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The Role of Nonopioid Analgesics in Managing Osteoarthritis Pain

OVERVIEW

Osteoarthritis (OA) is the most common form of arthritis in the United States.[1,2] More than 20 million people suffer from OA in the United States and joint pain is considered the most prevalent symptom bringing these patients into the healthcare system for treatment.[3] Radiologic evidence suggests that more than 50% of the population aged 65 years and older have OA in at least one joint.[2] Consistent with the aging of the population, the prevalence of OA is expected to double by 2020.[4] By 2030, about 20% of the population—70 million people—will be older than 65 years and therefore at higher risk for developing OA.[2] Although the prevalence of OA is higher in men than in women younger than 45 years of age, the overall prevalence of OA is higher in women than in men (20% vs 15%, respectively).[1,2] OA and other types of arthritis are associated with substantial morbidity and disability, producing considerable direct and indirect costs of approximately $65 billion annually. These expenses include 39 million physician visits and half a million hospitalizations, as well as the costs of medications and lost wages.[5] For OA itself, medical costs alone are estimated to range from $15.5 billion to $28.6 billion annually.[6]

Although OA is not yet curable, therapeutic interventions have been shown to relieve pain and minimize or reduce disability.[7] Appropriate analgesia is the cornerstone of a multimodal therapeutic approach. Recently, experts in pain management met under the auspices of the US Department of Health and Human Services Office on Women's Health to examine facets of mild-to-moderate pain. This issue of *Clinical Courier*® focuses on the etiology of OA and management of mild-to-moderate pain associated with this incurable disease by summarizing the presentations and discussions held during the roundtable meeting.

INTENDED AUDIENCE

Healthcare professionals

LEARNING OBJECTIVES

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

- Recognize the various risk factors for osteoarthritis
- Explain the principles of pain management for mild-to-moderate osteoarthritis pain
- Discuss practical, multimodal approaches to manage mild-to-moderate osteoarthritis pain
- Educate patients on the safe use of over-the-counter (OTC) pain medications for treating mild-to-moderate osteoarthritis pain

RECENT NEWS FROM FDA AS OF APRIL 7, 2005:

- FDA has asked Pfizer, Inc. to withdraw Bextra® (valdecoxib) from the market because the overall risk-versus-benefit profile for the drug is unfavorable. FDA has also asked Pfizer to include a boxed warning in the Celebrex® (celecoxib) label.
- FDA is asking manufacturers of all other prescription NSAIDs to revise their labels to include the same boxed warning highlighting the potential for increased risk of cardiovascular (CV) events and gastrointestinal (GI) bleeding associated with their use.
- FDA is asking the manufacturers of all OTC NSAIDs to revise their labels to include more specific information about the potential CV and GI risks, and information to assist consumers in the safe use of the drugs. FDA is also asking manufacturers of OTC NSAIDs to include a warning about potential skin reactions.

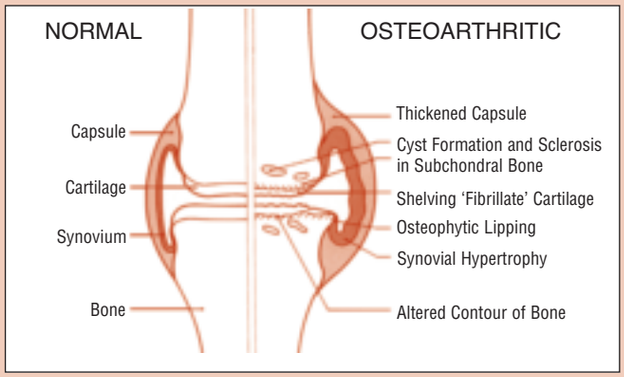
A CLOSER LOOK AT OA—PATHOPHYSIOLOGY AND PRESENTATION

OA affects synovial joints, causing progressive loss of articular cartilage coupled with reactive changes at the joint margins and in the subchondral bone. Mild synovitis may also be present.[8] Unlike rheumatoid arthritis (RA), systemic lupus erythematosus, and other probable autoimmune disorders, OA is not a systemic inflammatory disease. While evidence of mild inflammation may be present, it is not a hallmark of OA.[2,3] Whether OA is primary or secondary—it can be either—the pathophysiologic character is the same.

Articular damage tends to occur mostly in the main weight-bearing joints, typically the hips and knees. Other commonly affected sites include the spine, the distal interphalangeal joints (Heberden's nodes), and the proximal interphalangeal joints (Bouchard's nodes). When OA affects the ankle, the condition is usually secondary, such as from previous trauma.[9] Figure 1 illustrates the differences between a normal and an affected joint. In Figure 2a, radiologic findings of osteophytes, narrowing of the cartilage, and bony sclerosis can be seen to parallel OA physical findings. Disease progression, evidenced by complete loss of cartilage and bony eburnation, can also be seen on plain film (Figure 2b). Histologically, abnormal-appearing cartilage shows breakup at the surface (Figures 3a-d).

FIGURE 1

Comparative Illustration of a Normal and Osteoarthritic Knee Joint



Courtesy of D.O. Clegg, MD.

THE OSTEOARTHRITIC PROCESS

Both mechanical and biologic factors interact in the osteoarthritic process.[8,10] Early in the development of OA, chondrocytes proliferate and the water content of the cartilage matrix increases.[9] These changes, in turn, alter proteoglycan composition.[9] Eventually the cartilage matrix breaks down[8] to become more fibrous and then more cellular. Many of these transformations are age related.[9]

In addition to the cartilage degeneration seen in OA, the underlying bone also undergoes substantial alterations, such as formation of large osteophytes at the joint margins, and sclerosis. Osteophyte formation, which occurs in low-stress areas, extends the cartilage surface area, resulting in increased joint stability as a compensatory mechanism.[9] Stress-induced hypervascularity and venous engorgement of subchondral bone adjacent to affected cartilage may induce subchondral sclerosis. New bone deposition on pre-existing trabeculae, trabecular fractures, and callus formation all promote sclerosis.[9]

As OA progresses, subchondral cysts form between thickened subchondral trabeculae. Researchers have proposed alternative explanations for cyst formation[9,11]:

1. Cysts result from bony microcontusions leading to necrosis, increased intra-articular pressure, and extension of synovial fluid into the subchondral bone; or
2. Cysts result from proliferation of myxomatous tissue within bone marrow.

