Chapter 110: Osteoarthritis

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 2, Osteoarthritis.

KEY CONCEPTS

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1. Osteoarthritis (OA) is a common disease. OA prevalence increases with age and number of other chronic conditions, with women more commonly affected than men.
2. Contributors to OA are systemic (age, genetics, hormonal status, obesity, occupational or recreational activity) and/or local (injury, overloading of joints, muscle weakness, or joint deformity).
3. OA is primarily a disease of cartilage that reflects a failure of the chondrocyte to maintain proper balance between cartilage formation and destruction. This leads to loss of cartilage in the joint, local inflammation, pathologic changes in underlying bone, and further damage to cartilage triggered by the affected bone.
4. The most common symptom associated with OA is pain, which leads to decreased function and motion. Pain relief is the primary objective of medication therapy.
5. Manifestations of OA are local, affecting one or a few joints; the knees are most commonly affected, as well as the hips and hands.
6. Nonpharmacologic therapy is the foundation of the treatment plan for all patients with OA. Nonpharmacologic therapy should be initiated before or concurrently with pharmacologic therapy.
7. Based upon efficacy, safety, and cost considerations, scheduled acetaminophen, up to 4 g/day, should be tried initially for pain relief in knee and hip OA. If this fails, nonsteroidal anti-inflammatory drugs (NSAIDs; topical or oral) are recommended, if there are no contraindications.
8. Topical NSAIDs, in lieu of oral NSAIDs, are recommended for patients older than 75 years of age to decrease the risks of systemic toxicity.
9. Strategies to reduce NSAID-induced gastrointestinal (GI) toxicity include the use of nonacetylated salicylates, COX-2 selective inhibitors, or the addition of misoprostol or a proton pump inhibitor.
10. Other agents useful in treating knee OA include intra-articular injections of corticosteroids, duloxetine, or tramadol.

BEYOND THE BOOK

BEYOND THE BOOK

This activity is designed to build skills in developing a safe-and-effective patient-specific PLAN as part of the patient care process.

Create a table of drug treatment options for a patient with knee, hip, and hand osteoarthritis and a history of a myocardial infarction.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and one of the leading causes of disability in the United States.[1] Knee OA alone is as important a contributor to disability as cardiovascular (CV) disease and more important than other comorbidities. OA is a common co-occurrence with other chronic health conditions that adversely affect quality of life.[1]

The progressive destruction of articular cartilage has long been appreciated in OA, but OA involves the entire diarthrodial joint, including articular cartilage, synovium, capsule, and subchondral bone, with surrounding ligaments and muscles also playing important roles. Changes in structure and function of these tissues produce clinical OA, characterized by joint pain and tenderness, with decreased range of motion, weakness, joint instability, and disability.

This chapter will review the epidemiology, etiology, pathophysiology, and clinical presentation of OA. It then will focus on nonpharmacologic and pharmacologic treatments for OA. Because millions of persons take medications for OA, the overall risks posed by these medications require careful consideration, particularly by clinicians who treat or advise patients on drug therapy for OA. This chapter examines the risks and benefits of OA treatments, with emphasis on those individuals who have the highest risk for adverse events, to help clinicians maximize benefits and minimize risks to their patients with OA.

EPIDEMIOLOGY

1 During 2013 to 2015, an estimated 54.4 million adults in the United States reported doctor-diagnosed arthritis (osteoarthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia), with 23.7 million reporting arthritis-attributable activity limitation (AAAL).[1] The prevalence of AAAL among adults with arthritis increased by almost 20% over time (2002-2015).[1] Arthritis is projected to affect 78.4 million adults by 2040.[2] OA imposes a tremendous cost burden with combined arthritis-attributable medical expenditures and earnings losses totaling approximately $303 billion dollars in 2013.[3] The US Medical Expenditure Panel Survey found that arthritis-attributable medical expenditures were $139.8 billion, representing 11% of the total medical expenditures in 2013.[3] Among all adults in the US population, adults with arthritis had the highest overall average cost per person ($9,233), followed by adults with at least one nonarthritis chronic condition ($6,272) and those with no chronic conditions ($1,369).[3] Total hospital costs associated with the specific diagnosis of osteoarthritis were $16.5 billion attributed to 1 million hospital stays in 2013.[4] Arthritis-attributable lost earnings were $163.7 billion with almost half of lost earnings due to lower adjusted per-person earnings for those with arthritis.[3]

Prevalence by Age, Sex, and Race

Prevalence estimates for OA vary depending on the age group of interest, gender, ethnic group, and the specific joint involved. Estimates also depend on the specific means by which OA is assessed and documented. Clinical OA is based on physical exam and patient history, whereas radiographic OA is determined by x-ray or other imaging, and symptomatic OA is based on patient history and physical exam plus x-ray. OA is more prevalent with increasing age. In the United States, the prevalence of self-reported doctor-diagnosed arthritis in the 2013 to 2015 National Health Interview Survey (NHIS) is 22.7% for all persons over age 18, but 49.6% for persons age 65 and older.[1] Prevalence for AAAL among persons with doctor-diagnosed arthritis is 43.5% for all persons over age 18 and 44% for persons age 65 and older.[1] Radiologically confirmed hip OA shows clear trends through all age groups, affecting 1.6% of those between ages 30 and 39, up to a prevalence of 14% in those over 85 years of age.[5] Radiographic hand OA is found in 5% of those aged 40, but in 65% of those older than 80 years of age.[6]

Prevalence of physician-diagnosed arthritis is 26.3% in White populations, and ranges from 11.1% for Asian populations to 21.8% for Black

populations.[1] African American men are approximately 35% more likely to have radiographic knee OA and twice as likely to have more severe knee OA than White men.[7] No significant differences were found between the prevalence of knee OA in Black women and White women, but Black women were 50% more likely than White women to have more severe involvement.[7] Among adults with arthritis, the prevalence of severe joint pain is significantly higher in women (29.7%), non-Hispanic Blacks (45.6%), those with less than a high school education (40.2%), and those unable to work (51.9%).[8] Women are also more likely to have inflammatory OA of the proximal and distal interphalangeal joints of the hands, giving rise to the formation of Bouchard and Heberden nodes, respectively (Fig. 110-1).

FIGURE 110-1

Heberden nodes (distal interphalangeal joint) noted on all fingers and Bouchard nodes (proximal interphalangeal joint) noted on most fingers. *(Reproduced, with permission, from Johnson BE. Arthritis: Osteoarthritis, gout, and rheumatoid arthritis. In: South-Paul JE, Matheny SC, Lewis EL, eds. CURRENT Diagnosis and Treatment in Family Medicine. 4th ed. New York, NY: McGraw Hill; 2015.)*

Incidence

As the incidence of a disease describes the number of newly diagnosed cases each year, OA poses a challenging situation for determining disease incidence. These reasons include: (1) not all patients with OA seek medical treatment; (2) OA is common within the population; (3) many effective treatments are available over the counter, promoting self-treatment; (4) not all radiographically diagnosed OA is symptomatic and patients may not be formally diagnosed with OA; and (5) many patients have multiple affected joints, making it difficult to track the overall occurrence of OA in these individuals.

ETIOLOGY

2 The etiology of OA is multifactorial and complex, with development of OA depending on interplay between person-level risk factors and joint-level risk factors.[9] Many patients have more than one risk factor for the development of OA. The most common risk factors for the development of OA include age, obesity, sex, occupation, participation in certain sports, history of joint injury or surgery, and genetic predisposition.

Obesity

Obesity is the most important preventable risk factor for OA. This linkage is strongest for knee OA, although hip OA and even hand and wrist OA may be linked with obesity. The etiology of this association of OA in non-weight-bearing joints is thought to be the adverse metabolic and inflammatory effects produced by obesity.[10] As the epidemic of obesity spreads in the United States and in other developed countries, so will the burdens imposed by OA.

For every five unit increase in BMI, the risk of knee OA increases 35%.[9] Obesity often precedes OA and contributes to its development, rather than occurring as a result of inactivity from joint pain. In an 11-year study of approximately 30,000 Norwegian men and women, obesity significantly increased the risk of developing OA.[11] Men who were obese at baseline had a 2.8-fold increase in developing knee OA compared to the nonobese men, whereas women who were obese at baseline had a 4.4-fold increased risk in developing knee OA compared to the nonobese women. Also, there was an increased risk for severe knee OA in obese subjects.[11]

Occupation, Sports, and Trauma

OA risk is increased for people in occupations involving excessive mechanical stress. Work that involves prolonged standing, kneeling, squatting, lifting, or moving of heavy objects increases risk of OA. Such occupations include construction, mining, healthcare assistance, factory work, carpentry, and farming.[9] Repetitive motion also contributes to hand OA, with the dominant hand usually affected. Risk for OA depends on the type and intensity of physical activity and whether injury incurred in the activity. Increased risk of OA is associated with participation in activities such as wrestling, soccer, weight lifting, football, and hockey, although recreational participants do not have the increased risk seen in the professional athlete.[12] Studies that have included running, including long distances, have produced decidedly mixed results.[12] In the study of 30,000 Norwegians, exercise intensity was not associated with any increased risk in the obese subjects compared to those of normal weight.[11]

Traumatic knee injury, either during sports or in accidents, significantly increases the risk of knee OA over a 10-year period.[12] These injuries include anterior cruciate ligament tears, meniscal tears, and direct cartilage injuries.[9] Meniscal damage increases the risk of knee OA because of the loss of proper load bearing and shock absorption, and increased focal load on cartilage and on subchondral bone. Quadriceps muscle weakness is also recognized to increase the risk for knee OA, as these muscles are important in maintaining joint stability.[10] As proper alignment of the joint structures is critical to proper function of the joint, knee malalignment increases risk of developing OA. In the person who already has OA, knee malalignment is strongly associated with faster progression of OA.[10]

Genetic Factors

OA is a complex disease with a strong genetic component. The genetic contribution to OA has been supported by many studies and it is estimated that 30% of the risk of OA is genetically determined.[13] There is not a single genetic variant responsible for OA, but likely thousands of loci associated with the complex nature of the disease. Identification of these genetic loci may promote development of agents to prevent OA or to slow or halt its progression. Heberden nodes are 10 times more prevalent in women than in men, for example, with a twofold higher risk if the woman's mother had them. Genetic links have been shown with OA of the first metatarsophalangeal joint and with generalized OA. Twin studies indicate that OA can be attributed substantially to genetic factors.[14]

One approach OA researchers have used is the candidate gene approach which is hypothesis based and focuses on genes with known function which could be plausibly linked with the OA. This approach requires a priori knowledge of disease etiology and only very small regions of the genome can be studied at a time. Studies of 199 candidate genes found that only two variants (COL11A1 and VEGF genes) reached significance.[13] These results confirm that using existing joint biology knowledge to identify genetic variants is unlikely to facilitate the understanding of the genetic risks of OA.

Genome-wide association studies (GWAS) use a hypothesis-free methodology that involves scanning hundreds of thousands or millions of genetic markers, in the form of single-nucleotide polymorphisms (SNPs). Using GWAS studies, at least 21 independent susceptibility loci to OA have been found.[13] A meta-analysis of GWAS with 6,709 knee OA cases and 44,439 controls revealed that the Chrom7Q22 locus was highly significantly associated with knee OA. The locus also included six genes which code for proteins that are known to be expressed in joint tissues.[15]

It is quite likely that the genetic risk of developing OA, like many other diseases, is determined by a combination of genetic differences. This underscores the point that understanding of the genetics and pathology of OA is in its early stages.

PATHOPHYSIOLOGY

OA falls into two major etiologic classes. *Primary* (*idiopathic*) *OA*, the more common type, has no identifiable cause. *Secondary OA* is that associated with a known cause such as inflammation, trauma, metabolic or endocrine disorders, and congenital factors.[16]

The old view of OA as a “wear-and-tear” or degenerative disease, largely focused on joint cartilage, has long been superseded by an appreciation of the dynamic nature of OA and that it represents a failure of the joint and surrounding tissues.[10] Some changes in the OA joint may reflect compensatory processes to maintain function in the face of ongoing joint destruction. Not only biomechanical forces but also inflammatory, biochemical, and immunologic factors are involved. An appreciation of the biology and function of normal cartilage can aid in understanding osteoarthritic cartilage and is summarized below.

