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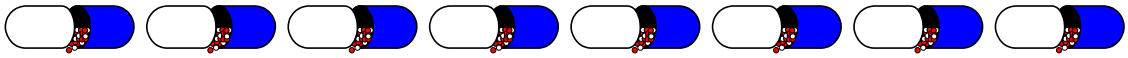
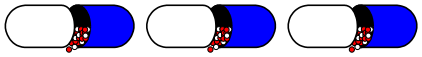


MISSOURI DUReport



ARTHRITIS: A BRIEF REVIEW

Currently, nearly 43 million Americans have arthritis. Musculoskeletal diseases such as arthritis cost the U.S. economy nearly 65 billion dollars per year. This figure represents both direct and indirect costs such as medical care, lost wages, and lost productivity at work.[1]

The two most common forms of arthritis are osteoarthritis (OA) and rheumatoid arthritis (RA). Approximately 21 million Americans have been diagnosed with OA and a majority of these patients are women over the age of 45. More than 7 million physician visits are attributed to OA annually.[2] Currently, rheumatoid arthritis affects 2.1 million Americans. It is more than twice as common in women than men and is non-specific with respect to race.[4] Onset of symptoms is usually between 30-50 years of age, but may occur at any time. Juvenile rheumatoid arthritis occurs before the age of 16 years and has some characteristics similar to adult rheumatoid arthritis.

Osteoarthritis

Osteoarthritis is the most common form of joint disease. It affects nearly 50% of the population older than age 65. There is no known cure for OA; however, treatment designed for individual patients may reduce pain, maintain or improve joint mobility, and limit functional impairment.[3] For this reason, therapeutic management of patients with OA depends on an accurate and early diagnosis and the extent of joint involvement.[4]

The clinical presentation of OA depends upon the duration of disease, type of joints affected, and severity of joint involvement. The predominant symptom is a

localized, deep aching pain associated with the affected joint. The joints most commonly affected in primary OA are the distal interphalangeal and proximal interphalangeal (DIP and PIP respectfully) joints of the hand, the first carpometacarpal (CMC) joint of the hand, knees, hips, cervical and lumbar spine, and the first metatarsophalangeal (MTP) joint of the toe.[4]

Contemporary management goals for patients with OA target relief of pain, functional improvement, and improvement in quality of life. Attempts should be made to achieve these goals while minimizing adverse effects.[3] Treatment strategies should be patient specific, and take into account severity of joint involvement as well as presence or absence of other comorbid disease states, concomitant medications, and allergies. Patients should initially receive nonpharmacologic therapy, which can then be supplemented by pharmacologic therapy. Nonpharmacologic therapy may include one or more of the following techniques:

- Social support, weight loss, dietary modifications, and aerobic exercise
- Rest
- Physical therapy, range of motion exercises, muscle-strengthening exercises, and occupational therapy
- Devices to assist with ambulation, appropriate footwear, bracing, and assistive devices for activities of daily living[3]
- Education. Patient education programs exist in many communities. If you are interested in locating a program, contact the Arthritis Foundation. (Arthritis Foundation Self Management programs are located at www.arthritis.org[5]

When patients do not adequately respond to nonpharmacologic therapy, the next step involves initiating pharmacologic therapy. Studies show that pharmacologic therapy is most effective when combined with nonpharmacologic strategies.[4] Pharmacologic therapies include the following:

Oral:

Oral agents are used in OA primarily as analgesics. They can provide consistent relief of chronic pain and are normally dosed around the clock. This dosing method is used to prevent chronic pain. The most common oral agents for OA include:

- Acetaminophen
- COX-2 specific inhibitors
- Nonselective Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) such as naproxen or ibuprofen. These drugs may also be given with misoprostol or a proton pump inhibitor if the patient has a history of GI bleed or is at risk of a GI bleed
- Nonacetylated salicylates such as choline magnesium trisalicylate or salsalate
- Pure analgesics such as tramadol or opioids[3]

Intra-articular:

Recently new intra-articular hyaluronan injection agents (hyaluronic acid approved for OA of knee) have become commercially available for the treatment of pain associated with OA of the knee. These products are intended to assist in the reconstitution of the synovial fluid, thereby improving joint function.[4] Intra-articular glucocorticoids produce an anti-inflammatory effect directly to the affected joint[3].