Increased bone turnover during the early phases of OA may reflect attempts to repair damage or adapt to altered joint mechanics.[8] This accelerated bone metabolism is probably mediated by cytokine signaling to cells, increased matrix synthesis, or enzymatically driven matrix breakdown.[8]

Risk Factors

A number of known risk factors increase susceptibility to OA and influence location and severity of the condition (Table 1).[10] Both modifiable and unmodifiable risks have been identified. The probability of developing OA increases with systemic risk factors such as advancing age, female gender, bone density, and nutritional and metabolic variables. Aging is perhaps the most significant risk factor for OA, with the prevalence in all joints increasing with age.[3] Because the prevalence of OA is greater in women who are postmenopausal, estrogen deficiency has been proposed as a risk factor for OA. Although data on the protective effects of estrogen are inconsistent,[3,10,12] some data suggest that estrogen replacement therapy may protect against large joint OA[13]; however, the Women's Health Initiative has shown significant health risks involved with its use.[14]

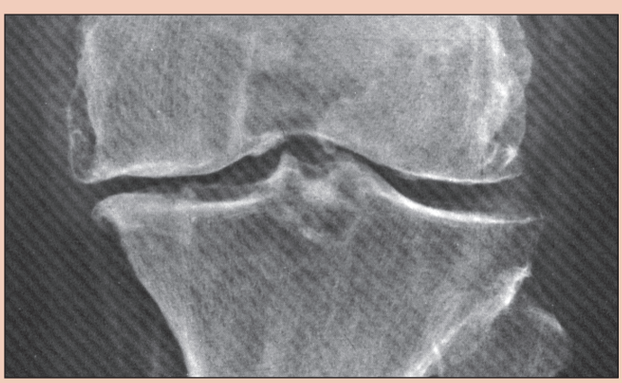
The relationship of bone density to OA is complex. A number of studies suggest an inverse relationship between OA and osteoporosis.[10] Most studies indicate an association between higher bone density and an increased prevalence of OA.[15] Women with OA may also be less likely to lose bone than women without radiographic evidence of OA, as suggested by a 3-year longitudinal study.[10,16] Once OA is established, however, higher bone density may mitigate disease progression.[10,17]

The relationship of race and ethnicity to the prevalence of OA is also complex and conflicting. The results of the National Health and Nutrition Examination Survey (NHANES) I, which compared rates of OA in blacks and whites, indicated that black women, but not black men, may have higher rates of knee OA.[10,18] No ethnic differences in OA of the hip were detected.[10] Other studies show no differences between blacks and whites or a higher rate of hip OA in black men.[19] The relative contribution of potentially confounding or predisposing factors—biologic/genetic, lifestyle, and socioeconomic variables, for example—is unknown. Factors such as ethnic differences in obesity may account for some differences in prevalence rates, but biologic [20] and genetic factors have also been implicated.

Nutritional and metabolic factors may contribute to the development of OA. Exposure to oxidants may increase the rate of OA and antioxidants may provide some degree of protection. The results of the Framingham study, which examined the possible inverse relationship between osteoporosis and OA by evaluating the

FIGURE 2a

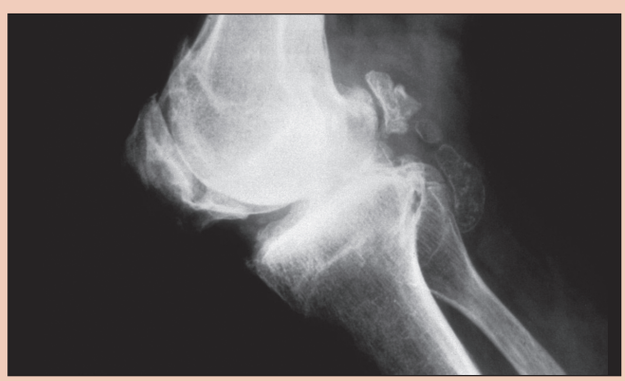
Radiologic Findings of Osteophytes, Narrowing of the Cartilage, and Bony Sclerosis



Courtesy of D.O. Clegg, MD.

FIGURE 2b

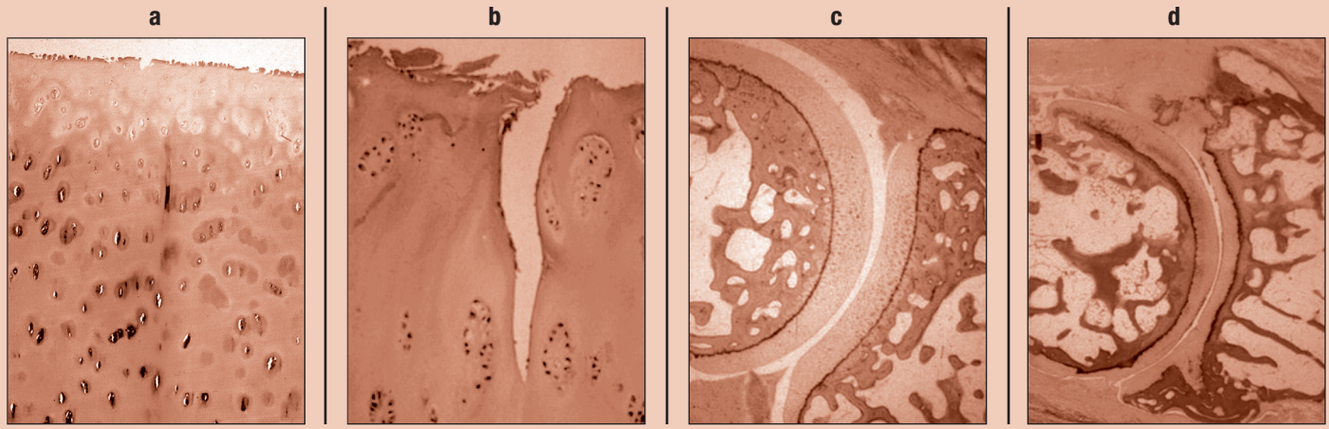
Disease Progression, as Evidenced by Complete Loss of Cartilage and Bony Eburnation



Courtesy of D.O. Clegg, MD.

