CONTINUING EDUCATION

New Options in the Treatment of Arthritis

Edwin H. Adams, Tracy S. Hunter, and Tanzania Williams

OBJECTIVE: To review the pathophysiology, treatments, and resource utilization of patients with osteoarthritis and rheumatoid arthritis.

DATA SOURCES: Literature references.

CONCLUSION: Nonsteroidal antiinflammatories (NSAIDs) remain the most commonly used drugs in the treatment of arthritis. Although the new COX-2 inhibitors appear to be associated with a lower risk of serious gastrointestinal-related problems, their cost per unit is substantially greater than NSAID therapy. As the strengths and weaknesses of COX-2 inhibitors become evident with continued use and as cost-effectiveness studies are conducted, decision makers will be able to make more-informed decisions.

KEYWORDS: Osteoarthritis, Rheumatoid arthritis, COX-2, NSAIDs, Prostaglandins

J Managed Care Pharm 1999: 443-448

Arthritis and other musculoskeletal conditions are among the most common chronic conditions in the United States. The two primary musculoskeletal conditions are osteoarthritis (OA) and rheumatoid arthritis (RA). Approximately 37.9 million people are estimated to be affected by arthritis in the United States, and by the year 2020, it is expected that 58.4 million people will suffer from these diseases.

These conditions can have a substantial impact on the use of health care resources and on patients’ quality of life. Modern drug therapy is effective in alleviating many of the symptoms of these two chronic conditions; however, drugs do not halt the disease progression. Drug-related problems are common and can significantly limit patient progress, but with the advent of tumor necrosis factor (TNF) modulators and the COX-2 inhibitors, physicians have an expanding treatment arsenal for osteoarthritis and rheumatoid arthritis.

Osteoarthritis

OA is primarily a disease of cartilage degeneration. Risk factors associated with OA include traumatic injury and wear-and-tear, increasing age, obesity, quadriceps muscle weakness, joint overuse/injury, genetic susceptibility, and development abnormalities. Approximately 12% of adults in the United States have symptomatic OA, and incidence rises sharply with age. The joints of the wrist and hand are most often affected, although arthritis of the hip and knee is common.

The pathogenesis of OA is multifactorial. Complex biomechanical and chemical changes cause both increased cartilage degeneration and decreased cartilage synthesis. The result is a thickened synovial capsule, a bone cyst, synovial hypertrophy, and fibrillated cartilage. These changes lead to joint instability, pain, subchondral microfractures, nerve compression, and sometimes inflammation of the joint. Drug therapy is targeted at pain control, with nonsteroidal antiinflammatories (NSAIDs) often used to treat pain.
Rheumatoid Arthritis

RA involves a poorly understood autoimmune process that destroys the synovial lining of the joint. While the disease can affect any organ system, it is manifested primarily within the joint capsule. RA has an estimated prevalence of 0.8%, and is three times more prevalent in females than males. The American College of Rheumatology classification criteria for RA requires that patients have at least four of the following seven criteria:

- morning stiffness lasting at least one hour for at least six weeks;
- swelling in three or more joints for at least six weeks;
- swelling in hand joints for at least six weeks;
- symmetric joint swelling for at least six weeks;
- erosions or decalcification on radiograph of hand;
- rheumatoid nodules; and
- abnormal amount of serum rheumatoid factor.

Although the exact etiology is unknown, environmental triggers may cause genetically susceptible individuals to develop RA. Current treatments for RA are three types of drug therapies: 1) disease-modifying antirheumatic drugs (DMARDs), which have been effective in slowing disease progression but are not without toxicity; 2) NSAIDs, which play a crucial role in treating the pain and inflammation associated with RA; and 3) newer therapies that focus on the immune response involved in the destruction of the synovial lining of the joint. A comparison of OA and RA may be found in Table 1.

Table 1. Comparison of Osteoarthritis and Rheumatoid Arthritis

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<tr>
<th>Sites</th>
<th>Osteoarthritis</th>
<th>Rheumatoid Arthritis</th>
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<tr>
<td>Pathogenesis</td>
<td>localized pain</td>
<td>articular, systemic, and extra-articular manifestations</td>
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<tr>
<td>Symptoms</td>
<td>biomechanical; leads to loss of cartilage matrix</td>
<td>autoimmune response; leads to joint destruction</td>
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<tr>
<td>Inflammation</td>
<td>pain; stiffness &lt;20 minutes; limited motion</td>
<td>pain; joint swelling; stiffness &gt;1 hour; limited motion</td>
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<tr>
<td></td>
<td>usually limited; may be present in advanced disease</td>
<td>chronic</td>
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A few studies have examined the costs associated with these conditions. In 1992, the cost of musculoskeletal conditions was reported to be $149.4 billion in the United States, of which 48% is attributable to direct medical costs; the rest represents indirect costs resulting from lost wages. Although the indirect costs do not affect the medical costs of a managed care organization (MCO), these costs do concern employer groups and, of course, patients.

