# COX-2–selective inhibitors in the treatment of arthritis

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## ABSTRACT

Therapy with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) has long been the cornerstone of pharmacologic management of patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Many patients with OA or RA, however, are at increased risk of developing clinically significant adverse events associated with NSAID therapy, particularly upper gastrointestinal (GI) complications including symptomatic and complicated ulcers. The introduction of cyclooxygenase (COX)-2–selective inhibitors (coxibs) represents a major advance in the pharmacologic approach to the signs and symptoms of arthritis. In addition to the first two members of this class, celecoxib and rofecoxib, other coxibs have been introduced or are in development (valdecoxib, etoricoxib). In numerous clinical trials, coxibs have been shown to be as effective as nonselective NSAIDs in relieving pain and inflammation associated with OA and RA, and notably, with a significantly lower risk of NSAID-type adverse events. The use of coxibs to treat OA and RA is recommended as first-line therapy when symptoms of pain and inflammation are present in patients vulnerable to potential NSAID-associated GI toxicity.


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Affecting nearly 43 million Americans, arthritis is one of the most prevalent diseases and major causes of disability in the United States.[1] By the year 2020, it is estimated that more than 18% of adults in America will have some form of arthritis.[2]

Rheumatoid arthritis (RA) is a systemic disease marked by inflammatory changes in synovial membranes and articular structures that lead to widespread degeneration of collagen fibers and destruction of bony structures. Osteoarthritis (OA) is believed to be caused by a combination of abnormal biomechanical stresses on the joint and abnormal biochemical and metabolic changes in the chondrocyte and articular cartilage. Unlike RA, when OA inflammation is present, it is usually mild and localized to the affected joint. Nevertheless, proinflammatory cytokines play a pivotal role in the development of OA disease.[3]

The disease process in OA affects the entire joint

and can result in inflammatory changes in the synovium similar to those of RA. These manifest as joint stiffness, loss of physical mobility, and occasionally as joint swelling or redness.[3] Synovial inflammation may be present in early stages of OA, but it is more often seen in advanced stages. OA joint pain, however, does not correlate with histologic evidence of joint inflammation.[4]

Most patients with arthritis are treated by primary care physicians. Therapy for OA is largely palliative, aimed at increasing physical function by relieving joint pain and reducing inflammation.[5] Control of systemic inflammation and prevention or slowing of disease progression are additional treatment goals in patients with RA. While no pharmacologic agents have been shown to prevent or delay the progression of structural damage in OA, disease-modifying antirheumatic drugs (DMARDs) appear to have the capacity to alter the clinical course of RA.[6,7]

Because of their analgesic and anti-inflammatory effects, nonsteroidal anti-inflammatory drugs (NSAIDs) are the class of medication most commonly used to treat joint pain and stiffness in patients with OA and RA.[4,8–10] Nonselective NSAIDs inhibit the isozymes of cyclooxygenase (COX), COX-1 and COX-2. (See articles by Bingham and Cronstein in this supplement.) Preclinical studies strongly suggest that inhibition of COX-2 is primarily responsible for many of the therapeutic benefits of NSAIDs, while inhibition of COX-1 can lead to toxic effects.[8,11,12] For this reason, the American College of Rheumatology (ACR) recently recommended replacing nonselective NSAID therapy with therapy with a coxib agent, a COX-2–selective inhibitor, when treating a patient with OA at increased risk of developing an NSAID-related toxicity.[5] Patients with OA or RA at increased risk of developing NSAID-related gastrointestinal (GI) toxicities include those who are older (65 years of age and above), have a history of a prior symptomatic or complicated ulcer, require chronic high-dose NSAID therapy, or take concomitant corticosteroid or anticoagulant therapy.[4,5,13–15]

The introduction of coxibs represents one of the most rapid development programs of a pharmacologic agent in rheumatology. The first two coxibs, celecoxib and rofecoxib, were approved for use in the United States only a few years after COX-2, the inducible form of COX, was first identified[16] and its pathogenic role in pain and inflammation proposed.[17] An aggressive program of clinical trials rapidly followed and provided the evidence-based proof of coxib efficacy in managing the signs and symptoms of OA and RA required by the regulatory approval process.

### The efficacy of coxibs in the treatment of osteoarthritis

Celecoxib, rofecoxib, and valdecoxib are approved for the treatment of OA in the United States.

The efficacy of celecoxib 100 mg twice daily, 200 mg once daily, and 200 mg twice daily in OA is comparable to that of diclofenac 50 mg three times daily and naproxen 500 mg twice daily and significantly superior to placebo.

The efficacy of rofecoxib 12.5 mg once daily and 25 mg once daily in OA is comparable to ibuprofen 800 mg three times daily, nabumetone 1,500 mg once daily, and diclofenac 50 mg three times daily and significantly superior to placebo.