FIGURE 3

Histology: Abnormal-Appearing Cartilage Demonstrates Breakup at the Surface



Courtesy of D.O. Clegg, MD.

association between bone mineral density and knee OA, demonstrated a 3-fold reduction in risk of progressive radiographic OA in those patients with higher intake of vitamin C. Low levels of vitamin D may also contribute to the progression of OA.[10] It appears that susceptibility to OA may have a genetic component, as suggested by the findings of a study of identical and fraternal female twins.[21] Correlations between disease trait and status were consistently higher in identical twins. The proportion of variance in OA of the hand and knee attributable to genetic factors was 39% to 65%.[21] Results of other population-based epidemiologic studies also demonstrate significant familial clustering for OA of the hand and knee.[22] The OA inheritance pattern appears to be polygenic; data from studies conducted to map OA genes to specific chromosomes indicate that genes on chromosomes 2, 7, and 11 may be involved.[10,22,23]

Local biomechanical factors can modulate the site and severity of OA (Table 1).[10] Obesity is a key risk factor for OA of the hip and knee. Increasing weight correlates with an increased prevalence of OA, and most evidence suggests that the relationship is primarily causal with obesity preceding the development of OA.[10] The relationship between body mass index (BMI) and OA risk is even higher in women than in men.[24] The relationship between body weight and OA is strongest for the knee joints; weight loss in women has been shown to lower the risk of OA of the knee.[25] Unilateral hip OA is not clearly associated with weight, whereas bilateral hip OA is.[10]

Acute joint injury and deformity, participation in certain sports, occupational factors, and muscle weakness—particularly of the quadriceps—have all been shown to increase the risk of OA. For example, after adjustment for body weight, age, and sex, lower quadriceps strength predicted symptomatic and radiographic OA of the knee.[26] 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 study indicated that knee extensor strength was 18% lower in women with incident OA.[27] 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, it also correlates with pain (P<.005).[28] 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; symptom onset may be insidious. Pain is the most important symptom to trigger a visit to the physician.[3] Morning stiffness or stiffness after inactivity (gel phenomenon) is common, but is usually of limited duration and resolves upon initiation of activity.[3] As use of the joints increases during the day, so does pain. Patients with OA also experience instability and buckling of the joints, as well as loss of function.

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 OA pain is not known, virtually all components of the joint can be sources of pain (Table 2).[8] Joint structural alterations alone are unlikely to explain pain. Rather, the pain experienced from OA appears to result from complex interactions among structural deterioration, central and peripheral pain mechanisms, and psychosocial determinants of pain perception.[3]

Physical findings are consistent with the radiographic findings described previously. 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.[3]

PRINCIPLES OF PAIN MANAGEMENT IN OA

Current management of OA is directed most often at symptom control—primarily pain—and risk modification.[3] The substantial number of interventions in clinical use encompasses both pharmacologic and nonpharmacologic approaches,

TABLE 1

Risk Factors for Osteoarthritis (OA)[10]

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	Muscle weakness
Genetics	
Nutritional factors	
Metabolic factors	

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

TABLE 2

Sources and Mechanisms of Pain in Osteoarthritis[8]

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.

including surgery. Although it is generally agreed that treatment plans should be multimodal and individualized, expert consensus and evidence-based support for definitive recommendations are limited.[7,29]

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 an evidence-based analysis of published literature.[7,29] Despite differences in the recommendations, areas of consensus have been achieved for several nonpharmacologic, pharmacologic, and surgical interventions (Table 3).[7,29,30]

Both organizations agree that recommendations are to be considered flexible and that a program tailored to each patient is necessary:

"Any management plan needs to be individualised to take into account holistic factors, such as patient attitudes and knowledge, constitutional features. . .risk factors for OA progression, degree of structural damage, comorbid disease and treatment, and treatment availability and costs."[29]

NONPHARMACOLOGIC INTERVENTIONS IN OA

Numerous nonpharmacologic interventions for OA have been implemented with varying degrees of success. Nevertheless, both the ACR and EULAR agree that nonpharmacologic options constitute the foundation of individualized treatment plans, but that in most instances, optimal therapy requires pharmacotherapy as well, especially for the alleviation of pain.[7,30] Exercise, weight loss, and patient education are among the most effective of the nonpharmacologic approaches.[30]

Exercise

The efficacy of exercise as an intervention for OA is supported both by expert opinion and by the results of clinical studies that include prospective, randomized, controlled trials (RCTs).[7,29,31] Various forms of exercise—muscle strengthening, aerobic activity, and physical therapy—have been proven to be beneficial. The findings of several RCTs have demonstrated pain reduction ranging from 8% to 56% (based on pain assessment scales) and functional improvement ranging from 8% to 17% (Table 4).[32-35] Study-to-study differences in the specifics of exercise programs and characteristics of patient populations may account for the wide variation in the extent of improvement shown in these studies.

Weight Loss

Obesity, particularly in women, is a strong risk factor for OA of the knee. Conversely, weight loss reduces the risk of OA.[3,25] Among women participating in the Framingham Knee Osteoarthritis Study, a weight loss of approximately 5.1 kg (about 2 BMI units) in the previous 10 years reduced the risk of developing OA by about 50% (odds ratio [OR]=0.46; 95% confidence interval [CI], 0.24-0.86; *P*=.02). The ORs were adjusted for age, baseline BMI, history of knee injury, and several other variables. Weight loss also significantly reduced the risk of OA among higher risk women—those with an elevated BMI at baseline (OR=0.41; CI, 0.18-0.88).[25]

The Arthritis Self-Management Program (ASMP)—A Self-Efficacy Model

Developed by Alfred Bandura, the ASMP is based on the concept of self-efficacy—the belief that people have the capacity to alter their own behavior.[36,37] The peer-led, 6-week program aims to reduce pain by focusing on 3 key elements: action planning, problem solving, and decision making. The techniques of skills mastery, modeling, reinterpretation, and social persuasion are used to foster self-efficacy. The integration of a patient-education program like the ASMP into the overall treatment plan can be important in reinforcing the guidance and counseling provided by the healthcare professional.

