

RHEUMATOLOGY



OSTEOARTHRITIS

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Learning Objectives

1. Demonstrate an understanding of the pathophysiology of osteoarthritis (OA).
2. Develop an individualized treatment plan for a patient with OA.
3. Devise an appropriate drug intervention for an individual patient with OA.
4. Assess the appropriateness of using gastroprotective strategies, including the use of cyclooxygenase-2 (COX-2)-specific nonsteroidal anti-inflammatory drugs (NSAIDs), in specific OA patients.
5. Justify an appropriate intervention in a patient who develops a complication from NSAIDs or other therapies for OA.
6. Evaluate the role of alternative therapies in treating OA.
7. Choose appropriate outcome measures and monitoring parameters for assessing drug efficacy.

Introduction

Osteoarthritis (OA) is by far the most common form of arthritis, causing symptoms in about 21 million Americans (12% of the adult population). With the population aging, OA is expected to affect 40 million people by 2020. It represents a significant cause of disability, second only to chronic heart disease as the primary diagnosis leading to Social Security disability payments, and a significant burden on quality of life and use of health care resources. In the past few years, the pathophysiology of OA has become better understood, but treatment is still limited to improving

symptoms. Several innovative treatments have been developed by the pharmaceutical industry, and treatments from the “alternative” health care industry, including glucosamine and chondroitin, have become widely used in treating OA.

Unfortunately, there is still limited knowledge about how OA starts and how to stop the process. The extent of inflammation continues to be a source of argument and the role of anti-inflammatory drugs versus plain analgesics remains controversial. Clinical trials of therapeutic agents rely on assessment of analgesia and quality of life; biochemical markers of cartilage damage do not yet have general applicability, and imaging techniques for affected joints provide only a crude reflection of disease progress.

Comprehensive management includes non-pharmacological, pharmacological (Table 1-1), and surgical approaches. Many treatments can now be offered, which allows tailoring a program for individual patients. The most influential guidelines for treating OA have been the American College of Rheumatology (ACR) Treatment Guidelines for hip and knee OA. These were published in 1995 and updated in 2000. Guidelines have been published in the past few years that address the use of opiates in chronic nonmalignant pain.

Pathophysiology

Definition

Osteoarthritis has been defined as a process of cartilage degeneration characterized primarily by focal loss of

Abbreviations in this Chapter

ACR	American College of Rheumatology	MMP	Matrix metalloproteinase
AGS	American Geriatric Society	NHANES	National Health and Nutrition Examination Survey
AIMS	Arthritis Impact Measurement Scale	NSAID	Nonsteroidal anti-inflammatory drug
ASU	Avocado/soybean unsaponifiables	OA	Osteoarthritis
CLASS	Celecoxib Long-term Arthritis Safety Study	OTC	Over-the-counter
CNS	Central nervous system	PG	Prostaglandin
COX	Cyclooxygenase	PUBs	Perforations, ulcers and bleeds
ESR	Erythrocyte sedimentation rate	RA	Rheumatoid arthritis
FDA	Food and Drug Administration	SAMe	S-adenoyl-methionine
GAG	Glycosaminoglycan	SELECT	Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies
GFR	Glomerular filtration rate	TGF	Transforming growth factor
GI	Gastrointestinal	TNF	Tumor necrosis factor
HA	Hyaluronan	VAS	Visual analog scale
HAQ	Health assessment questionnaire	VIGOR	Vioxx Gastrointestinal Outcomes Research
HAD	Hospital anxiety and depression scale	WOMAC	Western Ontario and McMaster Universities
IL	Interleukin		
MELISSA	Meloxicam Large-scale International Study Safety Assessment		
MHAQ	Modified Health Assessment Questionnaire		

cartilage (as seen by loss of joint space on radiography) as well as hypertrophic bone spurs due to overgrowth of bone at the margins and subchondral areas of the joint. Like many diseases, OA has several definitions. In many epidemiological studies, OA is assessed by radiological means only because it is the easiest way to assess prevalence on a large scale. However, fewer than half of patients with radiologic criteria for OA has symptoms. Symptomatic OA means presence of almost daily pain plus presence of radiographic change in the painful joint(s).

Etiology

In the past, OA was regarded as a “wear and tear” form of arthritis, in which weight-bearing joints simply wore out or “degenerated” with advancing age. However, the disease is now viewed as an active process in which specific biochemical changes occur in joint fluid, cartilage, and subchondral bone. Some of the biochemical processes are thought to be normal reparative responses to joint insult.

Only 5% of cartilage consists of living chondrocytes. It primarily consists of water and proteoglycans (aggrecans)

Table 1-1. Overview of Drug Treatments

Name	Usual Adult Dosage	Cautions
Acetaminophen	2400–4000 mg/day in divided doses	Risk of hepatotoxicity in overdose or in chronic alcohol abusers
NSAIDs	See Table 1-1	Risk of GI bleeding, nephrotoxicity
Capsaicin	Topically over affected joint 2–4 times/day in 0.025% or 0.075% cream	Local burning sensation initially
Glucosamine	500 mg 3 times/day	Efficacy and safety not evaluated by FDA
Chondroitin	400 mg 3 times/day	Efficacy and safety not evaluated by FDA
Tramadol	200–400 mg/day in divided doses	Low risk of physical and psychological dependence
Oxycodone	10–20 mg (sustained release) 2 times/day	Low risk of physical and psychological dependence
Sodium hyaluronate	20 mg/2 ml by intra-articular injection once weekly for 5 weeks	Local reactions, pain
Hylan G-F 20	2 ml by intra-articular injection once weekly for 3 weeks	Local reactions, pain
Triamcinolone acetonide	40 mg by intra-articular injection or hexacetonide	Possible risk of damage to cartilage no more than 3 or 4 times/year

FDA = Food and Drug Administration; GI = gastrointestinal.

Adapted with permission from Partnership for Self-Care: “Management of Osteoarthritis”. Washington, D.C. American Pharmaceutical Association, 2000:1–25.

compressed in a tight collagen network. The rigid collagen fibers are embedded in the subchondral bone to provide strength and stability. Proteoglycans are complex hydrophilic macromolecules that hold water osmotically and provide compressibility to allow cartilage to absorb impact to joints. Proteoglycans are made up of a protein core with glycosaminoglycan (GAG) side chains, predominately chondroitin sulfate and keratan sulfate. Proteoglycans form aggregates with hyaluronan (HA), another GAG, and link proteins. Biochemically, OA severity correlates with the amount of loss of GAGs from cartilage.

As cartilage loses its elasticity and ability to absorb forces, changes in OA involve not only loss of cartilage matrix but changes in the synovium, subchondral bone, and the periarticular muscles and ligaments. In healthy joints, there is a complex balance between anabolic and catabolic processes. Inflammatory cytokines and their inhibitors produced by the synovial membrane play an important role in this equilibrium, and activation of cytokine cascades are involved in the etiology of OA. Inflammation has been considered to play a minor role in OA but does occur locally in varying degrees. It is unclear if synovitis plays a primary role in joint destruction or is a secondary event. Synovitis may be initiated and perpetuated by mechanical and structural abnormalities.

Synovial fluid is a plasma ultrafiltrate that is modified by the addition of a high concentration of HA, which is synthesized and secreted into joint fluid by type B cells of the synovial lining. In OA, the concentration and molecular weight of HA are reduced, which compromises the viscoelastic properties of joint fluid. Synovial histology in at least some patients may show hyperplasia and a mononuclear cell infiltrate similar to that seen in rheumatoid arthritis (RA), but the inflammation is more focal, being most pronounced where synovium is adjacent to cartilage. The local response may be initiated by cartilage breakdown products phagocytized by synoviocytes.

Among the proinflammatory cytokines, interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF- α) seem to be most active in OA. Interleukin-1 stimulates matrix metalloproteinase (MMP) activity, release of collagenase and plasminogen activator from cartilage and synovial cells, catabolism of GAGs from cartilage, and secretion of IL-6 by chondrocytes. Interleukin-1 also inhibits synthesis of collagen and GAGs and induces prostaglandin and nitric oxide synthesis. Tumor necrosis factor stimulates collagenase and prostaglandin production. Interleukin-6 stimulates synthesis of metalloproteinase inhibitor, up-regulates IL-1 receptor antagonists and enhances chondrocyte proliferation, but at the same time it increases inflammatory cells in synovial tissue and enhances some effects of IL-1.

Of the various substances implicated in cartilage degradation, a family of structurally related MMPs are believed to be the most relevant. These protein-degrading enzymes are normally secreted by chondrocytes and synoviocytes. Increased expression and synthesis of MMPs in OA joints is related to the higher levels of proinflammatory cytokines such as IL-1 and TNF- α . Specific MMPs include collagenase and stromelysin (MMP-3).

It is uncertain what initiates degradation of cartilage, but it may be mechanical stress that leads to microfractures of cartilage, increased stress on surrounding tissue and induction

of altered chondrocyte metabolism to favor proteolytic enzymes such as MMPs. Once initiated, the process becomes self-perpetuating. The increased stress on subchondral bone leads to formation of osteophytes, or spurs of new bone. These bone spurs result in the hard, bony enlargement that is a clinical characteristic of OA. An overview of the etiopathogenesis of OA is found in Figure 1-1

Classification and Risk Factors

Osteoarthritis may be classified as primary (idiopathic) or secondary. Secondary OA is most often due to joint trauma (acute or chronic) and more rarely due to systemic metabolic or endocrine disorders.

Age is an obvious risk factor for primary OA; the incidence steadily increases with age, but there are other risk factors. Osteoarthritis is more common in women, especially African-American women after menopause. Obesity is a well established risk factor, and weight-bearing joints, including the hips, knees, feet, and lumbosacral spine, are commonly affected. Occupations or hobbies that subject particular joints to excessive stress predispose those joints to OA later in life. Prolonged kneeling, squatting, and lifting are associated with knee OA, especially in heavier people. Regular sports participation is also associated with OA. Low-impact recreational activity (e.g., jogging) does not seem to cause OA, but studies of elite long distance runners and tennis players have found a 2–3-fold increase in risk of hip or knee OA. Previous injury to a joint (including ligament ruptures) is also a risk factor for secondary OA. A study indicated that quadriceps muscle weakness may precede development of knee arthritis, and hip abductors are relatively weak in those with hip OA. Genetic factors also contribute. The disease sometimes runs in families, and mutations in the type II collagen gene have been identified within families prone to early onset of disease.

The Framingham Heart Study showed that both low intake of vitamin D and low serum levels of the vitamin were associated with increased risk for progression of existing knee OA but not with incidence of new OA. In another study, low vitamin D levels were associated with an increased incidence of radiographic hip OA. Low vitamin D levels are related to inadequate bone strength leading to greater adverse impact on subchondral bone and the joint in general. There is weaker evidence that low intake of antioxidant vitamins, such as vitamin C, vitamin E, and beta-carotene, may increase progression of established knee OA. Together, these findings suggest that nutrition may be a modifiable risk factor for OA.

Incidence increases in women after menopause, suggesting that estrogen loss plays a role. Indeed the Framingham Heart Study database and other epidemiological studies have found that women who use hormone replacement treatment are at a lower risk of developing OA.

Proven preventive measures for OA are maintaining ideal body weight, preventing injury, strengthening muscles that bridge joints, and modifying job tasks to minimize repetitive loading of joints.

Clinical Characteristics

The main symptom that patients complain of is pain, especially with use of the joint. Other symptoms include joint stiffness after inactivity, limitation of movement,

variable degrees of local inflammation, and loss of function. Stiffness lasts less than 15 minutes. On examination, joints may have some localized tenderness and firm swellings at the joint margins (due to the bony hypertrophy). Unlike RA, OA may affect joints asymmetrically. Crepitus (crackling or grinding sound) during motion is common. Patients with knee involvement may complain of instability or a tendency for the knee to buckle. There are no systemic symptoms outside the joint.

Cartilage is avascular and has no nervous innervation, so pain is unlikely to be due to cartilage destruction. Pain in OA is probably due to irritation of surrounding structures outside the joint. Production of prostaglandins in these structures sensitizes local nociceptors and modulates production of other inflammatory mediators. Joint instability may lead to stretching of the joint capsule and pain.

Weight-bearing joints, including the hips, knees, feet, and lumbosacral spine, are commonly affected. However, the cervical spine, and proximal and distal interphalangeal

joints of the hands are also affected. The hands are more often affected in women. The wrists, elbows, shoulders, and ankles are seldom involved.

The amount of inflammation in OA is controversial. Certainly, there is no systemic inflammation in OA, but there may be local signs of joint inflammation (e.g., effusion, warmth, and tenderness). Synovitis can be frequently demonstrated histologically in advanced OA. The amount of joint inflammation varies among patients and at different time points.

An arthritis module in the 1996–98 Behavioral Risk Factor Surveillance System surveyed people in 11 states. The survey revealed that health-related quality of life was worse in people with arthritis regardless of gender, age, or education level. Hip and knee OA accounted for most of this disability. The correlation among pain, disability, and structural change in OA was inconsistent and varied among joints. Pain and disability correlated with each other better than with structural change.

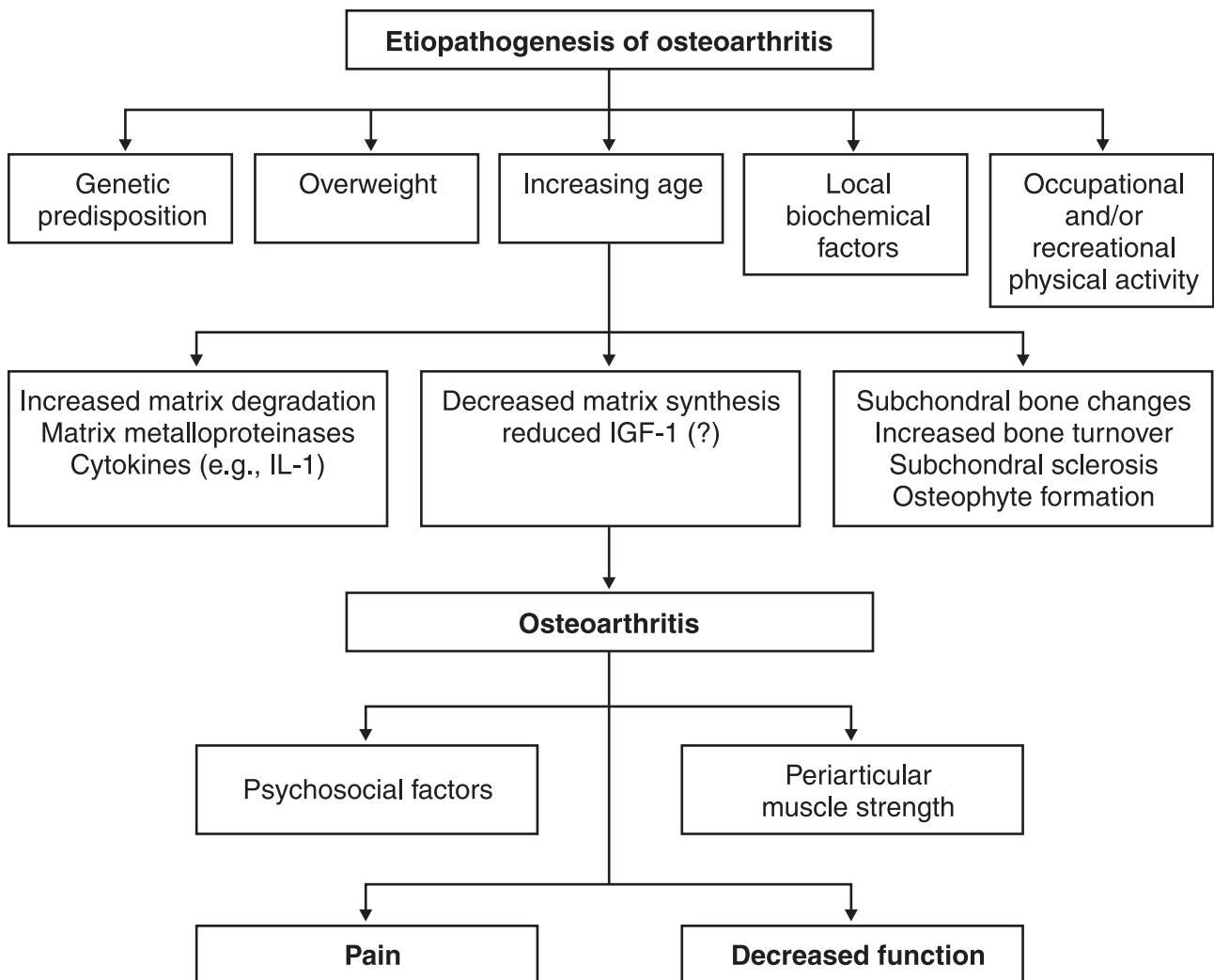


Figure 1-1. Etiopathogenesis of osteoarthritis.

OA = osteoarthritis; IL-1 = interleukin-1; IGF-1 = insulin-like growth factor.

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Diagnosis

Radiological diagnosis requires evidence of asymmetrical joint space narrowing, marginal osteophytes, subchondral bone sclerosis, or subchondral cyst formation. The first sign of OA is osteophyte formation, followed by loss of cartilage. However, fewer than 50% of subjects with radiographic OA have clinical symptoms. The clinical diagnosis of OA is suspected in patients with joint tenderness, bony nodules, joint crepitus, and limitations in movement, then confirmed by radiology. Routine laboratory tests are normal and are only helpful in ruling out related conditions.

Administrative databases are likely to be unreliable for accurately identifying patients with a diagnosis of OA. A study in a Massachusetts health maintenance organization found that among patients with an administrative diagnosis of OA only 62% were determined as having definite OA on chart review. On the other hand, 18% of those without an administrative diagnosis actually had definite OA.

Epidemiology

Estimating incidence and prevalence is difficult because OA can be defined either clinically or radiographically. Furthermore, the threshold for abnormality in radiographs has varied among studies, and radiographic screening studies usually focus on one or a few joints and not all possibly affected joints. Finally, various studies have often omitted or undersampled patients older than 75 years of age. Incidence and prevalence are strongly correlated with age.

Before age 50, men have a higher frequency of OA than women, but incidence accelerates in women after menopause. After age 50, some women develop “menopausal OA”, a rapidly progressive generalized OA.

Osteoarthritis prevalence by clinical examination was assessed in the National Health and Nutrition Examination Survey (NHANES) I in a sample of 6913 United States adults age 25–74. On the basis of these examinations, 12.1% of the population in that age group had OA.

