



InetCE

Volume 4

2000

Number 1

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Update on the Management of Common Musculoskeletal Conditions: Osteoarthritis, Rheumatoid Arthritis, and Fibromyalgia

InetCE 146-000-00-003-H01

Expires 03/14/2003

Kimberly A. Hunter, Pharm.D.

Assistant Professor of Pharmacy Practice
Albany College of Pharmacy
Clinical Specialist
Albany Family Practice
Albany, NY 12208

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Learning Objectives

After completing this continuing education program, the reader should be able to:

1. Differentiate between osteoarthritis, rheumatoid arthritis and fibromyalgia.
2. Recognize common presenting signs and symptoms of each disease.
3. Describe the proposed pathophysiology of each disease.
4. Recommend appropriate pharmacologic and nonpharmacologic therapies for each disease.

5. Recognize common side effects of the therapies used to treat these diseases.
6. Provide monitoring and education for patients with these illnesses.

Abstract: Musculoskeletal conditions affect over 40 million people in the United States. The 3 most common are osteoarthritis, rheumatoid arthritis, and fibromyalgia. Osteoarthritis is the most common form of all musculoskeletal conditions affecting more than 20 million people in the United States. Rheumatoid arthritis and fibromyalgia are not as common, but have a significant impact on a patient's quality of life and physical functioning. The exact etiologies of these conditions are not well understood, but research on these topics is providing important information about the pathophysiology of these diseases. Currently, therapy is aimed at reducing the pain and other symptoms associated with these conditions. Non-pharmacologic therapies play an important role in the treatment of these disorders including weight loss, exercise, and physical therapy. Pharmacologic therapy is aimed at pain relief and, in the case of rheumatoid arthritis, disease modification. In addition to therapies that have been available for years, new therapies with fewer side effects and more specific mechanisms of action are being studied and released. Pharmacists should become familiar with these therapies to help patients achieve optimal treatment outcomes.



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Update on the Management of Common Musculoskeletal Conditions: Osteoarthritis, Rheumatoid Arthritis, and Fibromyalgia

INTRODUCTION

There are over 100 different types of musculoskeletal conditions that can have a significant impact on a patient's physical and psychological functioning. They affect approximately 40 million Americans including men and women, young and old, and are the leading cause of work-related disability in people between the ages of 16 and 72 years.¹ One hundred and fifty billion dollars in medical costs were spent on these conditions in 1992 on over 315 million physician visits and 8 million hospital admissions.^{1,2} In addition to being costly both monetarily and physically, these diseases impact patients' quality of life with 42% of people experiencing limitations in their ability to participate in various activities.¹

Osteoarthritis (OA) is the most prevalent musculoskeletal condition in the United States affecting more than 21 million people.² However, this figure is thought to be underestimated because of the lack of a standard definition for the diagnosis of OA. In fact, many people have radiographic changes indicative of OA but do not have symptoms of the disease.² Approximately 70% of people over the age of 70 years have radiographic evidence of OA, but only half of these people will go on to develop clinical symptoms of the disease.³ The prevalence of OA is growing, most likely due to an increase in the average age of our population and better recognition and diagnosis of the disease. Although OA affects people of all ages, it is a condition whose incidence rises

greatly with age. It can affect both genders, but it is twice as common in women over 65 years of age than it is in their male counterparts.²

Rheumatoid Arthritis (RA) is the second most common musculoskeletal condition. It is significantly less prevalent than OA affecting approximately 2.1 million people.^{2,4} Although less common than OA, more than \$65 billion were spent in 1992 on the management of this illness.⁴ Three-quarters of the people afflicted with RA are women, and peak onset is between the ages of 20 and 45 years.⁴ Rheumatoid arthritis is a disease that fluctuates in severity leaving the patient unable to predict when flares will occur. Without aggressive and early treatment RA can progress to joint destruction and resultant deformity, disability, and premature death.⁵

Fibromyalgia (FM), previously referred to as fibrositis, is a complex musculoskeletal syndrome that has only been defined as a medical condition for approximately 20 years.⁶ It is characterized by a multitude of symptoms including chronic pain, fatigue, aching, and stiffness.⁷ FM affects 2% of the American population and it is 7 times more common in women than men, especially women of childbearing age.⁷ This condition is very controversial because it can mimic many other diseases like Lyme disease and systemic lupus erythematosus, and it often coexists with other illnesses, such as chronic fatigue syndrome, headaches, and depression.⁸ It can be difficult to diagnose as symptoms can be nonspecific. The etiology of FM is unknown, and there is no cure. Although painful, FM does not appear to cause permanent damage to connective tissues.⁷

PATHOPHYSIOLOGY

Osteoarthritis

The exact mechanism of OA is not known, but research has shown that it appears to result from an imbalance between the synthesis and degradation of articular cartilage, its extracellular matrix, and subchondral bone resulting in loss of integrity. Cartilage is responsible for absorbing stress placed on a joint and providing a smooth, friction-reducing surface to ease joint movement. It is able to perform these roles because of its composition consisting of chondrocytes and a matrix of collagen and proteoglycan.⁹ Cartilage is maintained through a process of synthesis and degradation. In people with osteoarthritis, this process appears to be off balance leading to decreased production or increased degradation. Matrix metalloproteinase enzymes, various cytokines, and nitric oxide have all been implicated in increased matrix degradation, since they are found in increased concentrations in osteoarthritic joints. Many compounds including growth factors influence cartilage synthesis. Insulin-like growth factor 1 and transforming growth factor beta may play a role in reduced production of cartilage, but their role is still unproven.⁹ In addition to this imbalance, other factors seem to play a part in the destruction of cartilage including metabolic, biomechanical, immunologic, and genetic influences. These changes result in cartilage that is fibrillated (as opposed to being smooth) and hypertrophied, inflamed in the underlying synovium, and has developed bony prominences known as osteophytes.⁹ Additionally, other surrounding structures may be involved. Subchondral bone may become brittle and develop cysts and microfractures, which can result in bone that is less efficient as a shock absorber. Many of these changes have been implicated as

sources of pain experienced by patients with OA.