The findings of clinical trials of the ASMP have shown that pain can be reduced after 4 months of participation. Furthermore, participants in the program increase their knowledge about OA and improve behaviors that contribute to improved functioning.[38] Pain experienced by program participants decreased by 23% from baseline on a visual analog scale and 20% when measured by an ordinal scale. There was no significant change in pain in the control group.[38] Improvement was maintained when assessed at 20-months' follow-up, and a comparison at 4 years found pain reduced by 18% for program participants versus 2% for control subjects. Visits to physicians were also reduced by approximately 40% as compared with 6%, respectively (baseline 3.6 visits for arthritis only).[38,39] Although the changes in pain could be considered relatively modest, patients' perceptions of their coping abilities rose substantially relative to baseline. In addition to providing sustained health benefits for persons with OA, self-help programs like the ASMP may also reduce healthcare costs.[39]

Other Interventions

Additional nonpharmacologic interventions include assistive walking devices (eg, canes, walkers), occupational therapy, and joint protection (eg, wedged insoles). The value of these in the management of OA has been reviewed extensively elsewhere.[7,8,29,31]

TABLE 3

ACR and EULAR Recommendations on the Management of OA: Areas of Consensus[7,29,30]

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.

TABLE 4

Effectiveness of Muscle-Strengthening Physical Therapy in OA: Results of Randomized Controlled Trials[32-35]

Study	N	Duration	Improvement in Pain, %	Improvement in Function, %
Deyle et al, 2000	83	4 weeks	56	13
O'Reilly et al, 1999	191	6 months	22	17
Ettinger et al, 1997	439	18 months	8	8
Thomas et al, 2002	786	24 months	11	11

OA, osteoarthritis.

ANALGESIA—THE CORNERSTONE OF PAIN MANAGEMENT IN OA

Drug therapy for OA is considered most effective when it is part of a multimodal treatment plan.[7,29] Current analgesic options for OA are: acetaminophen, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX)-2–selective NSAIDs, and, less commonly, centrally acting medications. In some cases, tricyclic antidepressants and muscle relaxants are used as adjuvant therapy.

Assessments of the safety of available agents have been complicated by the recent withdrawal from the market of rofecoxib and valdecoxib, both COX-2–selective NSAIDs, which were believed to have an improved gastrointestinal (GI) safety profile over traditional, nonselective NSAIDs.[40] However, studies have linked these agents, along with celecoxib and the over-the-counter (OTC) NSAID naproxen to increased cardiovascular (CV) adverse events.[40-42] **(See page 7 for information on the Reassessment of the Risk/Benefit Profile of Selective and Nonselective NSAIDs.)** These reports have raised concerns relating to the CV safety of all selective and nonselective NSAIDs, and prompted 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 events and GI bleeding associated with their use. Manufacturers of celecoxib and all other prescription NSAIDs have been asked to revise their labeling to include a Medication Guide for patients to help make them aware of the potential for CV and GI adverse events associated with the use of this class of drugs.

In addition, FDA is asking the manufacturers of all 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 the prescription NSAIDs already addresses potential skin reactions.[43]

An Evidence-Based Review of Analgesia for Mild-to-Moderate Pain

For mild-to-moderate pain, both ACR and EULAR guidelines recommend acetaminophen as a first-line oral therapy for OA.[7,29] Counseling and educating patients about this recommendation may be crucial because risk/benefit profiles and cost-effectiveness are important for properly individualizing treatment.

For mild-to-moderate pain, both ACR and EULAR guidelines recommend acetaminophen as first-line oral therapy for OA.

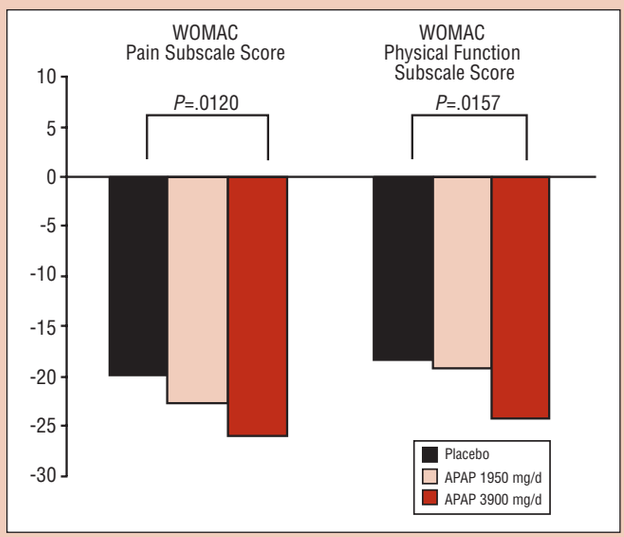
Several studies have assessed comparative efficacy of commonly used analgesics for the treatment of OA pain.[44-49] They were not, however, designed to examine risk profiles or consider cost-effectiveness. The findings of an early RCT by Bradley and colleagues suggested equivalent efficacy of acetaminophen 4000 mg/d and ibuprofen 1200 mg/d or 2400 mg/d for pain relief and improved mobility in patients with OA. Efficacy was similar after 4 weeks of treatment regardless of the dose of ibuprofen.[44] Except for pain at rest, which favored ibuprofen (P=.05), the treatment groups did not differ significantly in the degree of improvement on the various outcome measures.[44]

More recently, individual studies of acetaminophen and ibuprofen have provided conflicting results. In a meta-analysis of selective and nonselective NSAIDs in OA knee pain, investigators found that NSAIDs performed only slightly better than placebo.[45] In one of the trials that provided long-term data, results showed no significant effect of NSAIDs compared with placebo at 1 to 4 years.[45] 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 patients taking 3900 mg acetaminophen extended-release caplets daily (two 650-mg caplets 3 times daily) had significantly less pain and greater physical function than those patients taking placebo.[46] Acetaminophen 3900 mg was superior to placebo for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score and WOMAC physical function score (Figure 4),[46] with similar results for both knees and hips. Additionally, there were no significant differences among treatment groups with regard to total rescue medication ingested and WOMAC stiffness subscale scores. Although further controlled, comparative trials are warranted, acetaminophen provides safe and effective analgesia for OA pain for patients seeking an alternative to prescription analgesics[46] or for whom NSAID therapy is not recommended.

