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State-of-the-Art Management of Mild-to-Moderate Pain

Musculoskeletal Injuries and Osteoarthritis Pain: Optimizing Treatment Outcomes

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Continuing Medical Education
University of Colorado School of Medicine

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NEEDS ASSESSMENT

In the United States, approximately $3 billion per year is spent on over-the-counter (OTC) analgesics, including aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. These agents are often used for the relief of osteoarthritis (OA) and mild-to-moderate pain of musculoskeletal injuries. When used correctly, these medications can provide significant relief from pain. Prescription medications are also believed to be effective; however, recent studies have demonstrated that the cyclooxygenase (COX)-2 inhibitors have been linked to an increased risk of cardiovascular (CV) events. Although further study is needed to determine the exact relationship between these agents and CV events, many questions have emerged. Further complicating this issue is, that while many available NSAIDs are effective at relieving pain, these agents have been associated with gastrointestinal (GI) complications such as GI bleeding. Thus, a thorough understanding of non-NSAID analgesics is becoming even more important to clinicians.

Therapeutic interventions have been shown to relieve pain and reduce disability. Optimal therapy for OA and mild-to-moderate pain should be targeted to the individual. Despite the fact that pharmacologic measures are vital to the treatment of OA and mild-to-moderate pain, nonpharmacologic measures, such as exercise, weight loss, and patient education cannot be overlooked as they are essential to the overall, long-term management of these conditions. An understanding of the various physical therapies that can aid in the lessening of pain is critical.

This continuing medical education (CME) activity has been developed to educate primary care clinicians to evaluate the latest safety and efficacy issues regarding oral analgesic treatment strategies, including OTC agents, for the management of OA musculoskeletal injuries, and mild-to-moderate pain. The importance of nonpharmacologic measures will also be addressed as a keystone to the management of these conditions.

INTENDED AUDIENCE

Healthcare professionals

LEARNING OBJECTIVES

After reading this monograph, the healthcare professional should be able to:

- Discuss the role of inflammation in osteoarthritis and musculoskeletal injuries
- Differentiate between sprains and strains
- Describe how different patient populations impact the selection of a therapeutic regimen
- Examine efficacy and safety considerations in analgesic use for osteoarthritis and painful musculoskeletal conditions

CME CERTIFICATION

The University of Colorado School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education (CME) for physicians.

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The University of Colorado School of Medicine designates this educational activity for a maximum of 2.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This activity should take approximately 2.5 hours to complete. The participant should, in order, read the learning objectives contained in the monograph, read the activity, answer the multiple-choice posttest, and complete the Registration/Evaluation Form.

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This program has been approved for 2.5 contact hours of continuing education by the American Academy of Nurse Practitioners. Program ID 0506251.

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This program has been reviewed and is approved for a maximum of 2.5 hours of AAPA Category I (Preapproved) CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of November 1, 2005. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

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Musculoskeletal Injuries and Osteoarthritis Pain: Optimizing Treatment Outcomes is a certified continuing education activity providing an in-depth, expert review and analysis of recent scientific advances and clinical controversies in the management of mild-to-moderate pain. The views presented are those of the faculty and/or contributing editors and not necessarily those of the producer, commercial supporter, the US Department of Health and Human Services Office on Women's Health, or the University of Colorado School of Medicine. Some information presented in this monograph may be off label. Before using any product discussed in this publication, clinicians should consult the full prescribing information.

Musculoskeletal Injuries and Osteoarthritis Pain: Optimizing Treatment Outcomes reports highlights from a roundtable meeting presented by the US Department of Health and Human Services Office on Women's Health, under the auspices of the University of Colorado School of Medicine, and in cooperation with the American Geriatrics Society, the American Pharmacists Association, American Academy of Nurse Practitioners, and the American Academy of Physician Assistants.

This material is based upon a review of multiple sources of information, but is not exhaustive of the subject matter. Healthcare professionals and other individuals should review and consider other publications and material about the subject and not rely solely upon the information contained within this publication.

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Please look for the entire DHHS *State-of-the-Art Management of Mild-to-Moderate Pain* series, which can be found at http://www.medcme.org/

Overview

Approximately 25% of the population in the United States suffers from musculoskeletal injuries or disorders, reflecting annual indirect costs of $254 billion.[1] Musculoskeletal injuries are now the primary cause for clinician visits and result in approximately 153 million bedridden days per year for afflicted individuals.[1] In recognition of the worldwide impact of musculoskeletal conditions on health and quality of life, and the resultant economic impact, the current decade (2001 to 2010) has been declared the "Bone and Joint Decade" by a coalition including the United Nations, the World Health Organization, and 22 participating countries.[1] In a related demonstration of concern, the US Congress has declared this time to be the "Decade of Pain Control and Research."[2]

This monograph will present musculoskeletal pain management options associated with soft tissue injuries, which include overuse injuries, strains, sprains, chronic tendon lesions, and fracture-related damage. Overuse injuries, including delayed-onset muscle soreness (DOMS) and osteoarthritis (OA), may be more complex. These injuries can occur from repetitive use of a joint or muscle, but the pathophysiologies of DOMS and OA are not as well defined as other soft tissue injuries. Although pain resulting from tissue or overuse injuries may be adaptive in helping protect injured tissues, it may also interfere with rehabilitation during the recovery process. From the perspective of the injured patient, pain is likely to be the overriding initial concern, and prompt intervention for pain is the essential first step in managing musculoskeletal injury.

Recent approaches to pain management have been complicated by the withdrawal of rofecoxib and valdecoxib from the prescription drug market. These agents—both cyclooxygenase (COX)-2–selective nonsteroidal anti-inflammatory drugs (NSAIDs)—were believed to have an improved gastrointestinal (GI) safety profile over traditional, nonselective NSAIDs.[3] However, studies have linked these agents, along with celecoxib, to increased cardiovascular (CV) events.[3-5] These reports have raised concerns relative to the CV safety of all selective and nonselective NSAIDs and have prompted the US Food and Drug Administration (FDA) to ask the manufacturers of all prescription NSAIDs to revise their labeling to include a boxed warning highlighting the potential for increased risk of CV and GI adverse events associated with their use. Manufacturers of celecoxib and all other prescription NSAIDs have also been asked to revise their labeling to include a Medication Guide for patients to help make them aware of the potential CV and GI adverse events associated with the use of this class of drugs.

In addition, FDA is asking the manufacturers of all over-the-counter (OTC) NSAIDs to revise their labels to include more specific information about the potential CV and GI risks, along with information to assist consumers in the safe use of the drugs. FDA is also asking manufacturers of OTC NSAIDs to include a warning about the risk of potential skin reactions. The labeling of prescription NSAIDs already addresses potential skin reactions.[6]

The US Department of Health and Human Services Office on Women's Health assembled a group of pain management experts to examine the impact of mild-to-moderate pain on individuals, society, and the healthcare system. These experts were invited to present and discuss new clinical data before suggesting a multimodal treatment approach designed to help improve clinical outcomes. This issue of *CLINICIAN*® presents highlights of the roundtable proceedings.

Activity-Related Musculoskeletal Problems

Physical activity is beneficial—it improves flexibility and balance and builds strong muscles and bones throughout a person's lifespan. Physical fitness protects individuals from overexertion or strains and prevents consequences of overexertion, including muscle tears, tendon ruptures, bone fractures, and low back pain. Musculoskeletal fitness delays the onset of age-related disorders such as osteoporosis. In addition, physical fitness can lower the risk of chronic illnesses, including obesity and CV disease.

Despite the obvious health benefits that derive from physical fitness, there are also risks associated with physical activity. The most common health problems associated with physical activity are musculoskeletal injuries, which can occur with either excessive activity or sudden activity in an underconditioned individual. It has been estimated that nearly 29 million people in the United States sustain musculoskeletal injuries each year, more than half of all reported injuries.[1] Underconditioning is a problem in terms of athletic participation, but can also lead to injuries during the course of daily living.

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The health problems associated with extremely strenuous exercise or sports regimens are also significant. More than 30 million Americans participate in organized sports, and half of American adults exercise on a regular basis.[7] This has led to an increase in activity-related injuries, which has a substantial impact on the workforce. It has been estimated that musculoskeletal injuries are responsible for 147 million lost workdays each year, as well as 21 million lost school days for children.[1] Furthermore, 17 million people in the United States sustain a significant injury from sports or recreational participation each year.[7] In light of these statistics, it is clear that understanding the causes, prevention, and treatment of activity-related injury would be of enormous benefit.

Differentiating Between Sprains and Strains

A sprain is a stretching or tearing injury to a *ligament*, the severity of which depends on the extent of injury to

a single ligament (partial or complete tear) and the number of ligaments involved. A sprain can result from a fall, a twist, or a blow to the body that forces a joint out of its normal position.[8] Although sprains can occur in either the upper or the lower parts of the body, the most common site is the ankle.

The ankle joint is composed of 3 bones, the tibia, the fibula, and the talus (Figure 1).[8] The talus articulates with the tibia and the fibula to form the mortise joint of the ankle, which is supported by several lateral and medial ligaments. The most common type of sprain is an inversion injury, which happens when the foot turns inward as a person runs, turns, falls, or lands on the ankle after jumping.[8] With an inversion injury, 1 or more of the lateral ligaments are injured, most often the anterior talofibular ligament. The second most frequently torn ligament is the calcaneofibular ligament.

Sprains also frequently occur in the wrist, which is most commonly caused by falling on an outstretched hand. As with other types of sprains, wrist sprains are graded according to their severity. A grade I sprain is a mild injury that causes stretching and microtearing of ligament tissue, but the stability of the injured joint is not significantly affected. A grade II sprain is a partial tearing of ligament tissue in combination with mild instability of the joint. With a grade III sprain, the ligament is torn completely or avulsed, which causes significant instability of the joint.[8]

The knee is another common site for a sprain, which is usually caused by a blow, a fall, or sudden twisting. The knee joint is an articulation of 3 bones; the tibia and the femur meet to form a hinge joint, in front of which is the patella (Figure 2).[8] The 4 primary stabilizing ligaments of the knee are the anterior cruciate ligament, the posterior cruciate ligament, the medial collateral ligament, and the lateral collateral ligament.