Topical:

Topical treatment can be effective for arthritis. Some topical analgesics may be good alternatives for patients with mild arthritis or patients who prefer topical dosage forms or have difficulty taking oral medications. The most commonly used products are:

- Topical capsaicin
- Topical methylsalicylate[3]

Patients and physicians should discuss the best possible drug therapy to ensure proper treatment. Not all therapies are appropriate for everyone as certain patients will respond differently to various agents. Patients with severe symptomatic OA who have pain that has failed to respond to medical therapy should be referred to an orthopedic surgeon for evaluation. [4]

Alternative or Herbal Treatments for Osteoarthritis

Many patients with chronic pain due to conditions such as osteoarthritis turn to alternative or herbal treatments for relief. This may be due to a perceived failure of conventional medicine to alleviate the pain to the patient's satisfaction or patients may feel alternative medicines are safer. Table 1 lists some of the alternative therapies most commonly used in treating osteoarthritis.

Safety of alternative therapies:

S-adenosylmethionine (SAMe), glucosamine sulfate, and chondroitin are generally well tolerated.[7,11,12] Insufficient clinical data exists for methylsulfonylmethane and superoxide dismutase to make a conclusion on their tolerability.[10,11] Patients should be cautioned because the use of SAMe has been reported to induce mania and hypomania in clinical trials. Patients with a history of bipolar disorder should not use SAMe.[7] Ginger extracts should not be used in patients who are bleeding or on anticoagulation therapy.[11] Willow bark contains salicylates and carries the same precautions as aspirin and other salicylates. (e.g., hypersensitivity, asthma, active peptic ulcer disease, diabetes, gout, hemophilia, and kidney or liver disease).[11,12]

Rheumatoid Arthritis

Approximately one percent of the world's population has rheumatoid arthritis (RA), a chronic inflammatory condition that primarily affects the joints, but may also target other tissues and organ systems throughout the body. There is strong evidence of a genetic link for rheumatoid arthritis.[13]

The cause of rheumatoid arthritis is currently unknown. One theory suggests a microbe, such as Epstein-Barr virus, may serve as an antigen to trigger the inflammatory process in genetically predisposed individuals. Joint inflammation causes the synovium to thicken. The thickened synovium, also known as *pannus*, eventually protrudes through the cartilage and into bone. Bony ankylosis and joint deformities are the end result in severe RA.[13]

Diagnostic criteria for RA are based on the frequency of symptoms, laboratory parameters, and radiographic results. However, a diagnosis is not made up of any one specific test or physical finding. Signs and symptoms include joint stiffness and inflammation (often in the morning), fatigue, weakness, and mild fever. Most commonly, joint involvement tends to be symmetric. The presence of rheumatoid factor, non-

specific markers of inflammation, and hematological abnormalities are among the laboratory findings in RA.[4]

There is currently no cure for RA.[4] Treatment options are directed at controlling pain, inflammation, and slowing disease progression. Current treatment guidelines are somewhat outdated because they do not cover the more recent treatment options.[14] New guidelines are currently being established.[15] The present approach to treatment does not provide a specific algorithm to guide treatment options. Recent treatment guidelines, as well as alternative therapies, will be discussed.

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually the initial pharmacologic treatment used for RA, depending on disease severity.[14] Prostaglandin synthesis is blocked by NSAIDs therefore yielding analgesic and anti-inflammatory effects; however, NSAIDs do not prevent joint damage. Analgesic properties are seen almost immediately, but the onset of anti-inflammatory action can require up to 2 weeks.