Several risk factors are implicated in the development of OA. In addition to aging, obesity, female gender (although OA of the hip is more common in the male gender), previous joint injury, and repetitive occupational use, genetic predisposition and developmental abnormalities have been implicated in the development of OA.⁹ The most common sites of OA are the hands, knees, hips, cervical and lumbrosacral spine, and, less frequently, the shoulders and elbows. Joint involvement is usually unilateral and systemic manifestations are rare.¹⁰

Rheumatoid Arthritis

The exact etiology of RA is also unknown, but it is well established that this illness is an acquired autoimmune disorder that is genetically linked. It is a chronic, progressive disease that not only affects the joints but also can exhibit extraarticular manifestations including low-grade fever, lymphadenopathy, anorexia, weight loss, and muscle atrophy. Subcutaneous nodules may be present in about 25% of patients with RA, and are a result of circulating rheumatoid factor.¹¹ Rheumatoid factor is antibody to IgG and is present in 60% to 80% of adults with the disease.¹²

Rheumatoid arthritis can attack any joint in the body and tends to do so in a symmetric pattern. It more frequently affects the small joints of the hand, wrist, knees, and feet. As the disease worsens, it may affect the elbows, shoulders, hips, and ankles.¹¹ The damage to the joints caused by RA is thought to be caused by the interaction of many inflammatory cells and chemicals. Cytokines, like tumor necrosis factor (TNF), are secreted by synovial fibroblasts and other cells resulting in the inflammation and pain. TNF may also be responsible for

influencing other inflammatory compounds including interleukins, collagenase, and prostaglandins.¹³⁻¹⁵

Fibromyalgia

FM is a condition characterized by widespread muscle pain and point tenderness at various sites around the body including the upper back, buttocks, upper arms, and knees. The etiology of this illness is unknown, but it has been linked to psychological stress, immune or endocrine disorders, and biochemical abnormalities in the central nervous system.⁷ Elevations in substance P and nerve growth factor have been detected in patients with FM. Similarly, lower levels of serotonin have been documented in these patients. Activation of N-methyl-D-aspartate (NMDA) receptors that interact with excitatory amino acids and increase chronic pain may also play a role. Other abnormalities include reduced response of cortisol to physiologic stress, decreased nighttime hormone release, and disturbances in rapid eye movement (REM) sleep leading to daytime sleepiness.¹⁶ A second theory explaining FM focuses on it being a psychiatric disorder. One trial found that patients with FM were more likely to have histories of sexual, physical, or drug abuse; eating, anxiety, or panic disorders; phobias; depression; or alcoholism in their families.¹⁷

CLINICAL PRESENTATION

Osteoarthritis

The most common clinical manifestation of OA is pain that can limit activity. Patients will seek the advice of their health care providers for pain in a joint that is insidious in onset, mild to moderate in severity, worsened with use, and relieved with rest.⁹ In general, inflammation is not a common presenting factor of OA, but some patients

may have synovial swelling of the affected joint. Stiffness is not severe, but some patients may experience joint stiffness for as long as 15 to 30 minutes when awakening in the morning.¹⁰ Signs associated with OA include crepitus or the sound of bone rubbing against bone, bony hypertrophy, and tenderness. With more advanced disease and joint destruction, patients may experience limited range of motion, joint malalignment, and altered gait.

Rheumatoid Arthritis

Rheumatoid arthritis can fluctuate between being a mild illness to a chronic, progressive joint destroying condition. Early in the course of the disease inflammation of the synovium may occur leading to joint pain, stiffness, and limitation of motion. Patients may also have non-specific complaints of fatigue, malaise, and flu-like symptoms. Signs of osteoporosis in the ends of the bones forming the joint may also be present early in the disease process.

With more advanced disease patients may exhibit extraarticular manifestations. These include rheumatoid nodules; vasculitis; and lesions in the eyes, heart, lungs, and peripheral nerves. Patients may also complain of dry eyes (xerophthalmia) and dry mouth (xerostomia) due to chronic inflammation of the exocrine glands.¹¹

Fibromyalgia

Patients with FM will most frequently complain of widespread pain with tender points. The pain is characterized as burning, gnawing, radiating, or shooting and may be accompanied by weakness, fatigue, stiffness, nausea, numbness, poor sleep, and inability to concentrate.⁶ Stress, anxiety, and exertion may worsen symptoms.¹⁶ Because of the nonspecific nature of the symptoms associated with FM, patients can be easily diagnosed with other syndromes and

conditions. Twenty percent to 70% of people with FM also fit the criteria for chronic fatigue syndrome. Irritable bowel syndrome is present in 34% to 65% of patients with FM.¹⁶ FM has also been associated with tension headache, Gulf War Syndrome, premenstrual syndrome, substance abuse, chemical sensitivities, and other, sometimes controversial, syndromes.¹⁶

DIAGNOSIS

Osteoarthritis

Appropriate diagnosis of OA requires the collection of a complete patient history and physical. Radiographic changes consistent with OA include asymmetric joint space narrowing, subchondral bone sclerosis and cyst formation, osteophytes, and, in severe cases, deformity of bone ends. Surrounding joint structures may also exhibit radiographic changes.