A strain is an injury to either a *muscle* or a *tendon*. Depending on the severity of a strain, the muscle or tendon could simply be stretched, or it could sustain a partial or complete tear.[8] Strains are caused by the traumatic twisting or pulling of a muscle or tendon. Strains can be either acute or chronic—an acute strain is caused by the overstressing of muscles that occurs, for instance, with the improper lifting of heavy objects. Conversely, chronic strains are generally the result of prolonged, repetitive overuse of the muscles and tendons.[8]

Strains commonly occur in either the back or the hamstring muscle. People who are underconditioned or obese are at increased risk for strains because of diminished muscle tone, which decreases the body's ability to protect itself against strains.[8] People who engage in contact sports, such as soccer, football, hockey, boxing, or wrestling, are also at increased risk for strains.[8] Sports that require extensive gripping, such as tennis and golf, increase the risk of hand and forearm strains. Those who participate in racquet sports, throwing, and contact sports are at risk for elbow strains.[8]

Figure 1

LATERAL VIEW OF THE ANKLE[8]

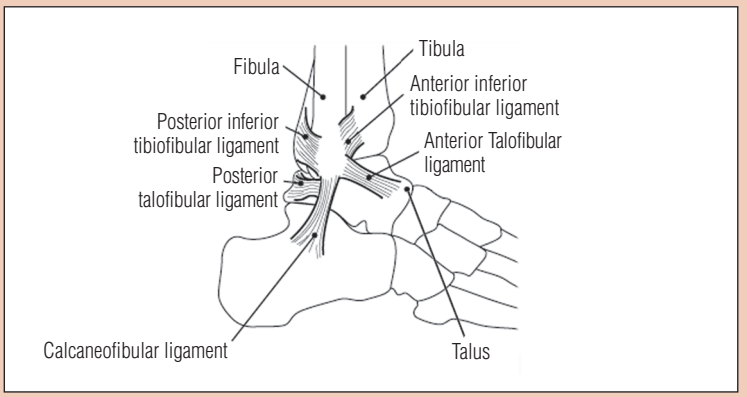
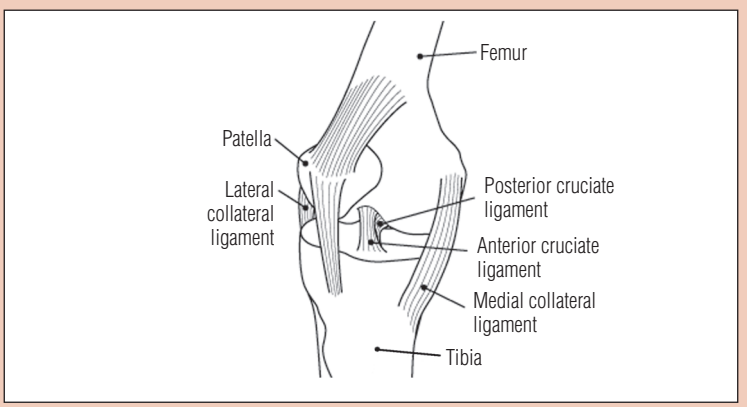


Figure 2

LATERAL VIEW OF THE KNEE[8]



Gender Differences

There appears to be a growing body of evidence suggesting that female athletes continue to show an increased anterior cruciate ligament injury rate in sports such as basketball and soccer.[9-11] Researchers theorize that gender differences in the performance of athletic maneuvers are a contributory factor. In general, females experience increased frontal plane moments and decreased sagittal plane moments during early deceleration. These differences are suggestive of an "at risk" pattern in that frontal plane support of the knee is afforded primarily by passive structures (including the anterior cruciate ligament). Furthermore, increased quadriceps and activity and smaller net flexor moments may suggest less sagittal plane protection (ie, increased tendency toward anterior tibial translation).[11] Prevention programs based on improving dynamic control of the knee by emphasizing hamstring strengthening may be appropriate in this patient population.

Fractures

In the United States, 5.6 million fractures occur per year, which corresponds to an incidence of 2%.[12] Fractures occur when external force applied exceeds the strength of the affected bone as a result of either direct or indirect trauma. Direct trauma involves lineal proximate force to the bone, which can include tapping fractures, penetrating fractures, and crush fractures. Indirect trauma arises from forces acting at a distance from the fracture site. Indirect mechanisms include tension, compressive, and rotational forces.[12]

Table 1

PATIENT FACTORS INFLUENCING FRACTURE HEALING[12]

Prognostic Factor	Enhancing Condition	Problematic Condition
Age	Youth	Advancing age (>40 y)
Trauma	Single limb	Multiple traumatic injuries
Comorbidities	None	Multiple medical comorbidities (eg, diabetes)
Medications	None	NSAIDs, corticosteroids
Social factors	Nonsmoking	Smoking
Local factors	No infection	Local infection
Type	Closed fracture, neurovascularly intact	Open fracture with poor blood supply
Nutrition	Well nourished	Poor nutrition

NSAID, nonsteroidal anti-inflammatory drug.

Used with permission from eMedicine.com, Inc., 2004: Buckley R, Arneja SA. General principles of fracture care. Available at: http://www.emedicine.com/orthoped/topic636.htm. Accessed July 20, 2004.

Table 2

RISK FACTORS FOR OSTEOARTHRITIS[18]

Systemic Factors	Local Biomechanical Factors
↓	↓
Increase Susceptibility to OA	Influence Site and Severity of OA
Age	Obesity
Gender	Joint injury/overuse
Ethnic characteristics	Joint deformity/shape
Bone density	Sports participation
Genetics	Muscle weakness
Nutritional factors	
Metabolic factors	

OA, osteoarthritis.

Adapted with permission from Felson DT et al. *Ann Intern Med.* 2000;133:635-646.

Pathology of Bone Fractures

Injury involves the actual fracture to the bone, with resultant insult to bone marrow, periosteum, and local soft tissues. Almost identical to the process of tissue healing and repair, there are 4 phases of fracture healing: (1) inflammation, (2) proliferation, (3) maturation, and (4) callus formation. Immediately after fracture, a hematoma forms at the fracture site. There is an inflammatory reaction that initiates cellular migration and proliferation and differentiation of cells at the site of injury.[13] Within 1 week, the body forms granulation tissue between the fracture fragments, which provides some stability to the fractured bone but not enough for the bone to support weight. In the maturation phase, the fracture unites. Activated osteoprogenitor cells deposit woven bone, and activated mesenchymal cells in the soft tissue surrounding the fracture differentiate into chondroblasts and deposit cartilage. This mixture of granulation tissue, woven bone, and new cartilage is called a callus. Finally, the meshlike callus of woven bone undergoes remodeling to form strong lamellar bone.[12]

There are a number of patient factors that can influence fracture healing, including age, degree of trauma, medication use, and nutrition (Table 1).[12] Patients who have poor prognostic factors for fracture healing are at increased risk for complications, including malunion, nonunion, osteomyelitis, and chronic pain.[12]

Because of the high prevalence and cost associated with soft tissue injuries, it is necessary to begin treatment early to effectively manage these injuries. This will help ensure more complete recovery of function and reduce the socioeconomic costs of lost workdays and prolonged morbidity.

Osteoarthritis

Despite the obvious benefits regarding physical fitness, there appears to be an increased risk of lower limb OA in participants of repetitive, high-impact sports that is strongly associated with joint injury.[14]

OA is the most common form of arthritis in the United States.[15,16] More than 20 million people suffer from OA in the United States, and radiologic evidence suggests that more than 50% of the population 65 years of age or older have OA in at least 1 joint.[16] Consistent with the aging of the population, the prevalence of OA is expected to double by 2020.[17]

More than 20 million people suffer from OA in the United States, and radiologic evidence suggests that more than 50% of the population 65 years of age or older have OA in at least 1 joint.

A number of known systemic and local biomechanical risk factors increase susceptibility to OA and influence location and severity of the condition (Table 2).[18] Both modifiable and unmodifiable risk factors have been

identified. The probability of developing OA increases with such systemic risk factors as advancing age, female gender, bone density, and nutritional and metabolic variables. Increasing age is perhaps the most significant risk factor for OA, with the prevalence in all joints increasing with age.[19] Another potential contributing factor for premature articular cartilage degeneration is lower extremity malalignment, which also can result in abnormal joint loading.[20]

Although sports that subject joints to repetitive high levels of impact and torsional loading increase the risk of articular cartilage degeneration and the resulting clinical syndrome of OA, moderate habitual exercise does not increase the risk of OA.[21] Increased risk is likely reserved for those with abnormal joint anatomy/alignment, previous significant joint injury or surgery, joint instability, above-average body weight, disturbances of joint or muscle innervation, or inadequate muscle strength.[21]

Injury and Healing: The Clinical Application of Basic Science

Musculoskeletal injuries generally do not all have the same pathophysiology and often heal differently.[22] Therefore, the clinician should consider the type of injury when selecting appropriate pain medication.

Injuries to tendons, ligaments, muscles, and bones can cause significant pain, which is often accompanied by inflammation. Although achieving pain relief is a key component of rehabilitation, the process of inflammation is fundamental to the healing of musculoskeletal injuries.[23] Historically, the anti-inflammatory effect of NSAIDs has been the rationale for using these analgesics in the treatment of musculoskeletal injuries; however, the clinician must evaluate the need for pain relief and how analgesic choice could interfere with healing. Proper management necessitates understanding the complex role of inflammation as an inherent part of the healing process. Specifically, inflammation plays a more active role in muscle strains and sprains (ligament/joint damage due to partial tears and direct contusions) than it does in tendinopathies or DOMS.

