

## Celecoxib: A COX- 2 Inhibitor

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This activity is designed to provide healthcare professionals involved in the management of osteoarthritis and rheumatoid arthritis with information about a new treatment option.

### GOAL

To inform health professionals about a new treatment option for the management of rheumatoid arthritis (RA) and osteoarthritis (OA).

### OBJECTIVES

1. Discuss the epidemiology, pathophysiology, and presentation of OA and RA.
2. List the nonpharmacologic and pharmacologic approaches to managing OA and RA.
3. Differentiate between the two cyclooxygenase isozymes and understand the clinical importance of each.
4. Discuss the mechanism of action by which nonsteroidal antiinflammatory drugs (NSAIDs) exert their toxic effect.
5. Review treatment strategies to decrease NSAID-related gastrointestinal toxicity.
6. Describe the appropriate use of Celebrex® (celecoxib), including pharmacology, pharmacokinetics, dosage, administration, efficacy, adverse effects, precautions, and drug interactions.



### CONTINUING EDUCATION CREDIT

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-000-99-204-H-01. This course expires on April 30, 2002.

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Arthritis and other rheumatic conditions are a leading cause of disability in the United States, second only to heart disease as a factor contributing to work inability.<sup>1</sup> It is estimated that 40 million Americans are affected, and by the year 2020, more than 59 million Americans could have arthritis.<sup>2</sup> Approximately \$15.2 billion is spent on direct medical costs, with the total costs of medical care and lost wages totaling nearly \$65 billion annually.<sup>1</sup>

The term “arthritis” encompasses more than 100 different diseases that affect areas in or around joints and other parts of the body.<sup>2</sup> This article will focus on two types: osteoarthritis (OA) and rheumatoid arthritis (RA). It will discuss the use of nonsteroidal antiinflammatory drugs (NSAIDs) as a treatment option, the toxicities of these agents, and possible solutions, including a new class of antiinflammatory drugs.

### ... RHEUMATOID ARTHRITIS ...

Rheumatoid arthritis is a chronic, inflammatory, autoimmune disorder characterized by symmetrical joint involvement, usually of the hands and feet. The etiology is unknown and the immunologic changes may be initiated by a number of factors. Rheumatoid arthritis is estimated to occur in 1% to 2% of the population and is three times more common in women than men. Onset may be at any age, but it most often occurs between the ages of 25 and 50 years.<sup>3</sup>

### Pathophysiology

In RA, the body's immune system can no longer differentiate foreign from nonforeign tissue and, therefore, begins to attack the synovial tissue lining the joint, resulting in proliferation of the tissue. The inflamed, proliferating tissue, referred to as pannus, begins to invade the cartilage and eventually the bone surface, producing erosions that lead to

destruction of the joint.<sup>4</sup> The factors that initiate this inflammatory process are unknown, although infectious agents, genetic factors, and unknown environmental factors have all been postulated as etiologies.

### Presentation

Symptoms have an insidious onset and usually develop over the course of several weeks to months. In addition to joint stiffness, early symptoms may include fatigue, malaise, low-grade fever, and loss of appetite. Morning stiffness and joint pain usually precede the swelling. Joint involvement is usually symmetrical and most frequently affects the hands and feet.<sup>4,5</sup>

### Diagnosis

In addition to these symptoms, other criteria for diagnosing RA include the presence of a serum rheumatoid factor and radiographic changes. The presence of a positive rheumatoid factor is the most reliable method of diagnosing RA; however, it is only present in about 70% of patients with RA. Radiologic evaluation usually shows uniform joint space narrowing and erosions at the joint margin.<sup>3,5</sup>

### Treatment

Goals of treatment are to relieve pain, reduce inflammation, slow down or stop joint damage, and maintain the patient's ability to function independently and to perform day-to-day activities.<sup>6</sup> Nonpharmacologic management may include rest (to reduce active inflammation and pain), coupled with exercise to preserve joint mobility and maintain flexibility. A healthful diet and stress reduction techniques also can be beneficial. Select patients may even find that a splint used around the joint is helpful to reduce pain and swelling.