Laboratory tests including a complete blood count and electrolyte panel are usually normal, and the erythrocyte sedimentation rate, a non-specific marker for inflammation, may be slightly elevated. Diagnostic tests that are available for other rheumatologic conditions, such as Rheumatoid factor (RF) and antinuclear antibody (ANA), will almost always be negative.^{9,10}

Rheumatoid Arthritis

A complete history should also be obtained from patients suspected to have RA. The evaluation should include documentation of symptoms and severity of active disease including joint pain, stiffness, and fatigue. A patient's functional status should also be assessed.⁵ Laboratory studies should include those listed for OA and an assessment of baseline renal and hepatic

functioning, since antirheumatic therapies have been shown to cause damage to these two organs. These tests are not specific for the diagnosis of RA, but an elevated RF is common in two-thirds of people with this disease. RF can be used as a prognostic indicator in RA, since patients with higher levels have more severe and active joint disease, greater systemic involvement, and a poorer prognosis for remission.^{12,18} The likelihood of a poor prognosis has also been associated with earlier age at onset, elevated erythrocyte sedimentation rate, and swelling of greater than 20 joints.⁵

Fibromyalgia

In 1990, the American College of Rheumatology (ACR) developed a list of criteria for FM to help practitioners accurately diagnose this disorder. These criteria require that patients have widespread pain (pain above and below the waist on both sides of the body) of at least 3 months' duration in combination with 11 of a possible 18 tender points.¹⁹ However, in 1993, the World Health Organization realized that many patients with FM may be missed using these criteria and suggested that FM was part of a wider spectrum of disorders.¹⁶ Muscle and joint evaluations as well as laboratory analysis are generally normal. Currently, there is no gold standard upon which to base a diagnosis of FM.⁶

NONPHARMACOLOGIC THERAPY

The goals of therapy for patients with OA, RA, or FM are to reduce symptoms, especially pain. Additionally, for patients with RA, early intervention is imperative to slow disease progression and prevent joint damage. Therapies should be implemented to minimize disability, maintain mobility, allow the patient to participate in activities of daily living, and to avoid complications

including loss of functioning or the development of subsequent psychological problems.

Nonpharmacologic therapy is aimed at reducing modifiable risk factors and educating patients about their disease and its management. These interventions include involving patients in support groups and self-help courses and referring patients to physical and occupational therapists to learn various exercises and mechanisms of joint protection and energy conservation.

Patients with OA, especially of weight-bearing joints, who are overweight should be encouraged to lose weight and use assistive devices, such as canes, grab bars, and splints. Aerobic exercise also plays an important role in maintaining function and flexibility. It may also help overweight patients lose weight. Water aerobic programs may be useful because of the reduced stress they place on weight-bearing joints. Additionally, they have been shown to increase mobility and reduce depression in patients with OA.²⁰ Muscle conditioning may also help to reduce the pain associated with OA by allowing the load placed on weight-bearing joints to be borne by the muscle.²¹ Patients with severe disease and limitation of motion may benefit significantly from surgery to replace the affected joint.

The patient with RA can also benefit from nonpharmacologic modalities. In addition to the suggestions listed above, patients with RA can reduce symptoms by resting. Also,

inflamed joints can be splinted to reduce unnecessary movement. Exercise can also be employed to maintain and improve muscle strength and joint mobility, as long as it doesn't exacerbate symptoms. Assistive and orthotic devices can be used to support deformed joints, in an effort to reduce pain and improve function.¹⁸

Similar approaches should be used in patients with FM. Education about rest and sleep hygiene is imperative due to the high rate of sleep disturbance in this population. Patients should be educated not to go overboard with activities on days when their disease is mild. Exercise has been shown to reduce objective measures of pain in these patients.²² Cognitive behavioral therapy and stress-reduction techniques may be beneficial in helping FM patients reduce stress.⁶

PHARMACOLOGIC THERAPY

Osteoarthritis

The ACR recommends that pharmacologic therapy should be individualized for each patient. Practitioners should evaluate the patient for concomitant renal, heart, and peptic ulcer disease and for drug therapy that may interact with the therapy prescribed for OA. A stepped approach to therapy for OA of the hip and knee is provided in Tables 1 and 2, respectively.^{23,24} However, there are agents not listed in these tables that may be helpful for certain patients and should not be precluded based upon their absence from these guidelines

Table 1. American College of Rheumatology Stepped Approach to Managing Osteoarthritis of the Hip²³

- Nonpharmacologic treatment
 - Simple analgesics (acetaminophen up to 1 gram 4 times per day)
 - Low-dose ibuprofen (up to 400 mg 4 times per day) or nonacetylated salicylates
 - Full-dose nonsteroidal antiinflammatory drugs (NSAIDs)
 - Referral for surgery
-

Table 2. American College of Rheumatology Stepped Approach to Managing Osteoarthritis of the Knee²⁴

- Nonpharmacologic treatment
 - Intraarticular steroid injection (if localized inflammation is present)
 - Simple analgesics (acetaminophen up to 1 gram 4 times per day)
 - Add topical capsaicin cream if acetaminophen provides inadequate relief
 - Low-dose ibuprofen (up to 400 mg 4 times per day) or nonacetylated salicylates
 - Full-dose nonsteroidal antiinflammatory drugs (NSAIDs)
 - Referral for joint debridement, lavage, or surgery
-