The **cyclooxygenase-2 (COX-2) inhibitors** are a recent addition to the NSAID class.[16] Their primary benefit is in the ability to selectively block only the prostaglandins involved in inflammation. This maintains the beneficial effects of other prostaglandins which protect the gastric lining. Celecoxib is currently the only COX-2 inhibitor approved for RA by the FDA.[16]

The **glucocorticoids** are another class of drugs used to fight inflammation. Given early in the course of the disease, they appear to reduce the progression of erosive joint damage.[4] Low doses are generally preferred, but higher doses may be required to manage disease flares.[14] Glucocorticoids can be administered orally for systemic effects or injected to target specific joints for temporary relief.[2] Despite providing symptomatic relief for disease flares, high doses of glucocorticoids do not slow the progression of joint
damage any better than low doses.[14]

Disease modifying anti-rheumatic drugs (DMARD) are pharmacologic agents used to alter the course of RA. Although patients might respond to one drug more than another, no DMARD is considered to be a first line agent.[14] DMARD therapy should be started within 3 months in patients with an established diagnosis of RA regardless of the level of symptom control.[14] Many practitioners prescribe these drugs as soon as possible because these drugs have the ability to slow the progression of the disease, therefore limiting the damage caused by RA.[16] Auranofin, gold sodium thiomalate, azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, methotrexate, leflunomide, penicillamine, and sulfasalazine are all drugs belonging in the DMARD class.[14] Minocycline, an antibiotic, has some activity similar to the DMARD class and is sometimes used in patients with RA.[16] Many rheumatologists initiate DMARD therapy with hydroxychloroquine because of safety, convenience and cost concerns.[14] For more severe RA, methotrexate is used as the initial treatment.[14] Combinations of DMARD are also used in treatment for synergistic effects.[16] The rationale for combining DMARD is smaller dosages of the individual drugs are more efficacious while minimizing side effects of the specific drugs.[2] DMARD should rarely be discontinued, even if the disease is in remission, as this may precipitate a disease flare. Therefore, a maintenance dose should be continued to help slow the progression of disease.[14]

A new drug class used in the treatment of RA is the Biological Response Modifiers. These drugs specifically bind to tumor necrosis factor.[16] Tumor necrosis factor is believed to be one of the specific components of the immune system that is

responsible for RA.[16] On January 2, 2001, the FDA granted marketing approval to infliximab, in combination with methotrexate, for inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.[17] Additionally, etanercept is FDA approved for monotherapy or in combination with methotrexate.[11]

> Other treatment options are on the horizon. Three hearings before the Food and Drug Administration are scheduled this year. Topics to be discussed include celecoxib for the treatment of RA and OA in adults, rofecoxib to treat OA and acute pain, and the use of leflunomide for active RA.[18]

Alternative Treatments for Rheumatoid Arthritis

In several surveys, RA patients report to use alternative and traditional therapies simultaneously; 81% of RA patients in one survey reported using alternative treatments.[19]

Despite widespread use of alternative therapies, conclusive evidence in the use in rheumatoid arthritis is lacking at this time. Some studies demonstrated that omega-3 fatty acids might be useful in the treatment of RA when combined with traditional treatments.[20] Type II collagen may also provide benefit to these patients.[21] Curcumin, bromelain, and ginger are among the plethora of natural products that are reported to alleviate symptoms of RA.[21,19] However, data on the safety of these products are lacking and more studies are needed before the use of these products can be recommended.

Osteoarthritis and rheumatoid arthritis both can be very problematic to the patient. With proper pharmacological and non-pharmacological therapies, patients will be able to minimize pain and maintain joint mobility, thus improving their quality of life.

This "DUReport" was prepared by
Nathaniel Roberts, Pharm D and
Michael Steinberg, Pharm D Drug Information Center, UMKC School of Pharmacy

Please send comments and suggestions regarding this newsletter to Jayne Zemmer, DUR Coordinator, Division of Medical Services, P.O. Box 6500 Jefferson City, MO 65102-6500

Table 1: Alternative Treatments for OA

Agent	Oral	Injectable	Topical	Typical Dosage	Effective
Superoxide Dismutase[6]		X		16 mg/week x 2 weeks	Yes
S-adenosylmethionine[7]	X	X†		200 mg PO 3x/day	Possibly
Glucosamine Sulfate[8]	X	X†		500 mg PO 3x/day	Possibly
Ginger extract[9]	X			500-1000 mg PO daily	No
Methylsulfonylmethane[10]	X		X	1000-3000 mg PO daily	Unknown
Chondroitin[11]	X	X		400mg PO 3x/day	Possibly
Willow bark[12]	X			1-3 g daily	Possibly

