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

either a commercially available magnetic bracelet with steel backing that creates a fluctuating magnetic field, a weak magnetic bracelet that is accepted to be nontherapeutic, or a nonmagnetic steel washer. Analysis of data showed that pain relief was greatest in the group using the strong, real magnets. This effect was unrelated to whether the patients could determine that they were using a real magnet. The problem with this report and all others that employ a group receiving placebo is that it is easy to tell whether a strong magnet is being used and therefore difficult to compensate for a self-fulfilling prophecy.

In the second research project, short-term leech therapy was compared with topical nonsteroidal anti-inflammatory drug (NSAID) treatment.<sup>7</sup> A single application of leeches gave relief of symptoms within 4 weeks. Leech saliva may contain various anti-inflammatory substances, but the placebo effect could be great because no sham leech therapy exists.

### Pharmacologic Management of Osteoarthritic Knee Pain

Pharmacologic treatment options available for pain relief in OA can be categorized in three separate groups: topical, intra-articular, and oral (Figure 1).

### Topical Treatment Modalities

Topical treatment modalities include capsaicin, NSAIDs, and lidocaine patch.

■ **Capsaicin**—Capsaicin is the compound in chili peppers that burns the mouth, but repeated use induces prolonged hypogeusia. When rubbed on the skin, capsaicin can produce initial burning but subsequent reduced sensitivity. Although it may be useful for the treatment of OA pain, controlled studies are difficult because of the burning seen with the active compound. Mason et al<sup>8</sup> reviewed placebo-controlled trials involving use of capsaicin cream 0.025% in treatment of patients with musculoskeletal pain and found that though capsaicin was statistically better than placebo (relative benefit from topical capsaicin compared with placebo 1.5; 95% confidence interval [CI] 1.1 to 2.0; statistical significance when CI lower limit  $> 1$ ), it was less efficacious than topical NSAIDs. In general, the role of capsaicin would be best described as adjunctive to more traditional modes of therapy.

■ **Topical Lidocaine**—Topical lidocaine patches may also offer adjunctive benefit. A brief open-label 2-week trial, sponsored by the manufacturer, was undertaken.<sup>9</sup> Although there appeared to be benefit with regard to pain relief, the small size of the study and lack of a control group make the use of lidocaine patches adjunctive at best, in my opinion.

■ **Topical NSAIDs**—Administration of NSAID creams in treatment of patients with OA of the knee is common outside the United States. A recent prospective double-blind placebo-controlled study of 5% ibuprofen cream in OA of the knee examined pain relief after 7 days.<sup>10</sup> At the end of the treatment period, 84% of patients treated with ibuprofen cream responded to the therapy, whereas only 40% of those in the group receiving placebo did. These results were highly significant ( $P = .0015$ ). Pain relief as measured by several visual analog scale scores was significant in the ibuprofen-treated group compared with the group receiving placebo.

The seemingly high rate of placebo response at 40% is not dissimilar to the approximately 35% placebo response rate in most oral NSAID studies. Side effects for this brief study were virtually nonex-

istent in either group<sup>10</sup>; however, with long-term use, local skin irritation and gastrointestinal (GI) upset may occur.

In the United States, topical NSAIDs are often compounded by local pharmacists and may offer adjunctive benefits to other modes of therapy.

■ **Local Intra-articular Agents**—Local intra-articular agents primarily include corticosteroids and hyaluronan.

Intra-articular corticosteroids have been used for decades as adjunctive therapy and are useful when local inflammation is present as noted by erythema and synovial effusion.<sup>11</sup> Relief of pain is short term, lasting days and usually not longer than a week. The presence of an effusion may help predict a better response to intra-articular corticosteroids because age, obesity, and the degree of radiographic change may be of little value in selecting patients who may benefit.

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 and in the normal joint have a property that allows synovial fluid to function differently depending on the load; ie, with low stress, hyaluronans are highly viscous, but when joint stress increases, hyaluronans become more elastic and absorb energy more efficiently. This function would be useful in an osteoarthritic joint.<sup>12</sup>

When intra-articular hyaluronans are used in clinical practice, one can expect between 3 months and 6 months of improvement from pain as measured in various ways. In at least one study,<sup>13</sup> pain relief was documented in a substantial proportion of patients for up to 1 year after a single course of treatment. Retreatment with a second course of intra-articular hyaluronan therapy was useful and not associated with any increase in adverse events. Unfortunately, patient selection is difficult, but it seems that this therapeutic option is most useful in earlier disease when radiographic changes are not severe.