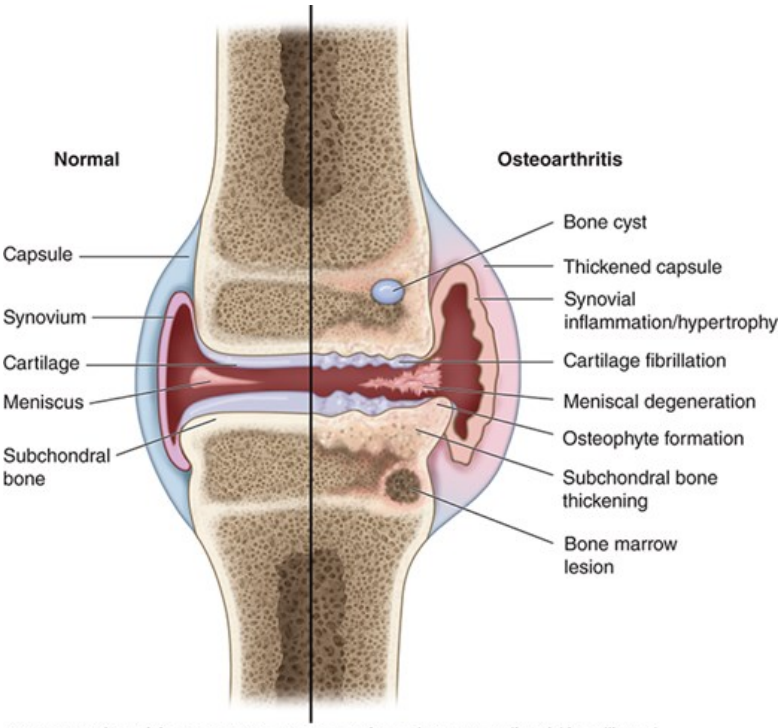
Normal Cartilage

Function, Structure, and Composition of Cartilage

Articular cartilage possesses viscoelastic properties that provide lubrication with motion, shock absorbency during rapid movements, and load support. In synovial joints, articular cartilage is found between the synovial cavity on one side and a narrow layer of calcified tissue overlying subchondral bone on the other side (Fig. 110-2).[16,17] The layer of cartilage is narrow, with human medial femoral articular cartilage being approximately 2 to 3 mm thick. Despite this, healthy articular cartilage in weight-bearing joints withstands millions of cycles of loading and unloading each year. Cartilage is easily compressed, losing up to 40% of its original height when a load is applied. Compression increases the area of contact and disperses force more evenly to underlying bone, tendons, ligaments, and muscles. In addition, cartilage is almost frictionless, and together with its compressibility, this enables smooth movement in the joint, distributes load across joint tissues to prevent damage, and stabilizes the joint.

FIGURE 110-2

Characteristics of osteoarthritis in the diarthrodial joint. *(Reprinted, with permission, from Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. Clin Geriatr Med. 2010;26(3):371-386.)*



Strength, a low coefficient of friction, and compressibility of cartilage derive from its unique structure. Cartilage is a complex, hydrophilic, extracellular matrix (ECM). It is approximately 70% water, 10% collagen, 8% proteoglycans, chondrocytes, other proteins, and long hyaluronic acid molecules.[18] The two major structural components in articular cartilage are type II collagen and aggrecans.[16] Type II collagen has a tightly woven triple helical structure, which provides the tensile strength of cartilage. Aggrecan is a proteoglycan linked with hyaluronic acid, providing the long aggrecan molecules a high

negative charge. These are squeezed together by surrounding fibrils of type II collagen. The strong electrostatic repulsion of proteoglycans held in close proximity gives cartilage the ability to withstand further compression. Within the cartilage ECM, chondrocytes, the only cells in cartilage, are responsible for laying down all the components of cartilage.

Normal cartilage turnover helps repair and restore cartilage in response to demands of joint loading and during physical activity. In adults, cartilage chondrocyte metabolism is slow and is regulated by growth factors, including bone morphogenetic protein 2, insulin-like growth factor-1, and transforming growth factor, and by catabolism and proteolysis stimulated by matrix metalloproteinases (MMPs), tumor necrosis factor-α (TNF-α), interleukin-1, and other cytokines. Tissue inhibitors of metalloproteinase (TIMP) also contribute to the balance by restraining the catabolic actions of MMPs. If cartilage is injured, chondrocytes react by removing the damaged areas and increasing synthesis of matrix constituents to repair and restore cartilage.[17]

Other components supporting healthy joints are the joint protective mechanisms, such as muscles bridging the joint, sensory receptors in feedback loops to regulate muscle and tendon function, supporting ligaments, and subchondral bone that has shock-absorbent properties.

Finally, note that adult articular cartilage is avascular, with chondrocytes nourished by synovial fluid. With movement and cyclic loading and unloading of joints, nutrients flow into the cartilage, whereas immobilization reduces nutrient supply. This is one of the reasons that normal physical activity is beneficial for joint health.

Osteoarthritic Cartilage

3 Important contributors to the development of OA are local mechanical influences, genetic factors, inflammation, and aberrant chondrocyte function leading to loss of articular cartilage.[16,19] At a molecular level, OA pathophysiology involves the interplay of dozens, if not hundreds, of extracellular and intracellular molecules with roles including chondrocyte regulation, phenotypic changes, proteolytic degradation of cartilage components, and interactions between articular cartilage, underlying subchondral bone, and the joint synovium.[10,19]

OA most commonly begins with damage to articular cartilage, through trauma or other injury, excess joint loading from obesity or other reasons, or instability or injury of the joint that causes abnormal loading. In response to cartilage damage, chondrocyte activity increases in an attempt to remove and repair the damage. Depending on the degree of damage, the balance between breakdown and resynthesis of cartilage can be lost, and a vicious cycle of increasing breakdown can lead to further cartilage loss and apoptosis of chondrocytes.[10,19] Studies have revealed several aspects of the complex nature of OA.

There is increased appreciation of the role of tissues beyond cartilage, within the joint and surrounding subchondral bone.[19] Subchondral bone undergoes pathologic changes that may precede, coincide with, or follow damage to the articular cartilage. In OA, subchondral bone releases vasoactive peptides and MMPs, and damage to subchondral bone may trigger further damage to articular cartilage.[18] Neovascularization and subsequent increased permeability of the adjacent cartilage contribute further to cartilage loss.

Joint space narrowing results from loss of cartilage, which can lead to a painful, deformed joint (Fig. 110-3). Remaining cartilage softens and develops fibrillations (vertical clefts into the cartilage), followed by splitting off of more cartilage and exposure of underlying bone.[18] During this time, adjacent subchondral bone undergoes further pathologic changes, cartilage is eroded completely, leaving denuded subchondral bone, which becomes dense, smooth, and glistening (eburnation). A more brittle, stiffer bone results, with decreased weight-bearing ability and development of sclerosis and microfractures. New bone formations or osteophytes also appear at joint margins, distant from cartilage destruction and are thought to arise from local and humoral factors. There is direct evidence that osteophytes can help stabilize osteoarthritic joints.[16]

FIGURE 110-3

Plain x-ray films of the knee demonstrating joint space narrowing. *(Reproduced, with permission, from Johnson BE. Arthritis: Osteoarthritis, gout and rheumatoid arthritis. In: South-Paul JE, Matheny SC, Lewis EL, eds. CURRENT Diagnosis & Treatment in Family Medicine. 4th ed. New York, NY: McGraw Hill; 2015.)*

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

In the joint capsule and synovium, inflammatory changes and pathologic changes can occur.[19] Contributors to inflammation may include crystals or cartilage shards in synovial fluid. Other possible factors are interleukin-1, prostaglandin E_2, TNF-α, and nitric oxide that are found in synovial fluid. With inflammatory changes in the synovium, effusions and synovial thickening occur.

4 The pain of OA is not related to the destruction of cartilage but arises from the activation of nociceptive nerve endings within the joint by mechanical and chemical irritants.[10,16] OA pain may result from distension of the synovial capsule by increased joint fluid, microfracture, periosteal irritation, or damage to ligaments, synovium, or the meniscus. Consequently, x-ray changes in OA correlate poorly with pain severity.

CLINICAL PRESENTATION

Diagnosis

5 The diagnosis of OA is made through history, physical examination, characteristic radiographic findings, and laboratory testing.[20] The major diagnostic goals are (1) to discriminate between primary and secondary OA and (2) to clarify the joints involved, severity of joint involvement, and response to prior therapies, providing a basis for a treatment plan. The American College of Rheumatology has published traditional diagnostic criteria and "decision trees" for OA diagnosis.[20] As with all guidelines, the authors stress these are for assisting the clinician rather than replacing clinical judgment. For example, traditional criteria are as follows: (1) For hip OA, a patient must have pain in the hip and at least two of the following three: an erythrocyte sedimentation rate <20 mm/hr (5.6 µm/s), femoral or acetabular osteophytes on radiography, or joint space narrowing on radiography. This provides a sensitivity of 89% and a specificity of 91%. For a clinical diagnosis of knee OA, a patient must have pain at the knee and osteophytes on radiography plus one of the following: age older than 50 years, morning stiffness no more than 30 minutes, crepitus on motion, bony enlargement, bony tenderness, or no palpable warmth. This provides a sensitivity of 95% and a specificity of 69%. The addition of laboratory or radiographic data further improves accuracy of diagnosis. Criteria for hand OA have also been published.[21]

Prognosis

The prognosis for patients with primary OA is variable and depends on the joint involved. If a weight-bearing joint or the spine is involved, considerable morbidity and disability are possible. In the case of secondary OA, the prognosis depends on the underlying cause. Treatment of OA may relieve pain or improve function but does not reverse preexisting damage to the joint.

CLINICAL PRESENTATION: OSTEOARTHRITIS

Age

- Usually occurs in older adults (≥65 years of age)

Gender

- Age <45 years more common in men
- Age >45 years more common in women

Symptoms

- Pain
- Deep, aching character
- Pain on motion
- Stiffness in affected joints
- Resolves with motion, recurs with rest ("gelling phenomenon")
- Usually duration <30 minutes
- Often related to weather
- Limited joint motion
- May result in limitations of activities of daily living
- Instability of weight-bearing joints

Signs, history, and physical examination

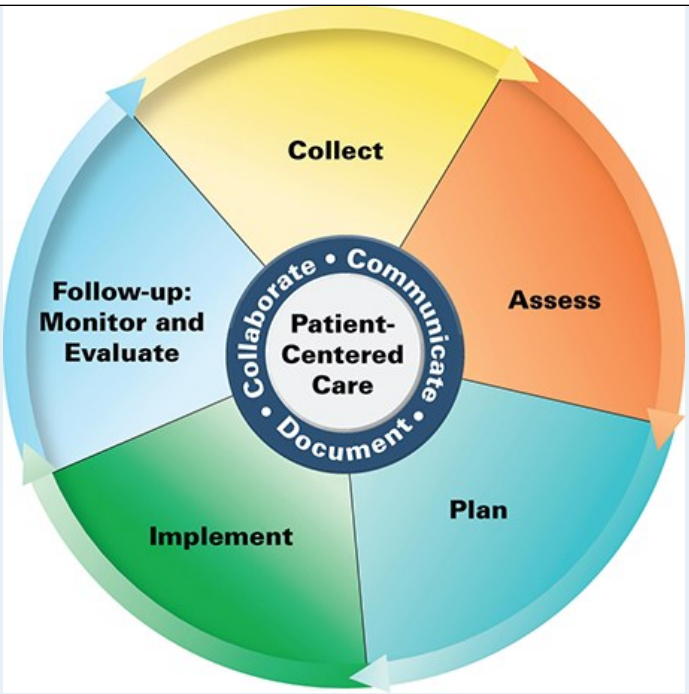
- Monoarticular or oligoarticular, asymmetrical involvement
- Hands
  - Distal interphalangeal joints
    - Herberden nodes (osteophytes or bony enlargements) (Fig. 110-1)
  - Proximal interphalangeal joints
    - Bouchard's nodes (osteophytes)
  - First metacarpal joint
    - Osteophytes give characteristic square appearance to hands
- Knee
  - Pain related to climbing stairs
  - Transient joint effusion
  - Genu varum ("bow-legged")
- Hips

- Groin pain during weight-bearing exercises
- Stiffness, especially after activity
- Limited joint movement