In direct comparisons in OA patients, rofecoxib 25 mg when given once daily in the morning was significantly more effective than celecoxib 200 mg once daily or acetaminophen 1,000 mg four times daily.

The efficacy of valdecoxib 5 mg once daily, 10 mg twice daily, or 10 mg once daily in OA is comparable to naproxen 500 mg twice daily and superior to placebo.

Etoricoxib 60 mg once daily and 90 mg once daily are significantly more effective than placebo and comparable to naproxen 500 mg twice daily in the treatment of OA.

COX-189, an experimental coxib, 50 mg, 100 mg, 200 mg twice daily or 400 mg once daily, provides relief of OA symptoms comparable to diclofenac SR 75 mg twice daily and is significantly superior to placebo.

## ■ OUTCOME MEASURES IN ARTHRITIS CLINICAL TRIALS

Clinical trials of pharmacologic agents in OA or RA employ several measures of efficacy recommended by Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT), a group endorsed by the International League of Associations of Rheumatology (ILAR) and the World Health Organization (WHO). These outcome measures are designed to detect minimal clinically significant changes in the severity of joint pain or physical disability associated with OA or RA.[18,19]

Many of these instruments, such as the Patient

Assessment of Pain, require evaluation by the patient. The sensitivity and reliability of these self-report measures have been validated by comparative and radiographic studies.[20–23] One commonly utilized self-rating scale is the visual analog scale (VAS), a continuous numerical scale that ranges from 0 mm, indicative of the best outcome (eg, no pain), to 100 mm for the worst outcome (eg, extreme pain). Another scale often employed in quantifying patient or physician global assessment of disease activity is the Likert scale, a 5-point scale in which 0 designates the best outcome and 4 designates the worst outcome. Minimal clinical significance is generally considered a Likert scale change of at least 0.4 units.[24]

Either the VAS or Likert scale can be used to quantify a patient's status following therapeutic intervention. Many recent OA clinical trials employ the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[18,25] The WOMAC OA Index is composed of 24 items in three subscales that evaluate pain (five questions), physical function (17 questions), and stiffness (two questions).[23,26] Minimal clinically significant change is considered a decrease of 9.7, 9.3, and 10 mm, respectively, in the WOMAC pain, physical function, and stiffness subscales (VAS).[24] The Lequesne Algofunctional Index, graded on a composite scale ranging from 0 to 24, with lower scores indicating better condition, is an outcome instrument commonly employed in clinical trials of hip or knee OA conducted in Europe.[26,27]

The common outcome measure used in RA trials is the ACR 20.[28] The ACR developed a binary outcome measure of response based on the seven items in the ILAR/WHO core set. These include the number of painful/tender and swollen joints determined by physical examination, the duration of morning stiffness, patient and physician global assessment of disease activity, severity of pain, a measure of physical disability (eg, Health Assessment Questionnaire [HAQ]), and a measure of an acute-phase reactant (eg, the erythrocyte sedimentation rate or C-reactive protein). To achieve an ACR 20 response, the patient must have at least a 20% improvement in the number of painful/tender and swollen joints as well as an improvement of 20% or more in three of the remaining five outcome measures. While originally developed for use in randomized placebo-controlled trials of DMARDs, the ACR 20 is now widely used in trials of NSAIDs, including COX-2–selective inhibitors.

With few exceptions, all clinical trials of coxib efficacy in OA or RA to date were designed to establish efficacy in patients who had been previously treated with an NSAID and who had experienced a "flare" in symptoms after discontinuing NSAID therapy shortly before study enrollment. (For further discussion of the "withdrawal flare" trial design, see Scott-Lennox et al, 2001[29]). When an NSAID was the active comparator, the higher anti-inflammatory dose of NSAID was generally employed. Most of these coxib trials were short-term, conducted for 6 or 12 weeks. The exceptions were two long-term studies, of 52 weeks' duration, in OA patients comparing rofecoxib with diclofenac,[11,30] and one 24-week study comparing celecoxib with diclofenac SR in patients with RA.[31] Two studies of the new coxib, etoricoxib, include a 46-week study versus diclofenac in OA patients[32] and a 52-week study comparing etoricoxib with naproxen in OA patients.[33] (See **Tables 1 and 2** for trial summaries.)