Most patients with RA will require pharmacologic treatment (Table 1). Nonsteroidal antiinflammatory drugs are the cornerstone of therapy because they reduce joint pain and swelling and improve function; however, they are not without limitations. Nonsteroidal antiinflammatory drugs do not prevent the progression of joint destruction and they can lead to gastrointestinal (GI) toxicities. Disease-modifying antirheumatic drugs are available when patients do not completely respond to NSAIDs. These agents have the potential to retard structural damage while continuing to alleviate symptoms. When choosing therapy, factors to be considered include cost, adverse effects, disease severity, and monitoring requirements of pharmacologic agents.<sup>7</sup>

In all patients with RA, it may be necessary to try various combinations of nonpharmacologic and pharmacologic modalities to achieve the most efficacious therapy with minimal adverse effects.

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## ... OSTEOARTHRITIS ...

Osteoarthritis is the most prevalent musculoskeletal disorder, characterized by joint pain, tenderness, and functional disability. Osteoarthritis primarily affects the weight-bearing joints of the body, including the spine, knees, and hips, but may also occur in joints that have suffered previous injury or have been damaged by prior infection.<sup>8</sup>

Osteoarthritis affects more than 16 million Americans, with essentially all persons affected in at least one joint by the age of 75 years. Men and women are equally affected, but onset may be earlier in women.<sup>9</sup> Although most people are asymptomatic, all persons usually have some pathologic changes in weight-bearing joints by the age of 40.<sup>10</sup>

### Pathophysiology

Osteoarthritis involves changes in the cartilage and joint; however, inflammatory, biochemical, and immunologic factors also may be involved. The disease begins with a progressive, structural breakdown of articular cartilage lining the joint surface in weight-bearing areas. Changes include a thickening of cartilage, an increase in cartilage water content, and possibly moderate inflammation. The biochemical changes result in a splitting of the noncalcified cartilage to expose underlying bone. This continuing process results in the cartilage being unable to repair itself, and cartilage thinning and erosions ultimately lead to abrasive wear on the joints.<sup>8</sup>

### Presentation

Initial symptoms are subtle and usually involve a limited number of joints with minimal swelling. Pain is the primary symptom. Stiffness usually follows but is relieved with motion. Range of motion of the joint becomes limited as the disease progresses, and tenderness or crepitus, a grating sensation, may develop. Joint enlargement or deformities become evident as inflammation develops and cartilage, bone, and tendons continue to proliferate.<sup>10</sup>

### Diagnosis

A diagnosis of OA usually is made based on signs and symptoms, primarily pain, or by radiologic findings. These findings include joint space narrowing,

an increase in the density of subchondral bone and osteophytes, or bony overgrowth formations.<sup>10</sup>

**Treatment**

Goals of treatment are to educate the patient and caregivers, relieve symptoms such as pain and stiff-

ness, preserve joint motion and function, and minimize disability. Treatment must be individualized and may include physical therapy, occupational therapy, dietary considerations, pharmacologic treatment, and surgery. Nonpharmacologic management may include patient education, weight man-

