

Practical Considerations for the Pharmacologic Management of Osteoarthritis

Roy Davis Altman, MD

Abstract

Pharmacologic treatment options for osteoarthritis (OA) are diverse both in terms of mechanisms of action and delivery formulations; however, no single agent has been demonstrated to consistently offer both a high level of tolerability and a sustained degree of efficacy across a broad OA patient population. Ultimately, a multimodal approach to OA treatment is the best option, offering a greater likelihood of tolerability by avoiding sustained exposure to higher risk agents while improving efficacy by combining agents with more than one mechanism of action. Such an approach should take into consideration the compatibility of different pharmacologic therapies while also taking advantage of nonpharmacologic treatments. Oral nonsteroidal anti-inflammatory drugs (NSAIDs), which are both easily accessible to patients and generally effective for pain relief, are the most popular pharmacologic therapies used in OA; unfortunately, these agents are associated with gastrointestinal and other cardiovascular risks. Combining these agents with other treatments possessing differing side-effect profiles and mechanisms of action will likely reduce the safety and tolerability risk. The recent availability in the United States of a topical NSAID gel with less systemic exposure than oral NSAIDs may offer clinicians an additional means of achieving effective analgesia in OA of superficial joints while minimizing the risk of adverse events.

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For author information and disclosures, see end of text.

Osteoarthritis (OA) is a joint disease characterized by the gradual loss of articular cartilage accompanied by bony remodeling, atrophy of periarticular muscles, and capsular stretching.^{1,2} Synovitis will occur in some OA patients, and is often accompanied by ligament laxity and, ultimately, bone marrow lesions.² There is an enormous variability between patients with regard to patterns of disease progression: many patients will experience remission or a relatively stable disease status while a minority will experience rapid joint deterioration and high levels of pain and loss of quality of life.² The most commonly affected joints are those of the hands, knees, spine, and hips.³

The primary goals of OA treatment are reducing pain and stiffness while avoiding drug toxicity, improving function and quality of life, and limiting disease progression to the greatest extent possible.^{4,6} Therapeutic options available for the treatment of OA include numerous nonpharmacologic (Table) and pharmacologic treatment modalities and the major clinical guidelines for managing OA encourage a combination of both therapeutic approaches.^{4,6} A proposed algorithm for the treatment of OA is reflected in the Figure.

Nonpharmacologic treatment approaches are quite diverse and include educational initiatives, physical exercises, and changes in lifestyle that should ideally be tailored to the specific needs of the patient.⁵ One of the most frequently recommended educational initiatives is the Arthritis Foundation Self-Management Program, which is widely regarded as a valuable and low-cost means of improving function and limiting pain.⁶⁻⁸ Physical exercises commonly applied to OA management include range-of-motion exercises, aerobic exercise, muscle strengthening (eg, quadriceps strengthening for knee OA), and physical therapy.^{4,6-8} Lifestyle changes most commonly consist of weight-loss programs (among overweight patients), as well as the use of devices, such as appropriate footwear, lateral wedged insoles, and canes for individuals with knee or hip OA.^{4,6-8}

This article examines the range of pharmacologic options for the management of OA which, as with nonpharmacologic options, are quite diverse. Available data on oral and topical treatments, including prescription agents and several over-the-counter options, are also reviewed.

Oral Agents for OA

Acetaminophen has anti-inflammatory activity yet acts as an

■ **Table.** Osteoarthritis Research Society International Recommendations for Pharmacologic Treatment of OA⁴

Treatment Type	OA Pain Severity	Timing	Administration Notes	Level of Consensus, %
Acetaminophen	Mild to moderate	Given initially	Up to 4 g/d	77
Oral NSAIDs	All	Given initially. Use with caution in patients with GI or CV risk	Administer at lowest possible dose. Avoid long-term use when possible	100
Topical NSAID	All	Given initially. Use alternatively or adjunctively with oral analgesia		100
Capsaicin	All	Given initially. Use alternatively or adjunctively with oral analgesia		100
Intraarticular corticosteroids	Moderate to severe	Given when oral analgesia and anti-inflammatory treatment has failed	Treatment appropriate when effusions or other signs of inflammation are present	69
Intraarticular hyaluronate	N/A	N/A	Delayed onset but prolonged duration	85
Glucosamine sulfate and/or chondroitin sulfate	N/A	Given for symptomatic knee OA	Lack of response after 6 mo should prompt discontinuation	92
Diacerein	N/A	Given for symptomatic hip OA	Recommended only for knee OA	69
Opioids and narcotic analgesics	<i>Weaker opioids:</i> moderate to severe <i>Stronger opioids:</i> severe	Given when other pharmacologic agents have failed	Strong opioids should only be used in exceptional circumstances	92