The findings of a 2-year prospective study comparing naproxen 375 mg bid and acetaminophen 650 mg qid also found similar efficacy in patients with OA of the knee for both physician-determined variables (knee pain on palpation or motion, effusion, crepitus, knee flexion and extension, assessment of disease activity) and patient-determined variables (knee pain at rest and on motion and assessment of disease activity).[47] Except for pain at rest, the results of between-group analyses indicated that acetaminophen and naproxen were equally effective (P=.008).[47] However, there was an extremely high dropout rate (65%) over the 2-year course of the study.

FIGURE 4

Acetaminophen Efficacy: Mean Change at Week 12 for Primary Endpoints[46]



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.

In a comparison of acetaminophen versus the prescription combination agent diclofenac and misoprostol (a gastroprotective agent), diclofenac/misoprostol demonstrated significantly improved pain scores (WOMAC and Multidimensional Health Assessment Questionnaire [MDHAQ]) for patients with hip or knee OA.[48] These validated instruments were consistent with patients' perceptions of the 2 treatments.[48] The investigators also noted that patients with more severe OA largely accounted for the difference in pain scores between the 2 treatments. In patients with mild OA, the degree of improvement was similar with both acetaminophen and diclofenac/misoprostol therapy on the WOMAC and MDHAQ scales.[48] Adverse events occurred significantly more frequently (P=.046)[48] in patients receiving diclofenac/misoprostol as compared with those receiving acetaminophen, even though the gastroprotective misoprostol was used.

In a 6-week study of patients with OA of the knee, the efficacy of the COX-2 inhibitor NSAIDs rofecoxib and celecoxib was compared with that of acetaminophen.[49] Rofecoxib 25 mg/d was significantly more effective in relieving pain than was rofecoxib 12.5 mg/d, celecoxib 200 mg/d, or acetaminophen 4000 mg/d. 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. Regarding global assessment, 39% of the acetaminophen group, 46% of the celecoxib group, 56% of the rofecoxib 12.5 mg/d group, and 60% of the rofecoxib 25 mg/d group assessed their response as "good" or "excellent."

Risks, Benefits, and Cost-Effectiveness

In general, patients with OA and other musculoskeletal diseases are heavy users of healthcare resources. One analysis found that patients with these chronic conditions have total medical expenditures that are 50% higher than those without musculoskeletal conditions.[50] Hospitalizations (37%), physician visits (23%), and prescription drugs (16%) were the major components of healthcare resource utilization.[50] 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, reinforcing the critical importance of risk/benefit evaluation and patient counseling in drug selection and use.[51]

Safety Considerations of Pharmacotherapy. As noted previously, GI complications are the most prevalent of NSAID-related adverse drug reactions.[51] An estimated 103,000 hospitalizations for severe GI complications were associated with annual direct costs in excess of $2 billion.[51] Even more alarming, 16,500 deaths per year were attributable to GI complications of NSAIDs in patients with OA or RA.[51]

. . . 16,500 deaths per year were attributable to GI complications of NSAIDs in patients with OA or RA.

OTC agents are included in the mass of data implicating NSAIDs in damage to both upper and lower GI tracts. Risk factors for GI bleeding include prior bleeding episodes, concurrent anticoagulant and corticosteroid use, older age, and high NSAID dose.[52-55] Moreover, many patients who experience GI complications with NSAID use do not have prior warning symptoms.[56]

In a preliminary report, data collected by the American College of Gastroenterology to evaluate the risk of GI bleeding associated with common OTC analgesics were analyzed by researchers.[57] Among recent users of aspirin, ibuprofen, and other NSAIDs, the risk of GI bleeding was dose related. After adjusting for age, sex, alcohol intake, dyspepsia, prior GI bleeding, corticosteroid/anticoagulant use, and use of other analgesics, the OR of GI bleeding was significantly increased for aspirin (OR=2.7) and for ibuprofen (OR=2.4) but there was no increased risk among users of acetaminophen.[57]

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 treatment after 6 months; the rates of these complications were highest in patients who were also taking aspirin.[58] However, there was no clear difference with celecoxib in the risk of GI complications at 12-months' follow-up and in patients taking aspirin therapy.[59]

When considering the large body of clinical evidence regarding the GI safety of analgesics, acetaminophen is the safest available OTC analgesic. Aspirin carries a much greater risk than do nonaspirin NSAIDs.[40,57] Enteric coating and buffering do not reduce aspirin-associated risks.[60] The GI effects of NSAIDs, particularly of aspirin, take on added importance in OA because of their widespread use and because the risks of both GI complications and OA increase with age. While a COX-2 inhibitor may offer a temporarily improved GI safety profile, until more definitive safety trials are complete, the relative CV risk should be determined for each patient when considering this agent.

Although further investigation into the CV safety of COX-2 inhibitors is warranted, the potential reduction in GI complications conferred by using these agents was considered to be economically advantageous in patients at high risk for GI adverse events. Because a significant number of OA sufferers live on fixed incomes, identifying patients who have an increased risk for GI complications can often be an important consideration in drug selection for patients with OA.

These observations were supported by a cost-utility analysis.[61] Spiegel and colleagues observed that although COX-2 inhibitors may reduce the risk of GI complications, the risk reduction is not enough to counter the increased cost of these agents compared with that of nonselective NSAIDs. They suggested that the incremental cost-effectiveness ratio (ICER) of COX-2 inhibitors was acceptable in high-risk patients, but questionable in the management of average-risk patients with chronic arthritis.[61] The results of this study may no longer be applicable in light of recent COX-2 inhibitor CV issues. Further studies are needed.