• Capsaicin

Capsaicin cream is the first of the non-prescription products available for the treatment of OA. It has been shown to be useful in reducing the pain associated with OA of the knee, and can be used alone or as adjunctive therapy to oral analgesics.^{25,26}

Capsaicin works by depleting substance P, a neurotransmitter involved in peripheral pain sensation.²⁷ It is available in several concentrations including 0.075% and 0.25%, and should be applied 2 to 4 times daily for best results. Patients should be informed that capsaicin cream may cause localized burning and that it may take several weeks to months to feel results. As well, they should be cautioned to wash their hands after using this agent and to avoid getting it in their eyes.

• Acetaminophen

Acetaminophen is the first-line pharmacologic agent recommended by the ACR for OA. It is inexpensive, available without a prescription, and effective in reducing pain. Patients should be counseled to use 500 mg to 1,000 mg up to 4 times daily to a maximum dose of 4 grams per day. Patients should also be advised that they might need to take this drug on a regular basis versus “as needed” to achieve maximal pain relief. Those with renal and/or hepatic dysfunction or who consume alcohol on a regular basis should check with their physicians before using this agent to verify an appropriate maximal daily dose. A study comparing 4 grams per day of acetaminophen with ibuprofen found that acetaminophen was equally efficacious to high and low doses of ibuprofen.²⁸

- **Nonsteroidal Antiinflammatory Drugs (NSAIDs)**

Despite the safety and efficacy of acetaminophen in the treatment of OA, NSAIDs are more frequently used to treat the pain associated with this disorder.²⁹ NSAIDs have been used in the U.S. for over 20 years, and there are currently over 25 agents available. The ACR recommends them as second line for OA after a trial of acetaminophen and/or capsaicin. These agents are very effective for the relief of pain, but have several serious side effects and drug interactions. Although there appears to be little difference between these agents with respect to efficacy, there are differences in their abilities to cause side effects. NSAIDs work by non-specifically inhibiting prostaglandin synthesis. Prostaglandins play a role in inflammation but also have protective roles in the body. NSAIDs have been implicated in causing renal disorders, hepatic dysfunction, and disturbances of the central nervous system through the non-specific systemic inhibition of protective (Cox-1) and inflammation-causing (Cox-2) prostaglandins in the gastric mucosa, kidneys, and platelets. The most serious side effect of NSAIDs is gastrointestinal toxicity. NSAIDs cause ulcers or ulcer complications in 2% to 4% of

patients per year.³⁰ They are responsible for approximately 100,000 hospitalizations and over 16,000 deaths per year.^{31,32}

- **Cox-2 Inhibitors**

To overcome some of these serious problems associated with traditional NSAIDs, researchers have developed new analgesic and antiinflammatory agents known as specific cyclooxygenase-2 inhibitors (Cox-2 inhibitors). Two of these agents were released into the U.S. market in 1999, celecoxib (Celebrex) from Searle and rofecoxib (Vioxx) from Merck. The Cox-2 inhibitors work by specifically inhibiting the Cox-2 isoenzyme while preserving Cox-1 function, thus reducing many of the toxicities listed above. Although they have a different mechanism of action, Cox-2 inhibitors are still classified as NSAIDs by the FDA and carry all of the warnings associated with these agents. However, experience, to date, has shown fewer, serious gastrointestinal (GI) complications than seen with NSAIDs.³³ It is important to remember that these agents are no more effective than standard NSAIDs for treating OA and may be most cost effective in patients who have risk factors for developing GI problems. These risk factors can be found in Table 3.^{31,32}

Table 3. Risk Factors for NSAID-associated GI Complications^{31,32}

- History of peptic ulcer disease
 - History of upper GI bleeding
 - History of hospitalization for a GI event
 - Concurrent use of prednisone
 - Older age
 - Higher NSAID dose/longer duration of therapy
 - History of cardiovascular disease
-

Celecoxib is approved for use in the treatment of OA and RA.³⁴ Rofecoxib is approved for the treatment of OA and acute pain, but not RA.³⁵ Both drugs should be used with caution in patients on concurrent warfarin therapy and they may reduce the effectiveness of ACE inhibitors.^{34,35} Additionally, celecoxib should be avoided in patients who have an allergy to sulfonamides.³⁴ Common side effects of the Cox-2 inhibitors include gastrointestinal upset, dyspepsia, nausea, and diarrhea. Patients can be instructed to take these agents with food if these side effects occur.^{34,35}

- **Narcotics**

Narcotics are not recommended by the ACR as first- or second-line therapy for OA.^{23, 24} Some practitioners feel that these agents are warranted in patients whose pain is uncontrolled with conventional therapies. Others feel that narcotics should be used in acute situations when patients experience flares in their pain associated with OA. If they are used, patients should be counseled about the side effects of these drugs including sedation, dizziness, constipation, and respiratory depression. With long-term use, physical and psychological dependence may occur. Patients should also be aware that many of the narcotics that may be used for OA contain acetaminophen, and that they should avoid taking additional acetaminophen while they are on the narcotic agent.