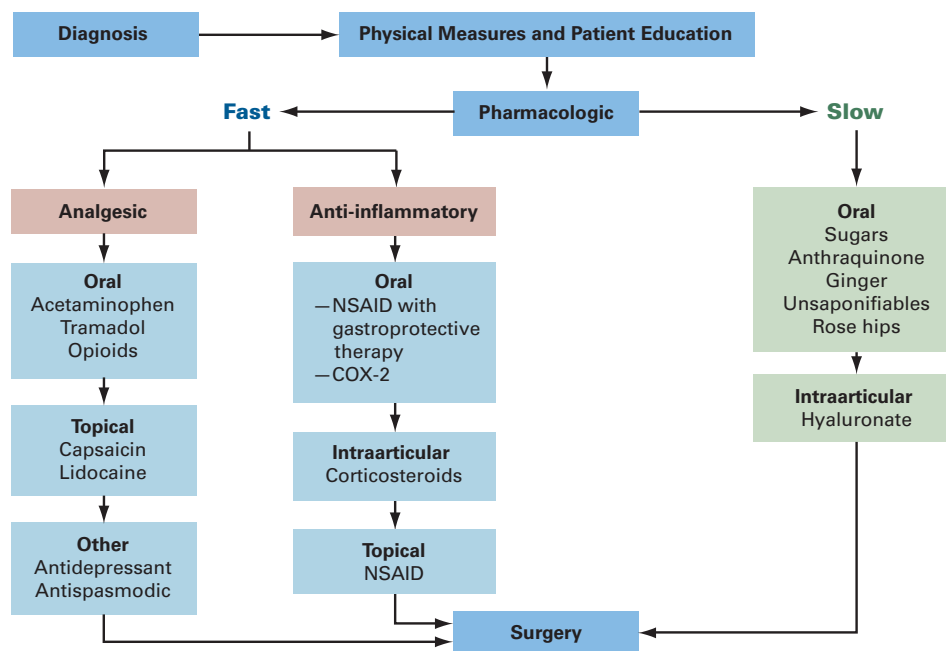
CV indicates cardiovascular; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis.

inhibitor of cyclooxygenase (COX)-1 and -2 in the central nervous system.⁹ Its use for the relief of mild-to-moderate OA pain is recommended by numerous OA clinical guidelines (typically ≤ 4 g/day), including those published by the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and Osteoarthritis Research Society International (OARSI).^{4,6} Whereas the ACR guidelines note that acetaminophen is among the safest oral analgesics, it does confer a degree of risk for hepatic toxicity, although rarely at doses of 4 g/day or less.⁶ It is therefore recommended that acetaminophen be avoided in patients with existing liver disease and those with chronic alcohol abuse. Caution should also be exercised in the use of high-dose acetaminophen because of its capacity to prolong the half-life of warfarin sodium and thereby induce excess anticoagulant effects.⁶ Because of the potential for hepatotoxicity, the US Food and Drug Administration (FDA) has issued a warning on the

use of acetaminophen. Patients need to be aware that many analgesics and “cold remedies” contain acetaminophen. Use of several of these agents at the same time as taking full doses of acetaminophen is potentially hepatotoxic.

A 2006 Cochrane review of acetaminophen in the treatment of OA found that although acetaminophen was significantly superior to placebo for pain relief, the clinical significance of the improvement was dubious.¹⁰ It is also worth noting that the superiority of acetaminophen versus placebo was based on a set of measures including pain response, pain on motion, physician global assessment, modified Health Assessment Questionnaire (HAQ), and patient global assessment; however, significant improvement was not seen for acetaminophen when measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Lequesne index.¹⁰ No significant differences were observed for safety issues among patients

■ **Figure.** Algorithm for Present-Day Therapy of Osteoarthritis^a



^aOnce the diagnosis is confirmed, a nonpharmacologic program is initiated. If not effective, a pharmacologic program is initiated that is most often multimodal in its execution. COX-2 indicates cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

receiving acetaminophen compared with those receiving placebo.