- Spine
  - Lumbar involvement is most common at L3 and L4
  - Paresthesia
  - Loss of reflexes
- Feet
  - Typically involves the first metatarsophalangeal joint
- Shoulder, elbow, acromioclavicular, sternoclavicular, temporomandibular joints may also be affected
- Observation on joint examination
  - Bony proliferation or occasional synovitis
  - Local tenderness
  - Crepitus
  - Limited motion with passive/active movement
  - Deformity
- Radiologic evaluation
  - Early mild OA
    - Radiographic changes are often absent
  - Progressive OA
    - Joint space narrowing (Fig. 110-3)
    - Subchondral bone sclerosis
    - Marginal osteophytes
- Late OA
  - Abnormal alignment of joints
  - Effusions

PATIENT CARE PROCESS

Patient Care Process for the Management of Osteoarthritis*



Collect

- Patient characteristics (eg, age, weight, height, race, sex, pregnant)
- Patient history (past medical, family, social—trauma, diet, exercise, alcohol use)
- Symptom information: type and location of pain, duration, effect of motion and rest, range of motion and limitations on activities, joint instability
- Current and past medications, including nonprescription agents and dietary supplements, and medications' relief of symptoms
- Objective data
  - Physical examination, appearance of joints
  - Radiologic evaluation—changes in joints, subchondral bone sclerosis, effusions
  - Body mass index (presence of overweight or obesity)

Assess

- Distribution and severity of joint involvement
- Impact of symptoms on patients' movements, health-related quality of life, amount of disability

Plan

- Patient education about disease, prognosis, treatment options, application and use of topical products
- Nonpharmacologic therapy (see Table 110-1)—weight loss (if overweight or obese), exercise, surgery (for severe pain or functional disability)
- Drug therapy regimen including specific analgesics, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Figs. 110-4 and 110-5 and Tables 110-2 and 110-3)

- Monitoring parameters including efficacy (eg, symptom relief) and safety (medication-specific adverse effects) (see Table 110-3)
- Self-monitoring of symptoms, exercise, and weight—where and how to record results
- Referrals to other providers when appropriate (eg, physician, orthopedic surgeon, physical therapist, dietician)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Assess symptom relief, effectiveness of weight loss and exercise programs
- Presence of adverse effects (see Table 110-3), including CV and renal effects of NSAIDs and hepatic effects of acetaminophen
- Closely monitor proper use of opioids, including dependence, addiction, tolerance, hyperalgesia, and diversion (see text); joint replacement may be preferred to chronic opioids
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

FIGURE 110-4

Treatment recommendations for knee and hip osteoarthritis. (CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.) [a]Selection of a medication should consider patient-specific characteristics. [b]The patient must be counseled regarding all acetaminophen-containing products. [c]When used for chronic management of OA, consider addition of a proton-pump inhibitor.

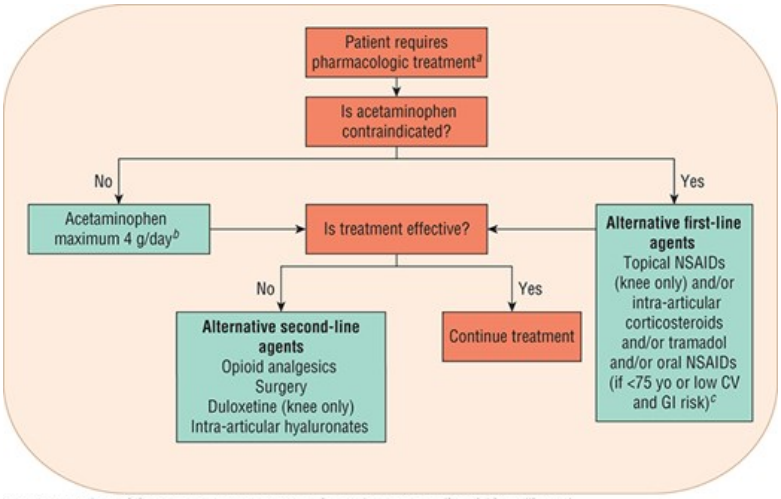
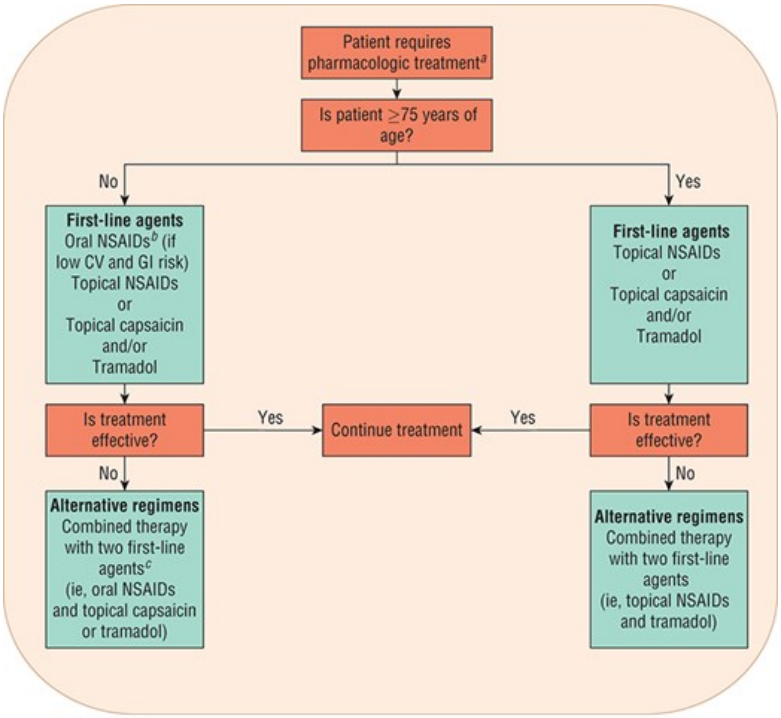


FIGURE 110-5

Treatment recommendations for hand osteoarthritis. (NSAID, nonsteroidal anti-inflammatory drug.) [a]Selection of a medication should consider

patient-specific characteristics. [b]When used for chronic management of OA, consider addition of a proton-pump inhibitor. [c]Should not combine topical NSAIDs and oral NSAIDs.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 110-1

Nonpharmacologic Interventions in the Treatment of OA

Intervention	Strength of Recommendation
Exercise	Strong
Weight loss (if overweight)	Strong
Patient education	Strong
Use of assistive device (ie, cane)	Moderate
Use of shoe insoles	Moderate
Application of heat	Moderate
Use of fitted knee braces	Minimal
Lateral patellar taping	Minimal
Passive exercise alone	Minimal

Data from References 24, 25.

Robustness of recommendation: Strong—fully supported by evidence-based guidelines; Moderate—supported by evidence-based guidelines; Minimal—little support by evidence-based guidelines.

TABLE 110-2

Dosing of Medications for Osteoarthritis

Drug	Brand Name	Starting Dose	Usual Range	Special Population Dose	Other
Oral analgesics					
Acetaminophen	Tylenol	325-500 mg three times a day	325-650 mg every 4-6 hours or 1 g three to four times/day	Chronic alcohol intake, hepatic disease	Contained in many combination analgesics
Tramadol Tramadol ER	Ultram Ultram ER	25 mg in the morning 100 mg daily	Titrate dose in 25-mg increments to reach a maintenance dose of 50-100 mg three times a day Titrate to 200-300 mg daily	Creatinine clearance <30 mL/min (0.5 mL/s)—maximum dose is 200 mg daily Do not use if	May need to taper dose upon discontinuation to prevent withdrawal symptoms

				creatinine clearance <30 mL/min (0.5 mL/s)	
Hydrocodone/acetaminophen	Lortab, Vicodin, Norco	5 mg/325 mg three times daily	2.5-10 mg/325-650 mg three to five times daily	Titrate dose slowly in older adults (age >65 years)	Maximum dose limited by total daily dose of acetaminophen
Oxycodone/acetaminophen	Percocet	5 mg/325 mg three times daily	2.5-10 mg/325-650 mg three to five times daily	Titrate dose slowly in older adults (age >65 years)	Maximum dose limited by total daily dose of acetaminophen
Topical analgesics					
Capsaicin 0.025% or 0.15%	Capzasin-HP		Apply to affected joint three to four times per day		—
Diclofenac 1% gel	Voltaren		Apply 2 or 4 g per site as prescribed, four times daily		
Diclofenac 1.3% patch	Flector		Apply one patch twice daily to the site to be treated, as directed		
Diclofenac 2% solution	Pennsaid		Apply 40 mg (two pump actuations) twice daily		
Intra-articular corticosteroids					
Triamcinolone	Kenalog	5-15 mg/joint	10-40 mg/large-joint (knee, hip, shoulder)	If multiple joints injected, maximum total dose is usually 80 mg	Often administered concomitantly with a local anesthetic

Methylprednisolone acetate	Depo-Medrol	10-20 mg/joint	20-80 mg/large-joint (knee, hip, shoulder)	10-40 mg for medium joints (elbows, wrists)	
Nonsteroidal anti-inflammatory drugs (NSAIDs)					
Aspirin, plain, buffered, or enteric-coated	Bayer, Ecotrin, Bufferin	325 mg three times a day	325-650 mg four times a day		Doses of 3,600 mg/day are needed for anti-inflammatory activity
Celecoxib	Celebrex	100 mg daily	100 mg twice daily or 200 mg daily		
Diclofenac XR Diclofenac IR	Voltaren-XR Cataflam	100 mg daily 50 mg twice a day	100-200 mg daily 50-75 mg twice a day		
Diflunisal	Dolobid	250 mg twice a day	500-750 mg twice a day		
Etodolac	Lodine	300 mg twice a day	400-500 mg twice a day		
Fenoprofen	Nalfon	400 mg three times a day	400-600 mg three to four times a day		
Flurbiprofen	Ansaid	100 mg twice a day	200-300 mg/day two to four divided doses		
Ibuprofen	Motrin, Advil	200 mg three times a day	1,200-3,200 mg/day in three to four divided doses		Available OTC and Rx
Indomethacin Indomethacin SR	Indocin Indocin	25 mg twice a	Titrate dose by 25-50 mg/day until pain		

	SR	day 75 mg SR once daily	controlled or maximum dose of 50 mg three times a day Can titrate to 75 mg SR twice daily if needed		
Ketoprofen	Orudis	50 mg three times a day	50-75 mg three to four times a day		
Meclofenamate	Meclomen	50 mg three times a day	50-100 mg three to four times a day		
Mefenamic acid	Ponstel	250 mg three times a day	250 mg four times a day		FDA approval for 1 week of therapy
Meloxicam	Mobic	7.5 mg daily	15 mg daily		
Nabumetone	Relafen	500 mg daily	500-1,000 mg one to two times a day		
Naproxen	Naprosyn	250 mg twice a day	500 mg twice a day		
Naproxen sodium Naproxen sodium DR	Anaprox, Aleve Naprelan	220 mg twice a day	220–550 mg twice a day 375-750 mg twice a day		Available OTC and Rx
Oxaprozin	Daypro	600 mg daily	600-1,200 mg daily		
Piroxicam	Feldene	10 mg daily	20 mg daily		
Salsalate	Disalcid	500 mg twice a	500-1,000 mg two to three times a day		

		day			

TABLE 110-3

Monitoring of Medications Used in Osteoarthritis Treatment

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Oral analgesics			
Acetaminophen	Hepatotoxicity	Total daily dose limits	Use caution with multiple acetaminophen-containing products—total 4 g limit (or less in patients with hepatic dysfunction)
Tramadol	Nausea, vomiting, somnolence	No routine labs recommended	Drug-drug interaction with other serotonergic medications
Opioids	Sedation, constipation, nausea, dry mouth, hormonal changes	No routine labs recommended	Risks of addiction, dependence, and drug diversion
NSAIDs	Dyspepsia, CV events, GI bleeding, renal impairment	BUN/Creatinine, Hgb/Hct, blood pressure	Risks higher in those older than 75 years of age
Topical analgesics			
Capsaicin	Skin irritation and burning	Inspection of areas of application	Wash hands thoroughly after application
NSAIDs	Skin itching, rash, irritated dyspepsia, CV events, GI bleeding, renal impairment	Inspection of areas of application. As needed: BUN/Creatinine, Hgb/Hct, blood pressure	Wash hands thoroughly after application. Avoid oral NSAID or aspirin other than cardioprotective dose. Ensure patient applies gel, solution, or patch correctly
Injectable drugs			
Intra-articular corticosteroids	Hypertension, hyperglycemia	Glucose, blood pressure	HPA axis suppression if used too frequently
Intra-articular hyaluronates	Local joint swelling, stiffness, pain	No routine labs recommended	Less effective than intra-articular corticosteroids; expensive

TREATMENT

Desired Outcome

Management of the patient with OA begins with a diagnosis based on a careful history, physical examination, radiographic findings, and an assessment of the extent of joint involvement. Treatment should be tailored to each individual. Goals are (1) to educate the patient, family members, and

caregivers; (2) to relieve pain and stiffness; (3) to maintain or improve joint mobility; (4) to limit functional impairment; and (5) to maintain or improve quality of life.[24,25] About half of the US population has one chronic health condition, with 25% having two or more conditions.[26] With nearly 25% of the US adults with at least one chronic health condition having arthritis, it is essential that comprehensive patient-centered medication management is provided to these patients to maximize treatment goals for OA and other chronic conditions, while minimizing medication-related adverse outcomes.