Theoretic Pathways of Sports-Induced Inflammation

Inflammation is always a potential response to musculoskeletal injury. As Leadbetter has stated, "inflammation can occur without healing, but healing cannot occur without inflammation."[23] When strains, sprains, or soft tissue damage associated with fracture occur, the healing process that ensues consists of 3 overlapping phases: inflammation, proliferation, and maturation.[24-26]

The Inflammatory Phase

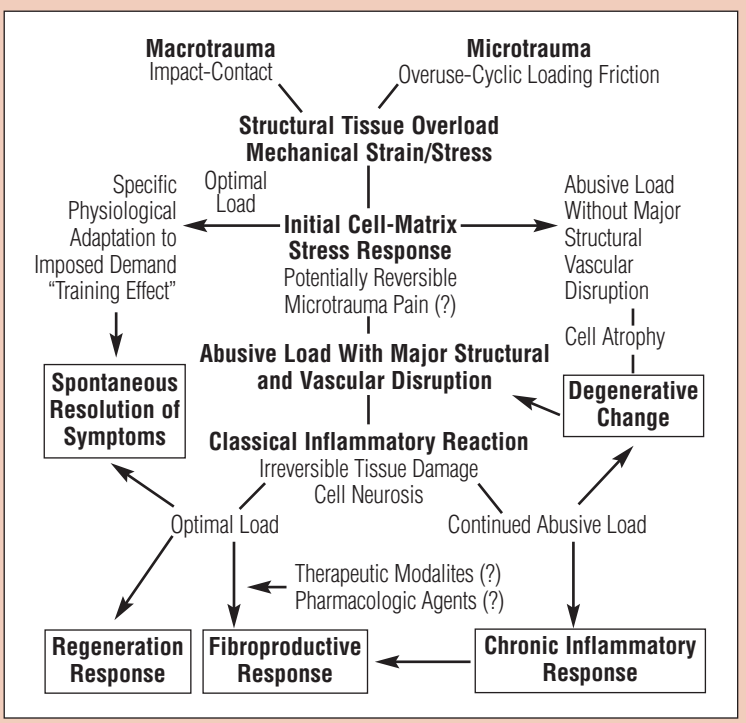
The healing process starts with the inflammatory phase, a localized, protective-tissue response that isolates injured tissue and destroys damaged cellular by-products or injurious agents, thus setting the stage for the rest of the healing process.[27] Inflammation is characterized by 5 cardinal signs: swelling, erythema, increased temperature, pain, and impaired function.[22,26,27] The complex inflammatory response comprises a number of events that immobilize the injured site, increase blood flow, and promote the entry of inflammatory cells[26]:

- Increased vascular permeability, leading to tissue edema
- Exudation of fibrin
- Infiltration of inflammatory cells (leukocytes, monocyte-lymphocyte line cells, macrophages)
- Production of fibronectin
- Thickening of capillary walls
- Occlusion of capillaries

The initial response of vascularized tissue to injury can last up to 7 days, depending on the severity and type of injury.[26] Figure 3[23] represents a proposed schema for the possible outcomes from sports-induced inflammation caused by macrotrauma (eg, strain, sprain) or microtrauma (eg, overuse).[23] Either form of damage overloads the tissues, producing mechanical strain and stress. The initial stress response in the cell matrix—although it may

Figure 3

THEORETIC PATHWAYS OF SPORTS-INDUCED INFLAMMATION[23]



Reprinted with permission from Leadbetter WB. In: Leadbetter WB, Buckwalter JA, Gordon SL, eds. *Sports-Induced Inflammation: Clinical and Basic Science Concepts*. Park Ridge, Ill: American Academy of Orthopaedic Surgeons; 1990:3-23.

be painful—is thought to be reversible, depending on the subsequent load on the tissue. Optimal loading of the tissue is likely to lead to spontaneous remission and full recovery.[23] However, when an abusive load is continued in the absence of major structural or vascular damage, cellular atrophy and degenerative changes are likely. If an abusive load is continued, but is associated with structural or vascular damage, further damage and sustained inflammation can result in local cell necrosis and irreversible tissue damage.

As part of the inflammatory responses, cytokines and growth factors (GFs) are released at the site of the injury.[24] This response is mediated in part by the production of prostaglandins (PGs), formed from arachidonic acid by the dual COX pathways, COX-1 and COX-2.[24] In a normal inflammatory response, vascular, cellular, and chemical mediators eventually lead to tissue regeneration and repair. In some settings, excessive inflammation and chronic degeneration can occur and produce scarring or adhesion formation.[26] Research suggests that a chronic inflammatory condition is most likely to result when the injury is subjected to continued abuse and irritation, which in turn stimulates additional local cytokine release that prolongs cellular activity.[27] The failure of the normal orderly healing progression in a wound can, in certain instances, lead to adverse granulation tissue formation or tissue degeneration.[27]

The Proliferative Phase

The proliferative phase generally occurs from 7 to 21 days following an injury. This phase is concerned with the elimination of damaged cellular material and laying down of new connective tissues to restore function. Typically, it is characterized by fibrin clotting, as well as macrophage- and GF-induced migration and proliferation of fibroblasts, myofibroblasts, synovial cells, and capillaries.[26] As the macrophages eliminate damaged material through phagocytosis, there is an increased production of fibronectin, collagens, and the proteoglycans and glycoproteins of the extracellular matrix. Gradually, healthy deposition of granulation tissue replaces the original fibrin clot.

The Maturation (Remodeling) Phase

During the maturation phase, fibroblasts continue to restructure the extracellular matrix.[24] The cellular and capillary material and the proteoglycan water content of the tissue are reduced. Simultaneously, the type I collagen (basic collagen of musculoskeletal tissues) becomes more organized, orienting normally so that it is stronger and better able to withstand stress. A substantial recovery of strength and stress resistance may occur approximately 6 to 8 weeks following an injury, but complete healing may require a period of 1 to 2 years.[26]

Other Injuries

Tendon Injuries

The traditional view of tendon injury, most frequently referred to as tendinitis, proposed that swelling and pain resulted from repetitive mechanical load with a subsequent inflammatory response, hence the suffix "itis." Therapy focused on reducing pain and inflammation with rest, ice, and anti-inflammatory medications. In tendinitis—more accurately called *tendinopathy* or *tendinosis*—there is actually no clinically apparent inflammation, so blocking inflammation is unlikely to be beneficial. Supporting this concept, a systematic literature review by Almekinders and Temple of 2326 articles on the etiology, diagnosis, and treatment of "tendinitis" concluded that actual inflammation of tendon tissue consistent with tendinitis has not been demonstrated clearly in pathoanatomic studies.[28]

Musculoskeletal injuries generally do not all have the same pathophysiology and often heal differently. Therefore, the clinician should consider the type of injury when selecting appropriate pain medication.

Chronic tendon injuries, such as tennis elbow, are often assigned the misnomer "tendinitis." However, researchers suggest that these injuries are due to microtrauma of the tendon rather than inflammation.[29,30] For tendon degeneration without signs of inflammatory response, the more appropriate term is tendinosis, and any pathology that arises in and around the tendons is a *tendinopathy*. The differences between these terms are not merely semantic; there are clinical implications as well. For instance, the treatment of tendinosis should target collagen breakdown—characterized by an increase in mucoid ground substance and an absence of inflammatory cells—rather than inflammation.[31]

Less is known about acute tendon injuries. One theory suggests that tissue damage in overuse tendinopathy may actually precede acute injury and overt symptoms.[32] In sports medicine, a typical scenario is a period of excessive training that precedes the development of symptoms. An athlete might complain of elbow pain after lifting a heavy suitcase, but there is really no way to determine whether this is an acute injury or simply the result of pre-existing tendon damage.

Muscle Injuries

The most frequent types of sports-related muscle injuries are strains and contusions.[26] As described earlier, strain injuries are the result of excessive tension on the muscle or tendon, which results in a tear, followed by inflammation, clearing of debris, and finally regeneration of the tissue. Contusions are the result of a direct blow to the muscle, resulting in a hematoma with inflammation in the muscle mass.

DOMS is a muscle strain injury characterized by decreased function occurring 24 to 48 hours after repeated eccentric exercise that causes the muscle to lengthen and contract simultaneously.[25,33] DOMS pathophysiology is less defined than that of other soft tissue injuries, such as strains and sprains.[25] In contrast to other soft tissue injuries, there is minimal inflammation in

DOMS, no fibroblast activation, and little correlation of inflammation with clinical symptoms. However, there is damage to the muscle fibers, as evidenced when sarcomeres are examined under electron microscopy. Additional evidence of muscle damage is reflected in elevated serum levels of creatine kinase (CK).[25] Currently, multiple theories exist to explain the etiology of DOMS, including lactic acid, muscle spasm, connective tissue damage, and inflammation.[33] The general consensus is that a complete explanation is likely to combine elements from each of these theories.[33]

Osteoarthritis

Acute joint injury and deformity, participation in certain sports, occupational factors, and muscle weakness—particularly of the quadriceps—all have been shown to increase the risk of OA. For example, a cross-sectional study was designed to explore the relationship between lower extremity weakness and OA of the knee. After adjustment for body weight, age, and gender, lower quadriceps strength predicted symptomatic and radiographic OA of the knee.[34] Each 10 lb-ft increase in the strength of knee extension was associated with 20% lower odds for radiographic OA and 29% lower odds for symptomatic OA. The findings of another prospective study to determine whether baseline lower extremity muscle weakness is a risk factor for radiographic OA of the knee indicated that knee extensor strength was 18% lower in women with incident OA than in controls without incident OA.[35] Moreover, body weight and extensor strength were negatively correlated (r=-0.740, P=.003). Not only is quadriceps weakness associated with an increased risk of OA, but it also correlates with pain (P<.005).[36] Within the group of patients with knee pain, strength of the quadriceps was inversely related to degree of disability.

Presentation and Physical Findings

The OA process likely begins before signs and symptoms become manifest, and symptom onset may be insidious. Pain is the most important symptom to trigger a visit to the clinician.[19] Morning stiffness or stiffness after inactivity (gel phenomenon) is common,[19] but it is usually of limited duration and resolves upon initiation of activity. In general, pain increases with an increase in physical activity.

Pain Mechanisms in OA

Pain is the principal symptom of OA. Characteristically mild to moderate in intensity, it worsens with joint use and improves with rest. Although the exact cause of pain is not known, virtually all components of the joint can be sources of pain (Table 3).[37] Joint structural alterations alone are unlikely to explain pain. Rather, the pain experienced in OA appears to result from complex interactions among structural deterioration, central and peripheral pain mechanisms, and psychosocial determinants of pain perception.[19]

Table 3

SOURCES AND MECHANISMS OF PAIN IN OSTEOARTHRITIS[37]

Site/Source	Mechanisms
Subchondral bone	Medullary hypertension, microfractures
Osteophytes	Stretching of nerve endings in periosteum
Ligaments	Stretching
Enthesis	Inflammation
Joint capsule	Inflammation, distension
Periarticular muscle	Spasm
Synovium	Inflammation

Adapted with permission from Dieppe P, Brandt KD. *Rheum Dis Clin North Am.* 2003;29:687-716.