## ■ CLINICAL TRIALS OF COXIBS IN OA

### Celecoxib

The first published trial of a coxib was a 2-week, placebo-controlled, dose-ranging study of celecoxib 40 mg, 100 mg, or 200 mg twice daily in 293 patients with OA of the knee. Although all three doses demonstrated clinical improvement, only the two higher doses maintained mean improvements significantly greater than with placebo ($P \leq .048$).[8]

Another study, conducted in 1,003 patients with OA of the knee, was reported the following year. In this 12-week trial, clinical improvements with celecoxib 100 mg or 200 mg twice daily were greater than with celecoxib 50 mg twice daily and comparable to naproxen 500 mg twice daily. Mean measures of efficacy with celecoxib 100 mg or 200 mg twice daily or naproxen 500 mg twice daily were significantly superior to outcomes with placebo ($P \leq .05$).[34]

Another placebo- and active-comparator controlled study of celecoxib in OA involved 600 patients with OA of the knee who were treated for 6 weeks with celecoxib 100 mg twice daily, diclofenac 50 mg three times daily, or placebo. Mean improvements with celecoxib or diclofenac were comparable and significantly superior to outcomes with placebo ($P < .001$).[35]

A 6-week, placebo-controlled study compared treatment with celecoxib 100 mg twice daily to

*Continued on page SI-26*

**TABLE 1**
CLINICAL STUDIES OF COXIB EFFICACY IN OSTEOARTHRITIS

| Author | N | Study drug | Comparator | Duration | Clinical response |
|---|---|---|---|---|---|
| Simon et al[8] | 293 | **Celecoxib**<br>40 mg BID (n = 73)<br>100 mg BID (n = 76)<br>200 mg BID (n = 73) | **Placebo** (n = 71) | 2 weeks | All 3 celecoxib regimens superior to placebo in mean improvements of disease status ($P \leq .048$) |
| Bensen et al[34] | 1,003 | **Celecoxib**<br>50 mg BID (n = 203)<br>100 mg BID (n = 197)<br>200 mg BID (n = 202) | **Naproxen**<br>500 mg BID (n = 198)<br>**Placebo** (n = 203) | 12 weeks | Celecoxib 100 mg and 200 mg BID comparable to naproxen, superior to placebo in mean improvements in WOMAC index, global assessments ($P \leq .05$) |
| McKenna et al[35] | 600 | **Celecoxib**<br>100 mg BID (n = 201) | **Diclofenac**<br>50 mg TID (n = 199)<br>**Placebo** (n = 200) | 6 weeks | Celecoxib comparable to diclofenac, superior to placebo in mean decrease in VAS pain, percent with 2-grade improvements in disease status ($P < .001$) |
| Singh et al[36] | 13,194 | **Celecoxib**<br>100 mg BID<br>200 mg BID | **Naproxen**<br>500 mg BID<br>**Diclofenac**<br>50 mg BID | 12 weeks | Celecoxib comparable to diclofenac in mean decrease in VAS pain |
| Williams et al[26] | 718 | **Celecoxib**<br>100 mg BID (n = 243) | **Celecoxib**<br>200 mg QD (n = 231)<br>**Placebo** (n = 244) | 6 weeks | Celecoxib QD, BID regimens comparable, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .05$) |
| Ehrich et al[39] | 672 | **Rofecoxib**<br>5 mg QD (n = 149)<br>12.5 mg QD (n = 144)<br>25 mg QD (n = 137)<br>50 mg QD (n = 97) | **Placebo** (n = 145) | 6 weeks | Rofecoxib 12.5-mg, 25-mg, 50-mg regimens produced dose-dependent efficacy superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .001$) |
| Ehrich et al[37] | 219 | **Rofecoxib**<br>25 mg QD (n = 73)<br>125 mg QD (n = 74) | **Placebo** (n = 72) | 6 weeks | Both rofecoxib regimens comparable, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .001$) |
| Day et al[40] | 809 | **Rofecoxib**<br>12.5 mg QD (n = 244)<br>25 mg QD (n = 242) | **Ibuprofen**<br>800 mg TID (n = 249)<br>**Placebo** (n = 74) | 6 weeks | Rofecoxib comparable to ibuprofen, superior to placebo in mean improvements in VAS pain, WOMAC index,global assessments ($P \leq .009$) |
| Geba et al[41] | 1,042 | **Rofecoxib**<br>12.5 mg QD (n = 424) | **Nabumetone**<br>1,000 mg QD (n = 410)<br>**Placebo** (n = 208) | 6 weeks | Rofecoxib superior to nabumetone ($P < .05$) and placebo ($P < .001$) in mean improvements in global assessment |
| Truitt et al[13] | 341 | **Rofecoxib**<br>12.5 mg QD (n = 118)<br>25 mg QD (n = 56) | **Nabumetone**<br>1,500 mg QD (n = 115)<br>**Placebo** (n = 52) | 6 weeks | In patients ≥80 years, rofecoxib comparable to nabumetone, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .05$) |
| Saag et al[30] | 736 | **Rofecoxib**<br>12.5 mg QD (n = 219)<br>25 mg QD (n = 227) | **Ibuprofen**<br>800 mg TID (n = 221)<br>**Placebo** (n = 69) | 6 weeks | Rofecoxib comparable to ibuprofen, superior to placebo in mean improvements in WOMAC index, global assessments ($P < .001$) |