The same Cochrane review analyzed study data comparing acetaminophen to nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, arthrotec, celecoxib, naproxen, diclofenac, and rofecoxib. For pain reduction, NSAIDs demonstrated superiority to acetaminophen in the areas of rest pain, overall pain, and pain measured by both WOMAC and HAQ, but not pain measured by the Lequesne index.¹⁰ In the area of physical function, NSAIDs also demonstrated superiority to acetaminophen on the WOMAC function scale, but not on the HAQ or Lequesne function index nor in the 50-foot walk time test.¹⁰ In terms of safety, patients taking “traditional” NSAIDs—that is, ibuprofen, diclofenac, and naproxen—were twice as likely as those taking acetaminophen to withdraw from studies based on adverse gastrointestinal (GI) events. There was, however, no overall difference in serious adverse events, including serious GI events—such as perforations, peptic ulcers, and GI bleeding—although such events are likely to be very rare in the short-term studies that comprised the subject matter of this Cochrane review.^{4,5,10}

NSAIDs

Oral NSAIDs may be broadly divided between those that are selective for COX-2 inhibition and those that are nonselective, indicating a degree of inhibition of both COX-1 and COX-2.¹¹ NSAIDs, which function both centrally and peripherally, are primarily effective in limiting pain by their capacity to reduce inflammation and nociceptor pain through COX-2 inhibition.¹² Anxiety surrounding the propensity for oral nonselective NSAIDs to cause serious GI events has led major guidelines to recommend that nonselective NSAIDs be prescribed along with gastroprotective agents such as a proton pump inhibitor or misoprostol when being given to patients with elevated GI risk.^{4,6} Oral NSAIDs have also been seen to possess renal risk as well as a risk of potential central nervous system adverse events and allergic reactions.¹³ The OARSI guidelines specifically recommend use of these agents at the lowest dose possible and to avoid long-term use when possible.⁴ It should also be noted that risk of adverse events increases when NSAIDs are combined.⁷

The desire to avoid GI side effects associated with nonselective NSAIDs was a key motivation

for the development of NSAIDs that were selective for COX-2, and it is this considerably reduced GI risk that has made the COX-2 inhibitors a treatment choice commonly recommended by OA clinical guidelines.^{4,6,14} However, extensive use of COX-2 inhibitors, after their initial introduction, revealed them to confer potentially substantial cardiovascular (CV) risk.¹⁵ Indeed, 2 widely distributed COX-2 inhibitors, rofecoxib and valdecoxib, were withdrawn from the market as a result of elevated CV risk.¹³

In terms of analgesic efficacy, COX-2 inhibitors appear to be roughly equivalent to nonselective NSAIDs based on a systematic review of randomized controlled trials.¹³ The review also found a greater rate of CV events for COX-2 inhibitors compared with nonselective NSAIDs, although it should be noted that data regarding CV risk for nonselective NSAIDs are very limited.¹³ Among COX-2 inhibitors, the greatest quantity of evidence for CV risk was seen with COX-2 agents having the greatest degree of patient exposure.¹³ At present, all NSAIDs, other than aspirin, both selective and nonselective, carry the same black box warning for CV risk.

Opioids and Related Analgesics

The opioid class of drugs constitutes a diverse grouping with various degrees of efficacy and adverse-event risks. Most opioids, morphine being the primary example, function mainly through mu receptor inhibition.¹⁶ Opioids appear to be more effective with neurogenic rather than nociceptive pain.¹⁷ The use of opioids in treating OA pain is typically limited, a caution borne of anxieties about side effects and the risk of dependency, but they are recommended when other pain treatments have proved ineffective.^{4,6} Clinical treatment guidelines state a preference for weaker opioids, such as codeine (often in combination with acetaminophen) or the synthetic opioid tramadol. To date, no long-term trials of opioids for the treatment of OA have been conducted.⁴ Shorter term data, however, suggest that opioids are effective for OA pain although they are associated with side effects that result in a high rate of discontinuation.¹⁸

Tramadol, regarded by many as a lower risk alternative to true opioids, is a centrally acting weak mu inhibitor that also inhibits uptake of

serotonin and norepinephrine, giving it opioid and nonopioid dual action.^{6,16} A Cochrane review of tramadol for OA pain found that while patients benefited from treatment, the benefits were relatively minimal.¹⁹ At the same time, as with standard opioids, tramadol adverse events lead to a high rate of discontinuation and, among other side effects, tramadol is associated with risk of seizures.^{16,19} Slow titration of tramadol will generally improve patient tolerance.