The side effects of intra-articular hyaluronans are usually related to injection site and pseudoseptic reactions, with erythema, pain, and effusion particularly

with hylan G-F 20. Often this pseudoseptic reaction occurs when the compound is injected into a bursa rather than intra-articularly, but it can occur even with good technique. Treatment may require oral NSAIDs or reaspiration of the knee with injection of corticosteroids.

### Oral Agents

■ **Acetaminophen, NSAIDs, and Cyclooxygenase Type 2 Inhibitors**—Many oral agents can be used to reduce osteoarthritic knee pain, beginning with acetaminophen in doses up to 1000 mg four times daily. Doses greater than 4000 mg/d may be associated with hepatotoxicity. Although this may be initial therapy, one can easily add intra-articular corticosteroids and even over-the-counter (OTC) NSAIDs to acetaminophen. If pain persists, then prescription-strength NSAIDs or the more specific cyclooxygenase type 2 (COX-2) inhibitors may be useful.

Although studies have been published to show the efficacy of the COX-2 inhibitors in relieving the pain from OA of the knee, recent developments include Merck & Co's voluntary removal of rofecoxib from worldwide markets and the FDA's asking Pfizer to withdraw valdecoxib from the market.

A major concern with both drugs is an increased incidence of cardiovascular adverse events, particularly in an at-risk population. To complicate an already very confusing situation for both physicians and patients, the FDA is requesting labeling changes for all nonselective NSAIDs, both prescription and OTC, to warn of potential cardiovascular and GI adverse events from these medications.

In addition, the FDA has urged both patients and physicians to adhere to dose and duration reminders as noted in a recent meta-analysis. Bjordal et al<sup>14</sup> examined 23 trials with a total of more than 10,000 patients and concluded that NSAIDs provide short-term pain relief in patients with OA of the knee. However, GI bleeding, hypertension, congestive heart failure, and renal failure are real risks and increase in frequency in elderly patients.

To mitigate GI side effects of NSAIDs but not rely simply on the COX-2 inhibitors, it may be preferable to use a

proton pump inhibitor with a nonselective NSAID.<sup>15</sup>

■ **Nutraceuticals**—Another option for many patients is the use of OTC nutraceuticals. The most frequent one used for OA of the knee is glucosamine sulfate either alone or in combination with chondroitin or other agents. This is a controversial issue because in the United States, it is an OTC nutritional supplement, whereas in Europe, it is a prescription drug.<sup>16</sup> Glucosamine, obtained from shrimp exoskeleton, is ubiquitous in animal cells and a component of many macromolecules such as hyaluronic acid (important in collagen formation).

Although many studies have examined potential mechanisms of action for glucosamine in OA, the exact nature of this effect remains unclear. Rubin et al<sup>17</sup> conducted a small clinical trial of a glucosamine preparation. In 12 weeks, the active treatment group fared better than a cohort receiving placebo. Side effects in this study conformed to literature reports indicating that glucosamine treatment is relatively safe. Although not stated in the published report, no side effects were observed in this study.

■ **Opioid Analgesics**—For patients with chronic OA of the knee who have not responded to any of the preceding therapeutic options (or in whom side effects that reduce efficacy have developed), opioids may be useful. These powerful analgesic drugs can be used as adjunctive therapy in addition to acetaminophen or NSAIDs, but certainly they may also be used as sole analgesics for appropriate patients (eg, when NSAIDs have caused adverse events, are poorly tolerated, or perhaps even contraindicated).

For patients with chronic pain (ie, pain present for more than 6 months), long-term use of opioids may be effective and actually improve overall quality of life. Although the World Health Organization and the Joint Commission on Accreditation of Healthcare Organizations have made "pain" another vital sign for physicians and other healthcare providers to assess when evaluating patients with OA and other chronic debilitating conditions,<sup>18</sup> certainly some physicians have fears about the use of these

drugs, the potential for abuse, and scrutiny of their practice patterns by licensing boards. Despite these concerns, however, there clearly are patients with chronic OA pain who will benefit from opioid analgesics.

It is therefore imperative that physicians have a basic understanding of which patients to treat, how to match opioid treatment with comparable pain severity, what routes of administration are appropriate, what opioid side effects may occur, and the difference between addiction—which is psychological dependence that is rare with opioids—and physical dependence, which occurs in any patient who takes opioids for more than a week.