The population-based National Health Examination Survey in 1960–62 included hand and foot radiographs. Results indicated OA was rare in people younger than 25 years of age, but by ages 65–74 almost all people had some evidence of OA in the hands and about half had evidence in the feet. The incidence of new OA defined radiographically in people older than 45 years of age is about 2% per year, whereas the incidence of symptomatic OA in the same population is about 1% per year.

Defining OA as symptoms plus radiographic change, studies in northern England found that 6.2% of adults older than 35 years of age had knee OA and 12.2% of women did. Among adults 55 years of age and older the prevalence of hip OA was 5.5% in men and 3.6% in women. In the Framingham Heart Study OA study, 9.5% of people age 63–93 had symptomatic knee OA, with a higher prevalence in women (11.4%) than men (6.8%).

Prognosis

The natural history of OA is highly variable. Most patients with radiographically mild OA have a stable course and do not progress to severe joint damage. In one study, 63 patients were followed for 11 years and more than half showed no radiological deterioration in their knees

regardless of the assessment method. Fewer than 10% of these patients required joint replacement. Symptoms also do not remain constant. In one study, 23% of patients reported an improvement in pain during a 2-year period. In placebo-controlled trials, many patients remained on placebo for prolonged periods, suggesting that nonsteroidal anti-inflammatory drugs (NSAIDs) can often be given as needed during exacerbations only.

The OA500 study was an observational study that followed 500 consecutive patients at a hospital-based rheumatology clinic in England. At the 8-year review, 17.2% reported worsening in all three subjective end points of pain severity, change in index joints, and global change, compared with 6.3% who improved in all three. Patients with knee disease had the worst outcome. Mean scores on the health assessment questionnaire (HAQ) and hospital anxiety and depression scale (HAD) were high after 8 years, especially in those with knee involvement. Forty-four percent of the 72 patients with only hand involvement at entry had acquired significant knee or hip involvement 8 years later. The disease resulted in high levels of disability, anxiety and depression, and use of health care resources, including the need for joint replacement. The authors concluded that patients with OA severe enough to require hospital referral had a heterogeneous, but generally poor, outcome 8 years later.

The factors that cause OA may not necessarily be the same that determine progression. One study found that knee pain and presence of hand involvement (Heberden’s nodes) at baseline predicted progression of knee OA. In the OA500 study, there was no strong predictor of clinical outcome but patients with knee involvement tended to have more disability.

Quality Pharmaceutical Care

Non-pharmacological Measures

Non-pharmacological interventions are generally safe, applicable to the elderly, and may give long-term as well as short-term benefits. There is evidence that anxiety, depression, and reduced muscle strength are related to pain and disability. Each of these factors is modifiable.

Lifestyle Changes and Adaptive Devices

Bed rest is not indicated in OA but patients should avoid standing, kneeling, or squatting for prolonged periods due to the load on joints. Modification of occupational and recreational activities, weight reduction, and muscle strengthening may reduce stress on joints. Weight loss through dietary change and increased exercise is recommended in patients who are overweight. Decreased weight reduces symptoms and may possibly reduce the rate of disease progression. Proper footwear, elastic knee supports, and assistive devices such as canes may also reduce the mechanical forces across the joint and are recommended by the ACR guidelines.

Exercise and Muscle Strengthening

Aerobic exercises, fitness walking, and strengthening exercises decrease pain and disability and improve physical

performance in patients with knee or hip OA. In addition, programs that include manual physical therapy procedures (e.g., passive and active range of motion exercises) can provide relief of symptoms. A systematic review of the literature found 11 published studies of exercise in OA, only two of which had both acceptable validity and sufficient power. The data support the benefit of exercise, with effect sizes for benefit being about 0.50 for improvement in pain, 0.35 for self-reported disability, and 0.30 for disability in walking. An effect size of 0.5 is generally considered moderate and a size of 0.8 is considered large. Although exercise can be recommended, further information is needed on the optimum form and duration of exercise and whether different programs are applicable based on patient criteria such as the joints involved or severity.

Medical Devices

Transcutaneous nerve stimulation has been found to be modestly effective in two clinical trials of knee OA. Both electromagnetic stimulation and pulsed electrical stimulation are efficacious in double-blind, clinical studies of knee OA.

Surgical Approaches

Focal articular cartilage defects are sometimes found in young adults and may lead to functional problems. Autologous cultured chondrocytes (Carticel) are most likely to benefit those with normal knee alignment, no ligamentous instability, and no arthritis on the opposite knee surface. Typically, these patients have normal knee radiographs. Carticel was initially approved by the Food and Drug Administration (FDA) for both primary and secondary therapy for repair of symptomatic, cartilaginous defects of the femoral condyle caused by acute or repetitive trauma. The manufacturer was unable to recruit enough patients for postmarketing studies of primary repair so the approved indication is now limited to secondary repair in patients with an inadequate response to a prior arthroscopic or other surgical repair procedure.

The procedure involves arthroscopically collected biopsy specimen of 200–300 mg of articular cartilage. The specimen is enzymatically digested and chondrocytes are cultured in the laboratory. At surgery, the focal defect is debrided, a periosteal graft from the proximal tibia is sutured to the edges of the cartilage defect, and cultured chondrocytes are injected under the periosteal graft. Long-term follow-ups have indicated sustained improvement in symptoms and function.

A different procedure may be used for small cartilage lesions no larger than 2 cm². Autogenous osteochondral grafting is a technique whereby cylinders of bone and cartilage from a lesser weight-bearing position on the distal femur are transferred into prepared tunnels on the articular surface defect of the femur. Good bonding of the graft and good clinical results were seen in early studies. Both of these procedures are used primarily in patients younger than 40 years of age and have little application to typical patients with OA.

Patients with knee OA may obtain relief with closed tidal irrigation using saline infused through a catheter. Arthroscopy and lavage to flush the joint of debris are alternatives. Patients with severe pain or disability

unresponsive to drug therapy are candidates for joint replacement surgery. Prosthetic joint replacement of the hip or knee improves quality of life and provides excellent improvement of both pain and function.

Pharmacotherapy

Acetaminophen

According to ACR guidelines, acetaminophen as needed up to 4 g/day should be the first-line pharmacological therapy for patients with mild to moderate OA, based on cost, efficacy, and safety. Adverse effects are minimal, although patients who consume alcohol regularly need to be monitored for developing liver toxicity. Long-term use of acetaminophen has been associated with renal failure but this also can occur with NSAIDs.

In a double-blinded, crossover study of 25 patients with knee OA, acetaminophen 4 g/day was preferred over placebo by 18 of the 19 patients with a treatment preference. Efficacy of acetaminophen is similar to NSAIDs for treating OA of the knee in several blinded studies. For example, one study compared acetaminophen 4 g/day, low-dose ibuprofen 1200 mg/day, or high-dose ibuprofen 2400 mg/day in 184 patients with OA of the knee and found all treatments to be equivalent in efficacy. Patients who had signs and symptoms of joint swelling were improved to a similar extent regardless of drug regimen. This implies the primary effect of each drug was analgesia.

Another study enrolled 187 patients with OA of the knee in a 2-year prospective, randomized trial comparing acetaminophen 650 mg 4 times/day with naproxen 375 mg 2 times/day. After 6 weeks, modest improvement in pain on motion and physician's global assessment was seen in both groups. Among 62 patients who completed 2 years in the study, radiographic progression in the knee was similar in each group. Withdrawal from treatment due to lack of efficacy was higher in the acetaminophen group (22% vs. 16%), but withdrawal due to adverse effects was higher in patients on naproxen (23% vs. 18%). Thus, there was little difference between drugs; however, the high 2-year withdrawal rate indicates that neither drug is completely satisfactory for most patients.

Analysis by the North of England guideline development group concluded that NSAIDs were modestly more effective than acetaminophen (better in controlling pain at rest and pain at night) but the risk of adverse gastrointestinal (GI) events was higher with NSAIDs. Pooled estimates of efficacy were statistically in favor of NSAIDs.

Capsaicin and Topical Products

Managing OA with topical agents is an attractive option for localized OA. Several NSAIDs are available in topical preparations in Europe and Canada, but none are marketed in the United States to date. A recent study found that 2% diclofenac gel was modestly effective in knee OA compared to placebo. However, the North of England guideline development group did not recommend topical NSAIDs for OA due to a lack of clinical trials comparing them with the oral route. Over-the-counter (OTC) topical salicylate-containing preparations are available, but evidence of their efficacy is also scanty.

Capsaicin is by far the best studied topical drug in OA. Capsaicin is an alkaloid that inhibits release of substance P, which transmits nociceptive stimuli from the periphery to the central nervous system. On application, capsaicin provokes release of substance P from peripheral nerves, and then prevents its reaccumulation in the terminal nerve endings. Because of this mechanism, capsaicin may induce pain or stinging with the first few applications. Analgesia will not be achieved until 2–4 weeks of continuous application. Capsaicin is not a counterirritant, although the stinging during early applications may resemble the effects of counterirritants. Cartilage does not have nerve endings, but substance P is expressed in the nerves supplying periarticular tissues.

Several trials have demonstrated efficacy of capsaicin in OA. One study demonstrated that capsaicin 0.075% decreased pain and tenderness by about 40% when applied to specific joints 4 times/day for a month. A high-strength (0.25%) formulation of capsaicin is available for 2 times/day application and provided faster and stronger pain relief than a 0.025% preparation. Patients should be warned about the need for frequent application and the local burning sensation that will occur for the first few days before significant pain relief occurs.

Nonsteroidal Anti-inflammatory Drugs

According to ACR guidelines, NSAIDs are indicated for patients with OA who do not respond to acetaminophen and topical analgesics. Nonsteroidal anti-inflammatory drugs were traditionally the drugs of choice in OA and most primary care physicians still use NSAIDs first. However, as previously discussed, randomized, comparative clinical

studies have not shown a substantial difference in response to NSAIDs compared to acetaminophen, probably because inflammation plays little role in OA.

It is possible that only patients with inflammation of the joint benefit more from NSAIDs. However, one study assessed knee swelling and tenderness in 182 patients with OA of the knee who were randomly assigned to receive acetaminophen, an analgesic dose of ibuprofen, or an anti-inflammatory dose of ibuprofen. The presence of clinical inflammation at baseline did not predict a better response to ibuprofen than to acetaminophen. Knee swelling was noted in 20% of patients but did not change substantially in any group.

All NSAIDs are effective analgesics even though they have mostly been developed and promoted primarily as anti-inflammatory drugs. There are many NSAIDs to choose from (Table 1-2), and no one agent is more effective than another in OA. Toxicities are comparable, but nonacetylated salicylates (e.g., salsalate and choline magnesium trisalicylate) have less renal toxicity and antiplatelet effects. Because intensity of OA pain varies from day to day and within a day, the use of short-acting NSAIDs as needed is a reasonable approach. The ACR guidelines also state that low doses of NSAIDs should be used before trying higher ones.

In vitro studies show that some NSAIDs (e.g., tolmetin) can promote and others (e.g., indomethacin, naproxen, and ibuprofen) inhibit cartilage breakdown by modifying proteoglycan and collagen synthesis, altering cytokine-induced cartilage resorption or by altering release of MMPs. In particular, indomethacin consistently inhibits

Table 1-2. Nonsteroidal Anti-inflammatory Drugs

Drug	OA Starting Dose	Maximum approved dose ^a	Half-life (hrs)	Generic/OTC	COX Selectivity
Aspirin	650 mg qid	1300 mg qid	3–20 ^b	yes/yes	COX-1
Celecoxib	200 mg qd	200 mg bid	12	no/no	COX-2
Choline salicylate	870 mg qid	1740 mg qid	3–20 ^b	no/yes	COX-2
Diclofenac	50 mg bid	75 mg tid	2	no/no	none
Diflunisal	250 mg bid	500 mg tid	12	yes/no	none
Etodolac	300 mg bid	400 mg tid	7	no/no	COX-2 preferential
Fenoprofen	300 mg tid	800 mg qid	3	yes/no	none
Flurbiprofen	50 mg qid	300 mg tid	6	yes/no	none
Ibuprofen	300 mg qid	800 mg qid	2	yes/yes	none
Indomethacin	25 mg bid	50 mg qid	4	yes/no	none
Ketoprofen	50 mg qid	75 mg qid	3	yes/yes	none
Meclofenamate	50 mg tid	100 mg qid	2	yes/no	none
Meloxicam	7.5 mg qd	15 mg qd	20	no/no	COX-2 preferential
Nabumetone	1 g qd	1 g bid	24	no/no	COX-2 preferential
Naproxen	250 mg bid	500 mg tid	13	yes/yes	none
Oxaprozin	600 mg qd	1800 mg qd	42	no/no	none
Piroxicam	10 mg qd	20 mg qd	45	yes/no	none
Rofecoxib	12.5 mg qd	25 mg qd	17	no/no	COX-2
Sulindac	150 mg bid	200 mg bid	18	yes/no	none
Salsalate	500 mg tid	1000 mg tid	3–20 ^b	yes/no	COX-2
Tolmetin	200 mg tid	400 mg tid	1–5 ^b	yes/no	none

^a Maximum dose is for any chronic rheumatic indication.

^b Dose-related half-life.

OA = osteoarthritis; qd = once daily; bid = twice daily; tid = three times daily; qid = four times daily; OTC = over-the-counter; COX = cyclooxygenase.

proteoglycan synthesis in human articular cartilage. Both cyclooxygenase (COX)-1 and COX-2 are synthesized by chondrocytes but it is not clear whether the findings are related to prostaglandin-mediated effects. Comparison and interpretation of these studies are difficult due to various concentrations and models used for testing the NSAID. The effect of NSAIDs on OA progression in humans is unclear. Indomethacin has been associated with accelerated joint destruction of the hip in two studies, and with faster progression of knee OA in a randomized study of 812 patients. Indomethacin probably should not be used in OA. No convincing studies have shown that other NSAIDs have a beneficial or harmful effect in human OA.

Nonsteroidal anti-inflammatory drugs have several actions, but primarily they inhibit the enzyme COX, which is the first enzyme in the pathway that converts arachidonic acid into various prostaglandins. Prostaglandins have a key role in pain and inflammation as well as many other body processes such as platelet aggregation. The nonspecific inhibition of prostaglandin synthesis throughout the body causes the range of adverse effects that are caused by NSAIDs. In 1990, it was discovered that two different forms of COX exist. The two forms are compared on Table 1-3. Cyclooxygenase-1 is always present at low levels in many organs, including platelets, the kidney, and the GI tract. Its synthesis can be up-regulated only slightly in some cells in response to hormones or growth factors. Under basal conditions, COX-2 is present only in a few loci, including the brain, reproductive tract, and kidney (Table 1-3). Cyclooxygenase-2 is induced up to 20-fold by inflammatory cytokines during tissue injury, and thus generates prostaglandins that cause pain and inflammation. Therapeutic activity of NSAIDs appears to be due to COX-2 inhibition, whereas toxicity may be primarily the result of COX-1 inhibition. Cyclooxygenase-1 appears to have no role in producing pain or inflammation, and highly selective COX-2 inhibitors have analgesic and anti-inflammatory activity equivalent to older NSAIDs.

Traditionally, NSAIDs have been grouped by arbitrary chemical categories, even though there is no evidence that such classification is useful in predicting important properties of the drugs. The advent of COX-selective NSAIDs has presented a much more clinically useful classification. Many assays have been used to describe the selectivity of NSAIDs for COX-2 versus COX-1.

Selectivity ratios are based on the concentration of drug needed for 50% inhibition of each enzyme using purified enzymes, cell culture, or animal tissues. Unfortunately, estimates of selectivity for any compound vary tremendously from one in vitro assay to the next, depending on tissue used, incubation time, and concentration of drug used; estimates also vary from one laboratory to another using the same assay (Figure 1-2). Selectivity ratios can and have been used selectively to suit the marketing purposes of drug manufacturers.

Selectivity may be somewhat better gauged from ex vivo whole blood assays in which therapeutic doses of the drug are given to patients and whole blood is drawn and tested for activity. The ability of platelets to produce thromboxane A_2 during clotting measures COX-1 activity because only COX-1 is made by platelets and prostaglandin (PG) E_2 synthesis from monocytes stimulated by lipopolysaccharide measures COX-2 activity. An International COX-2 Study Group has proposed that drugs may be called COX-2-“specific” if they have no ex vivo effect on COX-1 through the full range of potential human doses, but show significant dose-related activity versus COX-2. Drugs that show enzymatic preference for COX-2 but still inhibit COX-1 at therapeutic doses would be called COX-2 preferential. However, even the ex vivo whole blood classification needs to be verified as clinically meaningful. Other authoritative sources argue that tissue specificity can never be proven and the term “selective” is more meaningful than “specific”.

All older NSAIDs have activity against both forms of COX. Several of these drugs, including nabumetone, etodolac, and meloxicam, may be COX-2 preferential based on in vitro data. In the human whole blood assay, all three of these drugs have less than a 20-fold selectivity for COX-2. Celecoxib and rofecoxib meet the proposed criteria for being COX-2 specific.

Since the discovery of the two COX isoenzymes, it has become clear that COX-2 plays an important physiological role in many tissues. Thus, some commentators have questioned whether COX-2-selective drugs truly have a large safety advantage. For example, it is now well established that COX-2 plays an important role in the kidney and COX-2-selective drugs, contrary to early hopes, have little or no margin of safety on renal function. Cyclooxygenase-2 is expressed in the GI tract in the

Table 1-3. Comparison of COX Enzymes

	COX-1	COX-2
Production	Constitutive	Inducible, can increase 10–20 fold
Protein	602 amino acids	604 amino acids
Molecular weight	69,054 kilodaltons	69,093 kilodaltons
Chromosome	9	1
Role	Homeostatic	Response to stress or pathology
Tissue expression	Gastric mucosa Platelet activation Renal function Macrophage differentiation	Pain, fever, inflammation Tissue repair Renal function Reproduction Brain

COX = cyclooxygenase.