**Table 1.** Various Drugs Used in the Treatment of Rheumatoid Arthritis

Drug	Usual Dose	Common Side Effects
<b>Nonsteroidal antiinflammatory drugs</b>		
Aspirin	2600–5200 mg/day in 4–6 divided doses	Side effects that may be common to all NSAIDs include nausea, vomiting, diarrhea, GI bleeding and ulceration, rash, decreased platelet aggregation, tinnitus
Ibuprofen	1200–3200 mg/day in 3–4 divided doses	
Fenoprofen	300–600 mg/day in 3–4 divided doses	
Ketoprofen	50–75 mg 3–4 times daily	
Naproxen	500–1000 mg/day twice daily	
Sulindac	300–400 mg/day in 1–2 divided doses	
Diclofenac	150–200 mg/day in 3–4 divided doses	
Indomethacin	50–200 mg/day in 2–4 divided doses	
Salsalate	3000 mg/day in 2–3 divided doses	
Nabumetone	1000–2000 mg/day in 1–2 divided doses	
Oxaprozin	600–1800 mg/day	
Etodolac	200–1200 mg/day in 3–4 divided doses	
<b>Disease-modifying antirheumatic drugs</b>		
Azathioprine	50–150 mg/day	Bone marrow suppression, GI intolerance, hepatotoxicity
Hydroxychloroquine	200 mg twice daily	Nausea, diarrhea, retinal toxicity, rash
Sulfasalazine	1000 mg 2–3 times daily	Rash, bone marrow suppression, GI intolerance
D-Penicillamine	250–750 mg daily	Rash, stomatitis, bone marrow suppression, hypogeusia
Methotrexate	7.5–15 mg/week	Nausea, vomiting, diarrhea, stomatitis, thrombocytopenia, ↑ LFTs
Injectable gold compounds	25–50 mg IM every 2–4 weeks	Rash, stomatitis, conjunctivitis
Gold (oral)	3 mg once or twice daily	Metallic taste, rash, stomatitis, diarrhea
<b>Corticosteroids</b>		
Intraarticular corticosteroids	3–4 injections per year	Pain at injection site
Prednisone	10 mg/day preferred	Osteoporosis, fluid retention, glaucoma, cataracts, hypertension
<b>New agents</b>		
Leflunomide (Arava®)	100 mg every day ( 3 days, then 20 mg/day	Alopecia, hypertension
Etanercept (Enbrel®)	10–25 mg/dose SC twice weekly	Inflammation at injection site

Source: References 4, 6, and 7.

GI = gastrointestinal; IM = intramuscular; LFTs = liver function tests; SC = subcutaneous.

agement to reduce stress on the joints, exercise to help preserve range of motion and increase strength, and cold and heat application to reduce pain. Surgery to repair or replace damaged joints may be required to relieve pain and restore functional mobility.<sup>11</sup>

Pharmacologic management should begin with simple analgesics such as acetaminophen or aspirin used at analgesic doses (325 mg every 4–6 hours). Acetaminophen is the initial drug of choice because of a more favorable safety profile. Nonsteroidal anti-inflammatory drugs are indicated when those analgesics fail to relieve pain or when inflammation is present. Oral corticosteroid therapy is not recommended; however, intraarticular injections may provide temporary relief if inflammation is present. Opioid analgesics such as propoxyphene and codeine can be used short term for acute exacerbations of pain. Topical preparations, such as capsaicin, can be added at any time.<sup>8,12</sup>

counter aspirin and other NSAIDs are sold each year in the United States.<sup>13</sup> Use of NSAIDs tends to increase with age; studies have shown that 10% to 20% of persons aged 65 years or older have used or are currently using an NSAID.<sup>14</sup>

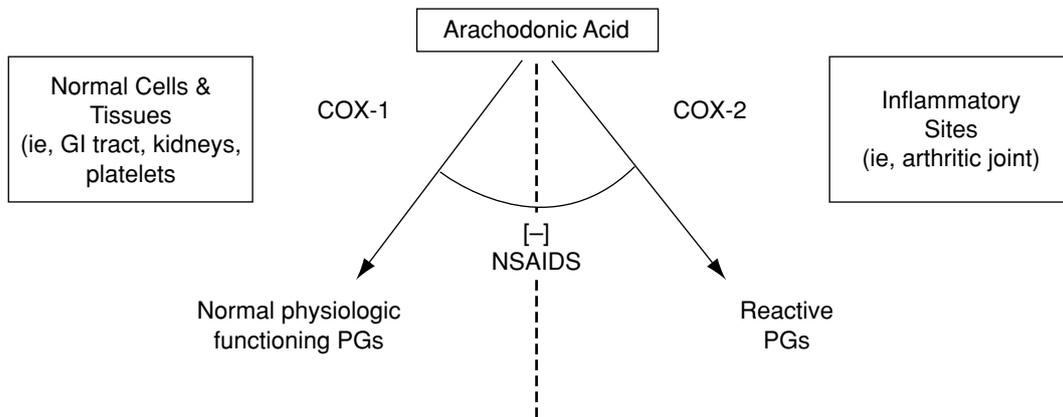
On the whole, NSAIDs provide analgesic effects at lower doses and antiinflammatory activity at higher doses.<sup>8</sup> Nonsteroidal antiinflammatory drugs from a variety of chemical classes are available and provide the same therapeutic properties. However, there is increasing concern about overuse of NSAIDs.