*(continued)*

**TABLE 1** *(continued)*

| Author | N | Study drug | Comparator | Duration | Clinical response |
|---|---|---|---|---|---|
| Saag et al[30] | 693 | **Rofecoxib**<br>12.5 mg QD (n = 231)<br>25 mg QD (n = 232) | **Diclofenac**<br>50 mg TID (n = 230) | 52 weeks | Rofecoxib 25 mg comparable to diclofenac, superior to placebo in mean improvements in WOMAC index, global assessments ($P < .001$) |
| Cannon et al[11] | 784 | **Rofecoxib**<br>12.5 mg QD (n = 259)<br>25 mg QD (n = 257) | **Diclofenac**<br>50 mg TID (n = 268) | 26 weeks | Rofecoxib comparable to diclofenac, superior to placebo in mean improvements in VAS pain, WOMAC index (taken to week 26), global assessments |
| Geba et al[42] | 382 | **Rofecoxib**<br>12.5 mg QD (n = 96)<br>25 mg QD (n = 95) | **Celecoxib**<br>200 mg QD (n = 97)<br>**Acetaminophen**<br>1,000 mg QID (n = 94) | 6 weeks | Rofecoxib 25 mg statistically superior to celecoxib, acetaminophen in mean improvements in VAS pain, WOMAC index, global assessments, onset of relief |
| Schnitzer et al[43] | 1,082 | **Rofecoxib**<br>25 mg QD (n = 471) | **Celecoxib**<br>200 mg QD (n = 460)<br>**Placebo** (n = 151) | 6 weeks | Rofecoxib statistically superior to celecoxib, placebo in mean improvements in VAS pain, WOMAC index, global assessments, onset of relief |
| Eskiyurt[46] | 138 | **Rofecoxib**<br>12.5 mg QD | **Rofecoxib**<br>25 mg QD | 6 weeks | In Turkish population, rofecoxib regimens comparable in mean improvements in WOMAC, Lequesne Algofunctional indices |
| Fiechtner et al[47] | 642 | **Valdecoxib**<br>0.5 mg BID<br>1.25 mg BID<br>2.5 mg BID<br>5 mg BID<br>10 mg QD<br>10 mg BID | **Naproxen**<br>500 mg BID<br>**Placebo** | 6 weeks | Valdecoxib produced dose-dependent efficacy comparable to naproxen at 5 mg BID, 10 mg QD, and 10 mg BID; superior to placebo at all dosages except .5 mg BID in mean improvements in VAS pain, WOMAC index, global assessments ($P \leq .004$) |
| Curtis et al[32] | 617 | **Etoricoxib**<br>5 mg QD (n = 117)<br>10 mg QD (n = 114)<br>30 mg QD (n = 102)<br>60 mg QD (n = 112)<br>90 mg QD (n = 112) | **Placebo** (n = 60) | 6 weeks (Part I) | Etoricoxib produced dose-dependent efficacy superior to placebo in mean improvements in VAS pain, global assessments ($P < .05$) |
| Curtis et al[32] | 617 | **Etoricoxib**<br>30 mg QD<br>60 mg QD<br>90 mg QD | **Diclofenac**<br>50 mg TID | 46 weeks (Part II) | Etoricoxib 60-mg, 90-mg regimens superior to 30-mg regimen in mean improvements in VAS pain, global assessments |
| Fisher et al[33] | 496 | **Etoricoxib**<br>60 mg QD (n = 222) | **Naproxen**<br>500 mg BID (n = 218)<br>**Placebo** (n = 56) | 12 weeks (Part I) | Etoricoxib 60 mg comparable to naproxen, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments |
| Fisher et al[33] | 496 | **Etoricoxib**<br>60 mg QD (n = 248) | **Naproxen**<br>500 mg BID (n = 248) | 40 weeks (Part II) | Etoricoxib 60 mg comparable to naproxen in mean improvements in VAS pain, WOMAC index, global assessments |
| Schnitzer et al[48] | 583 | **COX-189**<br>50 mg BID<br>100 mg BID<br>200 mg BID<br>400 mg QD | **Diclofenac SR**<br>75 mg BID<br>**Placebo** | 4 weeks | All regimens of COX-189 comparable to diclofenac, superior to placebo in mean improvements in VAS pain, WOMAC index, HAQ index, global assessments |