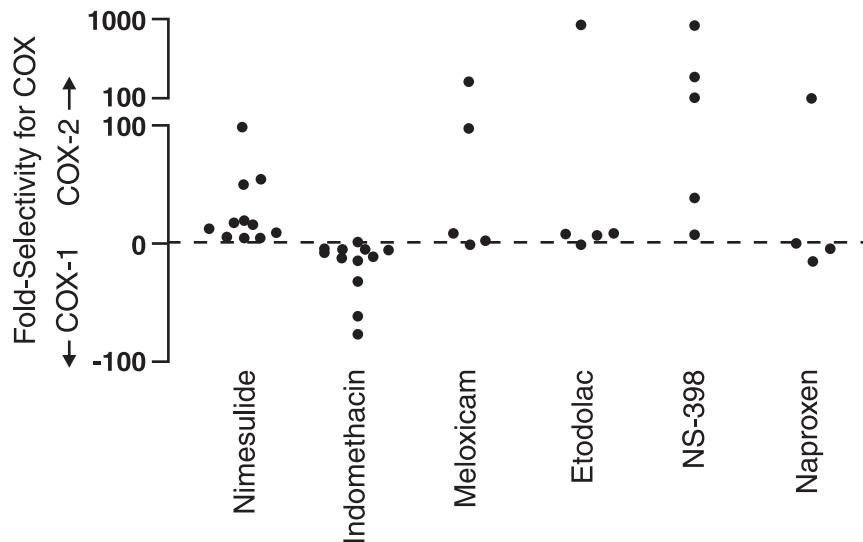


Figure 1-2. Selectivity of various compounds for COX-1 versus COX-2. Selectivity in vitro of various compounds for COX-1 versus COX-2 in a number of different studies. Each point represents the fold-selectivity for a compound from one study. Several different in vitro assays were used, although this does not entirely account for the high amount of variability. Note that for some drugs, the selectivity varies from one study to another, from indicating slight selectivity for one isoform to strong selectivity for the other. COX = cyclooxygenase. Reprinted with permission from Elsevier Science. Wallace JL. Distribution and expression of cyclo-oxygenase (COX) isoenzymes, their physiological roles, and the categorization of nonsteroidal anti-inflammatory drugs. *Am J Med* 1999;107(6A):11S-17S.

presence of mucosal inflammation. However, long-term comparative data from the Celecoxib Long-term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR) study support a lower rate of clinically important GI bleeding with selective drugs.

The potential efficacy of COX-2-selective drugs has also been questioned. In certain situations COX-1 is induced and plays a protective function or contributes to analgesic and inflammatory responses, and some in vitro studies have found that COX-1 selective compounds have anti-inflammatory activity.

Adverse Effects of NSAIDs

The greatest problems associated with NSAID use are GI bleeding and ulcers. Dyspepsia and abdominal pain are common side effects of all NSAIDs, but there is a poor relationship between symptoms and presence of serious GI complications. Bleeding from NSAID-induced ulcers often occurs without warning, so it is important to know which patients are at risk. The risk factors in Table 1-4 have appeared consistently in multiple studies. A previous history of GI bleeding is a strong risk factor. Although it is prudent to have patients avoid alcohol or smoking, few data support these as independent risk factors in NSAID users. The importance of *Helicobacter pylori* infection is controversial; some studies have found *H. pylori* to be protective, perhaps because its production of urease enzyme helps neutralize stomach acid. There is no need to eradicate *H. pylori* in patients without a previous history of peptic ulcer.

The incidence of NSAID-related upper GI complications depends on the type of outcome studied. Endoscopic studies generally find that about 20–25% of subjects who take

NSAIDs for more than 2 weeks have gastric or duodenal ulcers. The importance of these ulcers is questionable because they cause no symptoms, generally heal spontaneously on follow-up, and seldom cause complications. Nevertheless, endoscopic ulcer rate is often used as a surrogate end point in short-term studies for determining relative safety of NSAIDs. In general, GI complications follow a biological progression from asymptomatic (endoscopically diagnosed) ulcers to symptomatic ulcers to hemorrhage or perforation and the incidence of one effect will predict the incidence of others.

Table 1-4. Established Risk Factors for Developing NSAID-associated Gastroduodenal Ulcers

Age > 65 years ^a
Higher dose of NSAID, or use of more than one NSAID (including low-dose aspirin)
History of prior ulcer or upper GI bleeding
Concurrent use of corticosteroids
Concurrent use of anticoagulants
Significant comorbidity/disability, including cardiovascular disease

Based on *Am J Gastroenterology* 1998;93:2037-46, *Ann Intern Med* 1991;115:787-96, *Arthritis Rheum* 2000;43:1905-15

^a Although the increase in risk with age is probably linear, for the purpose of choosing patients for prophylaxis, an age of 65 is suggested. NSAID = nonsteroidal anti-inflammatory drug; GI = gastrointestinal. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. *Am J Gastroenterology* 1998;93:2037-46.

Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med* 1991;115:787-96. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;43:1905-15.

The FDA requires all NSAIDs manufacturers to include in their labeling a warning that a 2–4% incidence of “serious” upper GI events occur per year. These events include symptomatic ulcers or heme-positive stools that require a physician’s evaluation, and complications such as hospitalizations for hemorrhage or obstruction. The rate of GI events serious enough to require hospitalization is less than 2%. Data from the Arthritis, Rheumatism, and Aging Medical Information System, in more than 10,000 patient-years of observation, found that GI-related hospitalizations or deaths occurred at a rate of 1.3% per year. In a randomized, controlled, prospective study of NSAID-related GI complications, the annualized incidence of hospitalization or death was 1.9% in 8843 patients followed for 6 months.

A recent systematic review of upper GI complications from NSAIDs identified 15 randomized, controlled trials, three cohort studies, six case-control studies, and 20 case series. The review required studies to follow NSAID-treated patients for at least 2 months. The authors concluded the data were consistent with a biological model of progression because the ratios among various levels of harm were consistent. By comparing the rates of adverse effects in NSAID-treated patients to rates in control patients, the authors determined the following estimates for incidence of adverse effects. In randomized, controlled trials, the average risk for endoscopically diagnosed upper GI ulcers with NSAIDs was 21%; the risk for ulcers diagnosed due to symptoms was 1.48%; and the risk for a hemorrhage or perforation was 0.69%. Risk estimates for these events were lower in observational studies: 0.39% for symptomatic ulcers and 0.22% for bleeding or perforation. The risk of death from GI bleeding was low, and data from randomized, controlled trials and observational studies gave a combined risk estimate of 0.08%. About one in three symptomatic ulcers will bleed or perforate and about 12% of bleeders will die. Overall, about one in 1200 patients taking NSAIDs for at least 2 months will die.

Another analysis focused on epidemiological studies published in the 1990s. A systematic review of the literature identified 18 original case-control or cohort studies of nonaspirin NSAIDs. The pooled relative risk of upper GI bleeding or perforation after exposure to NSAIDs was 3.8. The increase in risk was consistent during treatment but returned to baseline once treatment was stopped. A clear dose-response relationship was observed. The variation in risk among NSAIDs was small when comparable daily doses were considered. Finally, advanced age, history of peptic ulcer disease, and male gender were independent risk factors for GI bleeding.

The relative risk for upper GI bleeding is fairly consistent across studies and patient groups, but patients with concurrent risk factors have the greatest absolute risk for serious NSAID-induced GI problems. Assuming a baseline rate of upper GI bleeding of one case per 1000 patient-years, patients older than 75 years of age taking NSAIDs would have an absolute incidence of about 20 per 1000 patient-years, and patients with a history of complicated ulcer may have an absolute risk of more than 30 per 1000 patient-years. Patients with multiple risks have at least additive absolute risk.

One method of protecting the stomach in high-risk patients is to use a concurrent drug that minimizes damage.

Misoprostol significantly reduces the incidence of both gastric and duodenal ulcers, and it reduces the risk of clinically serious GI bleeding by 38%. However, misoprostol adds cost to the NSAID regimen and frequently causes diarrhea or abdominal pain. Usual doses of histamine-2 receptor antagonists, such as cimetidine and ranitidine, only prevent development of duodenal ulcers, not gastric ulcers. A large, randomized study found omeprazole 20 mg/day or 40 mg/day as effective as misoprostol 800 µg/day in preventing both ulcer types, but misoprostol caused more diarrhea and abdominal pain. Diclofenac is now available with misoprostol in a single tablet. This dosage form is effective in OA and reduces risk of endoscopic ulcers by 50%.

Nonsteroidal anti-inflammatory drug therapy should be stopped in any patient who develops a serious GI complication, such as bleeding ulcer or gastric obstruction. However it is not absolutely necessary to stop the NSAID if an endoscopic ulcer is found in the context of mild to moderate abdominal pain in a patient who requires symptomatic relief from the NSAID. Healing of ulcers and resolution of symptoms can occur with appropriate antiulcer treatment. A recent study randomly assigned 350 patients with documented nonmalignant gastric ulcers of at least 5 mm in diameter to ranitidine 150 mg 2 times/day, lansoprazole 15 mg/day, or lansoprazole 30 mg/day for 8 weeks. All patients continued NSAIDs. At the end of the study, complete ulcer healing occurred in 53%, 69%, and 73% of patients, respectively. Both doses of lansoprazole were statistically better than ranitidine. Of interest, presence of concurrent *H. pylori* infection had no influence on healing rates.

Nonsteroidal anti-inflammatory drugs may affect kidney function because the kidneys synthesize PGs to help maintain blood flow when perfusion is reduced. Both COX-1 and COX-2 are found in the kidney. Problems are more common in patients who already have some intrinsic renal dysfunction or who have reduced renal blood flow (e.g., patients with congestive heart failure and the elderly). Some patients simply develop retention of sodium and water resulting in weight gain or mild leg edema. Some develop worsening of hypertension and heart failure. Occasionally, NSAIDs may cause acute renal failure. Nonsteroidal anti-inflammatory drugs can also decrease the response to antihypertensive agents, especially diuretics and angiotensin-converting enzyme inhibitors. Usually the increase in blood pressure is mild, less than 5 mm Hg.

A renal-sparing NSAID is useful in many situations. Nonacetylated salicylates (e.g., salsalate) have less effect than other NSAIDs on renal function. Sulindac is actually a prodrug, and the kidney can oxidize the active metabolite sulindac sulfide back to the parent drug and protect itself. Some clinical studies show no effect by sulindac on renal blood flow or renal prostaglandin synthesis, whereas other studies found that sulindac in usual doses affects sodium homeostasis and renal blood flow similar to comparator NSAIDs. Nabumetone may have renal-sparing effects. However, studies purporting to show renal-sparing effects with nabumetone have been flawed by inadequate sodium restriction of experimental subjects and measurement of renal indices too late after dosing.

Early in developing COX-2-selective drugs, it was hoped that these drugs would have little or no effects on kidney function. However, it was soon discovered that COX-2 is inducible in the kidney. The physiological role of COX-2 versus COX-1 in the kidney is not fully defined as there are species differences in animal models. Data from human nephrectomy specimens obtained from patients with cancer show quite a different expression of COX-2 compared to animal models.

Several studies have evaluated renal effects of COX-2-selective drugs in humans. A crossover study of 29 healthy, elderly subjects comparing celecoxib and naproxen showed that both drugs had similar effects to modestly decrease sodium excretion. Both drugs reduced urinary excretion of PGE₂ and 6-keto-PGF_{1α}. However, only naproxen caused a statistically significant reduction in glomerular filtration rate (GFR). Another study compared celecoxib 200 or 400 mg 2 times/day, naproxen 500 mg 2 times/day, or placebo administered for 7 days to 40 salt-depleted healthy men. Neither drug affected blood pressure. Both celecoxib and naproxen caused a sustained decrease in sodium excretion and urine output. Only the higher dose of celecoxib decreased GFR, but that occurred only on day 1. A separate study of 71 patients with stable chronic renal insufficiency also showed that celecoxib had the same effect as naproxen on fractional sodium excretion.

Rofecoxib was compared to indomethacin in 75 elderly subjects on a low-salt diet. After a single dose and multiple doses, both drugs caused small but statistically significant reductions in GFR. Both drugs caused small reductions in sodium excretion.

Thus, COX-2-selective NSAIDs clearly can cause sodium retention similar to older NSAIDs. Some, but not all, studies found less effect on glomerular blood flow. Cases of acute renal failure and worsening of hypertension have been reported with both celecoxib and rofecoxib. Therefore, it should be assumed that *all* NSAIDs have the potential to adversely affect renal function in at-risk patients.

With the exception of nonacetylated salicylates, older NSAIDs also interfere with platelet function. Inhibition of platelet aggregation may increase the risk of bleeding problems, including GI bleeding. Activated platelets produce thromboxane A₂ by way of COX-1, the only COX isoenzyme they contain. Because platelets are un-nucleated, they are incapable of COX-2 induction. Cyclooxygenase-2-selective drugs, by definition, should have no effect on platelets. Celecoxib did not inhibit platelet function at doses as high as 600 mg 2 times/day for 10 days. Meloxicam at 15 mg/day caused little effect on platelet aggregation compared to indomethacin. Meloxicam reduced serum thromboxane B₂ levels by 66% and caused a slight increase in bleeding time, and nabumetone 1 g/day reduced serum thromboxane levels by 70% by the third dose. Both of these drugs are COX-2 preferential.

The cardiovascular toxicity of COX-2-selective drugs has come under scrutiny. Cyclooxygenase-2 is inducible in vascular tissue to produce prostacyclin, a vasodilator and inhibitor of platelet function. By selectively inhibiting prostacyclin and not platelet-derived thromboxane, COX-2-selective drugs could shift the hemostatic balance

toward a prothrombotic state and increase the risk of thrombosis or ischemic heart disease. The risk of cardiovascular thromboembolic events was not increased in the clinical efficacy trials of celecoxib or rofecoxib. In CLASS, a 13 month, postmarketing outcomes study of 8000 patients, there was no increase in thromboembolic events in patients who took celecoxib compared to patients on ibuprofen or diclofenac. However, in the similar VIGOR study, patients who took naproxen had fewer myocardial infarctions (0.1%) than rofecoxib patients (0.4%). The latter finding could reflect a beneficial antiplatelet effect of naproxen rather than an adverse effect of rofecoxib. The results of the VIGOR study have raised safety concerns that need to be resolved in future trials.

Four cases of thrombosis developing within days of starting celecoxib in patients with connective tissue diseases have been published. Each of the four patients had evidence of ongoing inflammation as indicated by elevated erythrocyte sedimentation rate (ESR), hypocomplementemia, and/or elevated levels of anti-deoxyribonucleic acid antibodies. None of the patients were taking aspirin or adequate doses of warfarin. These cases suggest that patients with a known prothrombotic state should not receive COX-2-selective drugs without concomitant antiplatelet or anticoagulant therapy. In addition, all patients with risk factors for ischemic heart disease should receive concomitant antiplatelet therapy.

All NSAIDs can cause central nervous system (CNS) effects such as dizziness, drowsiness, or confusion. Indomethacin causes more severe CNS effects, especially headache, than other NSAIDs. Nonsteroidal anti-inflammatory drugs also cause small increases in aminotransferase activity. Serious hepatotoxicity occurs rarely; NSAIDs should be stopped if aminotransferase levels persist more than three times the upper limit. Nonsteroidal anti-inflammatory drugs should be avoided in pregnancy, especially during the last trimester, because of the importance of PGs in labor and delivery. In addition to increasing the risk of maternal and neonatal bleeding during delivery, NSAIDs may delay onset and prolong duration of labor. Cyclooxygenase-2 is involved in uterine contraction so selective drugs offer no advantage.

Clinically important drug interactions caused by NSAIDs are listed in Table 1-5. Combinations of two different NSAIDs are inappropriate because of increased toxicity with no additive effect. Absorption of NSAIDs may be delayed or somewhat decreased if given with antacids or cholestyramine.

Newly Released NSAIDs in OA

Three-dimensional x-ray crystallography has demonstrated the structure of COX enzymes and how NSAIDs work. Cyclooxygenase-1 and COX-2 are similar enzymes that consist of a long, narrow, lipophilic tunnel and a hairpin bend at the end. Although the two forms of COX are similar, COX-2 has a smaller valine amino acid substituted for an isoleucine that is present in COX-1. This leaves an opening to a “side pocket” in the COX-2 enzyme. Consequently, NSAIDs with a bulkier side group can fit into and block the COX-2 enzyme but not COX-1.

Regardless of any theoretical advantages ascribed to COX-2-selective drugs compared to nonselective, clinical

Table 1-5. Clinically Important Drug Interactions With NSAIDs

Interacting Drug	Mechanism	Outcome
Warfarin	NSAIDs may displace warfarin from protein binding, reduce platelet aggregation, induce GI bleeding	NSAIDs may increase INR and risk of bleeding
Diuretics	NSAIDs reduce natriuretic effect	Increased edema, increased blood pressure
Antihypertensives	NSAIDs may cause sodium retention	Increase blood pressure
Lithium	Reduced lithium clearance	Increased lithium effect
Methotrexate	Reduced renal elimination of methotrexate	Increased risk of methotrexate toxicity
Cyclosporine A	Reduced prostaglandin synthesis in kidney	Increased nephrotoxicity

GI = gastrointestinal; INR = international normalized ratio; NSAIDs = nonsteroidal anti-inflammatory drugs.

studies in OA clearly indicate the new drugs have therapeutic efficacy comparable to classic NSAIDs.

Because serious upper GI events are the most important adverse effect of NSAIDs, the benefit-to-risk ratio for COX-selective NSAIDs may be determined by the rate of serious GI events.

Celecoxib. Celecoxib (Celebrex) was approved in December 1998 for treating OA and RA. The dose in OA is 200 mg/day or 100 mg 2 times/day. Celecoxib is moderately long acting, with a half-life of 11 hours.

An OA dose-ranging study randomized 401 patients to receive placebo or celecoxib 25 mg 2 times/day, 100 mg 2 times/day, or 400 mg 2 times/day for 4 weeks. The investigators found that doses of 100 mg and 400 mg 2 times/day were equivalent in efficacy. Both celecoxib regimens were superior to placebo and the dose of 25 mg 2 times/day. Celecoxib was well tolerated at all doses with no side effect more common than in placebo.

A 12-week, randomized, double-blind study was conducted in 1003 patients who had a flare of knee OA. Primary end points were patient and physician global assessment, patient assessment of pain on visual analog scale, the Western Ontario and McMaster Universities (WOMAC) OA index, and American Pain Society questionnaires. A dose of 50 mg 2 times/day of celecoxib was better than placebo but not as good as naproxen 500 mg 2 times/day. However, doses of 100 mg 2 times/day or 200 mg 2 times/day of celecoxib were equivalent to each other and to naproxen in all end points. Incidence of dyspepsia and abdominal pain were low and comparable among all treatment groups. One patient on celecoxib 50 mg 2 times/day developed a symptomatic duodenal ulcer, and one patient on naproxen had melena and hematemesis from multiple ulcers.