General Approach to Treatment

Treatment for each OA patient depends on the distribution and severity of joint involvement, comorbid disease states, concomitant medications, and allergies. Management for all individuals with OA should begin with both oral and written patient education, a customized activity and exercise program, and weight loss, if the patient is overweight or obese.[24,25] A multidisciplinary intervention for knee OA initiated by pharmacists has been shown to improve adherence to OA guideline recommendations, decrease pain scores, and improve functional assessment scores.[27] These types of multidisciplinary disease state management programs that implement strategies to provide comprehensive care should be offered to all OA patients to maximize outcomes.

The primary objective of medication is to alleviate pain.[24,25] Scheduled acetaminophen, up to 4 g/day, should be tried initially (knee, hip), if contraindications are not present. Application of topical NSAIDs over specific joints (knee, hands) and topical capsaicin (hands) are recommended as initial therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) or possibly a cyclooxygenase-2 (COX-2)–selective inhibitor (celecoxib) can be prescribed after careful risk assessment if additional pain control is needed. Intra-articular corticosteroid injections (knee or hip) can relieve pain and are offered concomitantly with oral analgesics or after failed trials of first-line medications, depending on the practitioner's preference. With centrally acting serotonin reuptake inhibition and analgesic properties, tramadol can also be considered if acetaminophen or topical treatment is ineffective or not tolerated.

Consideration may also be given to duloxetine or, rarely, hyaluronic acid injections when additional pain control is needed for knee OA. When symptoms are persistent or there is significant loss of function, joint replacement can be appropriate if the patient is a surgical candidate.

There is general agreement that glucosamine and/or chondroitin and topical medications lack uniform efficacy in the treatment of hip and knee OA pain and are not preferred treatment options.

Nonpharmacologic Therapy

6 Nonpharmacologic therapy is an integral part of the treatment plan for all patients with OA.[24,25,28] Nonpharmacologic therapy is the only available treatment that has been shown to delay the progression of OA.[2,29] Delaying the progression of OA through active participation in nonpharmacologic therapy is critical to prevent future functional impairment. Patient-specific characteristics such as (1) number and location of affected joints, (2) degree of functional impairment, (3) body mass index, (4) motivation, and (5) overall health status determine which nonpharmacologic therapies should be offered. Nonpharmacologic therapy should be ongoing treatment for all patients, even those who require pharmacologic therapy for pain control (Table 110-1).[2,28,29]

Patient Education

The first step in OA treatment is patient education about the disease process, the extent of OA, the prognosis, and treatment options. Education is paramount, in that OA is often seen as a wear-and-tear disease, an inevitable consequence of aging for which nothing helps. Even worse, patients may resort to the use of alternative but unproven medications or treatments. Organizations such as the Arthritis Foundation provide a wealth of educational information for patients regarding OA, OA medications, and local clinics and agencies offering physical and economic assistance. Exercise, weight loss, and nutritional information are also available. Most educational information is readily available online for patient use. Several mobile applications are available to provide education, track symptoms and exercise, and encourage better self-management of OA.

The benefits of patient education have been documented in a variety of programs.[22,28] These programs are provided across a wide spectrum of delivery methods: from trained volunteers using telephone calls to group sessions for patient support to one-on-one educational sessions with physical therapists or nurse educators. While nearly all of these delivery methods are effective, cost of delivery is highly variable. Long-term cost-effectiveness is important for sustainability of these patient education programs.

Weight Loss

The association between OA and obesity has been well established. Studies also indicate a strong association between increasing BMI and surgical replacement of the hip and knee joints.[30] Weight loss of amounts as small as 4% body weight can lessen OA pain in the knee.[31] Greater amounts of weight loss, especially when associated with regular exercise improve joint function and substantially lessen pain.[2,29] Modest weight loss (5%) has been shown to provide some relief in obese patients with OA but the goal should be an initial decrease in body weight of at least 10% to provide significant reductions in pain.[30] The Intensive Diet and Exercise for Arthritis trial (IDEA) found that after 18 months, overweight and obese adults with knee OA who participated in the diet and exercise treatment group had less inflammation, less pain, better function, and better quality of life.[32] Weight loss requires a motivated patient, but all patients with OA who also have obesity and overweight should be encouraged and supported in their efforts to optimize their body size. Effective behavior change strategies should be employed to promote weight loss in patients with OA.[29]

Exercise

Exercise programs can improve joint function and can decrease disability, pain, and analgesic use by OA patients.[2,33] Low-impact aerobic exercise including both land- and water-based methods are preferred.[34] Exercises can be taught and then observed before the patient exercises at home. The frequency, types of exercise, and setting of exercise are still uncertain, but patients who exercise have decreased pain and increased physical function.[35] The patient should be instructed to decrease the number of repetitions if severe pain develops with exercise.

Some regular exercise should be encouraged for all patients with OA.[25] With weak or deconditioned muscles, the load is transmitted excessively to the joints; weight-bearing activities can exacerbate symptoms. Many patients fear that exercise will promote further joint damage and avoid exercise as a means to protect the joint. However, avoidance of regular exercise by those with hip or knee OA leads to further deconditioning and/or weight gain. Further weight gain and deconditioning leads to more pain and impaired joint function, promoting a downward spiral of disability. Exercise therapy in addition to patient education has been shown to decrease or postpone the need for hip replacement surgery in patients with hip OA.[36]

Referral to the physical and/or occupational therapist is especially helpful for developing a customized exercise plan for patients with functional disabilities. The therapist can assess muscle strength and joint stability and recommend exercises and assistive and orthotic devices, such as canes, walkers, braces, heel cups, splints, or insoles for use during exercise or daily activities. Heat or cold treatments help to maintain and restore joint range of motion and to reduce pain and muscle spasms. Warm baths or warm water soaks may decrease pain and stiffness. Heating pads should be used with caution, especially in the elderly. Patients should be warned not to fall asleep on the heat source or to lie on it for more than brief periods to avoid burns.

Surgery

Surgery can be recommended for OA patients with functional disability and/or severe pain unresponsive to medical therapy.[37] Total joint replacement surgeries are quite common and expected to increase. Over 1 million total hip and knee replacement procedures are performed each year in the United States. Seven million individuals are living with an artificial knee or hip, including 620,000 people who have both.[23] Although total knee arthroplasty can decrease pain and improve function for many patients, about 20% experience little or no improvement in pain, disability, and/or quality of life.[38] Patients who are obese are less likely to have improvement in symptoms from knee arthroplasty. Patients also experience less pain and decreased length of hospitalization after surgery if they participate in a supervised exercise program for the first two months that begins on the day of surgery.[39]

Total joint arthroplasty is responsible for a large portion of the direct medical costs associated with OA in the United States. The cost-effectiveness of total knee arthroplasty has been evaluated for a Medicare-age population.[40] Calculations were based on Medicare claims data and costs and outcomes data. Cost projections were calculated for lifetime costs as well as quality-adjusted life expectancy (QALE) for different risk populations and across low-volume to high-volume hospitals. Although total knee arthroplasty was found to be cost-effective across hospital settings and patient risk categories, the procedure was found to be most cost-effective when performed in high-volume centers. The cost-effectiveness of knee arthroplasty was evaluated against nonsurgical management. Knee arthroplasty was cost-effective at both low and high levels of improvement in pain and function in patients with severe knee OA.[41] Direct medical costs associated with joint replacement will continue to increase at a rate higher than predicted rates due to

increasing willingness of patients to undergo joint replacement surgery.[3]

Pharmacologic Therapy

Drug therapy in OA is targeted at relief of pain. OA is commonly seen in older individuals who have other medical conditions, and OA treatment is often long term. As such, a conservative and patient-centered approach to drug treatment is warranted (see Figs. 110-4 and 110-5).[24,25,28] Even when pharmacologic therapy is initiated, appropriate nondrug therapies should be continued and reinforced. Specific drug therapy recommendations depend on which joint(s) are affected, response to previous trials of medication, and patient comorbidities.

Knee and Hip OA

First-Line Treatments

Acetaminophen

7 The American College of Rheumatology, as well as others, recommend acetaminophen as a first-line treatment for knee and hip OA.[24,25,42] Acetaminophen has been extensively studied in the treatment of knee and hip OA and is more effective than placebo in controlling OA pain.[43] Compared with oral NSAIDs, acetaminophen may be modestly less effective, but have lower risk of serious GI and CV adverse events and as a consequence is preferred to oral NSAIDs as first-line treatment.[28,42]

Oral NSAIDs

The American College of Rheumatology and other key groups recommend nonspecific or COX-2 selective NSAIDs, depending on patient risk factors, as a first-line option for knee and hip OA if the patient fails acetaminophen.[25,26,41] Nonselective and COX-2 selective NSAIDs pose higher risks for GI, renal, and CV adverse events compared to acetaminophen. COX-2 inhibitors carry less risk for both minor and serious GI adverse events in comparison to nonselective NSAIDs (with the exception of diclofenac).[42]

Topical NSAIDs—Knee Only

8 The American College of Rheumatology and other authorities recommend topical NSAIDs as a first-line option for knee OA if the patient fails acetaminophen and is preferred to oral NSAIDs for those older than age 75 years.[24,25,42] Topical NSAIDs provide pain relief for OA similar to that obtained with oral NSAIDs but with fewer GI adverse events. Topical NSAIDs offer a favorable safety profile and aren't associated with systemic adverse effects. The most common adverse effect of topical NSAIDs is a localized skin reaction.[44]

Intra-articular Corticosteroids

Intra-articular corticosteroid injections are recommended as alternative first-line treatment for both knee and hip OA when pain control with acetaminophen or NSAIDs is suboptimal.[24,25] Injections can also be administered with concomitant oral analgesic therapy as needed for additional pain control. Intra-articular corticosteroids are generally safe and well tolerated, but should not be administered more frequently than once every 3 months due to risks of systemic adverse effects.

Tramadol

Tramadol is recommended as an alternative first-line treatment of knee and hip pain due to OA in patients who have failed treatment with scheduled full-dose acetaminophen and topical NSAIDs, who are not appropriate candidates for oral NSAIDs, and who are not able to receive intra-articular corticosteroids.[25] Tramadol can also be safely added to partially effective acetaminophen or oral NSAID therapy. Less data are available to support the use of tramadol as monotherapy for OA pain.

Second-Line Treatments

Opioid Analgesics

The American College of Rheumatology recommends opioid analgesics as the primary second-line medication for both knee and hip OA.[25] Opioids may be considered in patients who have not had an adequate response to both nonpharmacologic and first-line pharmacologic therapies. Patients who are at high surgical risk, precluding joint arthroplasty, are also candidates for opioid therapy. When compared to nonopioid medications in a 12-month randomized trial, opioids were not found to be superior in improving pain-related function.[45] Adverse effects, including serious events, limit the routine use of opioids in the treatment of OA pain.

Duloxetine—Knee Only

Duloxetine can be used as adjunctive treatment in patients with knee OA who have had a partial response to first-line analgesics.[24,25] It may be a preferred second-line medication in patients with both neuropathic and musculoskeletal OA pain. Duloxetine has demonstrated efficacy primarily as add-on therapy when there has been less than optimal response to acetaminophen or oral NSAIDs.[46,47] Reduction in pain occurs at about 4 weeks after initiation.[48] Adverse events associated with duloxetine in the treatment of knee OA are most commonly GI, with nausea, vomiting, and constipation being the most common. The recommended dose is 60 mg once daily. However, some patients may benefit from higher doses, up to a maximum dose of 120 mg daily.[48] Adverse events have been reported in OA trials that most commonly used doses of 60 mg/day. A higher dose is associated with an increased risk of adverse reactions.