Physical findings are consistent with the radiographic findings described earlier. Examination usually reveals local tenderness of the joints, often including tenderness of the tibial plateaus. Bony enlargement is also frequent, as is crepitus upon motion. Range of motion may become limited and joints may become misaligned and/or deformed.[19]

Clinical Implications of Injury: Pathophysiology and Healing

Not all injuries that are accompanied by pain will involve inflammation, and, as discussed earlier, in some injuries the role of inflammation remains unclear. In soft tissue injuries, where inflammation has resulted, the use of anti-inflammatory agents may actually retard the healing process.[25] However, it is essential to prescribe the appropriate analgesic for adequate pain management. This, in turn, enables the patient to heal and participate in a conditioning program that is important for a full recovery.[38]

Because the pain of a musculoskeletal injury usually requires prompt treatment, it is important to implement the following principles in order to select the most appropriate analgesic agent:

- Make an accurate diagnosis; various injuries involve different pathophysiologies and may necessitate specific treatment regimens
- Distinguish the injury itself from the pain and develop a treatment strategy that addresses pain and injury as separate, albeit related, clinical issues
- When selecting an analgesic, consider the potential side effects of treatment and their impact on healing

When appropriate analgesics minimize discomfort and pain, healing and a more rapid rehabilitation are enhanced.

Nonpharmacologic Considerations in the Management of Soft Tissue Injuries

When managing mild-to-moderate pain, both nonpharmacologic and pharmacologic interventions should be assessed. The traditional approach to managing soft tissue injuries includes rest, ice, compression, and elevation (RICE). Although widely used, RICE has not been rigorously examined in controlled clinical trials to see if it actually improves or hinders healing.

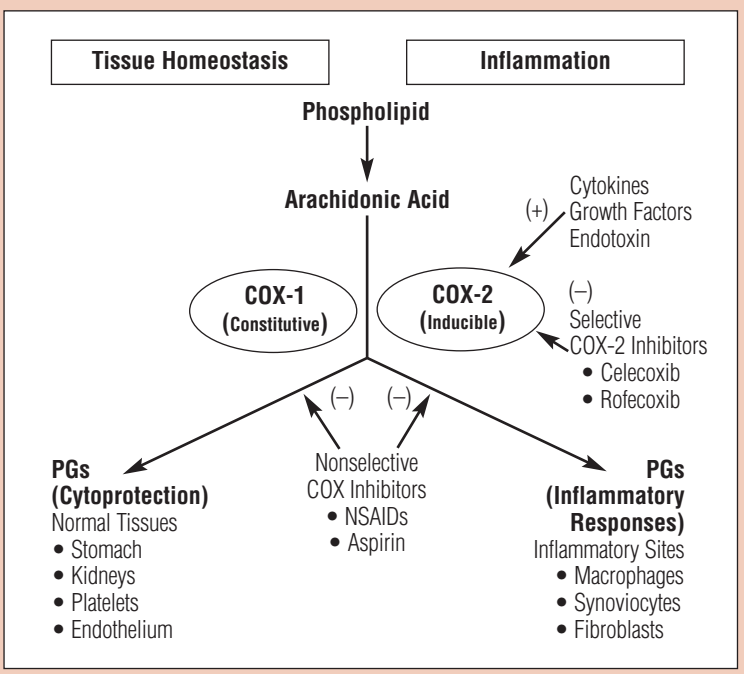
Rest and immobilization are appropriate to relieve initial pain and prevent re-injury, but have been shown to be detrimental if prolonged.[26] Extended immobilization can result in tissue atrophy, whereas controlled stretching and joint movement have been shown to improve collagen fiber orientation to parallel the stress lines of normal fibers.[26] Similarly, controlled mechanical load stimulates the bone remodeling process in healing fractures. *Ice* can relieve pain by affecting nerves and causing temporary vasoconstriction to reduce edema, but its ultimate effects on swelling are unclear. *Compression* retards swelling, but its effects on pain and ultimate clinical outcome have not been identified.[39] In fractures, there is the additional risk that compression may cause neurovascular complications. Finally, *elevation* is logical in the short term, because it may alleviate swelling by counteracting gravitational effects and improving venous return, but there are no data on its overall impact on the healing process.

Other interventions for the management of pain include patient education, relaxation/cognitive therapy, and hypnosis. For example, in the treatment of OA, the following nonpharmacologic measures may offer some benefits to patients:

- Exercise (CV, muscle-strengthening, range-of-motion)
- Weight loss (if obese)
- Assistive devices
- Lateral-wedged insoles
- Patellar taping
- Patient education/support

Figure 4

EFFECTS OF NSAIDS ON THE ARACHIDONIC ACID CASCADE[40-43]



The role of COX isoforms 1 and 2 in normal and inflamed tissue.

NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; PG, prostaglandin.

Selecting an Analgesic

The analgesic choices for the management of mild-to-moderate pain in sports-related injuries include NSAIDs, COX-2 inhibitors, and acetaminophen, with opioids and opioid combinations reserved for chronic severe pain. When selecting a specific medication for mild-to-moderate pain, the efficacy, overall risk and benefits need to be considered. This section will review the mechanisms of the various analgesic agents and their use in musculoskeletal injuries.

Mechanisms of NSAIDs

NSAIDs exert their analgesic and anti-inflammatory effects primarily through inhibition of the COX enzyme, which alters the conversion of arachidonic acid into a number of compounds, including PGs and thromboxanes. The COX enzyme exists in 2 isoforms, COX-1 and COX-2, with each performing various functions and being differentially expressed in different tissues (Figure 4).[40-43] COX-1 mediates PGs that maintain the integrity of the GI, renal, and vascular mucosa, and protect surface epithelial cells, whereas COX-2 induces pro-inflammatory PGs that cause the stiffness, swelling, and pain that accompany an illness or injury. Nonselective NSAIDs block the activity of both isoforms—blocking COX-1 leads to adverse GI effects, and the inhibition of COX-2 may account for their interruption of the inflammatory process. By inhibiting only the COX-2 isoform, COX-2–selective inhibitors may minimize the adverse GI effects associated with nonselective NSAIDs; however, they may have a negative effect on healing as they may impede inflammation, which is a necessary component of healing.

Mechanisms of Acetaminophen

The mechanism of action by which acetaminophen produces analgesia is not fully understood; however, it is believed to act centrally by increasing the pain threshold within the brain.[44] Like NSAIDs, acetaminophen has both analgesic and antipyretic properties

to provide relief to the patient, but acetaminophen has no anti-inflammatory activity and is not associated with adverse GI effects. Because it does not affect COX enzymes, acetaminophen has minimal effects on PG synthesis.[45] The analgesic potency of acetaminophen is similar to that of aspirin, but acetaminophen is devoid of anti-inflammatory effects. Overall, acetaminophen is an effective first-line agent, has fewer side effects than NSAIDs, and is recommended for use when NSAIDs are contraindicated (eg, in elderly patients or patients with asthma, peptic ulcers, or renal insufficiency).[46]

Analgesia

OTC analgesics are proven effective pain relievers, yet in certain circumstances comparative data in specific disease states are lacking. Furthermore, comparative efficacy trials are difficult to interpret because they often involve different patient populations, different disease states, dosing and duration variations, and different measures of effective analgesia, especially in their clinical relevance. This section will review select data from various musculoskeletal disorders.

Ligament and Muscle Injuries

NSAIDs

The clinical literature on ligament injuries focuses on joint function rather than ligament healing, with 2 principles having been validated repeatedly in studies. The first is that early mobilization of the joint results in faster healing; the second is that controlled rehabilitation with the avoidance of excessive stress helps speed recovery.

In soft tissue injuries, where inflammation is the result of tissue injury, the use of anti-inflammatory agents may actually retard the healing process.

Almekinders identified more than 35 articles that reported the use of NSAIDs in sprains and strains, but found that only 15 of them were sufficiently rigorous to permit valid conclusions.[47] Few differences were found among various NSAIDs unless they were being compared to a placebo-controlled group. Moreover, treatment effects were often confounded because injuries tend to improve over time, even without treatment.

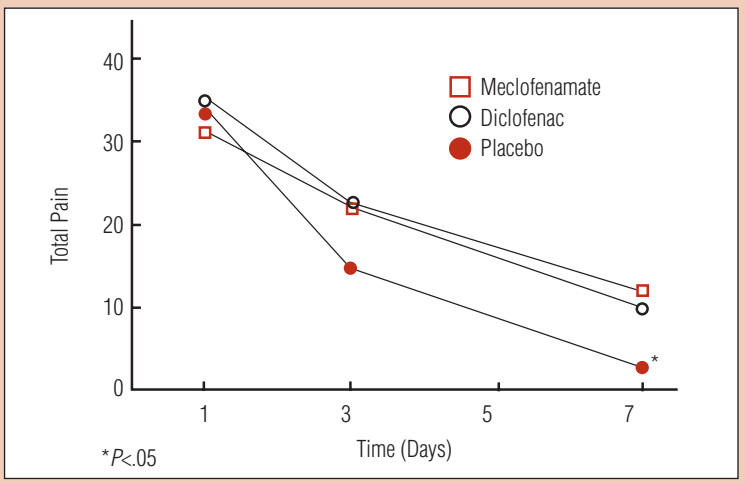
More recently, Almekinders and Temple conducted a review of the literature and concluded that NSAIDs did not offer major benefits for the treatment of soft tissue injuries.[28] This conclusion is supported by the findings of a randomized controlled trial on hamstring tears demonstrating that NSAIDs did not improve healing. In fact, for patients with severe pain, placebo-treated patients had significantly lower pain scores at day 7 than did those who received diclofenac or meclofenamate (Figure 5).[48] For patients with less severe pain, there were no differences among the groups evaluated.