A pooled safety analysis was conducted of 14 multicenter, double-blind North American randomized, controlled trials conducted to support the approval of celecoxib, and a separate analysis was done of one long-term open-label study of celecoxib in patients who completed the randomized, controlled trials. The randomized, controlled trials enrolled 11,008 patients with OA or RA for 2–24 weeks and principal outcome of the analyses was upper GI complications, defined as bleeding, perforation, or gastric outlet obstruction. Upper GI complications occurred at an annualized rate of 0 for placebo, 0.20% for celecoxib, and 1.68% for comparison NSAIDs (naproxen 500 mg 2 times/day, diclofenac 50 or 75 mg 2 times/day, or ibuprofen 800 mg 3 times/day). In the long-term open-label study of

5155 patients followed up to 2 years, the annualized incidence of upper GI complications on celecoxib 100–400 mg 2 times/day was 0.18%.

The above data provide strong evidence that upper GI complications will indeed be lower with celecoxib. The rates of complication with comparator NSAIDs were similar to previous studies, whereas both blinded and open-label data for celecoxib indicated about an 8-fold reduction in complications. If we assume the baseline incidence of upper GI complications with NSAIDs is 1.68%, and celecoxib reduces this rate to 0.2%, then the number of patients needed to treat with celecoxib to prevent one complication is $100/(1.68-0.20)$, or 67.

Another large GI safety study of celecoxib was CLASS. In this trial 400 mg 2 times/day of celecoxib (four times the OA dose) was compared to diclofenac 150 mg/day and ibuprofen 2400 mg/day. Despite the high dose of celecoxib, symptomatic GI event rates were lower than the two other NSAIDs (2.08% vs. 3.54%/year; $p=0.02$). The annualized rate of GI complications for celecoxib was also lower but not statistically significant (0.76% vs. 1.45%/year; $p=0.09$). However, symptomatic event rates and complication rates were similar between drugs among the subgroup of patients who concurrently used low-dose aspirin. The CLASS event rates may not be directly applicable in practice because higher than normal doses of celecoxib were used.

In a separate analysis of five premarketing randomized, controlled trials, the incidence of GI upset with celecoxib was contrasted to that with naproxen. Looking at a composite end point of moderate to severe abdominal pain, dyspepsia or nausea, the 12-week incidence with naproxen was 12% and placebo was 8.5%. The incidence for celecoxib was about 8% regardless of dose (50 mg–400 mg 2 times/day). Predictors of GI intolerance with celecoxib included prior NSAID intolerance or concurrent low-dose aspirin use.

Rofecoxib. Rofecoxib (Vioxx) was approved by the FDA in May 1999 for OA, acute pain in adults, and menstrual pain. The recommended dose for OA is 12.5 mg/day, increasing to 25 mg/day if necessary. Its half-life is about 17 hours.

Rofecoxib 12.5 or 25 mg 1 time/day was compared to ibuprofen 800 mg 3 times/day and placebo in a randomized, double-blind trial of 809 adults with knee or hip OA. Clinical efficacy and safety were monitored for 6 weeks. Primary end points were pain walking on a flat surface (a WOMAC index), patient global response to therapy, and investigator global assessment. Both rofecoxib doses and

ibuprofen were significantly better than placebo on all primary end points, and each dose of rofecoxib had efficacy comparable to ibuprofen. Each treatment was well tolerated, with no significant differences between them.

Another double-blind, randomized study in 784 patients compared 12.5 or 25 mg of rofecoxib 1 time/day to 50 mg of diclofenac 3 times/day for 1 year. Patients had either hip or knee OA and the end points were the same as those in the above study. Again, both doses of rofecoxib were virtually indistinguishable from each other and from diclofenac. Finally, rofecoxib had similar clinical efficacy to ibuprofen based on these same end points in a 6-week trial in 736 patients, and to nabumetone in a 6-week study of 341 patients.

The GI safety of rofecoxib has been assessed in separate studies. A randomized, double-blind study of 775 patients with OA compared 25 and 50 mg of rofecoxib 1 time/day, ibuprofen 800 mg 3 times/day, and placebo. Gastrointestinal ulceration was assessed by endoscopy at 6, 12, and 24 weeks of treatment. At 12 weeks, the cumulative incidences of gastroduodenal ulcers of 3 mm diameter or more were 7.34% with placebo, 4.69% with 25 mg rofecoxib, 8.07% with 50 mg rofecoxib, and 28.47% with ibuprofen. Placebo was discontinued at 12 weeks per protocol but at 24 weeks the cumulative incidence of ulcers was 46.36% for ibuprofen versus 9.74% and 13.53% for the two doses of rofecoxib, respectively. Rofecoxib patients also experienced lower rates of dyspepsia, and GI bleeding was not seen in any group.

The cumulative results from all premarketing studies of rofecoxib allowed estimates of the incidence of adverse upper GI events. The analysis combined eight double-blind, randomized studies lasting up to 12 months that compared rofecoxib in doses of 12.5–50 mg/day, ibuprofen 800 mg 3 times/day, diclofenac 50 mg 3 times/day, or nabumetone 1500 mg/day. Among 5435 patients, the 12-month cumulative incidence of upper GI perforations, symptomatic ulcers, or upper GI bleeding (perforations, ulcers, and bleeds [PUBs]) was 1.3% with rofecoxib versus a combined incidence of 1.8% with comparator NSAIDs ($p=0.046$), and the rate per 100 patient-years was 1.33 with rofecoxib compared to 2.60 with other NSAIDs ($p=0.06$). The cumulative rate of dyspepsia in the studies was 23.5% for rofecoxib versus 25.5% for comparators in the first 6 months, although one-third fewer rofecoxib patients had to discontinue therapy due to dyspeptic symptoms.

Although the rate of PUBs was lower with rofecoxib, it was not dramatically so, which is a contrast to the comparable analyses with celecoxib. However, the rofecoxib analysis may have been biased against rofecoxib. Because patients who had asymptomatic ulcers at endoscopy were regularly eliminated from the studies, the reported data probably underestimate the incidence of PUBs for patients in a usual setting, and because asymptomatic ulcers were higher with the comparator NSAIDs, the underestimation is greater for that group. In addition, the rate of PUBs was surprisingly high for placebo (cumulative incidence of 0.9% at 4 months).

The VIGOR study was a randomized, double-blind safety study in 8076 RA patients. Analogous to CLASS for celecoxib, its goal was to compare the rate of GI complications in patients taking 50 mg/day of rofecoxib

with those taking naproxen 500 mg 2 times/day for a median of 9 months. Patients in VIGOR were not allowed to use aspirin. The incidence of all upper GI events was lower for rofecoxib than for naproxen (annual rate of 2.1% vs. 4.5%; $p<0.001$), as was the rate of PUBs (annual rate of 0.6% vs. 1.4%; $p=0.005$). Rofecoxib patients also required statistically significantly fewer gastroprotective agents, GI procedures, and GI hospitalizations.

This large GI safety study served as the basis for a controversial FDA advisory committee meeting in February 2001. The panel felt that rofecoxib should receive revised labeling to reflect a significantly lower risk of GI events. The panel had reservations about giving the same labeling change to celecoxib, however, because the difference in rates of complicated GI events between celecoxib and its comparators was not statistically significant in the CLASS. Unfortunately, a direct comparison between the VIGOR study and CLASS is impossible because CLASS allowed concurrent use of aspirin.

Meloxicam. Meloxicam (Mobic), approved in April 2000 for treating OA, is chemically related to piroxicam but appears to inhibit COX-2 more than COX-1. It is less selective than celecoxib or rofecoxib. It has a half-life of 20 hours. Although new to the United States market it has been used in 50 other countries for several years.

Meloxicam has been studied extensively for OA. Meloxicam 7.5 or 15 mg 1 time/day was better than placebo in a study of 464 patients with knee or hip OA. Two large trials compared the efficacy and safety of meloxicam with other drugs. The Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) was a double-blind, randomized trial of 8656 patients with OA of the hip, knee, hand, or spine that compared meloxicam 7.5 mg/day with piroxicam 20 mg/day for 28 days. At the end of the trial period there was no significant difference in pain or other efficacy measures between drugs. Meloxicam caused a statistically significantly lower rate of dyspepsia, nausea, diarrhea, and abdominal pain (10% vs. 15%). Symptomatic ulcers, GI bleeds, or perforations occurred in seven meloxicam patients versus 16 piroxicam patients, but that difference was not statistically significant.

The Meloxicam Large-scale International Study Safety Assessment (MELISSA) of 9323 patients with hip of knee OA compared meloxicam 7.5 mg/day to sustained-release diclofenac 100 mg/day. At 28 days both groups of patients had relief of pain at rest or on movement. The differences in efficacy favored diclofenac but were not statistically significant. More patients stopped taking meloxicam than diclofenac (80 vs. 49) due to lack of efficacy. The rate of minor GI events such as dyspepsia was lower with meloxicam (13% vs. 19%) but there was not a statistical difference in PUBs (five with meloxicam vs. seven with diclofenac).

A meta-analysis of studies that measured PUBs, which was heavily influenced by the above large trials (particularly the piroxicam comparison), concluded that meloxicam was statistically less likely to cause PUBs than other NSAIDs (odds ratio 0.52). No large scale studies comparing the endoscopic safety of meloxicam to other NSAIDs have been published, but two smaller studies found a lower rate of endoscopically documented ulcers with meloxicam than piroxicam.

Viscosupplementation: Hyaluronic Acid Derivatives

Hyaluronan (hyaluronic acid) is a large GAG present in all mammalian connective tissue. It is composed of repeating units of glucuronic acid and *N*-acetylglucosamine. High-molecular weight HA molecules in solution form an extensive network that gives synovial fluid its viscoelastic properties. Joint fluid acts as a viscous lubricant at rest or during gentle movement of a joint, and as an elastic solid shock absorber at high shear rates. Hyaluronan has a variety of effects on cells *in vitro* that could modify joint disease. For example, it can inhibit prostaglandin synthesis induced by IL-1, decrease leukocyte activity, and suppress cartilage matrix degradation.

In OA, the concentration and molecular weight of HA are reduced, which compromises the viscoelastic properties of joint fluid. Thus, injection of exogenous HA into the joint may restore some of the normal protective properties of endogenous HA and has been reported to transiently increase the quantity and molecular weight of HA synthesized by the synovium. However, there is no evidence that joint damage in OA is caused by any change in synovial fluid properties.

Normally, HA constantly flows through the joint with a half-life of only 12–24 hours in animals. Therefore, it is surprising that the therapeutic effects of HA last several months. It has been suggested that HA acts as a chemical sponge to bind or entangle debris in the joint and assist with its clearance. However, experiments do not confirm that HA promotes clearance of exogenous molecules or augments fluid flow through the joint.

Technically, available HA products are classified as medical devices because of their purported mechanism as lubricating agents. Sodium hyaluronate is administered in a series of five joint injections. Hylan G-F 20, a longer lasting polymer of HA, is administered in these injections.

Clinical trials in OA of the knee have demonstrated that the products relieve pain and improve function better than placebo for several months. Good responses typically have occurred in 75% or more of studied patients, and benefits have lasted an average of 8 months in clinical practice. However, joint aspiration alone improves pain in patients with knee OA, and in some clinical trials the investigators were not blinded to treatment group. The benefits are comparable to relief from NSAIDs, but the differences between HA and placebo have not been large. The best responses have occurred in patients with milder changes on radiographs. Compared with intra-articular steroids, HA injections have less dramatic but longer lasting effects. Two studies have found intra-articular HA to be superior to intra-articular methylprednisolone, and one study found hylan G-F 20 to be better than lower molecular weight HA. There is inadequate evidence that HA has an effect on disease progression; in fact, forceplate studies in animals suggest that overloading of the joint that leads to increased damage could occur after HA injections. Trials of HA as a disease-modifier are in progress.

Hyaluronan preparations appear to be quite safe, with local reactions at the injection site (e.g., pain and swelling) generally mild and transient. Local flares may be more common with hylan G-F 20, the higher molecular weight preparation. The precise indications for

viscosupplementation are still unclear, although the best candidates would include patients with residual knee symptoms despite pharmacological therapy, poor compliers with oral drugs, patients at risk for GI complications from NSAIDs, patients who needed glucocorticoid injections, and patients with early, milder OA who fail acetaminophen therapy. Courses of treatment can be repeated about every 6 months for several years if effective, although limited data are available on the effectiveness of multiple courses.

Glucocorticoid Injections

Glucocorticoid injections are a fairly safe adjunct to managing OA but their efficacy is established primarily for OA of the knees (data for other joints are limited). Because inflammation plays a small role in the disease, efficacy in knee OA is greatest in joints with an effusion. Injections relieve pain and may increase quadriceps strength. Different steroid products have been used, including triamcinolone hexacetonide, methylprednisolone, and prednisolone acetate, but the choice makes little difference. Determination of glucocorticoid efficacy is confounded by a strong placebo effect seen in all studies. Duration of improvement is quite variable. Superiority to placebo (saline injection) is limited to 1–3 weeks, but the placebo response to injection may persist for several weeks. Not surprisingly, the experience of many rheumatologists is that injections may provide a significant and sustained response.

The long-term role of glucocorticoid injections is unclear pending further well-done studies, and better elucidation of their mechanism of action in OA. In general, steroid injections should not be used in a given joint more than 3–4 times in a given year due to concern about progressive cartilage damage and joint destruction. However, this concern is not well supported by published human data, and some animal work found glucocorticoids to reduce cartilage degeneration and osteophyte formation. Of interest, glucocorticoids can reduce production of HA by synovial cells.

Joints should be aseptically aspirated for synovial fluid first and then injected. Occasionally, patients may have a short-lived flare of synovitis due to the crystalline suspensions.

The ACR guidelines recommend glucocorticoid injections as a treatment of knee OA if effusion is present, either as monotherapy or for patients with moderate to severe knee OA not responding to acetaminophen or NSAIDs. Use in the hip is problematic due to limited data on efficacy and the difficulty to accurately administer the injection into the joint. The benefit of steroid injections is temporary. Patients who need frequent injections should be considered candidates for other treatments such as HA, joint lavage, or surgical intervention.

Opioids and Tramadol

The updated ACR guidelines suggest tramadol, propoxyphene, codeine, or oxycodone as appropriate for long-term use in patients with moderate to severe pain who have poor response or contraindications to other oral therapy. The guidelines suggest tramadol be used first due to its lower risk for abuse. Opioids work primarily in the CNS to reduce the perception of pain, are additive to NSAIDs in analgesia, and have no ceiling effect. However,

in practice, physicians are often reluctant to prescribe chronic opioids due to the potential for inducing physical and psychological dependence.

Oxycodone, alone in controlled-release form or with acetaminophen, has been demonstrated to be better than placebo in OA pain. Controlled-release codeine was also significantly better than placebo on measures of pain and sleep quality in a 4-week study, and tramadol 200 mg/day allowed a reduction in naproxen dose in an 8-week study of patients with OA. Another important study randomized 130 patients with OA who have moderate to severe pain to double-blind treatment with placebo or either 10 or 20 mg of controlled-release oxycodone every 12 hours for 14 days. The 40 mg/day dose was superior to both placebo and the 20 mg/day dose in measures of pain, sleep, mood, and enjoyment of life. In 106 patients who continued in an open-label extension trial for up to 18 months, the dose of controlled-release oxycodone leveled off at an average of 40 mg/day by week 16 and analgesia remained constant, indicating that tachyphylaxis did not occur. The most common adverse effects were nausea, pruritus, somnolence, and constipation.

In 1997, the American Academy of Pain Management and the American Pain Society published a joint consensus statement that encouraged a more liberal role of opioids in chronic nonmalignant pain. The American Geriatric Society (AGS) guidelines for chronic nonmalignant pain, published in 1998, also address the underuse of opioids to treat chronic pain, emphasizing that the comfort and well-being of the patient is the guiding force in chronic pain management. The guidelines emphasize that fear of tolerance or addiction for patients with physiological pain is grossly exaggerated and leads to undertreatment of pain.

A decision to prescribe these drugs for regular use should be based on the severity of pain, lack of effect of first-line drugs, and a clear understanding by the patient of guidelines for dosage titration. Opioids should be prescribed in controlled-release dosage forms that do not contain other analgesics so that dosage titration can be simplified. At the same time, the clinician should be sure that a short-acting analgesic is available for breakthrough pain. With careful supervision by a physician and pharmacist as part of a comprehensive pain management program, judicious use of opioids is a reasonable option for pain not relieved by any other manner. Individual dosage titration and appropriate management of side effects are important components of therapy. Because regular follow-up of such patients is essential, opportunities for pharmacist-managed chronic pain clinics should exist. The goal of opioid therapy should be to maintain or improve patient function and quality of life.

Glucosamine and Chondroitin

Glucosamine and chondroitin have become highly popular “nutritional supplements” for OA. Glucosamine is a hexosamine sugar used as a building block for all glycoproteins, including GAGs. Chondrocytes can synthesize glucosamine from glucose and glutamine, which is then combined with glucuronic acid to produce GAGs. Glucosamine is available in two salt forms; the hydrochloride provides more glucosamine by weight than

the sulfate. It is not clear that the salt form has any influence on efficacy.

Chondroitin is the most abundant GAG in human articular cartilage. It is large with a molecular weight, ranging from 5000 to 50,000 Daltons. Absorption is not high but the lower molecular weight chains are adequately absorbed. Some studies administered chondroitin intramuscularly but most used the oral route. Although chemically similar to heparin, chondroitin does not affect clotting times. It is believed to work by competitively inhibiting degradative enzymes in articular cartilage.

Both compounds have anti-inflammatory activity and can favorably affect cartilage metabolism in vitro. The rationale for their use was based on animal and in vitro studies in the 1980s that suggested they could slow cartilage breakdown. A key issue is whether glucosamine stimulates cartilage to rebuild, as is commonly claimed, or merely serves as a substrate to stimulate GAG synthesis in vitro. A more likely explanation for any structure-modifying effects is slowing of proteoglycan destruction by inhibition of IL-mediated actions. Several double-blind, randomized, controlled trials found glucosamine to be better than placebo and comparable to NSAID therapy, although the full efficacy of glucosamine is not seen until about 4 weeks.