Intra-articular Hyaluronic Acid

The American College of Rheumatology, NICE, and others do not routinely recommend the use of intra-articular hyaluronic acid injections for knee OA pain.[24,25,28] HA injections do not provide clinically meaningful improvement in pain and/or function scores, although some studies may report statistical differences in scores. These agents may be associated with serious adverse events such as increased pain, joint swelling, and stiffness. Limited efficacy and risks of serious events limit the routine use of these agents.

Hand OA

First-Line Treatments

NSAIDs

The American College of Rheumatology and NICE recommend topical NSAIDs as a first-line option for hand OA.[28] Application of diclofenac gel compared to placebo topical product for hand OA provided significant relief.[21] No difference was found between the efficacy of oral and topical NSAIDs. Local adverse effects were seen more with topical versus oral NSAIDs but GI adverse effects were more common with oral NSAIDs.[49,50] Efficacy with topical NSAIDs was reported quickly, within 1 to 2 weeks.[21]

Oral NSAIDs are recommended as an alternative first-line treatment for hand OA by the American College of Rheumatology and as second-line therapy in the NICE guidelines.[25,28] For the person who cannot tolerate local skin reactions or who received inadequate relief from topical NSAIDs, oral NSAIDs can offer relief, but the patient then faces increased risk for GI, renal, and CV adverse events.

Topical Capsaicin

Capsaicin cream is recommended as an alternative first-line treatment for hand OA.[25] Clinical trial data supporting the use of capsaicin for the treatment of hand OA is limited to small studies, but demonstrates about 50% reduction in pain scores.[21] Adverse effects associated with capsaicin are primarily skin irritation and burning; therefore, it is a reasonable therapeutic alternative for patients who are not able to take oral NSAIDs.

Tramadol

Tramadol is recommended by the American College of Rheumatology as an alternative first-line treatment for OA of the hand.[25] No studies in hand OA

with tramadol have been performed.[21] In clinical practice, tramadol is a therapeutic option for patients who do not respond to topical therapy and are not candidates for oral NSAID treatment due to high GI, CV, or renal risks. Tramadol may also be used in combination with partially effective acetaminophen, topical therapy, or oral NSAIDs.

Drug Class Information

Highlights of drug information is presented here. This section is not intended to be all inclusive but aims to provide pertinent drug information to facilitate the safe-and-effective use of these medications in patients with OA.

First-Line Treatments

Acetaminophen

Pharmacology and Mechanism of Action

Acetaminophen is understood to act within the central nervous system (CNS) by inhibiting synthesis of prostaglandins, agents that enhance pain sensations. Acetaminophen prevents prostaglandin synthesis by blocking the action of central cyclooxygenase (COX). Acetaminophen is well absorbed after oral administration, with bioavailability of 60% to 98%. It achieves peak concentrations within 1 to 2 hours. It is inactivated in the liver by conjugation with sulfate or glucuronide, and its metabolites are renally excreted.

Adverse Effects

Although acetaminophen is one of the safest analgesics for younger individuals without comorbidities, it carries greater risk in frail older adults.[51] Serious hepatotoxicity, including fatalities, have been well documented with acetaminophen overdose (see Chapter e8, "Clinical Toxicology," for treatment of acetaminophen overdose).[52] Unintentional overdoses of acetaminophen are due to a variety of circumstances including narrow therapeutic window at the maximum dose (4 g/day), interpatient differences in sensitivity to liver injury from acetaminophen, a wide array of nonprescription and prescription products that contain acetaminophen, which may be hard for patients to identify on the label, and consumers' lack of knowledge about the association of acetaminophen and serious liver injury.

Acetaminophen-related hepatotoxicity is dose-dependent. Even at therapeutic doses, acetaminophen may cause transient liver enzyme elevations and potentially hepatotoxicity.[53,54] The most common risk factor for liver failure in patients who take acetaminophen is chronic alcohol intake.[55] The FDA has recommended that chronic alcohol users (three or more drinks daily) avoid acetaminophen intake as it increases the risk of liver damage or GI bleeding. Other individuals are not at increased risk of GI bleeding.

Drug-Drug Interactions and Drug-Food Interactions

Drug interactions with acetaminophen can occur; for example, isoniazid can increase the risk of hepatotoxicity. Chronic ingestion of maximal doses of acetaminophen may intensify the anticoagulant effect for patients taking warfarin; such individuals may need closer monitoring. Although food decreases the maximum serum concentration of acetaminophen by approximately half, the overall efficacy is unchanged.

Dosing and Administration

When used for chronic OA, acetaminophen should be administered in a scheduled manner. It may be taken with or without food. Acetaminophen can be taken at 325 to 650 mg every 4 to 6 hours, but the total dose must not exceed 4 grams daily (see "Adverse Effects" section above). FDA labeling requirements warn patients about potential liver toxicity if they inadvertently ingest more than the recommended dose when using multiple products containing acetaminophen. Additionally, prescription analgesics containing acetaminophen are limited to 325 mg/tablet to further decrease the opportunity for inadvertent overdose. Acetaminophen should be avoided in the setting of chronic alcohol intake or in those with underlying liver disease.

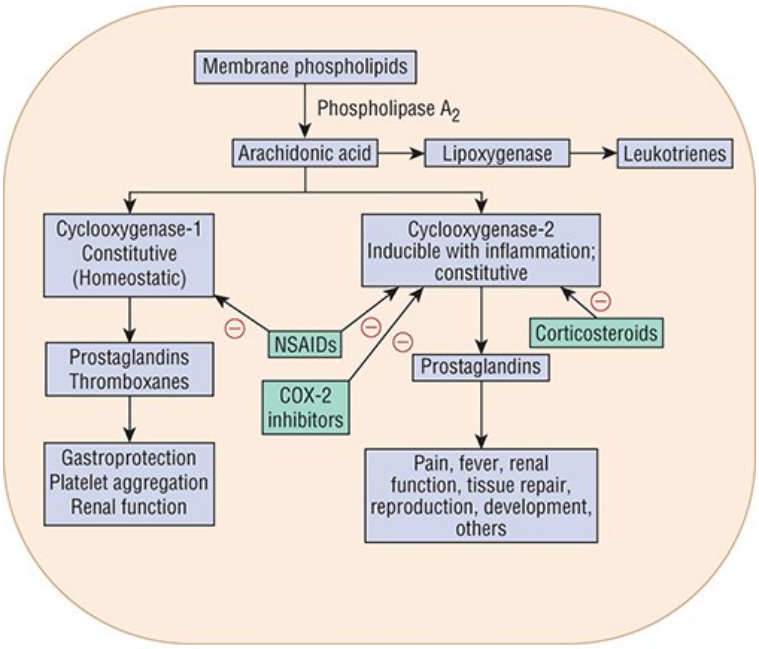
Oral Nonsteroidal Anti-inflammatory Drugs

Pharmacology and Mechanism of Action

NSAIDs reduce pain, inflammation, and fever by preventing synthesis of tissue prostaglandins and related prostanoids, which play a role in triggering these symptoms. All NSAIDs bind (reversibly) to the cyclooxygenase 2 (COX-2) enzyme, blocking its action and thus prostanoid production. Blockade of prostaglandin synthesis by inhibiting COX enzymes (mainly COX-2) is thought to account for NSAIDs ability to relieve pain and inflammation (Fig. 110-6).[56] Nonselective NSAIDs were developed prior to extensive knowledge of COX enzymes, but in fact they block both COX-2 and COX-1. COX-1 has required "housekeeping" functions such as gastroprotection. COX-2 inhibitors selectively block COX-2 but not COX-1 activity.

FIGURE 110-6

Pathway of synthesis for prostaglandins and leukotrienes. COX-1 and COX-2 are cyclooxygenase-1 and cyclooxygenase-2 enzymes, respectively. The minus (–) sign indicates inhibitory influence. Prostaglandins include PGE_2 and PGI_2; the latter is also known as prostacyclin.



The various NSAIDs exhibit several pharmacokinetic similarities, including high oral availability, high protein binding, and absorption as active drugs (except for sulindac and nabumetone, which require hepatic conversion for activity). There is a broad range of serum half-lives for different NSAIDs, which influence dosing frequency, and potentially, compliance with therapy.[57] Elimination of NSAIDs largely depends on hepatic inactivation, with a small fraction of active drug being renally excreted. NSAIDs penetrate joint fluid, reaching approximately 60% of blood levels.

Adverse Effects Gastrointestinal Effects of Nonselective NSAIDs

The most common adverse effects of NSAIDs involve the GI tract. NSAIDs can cause minor symptoms such as nausea and dyspepsia as well as more serious effects such as ulcers and bleeding.[58-60] All NSAIDs increase ulcer risk, but the serious GI complications associated with NSAIDs include perforations, gastric outlet obstruction, and bleeding. These important GI complications occur in 1.5% to 4% of patients per year. NSAIDs are so widely used that these small percentages translate into substantial morbidity and mortality. Moreover, the risk increases substantially for patients with risk factors including a longer duration of NSAID usage, higher dosage, age older than 60 years, past history of peptic ulcer disease of any cause, history of alcohol use, concomitant use of glucocorticoids, and/or anticoagulants.[56] A patient treated with NSAIDs has a three to five times higher risk of developing GI complications than a patient not treated with these medications.[61]

9 Options are available to reduce the GI risk of traditional NSAIDs. (1) Take the lowest dose possible and take only when needed. (2) Take the prostaglandin analog, misoprostol four times daily that reduces the rate of ulcers and serious GI complications. Many patients cannot tolerate the GI adverse events of misoprostol, especially diarrhea. (3) Take a proton pump inhibitor (PPI) or a full-dose H2 blocker daily. The PPI and the H2 blocker do

reduce minor GI complaints and reduce the risk of ulcers but are not rigorously proven to decrease the serious complications, possibly because of lack of power to detect rare events.[61]

Another choice that is available to reduce risk of GI events with an NSAID is to take a COX-2 selective inhibitor ("coxib").[58,60] Celecoxib is the only coxib available in the United States. Because this drug does not block the "housekeeping" gene, it may not have the same GI risks, but it is not without GI risk.[55] A meta-analysis showed that COX-2 selective inhibitors were associated with significantly fewer gastroduodenal ulcers and clinically important ulcer complications. Celecoxib has been shown to be as safe to the upper GI tract as a nonselective NSAID plus a PPI.[62] Another concern is the risk associated with NSAID use in patients taking aspirin for cardioprotection. The GI risk is lower in patients taking a coxib medication and low-dose aspirin than a nonselective NSAID. However, in patients with high GI risk the combination may still be harmful and gastroprotection is appropriate.[62]

Dosing and Administration

Administration of NSAIDs must be tailored to the individual patient with OA. Selection of an NSAID depends on the prescriber's experience, medication cost, patient preference, allergies, toxicities, and adherence issues. Individual patient response differs among NSAIDs, so if an inadequate response is obtained with one NSAID, another NSAID may yet provide benefit.[25,28]

Cardiovascular Risk of COX-2 Inhibitors and Traditional NSAIDs

Both nonselective and selective NSAIDs are associated with an increased risk for hypertension, stroke, myocardial infarction (MI), and death. NSAIDs should be avoided in patients with known active ischemic heart disease, cerebrovascular disease, and moderate-to-severe heart failure.[56] The mechanism for the CV effects of NSAIDs is not entirely clear.[61] NSAIDs are associated with hypertension, increased preload, volume expansion, and reduced sodium excretion.[63] A large meta-analysis showed some differences among NSAIDs in terms of vascular risk. The risks of diclofenac and ibuprofen were similar to that of coxibs but naproxen was not associated with an increased risk of major vascular events. Overall, coxibs were found to increase vascular risk by approximately one-third.[64] Several randomized controlled trials have compared NSAIDs to evaluate CV safety and found celecoxib to be noninferior to other NSAIDs in terms of CV events. However, the celecoxib dose in these trials was lower than the doses previously reported to be associated with increased CV risk. In these trials, more patients also discontinued celecoxib due to lack of efficacy compared to other NSAIDs.[64,65]