Acetaminophen

Acetaminophen was recently evaluated for the treatment of pain associated with sprains in a multicenter, randomized, double-blind trial conducted by Dalton and Schweinle.[49] The study followed patients with grade I or grade II lateral ankle sprains—involving either overstretching or partial tearing of supporting ligaments—who had moderate pain when walking. Patients were randomized to either acetaminophen (1300 mg extended-release, 3 times daily) or ibuprofen (400 mg, 3 times daily) for 9 days. Additionally, all patients were instructed to use RICE. At the conclusion of the trial, the acetaminophen and ibuprofen groups showed comparable findings by all endpoint measures (swelling, bruising, range of motion). Both medications were well tolerated, with no significant differences between treatment groups.[49]

Figure 5

PAIN SCORES ARE SIGNIFICANTLY LOWER IN PLACEBO-TREATED GROUP[48]



Changes in total pain scores in 3 groups of subjects with severe acute hamstring injuries treated with NSAIDs or placebo. Note that pain scores were significantly lower in the placebo group than in the meclofenamate group on day 7.

Adapted with permission from Reynolds JF et al. *S Afr Med J.* 1995;85:517-522.

Strains, Sprains, and Fracture-Associated Injuries

As part of their mechanism of action, NSAIDs may diminish the inflammatory response following soft tissue injuries, an effect that may retard healing.[25] Almekinders and Gilbert found that NSAIDs caused a delay in inflammatory response and muscle regeneration soon after injury in an animal model (rat tibialis anterior muscle) of experimental muscle strain.[50] Although NSAIDs can provide initial pain relief, they may also have an untoward effect on the healing process following an injury.[25]

Of the COX-2 inhibitors, the effect of celecoxib on healing was evaluated in a rat model following surgical ligament injury.[51] In a mechanical test of ligament strength, ligaments from celecoxib-treated rats failed at a 32% lower load than did those from untreated rats. While animal data cannot necessarily be extrapolated to humans, the authors concluded that the study did not support the use of COX-2–specific NSAIDs to treat ligament injuries. Additional studies in humans are needed.

Inflammation is a result of injury and a necessary step in the healing process. Soft tissue injuries tend to heal with controlled mobilization and rehabilitation. Research is very limited as to the role of pharmaceuticals in the healing of athletic injuries. Because chronic tendon injuries do not have an inflammatory component, the anti-inflammatory properties of NSAIDs are of little benefit in treatment. Pain relief likely has therapeutic benefit when it encourages mobilization and rehabilitation.

Healing in Bone Injuries

As with many other musculoskeletal injuries, inflammation is an inherent part of the healing process in bone injuries. In fractures, surrounding soft tissue trauma and the resultant inflammation and hypoxia contribute significantly to pain, which protects the injured structure from further use, but also induces gene expression pathways and facilitates cell proliferation and migration to the fracture site to promote healing.[13] Pain management is required for patient well-being and rehabilitation. Without adequate pain control, a patient is unlikely to put weight on an injured limb, which may slow down the process of tissue repair. Although opioids and opioid/acetaminophen combinations may be used initially for the management of severe pain, other analgesics may be necessary as the healing process continues.

A recent review of the effect of NSAIDs on bone healing found evidence that both nonselective and COX-2 –selective NSAIDs may be harmful to bone healing following repeated administration, as shown in both animal and in vitro studies.[52,53] Researchers theorize that, by inhibiting COX enzymes and the subsequent production of PGs, NSAIDs not only achieve their desired anti-inflammatory effects, but they also inhibit the increased production of PGs that is necessary for bone healing.[52] Supporting this theory is a retrospective analysis of patients with nonhealing diaphysis fractures of the femur. The study showed a highly significant association between the use of NSAIDs following the injury and impaired union of the fracture.[54] Furthermore, in those cases with united fractures, NSAID treatment was associated with delayed healing. In the absence of controlled studies to determine if these results are clinically significant, a clinician may want to consider using a non-NSAID analgesic that would not risk interference with bone healing for control of mild-to-moderate pain associated with fractures. Acetaminophen, a non-NSAID analgesic, may be an alternative; however, no studies have been undertaken to evaluate the efficacy of acetaminophen on pain associated with acute fracture.

Analgesics and Muscle Function in DOMS

Because of the complex pathophysiology of DOMS and the conflicting results of clinical studies, the role of common analgesics remains unresolved.[33] Some studies on NSAID use in DOMS suggest that there is no significant benefit for their use in treating muscle soreness. Because of the wide range of analgesics, dosages, and timing, it is difficult to draw any conclusions regarding the efficacy of NSAIDs in the treatment of this syndrome.[25,33,55-58]

Eccentric or excessive unaccustomed exercise has been shown to produce elevated serum CK levels.[58] Comparison of CK levels following strenuous exercise in humans and animals with or without NSAID therapy also has produced varied results. The results from an ibuprofen study suggest that serum CK levels were higher (a negative effect) after ibuprofen treatment than with placebo,[55] whereas other studies have reported that NSAIDs had no effect on CK levels.[58,59]

Comparative studies of ibuprofen and acetaminophen in the management of DOMS pain also produced conflicting outcomes. In a clinical study by Peterson and colleagues, investigators found that neither agent produced any anti-inflammatory effects (as shown by neutrophil or macrophage concentrations 24 hours after eccentric exercise),[60] which would suggest that these agents would be ineffective for muscle soreness and inflammation. However, another study reported that both ibuprofen and acetaminophen suppressed the increase in $PGF_{2\alpha}$ and protein synthesis that normally occurs following eccentric resistance exercise.[61,62] The contradictory results of these studies suggest the need for well-designed and controlled clinical trials of commonly used analgesics in DOMS for the purpose of accurate evaluation.

Tendon Injuries

Based on the assumption that there is an inflammatory component to tendon injuries (ie, tendinitis), NSAIDs have been widely prescribed in their treatment. A review of the literature reported that only 9 of 32 published studies on the use of NSAIDs in tendon injuries were prospective and placebo controlled.[28] Five of the 9 studies reported improved pain scores with NSAID therapy. However, because observation periods ranged from only 7 to 28 days, further studies are needed. There have been no recent studies addressing the use of acetaminophen for the treatment of tendon injuries.

Management of Tendon Injuries

Several factors should be considered in the management of tendinosis: recovery time is likely to be prolonged, whether the patient presents early or late in the injury, and controlled physical therapy can be very useful in

the development of collagen synthesis and maturation.[31] For example, in treating Achilles tendinosis, eccentric calf muscle training with a physical therapist helps strengthen the tendon and permits patients to resume normal activities more quickly.[38,63]

A review of the literature concluded that NSAIDs did not offer major benefits for the treatment of soft tissue injuries.

The precise mechanisms whereby these exercises improve tendinopathies are unknown. Researchers propose that eccentric loading may promote remodeling of the damaged tendon.[38,63] More specifically, exercise is thought to cause increased collagen production by stimulating mechanoreceptors in tenocytes.[31] The role of analgesia during rehabilitation would be to provide sufficient pain relief so that patients can participate actively in their rehabilitation.

Principles of Pain Management in OA

Current management of OA is directed at symptom — primarily pain—control and risk modification.[19] The substantial number of interventions in clinical use encompasses both pharmacologic and nonpharmacologic approaches, including surgery. Although it is generally agreed that a treatment plan should be multimodal and individualized, expert consensus and evidence-based support for definitive recommendations are limited.[64,65]

Management guidelines have been published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). Guidelines of both organizations have been developed from a combination of expert opinion and evidence-based analyses of published literature.[64,65] Despite differences in the recommendations, areas of consensus have been achieved for several nonpharmacologic, pharmacologic, and surgical interventions (Table 4).[64-66]

Drug therapy for OA is considered most effective when it is part of a multimodal treatment plan.[64,65] Based on its overall cost, efficacy, and toxicity profile, acetaminophen is recommended by the ACR as first-line therapy.[64] The American Geriatrics Society (AGS) Panel on the Management of Persistent Pain in Older Persons came to a similar conclusion stating "acetaminophen should be the first drug to consider in the treatment of mild to moderate pain of musculoskeletal origin."[67] Recent articles in the journal *American Family Physician*, published by the American Academy of Family Physician (AAFP), support the use of acetaminophen (up to 1000 mg doses, up to 4g per day) for first-line treatment of mild-to-moderate pain[68] and osteoarthritis.[69] Other analgesic options include analgesic doses of NSAIDs, and, for more severe pain, traditional NSAIDs, COX-2–selective NSAIDs and, less commonly, centrally acting medications. In some cases, tricyclic antidepressants and muscle relaxants are used as adjuvant therapy.

Table 4

ACR AND EULAR RECOMMENDATIONS ON THE MANAGEMENT OF OA: AREAS OF CONSENSUS[64-66]

Nonpharmacologic Therapy	Pharmacotherapy	Surgery
– Patient education	– Acetaminophen	– Arthroplasty
– Personalized social support	– NSAID	
– Weight loss	– IA corticosteroid	
– Aerobic exercise	– Topical NSAID	
– Muscle strengthening	– IA hyaluronate	
– Range-of-motion exercises		
– Walking aids		
– Insoles		

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; OA, osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; IA, intra-articular.

Comparative Efficacy of OTC Analgesics in OA

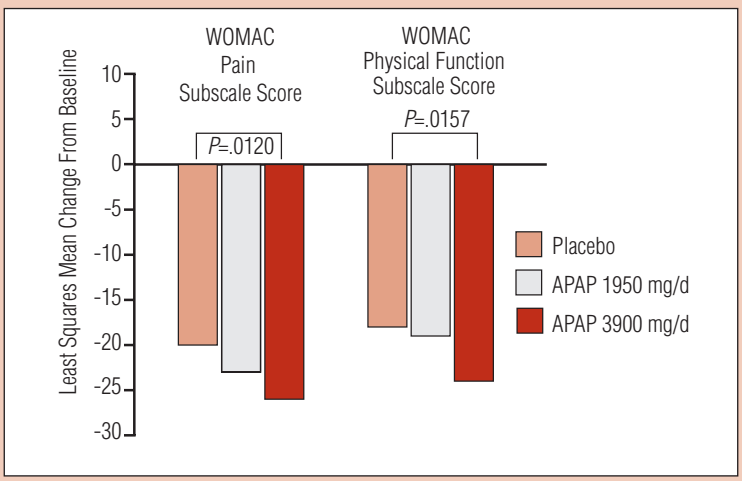
In a 4-week randomized, double-blind study, Bradley and colleagues compared the analgesic efficacy of acetaminophen 4000 mg/d, ibuprofen 1200 mg/d, and ibuprofen 2400 mg/d in patients with mild-to-moderate knee OA.[70] Results showed that all 3 groups had improvements in all major outcomes, including the Stanford Health Assessment Questionnaire (HAQ) pain and disability scores, and scores on the visual analogue scale (VAS). VAS scores did not differ significantly in the magnitude of improvement in most outcomes except pain at rest, which decreased to a greater extent in both ibuprofen groups. Each group had similar improvement in the HAQ pain scale, with a mean improvement of 0.33 with acetaminophen (95% confidence interval [CI], 0.14 to 0.52), 0.30 with low-dose ibuprofen (95% CI, 0.09 to 0.51), and 0.35 with high-dose ibuprofen (95% CI, 0.13 to 0.57).