A meta-analysis of chondroitin alone included 16 publications, of which seven were randomized, controlled trials. Each study was fairly small and had methodological problems. One confounding factor in all was the allowed use of analgesics or NSAIDs concurrently. However, all studies reported positive results; chondroitin was superior to placebo in pain and Lequesne index variables.

Another well-done meta-analysis evaluated the efficacy of both glucosamine and chondroitin in symptomatic management of knee and/or hip OA. This analysis included 15 placebo-controlled, double-blind, randomized, controlled trials of 4 weeks or longer duration. The analysis calculated effect sizes (mean difference between treatment and placebo divided by standard deviation for the outcome in the control group) for each treatment for pain and for functional outcomes. The aggregate effect size was 0.44 (95% confidence interval = 0.24–0.64) for glucosamine and 0.78 (95% confidence interval = 0.60–0.95) for chondroitin. An effect size of 0.5 is generally considered moderate and a size of 0.8 is considered large. However, effect sizes decreased when better designed trials were considered. Thus, the conclusion was that both are effective therapies, but the true benefit is likely to be less than in the published trials due to their methodological problems. Most studies had inadequate blinding and absence of intention-to-treat analyses, both of which exaggerate estimates of treatment efficacy. In addition, there was evidence of publication bias favoring publication of positive trials for the supplements. However, most studies of mainline pharmacological treatments in OA have similar limitations.

Additional studies have been published since the meta-analysis. A 2-month study of glucosamine was conducted in 98 veterans without any financial support from supplement manufacturers. Patients were randomly assigned to glucosamine 500 mg 3 times/day or placebo and assessed for pain at rest and during walking. This well-done

study found no difference between glucosamine and placebo. However, the patients tended to have more advanced OA than patients in other studies, which may have limited the opportunity for response.

A French study compared 1 g/day of oral chondroitin sulfate to placebo in a 3-month, double-blind, randomized study in 130 patients with knee OA. Patients who received chondroitin improved more on the Lequesne functional index and pain scales than did placebo patients. The difference was statistically significant on analysis of completers but not in the intention-to-treat analysis.

Recently published evidence suggests that both compounds may reduce radiological progression of OA. Pilot studies found that chondroitin may stabilize radiological progression of OA of the hand and knee. A double-blind study randomized 212 patients with knee OA to 1500 mg/day of glucosamine or placebo for 3 years. The patients taking glucosamine had no joint space narrowing throughout a 3-year period, whereas placebo patients lost about 0.1 mm/year. Thirty percent of placebo patients versus 15% of glucosamine patients had a large loss (greater than 0.5 mm) of joint space throughout 3 years. Osteoarthritis symptoms were assessed with the WOMAC index and scores improved by 20–25% in the glucosamine group while worsening slightly in the placebo patients. Of interest, there was correlation between joint space deterioration and relief of symptoms. No adverse effect was more common with glucosamine than placebo. This well-done study provides evidence for a sustained symptomatic benefit by glucosamine as well as the first evidence for a structure-modifying effect.

Glucosamine appears to be quite safe. Adverse effects occur with a frequency similar to placebo and include abdominal pain, loose stools, nausea, and dizziness. One concern is that glucosamine increases insulin resistance in experimental animals, although no change in glucose homeostasis was seen in the above 3-year glucosamine study. Patients with diabetes should be warned to observe for any effect on glucose control. Glucosamine should be avoided in patients with an allergy to shellfish because it is manufactured by hydrolysis of chitin. Chondroitin is also well tolerated, with GI effects being the predominant complaints. Theoretically, it could prolong clotting times through a heparin-like effect, but this has never been reported clinically.

The definitive study of these nutritional supplements is the Glucosamine/Chondroitin Arthritis Intervention Trial, a National Institutes of Health-sponsored 24-week, parallel group, double-blind, randomized, controlled trial with 1600 patients, comparing placebo, 500 mg glucosamine sulfate 3 times/day, 400 mg chondroitin 3 times/day, the combination, and celecoxib. Results should be available in 2003. Until that time, the long-term benefits and safety of these supplements seem adequately established to include them in the therapeutic armamentarium. One caveat is how much the purity and content of the products affects safety and efficacy. Independent laboratory tests have found highly variable content in brand name products and sometimes excessive levels of manganese.

The 2000 update to ACR OA guidelines made no recommendation regarding these products. However, in a

recent press release, the ACR has stated it is “not unreasonable” for physicians to concur in the use of the products after discussion with patients. Appropriate doses are 1500 mg/day of glucosamine and 1200 mg/day of chondroitin. If symptomatic benefits occur for patients, they should be evident within 2 months. Many patients are likely to take these supplements without any medical advice or regardless of advice. However, pharmacists can have an important role in counseling patients about the realistic benefits and risks of using them in conjunction with an overall treatment program. Pharmacists should also be sure that patients are self-treating OA and not another form of arthritis.

Potential Chondroprotective and Structure-modifying Drugs

The ultimate goal of OA therapy is to find a drug that alters the natural history of the disease to retard cartilage loss, and perhaps heal damaged cartilage. Chondroprotection may be achieved by inhibiting the rate of cartilage degradation or stimulating chondrocytes and matrix synthesis. An alternative term is “structure-modifying drugs” in recognition that OA affects the entire joint, not just cartilage. No drug at the present time is generally recognized as a structure-modifying drug for OA. However, several agents besides glucosamine and chondroitin have been touted as potentially disease-modifying.

A limiting problem with research in this area is the lack of reliable techniques to demonstrate structure-modifying effects. Presently, neither routine imaging technology nor biochemical markers are valid and reliable enough to easily demonstrate such effects. A disease-modifying effect in humans might be presumed if a drug can slow the rate at which joint space is lost compared to a concurrent control group. However, plain radiography is difficult to standardize, and changes occur gradually in most patients so that several years of observation are necessary. Magnetic resonance imaging is probably the most promising technique to assess the entire joint, but it is expensive and requires more experience to establish reproducibility. In assessing research results, one should keep in mind the poor correlation between radiographic change and symptoms.

The focus of current research is on drugs that inhibit MMPs. A problem with nonspecific inhibitors of MMPs, particularly collagenase, is their potential adverse effects on connective tissue outside the joint. Ideal drugs would selectively inhibit MMPs that are more highly expressed in cartilage.

Tetracycline and its derivatives have significant inhibitor effects on MMPs, possibly related to their ability to chelate calcium and zinc ions. Several *in vitro* studies have demonstrated that tetracycline inhibits collagenase and gelatinases. Animal studies have found that tetracyclines reduce OA severity. A clinical trial in men with knee OA is currently under way.

An investigational inhibitor of MMP-3, named BAY 12-9566, was discovered to selectively inhibit MMP-3 *in vitro* and *in vivo*. It can be administered 1 time/day without regard to food. To date, it has been tested in more than 300 OA patients for up to 3 months with good tolerability. Long-term (longer than 1 year) efficacy studies are under way.

Various exogenous GAGs have been used in animal studies. Some are available in other countries and/or are available in the United States for animal use. Pentosan polysulfate Na (Cartrophen) is a semisynthetic polysaccharide ester related to heparin that inhibits MMPs. Polysulfated GAG (Arteparon) is a heparinoid derived from trachea and lungs of cattle. It may inhibit MMPs and/or stimulate formation of new proteoglycans. Finally, GAG peptide complex (Rumalon) is made from an aqueous extract of bovine cartilage and bone marrow. It is given to patients in a series of intramuscular injections 2 times/week for 5–6 weeks, with the course repeated every 6 months. The mechanism of action of Rumalon may be through an immunostimulatory effect on helper T cells and in vitro and animal studies suggest evidence of a chondroprotective effect. It is licensed for use in some European countries. However, it has caused anaphylactic reactions, and adequate clinical randomized, controlled trial have not been done in human subjects to allow approval in the United States.

Diacerein is an anthraquinone derivative that inhibits synthesis of IL-1 β and MMPs in human cartilage in vitro. It has no inhibitory effect on prostaglandin synthesis. In placebo-controlled human studies, it demonstrated a slow onset of action starting 4–6 weeks after initiation of therapy, and a carryover effect up to 30 days after discontinuation. In a double-blind, randomized trial in hip OA, diacerein was as effective as tenoxicam, and the combination of the two was superior to the individual drugs. It was also as effective as naproxen in hip and knee OA in a 2-month study. Clinical studies are being conducted to test the structure-modifying properties of diacerein.

Cartilage Growth Factors and Cytokines

Many natural growth factors, including human growth hormone, fibroblast growth factors, insulin-like growth factors, hepatocyte growth factor, and transforming growth factor (TFG)- β , increase chondrocyte metabolism and stimulate proteoglycan synthesis. Local treatment with one of these factors could lead to restoration of a normal articular surface, especially in joints with limited damage. A specific growth factor studied in animal models is TGF- β , (cartilage growth factor). In rabbits with experimentally induced cartilage defects, TGF increased cellularity and cartilage repair. Unfortunately, growth factors have many pharmacological effects, and TGF- β can also stimulate joint inflammation and osteophyte formation. More research is needed to determine if these factors provide cartilage of normal mechanical integrity consistently in humans, especially older subjects.

Other Alternative and Complementary Therapies

Many therapies are touted in health food stores and on the Internet. Few are adequately tested in clinical studies. Claims of “clinically proven” for these therapies usually refer to testimonials rather than randomized studies.

S-adenoyl-methionine (SAMe) is a physiologic compound related to methionine that takes part in several biochemical reactions, including transmethylation, transsulfuration and aminopropylation reactions. It claims to improve joint mobility and relieve pain by boosting levels of adenosine triphosphate and supporting cartilage

production. It has also been reported to be an effective antidepressant and to have a gastric cytoprotective effect in animals.

In a 24-month, open-label study of 97 patients with OA of the hip, knee, or spine, SAMe 600 mg/day for 2 weeks followed by 400 mg/day reduced morning stiffness, pain at rest, and pain on movement. S-adenoyl-methionine was compared to NSAIDs in several large double-blind studies done in Europe in the 1980s. The comparative studies found 1200 mg/day to be similar in efficacy to naproxen 750 mg/day, piroxicam 20 mg/day, indomethacin 150 mg/day, and ibuprofen 1200 mg/day. The most commonly reported side effect is nausea.

Avocado/soybean unsaponifiables (ASU) are made of the unsaponifiable oil extracts of avocado and soybean in a one-third/two-thirds ratio, respectively. The product has in vitro inhibitor properties on the inflammatory cytokines IL-1, IL-6, IL-8, and on MMP. It stimulates in vitro collagen synthesis by articular chondrocytes in culture. The clinical efficacy of ASU has been demonstrated in two double-blind, placebo-controlled studies for treating knee and hip OA. In these studies, 300 mg/day of ASU was statistically superior to placebo for the outcomes of consumption of NSAIDs, pain visual analog scale (VAS), and Lequesne functional index, and patient satisfaction scale.

Ginger extract has been studied in one double-blind, three-way, crossover trial. Ginger extract was better than placebo and inferior to ibuprofen in the first period before crossover, but no significant difference was found between ginger and placebo for the study as a whole. No adverse effects of ginger were reported.

Devil’s Claw, a south African plant, is a folklore remedy for arthritis. Only one double-blind study of Devil’s Claw has been done. It found the herb to be better than placebo at relieving pain in patients with a variety of rheumatic complaints. Another study found Devil’s Claw to be as effective as diacerein at relieving pain. The herb may cause or aggravate peptic ulcers.

Only one study has been published of a homeopathic remedy for OA, that being *Rhus toxicum*. This poorly designed study with only 36 subjects reported no difference between the homeopathic drug and placebo.

Treatment Plan

Therapeutic Goals

The objectives in managing OA are to reduce symptoms, minimize functional disability, and maintain independence and quality of life. Inhibiting progression of the disease is a desirable goal that is not possible currently but may be feasible in the future. Treatment must be based on symptoms, not on radiological severity, and without inducing adverse effects. Therefore, the foundation of treatment is non-pharmacological therapy, supplemented by the lowest dose of analgesic drug that controls pain. Treatment must be individualized based on the degree and extent of symptoms and age and comorbidity of the patient. Usually, treatment outcomes can be assessed within 1 month of starting treatment.

The most influential guidelines in OA, the ACR treatment guidelines for hip and knee OA, were published in 1995 and updated in 2000. A complete revision of the ACR guidelines for OA is due to be published in late 2001. The North of England NSAID evidence-based guidelines focus on the use of NSAIDs and acetaminophen in OA. Other guidelines of relevance are the 1998 AGS chronic pain in the elderly guidelines and the European League Against Rheumatism recommendations for knee OA. The American

Pain Society will also publish guidelines on treating OA and RA pain by late 2001. A modified ACR algorithm for the knee is provided in Figure 1-3. The algorithm for the hip is similar except that use of capsaicin or intra-articular drugs are not options.

Considering the toxicities of NSAIDs in the elderly, there is no reason to use them before plain analgesics if inflammation is not a part of OA. Some patients obtain excellent pain relief with acetaminophen. Other patients will

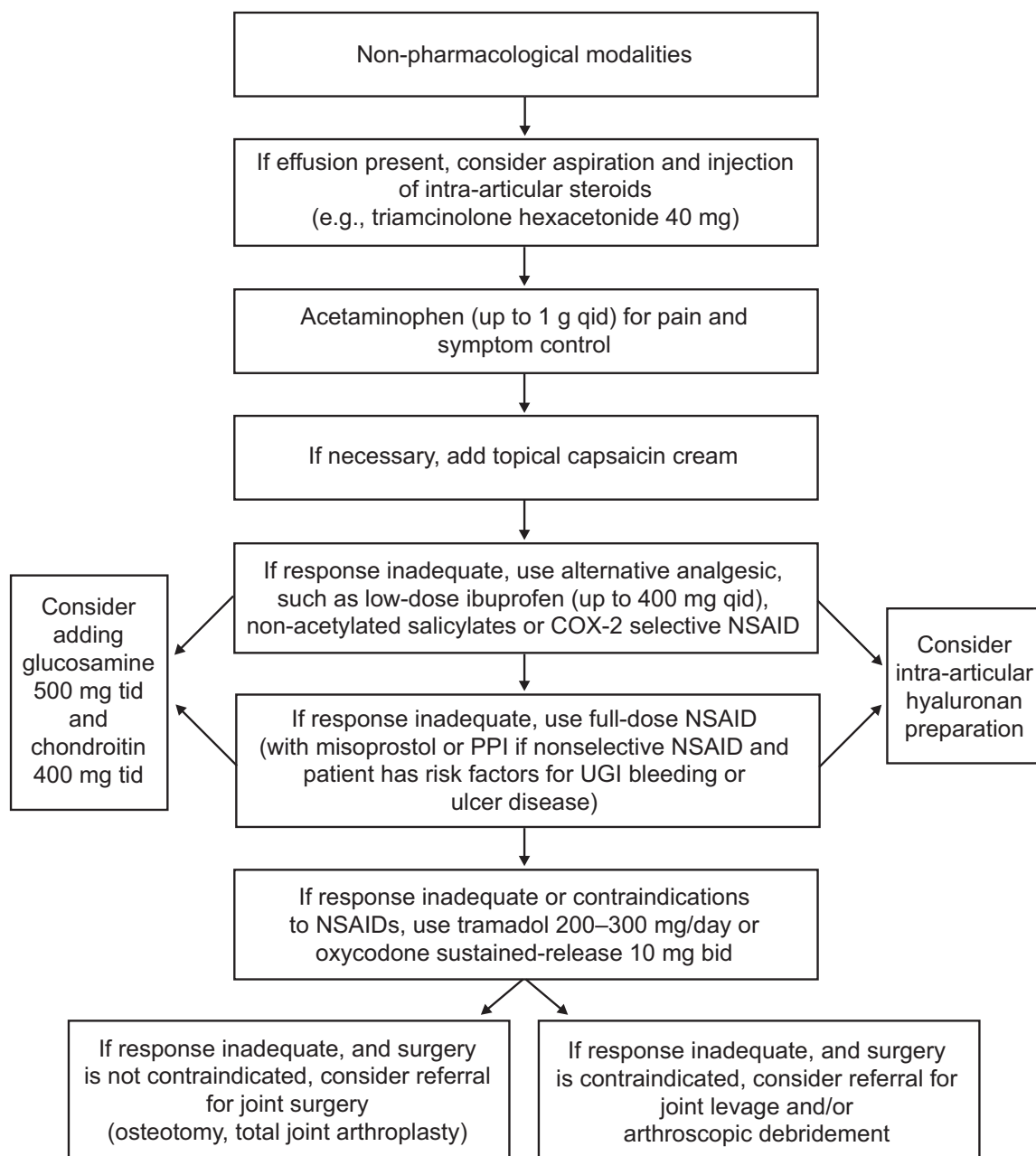


Figure 1-3. Modified American College of Rheumatology treatment algorithm for symptomatic osteoarthritis of the knee. bid = 2 times/day; tid = 3 times/day; qid = 4 times/day; UGI = upper gastrointestinal; PPI = proton pump inhibitor; NSAID = nonsteroidal anti-inflammatory drug; COX = cyclooxygenase. Adapted with permission from Lippincott Williams & Wilkins. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. *Arthritis Rheum* 1995;38:1541–6 and American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;43:1905–15.

not obtain complete relief with acetaminophen and at that point a NSAID must be considered. No drug therapy replaces the need for patients to lose weight (where applicable) and exercise to strengthen muscles. These non-pharmacological modalities must be used concurrently with drug treatment. When choosing additional therapy, patient comorbidities play a substantial role in drug selection.

In vitro studies have found that indomethacin, naproxen, and ibuprofen inhibit GAG synthesis but the selection of drug should not be based on these data alone. Indomethacin probably should be avoided in OA, due to increased propensity to cause adverse reactions, such as headache and GI bleeding, as well as its possible adverse effects on the outcome of OA.

Treating Special Populations

Aging affects the physiology of the gastric mucosa, with reduced synthesis of prostaglandins and bicarbonate. Older people are also more likely to develop complicated ulcers without warning symptoms such as abdominal pain. Because 95% of OA patients are older than 60 years of age, they are also at risk of GI bleeding from NSAIDs. Concurrent morbidity is another risk factor for GI bleeding in some studies. Choice of treatment in patients older than 75 years of age is important because these patients are often frail and at significant risk of GI bleeding with NSAIDs. The elderly may also be least able to afford expensive new treatments. In these patients, it is critical to use the lowest dose of any NSAID on an as-needed basis when possible. Piroxicam and indomethacin have been implicated as being more gastrotoxic than other NSAIDs in some studies and should be avoided.