In February 2014, an advisory committee to the FDA met to discuss the data relating the CV risk and NSAIDs. After their review it was decided to strengthen the warning label for nonaspirin NSAIDs, warning patients on the risk of heart attack and stroke. The updated labeling warns that CV events can happen at any point during NSAID therapy and the risk may increase with longer treatment and higher doses. The FDA concluded that there was insufficient evidence that the risk of any NSAID was higher or lower than another. An increased risk for CV events is present even in patients with no underlying CV disease. The data reviewed also showed patients taking an NSAID following a first MI were more likely to die in the first year following the MI.[66] Strategies to reduce CV risk with NSAIDs are not well documented. Naproxen may present less CV risk than coxibs and diclofenac at higher doses and therefore seems prudent to consider this when choosing a specific NSAID.[61,62,66]

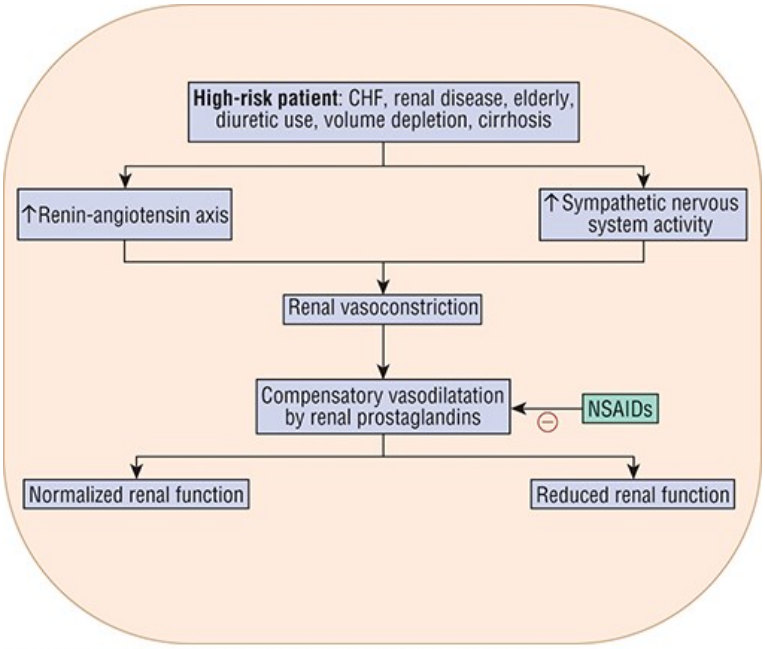
Other Toxicities Associated with NSAIDs

NSAIDs may cause kidney diseases, including acute renal insufficiency, sodium retention, acute interstitial nephritis, renal papillary necrosis, and accelerated chronic kidney disease. In a trial evaluating NSAID safety, serious renal events occurred at a significantly lower rate in the celecoxib group compared to the ibuprofen group but when celecoxib was compared to naproxen the difference in renal events was not significant.[67] Sodium retention has been reported to occur in up to 25% of NSAID-treated patients. This effect may be clinically important to cause exacerbations of congestive heart failure.[63] Clinical features of these NSAID-induced renal syndromes include increased serum creatinine and blood urea nitrogen, hyperkalemia, elevated blood pressure, peripheral edema, and weight gain. Patients at high risk are those with conditions associated with decreased renal blood flow or taking certain medications. Examples are those with chronic renal insufficiency, congestive heart failure, severe hepatic disease, and nephrotic syndrome, those of advanced age, or those taking diuretics, angiotensin-converting enzyme inhibitors, cyclosporine, or aminoglycosides (Fig. 110-7).

FIGURE 110-7

Mechanisms implicated in NSAID-induced renal injury. The minus (–) sign indicates inhibitory influence. (CHF, congestive heart failure; NSAIDs,

nonsteroidal anti-inflammatory drugs.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Close monitoring is advisable for high-risk patients taking an NSAID, with monitoring of serum creatinine at baseline and within 3 to 7 days of drug initiation. For those with impaired renal function, the National Kidney Foundation recommends acetaminophen over NSAIDs, although acetaminophen may pose risks, as discussed above.

Coxibs and NSAIDs uncommonly cause drug-induced hepatitis; the two NSAIDs most frequently implicated are diclofenac and sulindac. Patient monitoring should include periodic liver enzymes (aspartate aminotransferase and alanine aminotransferase), with cessation of therapy if these values exceed two to three times the upper limit of normal. Hepatotoxicity associated with NSAIDs is responsible for about 10% of medication-induced liver injury.[68]

Other toxic effects of NSAIDs include hypersensitivity reactions, rash, and CNS complaints of drowsiness, dizziness, headaches, depression, confusion, and tinnitus.[57] NSAIDs should be avoided for patients with asthma who are aspirin-intolerant.

All nonspecific NSAIDs inhibit COX-1–dependent thromboxane production in platelets and thus increase bleeding risk. Unlike aspirin, celecoxib and nonspecific NSAIDs inhibit thromboxane formation reversibly, with normalization of platelet function 1 to 3 days after the drug is stopped. Warfarin and celecoxib are metabolized by the cytochrome P450 isoenzyme CYP2C9; thus, patients receiving warfarin and COX-2 inhibitors should be followed closely.

Finally, if misoprostol is taken for GI protection, great care is indicated. Because of its abortifacient properties, misoprostol is contraindicated in pregnancy and in women of childbearing age who are not maintaining adequate contraception. It must be dispensed in its original container, which carries a warning for these individuals. Misoprostol is also available in a combination product with diclofenac, which bears the same restrictions as misoprostol alone.

Drug-Drug Interactions

Avoidance of concomitant use, or anticipation and careful monitoring, can often prevent serious events when potentially interacting drugs are being considered. The most potentially serious interactions include the use of NSAIDs with lithium, warfarin, other agents that increase bleeding risk, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.[57] In addition, there are probable drug interactions with tacrolimus for ibuprofen, naproxen, diclofenac, and possibly other NSAIDs.

Specific drug interactions are also seen with celecoxib.[69] Celecoxib metabolism is primarily via CYP2C9.[69] Cytochrome P450 inducers such as rifampin, carbamazepine, and phenytoin have the potential to reduce celecoxib levels. Concomitant administration of celecoxib with fluconazole can increase plasma concentrations of celecoxib, due to fluconazole inhibition of the CYP2C9 isoenzyme. Because warfarin and celecoxib are both metabolized by CYP2C9, patients receiving warfarin and COX-2 inhibitors should be followed closely. Because celecoxib inhibits CYP2D6, it has the potential to increase concentrations of a variety of agents, including antidepressants. Celecoxib is a sulfonamide and is thus noted to be contraindicated for those with sulfa allergies.[69]

Another drug interaction has been noted for those taking some NSAIDs and cardioprotective doses of aspirin. Ibuprofen, used at doses of 400 mg or more, may block aspirin's antiplatelet effect if it is taken prior to aspirin. Patients taking ibuprofen have been advised to take a single dose of ibuprofen at least 30 minutes after taking aspirin, or to take their aspirin at least 8 hours after taking ibuprofen. It is possible that other nonselective NSAIDs, such as naproxen, also may cause such interactions. The ACR recommends that patients taking aspirin who need an oral NSAID for OA choose an NSAID other than ibuprofen or COX-2 selective inhibitors.[25] Acetaminophen does not interfere with the antiplatelet effect of aspirin.

Topical NSAIDs

Pharmacology and Mechanism of Action

The mechanism of action of topical NSAIDs is considered to be through inhibition of the COX-2 enzyme in tissues near the site of application. Studies show significant placebo effects which could result from rubbing the product into the skin, which may have a counterirritant effect. Topical NSAIDs are significantly more efficacious compared to placebo vehicle in reducing pain due to musculoskeletal conditions, including osteoarthritis. Most trials have shown topical diclofenac to be as effective as oral NSAIDs, including both oral diclofenac and other comparators.[42,50,70] Diclofenac 1% gel as well as the newer diclofenac solution and diclofenac patches are approved in the United States for osteoarthritis.

Adverse Effects

Compared to oral NSAIDs, topical NSAIDs are associated with many fewer GI adverse events and fewer adverse events overall, except for local application site reactions. In comparison to placebo or oral NSAIDs, topical NSAID use is associated with more local adverse events, most often mild skin reactions such as itching or rash, but with few serious adverse effects. Meta-analyses and reviews have found similar tolerability between topical NSAIDs and placebo. Topical NSAIDs have not shown a significant link between their use and increased risk of CV events.[44] From 1% to 15% of topical NSAIDs enter the systemic circulation, but usually less than 5% contribute to its greater safety profile.[70,71]

Drug-Drug Interactions

Interactions listed for topical diclofenac are the same as those listed above for oral NSAIDs. The most potentially serious interactions include the use of NSAIDs with lithium, warfarin, and other agents that increase bleeding risk, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics. Other topical agents have not been studied with the product and there could be changes in tolerability and absorption of diclofenac. For all of these interactions, as there is only a small percentage of diclofenac absorbed, the risks are likely significantly less than that with oral drug, but the patient and provider should monitor appropriately for these interactions with any of these drugs the patient is taking. Patients should avoid oral NSAIDs while using topical products to minimize additive adverse effects. Care should be taken to avoid contact with the eyes or open wounds and to wash hands after application (except when treating hand OA).

Dosing and Administration

Diclofenac 1% gel (Voltaren®) can be used for hand or knee OA or other joints amenable to topical application (eg, not the hip or shoulder) and is available as an OTC product. It is applied four times daily using the dose measuring cards provided by the manufacturer. Four grams of gel is recommended for application to the affected area in the lower limb (eg, foot, ankle, knee) four times daily. For use on the upper extremities (eg, hand, wrist, elbow), the dose is 2 g four times daily. Diclofenac solution (Pennsaid®), only approved for knee OA, is available as a 2% solution. The 2% diclofenac solution is available in a meter-dose pump. It is applied as two actuations or 40 mg twice daily to the affected knee(s). The entire dose should be pumped into the palm of the hand then applied evenly to the knee. The diclofenac patch (180-mg diclofenac epolamine) is applied twice daily. If the patch doesn't stick well, the patient can tape edges with first-aid tape. Patient counseling is important to carefully explain how to apply the topical products. Other counseling points include hand washing after use, avoidance of touching the eyes, nose, or mouth directly after use, and how long to wait before dressing, putting on gloves, showering, and so forth.

Pharmacoeconomic Impact of NSAIDs

The highest costs associated with the pharmacotherapy of OA are hospitalization for treatment of NSAID-related complications, particularly serious GI

adverse events. Historically, gastroprotective therapy or the use of COX-2–selective inhibitors for low-risk patients has not been cost-effective because of the number needed to treat to prevent serious events is large, but most PPIs are generic, multisource products, making concomitant treatment with PPIs effective.[72] Pharmacoeconomic considerations for OA involve the selection of therapy for the initial treatment of patients with OA. Use of the nonprescription analgesic acetaminophen as initial therapy has greatly reduced medication costs in comparison with the use of NSAIDs, many of which are by prescription only. Oral NSAID costs vary considerably, depending on the medication, daily dose, and regimen selected. As oral NSAIDs as a class are therapeutically similar, the use of a less-expensive agent such as nonprescription ibuprofen or naproxen or a multisource generic product may minimize the cost. More expensive NSAIDs can be prescribed if neither of these offers benefit after a 2-week trial at sufficient doses. Prescription-only topical NSAIDs are significantly more costly than oral agents. Over-the-counter diclofenac products are likely to have a similar cost compared to many generic prescription oral NSAIDs. Costs related to the serious complications associated with oral NSAID therapy are likely to outweigh the costs associated with topical diclofenac in any form, making prescription status products cost-effective.