The most recognized adverse effects associated with NSAID use relate to the GI system, including nonulcer dyspepsia and peptic ulcers. In addition, any ulcer that forms has the potential to cause perforation or malabsorption.<sup>14</sup> Endoscopic studies have shown that 20% of long-term NSAID users have evidence of peptic ulcer disease. Clinical experience demonstrates that only a small percentage of these users are admitted and treated for GI ulcer or GI bleeding. Hospitalization rates continue to increase proportionally with increasing age. Risk factors for NSAID-induced GI injury include a past history of GI ulceration, high-dose and multiple NSAID use, and concurrent use of cigarettes and alcohol or concomitant medications like warfarin and steroids because of anticoagulation and ulcerogenic properties, respectively. Other risk factors include older

... NONSTEROIDAL ANTIINFLAMMATORY DRUGS ...

Nonsteroidal antiinflammatory drugs are generally accepted as first-line therapy for the symptomatic treatment of RA and are widely used for the treatment of OA.<sup>8</sup> It is estimated that over 35 million NSAID preparations and billions of over-the-

**Figure.** Mechanism of Action of NSAIDs



Source: Reference 17.

age and end-stage liver or kidney disease. Nonsteroidal antiinflammatory drugs also have been associated with adverse effects such as the inhibition of platelet aggregation, bronchospasms, and rarely, aseptic meningitis. Borderline idiosyncratic elevations of liver function tests can occur. These abnormalities may progress or may be transient with continued therapy but do not appear to require intervention.<sup>15</sup>

The mechanism of action by which NSAIDs exert their effect has only been studied since the early 1970s.<sup>16</sup> Although this exact mechanism is unknown, a major component of the activity of all NSAIDs is believed to be the inhibition of cyclooxygenase (COX), the enzyme that converts arachidonic acid to prostaglandins (see Figure).<sup>4</sup>

It was recently discovered that COX exists as two different isozymes: COX-1 and COX-2.<sup>5</sup> Concentrations of COX-1 are relatively constant within the body and are present in the stomach, kidneys, and platelets. COX-2 concentrations, which are present in a number of cells, are relatively low but increase in response to external stimuli, particularly the inflammatory process.<sup>16</sup> Both forms of COX ultimately produce the same prostaglandins; however, the effects of the prostaglandins vary, depending on the stimulus and the tissue in which they are located.<sup>18</sup> For example, activation of COX-1 leads to the production of prostacyclin and prostaglandin, which reduce gastric acid secretion, increase duodenal bicarbonate secretion, and stimulate the secretion of gastric mucosa. This increased mucus provides a physical barrier to the gastric mucosa, which, in turn, is cytoprotective. Prostaglandin also is produced by COX-2 in response to inflammatory stimuli, causing vasodilation and pain. In addition to the GI system, prostaglandins are important in other areas of the body. For example, prostaglandins produced in the kidney maintain renal perfusion by causing vasodilation and also inhibit the reabsorption of sodium and chloride.<sup>16</sup> Therefore, NSAIDs may produce renal failure or insufficiency and hyperkalemia by means of prostaglandin inhibition. However, the effects of COX-2 inhibition on renal function are unknown.

### Treatment Strategies for Reducing NSAID-Induced Toxicity

Some patients at high risk for gastroduodenal ulceration are unable to discontinue NSAID therapy. Over the last several years, various attempts have been made to reduce potential GI complications

that may arise from the use of NSAIDs. Data suggests that different NSAIDs have varying degrees of selectivity for COX-1 and COX-2.<sup>16</sup> One option is to use a NSAID with greater COX-2 selectivity. Those that inhibit COX-1 to a greater extent (indomethacin, piroxicam, ketoprofen) produce more GI side effects and renal toxicity than those with greater selectivity for COX-2 (diclofenac, salsalate, and ibuprofen).<sup>15</sup> In addition to the degree of selectivity, the use of these NSAIDs at low or high doses may play a role in the rate of GI toxicity.<sup>19</sup>