Because physicians tend to look for reproducible “tests,” “scans,” or “lab results” to quantitate a patient’s disease burden and to follow treatment outcomes, most will be disconcerted by the fact that when it comes to pain, the patient’s self-report of pain is the most accurate measure for determining the amount of pain relief needed. For most patients, the oral route of administration is easiest and least expensive. For a substantial number of osteoarthritic patients who take too many other medications or have esophageal irritation, a transdermal opioid is preferable. Clearly, around-the-clock opioid administration is the preferred method for obtaining maximal benefit. Therefore, long-acting opioids—either oral (eg, morphine sulfate or oxycodone hydrochloride controlled-release tablets) or transdermal—are useful.

In contrast, for short-acting agents to provide continuous pain relief, they must be taken every 4 hours; if they are combined with acetaminophen, hepatic toxicity becomes a concern. Therefore, the preferred alternative may be the use of the long-acting agents either once or twice daily, or the use of the transdermal system applied every 3 days.

Sustained-release oxycodone, morphine, and even once-daily morphine are effective. They provide more level analgesia and clearly improve quality of life for osteoarthritic patients by providing long-term analgesia. Consequently, patients have less worry and need to “watch the clock” to schedule

activities around short intervals that must be timed to coincide with their need to take more short-term opioids.

Fentanyl is a transdermal patch that can be useful. The adhesive may irritate the skin in some. In July 2005, the FDA issued an advisory after reports of death from overdoses of fentanyl. The FDA advised that fentanyl skin patches be reserved for severe, chronic pain. In addition, the patches should not be cut, and patients should avoid using other medications or substances (eg, alcohol) that can affect brain function.

Breakthrough pain can be easily controlled with short-acting opioids. Cost is always a consideration; therefore, generic acetaminophen with codeine, hydrocodone with acetaminophen, and methadone hydrochloride play a role, too.

Methadone is highly effective, and its low cost and long half-life have allowed it to become a good alternative opioid for the treatment of patients with OA.<sup>19</sup> Methadone hydrochloride is usually prescribed to be taken every 8 to 12 hours for analgesia; for example, beginning with a low dose of 5 mg twice daily and slowly titrating up.

It is important to be aware of opioid side effects for all these medications, as well as potential drug-drug interactions. Side effects include constipation, nausea and vomiting, sedation, respiratory depression, tolerance, and physical dependence. Constipation is so common that physicians should anticipate it and routinely prescribe laxatives. Nausea and vomiting usually occur early in treatment and spontaneously subside. Impaired cognition also occurs early in treatment or when the dose of drug is increased. The most serious side effect is respiratory depression. Methadone particularly can be associated with central apnea, often when the dose is increased too quickly or if given too frequently. Concomitant use of ethanol or benzodiazepines or both has been associated with increased respiratory depression. Less common side effects include weight gain and sexual dysfunction, but the etiology 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

currently in use, but the basic principles are that patients acknowledge:

- they will receive their analgesics only from one office;
- they will keep regular appointments;
- they will obtain a full month’s quantity of drug at every regularly scheduled visit; and
- their healthcare provider will not tolerate any excuses for “lost” prescriptions.