Kamath and colleagues performed an economic evaluation of selective and nonselective NSAIDs and acetaminophen in OA of the knee.[62] In an average-risk patient population, acetaminophen was superior to the nonselective (ie, ibuprofen) and COX-2–selective (ie, rofecoxib) NSAIDs in averting GI complications. For patients unresponsive to acetaminophen for pain control, ibuprofen had an ICER of $610 relative to acetaminophen; rofecoxib had an ICER of $12,000 relative to ibuprofen. (The ICER measured the cost per additional patient to achieve minimal perceptible clinical improvement relative to the comparator.[62])

Cardiovascular and renal diseases. Cardiovascular and cardiorenal risk profiles must also be considered when selecting an analgesic for pain management in OA. The mechanisms of action of all NSAIDs may increase salt and water retention, thereby elevating blood pressure.[63-66] The increase in blood pressure is also caused by the blocking of prostacyclin, which is a vasodilator.[67] At recommended dosages (≤4000 mg/d), acetaminophen has an excellent renal safety profile and does not affect fluid and electrolyte levels.[68-70] In addition, acetaminophen is the preferred analgesic/antipyretic for patients with liver disease because of a lack of platelet impairment, GI toxicity, and nephrotoxicity.[71]

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 study by Catella-Lawson and colleagues demonstrated that inhibition of serum thromboxane B_2 formation and platelet aggregation were blocked by a single dose of ibuprofen given before aspirin or multiple daily doses, regardless of when aspirin is taken.[72] 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% when patients took diclofenac after aspirin.[72] This observation suggests that while diclofenac did not influence the antiplatelet effects of aspirin, enough ibuprofen remained in the bloodstream from the evening dose to interact with aspirin in the morning.[72]

REASSESSMENT OF THE RISK/BENEFIT PROFILE OF SELECTIVE AND NONSELECTIVE NSAIDs

On September 30, 2004, Merck & Co., Inc., voluntarily withdrew rofecoxib, a selective inhibitor of cyclooxygenase-2 (COX-2), from the market after preliminary data from its most recent trial, Adenomatous Polyp Prevention on Vioxx (APPROVe), demonstrated an increased risk of myocardial infarction (MI) and stroke. In this trial of 2600 patients with colon polyps and no history of cardiovascular (CV) disease, it was discovered that 3.5% of rofecoxib-treated patients had experienced MI or stroke, compared with 1.9% of placebo-treated patients ($P<.001$).[1]

More recently, it has been reported that 2 other coxibs, valdecoxib and celecoxib, as well as the over-the-counter (OTC) nonselective nonsteroidal anti-inflammatory drug (NSAID) naproxen, have been associated with an increased risk of CV events, which underscores the urgency in determining if the CV effects of rofecoxib are actually a class effect for all selective and nonselective NSAIDs.

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

In 2000, Bombardier and colleagues first identified the potential for an increased risk of CV events with rofecoxib use in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, which compared the GI toxicity of rofecoxib with that of naproxen, a nonselective inhibitor.[2] Although not designed to assess CV events, investigators found a 4-fold increase in the incidence of MI associated with rofecoxib. In the following year, Mukherjee and colleagues analyzed CV event data from the VIGOR and the Celecoxib Long-term Arthritis Safety Study (CLASS) trials, as well as 2 smaller trials.[3] In their review of the CLASS data, they found no significant difference in CV event rates between celecoxib and NSAIDs; however, the annualized MI rates for COX-2 inhibitors in both VIGOR and CLASS were significantly higher than those found in the placebo group of a recent meta-analysis of 23,407 patients in primary prevention trials: 0.74% with rofecoxib ($P=.04$) and 0.80% with celecoxib ($P=.02$).

Although the FDA implemented labeling changes in 2002 to reflect safety results in the VIGOR trial, Merck & Co., Inc., responded by proposing that the explanation for differences in MI rates between rofecoxib and naproxen were due to the cardioprotective effect of naproxen, a theory that has been reiterated in 3 case-control studies.[4-6] However, a much larger, more rigorous cohort study by Ray and colleagues found no protective effect of naproxen or other nonaspirin NSAIDs on the risk of coronary heart disease.[7] On the contrary, an Alzheimer's disease prevention trial was recently suspended after 3 years when researchers found that patients taking naproxen had a 50% greater incidence of heart attack or stroke than patients taking placebo.[8] As this is the first study to show that naproxen might increase the risk of heart attack or stroke, and because other studies have supported a modest degree of cardioprotection, it seems premature to judge any possible untoward cardiovascular effect of naproxen.[9] However, until further studies are complete, it is important to remember that naproxen use is not recommended for more than 10 days,[8] and patients should be counseled about the risks of exceeding the recommended dosing and duration of therapy for all analgesics.

Although further study is necessary to determine the exact relationship between NSAID use and CV events, currently there are more questions than answers. As physicians consider how to counsel patients who take selective and nonselective NSAIDs, more and more safety concerns are emerging for these analgesics. For example, a recent study demonstrated that the risk of acute MI is actually increased during several weeks after the cessation of NSAID therapy.[10] The reality is that many patients must continue to take analgesics over the long term. Because of the lack of definitive safety profiles for NSAIDs, it is important to carefully evaluate each patient's relative CV risk profile before prescribing or discontinuing NSAID therapy, and to consider other analgesics with better established safety profiles, if appropriate.