In high-risk patients, H<sub>2</sub> antagonists and proton pump inhibitors are frequently coadministered with NSAIDs in an attempt to reduce GI adverse events; however, these agents are not indicated for prophylaxis but only for treatment of ulcers.<sup>15</sup> One option has been the addition of a prophylactic medication that will help protect the mucosa. Misoprostol, a prostaglandin E1 analog, can be used in conjunction with an NSAID to replace GI prostaglandins that NSAIDs deplete. Misoprostol increases secretion of gastric mucus and regulates gastric mucosal blood flow to decrease the risk of NSAID-induced ulceration and perforation. A combination product of diclofenac sodium and misoprostol is available from Searle (Arthrotec®). Tolerability is a factor that sometimes limits the use of misoprostol because it can cause abdominal pain, diarrhea, dyspepsia, and flatulence.<sup>20</sup> In addition, sucralfate exhibits protective properties by adhering to the gastric mucosa and forming a coating. However, its clinical benefits appear to be minimal. Finally, it is important to remind all patients to take NSAIDs with food.

In summary, NSAIDs play a great role in the treatment of OA, RA, and other inflammatory conditions. However, their use (especially at antiinflammatory doses) is sometimes limited because of their adverse effects. New advances in treatment have projected ways to reduce the risks and maximize the benefits of NSAID therapy. The development of selective COX-2 inhibitors, which produce an antiinflammatory and analgesic effect without interfering with GI and renal tracts, provide promising new approaches to management. However, lifestyle modifications and other non-pharmacologic strategies should also be used.

### ... CELECOXIB (CELEBREX®) ...

Celecoxib is the first NSAID selective for COX-2 inhibition approved by the FDA. Celecoxib does not inhibit COX-1 at therapeutic concentrations in humans; however, at higher doses there does appear to be some COX-1 inhibition.<sup>21</sup> Unless otherwise

indicated, all materials in this section are derived from Simon.<sup>21</sup>

### Approved Indication

Celecoxib is indicated for the relief of signs and symptoms of OA and RA in adults. It is contraindicated in patients allergic to sulfonamides because the chemical structure contains a sulfonamide component. It also should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions with aspirin or other NSAIDs. The safety and efficacy of celecoxib has not been investigated in patients younger than 18 years of age.

### Pharmacokinetics

*Absorption.* Peak plasma drug concentrations are reached in approximately 3 hours after an oral dose. Food does not affect its bioavailability.

*Distribution.* In plasma, 97% of the drug is bound to protein, primarily albumin, and it has substantial distribution into compartments. The drug is excreted in the milk of lactating animals at concentrations similar to those in plasma.

*Metabolism.* Celecoxib is metabolized primarily by the cytochrome P-450 2C9 isozyme (CYP2C9), producing inactive metabolites.

*Elimination.* Celecoxib and its metabolites are excreted primarily by hepatic metabolism. After administration of radiolabeled celecoxib, approximately 57% of the dose was excreted in the feces and 27% was excreted in the urine.

### Drug Interactions

In vitro studies show that celecoxib is an inhibitor of the isozyme CYP2D6. Therefore, drugs metabolized by isozyme CYP2D6 should be used with caution in patients taking celecoxib until in vivo studies are performed. Also, drugs known to inhibit isozyme CYP2C9 should be used with caution in patients taking celecoxib because this is its primary route of metabolism. Twofold increases in plasma celecoxib concentrations have been observed after concomitant administration of fluconazole, a CYP2C9 inhibitor. Patients taking NSAIDs (including celecoxib) along with an angiotensin-converting enzyme inhibitor, diuretic, or lithium should be monitored closely for drug interactions. Celecoxib may diminish the antihypertensive effect of angiotensin-converting enzyme inhibitors, reduce the natriuretic effect of diuretics, and increase lithium levels. In addition, celecoxib has not been shown to alter the anticoagulant effects of warfarin, but because patients would be at an

increased risk for bleeding complications, caution should be used. No significant interactions have been found in studies with methotrexate, glyburide, ketoconazole, phenytoin, and tolbutamide.