Fishman et al. found that within a single health care plan, arthritis was the sixth most prevalent chronic condition and that the cost to treat members diagnosed with arthritis was 1.5 times higher than the cost for members without this diagnosis, after controlling for age, gender, and other chronic conditions. In addition, a diagnosis of OA was associated with 111% higher gastrointestinal (GI) costs. The average cost of treating OA was estimated at just under $550 per patient per year. The cost of ambulatory care was $110; medications ($173 per person) represented about one-third of expenditures, of which almost half was spent to protect against the GI complications of NSAID treatment. Although only 5% of these patients required hospital care, hospitalizations represented almost 46% of total annual cost; half of this was for hip and knee replacement surgery.

The cost and treatment profile of RA is considerably different. In 1992, the annual cost of treating a patient with RA was $2,162 per patient. RA patients average 7.7 physician office visits per year—twice as many as for OA patients. Prescription medications accounted for more than 50% of the total cost of treating RA. The most expensive drug category was DMARDs, which accounted for about half of the money spent on prescriptions for RA. NSAID agents were the second most expensive class, representing one-third of the medication cost. Medications to protect against adverse GI effects consumed approximately 16% of the medication budget for RA patients.

Pharmacotherapy

The goals of treatment are similar for OA and RA:

- Control pain, inflammation, morning stiffness, and other symptoms;
- Maintain or improve joint function;
- Prevent or slow further joint destruction;
- Minimize disability;
- Enhance quality of life and functional independence;
Minimize any risks of therapy; and
Educate patients and their families.

Drugs used in the management of OA include analgesics, over-the-counter and prescription NSAIDs, topical agents, intraarticular glucocorticoids, and intraarticular hyaluronan. Patient education, physical and occupational therapy, use of assistive devices, weight loss, and aerobic exercise are highly recommended as well. All these components of therapy may be used early in the management of the disease or as adjunct therapy in later stages.

The approach taken to the management of RA during the 1980s emphasized improving the measures of disease activity, providing less-aggressive treatment in early stages, and the use of NSAIDs as the least-toxic means of treating patients. These attitudes have changed. The new approach emphasizes improving the risk-benefit ratio associated with NSAID use, limiting the destruction of joints, and using DMARDs earlier in the disease progression (see Table 2). Methotrexate is the DMARD of choice because of its safety profile. New therapies targeting TNF (i.e., Enbrel [etanercept] and Arava [leflunomide]) show promise in the management of RA but are not yet considered first-line therapy.

**NSAIDs**

NSAIDs are the common therapy link between OA and RA. In both conditions, NSAIDs provide symptom control but do not alter disease progression. In OA, NSAIDs are used in low doses for pain control; in RA, they may be used in low or high doses to manage both pain and inflammation.

NSAIDs treat the symptoms of OA and RA by inhibiting the production of prostaglandins (PG), the mediators of pain and inflammation. NSAIDs inhibit PG production by blocking the enzyme cyclooxygenase (COX). Unfortunately, inhibiting COX has deleterious effects on organ systems that require PG for normal functioning. Although most of the side effects associated with NSAID therapy are mild and abate when therapy is discontinued, GI side effects can be more serious.

It has been estimated that up to 20% of patients on NSAIDs experience GI problems. NSAID users are at nearly three times greater risk for developing gastric ulcers, bleeding, and death from these complications than nonusers. The Food and Drug Administration (FDA) estimates that these complications cause between 10,000 and 20,000 deaths and approximately 76,000 hospitalizations annually. Patients who may run an increased risk of developing serious NSAID-induced GI complications include those who are older than 65; have a history of peptic ulcer disease, upper-GI bleeding, or GI hospitalization; suffer arthritis-related disability; take higher doses of NSAIDs; use prednisone concurrently with NSAIDs; have previously suffered GI side effects from NSAIDs; and have a history of cardiovascular or renal disease.