Among other analgesics, propoxyphene is not recommended because of its relatively weak efficacy compared to other narcotic derivatives as well as its side-effect profile, particularly in elderly patients.^{20,21} Recent clinical trials (single-blind, placebo-controlled, 10 weeks in duration) of 2 selective norepinephrine-serotonin reuptake inhibitors for OA pain—venlafaxine XR and duloxetine—observed mixed results, with some degree of pain relief occurring with both drugs.^{22,23}

Topical Agents for OA

The primary rationale for applying a topical agent for pain management in OA is based on the notion that the potentially severe side effects associated with systemic oral agents may be avoided in a topical agent with limited risk of systemic exposure. Other potential advantages include the fact that analgesia may be applied to superficial joints in a targeted fashion. Moreover, to the extent that a topical agent may be associated with fewer side effects than an oral agent, this allows for more flexible dosing. Topical agents that have been used to treat OA pain include NSAID solutions, salicylates, and capsaicin.

Salicylates

Although widely available and used for the treatment of joint disease pain, salicylates are limited by variable and frequently poor absorption into the skin.²⁴ This may explain why clinical trial data do not support the efficacy of these agents for pain relief in OA.^{25,26}

Capsaicin

The analgesic effect of capsaicin arises from its ability to irritate the nerve endings, causing depletion of nociceptor pain transmitters such as substance P.²⁷ Consequently, application of capsaicin, which is derived from chili peppers, is associ-

ated with a burning sensation for several days upon starting application.²⁸ Data supporting the utility of capsaicin for OA pain are mixed. Significant pain improvement of capsaicin compared with placebo was seen in 1 small clinical trial in patients with hand OA.²⁹ Two other small trials did not show significant improvement.²⁸ A larger study that included patients with hip, knee, and shoulder OA found a significant improvement in pain scores when capsaicin was combined with glyceryl trinitrate.³⁰ The EULAR, OARSI, and ACR guidelines all recommend the use of capsaicin.^{4,6}

Topical NSAIDs

At present, 1 topical NSAID, diclofenac sodium gel (DSG), has been approved by the FDA for treatment of OA pain.³¹ Similar to oral NSAIDs, DSG functions by inhibiting COX; however, while DSG functions through peripheral action, its systemic exposure is approximately 17 times lower than that of oral administration, and average peak plasma is 158 times lower than an oral agent.³¹

Several topical NSAIDs have long been used in Europe for OA pain. Both the EULAR and OARSI guidelines recommend the use of topical NSAIDs for pain management for hand and knee OA.^{4,5} Use of a topical NSAID for OA pain was not included in either the American Pain Society or ACR OA treatment guidelines because both were published well before the FDA approved DSG. Earlier studies of topical NSAIDs for OA pain, conducted prior to FDA approval of DSG, had suggested that pain relief might only persist for approximately 2 weeks³²; however, numerous subsequent studies have demonstrated a more enduring effect, which is likely a result of different formulations providing greater bioavailability.^{31,33-36}

The first of 2 pivotal studies for DSG was a 12-week, multicenter, double-blind, parallel-group trial in which 4 mg of DSG was applied 4 times daily for treatment of knee OA.³¹ Significant improvement versus placebo for pain based on WOMAC scores was seen in the DSG group during the course of 12 weeks. The second pivotal 8-week trial similarly showed significant WOMAC score improvement for pain at weeks 4 and 6 for topical DSG versus placebo.³¹

Topical NSAIDs, similar to other NSAIDs, do involve the risk of side effects associated with