- **Corticosteroids**

In patients with clinical evidence of synovial inflammation and fluid accumulation, joint aspiration should be performed and corticosteroids injected to relieve the pain and reduce the inflammation. Intraarticular injections can be performed up to 3 to 4 times per year, but more frequent injections have been associated with progressive joint

damage especially in weight bearing joints.³⁶ Oral corticosteroids are not recommended for the treatment of OA, since it is not a systemic inflammatory condition, and oral steroids have many serious side effects.³⁶

- **Hyaluronic Acid**

Two agents containing hyaluronic acid were released to the U.S. market in 1997, Synvisc and Hylagan. These agents are referred to as viscosupplementation and are injected into osteoarthritic knees to improve the cushioning properties of the synovial fluid. Injections must be given weekly over a period of 3 to 5 weeks, and patients with mild to moderate OA appear to receive the most benefit. This therapy is expensive and is classified as a device versus drug therapy, and may not be covered by all insurance plans. Experience, thus far, with these agents has shown mixed results. Patients may need to wait several weeks after their last injection before seeing a response, and in those that do respond, the effects may last only 3 to 5 months. These agents are for symptomatic relief only.³⁷

- **Alternative Therapies**

Glucosamine is an endogenous compound synthesized from sugar. It is an essential component for the synthesis of glycosaminoglycans (GAGs), important building blocks in the formation of connective tissues throughout the body. Specifically in the cartilage, GAGs complex with proteins to form proteoglycans. Proteoglycans are present as a gel in the cartilage and aid in the absorption of mechanical stress placed on the joint. Glucosamine is available in the U.S. as a dietary supplement, and has gained great favor for the relief of pain associated with OA. It is associated with few side effects, namely GI symptoms, and appears to be efficacious for many people with OA.³⁸ For optimal efficacy, 500 mg of glucosamine

taken three times per day is needed, and it may take up to 4 to 6 months for full benefits to be realized by the patient. Although glucosamine is often combined with chondroitin, there is no evidence that supports any benefit of this combination versus glucosamine alone.³⁸

S-Adenosylmethionine, more commonly referred to as SAM-e, is gaining increased recognition for the treatment of OA as well as other conditions. First introduced to the U.S. market in February 1999 as a dietary supplement, SAM-e is responsible for many biochemical reactions. It is a naturally occurring substance containing 2 amino acids and is found in almost all body tissues and fluids. It acts as a methyl donor when it reacts with vitamin B₁₂ and folic acid. Some evidence suggests that SAM-e may work as well as NSAIDs for OA but with fewer side effects, and it may stimulate cartilage growth and repair.^{39,40} The most common side effect of this therapy is nausea, especially with higher doses. There are no known drug interactions with SAM-e, and doses of 200 mg orally 3 times per day are needed for optimal effects in OA.³⁸

Some research supports the benefits of dietary therapy for OA.⁴¹ A well-balanced diet is important in helping patients to maintain a healthy weight or to lose weight, if needed. However, some researchers promote a diet that is rich in essential fatty acids and fish oils for their supposed ability to reduce inflammation and allergic responses. Other researchers promote the dramatic reduction of fatty foods, eggs, dairy products, caffeine, and sugars in the diet of the OA patient, since these foods have been implicated in food allergies that can result in pain.⁴¹

Other therapies that have been tried for OA include acupuncture, magnetic therapy, and

chiropractic care.⁴¹ It is important that if alternative therapies are tried they should cause no harm to the patient or delay the time in seeking appropriate medical care. While this list is not all-inclusive, it provides the pharmacist with useful information that can be used to answer patients' questions. Though many of these agents look promising, the pharmacist should keep in mind that more rigorous, clinical studies are needed before these therapies should be recommended on a widespread basis.

• **Experimental Therapy**

Several experimental therapies are being studied for the treatment of OA. Since cytokines have been potentially implicated in the imbalance that leads to OA, modulation of these compounds may be useful. Tenidap has been looked at for its potential ability to do this.⁴² Tissue transplants are also being reviewed for their potential role in the management of OA. In patients with a specific defect in the knee joint, known as osteochondritis dissecans, autogenous cartilage implantation is being studied. Results, to date, look promising, but caution is advised while more long-term and better-designed studies are conducted.⁴³ A second procedure being studied is referred to as autogenous osteochondral grafting. Only 57 patients have been studied so far, but results have been encouraging. In this procedure, cylinders of bone and cartilage are transferred from a lesser weight-bearing position to the articular surface of knee joint. The procedure is limited to areas where cartilage lesions are small.⁴⁴

Rheumatoid Arthritis

There is no cure for RA, nor is there a way to prevent it by reducing risk factors. Since this disease can cause great disability and premature death, early diagnosis and aggressive treatment are imperative to prevent impairment and joint damage.⁴ As

with OA, the ACR recommends that pharmacologic therapy should be individualized for each patient. The goals of therapy for patients with RA should be to maintain and/or improve joint function, reduce symptoms including pain, and slow disease progression. Ultimately, helping the patient to achieve full remission is desirable, but few are ever able to do so.⁵

- **NSAIDs/Cox-2 Inhibitors**

NSAIDs are used in RA to reduce joint inflammation and resultant pain and to improve function. The antiinflammatory property of these agents may take several weeks to reach maximal efficacy, while their pain relieving property is more immediate. Patients should be counseled about the importance of taking these agents as prescribed and not combining them with nonprescription agents without the approval of their physicians. NSAIDs cannot alter disease progression but play an important role in symptom relief for patients with RA. For patients with risk of gastrointestinal toxicity from NSAIDs, the prostaglandin analog, misoprostol, or a proton-pump should be added to prevent ulceration.⁵ An alternative would be to use celecoxib, the COX-2 inhibitor approved for the treatment of RA.