The damage that NSAIDs inflict on the GI tract occurs in two ways. Direct mucosal injury can occur when a drug, such as aspirin, causes mucosal erosions or hemorrhages, which can be locally irritating. Inhibiting endogenous gastric PG synthesis, specifically COX-1, significantly increases the likelihood of mucosal injury. Naturally occurring PGs like COX-1 and COX-2 are important in the production of gastric bicarbonate and mucus—key components of the stomach’s protective barrier—and in the maintenance of submucosal blood flow.

One of the dangers associated with NSAID-induced gastric ulcers is that most patients remain asymptomatic until complications arise. Approximately 81% of the serious GI complications with NSAIDs occur asymptotically. Although perforation can occur within a few days of the initiation of therapy, most complications occur during chronic NSAID use. Taking NSAIDs with food does not appear to reduce the overall risk of ulceration; however, food may help decrease the direct mucosal irritation.

Prophylactic treatment with H2-receptor antagonists, antacids, and sucralfate has not been shown to be effective in reducing the frequency or severity of these problems. Proton pump inhibitors have shown some benefit in reducing gastric ulceration; however, studies are inconclusive. In the United States, misoprostol (Cytotec, Searle) is the only agent approved as prophylactic therapy with NSAIDs. Misoprostol has been documented as both effective treatment and effective long-term protection against NSAID-induced GI injury.

Misoprostol is a synthetic prostaglandin E1 analogue that replenishes endogenous PG inhibited by NSAIDs. Its major limitation is its tolerability: Diarrhea, abdominal pain, dyspepsia, and flatulence are the rate-limiting steps. Doses of misoprostol should be titrated slowly to a dose of 200 mcg three to four times daily. A combination of diclofenac sodium and misoprostol is available (Arthrotec, Searle).

NSAIDs exhibit varying degrees of antiplatelet activity by inhibiting platelet COX. The resulting thrombocytopenia may contribute to the bleeding associated with GI mucosal damage. Several parameters determine the amount of time required for normal platelet function to return. One factor is the extent to which a drug binds to COX. Aspirin, for example, binds to the enzyme irreversibly, inhibiting functioning

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<th>Table 2. Disease-modifying Antirheumatic drugs (DMARDs)</th>
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<tr>
<td>▲ Hydroxychloroquine</td>
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<td>▲ Methotrexate</td>
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<td>▲ Sulfasazine</td>
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<td>▲ Intramuscular/oral gold</td>
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for the entire life of the thrombocyte. Platelet activity is then dependent on the production of new cells, which takes seven to 12 days. Ibuprofen and the other NSAIDs bind to COX reversibly, allowing normal platelet function to return once the drug has been eliminated. For these products, the half-life of the drug ultimately determines when platelet function returns.

Although NSAID therapy rarely has adverse effects on the kidneys, patients with congestive heart failure, cirrhosis, hypovolemia, or a renal condition are at increased risk of renal complications. In elderly patients or those with a history of kidney problems, urine output, blood urea nitrogen, and serum creatinine levels should be closely monitored.21

Two processes associated with NSAIDs can adversely affect kidney function. The first has an indirect effect on renal perfusion. PGs enhance the vasodilation of renal vasculature. When NSAIDs inhibit endogenous PG production, there is a decrease in renal perfusion, which can cause ischemic injury. For patients at risk, acute renal failure can occur soon after NSAID therapy begins. Reduction in renal perfusion, not the decrease in basal PG production, is responsible. The second mechanism is an idiosyncratic reaction that causes an interstitial nephritis, which can occur within days of the initiation of therapy or several months later; it appears to be immunologically mediated. Renal function generally recovers after therapy is discontinued.19

**COX-2 Inhibitors**

Tablet coating, encapsulation, and combination products have all been used to improve the safety of NSAIDs. Although agents such as sucralfate, H2-receptor antagonists, proton pump inhibitors, and PG analogues often are used to reduce the side effects caused by NSAIDs, the problem of GI toxicity remains. Accordingly, recent research has investigated ways to prevent gastric mucosal damage attributable to inhibition of PG formation by interference with COX.10