### Clinical Effectiveness

A recent study involving four trials conducted by Simon et al<sup>22</sup> evaluated the efficacy and safety of celecoxib in treating OA and RA. In addition, this study determined the effect of celecoxib on the GI mucosa and on platelet function. Two of the trials compared the efficacy of three dosages of celecoxib with placebo in treating RA and OA. Fewer patients withdrew from the studies because of lack of efficacy in the celecoxib groups compared with the placebo group. Also, reductions in the signs and symptoms of arthritis were observed with all dosages of celecoxib studied. The third trial was performed in healthy subjects to compare the gastroduodenal mucosal effects of celecoxib with those of naproxen and placebo. The doses of celecoxib used were 100 mg or 200 mg twice a day compared with naproxen 500 mg twice a day. No gastric ulcers were reported in any subjects receiving placebo or celecoxib, but in the naproxen group, six subjects (19%) had at least one gastric ulcer. The incidence of gastric erosions, ulcers, or both ranged from 9% to 13% in the celecoxib-treated and placebo-treated subjects, whereas naproxen-treated subjects had a 72% incidence. The final trial was performed to compare the platelet effects of celecoxib with those of aspirin. After administration of celecoxib 400 mg twice a day, platelet aggregation remained essentially unchanged from the pretreatment values, but after a single 650-mg dose of aspirin, the differences between predose and postdose values were statistically significant. The authors concluded that celecoxib achieves analgesic and antiinflammatory efficacy in arthritis through selective COX-2 inhibition, without demonstrating any evidence of the two predominant toxic effects of COX-1 inhibition associated with NSAIDs.

The package insert for celecoxib states, "In three 12-week studies of pain accompanying OA flare CELEBREX® doses of 100 mg BID and 200 mg BID provided significant reduction of pain within 24–48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of CELEBREX® was shown to be similar to that of naproxen 500 mg BID." Similar effects were seen in RA.<sup>21</sup>

### Precautions

Until long-term trials are performed to gather more information about COX-2 inhibitors, the same

warnings and precautions that apply to NSAIDs should be considered in patients taking celecoxib. Infrequent, but serious, upper GI toxicity has been observed in patients receiving celecoxib; therefore, signs and symptoms (ie, bleeding, ulceration, perforation) should be monitored, especially in high-risk patients. The lowest effective dose should be used to minimize the potential risk for an adverse GI event. Clinicians should be aware that NSAIDs can cause renal or hepatic dysfunction and that celecoxib may be expected to cause similar effects, especially at higher doses. If clinical signs and symptoms consistent with liver or kidney disease develop, celecoxib should be discontinued. In addition, it should be used cautiously in patients with fluid retention, hypertension, or heart failure.

Celecoxib is classified in FDA pregnancy category C. In late pregnancy, it should be avoided, along with all NSAIDs, to prevent premature closure of the ductus arteriosus.

**Adverse Effects**

According to FDA labeling, celecoxib was administered to more than 8500 patients with OA and RA, including 3900 patients who received it for 6 months or longer. The most common adverse reactions were dyspepsia, diarrhea, and abdominal pain, but the overall incidence of GI side effects appears to be equal to or less than that with the traditional NSAIDs. Collected data now exist for the utilization of celecoxib in over 14,000 patients (Table 2).

**Dosage and Administration**

The recommended oral dose in patients with osteoarthritis is 200 mg per day administered as a single dose or as 100 mg twice per day. For patients with RA, 100 to 200 mg twice per day is rec-

ommended. No dosage adjustment is required for patients who are elderly or who have mild to moderate renal impairment. A reduced dose should be used in patients with moderate hepatic impairment, and celecoxib is not recommended in patients with severe hepatic impairment.

... SUMMARY ...