Although studies comparing the efficacy of OTC analgesics for the treatment of OA are largely equivocal when it comes to reporting the differences among the various agents, the results of 2 recent studies provide further insight into the efficacy of OTC analgesics in the treatment of OA pain. In a recent meta-analysis that assessed the analgesic efficacy of selective and nonselective NSAIDs in OA knee pain, investigators found that NSAIDs performed only slightly better than did placebo. In the trial that provided long-term data for pain, there was no significant effect of NSAIDs compared with placebo at 1 to 4 years.[71] Conversely, a recent 3-month multicenter, randomized, double-blind, parallel-group trial of 483 patients with moderate-to-severe OA of the hip or knee found that subjects taking 3900 mg of acetaminophen extended-release caplets (two 650-mg caplets, 3 times daily) had significantly less pain and greater physical function than did those taking

placebo.[72] Acetaminophen 3900 mg/d was superior to placebo for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score and WOMAC physical function score (Figure 6).[72] Additionally, there were no significant differences among treatment groups with regard to total rescue medication ingested and WOMAC stiffness subscale scores.

Figure 6

ACETAMINOPHEN EFFICACY: MEAN CHANGE AT WEEK 12 FOR PRIMARY ENDPOINTS[72]



WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; APAP, acetaminophen.

Reprinted with permission from Altman R et al. Presented at: 9th World Congress of the Osteoarthritis Research Society International (OARSI); December 2-5, 2004; Chicago, Ill.

Table 5

EFFICACY OF ROFECOXIB, CELECOXIB, AND ACETAMINOPHEN IN OA OF THE KNEE[73]

	WOMAC (Mean Change, mm)			
Variable	**Acetaminophen 4000 mg**	**Celecoxib 200 mg**	**Rofecoxib 12.5 mg**	**Rofecoxib 25 mg**
First 6 days				
Night pain	-18.8	-18.7	-22.0	-25.2*†
Walking pain	-20.6	-26.4*	-29.0‡	-32.2†§
Rest pain	-12.5	-15.5	-18.6*	-21.8†§
Morning stiffness	-20.9	-25.7	-28.4*	-30.4‡
6 weeks				
Night pain	-23.6	-22.6	-25.2	-32.7‡‖
Walking pain	-30.3	-36.2	-35.1	-42.0‡
Rest pain	-21.7	-23.4	-24.8	-31.1‖
Morning stiffness	-22.3	-29.1	-29.0	-36.2§

OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

*P<.05 vs acetaminophen. †P<.05 vs celecoxib. ‡P<.01 vs acetaminophen.

§P<.001 vs acetaminophen. ‖P<.001 vs celecoxib.

Adapted with permission from Geba GP et al. *JAMA*. 2002;287:64-71.

Comparative Efficacy of Acetaminophen and COX-2–Selective NSAIDs

The therapeutic efficacy of rofecoxib, celecoxib, and acetaminophen was assessed in a 6-week, randomized, active comparator–controlled trial.[73] Adult patients at least 40 years of age, with symptomatic OA of the knee for at least 6 months, were randomized to receive either rofecoxib 12.5 mg/d, rofecoxib 25 mg/d, celecoxib 200 mg/d, or acetaminophen 4000 mg/d. Study endpoints were pain on walking, night pain, pain at rest, and morning stiffness as assessed by the WOMAC scores. Also, patients' global responses to treatment were assessed.

Across multiple clinical endpoints, rofecoxib 25 mg/d provided greater benefit in adult patients with OA of the knee than did the maximal daily doses of acetaminophen or celecoxib. However, after 6 weeks of treatment, there were no statistically significant differences between acetaminophen, celecoxib, and rofecoxib 12.5 mg/d in all efficacy variables (Table 5).[73] With regard to global assessment, at the end of the 6-week treatment, 39% of the acetaminophen group versus 60% of the rofecoxib 25-mg/d group assessed their response as good or excellent.

Although additional controlled, comparative trials are needed, acetaminophen and analgesic doses of NSAIDs appear to be equally efficacious in treating pain associated with mild-to-moderate OA.[70] Acetaminophen can provide effective pain relief for patients seeking an alternative to prescription analgesics,[72] or for whom NSAID therapy is not recommended.

Other Considerations

In selecting the appropriate analgesic, the clinician should balance overall risks, benefits, and costs. Patients should understand that all medications, including OTC drugs, have side effects and can interact with other medications. Patients should be advised to use OTC medications carefully because ingredients may be duplicated in various preparations. In their quest for relief of pain, many patients exceed the recommended daily dose of OTC medications. Patients need to be advised that the risk of side effects and adverse events increases dramatically when the maximum recommended daily dose is exceeded or the recommended duration of therapy is extended.

Safety Considerations of Pharmacotherapy

In general, patients with OA and other musculoskeletal diseases are heavy users of healthcare resources. One analysis found that patients with these chronic condi-

tions have total medical expenditures that are 50% higher than those in patients without musculoskeletal conditions.[74] Importantly, patients with arthritis are the single largest subgroup of daily NSAID users, and NSAID-related GI complications are the most prevalent category of NSAID adverse drug reactions. This reinforces the critical importance of risk/benefit evaluation and patient counseling in drug selection and use.[75]

GI Adverse Events

As noted previously, GI complications are the most prevalent of NSAID-related adverse drug reactions,[75] and OTC agents are included in the mass of data implicating NSAIDs in damage to both upper and lower portions of the GI tract. Researchers estimate that, in the United States, there are approximately 103,000 hospitalizations for severe GI complications associated with 16,500 deaths per year at the cost of over $2 billion.[75] Risk factors for GI bleeding include prior bleeding episodes, anticoagulant and corticosteroid use, older age, and high NSAID dose. The relative risks of serious GI adverse events are listed in Figure 7.[76-80] Many patients who experience GI complications with NSAID use do not have obvious risk factors, such as prior bleeding,[81] and patients should be informed that the majority of serious GI effects occur without any prior symptoms.[75]

Many patients who experience GI complications with NSAID use do not have obvious risk factors, such as prior bleeding, and patients should be informed that the majority of serious GI effects occur without any prior symptoms.

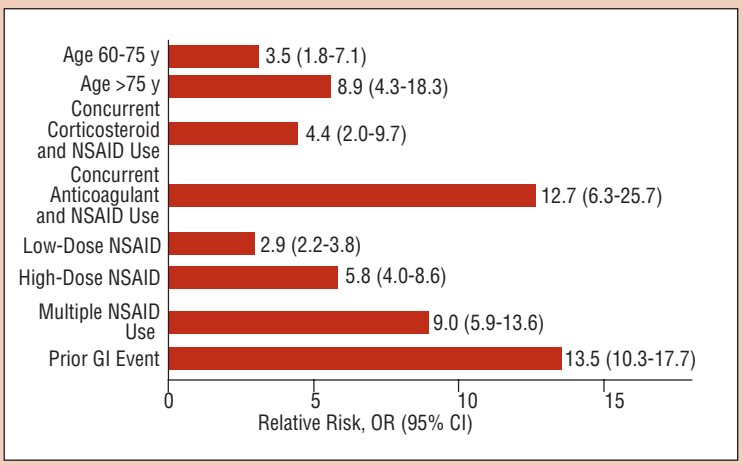
Researchers analyzed data collected by the American College of Gastroenterology to evaluate the risk of GI bleeding associated with common OTC analgesics.[82] Among recent users of aspirin, ibuprofen, and other NSAIDs, the risk of GI bleeding was dose related, but no excess risk of GI bleeding was observed among users of acetaminophen (Table 6).[82] The use of aspirin and nonaspirin NSAIDs by themselves increase the risk for GI adverse effects, but a national cohort study in Denmark showed that there is an even greater risk of upper GI bleeding when using these agents together.[83] The investigators did not find that enteric coating reduced these risks.

Findings of the Celecoxib Long-term Arthritis Safety Study (CLASS) revealed a lower incidence of combined upper GI ulcer complications and symptomatic ulcers associated with celecoxib treatment than with ibuprofen or diclofenac.[84] However, the concomitant use of aspirin negated any advantage of celecoxib over the comparator agents. This is an especially important consideration because it has been shown that COX-2 inhibitors are more likely to be used in elderly patients who commonly use prophylactic aspirin.[85] Furthermore, at 12 months follow-up, there was no clear difference in GI symptoms among the agents.[86]

In summary, the large body of clinical evidence regarding the GI safety of analgesics suggests that acetaminophen is the safest OTC analgesic available. Although COX-2 inhibitors may offer an improved GI safety profile compared to traditional NSAIDs, their use should be reserved for those patients at high risk for GI adverse effects and with no risk of CV events until more definitive safety trials are complete. The effects of NSAIDs, particularly of aspirin, take on added importance in OA because of their widespread use among the elderly and because the risk of both GI complications and OA increases with age.

Figure 7

RISK FACTORS FOR SERIOUS GI ADVERSE EVENTS: RELATIVE RISKS[76-80]



GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; CI, confidence interval.

Table 6

GI BLEEDING ASSOCIATED WITH ANALGESICS[82]

Analgesic	Case, % (n=627)	Control, % (n=590)	OR*	95% CI
OTC use of				
Aspirin	27.0	12.0	2.7	1.9-3.8
Ibuprofen	10.1	5.8	2.4	1.5-3.9
Acetaminophen	4.5	6.3	0.9	0.5-1.6
Total OTC NSAIDs	36.2	17.5	3.0	2.2-4.1
Rx NSAIDs	9.3	5.9	2.1	1.2-3.4
Total NSAIDs	42.9	22.0	3.1	2.3-4.1

GI, gastrointestinal; OR, odds ratio; CI, confidence interval; OTC, over-the-counter; NSAID, nonsteroidal anti-inflammatory drug; Rx, prescription.