The existence of two distinct isozymes of COX, which convert arachidonic acid to PGs, is well established.17 In 1990, Needleman and colleagues described the induction as suppression of COX function in human monocytes by bacterial lipopolysaccharides and dexamethasone, suggesting the existence of two separate isozymes.4 COX-1 produces PGs that regulate many physiologic processes under normal resting conditions, including gastric cytoprotection, platelet aggregation, vascular homeostasis, and renal sodium and water balance.9 In contrast, COX-2 is an inducible enzyme expressed in response to a variety of stimuli, such as inflammatory cytokines. COX-2 is upregulated at sites of inflammation, mediating the production of PGs involved in pain and inflammation in diseases such as arthritis. Recent animal research has shown that COX-2 is also expressed under basal conditions or in response to a variety of physiologic stimuli in organs such as the ovary, uterus, brain, kidney, cartilage, and bone. These data suggest a much more complex role for COX-1 and COX-2 than was originally thought.4

**Figure 1. Mechanism of Action of Conventional NSAIDs and COX-2 Inhibitors**

Traditional NSAIDs inhibit both COX-1 and COX-2 at therapeutic concentrations (Figure 1).21 Thus, NSAIDs inhibit inflammatory PG production derived from the activity of COX-2, as well as the homeostatic PGs in tissues like the stomach and kidney.22 Inhibition of PGs by nonspecific COX can result not only in antiinflammatory effects but also in potential GI toxicity and alterations in renal and platelet function. Inhibition of COX-2 plays an important role in the analgesic and antiinflammatory properties of an NSAID.9 In theory, compounds that specifically inhibit COX-2 could be antiinflammatory and analgesic with relatively few gastric side effects.10 The FDA approved one such compound, celecoxib (Celebrex, Searle), in December of 1998.

Celecoxib is a diaryl-substituted pyrazole sulfonamide nonsteroidal anti-inflammatory drug approved for the treatment of OA and RA.23 It exhibits antiinflammatory, analgesic, and antipyretic activities in animal models. Celecoxib is readily absorbed, with peak plasma levels occurring approximately three hours after administration, and can be administered without regard to timing of meals. In healthy subjects, celecoxib is 97% protein bound and is metabolized via cytochrome P450 2C9, with an elimination half-life of approximately 11 hours under fasting conditions. Celecoxib is primarily eliminated by hepatic metabolism, with less than 3% excreted unchanged in the urine and feces.

Dose adjustment in the elderly is generally not necessary. However, patients who weigh less than 50 kilograms initially should receive the lowest recommended dose of celecoxib. Celecoxib has not been clinically evaluated in pediatric patients or in patients with severe renal or hepatic impairment.

Significant drug interactions may occur when celecoxib is administered with drugs that inhibit cytochrome P450 2C9
such as zafirlukast (Accolate), fluconazole (Diflucan), and flu-
avastatin (Lescol), leading to increased serum concentrations of
celecoxib. In vitro studies indicate that celecoxib is not an
inhibitor of cytochrome 2C9, 2C19, or 3A4. However, cele-
coxib inhibits the activity of 2D6, and therefore may increase
the concentrations of drugs metabolized by 2D6, such as some
beta-blockers, antidepressants, and antipsychotic drugs.11,24

Celecoxib was evaluated in 4,200 patients for the treat-
ment of OA of the knee and hip in placebo in active con-
trolled trials of up to 12 weeks.19 Treatment with celecoxib,
100 mg twice a day or 200 mg daily resulted in improvement
in multiple measures of efficacy, with efficacy similar to
naproxen 500 mg twice a day. In three 12-week studies, cele-
coxib also was effective in reducing pain accompanying OA
flare at doses of 100 mg twice a day and 200 mg twice a day
within 24-48 hours of dosing.

In the treatment of RA, celecoxib has demonstrated effica-
cy compared to placebo in reducing joint pain, swelling, and
stiffness. In placebo and active controlled clinical trials, cele-
coxib was studied in 2,100 patients for up to 24 weeks.
Celecoxib 100 mg twice a day and 200 mg twice a day were
similar in effectiveness to naproxen 500 mg twice a day, with
superior improvement compared to placebo by multiple mea-
sures of efficacy.11

Upper GI endoscopic evaluations have been conducted in
over 4,500 arthritis patients enrolled in five randomized con-
trolled trials12,21 that have compared various doses of celecoxib
with placebo as well as naproxen, ibuprofen, and diclofenac.
In all studies conducted with naproxen and ibuprofen, cele-
coxib had a statistically significant lower incidence of endo-
scopic ulcers. In the two clinical trials comparing celecoxib
with diclofenac, one study showed a statistically significant
lower ulceration rate for celecoxib; the other study revealed
no statistical difference. The correlation between these endo-
scopic studies and the reduction in clinically significant GI
events has not been established.