Patients at risk of renal adverse effects with NSAIDs might cautiously be started on nonacetylated salicylates or sulindac, but only with appropriate monitoring. Nonacetylated salicylates should receive consideration for patients at risk of GI or renal toxicity, or if the patient is on warfarin.

Efficiency

Pharmacists and patients working together with nonprescription treatments can greatly increase the efficiency of the health care system. Once a diagnosis is established and the patient is educated about treatment goals and guidelines, a high degree of self-treatment is possible. The pharmacist should guide and advise on therapy until treatment becomes ineffective or drug toxicities require a physician to change treatment.

Efficacy of Major Treatments

A systematic review has been undertaken of all randomized, controlled trials of pharmacological therapy for knee OA published up to August 1994. A total of 80 trials were found. Acetaminophen was superior to placebo and comparable to naproxen or ibuprofen. Nonsteroidal anti-inflammatory drugs were clearly better than placebo but only five of 32 comparative NSAID trials found one superior to another. Few studies have compared one class of drug to another. Two studies have found intra-articular HA to be superior to intra-articular methylprednisolone.

The same authors published a review of studies in hip OA. Only five of 29 NSAID comparisons found a preference for one drug over another, whereas all comparisons of NSAID to placebo favored the NSAID. Low-dose ibuprofen (less than 1600 mg/day) or naproxen (less than 750 mg/day) was more likely to be less effective versus other NSAIDs as standard doses, whereas indomethacin was most likely to be superior in comparison to other NSAIDs. However, indomethacin was also more toxic in seven of nine comparisons. No randomized trials compared acetaminophen to NSAIDs in hip OA.

Two systematic reviews by the Cochrane Collaboration found no clear differences among various NSAIDs in 39 trials of OA of the hip or 16 trials of OA of the knee. Numerous studies have found that consistent preference for a particular NSAID may occur in *individual* patients, but no NSAID was clearly superior in large *groups* of patients. Thus, there is no reason to recommend one NSAID over another for efficacy, but changing from one NSAID to another may improve individual response.

Thus all pharmacological interventions are efficacious treatments. A choice must be based more on safety, convenience, cost, and patient preference. Consequently, acetaminophen should always be used first, with intermittent low-dose NSAID substituted or added occasionally. Nonsteroidal anti-inflammatory drugs are indicated once response to full-dose acetaminophen and non-pharmacological measures are proven inadequate. The American College of Rheumatology recommends beginning with low doses of a NSAID with a short half-life (e.g., ibuprofen) on an as-needed basis because pain varies with time. For a given patient, lack of response to one NSAID does not preclude a response to another. Cyclooxygenase-2-selective drugs should be used in patients with two or more risk factors for GI bleeding (see Table 1-4), and *not* on the basis of efficacy.

Effectiveness in Practice

Although guidelines recommend acetaminophen as the drug of first choice based on clinical studies finding no difference in efficacy between acetaminophen and NSAIDs, a recent survey of primary care physicians found that two-thirds would start therapy with a NSAID instead of acetaminophen. Many physicians may overestimate the effectiveness of NSAIDs and underestimate their toxicity.

A telephone survey was done of 300 patients with OA regarding their experience with four specific drugs. Of patients who had taken diclofenac, 56% rated it “very helpful”, which compared to a “very helpful” rating in 31% of patients taking ibuprofen, 30% taking naproxen, and 24% for acetaminophen. Of patients who named one drug as “most helpful”, 80% chose a NSAID compared to 20% for acetaminophen or other analgesic. However, drug continuation for greater than 24 months was reported for acetaminophen by 33% of patients, for ibuprofen by 21%, for naproxen by 17%, and for diclofenac by 19%. Acetaminophen was significantly less likely to be discontinued for adverse effects.

Similar results were found in a mail survey by different investigators of 1799 patients with OA, RA, or fibromyalgia. Patients with OA were more likely to have a preference for acetaminophen than those with the other two

diseases. Looking at just the 668 responders with OA, 41% found acetaminophen to be moderately or very effective, 14% found it more effective than NSAIDs, and 46% found NSAIDs more effective than acetaminophen.

These two surveys revealed that most patients with OA use many different drugs throughout time. Nonsteroidal anti-inflammatory drug therapy is more effective than acetaminophen for many patients but is more likely to cause adverse effects and is more costly. Thus, the recommendation to use acetaminophen first is strongly supported by these surveys. Acetaminophen can be used with NSAIDs and often is. In the above telephone survey, 30% of people taking acetaminophen were using a NSAID concurrently.

A high discontinuation rate is common with all NSAIDs. In a retrospective cohort study of health maintenance organization enrollees, a 12-month treatment period of 1405 patients with OA aged 45 years old or older who received a new prescription for one of four NSAIDs were reviewed. Rates of discontinuation during the 12-month period were high; only 15–20% of those who started a NSAID were taking the same drug 12 months later. Physicians probably overestimate the benefit of NSAIDs because there are so many available that patients can continue treatment with a drug in the category for long periods despite less than ideal results.

Opioid use was studied retrospectively in a cohort of 644 rheumatology clinic patients. Opioid prescriptions for codeine or oxycodone for longer than 3 months were found for 137 patients. Opioids significantly reduced pain, from 8.2–3.6 on a 10-point scale, with only mild side effects. The mean dose was 80 mg/ day of codeine or equivalent. Only four patients appeared to display abuse behavior; for other patients, dosage escalation coincided with medical complications or worsening of the rheumatic condition. The authors concluded opiates were safe and effective in practice.

Glucocorticoid injections are used in practice more than is expected from their limited proof of efficacy. A survey found that more than 95% of United States rheumatologists in 1996 used steroid injections in OA at least occasionally and 53% used them frequently. Their popularity may stem from the high placebo effect associated with injection of a joint.

Management Errors

One of the most important problems with managing OA patients is that they are not being managed within the organized health care system. Many people believe they know enough about arthritis to self-diagnose and treat. These impressions are increased by the reality that OA prevalence increases with age so it is perceived as a minor inconvenience of the elderly. First-line treatment with OTC drugs reinforces the perception of an inconsequential condition. At the same time, the popularity of books such as *The Arthritis Cure* and misinformation on the Internet lead people to believe that simple, natural approaches can completely treat their condition. The pharmacist in all settings is critical to getting patients within the mainstream of medical care. All arthritis patients should have an accurate medical diagnosis to guide appropriate treatment.

Pharmacists should screen patients by asking about their diagnoses and referring them to medical care if they do not have one. Next, pharmacists need to provide objective advice on selecting and monitoring of appropriate therapies.

Many patients receive NSAIDs inappropriately. Acetaminophen and non-pharmacological measures are often not given an adequate opportunity to control symptoms. In fact, studies have shown that physicians underestimate the importance that arthritis patients place on education, exercise, and diet instruction. If small doses of acetaminophen are not adequate, the dosage can safely be increased to 1 g 4 times/day for a month. If it is still ineffective, a low-dose NSAID can be *added* to the regimen. If pain develops primarily after physical activity, therapy should be directed at reducing mechanical stress on the joint through ergonomic adaptation and occupational therapy, or physical therapy and muscle strengthening, with drug therapy delayed or used only temporarily.

Another problem in treatment is that many patients receive inappropriate NSAID doses.

One study showed no difference between low and high doses of ibuprofen. Because most patients with OA need analgesia and not anti-inflammatory activity, doses of NSAIDs in OA should start low (Table 1-2). The risk of serious GI bleeding due to NSAIDs is dose-related. Therefore, it is imperative to use the lowest effective dose of NSAIDs when treating OA. In addition, many patients can use NSAIDs *as needed* because the intensity of pain is variable.

Although OA is usually thought of as a steadily progressive, unrelenting condition, patients in fact have exacerbations and periods of quiescence that occur without specific intervention. Periodically, any patient's drug regimen should be reviewed with a goal of stopping unneeded drugs.

Despite warnings to physicians since the late 1980s to avoid NSAIDs in the elderly and patients with a history of peptic ulcer, inappropriate prescribing still occurs. In a 1997 study in Montreal, Canada, patients with OA who visited physicians' offices were found to have unnecessary NSAID prescriptions written at more than one-third of visits. Furthermore, therapy was usually started at or close to the maximum adult dose.

When NSAID therapy becomes essential in at-risk patients, a COX-2-selective drug or concurrent gastroprotective therapy should be prescribed. In the Montreal study, the majority of high-risk patients received NSAID therapy with no or inappropriate gastric protective therapy. The dominant reason for this appeared to be inadequate assessment of risk factors for NSAID-related GI complications. Another common mistake is prescribing concurrent gastroprotective drugs with COX-2-selective NSAIDs. There are no data to support this excessively costly approach.

From these data, it is apparent that there is great potential to establish collaborative agreements with physicians to monitor and adjust therapy in OA.

Economic Considerations

There is a marked difference in cost between NSAID products. One way to reduce costs is to use a restrictive

closed formulary. Although there is individual variability in response to NSAIDs, few patients would try more than four or five in addition to the other treatments reviewed in this chapter. Selection of a small number of NSAIDs for a formulary will reduce inventory costs and promote rational therapy. Another economic approach is a stepped care approach. A study at a military medical center found that requiring a trial of an inexpensive NSAID before more costly ones reduced costs by 30% without causing patient care problems.

Several economic evaluations of NSAID therapy have concluded that attempting to prevent GI complications of NSAIDs is reasonable only for patients at high risk of ulcers and bleeding. One review of misoprostol cost-effectiveness studies concluded that estimates of cost-effectiveness are highly sensitive to the assumed incidence of serious upper GI complications. We now have good data that this complication rate is 1.5–2%/year in the overall OA population. Cost studies should not be based on rates of asymptomatic ulcers. Another important determinant of cost-effectiveness is the absolute risk of a GI event in the individual patient. Several studies have indicated that cost-effectiveness of prophylaxis becomes far more favorable when a patient has two or more risk factors for GI bleeding. The absolute risk in patients with multiple risk factors may exceed 5%/year compared with less than 1%/year in low-risk patients. The same principle applies to use of COX-2-selective drugs; use is economically justified only in patients with at least two risk factors.

Starting therapy with acetaminophen or a low-dose generic NSAID is not only clinically appropriate, but a logical way to minimize costs. This approach lowers direct cost and also lowers the cost of treating NSAID-related GI events. One cohort study found that \$0.66 was spent on preventing or treating GI side effects for every \$1 spent on NSAID acquisition cost. However, for some patients who have insurance coverage for prescription but not OTC drugs, this approach may actually increase their out-of-pocket expenses.

Safety Considerations

Both the AGS and ACR guidelines recommend to avoid high-dose, long-term NSAIDs in the elderly, and to give preference to short-acting NSAIDs on an as-needed basis. Nonsteroidal anti-inflammatory drugs must be used cautiously or avoided in patients with a history of peptic ulcer disease, bleeding diathesis, or renal dysfunction. The COX-2-selective drugs should be the preferred NSAIDs in patients at high risk of GI bleeding. Combinations of NSAIDs (including COX-selective with nonselective drugs) are inappropriate and should never be used. Even low-dose aspirin for cardiovascular protection may negate the GI safety advantage of COX-selective NSAIDs (a particular dilemma for elderly OA patients). Thus, for patients who need to take low-dose aspirin, prescription of a nonselective NSAID with misoprostol or a proton pump inhibitor may be considered.

Monitoring

Measuring the outcomes of OA is difficult because the disease can affect many dimensions of a patient's life.

There are several methods to monitor outcomes in OA and there is no agreement on a standard set of methods, either for clinical trials or for clinical use. It is important to know how OA affects not only pain but also functional ability and quality of life. Several generic questionnaires may be used for overall quality of life, whereas others have been developed specifically to address function in OA.

Unlike the ACR 20 criteria for RA, there is no standard threshold for assessing the effectiveness of OA treatment. Probably a 50% or more reduction in pain is a reasonable goal of therapy in most patients. When using functional or quality of life indices, a 20% improvement may be significant.

Patients on NSAIDs should have baseline and periodic determinations of serum creatinine, complete blood cell count, and hepatic transaminases.

Pain Measures

Joint pain is the main symptom in OA and the most important to assess. It is usually measured on a Likert scale or VAS that grades pain severity in one or more situations (nocturnal, walking, at rest, stair climbing, or global). In conversations with a patient, pain can be described simply on a scale from 0 to 10. Ideally, patients should always be asked about pain at the same time of day because of circadian cycles; pain may be higher in the evening and on weekends. Keeping a regular pain diary using any of the above scales may assist patients and health care professionals in determining effectiveness of therapy. Patients should also be asked about the extent and pattern of analgesic and NSAID use. Changes in pain measures can be assessed within a few days of changing treatment with most drugs.

General Symptoms

Patient and physician global assessments are commonly used in clinical trials. They take into account a variety of consequences of the disease and are easily done. Patients' perceptions of the overall clinical severity of their condition is usually assessed by a question such as "Considering all the ways your OA affects you, how would you rate your condition today?" Ratings are again assessed on a VAS or Likert scale. There is no standard question or response format.

Quality of Life Measures

Severe disease will affect patients' overall quality of life. Health-related quality of life measures are being considered increasingly important, especially for long-term follow-up of patients. They assess those aspects of a disease that are important to patients, such as social functioning, activities of daily living, and work disability, even if they are not part of a physician's or pharmacist's routine clinical assessment. Another advantage of general measures is that they allow comparisons of outcomes across diseases. One of the concerns with these measures is the time required to complete the questionnaire. However, the short (typically two pages) versions of the questionnaires can be completed by the patient in a waiting room before a clinic visit. Any of the standard questionnaires can be administered to every patient with

rheumatic disease at every clinic visit to provide quantitative data for comparisons between visits or to compare different patients. These data allow accurate description of changes in status over months or years. They not only correlate well with traditional measures of clinical status, but they are the best measures to identify and predict work disability.

An example of a widely used and psychometrically sound, generic quality of life assessment is the Medical Outcomes Study Short Form-36, which is a 36-item short-form general health survey. Designed for self-completion, it measures health on eight multi-item dimensions that cover functional status, social and emotional health, well-being, and overall evaluation of health. It is easy to use in an elderly population, sensitive to treatment improvement, and is comprehensive, reliable, and valid. The Medical Outcomes Study Short Form-36 data have shown that quality of life in elderly OA patients is significantly poorer than their healthy peers and that decreases in quality of life are affected mainly by amount of pain. Changes in quality of life indices could routinely be assessed about every 6 months.

Disease-specific Functional Indices

Other measures of health status focus on arthritis-related physical function or the presence of physical limitations. Two widely used measures have been developed, the HAQ or modified HAQ (MHAQ), and the Arthritis Impact Measurement Scale (AIMS). The HAQ assesses eight areas: dressing, arising, eating, walking, hygiene, reaching, gripping, and other activities. The MHAQ uses just a single question for each area. Scores for all eight areas are summed into a total score. The AIMS1 assesses nine similar domains, and the AIMS2 has 12 domains.

The WOMAC index is a disease-specific, multidimensional, self-administered, health-related quality of life measure that can be used with either a five-point Likert scale or a 100 mm VAS. It has been subjected to two major validation studies. It has 24 questions in three subsections to assess pain, stiffness, and physical dysfunction. Again, symptoms are assessed during various activities of daily living.

Lequesne, a French rheumatologist, developed indices for severity of hip and knee OA. Points are assigned to the responses to questions pertaining to pain in different situations, distance able to walk, and ability to perform activities of daily living. The questions are easy to administer and the indices are also reliable and valid. However, one small study found the Lequesne functional index was less sensitive to change than the WOMAC subscale for function.

Imaging Techniques

Radiographic features of OA are important to assess independent of symptoms because “structure-modifying” or “chondroprotective” drugs could have a positive effect without affecting symptoms. Radiographs assist in establishing baseline severity of disease and they may be repeated when the clinical course indicates.

With loss of cartilage there is a loss of joint space that can be detected with radiography. Plain radiographs are not sensitive for measuring changes in cartilage over a short (less than 1 year) time. Furthermore, attention to detail is

needed, as assessment of knee radiographs can be affected by small differences in knee rotation and flexion. Patients with decreased pain may be able to more fully extend their knee, altering the apparent joint space and falsely implying a chondroprotective effect by drugs they are taking. Magnetic resonance imaging could be used for greater accuracy and can assess the entire joint structure, but it is not practical outside of a research setting.

Patient Education

Patients often have misconceptions about the different types of arthritis. Some believe that arthritis is a minor inconvenience to be ignored whereas others worry that their OA will cause crippling and joint deformity. Patients should be reassured that, whereas OA can sometimes cause significant disability, it is not inflammatory or autoimmune, and most patients have a fairly stable course. At the same time, they should know that OA is more than just aches and pains that inevitably come with aging. Patients need to have medical follow-up and participate actively in managing their disease. Patients need to understand the different drug choices and that OTC products may be as appropriate and as effective as prescription medicine.

Appropriate aspects of education should include information about the disease, proper use of drugs, drug side effects, avoidance of joint overuse, and appropriate use of joint protection devices. Several studies reported the follow-up of patients enrolled in the Arthritis Foundation’s Arthritis Self-Management Program. The program consists of 2 hours of education for 6 weeks, for mixed patient populations with RA and systemic lupus as well as OA. Studies suggest that this intervention had substantial and long-lasting benefits on perceived ability to manage arthritis, reduction in pain, and improved psychological well-being. The Arthritis Foundation’s local chapters also sponsor informal support groups. Patients should be encouraged to take an active role in managing their disease, as this behavior has been correlated to better outcomes in arthritis. Arthritis Foundation chapters gladly use pharmacists as leaders for these groups or as speakers for short lectures on drugs for arthritis.

Advice on self-treatment, including the use of OTC medicines and alternative therapies, is essential. As long as patients are educated and monitored within the health care system, patients can be encouraged to take an active role in titrating their own drug doses within preset limits. Education can prevent unnecessary drug doses from being taken, and self-treatment is empowering.

Patients who take acetaminophen should know not to exceed 4 g/day and patients on acetaminophen or NSAIDs should be discouraged from drinking alcohol regularly. Patients should be warned to seek attention for signs of GI bleeding from NSAIDs (e.g., black tarry stools and persistent GI pain) or fluid retention.

Patients should be informed that COX-2-selective drugs *can* cause GI bleeding (although probably at a lower rate than older NSAIDs) and can cause renal impairment. The cardiovascular toxicity of COX-2 drugs needs further evaluation, but it is wise to ensure that patients at risk of myocardial infarction are taking antiplatelet therapy concurrently.