Intra-articular Corticosteroids

Pharmacology and Mechanism of Action

10 The anti-inflammatory properties of corticosteroids as a class are the primary mechanism of pain relief in the treatment of OA. These properties decrease the formation and release of prostaglandins, kinins, liposomal enzymes, and histamine. These actions decrease erythema, swelling, heat, and tenderness of the inflamed joints.[25,73] Aspiration of the effusion and injection of glucocorticoid are carried out aseptically, with examination of the aspirate recommended to exclude crystalline arthritis or infection. Several randomized, placebo-controlled, double-blind studies have shown that intra-articular corticosteroids are superior to placebo in alleviating knee pain and stiffness caused by OA but with a relatively short duration.[73] The most commonly used corticosteroids for intra-articular use are triamcinolone acetonide and methylprednisolone acetate. The branched esters of triamcinolone and methylprednisolone are preferred by practitioners because of the reduced solubility that allows the agents to remain in the joint space longer.[74,75]

Adverse Events

Adverse events associated with intra-articular injection of corticosteroids can be local or systemic in nature. Systemic adverse events are the same as with any other systemic corticosteroid and can include hyperglycemia, edema, elevated blood pressure, flushing, dyspepsia, and hypercortisolism. There is an acute 2- to 3-day rise in blood glucose in patients with diabetes following a single corticosteroid injection. The risk of systemic side effects can be lessened by limiting the dose of the corticosteroid since doses greater than 40 mg for triamcinolone or methylprednisolone have not been shown to provide any additional benefit.[74] Local adverse effects can include infection in the affected joint, osteonecrosis, tendon rupture, and skin atrophy at the injection site. Systemic corticosteroid therapy is not recommended in OA, given the lack of proven benefit and the well-known adverse effects with long-term use.

Dosing and Administration

Average doses for injection of large joints in adults are 40 mg of triamcinolone and methylprednisolone acetate. Local anesthetics such as lidocaine or bupivacaine are commonly combined with corticosteroids to provide rapid pain relief.[74] This therapy is generally limited to three or four injections per year due to the potential systemic effects of corticosteroids and because the need for more frequent injections indicates little response to the therapy.

After injection, the patient should minimize activity and stress on the joint for several days. Initial pain relief may be seen within 24 to 72 hours after injection, with peak pain relief about 7 to 10 days after injection and lasting up to 4 to 8 weeks.

Capsaicin

Pharmacology and Mechanism of Action

Capsaicin, isolated from hot peppers, releases and ultimately depletes substance P from afferent nociceptive nerve fibers. Substance P has been implicated in the transmission of pain in arthritis, and capsaicin cream has demonstrated to have moderate efficacy compared to placebo in clinical trials.[51] Due to the larger surface area and distance from the site of application to the joint, it is not expected that application of capsaicin would provide efficacy in the treatment of hip OA.

Adverse Effects

Adverse events associated with capsaicin are primarily local, including burning, stinging, and/or erythema that usually subsides with repeated

application. Systemic effects are rare.[51] The FDA has issued a public drug safety communication notifying consumers that rare cases of severe burns have been reported.[76] Some patients may experience coughing associated with application.

Dosing and Administration

To be effective, capsaicin must be used regularly, and it may take up to 2 weeks to take effect. Use is recommended four times a day.[51] Patients should be counseled not to get the cream in their eyes or mouth. Patients should also notify their healthcare provider immediately if they experience pain, swelling, or blistering skin at the site of application.

Capsaicin is a nonprescription product available as a cream, gel, solution lotion, or patch in concentrations ranging from 0.025% to 0.15%.

Tramadol

Pharmacology and Mechanism of Action

Tramadol, an analgesic with affinity for the μ-opioid receptor, as well as weak inhibition of the reuptake of norepinephrine and serotonin neurotransmitter, has shown moderate pain improvement for patients with OA when compared with placebo.[77,78] Tramadol is also modestly effective as add-on therapy for patients taking concomitant acetaminophen, NSAIDs, or COX-2–selective inhibitors. Tramadol may be helpful for patients who cannot take NSAIDs or COX-2–selective inhibitors.

Adverse Events

Opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence are common with tramadol. These occur in 45% to 84% of treated patients.[79] Although the frequency of adverse effects is high, the severity of these effects is less than for NSAIDs, as tramadol use is not associated with life-threatening GI bleeding, CV events, or renal failure. The most notable serious adverse event associated with tramadol use is seizures. Withdrawal symptoms can occur if tramadol is stopped abruptly. Older adults are significantly more likely to experience adverse events.[79] Tramadol was initially not classified as a controlled substance but was rescheduled as a class IV controlled substance due to its potential for dependence, addiction, and diversion.

Drug-Drug Interaction

Medications that lower the seizure threshold should be used with caution in patients taking tramadol. These include tricyclic antidepressants, first-generation antipsychotic medications, and cyclobenzaprine, as well as others. There is also an increased risk of serotonin syndrome (see Chapter 88, “Depressive Disorders,” for description) when tramadol is used concomitantly with other serotonergic medications, including duloxetine.

Dosing and Administration

Tramadol should be initiated at a lower dose (100 mg/day) and may be titrated as needed for pain control to a dose of 200 mg/day, with a maximum dose of 400 mg/day. Tramadol is available in a combination tablet with acetaminophen and as an extended-release tablet or capsule.

Second-Line Treatments

Opioid Analgesics

Opioid analgesics may be useful for patients who experience limited pain relief with acetaminophen, oral NSAIDs, intra-articular injections, or topical therapy or who cannot tolerate the side effect profile of these agents.[55] For patients with underlying conditions that limit the use of first-line analgesics, opioid analgesics can effectively relieve acute OA pain. A common clinical scenario includes the patient who cannot take oral NSAIDs because of renal failure or CV disease. Patients in whom all other treatment options have failed and who are at high surgical risk, precluding joint arthroplasty, are also candidates for opioid therapy. It is important to carefully use opioids to promote safety. The CDC recommends only prescribing opioids if the benefits from pain control and function outweigh the risk. The best practices for prescribing opioid include using the lowest effective dose and the smallest quantity needed; providing patients with information on how to use, store, and dispose of opioid medications; and avoiding combinations of opioids and sedating medications unless there is a specific indication to do so. Opioid use should be assessed at least every 3 months, evaluating patient progression toward functional treatment goals, risks of harm, and adverse effects.[80]

Adverse effects are common in opioid-treated patients with OA. More than 75% of patients in clinical trials experience at least one typical opioid-related (ie, nausea, somnolence, constipation, dry mouth, and dizziness) adverse effect. Although this is not an unexpected finding, it serves as a reminder to use opioids cautiously in elderly patients who may be more susceptible to adverse effects.

Opioid dependence, addiction, tolerance, hyperalgesia, and issues surrounding drug diversion are more serious adverse effects associated with long-term treatment. Prescription opioid misuse/abuse/addiction is a major public health concern with the CDC reporting around 46 deaths every day from prescription opioid overdose.[81] Patients should be educated on the risks of taking opioids, including addiction, overdose, and death.

If pain is poorly controlled and limits activities of daily living, and the patient has sufficiently good cardiopulmonary health to undergo major surgery, joint replacement may be preferable to continued reliance on opioids.

Duloxetine

Duloxetine is a centrally acting dual-reuptake inhibitor of both serotonin and norepinephrine, although norepinephrine reuptake inhibition does not occur until doses reach 60 mg/day. While the most common pain target in OA is peripheral nociceptive pain, there is some evidence that chronic nociceptive pain leads to central pain sensitization thereby lowering the pain threshold.[47] Duloxetine provides pain relief through the blocking of central pain transmitters, including serotonin and norepinephrine.

Adverse effects commonly associated with duloxetine therapy include nausea, dry mouth, constipation, and anorexia. Expected neurologic adverse effects include fatigue, somnolence, and dizziness. Rare, but serious adverse events associated with duloxetine include Stevens-Johnson syndrome and liver failure. Patients should be notified to contact their healthcare provider immediately if they develop a rash while taking duloxetine.

Particular care should be taken to avoid the use of duloxetine with other serotonergic medications including tramadol. As tramadol is a first-line treatment recommendation for OA, the likelihood of encountering this combination is high. Concomitant use of duloxetine with other medications that increase serotonin concentrations increases the risk of serotonin syndrome.

Hyaluronic Acid Injections

Hyaluronate is a naturally occurring component of cartilage and synovial fluid. Exogenous intra-articular hyaluronate is available as a treatment for the symptoms of knee OA. The goal of intra-articular HA is to provide and maintain intra-articular lubrication. HA may also have anti-inflammatory, analgesic, and chondroprotective effects on the articular cartilage and joint synovium.[82] Evidence has not shown intra-articular HA to have a clinically significant benefit involving pain relief and functional improvement and therefore does not support the routine use of HA.[83] Most HA products are injected once weekly for either 3 or 5 weeks, depending on the specific agent administered. Patients are generally advised to repeat the injection schedule by six months if they are satisfied with the previous course.[73] Strenuous or prolonged weight-bearing activities should be avoided for 48 hours after treatment. Routinely, most of the improvement is expected from 5 to 13 weeks after injection with some effect still occurring at 24 weeks.[82] Injections are generally well tolerated, although acute joint swelling, effusion, and stiffness can occur. Local skin reactions, including rash, ecchymosis, and pruritus, have also been reported. Local adverse effects are more frequent in products from animal origin. Rarely, systemic adverse events including hypersensitivity reactions have occurred. Joint infections are rare but have been reported.

At this time, the effect of HA injections on knee OA is modest at best.[82] These agents are expensive because the treatment includes both drug costs and administration costs. Patient expectations and cost effectiveness must be considered before choosing HA injection.[73]

Glucosamine and Chondroitin

Interest in chondroitin and glucosamine was spurred initially by anecdotal reports of benefit in animals and humans and by the ability of these substances to stimulate proteoglycan synthesis from articular cartilage in vitro. Over the past decade, enthusiasm for these agents has waned as additional efficacy data has become available to the point that the American College of Rheumatology conditionally recommends against the use of glucosamine and chondroitin.[25] Glucosamine, alone or in combination, has not been shown to provide uniform improvements in pain control or functional status in patients with OA of the knee or hip.[84]

Numerous trials have examined the safety and efficacy of glucosamine and chondroitin; however, the duration of these studies has been relatively short. The efficacy of glucosamine and chondroitin was evaluated after 2 years and was found not to be statistically superior to placebo.[85] The combination of glucosamine and chondroitin was well tolerated. There has previously been some concern that glucosamine may worsen diabetes or asthma; however, with 2-year follow-up this was not substantiated.[85] When the combination of glucosamine and chondroitin was compared to

celecoxib in patients with knee OA, it was noninferior in the reduction of pain at 6 months. The combination was well tolerated and the authors suggest glucosamine and chondroitin as a potential safe alternative for patients with CV or GI conditions.[86]

Because glucosamine and chondroitin are marketed in the United States as dietary supplements, neither the products nor their purity is adequately regulated by the FDA. The potential consequences related to the lack of regulatory oversight for these products can affect both efficacy and safety. Products containing less than labeled doses can compromise efficacy, while those containing ingredients not included on the labeling can compromise safety. A variety of brand name and generic products are available in various doses and formulations.

EVALUATION OF THERAPEUTIC OUTCOMES

For persons with OA, treatment decisions and pharmacotherapy monitoring are patient specific. The patient's situation and individual needs should be considered when devising a treatment plan. Is the patient bothered primarily by pain, by limitations in activity, or with concerns about side effects from medications? Does the patient understand what OA is and why certain treatments are useful?

When the patient is first being assessed for the possibility of OA, the diagnosis is often straightforward, including history and physical exam, plain films of the affected joint(s), and lab tests. The older patient with unilateral knee pain, limited range of motion, no palpable warmth, crepitus, and without prolonged morning stiffness and other suspicious findings is highly likely to have knee OA. It is still reasonable to obtain x-rays that may help follow disease over time (although joint space narrowing often does not correlate with the extent of pain or difficulty walking). Basic labs to help decide what pharmacologic therapy is possible (eg, no NSAIDs with poor renal function), assessment of pain using a visual analog scale, range of motion for affected joints. Additional tests of OA severity may include measurement of grip strength, 50 ft (~15 m) walking time, patient and physician global assessment of OA severity, and assessment of ability to perform activities of daily living. Once the patient is assessed and diagnosed, patient and family education is essential. Nondrug therapy may include a referral for physical and/or occupational therapy services, where the therapists can help to maintain and improve range of motion. Referral for nutritional counseling and weight loss may also be necessary if the patient is overweight or obese. These interventions may decrease pain and facilitate improved activity for OA patients.