*After adjustment for age, gender, alcohol intake, dyspepsia, prior GI bleeding, use of corticosteroids and anticoagulants, and each analgesic for use of the others.

Adapted with permission from Blot WJ, McLaughlin JK. *J Epidemiol Biostat.* 2000;5:137-142.

Analgesics for Patients With Risk Factors

Renal Considerations

In healthy patients, the risk of developing renal failure with OTC analgesics (aspirin, nonaspirin NSAIDs, or acetaminophen) is minimal.[87] Conversely, patients with hypertension, severe renal insufficiency, congestive heart failure, or other disorders of salt and water retention should be reminded of the potential risk of analgesic use. Patients with these conditions are likely to rely more heavily on renal PGs to maintain normal renal blood flow and function compared to otherwise healthy individuals.[88]

Inhibition of PG synthesis in such patients can reduce renal blood flow and glomerular filtration rate (resulting in increased blood urea nitrogen and creatinine levels), increase chloride absorption and sodium retention (resulting in edema and hypertension), reduce renin and aldosterone activity (resulting in elevated potassium levels), and increase the effect of antidiuretic hormone (resulting in water retention and hypervolemia).

The mechanisms of action of NSAIDs suggest that they could influence salt and water retention and hypertension.[88] In meta-analyses, increases in blood pressure occurred in patients with hypertension using NSAIDs, including those on treatment.[89] In one analysis, indomethacin and naproxen were associated with the greatest increases in blood pressure.[90] A multicenter, randomized, controlled trial indicated that both celecoxib and rofecoxib were associated with the development of edema and hypertension.[91] Acetaminophen does not affect the function of the kidneys or heart and can be used as an alternative in these patients.

Underlying Cardiovascular Disease

The need for an NSAID with an improved GI safety profile led to the development of COX-2 inhibitors. These agents are purported to selectively inhibit the enzymes responsible for synthesizing the PGs that induce inflammation and cause pain, while sparing COX-1 enzymes, which are not associated with adverse GI effects.

However, the recent withdrawal of rofecoxib and valdecoxib from the market due to adverse CV events and the subsequent FDA announcement that all manufacturers of NSAIDs should revise their labeling to include warnings for increased risk of CV and GI adverse events associated with their use has brought to light the need for greater scrutiny of all NSAIDs (Table 7). Although further study is necessary to determine the exact relationship between NSAID use and CV events, currently there are more questions than answers. For example, a recent study demonstrated that the risk of acute myocardial infarction (MI) is actually increased following the several weeks after the cessation of NSAID therapy.[92] Yet many patients who take NSAIDs have underlying CV disease and require analgesia for their pain. Until more definitive safety profiles for NSAIDs emerge, it is critical that each patient's relative CV-risk profile be evaluated prior to prescribing or discontinuing therapy and that other analgesics with better established safety profiles be considered, if appropriate.

A reasonable approach to pain management would include acetaminophen as the first-line agent for mild-to-moderate pain because it is not associated with significant CV or renal effects.[93,94] Ibuprofen would be recommended for patients who do not respond to the maximum recommended dose of acetaminophen (4000 mg/d) and who are not at risk for heart disease,[93] kidney disease,[94] or GI side effects.[75] Although COX-2 inhibitors remain a practical choice for patients at high risk for GI events and who are at low risk for CV events, it would seem sensible to avoid prescribing these agents to patients who are at risk for CV events until further long-term studies have been evaluated.

OTC Analgesia and Hypertension

Recently, 2 prospective cohort studies were conducted among women from the Nurses' Health Study (NHS), analyzing the association of incident hypertension and the dosing of OTC analgesia.[95] An earlier study had already reported on the association between the frequency of analgesic use and the risk of developing hypertension.[96] Women were considered to have incident hypertension if they had not been diagnosed with hypertension at baseline. Older women (51 to 77 years of age) who used higher daily doses of acetaminophen (>500 mg/d) showed a 93% increased risk of developing hypertension, compared with nonusers. Older women who used a higher daily dose of NSAIDs (>400 mg/d) showed a 73% increased risk. When the NSAID dose was further analyzed, women whose usual dose of NSAIDs was >800 mg/d showed a 2.2-fold higher risk of incident hypertension than nonusers.[95]

The increased risk of hypertension was also seen among younger women (34 to 53 years of age). Younger women whose average daily dose of acetaminophen was >500 mg/d, showed a 2-fold higher risk of developing hypertension compared with nonusers, and younger women whose intake of NSAIDs was >400 mg/d had a 60% increased risk. Aspirin use was not associated with incident hypertension in older women and only marginally in younger women.[95] This epidemiologic study relied on patient-reported analgesic use. Because of its observational design, some of the data may be confounded by uncontrolled variables.

Aspirin Use

An emerging issue is whether NSAIDs interfere with the cardioprotective effects of low-dose aspirin. Some reports suggest that NSAIDs, particularly ibuprofen, may diminish the cardioprotective effects of aspirin. For example, the results of a randomized study by Catella-Lawson and colleagues demonstrated that inhibition of serum thromboxane B_2 formation and platelet aggregation by aspirin were blocked by a single

dose of ibuprofen given before aspirin or multiple daily doses of ibuprofen, regardless of when aspirin is taken.[97] Concomitant administration of rofecoxib or acetaminophen, however, did not affect the pharmacodynamics of aspirin. In the second portion of the study, enteric-coated aspirin was administered in the morning, followed by multiple doses of ibuprofen or diclofenac, a dosing schedule more typical for patients with arthritis. On the morning of day 7, serum thromboxane B_2 was only 67% inhibited in patients receiving ibuprofen as compared to 92%, for patients who took diclofenac after aspirin.[97] This observation suggests that while diclofenac did not influence the antiplatelet effects of aspirin, ibuprofen blocked the antiplatelet effects of aspirin when taken under these conditions.[97]

A subgroup analysis from the Physicians Health Study (PHS) provides some additional data on the primary cardioprotective effects of aspirin and the concomitant use of NSAIDs in general.[98] This study randomized 22,071 apparently healthy male physicians to 325 mg aspirin or placebo on alternating days. Investigators then prospectively collected data on medical condition, compliance, and concomitant NSAID use. NSAID use in addition to aspirin/placebo was categorized as never, intermittent (1 to 59 d/y), or regular use (≥60 d/y). During a follow-up period that averaged 5 years, the study findings demonstrated a highly significant 44% reduction in the risk of first MI with aspirin *(P*<.00001) as compared to placebo. Intermittent use of NSAIDs had no material effect on aspirin's cardioprotective effect; however, in those who took NSAIDs 60 days or more per year, there was no protective effect of aspirin use.

While chance, bias, and confounding factors remain possible alternate explanations, study data suggest that, when low-dose aspirin is used with NSAIDs long term, there may be a reduced ability of aspirin to protect against CV disease.[100] Acetaminophen has not been shown to interfere with aspirin; however, additional studies are warranted, particularly in women, with larger numbers of patients and a variety of analgesics.

Aspirin Use in Women

Ridker and colleagues recently published the Women's Health Study (WHS), which assessed whether the use of 100 mg of aspirin every other day decreases the risk of a first MI.[99] The results of this study were somewhat different from data that have been reported in men. The study reported only a 9% reduction in major CV events in the aspirin group vs placebo (*P*=.13). Furthermore, it was noted that there was no decrease in death from CV causes (*P*=.68). Aspirin had no statistically significant effect on the risk of fatal or nonfatal MI (*P*=.83). However, a subgroup analysis of women 65 years of age or older demonstrated a 34% reduction in first MI. When aspirin was compared to placebo, there was a 17% reduction in the risk of stroke (*P*=.04) and a 24% reduction in the risk of ischemic stroke (*P*=.009). In women 65 years of age or older, there was a 30% reduction in stroke.

Table 7

NSAID BLACK BOX WARNINGS REQUIRED BY FDA

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- [Drug Name] is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- NSAIDs may cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

The researchers noted that there are risks associated with aspirin therapy (eg, an increased risk of GI bleeds requiring transfusion in the aspirin group [*P*=.02] and a statistically insignificant increase in hemorrhagic stroke [*P*=.31]). The results of this study differ from those of the PHS and may be attributed to the different doses of aspirin given: 100 mg in the WHS vs 325 mg in the PHS. The differences in the gender of the subjects in the 2 trials may also be a factor.

Hepatic Considerations

Patients with a history of compromised liver function—for example, those with a history of liver disease or alcohol abuse—are thought to be more prone to analgesic liver injury. The data do not support this theory. Following ingestion of a therapeutic dose, acetaminophen is metabolized to nontoxic glucuronide or sulfated metabolites. A large overdose of acetaminophen can lead to hepatic toxicity in patients with or without liver disease primarily because of reactive metabolites, especially *N*-acetyl-*p*-benzoquinone imine (NAPQI). This metabolite is normally detoxified by glutathione, but if a large dosage is taken at one time or if repeated large dosages are taken, it can cause liver injury. Contrary to popular presumptions, chronic liver disease does not generally cause substantial glutathione deficiency nor does it shift metabolism to the oxidated pathway producing NAPQI.

Another misconception is that acetaminophen somehow accumulates in patients with liver cirrhosis who use acetaminophen repeatedly. Although the half-life is increased somewhat in these patients, accumulation does not occur, as demonstrated in a randomized trial.[101]

In alcoholic patients, it has been theorized that alcohol can increase the production of NAPQI by inducing cytochrome P450 2E1 and simultaneously depleting glutathione. This would theoretically increase the potential for injury. A systematic review by Dart and colleagues

identified articles involving the use of recommended dosages (≤4000 mg/d) of acetaminophen by adult alcoholic patients.[102] An interesting dichotomy is revealed when examining prospective and retrospective data on this topic. Only retrospective case reports exhibit an association of therapeutic acetaminophen ingestion with liver injury in alcoholic patients.[102] In contrast, all prospective data demonstrate no risk of liver injury in alcoholic patients who repeatedly ingest the recommended maximum dosage of ≤4000 mg/d for 2 to 5 days.[102] There are no prospective studies of large overdosage in alcoholic patients, and retrospective studies have yielded conflicting data.