† Intravenous loading before oral maintenance therapy may be advantageous

MISSOURI MEDICAID STATISTICS (June 2000 through May 2001)

# Total patients with arthritis	# Patients with rheumatoid arthritis	# Patients with osteoarthritis	# Patients with other arthropathies
15,068	1,474	7,216	6,378

# Patients taking Celecoxib (user months)	Paid / Rx	Total Paid
141,735	$90.59	$12,530,038
# Patients taking Rofecoxib (user months)	Paid / Rx	Total Paid
111,838	$78.98	$8,677,894

References

1. Arthritis Foundation Resource Page. Arthritis Foundation Web Site. Available at www.arthritis.org/answers/diseasecenter/ra.asp. Accessed January 17, 2001.
2. Arthritis Foundation Resource Page. Arthritis Foundation Web Site. Available at www.arthritis.org/answers/diseasecenter/oa.asp. Accessed January 17, 2001.
3. Altman RD, Hochberg MC, Moskowitz RW, et al. Recommendations for the Medical Management of Osteoarthritis of the Hip and knee. *Arthritis and Rheumatism.* 2000;43(9):1905-15.
4. Dipiro JT, Talbert R, Yee G, et al. Pharmacotherapy: A Pathophysicolgic Approach. 5th Edition, Stamford, CT, Appleton and Lange, 1999.
5. Arthritis Foundation Resource Page. Arthritis Foundation Web Site. Available at www.arthritis.org/ Accessed January 23, 2001.
6. McIlwain H. Intra-articular Orgotein in osteoarthritis of the Knee: a placebo-controlled efficacy, safety, and dosage comparison. *Am J Med.* 1989;87(3):295-300.
7. Bradley JD. A Randomized, Double blind, Placebo Controlled Trial of Intravenous Loading with S-adenosylmethione (SAM) followed by oral SAM therapy in patients with knee osteoarthritis. *J Rheum.* 1994;21(5):905-11.
8. DaCamara CC, Djowlee GV. Glucosamine sulfate for osteoarthritis. *Ann Pharmacotherapy.* 1998;32(5): 580-7.
9. Bliddal H. A Randomized, Placebo-Controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. *Cartilage.* 2000;8(1):9-12.
10. Burnham TH, Schweain SL, editors. Methylsulfonylmethane. The review of Natural Products by Facts and Comparison. St Louis: Wolters Kluwer Company; 1999.
11. Natural Medicines Comprehensive Database. www.naturaldatabase.com Edition expires 3/2001. Accessed January 23, 2001.
12. Micromedex Healthcare Series: MICROMEDEX, Inc. Englewood, CO. Edition expires 2/2001.
13. Cotran R, Kumar V, Robbins S, et al. Pathologic Basis of Disease, 5th Edition. Philadelphia, PA. W.B. Saunders and Co. 1994:1249-53.
14. ACR Clinical Guidelines Committee. Guidelines for RA management. *Arthritis and Rheumatism.* 1996;39(5):713-22.
15. American College of Rheumatology Resource Page. American College of Rheumatology Web Site. Available at www.rheumatology.org/acrnews/2000/oct00.htm#oaguidelines. Accessed January 12, 2001.
16. Arthritis Foundation Resource Page. Arthritis Foundation Web Site. Available at www.arthritis.org/answers/drugguide. Accessed January 17, 2001.
17. Remicaide[7] Resource Page. Available at www.remicade.com/c5b_press.html. Accessed January 31, 2001.
18. American College of Rheumatology Resource Page. American College of Rheumatology Web Site. Available at www.rheumatology.org/aac.htm. Accessed January 12, 2001.
19. Gerber L, Hicks J. Surgical and Rehabilitation options in the Treatment of the Rheumatoid Arthritis Patient Resistant to Pharmacologic Agents. *Rheumatic Disease clinics of North America.* 1995:21(1):19-39.
20. Kremer J. N-3 fatty acid Supplements in Rheumatoid Arthritis. *Am J Clin Nutr.* 2000;71(Sup 1):349S-51S.

21. Murray M, Pizzorno J. Encyclopedia of Natural Medicine. 2nd Edition. Rocklin, California. Prima Health. 1998.