Although all patients must be provided with nonpharmacologic therapies, results from these interventions usually require weeks to months. In the meantime, the patient needs pain relief. First-line therapy continues to be acetaminophen. Adverse events with acetaminophen are uncommon, although it is important that the patient understand the maximum daily dose limits and all possible sources of acetaminophen-containing products. Although some do well on acetaminophen, many do not achieve sufficient pain relief. A step up to oral NSAIDs or second-line therapy might be necessary but poses significant risks beyond acetaminophen. A switch to NSAIDs requires careful consideration of the patient's age and comorbidities, renal function, history of GI problems, hypertension, and CV health. Periodic monitoring would include open-ended questions followed by direct questions relating to the commonest adverse effects associated with the respective medication. For an oral NSAID, symptoms of abdominal pain, heartburn, nausea, or change in stool color provide valuable clues to the presence of GI complications, although serious GI complications can occur without warning. Patients should be monitored for the development of hypertension, weight gain, edema, skin rash, and CNS adverse effects such as headaches and drowsiness. Baseline serum creatinine, complete blood count, and serum transaminases are repeated at 6- to 12-month intervals to identify GI, renal, and hepatic toxicities.

Topical NSAIDs have demonstrated efficacy in OA of the hand and knee and are as effective as oral NSAIDs. Although they carry the same CV, renal, and GI warnings, their area under the concentration–time curve (AUC) for a typical dose is only a few percent of the AUC from an equivalent dose of oral NSAID. Topical NSAIDs' most common side effects are local, with irritated skin, rash, or itching, usually mild, and with many fewer adverse effects of CV, GI, or renal nature. These agents are a welcome addition to the limited treatment modalities for the common, costly, painful, and often disabling disease of OA. It is important that the patient apply the topical products appropriately to achieve maximum benefit and avoid adverse events.

For patients receiving intra-articular corticosteroids, pain relief should begin with 2 to 3 days and last 4 to 8 weeks. Patients should be advised about possible injection site reactions, as well as possible systemic effects, especially for those with hypertension or diabetes, as there is a potential for increased blood pressure or blood glucose. For patients receiving opioids or tramadol, relief from pain should occur rapidly. Frail or elderly patients should be monitored carefully and cautioned about sedation, dysphoria, nausea, risk of falls, and constipation. Special additional monitoring should include strategies to assess development of opioid tolerance, addiction, misuse, and diversion.

CONCLUSION

OA is a common, slowly progressive disorder that affects diarthrodial joints and is characterized by progressive deterioration of articular cartilage, subchondral sclerosis, and osteophyte production. Clinical manifestations include gradual onset of joint pain, stiffness, and limitation of motion. The primary treatment goals are to reduce pain, maintain function, and prevent further destruction. An individualized approach based on education, rest, exercise, weight loss as needed, and analgesic medication can succeed in meeting these goals. Recommended drug treatment starts with acetaminophen ≤4 grams/day and topical analgesics as needed. If acetaminophen is ineffective, oral NSAIDs may be used in appropriately selected patients, often providing satisfactory relief of pain and stiffness. Individuals at increased risk for toxicity from NSAIDs, especially for GI, CV, or renal events, deserve special attention. Celecoxib may have safety advantages in some OA patients, but its safety relative to other NSAIDs and its role in OA remains poorly defined. Adjunctive therapy with tramadol, intra-articular corticosteroids, and duloxetine may be helpful in patients with poorly controlled pain. Experimental therapy aimed at preventing the progression of OA requires further clinical investigation before entering widespread clinical use.

ABBREVIATIONS

AAAL	arthritis-attributable activities limitations
AUC	area under the concentration–time curve
BMI	body mass index
CNS	central nervous system
COX	cyclooxygenase
CV	cardiovascular
ECM	extracellular matrix
FDA	Food and Drug Administration
GI	gastrointestinal
GWAS	genome-wide linkage studies
HA	hyaluronic acid
IDEA	Intensive Diet and Exercise for Arthritis
IR	immediate release
MI	myocardial infarction
MMP	matrix metalloproteinase
NICE	National Institute for Health and Clinical Excellence
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
OARSI	Osteoarthritis Research International
PPI	proton pump inhibitor
QALE	quality-adjusted life expectancy
SNPs	single-nucleotide polymorphisms
SR	sustained release
TIMP	tissue inhibitors of metalloproteinase
TNF-α	tumor necrosis factor-α

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SELF-ASSESSMENT QUESTIONS

1. Risk factors for the development of osteoarthritis (OA) include:
   A. Smoking
   B. Participation in running
   C. Being underweight
   D. Advanced age
   E. B and D
2. Patient education for OA, such as programs in which volunteers regularly contact patients:
   A. Has not yet been demonstrated to provide benefit to OA patients
   B. Is too expensive to recommend for general use by OA patients
   C. Should emphasize the “wear and tear” nature of OA as part of the educational message
   D. Has been shown to improve pain and functional status of OA patients
   E. All of the above
3. Matrix metalloproteinases (MMPs):
   A. Are naturally occurring chemokines that work primarily by recruiting neutrophils and macrophages to the inflamed synovium
   B. Help trigger degradation of articular cartilage by cleaving peptide bonds in proteoglycans
   C. Are stimulated by tissue inhibitors of metalloproteinases (TIMPS)
   D. Must be activated before they can ease the pain of OA
   E. B and C
4. Which of the following are required for an accurate and appropriate diagnosis of OA?
   A. Patient history and physical examination
   B. Patient history, physical examination, and radiologic evaluation
   C. Physical examination and magnetic resonance imaging
   D. Patient history, physical examination, and positive response to pharmacologic treatment
   E. Any of the above is accurate and appropriate
5. Acetaminophen:
   A. Is recommended as an appropriate initial treatment in OA
   B. Should be given on a scheduled basis for optimal pain control
   C. Can be associated with hepatotoxicity at doses below 4 g/day

D. Provides mild analgesia

E. All of the above

6. Traditional, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs):

A. Block access of arachidonic acid to both COX-1 and COX-2 enzymes

B. Promote platelet aggregation through blockade of COX-2 activity

C. Promote prostaglandin and bicarbonate production in gastric mucosa through blockade of COX-2 activity

D. Counteract renal vasoconstriction by promoting formation of renal prostaglandins

E. Are anti-inflammatory at low doses and analgesic at higher doses

7. NSAIDs:

A. Are associated with thousands of serious or life-threatening GI adverse events every year

B. Provide superior relief of OA pain in some individuals

C. Will usually produce symptoms of dyspepsia or abdominal discomfort as a prelude to serious GI adverse events

D. When used in anti-inflammatory doses, should be consistently monitored by serum levels

E. A and B

8. NSAIDs:

A. Are recommended as an alternative to acetaminophen for controlling inflammation associated with OA

B. Provide pain relief by the inhibition of prostaglandins

C. Provide cardioprotective effects similar to aspirin

D. Increase renal blood flow, causing sodium and potassium excretion

E. B and C

9. Celecoxib, a COX-2 selective inhibitor:

A. Blocks the COX- 2 enzyme with little or no inhibition of COX-1

B. Is more effective at relieving pain than nonselective NSAIDs

C. Is much safer to use in patients with cardiovascular disease

D. Carries a manufacturer's warning against use in sulfa allergic patients

E. A and D

10. Intra-articular corticosteroids:

A. Have no role in OA, as this disease does not have any inflammatory component

B. Are recommended as maintenance therapy for patients who cannot tolerate NSAIDs and who have severe OA

C. Can be administered up to 12 times per year for the treatment of severe OA pain

D. Are associated with hyperglycemia in patients without diabetes mellitus

E. Should not be used for the treatment of hip OA

11. Hyaluronic acid injectable material:

A. Is made using recombinant technology

B. Provides a long-term increase in viscosity of synovial fluid

C. Is a low cost pharmacologic therapy

D. Is highly effective when compared to placebo vehicle injections

E. Is less effective than intra-articular corticosteroids

12. Recommended treatment options for hip and knee OA patients who have failed acetaminophen include:

A. Nonselective NSAIDs used at analgesic doses, if the patient is not at high risk for GI bleeding

B. Nonselective NSAIDs with an H2 antagonist to prevent GI bleeding in the high-risk patient

C. COX-2 selective inhibitors with sucralfate in the high-risk patient

D. COX-2 selective inhibitors with misoprostol in the high-risk patient

E. None of the above

13. Knee replacement surgery should be considered in the patient with OA:

A. If the patient prefers not to try oral medications such as acetaminophen

B. If there is significant disability and interference with daily functioning

C. If the patient refuses treatment with low-dose NSAIDs

D. If the patient is at high risk for NSAID-related GI bleeding

E. If the patient does not respond to topical therapy with NSAIDs

14. Topical capsaicin therapy for the treatment of OA pain:

A. Produces systemic adverse effects

B. Provides therapeutic results within 48 hours

C. Is most effective when used on an as-needed basis

D. Must be used three times daily for best results

E. Is most appropriate for the treatment of hand OA

15. Which of the following patients is best suited to opioid analgesic therapy for their OA symptoms that have failed scheduled acetaminophen dosing?

A. History of alcoholism

B. History of small bowel obstruction

C. History of traumatic fall on home stairs

D. History of myocardial infarction

E. History of poor adherence to medications

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Participation in sports and advancing age are both independent risk factors for the development of OA. Refer to "Etiology" section.

2. **D.** A variety of patient education programs have been shown to improve pain and function in OA patients, including volunteer programs. Refer to "Nonpharmacologic Therapy" section.

3. **B.** MMPs are an important catalyst to normal cartilage turnover and repair. Refer to "Normal Cartilage" ("Function, Structure, and Composition of Cartilage") section.

4. **B.** A patient history to elicit symptoms, a physical exam to examine the affected joint, and basic x-ray examination to review for signs of joint space narrowing and other signs of osteoarthritis are the elements needed to diagnose osteoarthritis. Refer to "Diagnosis" section.

5. **E.** Acetaminophen is guideline-recommended, first-line therapy for all types of OA. Due to short duration of action, scheduled dosing is optimal. The most important toxicity is hepatoxicity. Refer to "Drug Class Information" ("Acetaminophen") section.

6. **A.** The mechanism of action of NSAIDs is the blockade of both COX-1 and COX-2. Refer to "Drug Class Information" ("Oral Nonsteroidal Anti-inflammatory Drugs [Pharmacology and Mechanism of Action]") section.

7. **E.** Due to the mechanism of action, risks of GI adverse events are inherent to NSAID use. Some patients are at higher risk of serious GI adverse events than others. Due to interpatient variability in response to analgesics, some patients have superior relief with NSAID use. Refer to "Drug Class Information" ("Oral Nonsteroidal Anti-inflammatory Drugs [Adverse Effects]") section.

8. **B.** Prostaglandins can generate pain signals. NSAIDs inhibit prostaglandins. Refer to "Drug Class Information" ("Oral Nonsteroidal Anti-inflammatory Drugs [Pharmacology and Mechanism of Action]") section.

9. **E.** Celecoxib is a COX-2 selective NSAID and as such has little to no inhibition of COX-1 enzyme. It also has a sulfonamide chemical structure, leading to a warning against use in sulfa allergic patients. Refer to "Drug Class Information" ("Oral Nonsteroidal Anti-inflammatory Drugs [Pharmacology and Mechanism of Action and Drug-Drug Interactions]") sections.

10. **D.** Intra-articular corticosteroids are associated with the same toxicities as systemic corticosteroids, including hyperglycemia in patients with and without preexisting diabetes mellitus. Refer to "Intra-articular Corticosteroids" ("Adverse Events") section.

11. **E.** Hyaluronic acid injections are less effective than other therapies; in some studies, no more effective than placebo. Refer to "Drug Class Information" ("Hyaluronic Acid Injections") section.

12. **A.** After acetaminophen failure, the next step in therapy is nonselective NSAIDs alone in a patient not at high risk for GI bleeding. H2 antagonists are not effective at preventing GI bleeding in high-risk patients and COX-2 selective inhibitors do not offer a therapeutic advantage in a low-risk patient. Refer to "Drug Class Information" ("Oral Anti-inflammatory Drugs [Adverse Effects (Gastrointestinal Effects of Nonselective NSAIDs)]") section.

13. **B.** Surgery is the best therapeutic option to improve significant disability and interference with activities of daily living. Refer to "Nonpharmacologic Therapy" ("Surgery") section.

14. **E.** Topical capsaicin is guideline-recommended alternative first-line therapy for hand OA. Refer to "Hand OA, First-Line Treatments and Drug Class Information" ("First-Line Treatments [Capsaicin]") section.

15. **D.** All NSAIDs are contraindicated in a patient with a history of a myocardial infarction. Refer to adverse effects under "Drug Class Information" ("Second-Line Treatments [Opioid Analgesics]") section.