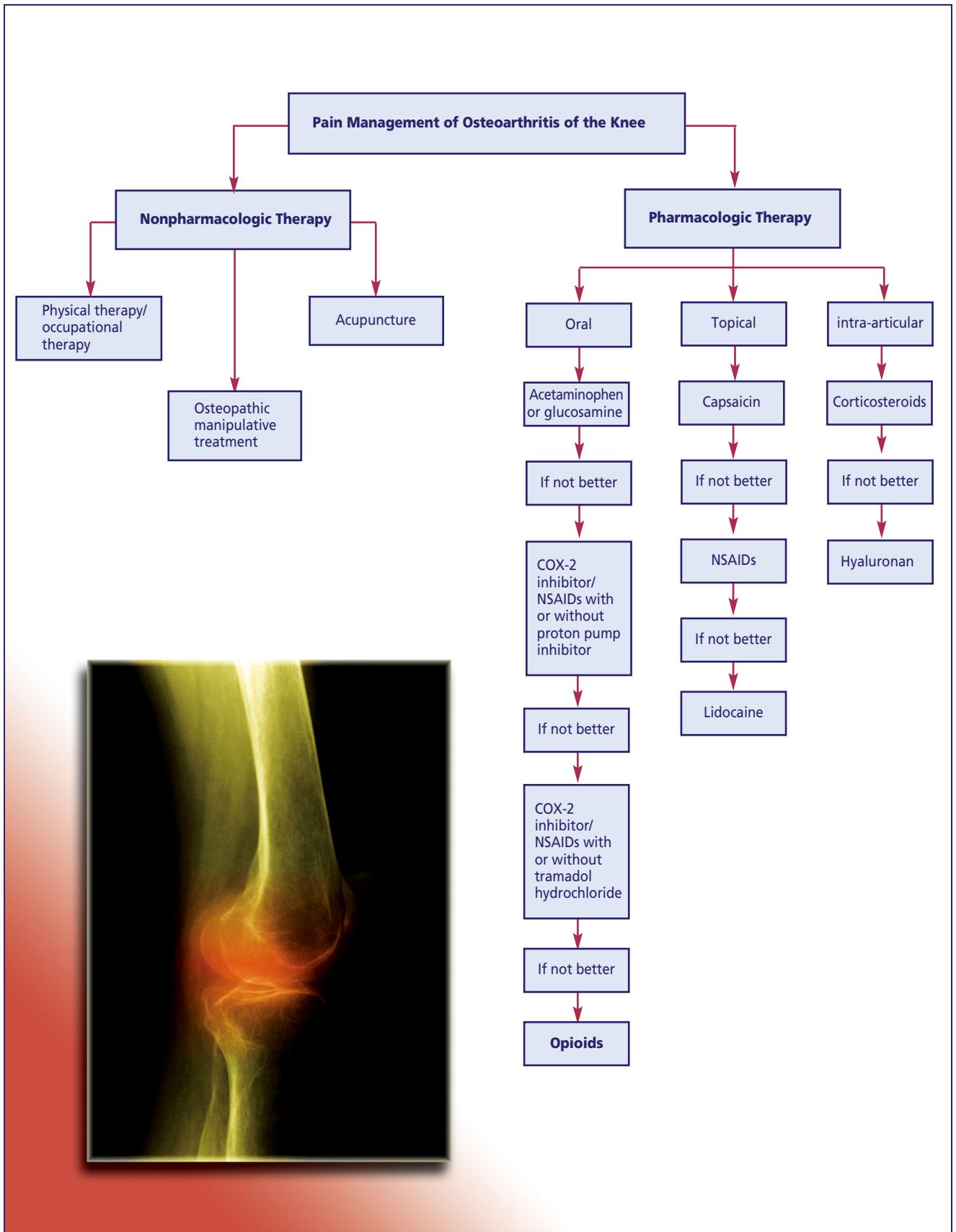
If patients are found to be obtaining opioids from another office, the “contracting” office will refuse to prescribe further opioids. This policy allows office staff to have a nonconfrontational framework from which to deal with these often difficult patients and yet be responsive to the need for compassionate care of osteoarthritic patients. Thus, physicians can assess pain systematically, educate patients and staff to ensure appropriate prescribing, educate both patients and families about the need for pain control and their responsibilities in the process, and monitor the process to ensure that the goal of adequate relief of chronic nonmalignant pain is achieved.

■ **Synthetic Opioid Analgesic**—Tramadol hydrochloride, a synthetic opioid, has a lower addiction potential than other opioid analgesics and has been used both as monotherapy and in combination with NSAIDs for osteoarthritic pain. Emkey et al<sup>20</sup> studied the efficacy of tramadol combined with acetaminophen as additional therapy for patients already receiving a COX-2 inhibitor. They found that on average, a daily addition of four tablets of the tramadol-acetaminophen combination led to a decrease in reported pain as determined by various self-reported qualitative measures. Side effects were modest and their reported incidence lower than that seen with acetaminophen-codeine compounds.<sup>20</sup>

Figure 2 provides an algorithm for management of OA of the knee.

## Comment

Although nonpharmacologic measures are important in the management of OA, most patients require various oral agents either alone or in combination, such as acetaminophen, NSAIDs, COX-2 inhibitors, nutraceuticals, and opioids. In addition, transdermal NSAIDs and opioids plus intra-articular corticoste-



**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 nonselective NSAIDs via documents posted to the FDA Web page at [www.fda.gov/cder/drug/infopage/COX2](http://www.fda.gov/cder/drug/infopage/COX2).

roids or hyaluronans are indicated in certain patients with OA of the knee (Figure 2). Physicians must individualize the treatment program for each patient and focus on pain relief because any data about disease retardation or modification in OA are scant and preliminary.

The FDA is requesting label changes to celecoxib and all nonselective NSAIDs, including OTC NSAIDs. The label change will emphasize an increased awareness of potential cardiovascular and GI risks and remind patients to adhere to instructions regarding dose and duration of treatment

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