NSAIDs, particularly in the area of GI events. It has been hypothesized, however, that a topical NSAID would confer a low risk of adverse events. That hypothesis has been supported by data from a variety of studies with topical diclofenac for OA pain. In the 2 pivotal studies described above, the most common side effects were reactions at the application site, mainly dermatitis, which occurred in 4% of study subjects³¹; GI side effects were not observed in either the 12- or 8-week studies. A long-term, open-label study of DSG observed similar rates of side effects. These data are consistent with other studies of topical diclofenac for OA pain.³³⁻³⁶

Injectable Agents

Intraarticular Corticosteroids

Intraarticular corticosteroids (IACs) have a long history in the treatment of OA pain, their efficacy being primarily a function of their anti-inflammatory effects.³⁷ These agents are generally recommended in clinical guidelines for moderate-to-severe pain when oral and/or other anti-inflammatory agents have failed.^{4,6} The guidelines are not in agreement, however, whether corticosteroid use should be limited to patients with physical signs of inflammation and/or effusion.^{4,6} A Cochrane review of IAC treatment for OA of the knee found benefit and limited side effects with short-term use.³⁸ Limited data are available for long-term use of IACs in OA; however, there are data from a 2-year placebo-controlled trial of triamcinolone acetonide injections in patients with knee OA showing relief of night pain and stiffness and no significant safety issues.³⁹ However, corticosteroid use in general is associated with risk for a variety of side effects, and injection of corticosteroids more than 4 times per year is not recommended.⁴ Systemic administration of corticosteroids in OA should be avoided.

Hyaluronates

Intraarticular hyaluronate (IAH) (sometimes called viscosupplementation) involves injections of hyaluronic acid into OA-affected joints. Compared with corticosteroid injections, IAH is associated with a delay in efficacy but of prolonged duration.⁴ IAH is included as a recommended treatment by ACR and OARSI clinical guidelines.^{4,6}

There are currently 5 different hyaluronic acid products approved by the FDA for knee pain,

requiring 3 to 5 weekly injections, as well as a recently approved formulation of one of these treatments—hylan G-F 20—as a single injection.^{40,41} The data supporting pain alleviation from viscosupplementation is somewhat conflicting.⁴²⁻⁴⁵ A 2005 meta-analysis of 22 trials of IAH injections for OA of the knee found that, although pain was reduced, it was not a clinically meaningful reduction.⁴⁶ Side effects were more common in patients receiving IAH, but these were minor and local in nature.⁴⁶ A 2006 Cochrane review of 76 trials, in contrast, found significant benefit from IAH injections in knee OA, with some local side effects but no meaningful systemic effects.⁴⁷ A 2008 review of IAH in knee OA concluded that IAH has demonstrated efficacy in terms of improved pain and function scores for up to 1 year, and that treatment was associated with minimal side effects.⁴⁸ A systematic review of IAH in hip OA arrived at a somewhat ambiguous conclusion, with most studies reviewed showing a 40% to 50% rate of pain relief, but with a duration of effect not clearly identified; reports of adverse events were few.⁴⁹ There are a limited number of publications demonstrating the benefit of IAH in other joints, such as the shoulder, ankle, base of the thumb (first carpometacarpal joint), and bunion (first tarsometatarsal joint).

Conclusions

Clinicians currently treating OA have a large and diverse set of therapeutic options from which to choose, including pharmacologic agents with differing means of delivery and mechanisms of action, as well as a spectrum of nonpharmacologic approaches. Unfortunately, no single treatment approach is entirely satisfactory. The number and variations in treatment options, however, offer the clinician excellent opportunities to combine treatments—to take a multimodal approach—to maximize benefits and minimize treatment risks, particularly with regard to toxicities associated with a number of pharmacologic agents.⁵⁰ The popularity of oral NSAIDs, combined with their propensity to produce adverse events, has made these drugs a particular cause for concern, particularly when used long term and as monotherapy. The availability of a topical NSAID with limited systemic effects provides an additional option for those patients for whom oral NSAIDs are contraindicated, such

as those who have experienced tolerability issues, elderly patients, and those at an elevated risk for GI toxicity.⁵¹

Author Affiliation: From the Division of Rheumatology and Immunology, University of California, Los Angeles.

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Address correspondence to: Roy Altman, MD, 9854 W. Bald Mountain Ct, Agua Dulce, CA 91390. E-mail: journals@royaltman.com

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