Quality Improvement

It would be ideal to detect the earliest signs of OA and predict which patients will have progressive disease so that early preventive interventions can be implemented. Unfortunately, this is not currently possible.

Little information exists in the literature about objective measures of quality care for OA. However, there are several areas where pharmacists can have an impact on improving treatment. One of these is to ensure that patients receive an adequate trial of acetaminophen and topical treatments before NSAIDs. Pharmacists should encourage patients to use a pain diary and set a goal for treatment to help determine effectiveness of drugs. Studies have shown that few primary care physicians recommend non-pharmacological treatments in OA. Therefore, the pharmacist should ask patients about their knowledge of the role of weight loss, muscle strengthening, and occupational factors in managing their OA.

Pharmacists need to be advocates for patients in their goal of seeking pain relief. Pharmacists should encourage a prescription of opioid analgesics where indicated, pointing out that achieving the goal of improved function and quality of life does not carry the risk of drug addiction.

Another area for pharmacists to emphasize is the proper use of COX-2-selective NSAIDs. They have an important role for patients with two or more risk factors for GI bleeding but many patients without risk factors are satisfactorily managed on low doses of older NSAIDs. Similarly, pharmacists should discourage the co-prescription of unnecessary prophylactic drugs for GI events.

Patients have ready access to most forms of OA pharmacotherapy because many are OTC preparations. Therefore, pharmacists may be approached by patients with questions about treatment, and pharmacists should initiate conversations with their patients who have OA. Many older people will self-diagnose arthritis based on their perceptions of normal aging. It may be important for pharmacists to refer patients to a physician for a correct diagnosis. A complete drug history is essential to determine use of prescription drugs, OTC products, and dietary supplements. Drug interactions or duplications can easily occur by self-treatment or seeing multiple physicians.

Pharmacists should advise patients about using medicine as needed (which is appropriate for many patients) or on a scheduled basis. Patients may be incorrectly labeled as “noncompliant” with analgesic drugs when, in fact, they are probably treating themselves quite intelligently on an as-needed basis to avoid adverse effects of drugs. It is essential to involve patients in the decision-making process about use of their drugs.

An opportunity for pharmacist involvement is in nursing home consulting, where a large proportion of patients is affected by OA, and inappropriate therapy may be common. Another opportunity is in the public health arena. Three national agencies—the Arthritis Foundation, the Association of State and Territorial Health Officials, and the Centers for Disease Control and Prevention—recently joined forces to lead an attack on the public health challenges of arthritis. The result of their collaboration is the National Arthritis Action Plan: A Public Health Strategy. The plan organizes the use of the nation’s health resources to combat OA among Americans, whereas

increasing awareness—among the general public, people with arthritis and their families, medical care providers, and policy makers—of the impact of arthritis, what can be done to prevent or delay its onset, and the effective interventions available to reduce disability and improve the quality of life of people with arthritis.

Conclusion

The understanding of OA has increased substantially in the past decade. Development of hyaluronan injections and COX-2-selective NSAIDs has expanded the number of well-tolerated options for treatment. Glucosamine and chondroitin have brought hope and relief to many patients, regardless of whether they have an effect on the underlying disease.

The future will undoubtedly see development of metalloproteinase inhibitors and perhaps IL-1 antagonists. Hopefully, these advances will improve the natural history of OA and provide improvement in quality of life. However, at the present time all available treatments are directed to the symptoms of the disease. With the high prevalence of OA and the numerous available treatments of similar efficacy, pharmacists can play an important role in advising both patients and physicians about optimal therapy.

Resources

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
(404) 633-3777
www.rheumatology.org

Arthritis Foundation
PO Box 7669
Atlanta, GA 30357-0669
(800) 283-7800
www.arthritis.org

American Academy of Pain Medicine
4700 W. Lake Avenue
Glenview, IL 60025
(847) 375-4731
www.painmed.org

American Pain Society
4700 W. Lake Avenue
Glenview, IL 60025
(847) 375-4715
www.ampainsoc.org

American Geriatrics Society
The Empire State Building
350 Fifth Avenue, Suite 801
New York, NY 10118
(212) 308-1414
www.americangeriatrics.org

Annotated Bibliography

Pathophysiology and Risk Factors

1. Saha N, Moldovan F, Tardif G, et al. Interleukin-1 β -converting enzyme/caspase-1 in human osteoarthritic tissues: localization and role in maturation of interleukin-1 β and interleukin-18. *Arthritis Rheum* 1999;42:1577–87.

This study adds to our appreciation of osteoarthritis (OA) as an active disease with cytokine up-regulation. In animal models of OA, interleukin (IL)-1 β is an important cytokine contributing to cartilage catabolism. Interleukin-1 β -converting enzyme is a protease that generates active IL-1 β and IL-18 from precursor forms. In this study, human OA cartilage was obtained from patients undergoing knee replacement or from autopsy controls. Increased expression of IL-1 β -converting enzyme was demonstrated in both the synovium and cartilage of OA patients compared to controls. Immunohistochemistry showed increased IL-1 β -converting enzyme expression as well as increased IL-1 β and IL-18 staining more prominently in the superficial zone than the deeper zone of cartilage. When IL-1 β -converting enzyme activity was inhibited in cartilage explants, immunostaining for IL-1 β and IL-18 was decreased, suggesting IL-1 β -converting enzyme was functional. These results suggest IL-1 β -converting enzyme expression may be important in the pathogenesis of OA. This is a good reference for those interested in the pathophysiology of OA.

2. Cooper C, Snow S, McAlindon TE, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis Rheum* 2000;43:995–1000.

Few studies have examined older populations prospectively for incidence and progression of OA. This study recruited 354 people 55 years of age or older (99 men; 255 women) in England, with and without baseline knee pain, and followed them for an average of 5.1 years. Risk factors assessed at baseline were tested for their association with incidence and progression of radiographic knee OA by logistic regression. Rates of incidence and progression were 2.5% and 3.6% per year, respectively. Incidence was influenced by obesity, previous knee injury, and a history of regular sports participation. Only knee pain at baseline and Heberden's nodes were weakly associated with progression. The authors conclude that different factors may be responsible for incident and progressive OA. Knee OA may be initiated by joint injury, whereas progression is related to impaired intrinsic repair capacity.

3. Dieppe P, Cushnaghan J, Tucker M, et al. The Bristol OA500 study: progression and impact of the disease after eight years. *Osteoarthritis Cartilage* 2000;8:63–8.

This study, which recruited 500 consecutive patients from a hospital-based rheumatology clinic in England, is probably the largest and longest prospective study of OA progression. All patients were invited for reassessment 3 and 8 years after initial evaluation. At the 8-year review, 349 patients (90% of those still alive) were available. Sixty patients (17.2%) reported worsening in all three subjective end points of pain severity, change in index joints, and global change, whereas 22 patients (6.3%) improved in all three. Based on this classification of patients, there was no strong predictor of clinical outcome. Patients with knee disease had the worst outcome. Mean scores on the health assessment questionnaire (HAQ) and hospital anxiety and depression (HAD) scale were high after 8 years, especially in those with knee involvement.

Forty-four percent of the 72 patients with hand disease alone at entry had acquired significant knee or hip involvement 8 years later. The authors concluded that patients with OA severe enough to require hospital referral had a heterogeneous, but generally poor outcome 8 years later. The disease resulted in high levels of disability, anxiety, and depression, and high use of health care resources, including joint replacement.

4. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum* 1998;41:1343–55.

Information on the epidemiology of OA and risk factors for the disease can be somewhat confusing because of the multiple studies using different definitions of disease. These authors have provided a well-written and informative review article based on a systematic review of the literature. It starts by reviewing general epidemiology studies and the different possible disease definitions. It then reviews data on various systemic risk factors for OA, including age, sex, race, genetics, nutrition, and estrogen loss. Local biomechanical factors, including weight, joint injury, and muscle weakness, are discussed next. The paper concludes by reviewing the feasibility of preventing OA. Overall, the paper provides useful information and is a key article for one's files.

5. Ettinger WH, Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. *JAMA* 1997;277:25–31.

This randomized, single-blind trial examined the effect of aerobic and resistance exercise training compared to an education program alone in 365 community-dwelling adults older than 60 years or age with knee OA. All patients reported some physical disability at baseline, so exercises were tailored to the individual needs. During a period of 18 months, there were modest (about 10%) improvements in measures of disability, pain, and physical performance after participating in either exercise program compared to the education group. There were no differences in radiographic scores among the three groups at the end of the study. Overall compliance in each exercise group was about 70%, suggesting the interventions were used similarly to how patients might use them in everyday practice. The data seem generally applicable and suggest that exercise should be prescribed as part of treating knee OA, but they do not tell us which type should be preferred.

General Guidelines

6. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip. *Arthritis Rheum* 1995;38:1535–40.
7. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. *Arthritis Rheum* 1995;38:1541–6.

These two guidelines (References 6 and 7) were developed simultaneously and are quite similar to each other. They differ only in the specific recommendations pertinent to each type of OA. Relatively brief and to the point, they review goals of therapy, non-pharmacological and pharmacological therapy, and surgical treatment. The guidelines were developed by consensus and are not evidence-based, although they are referenced in the style of a review article. The algorithms for treatment are clear and supported by evidence. Most of the recommendations are still relevant but they do not

address the use of hyaluronan injections or cyclooxygenase (COX)-specific nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, the cautionary tone about opioids in these guidelines may be unwarranted.

8. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;43:1905–15.

This is an update to the above guidelines and not a complete rewrite (a complete revision is scheduled for publication in late 2001). Overall, these guidelines are disappointing. Although they claim to follow principles of evidence-based medicine, the guidelines are heavily based on expert opinion. Although well referenced, strength of evidence is not cited for any recommendation and most recommendations are vague because they mainly provide alternatives that allow individualizing therapy to specific patients. No updated algorithm or decision tree is provided. For treating patients NOT at an increased risk of an upper gastrointestinal (GI) adverse event, these guidelines simply suggest management similar to those who ARE at an increased risk, thereby implying but not explicitly suggesting that COX-2-selective drugs are NSAIDs of choice for all patients. Some key changes from the 1995 guidelines include: COX-2-selective drugs are recommended for patients at high risk of GI complications; gastric protection with misoprostol or proton pump inhibitors is now recommended for all patients at high GI risk on nonselective NSAIDs, even at low doses; and they suggest tramadol, propoxyphene, codeine, or oxycodone for long-term use in patients with moderate to severe pain and poor response or contraindications to other oral therapy. The guidelines decline to make specific recommendations on use of glucosamine and chondroitin, other dietary supplements, or acupuncture.

9. American Geriatrics Society Panel on Chronic Pain in Older Persons. The management of chronic pain in older persons. *J Am Geriatr Soc* 1998;46:635–51.

This article focuses on analgesics and NSAIDs for any chronic pain in the elderly. Its goal was to develop guidelines in a practical format that take into account the special needs of the elderly. The recommendations are based on the consensus of a panel of experts in pain management, geriatrics, pharmacology, psychology, and nursing. Several recommendations are made for the appropriate use of NSAIDs that are consistent with other guidelines. It also addresses the underuse and appropriate prescription of opioids in the elderly. Some of the key parts of this guideline are recognition and assessment of pain in older people, pharmacological treatment, non-pharmacological treatment, and recommendations for health systems.

10. American Academy of Pain Medicine and the American Pain Society. The use of opioids for the treatment of chronic pain. *Clin J Pain* 1997;13:6–8.

This consensus statement addresses the need to consider opioids in chronic nonmalignant pain. Detailed recommendations are not given and the statement is not referenced but it attempts to establish a national consensus on principles for use of opioids. The statement addresses several misconceptions and assumptions about risks of addiction, tolerance, and respiratory depression. It also addresses principles of good medical practice in prescribing opioids. This article is a valuable addition to one's files.

Clinical Assessments

11. Lequesne M. Indices of severity and disease activity for osteoarthritis. *Semin Arthritis Rheum* 1991;20(suppl 2):48–54.

This paper describes several methods for assessing disease severity in OA. It provides all the items included in the Lequesne and Western Ontario and McMaster Universities (WOMAC) indices, as well as descriptions of pain scales, global evaluations of change, and the Doyle articular index. The paper describes evidence for the reliability and validity of the methods. Although it is an older reference, it is still the most accessible and useful description of these indices. It is essential for those involved in clinical studies of OA.

Drug Treatments

12. Towheed TE, Hochberg MC. A systematic review of randomized trials of pharmacologic therapy in osteoarthritis of the knee, with an emphasis on trial methodology. *Semin Arthritis Rheum* 1997;26:755–70.

Despite its relative age, this article is an excellent gateway into all randomized, controlled trials of pharmacological therapy for knee OA published up to August 1994. It also assesses and critiques the methodology of the trials. A total of 80 trials were found. Acetaminophen was superior to placebo and comparable to naproxen or ibuprofen. Nonsteroidal anti-inflammatory drugs were clearly better than placebo, but only five out of 32 comparative NSAID trials found one superior to another. Intra-articular steroids were better than placebo only in the first 3 weeks, whereas two studies found intra-articular hyaluronic acid to be superior to intra-articular methylprednisolone. Trials of several alternative therapies are also included. Overall, studies support the use of acetaminophen, topical capsaicin, intra-articular steroids, intra-articular hyaluronan, and NSAIDs in knee OA.

13. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacologic therapy in osteoarthritis of the hip. *J Rheumatol* 1997;24:349–57.

Similar to the previous article, this paper reviews all randomized, controlled trials of pharmacological therapy for hip OA published up to August 1994. It also assesses and critiques the methodology of the trials. Of 43 randomized, controlled trials identified, 39 studied NSAIDs and four compared only analgesics. Nonsteroidal anti-inflammatory drugs were better than placebo in all comparisons. Indomethacin was most often identified as a superior NSAID in efficacy but was also the most toxic drug in most comparisons. The authors were unable to recommend any specific NSAID based on available studies. However, they noted that trials in hip OA were often marred by lack of standard definition for hip OA, and by lack of standard outcome assessments.

14. Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: summary guideline for nonsteroidal anti-inflammatory drugs versus basic analgesia in treating the pain of osteoarthritis. *BMJ* 1998;317:526–30.

This guideline considers the evidence for efficacy, safety, and economic considerations of using acetaminophen and NSAIDs for OA. The development group did a systematic review of the literature for randomized, clinical trials and produced guidelines that are strictly evidence-based. Strength of evidence is provided with each recommendation. It reviews the management of GI symptoms from NSAIDs but it does not mention the COX-2-selective drugs. Statements on pharmacoeconomic considerations and use of topical NSAIDs are also of interest.

15. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain. *Arch Intern Med* 2000;160:853–60.

The use of chronic opioids in nonmalignant pain has always been looked on with skepticism. This study is an important contribution to understanding their proper use. The study included 130 OA patients with moderate to severe pain. Patients could use no other analgesics except NSAID therapy at a stable dose. Patients with a history of drug or alcohol abuse were excluded. Subjects were randomized to double-blind treatment with placebo, 10 mg or 20 mg of controlled-release oxycodone every 12 hours for 14 days. The 40 mg/day dose was superior to both placebo and the 20 mg/day dose in measures of pain, sleep, mood, and enjoyment of life. The investigators enrolled 106 of the same patients in an open-label extension trial for up to 18 months. During the open-label phase, the dose of controlled-release oxycodone leveled off at an average dosage of 40 mg/day by week 16 and analgesia remained constant, indicating that tachyphylaxis did not occur. The most common adverse effects were nausea, pruritus, somnolence, and constipation.

16. Brandt KB, Smith GN, Simon LS. Intra-articular injection of hyaluronan as treatment for knee osteoarthritis. *Arthritis Rheum* 2000;43:1192–203.

This review article summarizes the role of hyaluronan in normal joint physiology and the safety and efficacy of hyaluronan products in OA. It reviews all the key research with the products, a critical evaluation of clinical studies to date, and recommendations on the use of the products. The authors are not impressed with the efficacy of hyaluronan. However, the tone of the review appears overly critical, as the concerns addressed about the quality of research studies on hyaluronan are common to most OA interventions. Their opinion on the effectiveness of hyaluronan is more negative than other authors.

17. Creamer P. Intra-articular corticosteroid injections in osteoarthritis: do they work and if so, how? *Ann Rheum Dis* 1997;56:634–6.

This article is an excellent and concise editorial/review of the subject. Based on a review of seven controlled studies of steroid injections, the author concludes that efficacy beyond 3 weeks is unproven. The article also reviews the mechanism of action of steroids in OA. Although several mechanisms have been suggested, none have been proven. The article shows that the efficacy of steroid injections is overestimated by most clinicians due to the strong placebo effect induced by any injection.

18. McAlindon TE, Lavalley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and analysis. *JAMA* 2000;283:1469–75.

This meta-analysis is an excellent summary of research with glucosamine and chondroitin. After an exhaustive search for literature on the topic, studies were independently reviewed and scored for quality by two rheumatologists. Effect sizes were calculated for each supplement on pain and functional outcomes. Effect sizes were moderate to large in value (0.44–0.78) when all studies were combined but were lower when only high-quality studies were included. Furthermore, there was evidence of publication bias, and almost all available studies were sponsored by supplement manufacturers. Thus the actual benefit of glucosamine and chondroitin may be less

than indicated by the studies. Although this is a good analysis, clinicians must stay up with additional literature as newer, better designed, studies become available.

19. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulfate on osteoarthritis progression: a randomized, placebo-controlled trial. *Lancet* 2001;357:251–6.

This study of the long-term structural effects of glucosamine in knee OA is a meticulous and valuable contribution to the literature. In this study, 212 patients were randomized to receive 1500 mg glucosamine sulfate orally 1 time/day or placebo for 3 years. A limited number of NSAIDs could be used concurrently, if symptoms required. Weight-bearing, anteroposterior radiographs of each knee in full extension were taken at enrollment and after 1 and 3 years. The main outcome measure was mean joint space at the medial compartment of the tibiofemoral joint. Osteoarthritis symptoms were also measured using the WOMAC index. The 106 patients on placebo had a mean joint space loss of 0.31 mm for 3 years, whereas a nonsignificant loss of 0.06 mm occurred in the 106 glucosamine patients. A statistically significant difference between treatments occurred in both intention-to-treat and on-treatment analysis. Symptoms were also significantly better controlled by glucosamine. Furthermore, glucosamine caused no adverse reactions at a greater rate than placebo. There was no correlation between structural and clinical outcomes, which could lead one to question the relevance of the structural benefit from glucosamine. However, it is well known that OA symptoms correlate poorly with radiographic change. For now, this is the most definitive study of glucosamine.