**TABLE 2**
CLINICAL STUDIES OF COXIB EFFICACY IN RHEUMATOID ARTHRITIS

| Author | N | Study drug | Comparator | Duration | Clinical response |
|---|---|---|---|---|---|
| Simon et al[8] | 330 | **Celecoxib**<br>40 mg BID (n = 81)<br>200 mg BID (n = 82)<br>400 mg BID (n = 82) | **Placebo** (n = 85) | 4 weeks | Celecoxib 200-mg, 400-mg regimens superior to placebo in mean improvements in global assessment ($P < .001$); number tender, swollen joints ($P \leq .005$); percent improved by ACR 20 criteria ($P \leq .025$) |
| Simon et al[12] | 1,149 | **Celecoxib**<br>100 mg BID (n = 240)<br>200 mg BID (n = 235)<br>400 mg BID (n = 218) | **Naproxen**<br>500 mg BID (n = 225)<br>**Placebo** (n = 231) | 12 weeks | Celecoxib 200 mg, 400 mg regimens comparable to naproxen, superior to placebo in mean improvements in global assessments; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .05$) |
| Emery et al[31] | 655 | **Celecoxib**<br>200 mg BID (n = 326) | **Diclofenac SR**<br>75 mg BID (n = 329) | 24 weeks | Celecoxib comparable to diclofenac in mean improvements in VAS pain; global assessments; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria |
| Bensen et al[51] | 1,089 | **Valdecoxib**<br>10 mg QD<br>20 mg QD<br>40 mg QD | **Naproxen**<br>500 mg BID<br>**Placebo** | 12 weeks | Valdecoxib, all doses, comparable to naproxen, superior to placebo in ACR 20 response |
| Schnitzer et al[15] | 658 | **Rofecoxib**<br>5 mg QD (n = 158)<br>25 mg QD (n = 171)<br>50 mg QD (n = 161) | **Placebo** (n = 168) | 8 weeks | Rofecoxib 25-mg, 50-mg regimens superior to placebo in mean improvements in VAS pain; global assessments; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .001$) |
| Truitt et al[49] | 1,058 | **Rofecoxib**<br>25 mg QD (n = 315)<br>50 mg QD (n = 297) | **Naproxen**<br>500 mg BID (n = 147)<br>**Placebo** (n = 299) | 12 weeks | Rofecoxib comparable to naproxen, superior to placebo in mean improvements in VAS pain; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .05$) |
| Truitt et al[50] | 909 | **Rofecoxib**<br>12.5 mg QD (n = 148)<br>25 mg QD (n = 311) | **Naproxen**<br>500 mg BID (n = 149)<br>**Placebo** (n = 301) | 12 weeks | Rofecoxib 25 mg comparable to naproxen, superior to placebo in improvements in VAS pain; global assessments; number tender, swollen joints; percent improved by ACR 20 criteria; rofecoxib 12.5 mg superior to placebo in VAS pain, global assessments, and percent improved by ACR 20 criteria |
| Curtis et al[52] | 581 | **Etoricoxib**<br>10 mg QD (n = 78)<br>60 mg QD (n = 126)<br>90 mg QD (n = 134)<br>120 mg QD (n = 120) | **Placebo** (n = 123) | 8 weeks | Etoricoxib 90-mg and 120-mg regimens superior to placebo in mean improvements in VAS pain, global assessments, HAQ index ($P < .05$) |
| Melian et al[53] | 816 | **Etoricoxib**<br>90 mg QD (n = 323) | **Naproxen**<br>500 mg BID (n = 170)<br>**Placebo** (n = 323) | 12 weeks | Etoricoxib superior to naproxen, placebo in mean improvements in HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .05$) |

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### The efficacy of coxibs in the treatment of rheumatoid arthritis

Celecoxib and valdecoxib are the only coxibs currently approved for the treatment of RA in the United States.

Celecoxib 200 mg twice daily or 400 mg twice daily is as effective as naproxen 500 mg twice daily in the treatment of RA.

Celecoxib 200 mg twice daily is as effective as diclofenac SR 75 mg twice daily in the treatment of RA.

Rofecoxib 25 mg once daily or 50 mg once daily is as effective as naproxen 500 mg twice daily in the treatment of RA.

Valdecoxib 10 mg once daily is as effective as naproxen 500 mg twice daily in the treatment of RA.

Etoricoxib 90 mg and 120 mg once daily is significantly more effective than placebo in the treatment of RA.

Etoricoxib 90 mg once daily is as or more effective than naproxen 500 mg twice daily in the treatment of RA.

celecoxib 200 mg once daily in 718 patients with OA of the knee. Both regimens achieved comparable outcomes ($P < .05$).[26] In a recent 12-week study designed to examine safety, 13,194 patients with OA of the knee, hip, or hand were treated with celecoxib 100 mg or 200 mg twice daily, naproxen 500 mg twice daily, or diclofenac SR 50 mg twice daily. Mean improvements with either regimen of celecoxib were comparable to those achieved with diclofenac or naproxen.[36]

## Rofecoxib

Ten studies of the efficacy of rofecoxib in the treatment of OA have been reported to date.