The difference in results involving therapeutic use is probably related to the fact that retrospective data are susceptible to inaccurate patient histories of ingestion. Alcoholic patients who develop liver injury during "therapeutic" use have most likely inadvertently or intentionally ingested an acetaminophen overdose. Many of the reported cases have serum acetaminophen levels that are consistent with acute large overdosage of acetaminophen.

Although aspirin and nonaspirin NSAIDs are not contraindicated in alcoholics, available data suggest that they should be used with caution in patients who consume alcohol regularly, and their use should be carefully monitored because of concerns regarding GI bleeding. In an interview-based case-control study of 1224 patients hospitalized for acute major upper GI bleeding and 2945 neighbor controls, the risk for upper GI bleeding rose with increasing alcohol consumption in the entire study population, with relative risks (95% CI) of 0.9 (0.8-1.2), 1.3 (1.0-1.7), 1.4 (1.0-2.0), and 2.8 (2.0-3.9) for 1-6 drinks/week, 7-13 drinks/week, 14-20 drinks/week, and ≥21 drinks/week, respectively, compared with 1 drink/week.[103] Among regular aspirin users (at least every other day during the week prior to the event), any level of drinking increased the risk for acute major upper GI bleeding (multivariate relative risk [MVRR], 2.8; 95% CI 2.1-3.8, and MVRR 7.0, 95% CI 5.2-9.3 for regular users of ≤325 mg and >325 mg, respectively). Among current drinkers, even occasional aspirin use was associated with increased risk for upper GI bleeding (MVRR 2.4; 95% CI 1.9-3.0) at all levels. In a separate mail survey conducted by the American College of Gastroenterology, drinking (level not described) was associated with a 2-fold increased risk for GI bleeding that appeared to be at least additive to that associated with recent NSAID use.[82]

In summary, available data from prospective studies indicate that recommended dosages of acetaminophen may be taken by alcoholic patients without added risk of liver injury.[102,104] Chronic heavy alcohol abusers may have an increased risk of hepatotoxicity following a large overdose of acetaminophen.[102] Patients should be cautioned not to exceed the recommended dose. It should also be noted that all OTC analgesics carry an alcohol warning that advises patients who consume 3 or more alcoholic drinks every day to consult their clinician.

Summary and Conclusions

Musculoskeletal injuries are frequently accompanied by pain, the alleviation of which is likely to be the most urgent patient concern. Optimal management of the injury requires a thorough understanding of injury pathophysiology and the healing process. This will allow the clinician to prescribe an appropriate pain management regimen. The preponderance of literature on the pathophysiology of injuries and healing demonstrates that, from the time of injury, the repair process consists of a continuum of healing events that differ according to the type of injury. Inflammation is an initial and fundamental component of healing for the repair of strains, sprains, and fracture-associated tissue damage. In contrast, inflammation may have a minimal role in the repair of common tendon injuries or tendinosis. Although our understanding of injury in DOMS is less precise, inflammation does not seem to play a key role in recovery.

For those injuries where inflammation is an essential component for healing, some NSAIDs have been shown to interfere with the healing process, according to the results of studies of muscle and ligament injury.

Although additional controlled, comparative trials are needed, acetaminophen and NSAIDs appear to be equally efficacious in treating patients with mild-to-moderate OA.[70] In patients who are young, in good health, and without risk factors contraindicating NSAIDs, the use of acetaminophen or NSAIDs is a reasonable treatment option.

However, the risk of developing GI complications with NSAID use cannot be downplayed. It is well documented that NSAIDs are associated with an increased risk of developing GI complications. This risk is clinically significant because of the widespread use of these analgesics. These risks increase when patients take aspirin and nonaspirin NSAIDs concomitantly, even though patients may be using the proper dosages of these medications. To reduce the burden of GI complications, aspirin and nonaspirin NSAIDs should be used cautiously and their use should be carefully monitored, especially in high-risk patients such as the elderly. In order to use these medications safely, patients should be educated about the signs and symptoms of serious GI complications and the importance of following labeling instructions, such as not exceeding recommended doses and/or duration. It also should be made clear to patients that GI complications may develop without any warning symptoms.

When prescribing an analgesic, clinicians should recognize that some agents are associated with serious CV and cardiorenal side effects. Although some medications are taken indiscriminately by patients, clinicians are well positioned to help patients evaluate the benefits and limitations of various analgesics and determine how to use them safely by discussing the relevant pathophysiology of injury and the potential side effects of available agents.

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Answer Key:

1.a 2.b 3.d 4.a 5.a 6.c 7.c 8.b 9.a 10.c 11.a 12.b 13.a 14.d 15.c 16.d 17.d 18.a 19.d 20.b

STATE-OF-THE-ART MANAGEMENT OF MILD-TO-MODERATE PAIN
MUSCULOSKELETAL INJURIES AND OSTEOARTHRITIS PAIN: OPTIMIZING TREATMENT OUTCOMES

POSTTEST SELF-ASSESSMENT/CME VERIFICATION

Instructions:

For each of the following questions or incomplete statements, indicate the most appropriate response on the following page.

Physician Assistants:

Successful completion of the self-assessment is required to earn Category I (Preapproved) CME credit. Successful completion is defined as a cumulative score of at least 70% correct.

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CME-UCHSC
4200 East 9th Avenue, #C295 Denver, CO 80262

1. In the United States, musculoskeletal injuries affect how many individuals annually?
   a. 1 of 4
   b. 1 of 6
   c. 1 of 10
   d. 1 of 15

2. In strains and sprains, the 3 phases of the body's response to injury include all but which one of the following?
   a. Inflammatory
   b. Degenerative
   c. Proliferative
   d. Maturation

3. Why is inflammation an important part of the healing process?
   a. It protects the injured structure from further use.
   b. It induces gene expression pathways.
   c. It facilitates cell proliferation and migration.
   d. All of the above

4. Which one of the following is not a factor influencing fracture healing?
   a. Obesity
   b. Age
   c. Smoking
   d. Nutrition

5. In the healing process, granulation tissue replaces the original fibrin clot during the proliferation phase.
   a. True
   b. False

6. In soft tissue injury, the maturation/remodeling phase of healing can last up to how long?
   a. 6 to 8 weeks
   b. 3 to 6 months
   c. 1 to 2 years
   d. None of the above

7. Which one of the following statements best describes common tendon injuries?
   a. The histopathology of overuse in tendons is consistent with tendinitis and is characterized by microtraumatic injury and inflammation.
   b. The histopathology of overuse in tendons is consistent with tendinosis and is characterized by microtraumatic injury and inflammation.
   c. The histopathology of overuse in tendons is consistent with tendinosis and is characterized by microtraumatic injury and lack of inflammation.

8. The pathophysiology of DOMS is characterized by fibroblast activation and elevated plasma CK levels.
   a. True
   b. False

9. Which one of the following statements about RICE is <u>not</u> true?
   a. Compression is clinically proven to improve outcome.
   b. The efficacy of RICE is generally well accepted clinically.
   c. Extended immobilization may result in tissue atrophy.
   d. Controlled stretching and joint movement may improve collagen fiber orientation.

10. Which of the following statements about results of NSAID treatment for DOMS in animal and human studies is the most accurate?
    a. Serum CK levels are higher after treatment.
    b. Serum CK levels are lower after treatment.
    c. Serum CK levels are higher or are unchanged.
    d. Serum CK levels are higher in animal studies only.

11. The primary mechanism of action of NSAIDs is:
    a. Inhibition of prostaglandin synthesis
    b. Stimulation of endorphins
    c. Receptor-mediated
    d. Unknown

12. After rheumatoid arthritis, OA is the next most common form of arthritis in the United States.
    a. True
    b. False

13. The mechanism of action of NSAIDs suggests that NSAIDs could influence salt and water retention and hypertension.
    a. True
    b. False

14. In the context of multimodal interventions for OA, which one of the following analgesics is recommended as first-line pharmacologic therapy?
    a. Aspirin
    b. COX-2–selective NSAIDs
    c. Nonselective NSAIDs
    d. Acetaminophen

15. Which one of the following statements about the use of OTC NSAIDs is true?
    a. The use of OTC NSAIDs causes only nuisance GI symptoms such as nausea and dyspepsia.
    b. OTC doses of ibuprofen do not have an increased risk of upper GI bleeding.
    c. The use of enteric-coated or buffered aspirin does not reduce GI bleeding risks.
    d. The addition of OTC low-dose aspirin does not increase the risk of serious upper GI bleeding in patients chronically taking NSAIDs.

16. The primary mechanism of action of acetaminophen is:
    a. Inhibition of prostaglandins
    b. Stimulation of endorphins
    c. Receptor-mediated
    d. Unknown

17. Which of the following statements about analgesic efficacy is/are true?
    a. Acetaminophen 4000 mg/d has demonstrated similar improvement on the Stanford Health Assessment Questionnaire pain scale to that of low-dose and high-dose ibuprofen.
    b. Recommended daily doses of acetaminophen and naproxen have demonstrated similar efficacy in relief of pain.
    c. Acetaminophen 4000 mg/d and rofecoxib 25 mg/d have demonstrated similar efficacy in relief of pain.
    d. Both a and b
    e. All of the above

18. At doses of 4000 mg/d or less, acetaminophen has not been shown to increase the risk of bleeding in patients with chronic liver disease or a history of alcohol intake.
    a. True
    b. False

19. Which of the following statements is/are true?
    a. FDA has asked the manufacturers of all prescription NSAIDs to revise their labeling to include a boxed warning highlighting the potential for increased risk of CV events and GI bleeding.
    b. FDA has asked the manufacturers of all OTC NSAIDs to revise their labels to include more specific information about the potential CV and GI risks.
    c. FDA has asked the manufacturers of OTC NSAIDs to include a warning about the risk of potential skin reactions.
    d. All of the above

20. Which of the following statements about aspirin use is false?
    a. Some evidence exists that NSAIDs may interfere with the cardioprotective effects of aspirin.
    b. Enteric coating reduce aspirin-associated GI risks.
    c. Aspirin has not been associated with increased hypertension.

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MUSCULOSKELETAL INJURIES AND OSTEOARTHRITIS PAIN: OPTIMIZING TREATMENT OUTCOMES

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Please see page 18 for the Answer Key.

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