- **Disease-modifying Antirheumatic Drugs (DMARDs)**

DMARDs should be used for patients, who, despite the use of an adequate trial of NSAIDs, continue to experience pain and swelling in their joints, morning stiffness or fatigue, or elevations in other indicators of inflammation, such as the erythrocyte sedimentation rate.⁵ While they relieve pain and inflammation, NSAIDs cannot prevent the irreversible joint damage that can occur even early in the disease. DMARDs, on the other hand, are effective at reducing or preventing joint damage, maintaining and

improving joint function, and improving the overall care of the RA patient.⁴⁵ These agents should be started during the first 3 months following diagnosis of RA if NSAIDs are ineffective. Currently available DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, gold salts, D-penicillamine, azathioprine, and a recently released agent, leflunomide. Hydroxychloroquine and sulfasalazine are often the first DMARDs used in therapy because of their low side-effect profiles. However, it appears that these agents may be less efficacious than some of the other DMARDs, and that they often need to be replaced by other agents.^{5,45}

Despite the many side effects that may occur with DMARD therapy, current evidence supporting the use of these agents early in therapy to prevent inflammation is paramount to preserving joint function.⁴⁶ Methotrexate has become the most widely prescribed DMARD for RA.⁴⁵ It has several side effects that include gastrointestinal problems, liver and pulmonary toxicity, and lymphoma. Patients prescribed this agent should be monitored closely for these side effects and educated about ways to monitor themselves for toxicity. Despite these side effects, more patients continue on methotrexate therapy than any other DMARD.⁴⁷

DMARDs do not have an immediate onset of action. They may take up to 6 to 10 weeks to see improvements in symptoms, and concomitant therapy with steroids should be employed during this time. Patients should understand how these agents work and the importance of taking them on a regular basis for maximal benefit. Even though DMARDs have been available for the treatment of RA for a long time, newer studies are looking at different ways to use

these agents, ways to reduce side effects, and the importance of early intervention.⁴⁸

- **Steroids**

Steroids can be used at anytime in the management of RA. They are often applied for symptomatic relief of inflammation, but can be combined with DMARD therapy for a more aggressive treatment approach.⁴⁶ Steroids can be given orally or injected into swollen joints. Long-term administration of oral steroids has many serious side effects, and may limit their use in treatment. It is important, therefore, that the lowest possible dose be used for the shortest possible time. When these agents are prescribed for patients they should be aware of the importance of taking them as prescribed, especially during tapering. Locally injected steroids are unlikely to cause systemic side effects, but the antiinflammatory effect of the injection is often short-lived.⁵

- **Tumor Necrosis Factor Receptor Antagonist**

In 1999, etanercept (Enbrel, Immunex), a tumor necrosis factor (TNF) receptor antagonist, was found to be effective in reducing the signs and symptoms of moderate-to-severe, active rheumatoid arthritis in patients who have had an inadequate response to 1 or more disease-modifying antirheumatic drugs.⁴⁹ It has been studied in children as young as 4 years of age, and is given as a 25 mg subcutaneous injection twice weekly. In one study, patients experienced a 50% reduction in swollen joints after 3 months of therapy.⁴⁹

Etanercept should not be given to patients with sepsis, and its use should be discontinued if patients develop serious infections. It is possible that etanercept could reduce host defenses against infections and malignancies, since TNF mediates inflammation and

modulates cellular immune responses. It is pregnancy category B, and the risks versus benefits of therapy should be weighed before using this drug in nursing mothers.

Common side effects of etanercept include pain at the injection site, upper respiratory tract infections, headache, rhinitis, dizziness, rash, dyspepsia, and cough.⁴⁹ Although this agent appears promising for patients with severe RA, it is important to follow its progress now that it is available for widespread use.

Experimental Therapy

Therapies aimed at reducing the effects of inflammatory mediators in RA are currently being studied. These agents, referred to as biological response modifiers, are being developed to target specific mediators of the inflammatory response, especially cytokines.^{45,50} Infliximab, an anti-TNF alpha monoclonal antibody approved in the U.S. for the treatment of Crohn's disease and enterocutaneous fistulas, is also being studied in RA. Recent evidence suggests efficacy with few side effects when compared to placebo.⁵¹ Other agents in development include an interleukin-1 (IL-1) receptor antagonist developed through recombinant technology and anti-CD4 monoclonal antibodies.⁵⁰ It is not likely that these agents will take the place of DMARDs in the treatment of RA anytime soon. However, they may play an important part in slowing the progression of the disease, especially in patients with severe, refractory RA.^{44,50}

Fibromyalgia

Many of the treatment options for FM center around nonpharmacologic therapies. Although this syndrome has a pain aspect, conventional treatments for pain are not always effective. One of the most important aspects of the management of this disease is

ensuring that patients understand the illness as much as possible and the importance of trying nonpharmacologic treatment approaches including exercise and relaxation techniques.