Two phase II studies tested a range of rofecoxib dosages during a 6-week period.[37–39] In the first, the efficacy of rofecoxib 5 mg, 12.5 mg, 25 mg, or 50 mg once daily was compared with a placebo in 672 patients with OA of the hip or knee.[39] Mean improvements with rofecoxib at all doses were superior to those with placebo. The outcomes with rofecoxib 12.5 mg, 25 mg, and 50 mg once daily were superior to those seen with rofecoxib 5 mg once daily. The second study was conducted in 219 patients with OA of the knee treated with rofecoxib 25 mg or 125 mg once daily, or placebo. Both rofecoxib regimens demonstrated comparable efficacy, each resulting in significantly better responses than seen with placebo ($P < .001$).[37]

Six phase III studies compared the efficacy of rofecoxib with a nonselective NSAID and/or placebo. Two 6-week trials enrolled patients with OA of the hip or knee who were treated with rofecoxib 12.5 mg or 25 mg once daily, ibuprofen 800 mg three times daily, or placebo. Mean improvements seen with rofecoxib were comparable to those with ibuprofen and significantly superior to those with placebo ($P \leq .009$ and $P < .001$, respectively).[29,40]

Another 6-week trial compared the efficacy of rofecoxib 12.5 mg once daily with nabumetone 1,000 mg once daily or placebo in 1,042 patients with OA. In this study, the efficacy of rofecoxib was significantly superior to nabumetone ($P < .05$), and both treatments had greater efficacy than placebo ($P < .001$).[41] In an elderly population of 341 patients at least 80 years of age with OA of the hip or knee who were treated for 6 weeks with rofecoxib 12.5 mg or 25 mg once daily, nabumetone 1,500 mg once daily, or placebo, the mean improvements with rofecoxib were comparable to those with nabumetone and significantly superior to placebo ($P < .05$).[13]

Two 1-year trials evaluated the efficacy of rofecoxib 12.5 mg or 25 mg once daily and diclofenac 50 mg three times daily in patients with OA of the knee or hip. The efficacy of both rofecoxib regimens was comparable to that with diclofenac.[11,30]

## Comparative trials of rofecoxib and celecoxib

Several phase IV studies comparing the efficacy of rofecoxib with that of celecoxib have been done. In one study, patients with OA of the knee were treated for 6 weeks with rofecoxib 12.5 mg or 25 mg once daily, celecoxib 200 mg once daily, or acetaminophen 1,000 mg four times daily; no rescue analgesics were allowed, and all medications given once daily were dosed in the morning. By all outcome measures, rofecoxib 25 mg once daily was significantly superior to acetaminophen. In addition, rofecoxib 25 mg once daily was significantly more efficacious than celecoxib 200 mg once daily as assessed by patient global assessment of response to therapy and by mean improvement on the WOMAC pain and stiffness scales.[42]

A second, larger study involving 1,082 patients with OA evaluated rofecoxib 25 mg once daily, celecoxib 200 mg once daily, or placebo after 6 weeks of treatment; again, all medications were dosed in the morning. All outcome measures were significantly superior with rofecoxib than with celecoxib or placebo.[43]

Such findings have clinical significance, bolstering their statistical significance. Another study, however, found the efficacy of celecoxib 200 mg once daily and rofecoxib 25 mg once daily in treating OA of the knee to be comparable (both were superior to placebo).[44] However, in this study, all medications were dosed once in the evening. These results are consistent with the half-life of each of the two agents.

The findings that the recommended dose of rofecoxib for the treatment of OA was significantly more effective than the recommended dose of celecoxib for the treatment of OA may be related to the fact that rofecoxib has a longer half-life compared with that of celecoxib.[45] It is likely that this results in clinically significant sustained relief of pain and stiffness throughout the day with rofecoxib when both drugs are dosed once daily in the morning.

### Valdecoxib

Valdecoxib was recently approved in the United States for the treatment of OA at a dosage of 10 mg once daily, making it the third coxib available for that indication. The efficacy of valdecoxib in OA was shown in a 6-week, dose-ranging trial conducted in 642 patients with OA of the knee. Patients were treated with valdecoxib 10 mg either twice daily or once daily, 0.5 mg, 1.25 mg, 2.5 mg, or 5 mg twice daily; or naproxen 500 mg twice daily; or placebo. Maximum efficacy with valdecoxib was achieved with the 5 mg once daily, 10 mg twice daily, and 10 mg once daily regimens. These were comparable to naproxen and superior to placebo in all outcome measures.[47]

### Etoricoxib

Currently under investigation, etoricoxib is a second-generation coxib that has demonstrated efficacy for the treatment of OA. A 6-week, dose-ranging study was conducted in 617 patients with OA of the knee. Treatment with etoricoxib 5 mg, 10 mg, 30 mg, 60 mg, and 90 mg once daily produced dose-dependent efficacy that was superior to placebo and maximal at a dosage of 60 mg once daily ($P < .05$). Patients receiving either placebo or etoricoxib 5 mg or 10 mg once daily were then reallocated to treatment with etoricoxib 30 mg, 60 mg, or 90 mg once daily or diclofenac 50 mg three times daily for an additional 46 weeks. Etoricoxib 60 mg once daily or 90 mg once daily was more effective than 30 mg once daily in all outcome measures and comparable to diclofenac.[32]