Celecoxib has a favorable adverse event profile, with head-
ache reported as the most common adverse event.11 In a clin-
a trial of healthy patients, no difference in platelet function
was noted between celecoxib and placebo. The dosage recom-
manded for treatment of OA is 200 mg daily as a single dose or
100 mg twice a day. The dose for RA is 100-200 mg bid.

In November 1998, Merck and Co. submitted a New Drug
Application for its COX-2 inhibitor, rofecoxib, currently mar-
keted under the trade name Vioxx. Two studies were conduct-
ed to obtain evidence that rofecoxib selectively inhibits COX-
2 in humans. In an OA efficacy trial, rofecoxib 25 mg and 125
mg significantly improved Western Ontario and McMaster
Universities Osteoarthritis Index pain subscale score com-
pared with placebo. In a dental pain study, rofecoxib 50 mg
daily, rofecoxib 500 mg daily, ibuprofen 400 mg daily, and
placebo were compared.25 The efficacy of rofecoxib was not
significantly different from ibuprofen on the basis of sum pain
intensity difference or total pain relief, or via global ratings, but
both were superior to placebo. These results suggest that rofe-
coxib was sufficient for analgesic efficacy similar to ibuprofen.

The first specific COX-2 inhibitor marketed was meloxi-
cam, launched in the United Kingdom in 1996. Although
meloxicam is not marketed in the United States, many other
COX-2 inhibitors are in various stages of development.8

Pharmacoeconomic Issues

The availability of the traditional NSAIDs and of COX-2 in-
hibitors poses a classic pharmacoeconomic question. Although
the NSAIDs are less expensive, they appear to have a greater
incidence of drug-related GI problems, which may be associ-
ated with greater overall direct medical costs. The MUCOSA
(Misoprostol Ulcer Complications Outcomes Safety Assess-
ment) trial found that 1.3% of patients using NSAIDs report-
ed "definite" GI complications over one year. When "prob-
able" complications were included, the rate increased to 45%.
The most common complications were GI bleeding (76%),
perforated ulcer (17%), and gastric outlet obstruction (7%).
The average cost of hospitalizing a patient with a bleeding or
perforated ulcer was estimated at approximately $13,000.26

Secondary problems with NSAID therapy that may be
important in a pharmacoeconomic analysis of these products
include premature discontinuation due to adverse effects and
the increased incidence of dyspepsia, which in one study was
associated with higher medical costs.27

The following example helps illustrate the comparative costs
of therapy with NSAIDs and COX inhibitors. Assuming an
80% generic fill rate, NSAID products would cost the payor
$0.60 per day (assuming a generic cost of $0.25/day and a
brand cost of $2.00/day). A month's supply would cost $18
per user. The cost of GI protective care, based on published
figures, brings the total cost of care to approximately $115 per
patient per month, assuming 100% of patients will use pro-
tective care.7 The manufacturer of celecoxib reports an average
therapeutic cost of $2.35 per patient per day. Direct acquisition
costs for one month would be about $70 per patient with no
additional GI protective cost. Under such assumptions, cele-
coxib appears to be less expensive and equally efficacious, and
seems to have a similar, if not improved, side effect profile.

In reality, substantially less than 100% of patients taking
NSAIDs use a GI protective medication. Accordingly, the av-
average monthly drug acquisition cost for an NSAID/GI protective
will be less than $115 in a typical population. Depending on
the actual percentage of patients using a GI protective medica-
tion, the average drug cost could be less than the acquisition
cost of celecoxib. However, as fewer NSAID patients use a GI
protective, research would suggest that the incidence of GI
adverse events and related costs would increase. Pharma-
ecoconomic studies are needed to compare the relative cost-
effectiveness of celecoxib and NSAIDs with and without a GI
protective medication.
The full economic impact of this new class of drugs in the managed care setting is difficult to assess due to the paucity of utilization data and the limitations of clinical trials data. Ideally, a natural-history trial of the COX-2s compared to the traditional NSAIDs should be conducted to better understand the relative cost-effectiveness of these products. One advantage of such an approach, among others, is that it would better reflect compliance with these medications as seen in routine care.

CONCLUSION

The NSAIDs remain the group of drugs most frequently used in the treatment of arthritis. While the new COX-2 inhibitors appear to be associated with a lower risk of serious GI-related problems, their cost is substantially greater than traditional NSAID therapy. As their strengths and weaknesses become evident with continued use and as cost-effectiveness studies are conducted, decision makers will be able to make more informed decisions.