Since the withdrawal of rofecoxib from the market, the manufacturer of valdecoxib has announced the results of a study that demonstrated an increased risk of heart attack, stroke, and blood clots in heart bypass surgery patients taking valdecoxib. Furthermore, the National Institutes of Health announced that the use of celecoxib has been suspended in a large colorectal cancer prevention clinical trial because an independent analysis by the Data Safety and Monitoring Board showed a 2.5-fold increased risk of major fatal and nonfatal CV events for patients taking high doses of celecoxib (400 mg/d) versus placebo, and a 3.4-fold increase in those patients taking 800 mg/d versus placebo.[11,12] Although further study is necessary to determine the CV effects of these agents more definitively, the possibility that these agents have negative CV effects is not new. In 1999, Fitzgerald and colleagues first found evidence that all COX-2 inhibitors could theoretically cause CV events.[13] Nonselective NSAIDs reduce the formation of thromboxane A_2, which increases platelet aggregation, and prostaglandin I_2, which is a potent vasodilator and inhibits platelet aggregation. COX-2–selective agents also inhibit the production of prostaglandin I_2, but have no effect on thromboxane A_2, which may upset the balance between COX-1 and COX-2 isoforms and platelet inhibition and activity. This imbalance could potentially increase platelet aggregation and predispose patients to MI or thrombotic stroke.[13]

There have also been reports demonstrating that COX-2 inhibitors may have adverse cardiorenal effects. The Successive Celecoxib Efficacy and Safety Study VI (SUCCESS VI) showed that rofecoxib and celecoxib increased systolic blood pressure in 17% and 11% of patients, respectively, and increased edema in 9.5% and 4.9% of patients, respectively.[14] Other evidence has shown that COX-2 inhibitors impair renal function and cause sodium retention in patients with mild pre-existing renal failure and, potentially, in elderly patients with, for example, volume depletion.[15]

In addition to the possible CV and cardiorenal class effects of COX-2 inhibitors, valdecoxib labeling had been updated to include a black box warning regarding the risk of Stevens-Johnson Syndrome, a rare, serious, and potentially fatal skin reaction. Although this is a rare adverse event, the risk of this skin reaction is reportedly greater than with other COX-2 inhibitor products, such as celecoxib.[16]

In light of the recent withdrawal of rofecoxib and valdecoxib, and reports linking celecoxib and naproxen to an increased risk of CV events, there is a need for greater scrutiny of all NSAIDs. With this in mind, Muhammed Mamdani, PharmD, has proposed the following stepwise approach to pain management.[17] Acetaminophen, which is not associated with significant CV or cardiorenal effects,[18,19] as the first-line agent for mild-to-moderate pain. Ibuprofen is recommended for those patients who do not respond to the maximum recommended dose of acetaminophen (4000 mg/d), and are not at risk for heart disease,[18] kidney disease,[19] or GI side effects.[20] Although COX-2 inhibitors remain a rational choice for patients at high risk for GI events 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 are complete. Furthermore, the cost of these agents may be prohibitive for some patients, and their potential clinical benefit must be assessed in light of their added expense. The withdrawal of rofecoxib and valdecoxib from the market, and the suggested labeling revisions for celecoxib and both OTC and prescription NSAIDs have created more questions about the safety profiles of these drugs and shifted the onus of proof to the manufacturers of these agents. Clear evidence about the safety and efficacy of selective and nonselective NSAIDs is needed before confidence in these classes of drugs can be restored.

Additional evidence that ibuprofen may interfere with aspirin's antithrombotic effects comes from a study of 7107 patients who were taking low-dose aspirin (<325 mg/day) for secondary prevention following discharge from the hospital for CV disease.[73] After a median of 3.3 years of follow-up, those taking low-dose aspirin and concomitant ibuprofen had an almost 2-fold increased risk for all-cause mortality. When compared to those taking low-dose aspirin alone, there was a more than 70% increased risk for CV mortality compared to aspirin plus other NSAIDs.

Further evidence of the impact of NSAIDs when taken concomitantly with aspirin was shown in a recent case-controlled study by Kimmel and colleagues, which evaluated the effects of OTC and prescription NSAID use on CV events, both alone and in combination with aspirin.[74] The study compared nearly 1055 patients recently discharged from the hospital with a first myocardial infarction (MI) with 4153 matched control subjects randomly identified from the community. Results showed that the use of either aspirin or NSAIDs alone was associated with a reduced risk of MI, but that when combined with NSAIDs, aspirin exerted no cardioprotective effects (OR=1.28). For patients classified as frequent users of NSAIDs, aspirin users had a significantly higher risk of MI than nonaspirin users. Much of this effect seemed to be ibuprofen related, reinforcing the impression that there are differences in the interactions with various NSAIDs.

A subgroup analysis from the Physicians Health Study provides some additional data on the primary cardioprotective effects of aspirin and the concomitant use of NSAIDs in general.[75] 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 days/year), or regular use (≥60 days/year). 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.

In summary, the studies suggest that when low-dose aspirin is used with NSAIDs, primarily ibuprofen, there is a reduced ability of aspirin to protect against CV disease.[76] However, more studies are needed in women, larger numbers of patients, and with a variety of different NSAIDs.

OTHER MODALITIES

In addition to lifestyle modifications and analgesic therapy, other options for the management of OA include intra-articular injections of sodium hyaluronate, glucosamine, chondroitin, and arthroscopic surgery. Supporting data for all these modalities are limited and inconsistent.[77-80]

Some evidence supports careful use of intra-articular steroids for selected patients, although the benefit may be short-lived. Repeated use, moreover, can accelerate damage to cartilage.[31] Findings of an arthroscopic study follow-up after 2 years showed no differences in benefit comparing debridement, lavage, and placebo.[81]

Glucosamine and chondroitin are utilized widely for treating OA. Efficacy data are mixed and results of carefully designed studies are pending. Interestingly, recent data suggest the possibility of chondroprotection with glucosamine and chondroitin. For example, patients receiving glucosamine for OA of the knee had significantly greater reductions in WOMAC pain and function scores after 3 years than those patients receiving placebo. Additionally, joint-space narrowing progressed in the placebo group, but not in the glucosamine-treated group.[82] In another 3-year RCT comparing glucosamine with placebo, patients assigned to placebo experienced progressive joint-space narrowing. In contrast, glucosamine treatment retarded both symptom and joint-space narrowing progression of OA in the knee. Differences between the groups were statistically significant (P<.001), suggesting that glucosamine may have potentially important disease-modification effects.[83]