A second study of etoricoxib efficacy was conducted in 496 patients with OA of the knee or hip. In the initial phase of the trial, patients were treated with etoricoxib 60 mg once daily, naproxen 500 mg twice daily, or placebo for 12 weeks. Placebo-treated patients were then reallocated to treatment with either etoricoxib 60 mg once daily or naproxen 500 mg twice daily for an additional 40 weeks. By all outcome measures, the efficacy of etoricoxib at week 12 was significantly superior to the outcomes with placebo, and at week 12 and week 52 was comparable to that of naproxen.[33]

### COX-189

A multinational, dose-ranging trial evaluated the efficacy of an experimental coxib, COX-189, in 583 patients with OA of the hip or knee. Patients were treated for 4 weeks with COX-189 400 mg once daily; COX-189 50 mg, 100 mg, 200 mg twice daily; diclofenac SR 75 mg twice daily; or placebo. The minimum effective COX-189 dosage was 50 mg twice daily. By both primary and secondary outcome measures, all regimens of COX-189 provided comparable efficacy to diclofenac and significantly better improvement than placebo ($P < .05$).[48]

## ■ CLINICAL TRIALS OF COXIBS IN RA

### Celecoxib

Celecoxib is approved for the treatment of RA in the United States. Efficacy of celecoxib was established in a dose-ranging study and two phase III trials. In a 4-week dose-ranging study, 330 patients with RA were treated with celecoxib 40 mg, 200 mg, or 400 mg twice daily, or placebo. Mean improvements with celecoxib 200 mg or 400 mg twice daily were significantly superior to placebo.[8]

A 12-week phase III trial compared the efficacy of celecoxib 100 mg, 200 mg, or 400 mg twice daily with naproxen 500 mg twice daily or placebo in 1,149 patients with RA. Treatment with celecoxib 200 mg or 400 mg twice daily produced mean improvements comparable to those with naproxen and significantly superior to outcomes with placebo ($P < .05$).[12]

In a second phase III study, 655 patients with RA were treated for 24 weeks with celecoxib 200 mg twice daily or diclofenac SR 75 mg twice daily. Mean improvements with celecoxib were comparable to outcomes with diclofenac.[31]