Despite toxicities, NSAIDs still play a major role in patients with RA and OA. Researchers have pro-

**Table 2.** Adverse Events Occurring in  $\geq 2\%$  of Patients Receiving Celecoxib

	Drug (%)				
	Celecoxib	Placebo	Naproxen	Ibuprofen	Diclofenac
<b>Gastrointestinal</b>					
Abdominal pain	4.1	2.8	7.7	7.7	9.0
Diarrhea	5.6	3.8	5.3	5.3	9.3
Dyspepsia	8.8	6.2	6.2	12.2	10.9
Flatulence	2.2	1.0	1.0	3.6	4.1
Nausea	3.5	4.2	4.2	6.0	3.4
<b>Body as a whole</b>					
Back pain	2.8	3.6	2.2	2.2	0.9
Peripheral edema	2.1	1.1	2.1	2.1	3.5
Injury—accidental	2.9	2.3	3.0	2.6	3.2
<b>Central and peripheral nervous system</b>					
Dizziness	2.0	1.7	2.6	1.3	2.3
Headache	15.8	20.2	14.5	15.5	15.4
<b>Psychiatric</b>					
Insomnia	2.3	2.3	2.9	1.3	1.4
<b>Respiratory</b>					
Pharyngitis	2.3	1.1	1.7	1.6	2.6
Rhinitis	2.0	1.3	2.4	2.3	0.6
Sinusitis	5.0	4.3	4.0	5.4	5.8
Respiratory tract infection	8.1	6.7	9.9	9.8	9.9
<b>Skin</b>					
Rash	2.2	2.1	2.1	1.3	1.2

Source: Reference 21.

gressed to understanding the differences between the two isozymes inhibited by NSAIDs. This has led to the development of agents that will only inhibit the enzyme (COX-2) responsible for the production of proinflammatory prostaglandins and not the enzyme (COX-1) responsible for the production of cytoprotective prostaglandins. Early studies demonstrate that celecoxib is efficacious in treating OA and RA. Celecoxib appears to have a more favorable side effect profile than traditional NSAIDs. However, more information and research is needed to ensure optimal use of COX-2 inhibitors.

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**CONTINUING PHARMACY EDUCATION**

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-000-99-204-H-01. This course expires April 30, 2002.

**Instructions**

After reading the article "Celecoxib: A COX-2 Inhibitor," select the best answer to each of the following questions.

**1. The best overall approach to nonpharmacologic management of osteoarthritis and rheumatoid arthritis is:**

- a) education, weight loss, strenuous exercise
- b) exercise, education, good nutrition
- c) stress reduction class, exercise, weight gain
- d) good nutrition, occupational therapy, jogging

**2. Rheumatoid arthritis is:**

- a) a viral infection
- b) a disease of the weight-bearing joints
- c) more common in men
- d) a chronic, inflammatory, autoimmune disorder

**3. Detection of rheumatoid factor is useful in the diagnosis of rheumatoid arthritis:**

- a) true
- b) false

**4. Which statement is true regarding nonsteroidal antiinflammatory drugs (NSAIDs)?**

- a) NSAID therapy is the initial drug of choice for the treatment of osteoarthritis
- b) NSAIDs share the properties of being antiinflammatory and analgesic
- c) NSAIDs produce gastrointestinal toxicity through the inhibition of COX-2
- d) all NSAIDs affect COX-1 and COX-2 to the same degree

**5. Which NSAID has the tendency to produce more gastrointestinal toxicity?**

- a) indomethacin
- b) ibuprofen
- c) salsalate
- d) diclofenac

**6. Which factor does not need to be considered when initiating NSAID therapy?**

- a) the patient's age
- b) use of over-the-counter pain medications
- c) the patient's activity level
- d) past medical history of peptic ulcer disease

*(CPE QUESTIONS CONTINUED ON FOLLOWING PAGE)*

**Celecoxib: A COX-2 Inhibitor**

(PLEASE PRINT CLEARLY)

Name \_\_\_\_\_

Home Address \_\_\_\_\_

City \_\_\_\_\_

State/ZIP \_\_\_\_\_

Daytime Phone # \_\_\_\_\_

States in which CE credit is desired: \_\_\_\_\_

Social Security # \_\_\_\_\_

Please circle your answers:

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

Please complete the Program Evaluation on following page, and send with \$15 fee, payable to University of Tennessee, to:

Glen Farr, PharmD  
University of Tennessee College of Pharmacy  
600 Henley Street, Suite 213  
Knoxville, TN 37902

## ...CPE QUIZ...

**7. Regarding osteoarthritis, which statement is false?**

- a) pain is usually present as the initial symptom
- b) osteoarthritis is an autoimmune disease
- c) osteoarthritis will affect essentially every person by the age of 75 years
- d) treatment must be individualized and include nonpharmacologic management

**8. Which pharmacologic treatment is not indicated for osteoarthritis?**

- a) intraarticular injections
- b) aspirin
- c) ketoprofen
- d) oral corticosteroids

**9. Although NSAIDs are the most widely used pharmacologic agent for the treatment of arthritis,**

- a) they only reduce signs and symptoms of arthritis
- b) they can be extremely toxic to the gastrointestinal tract
- c) both a and b
- d) neither a nor b

**10. Which of the following statements are true?**

- a) osteoarthritis affects more than 16 million Americans
- b) the onset of rheumatoid arthritis most often occurs between the ages of 25 and 50
- c) maintaining the ability to function independently is a goal in the management of rheumatoid arthritis
- d) all of the above

**11. The mechanism of action of traditional NSAIDs includes:**

- a) the inhibition of COX-1 to prevent the production of prostaglandins
- b) irreversible binding to arachidonic acid
- c) the inhibition of COX 2 to prevent the production of prostaglandins
- d) both a and c

**12. H<sub>2</sub> antagonists prevent NSAID-induced gastric ulcers.**

- a) true
- b) false

**13. Which of the following is false concerning COX inhibition?**

- a) COX-1 concentrations remain relatively constant in cells and tissues
- b) activation of COX-2 leads to vasodilation and pain
- c) Cyclooxygenase is an enzyme responsible for catalyzing the conversion of arachidonic acid to prostaglandins
- d) COX-2 is primarily found in the GI tract

**14. Misoprostol**

- a) decreases gastric mucus production and gastric blood flow
- b) has a side effect profile similar to that of placebo
- c) is a prostaglandin analog
- d) can cause GI ulceration and perforation if used in conjunction with an NSAID

(CPE QUESTIONS CONTINUED ON FOLLOWING PAGE)

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### CPE PROGRAM EVALUATION

The University of Tennessee College of Pharmacy would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CPE test form. We thank you for your evaluation, which is most helpful.

*Please circle your answers:*

My pharmacy practice setting is:	Independent	Chain	Hospital	Consultant
The objectives of the lesson were achieved:	Yes	No		
The quality of presentation of the material was:	Excellent	Good	Fair	Poor
The information presented will be useful to me in my practice.	Strongly agree	Mildly agree	Mildly disagree	Strongly disagree

How long did it take you to read the material and respond to the Continuing Education questions: (Please specify the number of hours.)

\_\_\_\_\_

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*(CPE questions continued from previous page)*

**15. Which of the following adverse effects would a patient on celecoxib most likely experience?**

- a) dyspepsia
- b) insomnia
- c) dizziness
- d) rhinitis

**16. At therapeutic doses, celecoxib selectively inhibits COX-2.**

- a) true
- b) false

**17. Which of the following is true concerning celecoxib?**

- a) it will potentiate the anticoagulant effects (increase prothrombin time) in patients on warfarin
- b) it is classified in pregnancy category B
- c) it should always be taken on an empty stomach
- d) it is indicated for the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults

**18. Which of the following has the potential to interact with celecoxib?**

- a) lithium
- b) fluconazole
- c) furosemide
- d) all of the above

**19. The most appropriate initial dose of celecoxib for a rheumatoid arthritis patient would be:**

- a) 200 mg three times per week
- b) 50 mg three times per day
- c) 100 mg twice per day
- d) 10 mg every day

**20. Which of the following statements are true?**

- a) the same warnings and precautions that apply to NSAIDs should be considered in patients taking celecoxib
- b) monitoring for gastrointestinal complications is not required with celecoxib
- c) celecoxib is only selective for COX-2
- d) both a and c