Finally, regarding arthroplasty, the ACR guidelines concluded that total joint replacement could be highly beneficial and cost-effective in selected patients with OA.[7] Similarly, the recommendations of EULAR agree that strong evidence supports joint replacement for patients with disability and radiologic evidence of deterioration.[29] Additional data indicate that joint replacement should be considered early, before there has been substantial functional decline in order to optimize the outcome.[84]

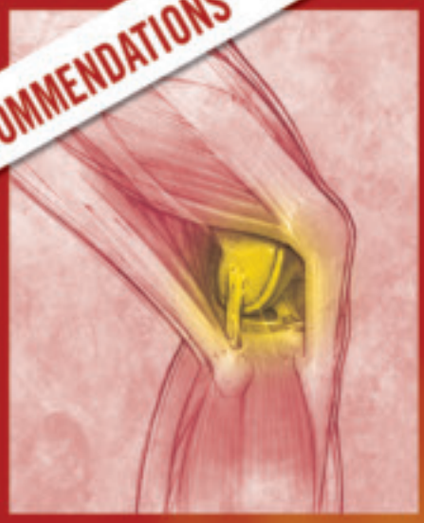
SUMMARY AND CONCLUSIONS

OA, the most prevalent form of arthritis, exerts a considerable burden on individual sufferers, the healthcare system, and the economy. OA is the result of many modifiable and nonmodifiable risk factors and currently cannot be cured. The pain of OA is the symptom that typically brings a patient into the healthcare system for treatment. OA is best managed by a multimodal therapeutic approach to symptom control.

Guidelines published by the ACR and EULAR agree that evidence and expert opinion support an individualized approach utilizing both nonpharmacologic and pharmacologic management modalities. Among nonpharmacologic options, exercise, patient education, and weight loss in particular should be considered when devising an overall treatment plan—all three have been shown to reduce pain and disability associated with OA. Pharmacotherapy with common analgesics is also a key element in optimizing therapeutic success and is considered most effective when it is combined with nonpharmacologic approaches. For mild-to-moderate OA pain, OTC analgesics—such as acetaminophen and, if tolerated, nonselective NSAIDs in analgesic and anti-inflammatory doses, as necessary—are often sufficient. Healthcare providers play an important role in educating patients about the importance of lifestyle changes and the risks and benefits of pain medications and modalities, and can significantly guide patients in developing personalized treatment strategies.

Answer Key: 1 b, 2 c, 3 d, 4 b, 5 d, 6 d, 7 d, 8 e, 9 a, 10 b

INCLUDES RECENT FDA RECOMMENDATIONS



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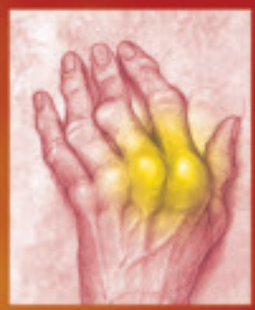

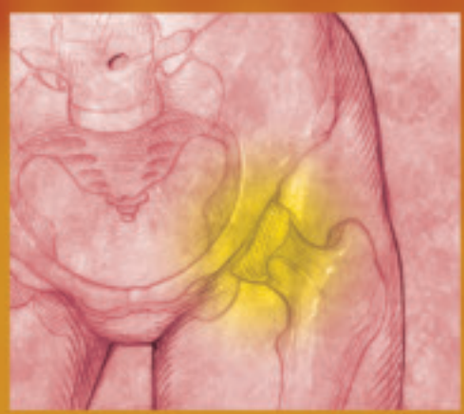

The Role of Nonopioid Analgesics in Managing Osteoarthritis Pain

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The Role of Nonopioid Analgesics in Managing Osteoarthritis Pain 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 newsletter may be off label. Before using any product discussed in this publication, clinicians should consult the full prescribing information.

The Role of Nonopioid Analgesics in Managing Osteoarthritis Pain 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 Pharmacists Association, the 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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Reassessment of the Risk/Benefit Profile of Selective and Nonselective NSAIDs

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THE ROLE OF NONOPIOID ANALGESICS IN MANAGING OSTEOARTHRITIS PAIN

Posttest Self-Assessment/CME Verification

If you wish to receive CME credit and confirmation of your participation, please mail a photocopy of this completed form before May 31, 2006, to:

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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.

Instructions: For each of the questions or incomplete statements below, indicate the most appropriate response on the Registration/Evaluation Form below.

1. In the United States, OA is the most common form of arthritis after rheumatoid arthritis.
   a. True b. False

2. Which one of the following statements about the pathophysiology of OA is false?
   a. OA is a disease of the synovial joints.
   b. The pathophysiology of primary and secondary OA is the same.
   c. Inflammation is a hallmark of OA.
   d. All statements are true.

3. Which one of the following interventions is not well-supported by evidence in the management of OA?
   a. Weight loss c. Exercise
   b. OTC analgesia d. Debridement

4. Many patients who develop serious GI complications with the use of NSAIDs have prior warning symptoms.
   a. True b. False

5. Which one of the following statements is 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 labeling 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 statements are true.

6. Which one of the following statements is false?
   a. Approximately 16,500 deaths per year are associated with GI complications of NSAID use in patients with OA and RA.
   b. Patients with musculoskeletal conditions are 50% more likely to utilize healthcare services than those without such chronic conditions.
   c. GI complications related to NSAID therapy are the most prevalent category of adverse drug reactions.
   d. All statements are true.

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

8. In a risk/benefit assessment of analgesics for OA pain, which one of the following factors should be considered?
   a. Risk of GI bleeding d. Both a and c
   b. Severity of pain e. All of the above
   c. Presence of CV and/or renal disease

9. Clinical studies suggest that when low-dose aspirin is used with NSAIDs, there is a reduced ability of aspirin to protect against CV disease.
   a. True b. False

10. Enteric coating and buffering reduces aspirin-associated GI risks.
    a. True b. False

Please record your posttest answers: 1._____ 2._____ 3._____ 4._____ 5._____ 6._____ 7._____ 8._____ 9._____ 10._____ Please see page 8 for the Answer Key.

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The University of Colorado School of Medicine would appreciate your comments regarding the quality of the information presented and thanks you for your participation.

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