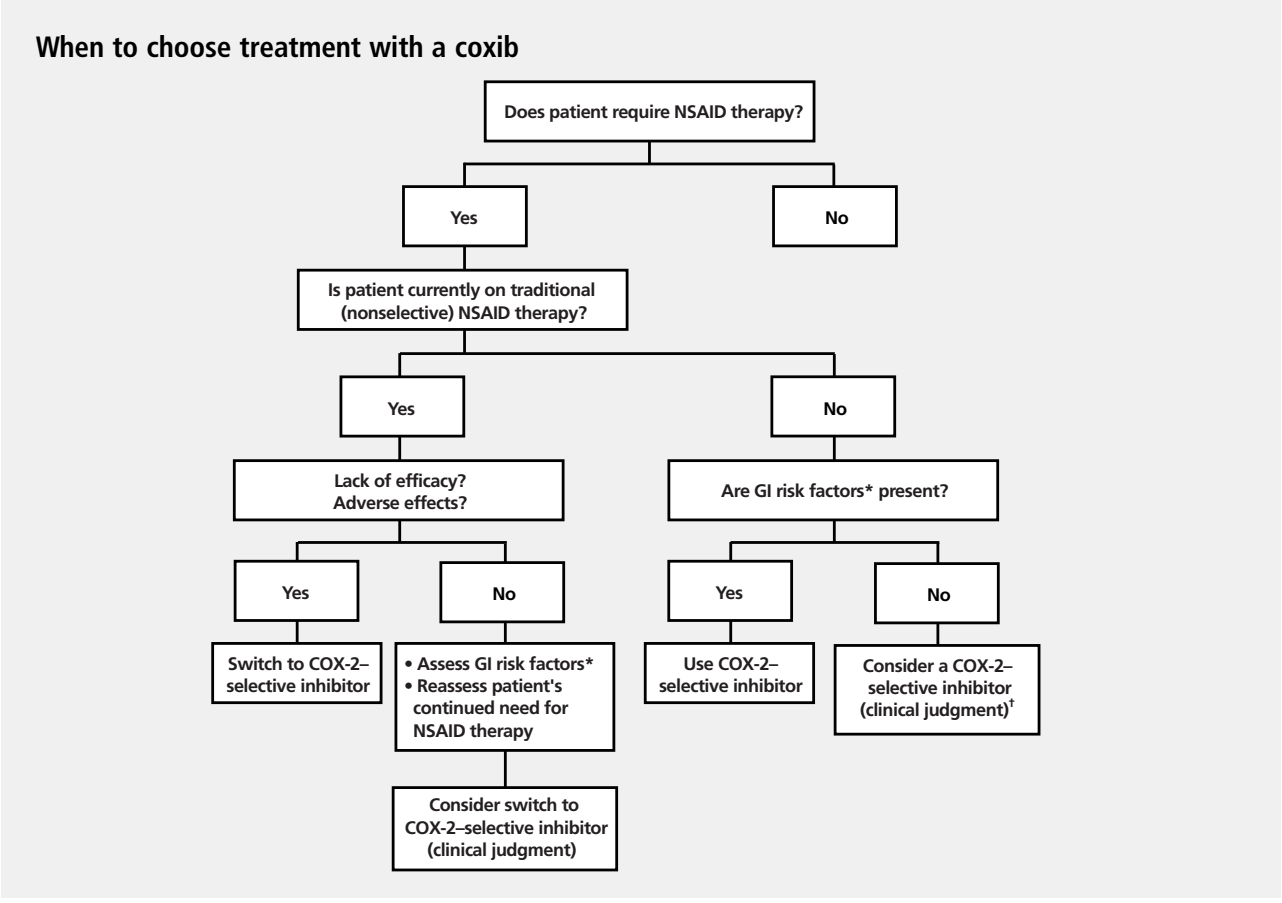


**FIGURE 1. The recommendation to "Switch to COX-2–selective inhibitor" for lack of efficacy and adverse effects of nonselective NSAIDs is based in part on numerous studies that have shown treatment with coxibs to be associated with lower rates of discontinuations, less need for GI (protective) cotherapy, less need for GI procedures, and lower risk of developing perforations, ulcers, and bleeds (PUBs). *Risk factors for serious upper GI complications from traditional NSAIDs include age above 65 years, the need for chronic high-dose NSAID therapy, history of peptic ulcer disease, and concomitant treatment with an anticoagulant or glucocorticoid agent. † Includes discussion of risks and benefits with the patient. (Reprinted from the *American Journal of Medicine*, vol. 110(3A), P.E. Lipsky, "Recommendations for the clinical use of cyclooxygenase-2–specific inhibitors," pp 3S-5S, copyright 2001, with permission from Excerpta Medica Inc.[14])**

## Rofecoxib

The efficacy of rofecoxib in the treatment of RA has been studied, and a claim for use in RA is pending. In an 8-week dose-ranging trial, 658 patients with RA were treated with rofecoxib 5 mg, 25 mg, or 50 mg once daily, or placebo. Mean improvements with rofecoxib 25 mg or 50 mg once daily were significantly superior to the responses to placebo ($P < .001$).[15]

Two phase III studies were conducted in approximately 2,000 patients with RA. In one study, participants were treated with rofecoxib 25 mg or 50 mg once daily, naproxen 500 mg twice daily, or placebo for 12 weeks.[49] In the other study, patients were treated with rofecoxib 12.5 mg or 25 mg once daily, naproxen 500 mg twice daily, or placebo for 12 weeks.[50] In all outcome measures, rofecoxib at doses of 25 and 50 mg once daily was comparable to naproxen and significantly superior to placebo ($P < .05$).

## Valdecoxib

The recent approval of valdecoxib also includes its use for the treatment of RA at a dosage of 10 mg once daily. At this dosage, a 12-week study found the efficacy of this agent superior to placebo and similar to that of naproxen (500 mg BID) but with improved GI tolerability compared with naproxen.[51]

### Etoricoxib

Etoricoxib is under investigation also for the treatment of RA. An 8-week dose-ranging study was conducted in 581 patients with RA. Patients were treated with etoricoxib 10 mg, 60 mg, 90 mg, or 120 mg once daily, or placebo. Etoricoxib 90 mg and 120 mg once daily were significantly superior to placebo in all outcome measures ($P < .05$).[52] Maximal improvement was noted with etoricoxib 90 mg once daily.

A 12-week study compared the efficacy of etoricoxib 90 mg once daily with naproxen 500 mg twice daily or placebo in patients with RA. Mean improvements in all primary and key secondary measures were significantly better with etoricoxib compared with naproxen or placebo ($P < .05$).[53]

## ■ CLINICAL GUIDELINES FOR THE USE OF COXIBS

Celecoxib and rofecoxib, the first-generation coxibs, both demonstrate efficacy in OA and RA and have been included in the updated ACR recommendations for OA management.[54] Newer entrants to the coxib class, valdecoxib, etoricoxib, and others, will provide further treatment options whose value will be assessed after additional data are available. Simple analgesics, such as acetaminophen, are still recommended as first-choice agents for pharmacologic management of patients with OA.[5] An algorithm for the use of coxibs in patients with OA and RA is shown in **Figure 1**. The guidelines recommend coxibs as an alternative to nonselective NSAIDs in patients at risk of developing GI toxicity associated with NSAID therapy.[5]

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