- **Analgesics/Antiinflammatories**

NSAIDs and other analgesics only partially improve symptoms for some patients with FM. Narcotics are not recommended because of their potential for dependence and addiction with long-term use. Glucocorticoids have been of little benefit, and should be avoided.⁶

- **Antidepressants**

Various other therapies have shown benefit in some patients with FM. The tricyclic antidepressants and the muscle relaxant, cyclobenzaprine, used before bedtime may help to restore a normal sleep pattern helping the patient to feel less fatigued. Patients should be started on regular doses of these medications and titrated upwards, based upon efficacy and side effects. Depression and anxiety should be treated with appropriate interventions including psychotherapy and drugs. Trazodone may be a useful addition in a patient with concomitant sleep disturbance and depression. Other than alprazolam, benzodiazepines should be avoided in patients with FM because of their negative effects on the sleep cycle.⁶

- **Others**

First and foremost, before any therapy is recommended for FM, patients should be educated about the disease itself. Practitioners should help sufferers to understand that this condition is not life threatening or crippling. Patients should understand that this disease is not one that progresses to the point of immobility, deformity, or early death like some other rheumatologic conditions. In addition to the

general nonpharmacologic measures listed above, patients with FM may benefit from stress- and pain-relieving therapies, such as biofeedback, hypnotherapy, and massage.⁶ As mentioned previously, S-adenosylmethionine (SAM-e) may play a role in the treatment of musculoskeletal conditions. Early evidence shows that some patients with FM may benefit from the addition of SAM-e to their therapeutic regimen.⁵²

CONCLUSION

Pharmacists should become part of a multidisciplinary team that helps to set therapeutic goals for patients with OA, RA, and FM. They should also be familiar with the differences between these conditions and variety of therapies—pharmacologic and nonpharmacologic—available for treatment. Table 4 provides the pharmacist with a comparison of these 3 conditions. With this knowledge, pharmacists should be prepared to make therapeutic recommendations, monitor therapies for efficacy and toxicity, and provide education and counseling for patients and their caregivers. This is especially true with the new prescription therapies that are entering the market and alternative modalities that are being promoted for their pain and inflammation-reducing properties for musculoskeletal conditions.

Osteoarthritis is a prevalent disease that remains underdiagnosed and undertreated. Pharmacists can play an important role in helping patients to achieve optimal therapeutic outcomes from the variety of therapeutic options available. Rheumatoid arthritis is a severely debilitating disease. If treated early and appropriately, many of the negative outcomes including joint deformity and destruction can be slowed. Fibromyalgia is a very complex syndrome

making it difficult to diagnose and treat. Pharmacists should be familiar with the variety of symptoms associated with FM, so that they may refer their patients to their physicians when this condition is suspected. By becoming active members of the

healthcare team and helping patients and caregivers to set and achieve reasonable therapeutic goals, pharmacists can make valuable contributions to the care of their patients with musculoskeletal conditions.

Table 4. Comparison of Osteoarthritis, Rheumatoid Arthritis, and Fibromyalgia

	Osteoarthritis	Rheumatoid Arthritis	Fibromyalgia
Etiology	Imbalance in cartilage degradation/synthesis	Autoimmune process	Unknown, but may be a biochemical imbalance
Common Presentation	Pain in one joint, minor or no stiffness	Pain, joint inflammation (usually symmetrical), fatigue, malaise, early morning stiffness	Widespread pain, tender points, weakness, fatigue, nausea, numbness, sleep problems
Diagnostic Factors	Patient history, radiographic changes	Patient history, rheumatoid factor, ESR	Patient history, location of tender points/pain, labs generally normal
Non pharmacologic Therapy	Weight loss, aerobic exercise, muscle conditioning,	Rest, exercise (if doesn't worsen symptoms), splinting, orthotics	Aerobic exercise, stress reduction/management, cognitive behavioral therapy
Pharmacologic Therapy	Capsaicin, acetaminophen, NSAIDs, Cox-2 Inhibitors, steroid injections, hyaluronic acid, glucosamine, SAM-e	NSAIDs, celecoxib, DMARDs, oral and injectable steroids, anti-TNF	NSAIDs, acetaminophen, cyclobenzaprine, alprazolam, antidepressants

REFERENCES

1. Yelin E, Callahan LF, for the National Arthritis Data Work Group. The economic and societal and psychological impact of musculoskeletal conditions. *Arthritis Rheum.* 1995;38:1351-62.
2. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998;41:778-799.
3. American College of Rheumatology website. www.rheumatology.org/patients/factsheet.oa.html. Accessed 12/28/99.
4. American College of Rheumatology website. www.rheumatology.org/patients/factsheet.ra.html. Accessed 12/28/99.
5. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum.* 1996;39:713-22.
6. Gordon S, Morrison C. Fibromyalgia and its primary care implications. *Medsurg Nursing.* 1998;7:207-16.
7. American College of Rheumatology website. www.rheumatology.org/patients/factsheet.fibromya.html. Accessed 12/28/99.
8. Goldenberg DL. Fibromyalgia syndrome a decade later. *Arch Intern Med.* 1999;159:777-85.
9. Creamer P, Hochberg MC. Osteoarthritis. *Lancet.* 1997;350:503-9.
10. Brandt KD. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, Inc;1998.
11. Firestein GS, Zvaifler NJ. Rheumatoid Arthritis. In: Gallin JI, Goldstein IM, Snyderman R, eds. Inflammation: Basic Principles and Clinical Correlates. 2nd ed. New York: Raven Press, Ltd.;1992.
12. Duquense University website. www.duq.edu/PT/RA/TableOfContents.html. Accessed 1/4/00.
13. Wallis WJ, Furst DE, Strand V, et al. Biologic agents and immunotherapy in rheumatoid arthritis. *Rheum Dis Clin North Am.* 1998;24:537-65.
14. Roux-Lombard P, Punzi L, Hasler F, et al. Soluble tumor necrosis factor receptors in human inflammatory synovial fluids. *Arthritis Rheum.* 1993;36:485-89.
15. Koopman WJ, Moreland LW. Rheumatoid arthritis: anticytokine therapies on the horizon. *Ann Intern Med.* 1998;128:231-3.
16. Wallace DJ, Shapiro S, Panush RS. Update of fibromyalgia syndrome. *Bull Rheum Dis.* 1999;48:1-4.
17. Epstein SA, Kay G, Clauw R, et al. Psychiatric disorders in patients with fibromyalgia: a multicenter investigation. *Psychosomatics.* 1999;40:57-63.
18. Lipsky PE. Rheumatoid Arthritis. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, Inc;1998.
19. Wolfe F, Smythe HA, Yunus MB et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160-72.
20. Minor MA, Hewitt JE, Webel RR, et al. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. *Arthritis Rheum.* 1989;32:1396-1405.
21. Block JA, Schnitzer TJ. Therapeutic approaches to osteoarthritis. *Hosp Pract.* 1997;32:159-164.