References

Upon completion of this article, the successful participant should be able to:

1. Compare and contrast osteoarthritis (OA) and rheumatoid arthritis (RA).
2. Appreciate the health care resource utilization of OA and RA.
3. Describe the pharmacotherapy of OA and RA.
4. Understand the rationale for COX-2 inhibitors and how they differ from conventional NSAID therapy.

SELF-ASSESSMENT QUESTIONS

1. Which of the following statement about the metabolism of celecoxib is TRUE?
   a. It is predominantly metabolized by the cytochrome P450 CYP2C19.
   b. It is predominantly metabolized by the cytochrome P450 CYP2C9.
   c. It has demonstrated saturable kinetics when studied at supratherapeutic doses.
   d. None of the above.

2. Which statement is TRUE?
   a. The prostaglandins produced by COX-1 regulate many physiologic processes under normal resting conditions.
   b. COX-2 plays a role in platelet aggregation.
   c. Both COX-1 and COX-2 have protective effects on the GI mucosa.
   d. Both COX-1 and COX-2 play a role in inflammation and pain.

3. The rationale for research and development of COX-2 inhibitors includes which of the following statements?
   a. Conventional NSAID therapies were ineffective in relieving the pain and inflammation associated with arthritis.
   b. Conventional NSAID therapies, while effective, have tolerability problems, particularly GI toxicity.
   c. The recent discovery of a second, inducible, form of cyclooxygenase, COX-2, stimulated research and interest in producing NSAIDs that are inherently safer while maintaining efficacy.
   d. b and c

4. What are the PG-dependent protective factors in the gastric mucosa?
   a. Mucous production
   b. Bicarbonate secretion
   c. Mucosal blood flow
   d. All of the above

5. Which of the following statements is TRUE?
   a. OA and RA are similarly distributed in the population.
   b. About 5% of OA patients require hospitalization.
   c. Pharmaceuticals represent the most expensive treatment category for OA.
   d. Generally, patients with RA require fewer visits to physicians than patients with OA.

6. The most common serious complication of NSAID therapy often is reported to be:
   a. Perforated ulcer
   b. Gastric outlet obstruction
   c. GI bleeding
   d. Dyspepsia

7. What complications for NSAID therapy add to the overall cost of treatment?
   a. Dyspepsia
   b. Perforated ulcer
   c. Gastric outlet obstruction
   d. All of the above

8. Which of the following statements is TRUE?
   a. Osteoarthritis is primarily a disease of joint inflammation.
   b. Risk factors for developing OA include obesity and joint overuse and injury.
   c. Drug therapy for osteoarthritis includes methotrexate and NSAIDS.
   d. All of the above

9. Which of the following statements about NSAID therapy is TRUE?
   a. Most side effects of the NSAIDs are mild and abate upon discontinuation of the drug.
   b. A serious side effect involves the GI tract.
   c. Traditional NSAIDs inhibit COX-1 and COX-2.
   d. All of the above

10. The new approach to RA management includes:
    a. Less aggressive treatment in early stages.
    b. An emphasis on limiting the destruction of joints.
    c. Use of NSAIDs to provide the least toxic means of treating patients.
    d. All of the above
11. In what type of setting do you work (leave blank if none of the responses below applies)?
   a. HMO.
   b. PPO.
   c. Indemnity insurance.
   d. Pharmacy benefits management.
   e. Other.

12. Did this program achieve its educational objectives?
   a. Yes.
   b. No.

13. How many minutes did it take you to complete this program, including the quiz (fill in on answer sheet)?

14. Did this program provide insights relevant or practical for you or your work?
   a. Yes.
   b. No.

15. Please rate the quality of this CE article.
   a. Excellent.
   b. Good.
   c. Fair.
   d. Poor.

INSTRUCTIONS

This quiz affords 1 hour (.1 CEU) of continuing pharmaceutical education in all states that recognize the American Council on Pharmaceutical Education. To receive credit, you must score at least 70% of your quiz answers correctly. To record an answer, darken the appropriate block below. Mail your completed answer sheet to: Academy of Managed Care Pharmacy, 100 N. Pitt Street, Suite 400, Alexandria, VA 22314. Assuming a score of 70% or more, a certificate of achievement will be mailed to you within 30 days. If you fail to achieve 70% on your first try, you will be allowed only one retake. The ACPE Provider Number for this lesson is 233-000-99-005-H01. This offer of continuing education credits expires October 31, 2000.

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[ ] Student    [ ] Nonmember

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I verify by my signature above that I have completed this examination independently.