22. Clauw D. Fibromyalgia: more than just a musculoskeletal condition. *Am Fam Physician*. 1995;52:843-51.
23. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part I: osteoarthritis of the hip. *Arthritis Rheum*. 1995;38:1535-40.
24. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II: osteoarthritis of the knee. *Arthritis Rheum*. 1995;38:1541-46
25. Deal CL, Schnitzer TJ, Lipstein E, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther*. 1991;13:383-95.
26. Altman RD, Aven A, Holmburg CE, Pfeifer LM, et al. Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. *Semin Arthritis Rheum*. 1994;23(suppl 3):25-33.
27. Schnitzer TJ, Posner M, Lawrence ID. High strength capsaicin cream for osteoarthritis pain: rapid onset of action and improved efficacy with twice daily dosing. *J Clin Rheumatol*. 1995;1:268-273.
28. Bradley JD, Brandt KD, Katz BP, et al. Comparison of an anti-inflammatory dose of ibuprofen and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med*. 1991;325:87-91.
29. Mamlin LA, Melfi CA, Parchman ML, et al. Management of osteoarthritis of the knee by primary care physicians. *Arch Fam Med*. 1998;7:563-7.
30. Labeling Revisions for NSAIDs. FDA Drug Bulletin 1989;19:3-4.
31. Fries JF. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. *J Rheumatol*. 1991;18(suppl 28):6-10.
32. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med*. 1998;105(suppl 1B):31s-38s.
33. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet*. 1999;354:2106-11.
34. Celebrex Detailed Prescribing Information.
35. Vioxx Detailed Prescribing Information.
36. Neustadt DH: Intraarticular steroid therapy. In: by Moskowitz RW, Howell DS, Goldberg VM, et al, eds. Osteoarthritis: Diagnosis and Medical/Surgical Management. Philadelphia, WB Saunders, 1992.
37. Simon LS. Arthritis: new agents herald more effective symptom management. *Geriatrics*. 1999;54:37-42.
38. Jellin JM, Batz F, Hitchens K. Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database. Stockton, CA: Therapeutic Research Facility; 1999:388-9, 743-4.
39. Di Padova C. S-adenosylmethionine in the treatment of osteoarthritis. Review of the clinical studies. *Am J Med*. 1987;83(suppl 5A):60-5.
40. Stramentinoli G. Pharmacologic aspects of S-adenosylmethionine. Pharmacokinetics and pharmacodynamics. *Am J Med*. 1987;83(Suppl 5A):35-42.
41. The Burton Goldberg Group. Alternative Medicine. Tiburon, CA: Future Medicine Publishing, Inc.;1997:532-7.
42. Sipe JD, Bartle LM, Loose LD. Modification or proinflammatory cytokine production by the antirheumatic agents tenidap and naproxen: a possible correlate with clinical acute phase response. *J Immunol*. 1992;148:480-4.
43. LaPrade RF, Swiontkowski MF. New Horizons in the treatment of

- osteoarthritis of the knee. *JAMA*. 1999;10:876-8.
44. Hangody L, Kish G, Karpati Z, et al. Mosaicplasty for the treatment of articular cartilage defects: application in clinical practice. *Orthopaedics*. 1998;21:751-6.
45. Weinblatt ME. The role of current strategies in the future treatment of rheumatoid arthritis. *Rheumatol*. 1999;38:19-23.
46. Emery H, Proudman MS. Management of patients with newly diagnosed rheumatoid arthritis. *Rheumatol*. 1999;38:27-31.
47. Pincus T, Marcum SB, Callahan LE. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: eleven second line drugs and prednisone. *J Rheumatol*. 1992;19:1885-94.
48. O'Dell JR, Scott DL. Rheumatoid arthritis: new developments in the use of existing therapies. *Rheumatol*. 1999;38:24-6.
49. Weinblatt ME, Kremer JM, Bankhurst AD et al: A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med*. 1999; 340(4):253-259.
50. Breedveld FC. Future trends in the treatment of rheumatoid arthritis: cytokine targets. *Rheumatol*. 1999;38:11-13.
51. Maini R, St. Clair EW, Breedvald F, et al. Infliximab(chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomized phase III trial. *Lancet*. 1999;354:1932-9.
52. Jacobsen S, Danneskiold-Samsoe B, Anderson RB. Oral s-adenosylmethionine in primary fibromyalgia. Double-blind clinical evaluation. *Scand J Rheumatol*. 1991;20:294-302.