20. Pelletier JP, Yaron M, Haraoui B, et al. Efficacy and safety of diacerein in osteoarthritis of the knee: a double-blind, placebo-controlled trial. *Arthritis Rheum* 2000;43:2339–48.

Diacerein is an interesting new treatment for OA that inhibits synthesis of IL-1 β and metalloproteinases in human cartilage cells. Therefore, it offers a unique approach to treating OA that could be disease-modifying. In this large, 16-week Phase II study, diacerein was compared to placebo at doses of 50, 100, or 150 mg/day divided into two doses. Although marred by a high dropout rate, the drug was better than placebo by intention-to-treat analysis as assessed by visual analog scale, pain on movement and the WOMAC indices. The major side effects of diacerein were diarrhea and abdominal pain. The optimal dose for benefit-to-safety ratio was 100 mg/day. The efficacy of diacerein was similar in magnitude to that of NSAIDs, but onset of action was delayed and began around week 4 of the study. Unfortunately, this study was not designed to test a disease-modifying effect for OA, but future trials with this drug will be eagerly awaited.

NSAIDs

21. Tramier MR, Moore RA, Reynolds DJ, et al. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000;85:169–82.

This is an excellent, up-to-date systematic review of upper GI complications with NSAIDs. The authors did a systematic search for studies with data on chronic (2 months or more) use of NSAIDs and located 15 randomized, controlled trials with 19,364 patients, three cohort studies with 215,076 patients, six case-control studies with 2957 cases, 20 case series with 7406 cases, and 447 additional case reports. In randomized,

controlled trials, the average risk for endoscopically diagnosed upper GI ulcers with NSAIDs was 21%, the risk for ulcers diagnosed due to symptoms was 1.48%, and the risk for a hemorrhage or perforation was 0.69%. Risk estimates for events were lower in observational studies: 0.39% for symptomatic ulcers and 0.22% for bleeding or perforation. The risk of death from GI bleeding for randomized, controlled trials and observational studies combined was 0.08%. This review found that about one in three symptomatic ulcers bleed or perforate, and about 12% of bleeders die. About one in 1200 patients taking NSAIDs for at least 2 months die. This review is important not only for its completeness but also because it addresses the “biological progression model” of GI damage, which suggests that all forms of NSAID-induced damage are related to each other along a reproducible continuum.

22. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation. *Arch Intern Med* 2000;160:2093–99.

Another good review of NSAID-related upper GI complications, this study focuses on epidemiological studies published in the 1990s. A systematic review of the literature retrieved 18 case-control or cohort studies of nonaspirin NSAIDs. The pooled relative risk of upper GI bleeding or perforation after exposure to NSAIDs was 3.8. The increase in risk was consistent during treatment but returned to baseline once treatment was stopped. A clear dose-response relationship was observed. The variation in risk among NSAIDs was small when comparable daily doses were considered. Advanced age, history of peptic ulcer disease, and male gender were independent risk factors for GI bleeding.

23. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1999;340:1888–99.

This is the most recent comprehensive review of this subject and an often quoted source of statistics on NSAID-induced GI toxicity. It covers the epidemiology of GI complications, risk factors, pathogenesis of gastroduodenal mucosal injury, treatment of NSAID-induced dyspepsia, and prevention and management of NSAID-related ulcers. Several excellent figures and tables help communicate key information. The paper also provides some insight into developing the NSAID molecules that contain nitric oxide that could be potentially safer to the GI tract.

24. Lipsky PE, Abramson SB, Crofford L, et al. The classification of cyclooxygenase inhibitors. *J Rheumatol* 1998;25:2298–303.

Precise classification of NSAIDs into meaningful categories has major implications for selection of therapy. This editorial by the International COX-2 Study Group reviews the various ways in which NSAIDs can be classified by COX activity. The group proposes and justifies a classification into four categories: COX-1 specific, COX nonspecific, COX-2 preferential, and COX-2 specific. The proposed classification uses three levels of data: enzymatic or biochemical, biological and pharmacological, and clinical. The authors acknowledge the limitations of available data. Despite the impressive title of the working group, it is not clear what authority initiated the classification. Although the authors are all respected rheumatologists and researchers, the group was supported by a grant from the manufacturers of COX-2 specific drugs. Other authors have argued that

complete specificity is impossible to prove, and the term “COX-selective” is more appropriate than “COX-specific”.

25. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Treatment of knee osteoarthritis: relationship of clinical features of joint inflammation to the response to a nonsteroidal antiinflammatory drug or pure analgesic. *J Rheumatol* 1992;19:1950–4.

This is a classic reference on the importance (or lack thereof) of inflammation in selecting treatment. The investigation was based on a randomized, double-blind comparison of acetaminophen 4 g/day with ibuprofen 1200 mg/day or ibuprofen 2400 mg/day in 182 patients with knee OA. An improvement in signs of joint inflammation (indicated by soft tissue tenderness and joint swelling) was associated with decreased disability and resting pain but not with the treatment regimen. Therefore, the study suggests that joint tenderness and swelling do not predict a better response to anti-inflammatory drug therapy than to pure analgesics. Unfortunately, this study has not been replicated, and it may have been underpowered to detect a true difference, but it gives no support to automatically choosing a NSAID over acetaminophen in patients with a swollen knee due to OA.

26. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. *Am J Med* 1999;107(6A):65S–71S.

This article reviews the various effects that NSAIDs can have on renal function and electrolyte homeostasis. It reviews solute homeostasis and normal renal blood flow and describes the various renal toxicities of NSAIDs, including interstitial nephritis, analgesic nephropathy, and alterations in renal blood flow. It examines the case for “renal sparing” NSAIDs and reviews data on the COX-2-selective drugs. The conclusion that COX-selective drugs have the same potential for adverse effects as older NSAIDs is well supported.

27. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282:1929–33.

This is a key article in describing the rate of clinically important adverse GI events with rofecoxib. The analysis reviewed eight double-blind, randomized studies lasting up to 12 months that compared rofecoxib in doses of 12.5–50 mg/day with ibuprofen 800 mg 3 times/day, diclofenac 50 mg 3 times/day, or nabumetone 1500 mg/day. Patients in these studies were not allowed to use low-dose aspirin. Among 5435 patients, the 12-month cumulative incidence of upper GI perforations, symptomatic ulcers, or upper GI bleeding (PUBs) was 1.3% with rofecoxib versus 1.8% with the comparator NSAIDs ($p=0.046$) and the rate per 100 patient-years was 1.33 with rofecoxib compared to 2.60 with other NSAIDs ($p=0.06$). The rate of dyspepsia in the studies was 23.5% for rofecoxib versus 25.5% for comparators in the first 6 months. However, the analysis probably had some biases against rofecoxib. Because patients who had asymptomatic ulcers at scheduled endoscopy were eliminated from the studies, the reported data probably underestimated the incidence of PUBs for patients in a usual setting, and because asymptomatic ulcers were higher with the comparator NSAIDs, the underestimation is greater for that group. In addition, the rate of PUBs was surprisingly high for placebo (cumulative incidence of 0.9% at 4 months) and the rate of complications with rofecoxib was not significantly higher than on placebo.

28. Goldstein JL, Silverstein FE, Agrawal NM, et al. Reduced risk of gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J Gastroenterol* 2000;95:1681–90.

This article complements the one above (Reference 27) by reviewing GI complications with celecoxib. It is a pooled analysis of 14 multicenter randomized, controlled trials with a median duration of 12 weeks that enrolled 11,008 patients, and an analysis of one long-term, open-label trial with 5155 patients who received celecoxib for up to 2 years. The principal outcome analyzed was developing bleeding, perforation, or gastric outlet obstruction. Baseline characteristics of the comparison groups in the randomized studies were similar. In these studies, the annualized incidence of complications was 0.20% for celecoxib, versus 0% on placebo and 1.68% on comparison NSAIDs (naproxen 500 mg 2 times/day, diclofenac 50 or 75 mg 2 times/day, or ibuprofen 800 mg 3 times/day). During the open-label trial with celecoxib 100–400 mg 2 times/day, the annual incidence was 0.18%. In the randomized, controlled trials, 11% of patients took aspirin concurrently and 16% used it in the open-label study. This study is more reassuring than the rofecoxib analysis because the rate of complications with celecoxib was 8-fold lower than other NSAIDs, and the rates were consistent between short- and long-term studies.

29. Crofford LJ, Oates JC, McCune WJ, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase inhibitors: a report of four cases. *Arthritis Rheum* 2000;43:1891–6.

A concern that may limit the usefulness of COX-2 inhibitors is potential cardiovascular toxicity. Cyclooxygenase-2 specific drugs inhibit production of vascular prostacyclin but not platelet thromboxane, thus theoretically shifting the body toward a prothrombotic state. This case series is the first to give credibility to an actual clinical risk. All four patients described developed ischemic complications a short time after starting celecoxib therapy. All had several risk factors for thrombosis, including connective tissue diseases, Raynaud's phenomenon, anticardiolipin antibodies, lupus anticoagulant, or a history of antiphospholipid syndrome. None were taking antiplatelet drugs or receiving adequate anticoagulation. Therefore, the risk may be minimal in a healthier population, but caution is suggested in prescribing COX-2 drugs to patients at risk of thrombosis.

30. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled study. *JAMA* 2000;284:1247–55.

This double-blind, randomized study was designed to compare the incidence of clinically meaningful adverse GI events with a supratherapeutic dose of celecoxib (400 mg 2 times/day) versus ibuprofen 800 mg 3 times/day or diclofenac 75 mg 2 times/day. More than 8000 adult patients were enrolled; 7968 of those patients received at least one dose of study drug, and 4573 patients completed 6 months of therapy. Baseline characteristics of patients were well matched. Concurrent low-dose aspirin for cardiovascular prophylaxis was allowed and used in 22% of participants. The annualized rate of GI bleeding, perforation, and obstruction for celecoxib and the two NSAIDs was 0.76% and 1.45% ($p=0.09$), respectively, and the rate of all symptomatic ulcers was 2.08% on celecoxib versus 3.54% on NSAIDs ($p=0.02$). Of note, the safety advantage of celecoxib was virtually lost in patients taking concurrent low-dose aspirin. The outcome

rates in aspirin users in the celecoxib and NSAID groups were 2.01% versus 2.12% for bleeding, perforation, and obstruction, and 4.70% versus 6.00%, respectively, for all symptomatic ulcers. In a secondary outcome analysis, the rate of cardiovascular events did not differ between drugs regardless of aspirin use.

31. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520–8.

This study was strongly analogous to the Celecoxib Long-term Arthritis Safety Study (CLASS) because each consulted with the Food and Drug Administration (FDA) about study design to prove better GI safety versus older NSAIDs. A total of 8076 patients were randomized to receive rofecoxib 50 mg/day or naproxen 500 mg 2 times/day. Patients were not allowed to take aspirin or other antiplatelet drugs concurrently. Study groups were well matched and 5742 patients continued their drugs for at least 8 months. Clinical efficacy in RA was similar between groups. Total GI events per 100 patient-years were 2.1 with rofecoxib versus 4.5 on naproxen ($p<0.001$). Respective rates of complicated events (e.g., perforation, obstruction, and severe upper GI bleeding) were 0.6 and 1.4 per 100 patient-years ($p=0.005$). Because patients in this study were not allowed to use aspirin, it is unknown how low-dose aspirin would affect GI outcome rates. The incidence of myocardial infarction was 0.4% on rofecoxib versus 0.1% on naproxen, although overall mortality and death from all cardiovascular causes were similar.

SELF-ASSESSMENT QUESTIONS

Questions 1–3 pertain to the following case.

You are working in a family medicine clinic with several physicians when you see a 63-year-old woman who presents with a history of chronic pain of the right knee with no synovial swelling or tenderness. On questioning, she states that she recently retired from a job as an executive secretary. Her past medical history consists of hypothyroidism treated with levothyroxine 0.15 mcg/day and depression treated with sertraline 50 mg/day. She also takes estrogen replacement therapy. She is 5 feet tall and weighs 159 pounds. She does not smoke but drinks socially with her friends. Laboratory studies reveal an erythrocyte sedimentation rate of 33 (normal less than 30) and a negative rheumatoid factor. Physical examination reveals Heberden's nodes in her fingers, but the examination is otherwise unremarkable. Knee radiology supports a diagnosis of osteoarthritis (OA).

1. Which one of the following is the *major* risk factor disposing this patient to OA?
 - A. Her age.
 - B. Her occupation.
 - C. Her weight.
 - D. Her gender.
2. Which one of the following factors is most likely to be predictive of the long-term prognosis of this patient's OA?
 - A. The knee involvement.
 - B. Her weight.
 - C. Her erythrocyte sedimentation rate.
 - D. Her gender.
3. Her physician suggests several possibilities as the initial drug treatment. When asked for your opinion, which one of the following drugs should you recommend?

- A. Acetaminophen 1 g 4 times/day.
- B. Naproxen 500 mg 2 times/day.
- C. Celecoxib 200 mg 1 time/day.
- D. Intra-articular sodium hyaluronate for five weekly injections.

Questions 4–7 pertain to the following case.

Later the same day you see a 73-year-old man with chronic OA of the knee. He visits the clinic due to severe knee pain at rest, made worse by walking. A total knee replacement is being considered for the near future but he may be a poor surgical risk. The patient currently takes acetaminophen 900 mg 4 times/day for the arthritis. His past medical history includes renal insufficiency (serum creatinine 2.1 mg/dl), gastroesophageal reflux disease, coronary artery disease, and congestive heart failure. Current drugs are ranitidine 150 mg 2 times/day, atenolol 100 mg/day, lisinopril 10 mg/day, furosemide 40 mg 2 times/day, and digoxin 0.125 mg/day. His is 5 feet, 8 inches tall and he weighs 160 pounds.

4. Which one of the following treatments should you recommend?
 - A. Celecoxib 200 mg 1 time/day.
 - B. Naproxen 500 mg 2 times/day.
 - C. Intra-articular triamcinolone hexacetonide in one injection.
 - D. Intra-articular sodium hyaluronate for five weekly injections.
5. Which one of the following interventions is most useful to include as an addition to this patient's OA treatment plan?
 - A. Quadriceps muscle strengthening exercises.
 - B. Chondroitin 400 mg 3 times/day.
 - C. S-adenoyl-methionine (SAME) supplements.
 - D. Tetracycline 500 mg 4 times/day.

6. This patient can best be monitored for long-term changes in OA symptoms and OA-related disability by which one of the following?
- Visual analog scale (VAS) for arthritis pain.
 - The Medical Outcomes Study Short Form-36 questionnaire.
 - The Western Ontario and McMaster Universities (WOMAC) index.
 - Physician global assessment.

The physician decides to order celecoxib 200 mg 1 time/day. One month later, the patient returns to clinic for follow-up. He states he obtains good pain relief with this drug and he is quite happy with it except for occasional abdominal discomfort. A physical examination and routine laboratory work done to monitor celecoxib shows no change in any parameters.

7. However, on reviewing his drug profile, which has not changed from above except for the celecoxib, you should recommend what alteration in drug regimen?
- Discontinue ranitidine.
 - Add clopidogrel 75 mg/day.
 - Add glucosamine 500 mg 3 times/day.
 - Discontinue ranitidine and add omeprazole 20 mg 1 time/day.
8. A 70-year-old man visits your community pharmacy to ask your advice. He was diagnosed with OA of the hip 1 year ago. He has found that over-the-counter (OTC) ibuprofen 600 mg 4 times/day provides excellent relief and allows him to perform normal daily activities. However, he increased the dose on his own to effective amounts and has developed considerable nausea and bloating. He has no history of peptic ulcer and there has been no change in stool color. Which one of the following interventions should you recommend he discuss with his physician?
- Add ranitidine 150 mg 2 times/day.
 - Change treatment to naproxen 500 mg 2 times/day.
 - Change treatment to rofecoxib 25 mg/day.
 - Obtain a prompt endoscopy.
9. Mrs. Jones is a 67-year-old woman with OA of the hands, knees, and hips. She has not responded at all to acetaminophen in the past but has been almost pain-free since starting etodolac 400 mg 2 times/day 11 months ago. Recently, she has complained of persistent abdominal pain, and a 2 g/dl drop in hemoglobin was noted on a complete blood cell count in the physician's office. Subsequent endoscopy confirmed a gastric ulcer 7 mm in diameter in the antrum of the stomach. Biopsy of the ulcer crater was negative for malignancy but positive for *Helicobacter pylori*. She has never had a peptic ulcer before. Which one of the following should you recommend to Mrs. Jones and her physician?
- Discontinue all nonsteroidal anti-inflammatory drug (NSAID) therapy and begin ranitidine 150 mg 2 times/day for 8 weeks.

- Continue etodolac and begin ranitidine 150 mg 2 times/day for 8 weeks.
- Discontinue all NSAID therapy and begin *H. pylori* treatment with ranitidine, bismuth citrate, and clarithromycin for 2 weeks.
- Continue etodolac and begin lansoprazole 15 mg/day for 8 weeks.

Questions 10 and 11 pertain to the following case.

A 57-year-old woman who had symptomatic OA for about 1 year is referred to you for counseling due to noncompliance. Although she has a prescription for etodolac 300 mg 3 times/day to treat her OA in the hip, she says that she only takes it when she feels enough pain to interfere with taking care of her garden. When she does take it she gets excellent relief with no adverse effects.

10. Which one of the following is the best intervention at this time?
- Complement the patient for her wise use of drugs and encourage her to continue in the same way.
 - Explain the importance of taking NSAIDs regularly and encourage her to take the etodolac exactly as prescribed.
 - Ask her physician to change drugs to a 1 time/day NSAID such as nabumetone 1 g/day.
 - Recommend that she apply capsaicin cream to her hands regularly so she can discontinue the etodolac.
11. The patient mentions to you that her younger sister is concerned about getting OA and would like do something to prevent the disease. Which one of the following prophylactic measures can you recommend?
- Glucosamine 500 mg 3 times/day.
 - A nutritional supplement containing antioxidant vitamins.
 - Aerobic exercise.
 - Rofecoxib 12.5 mg 1 time/day.

Questions 12 and 13 pertain to the following case.

M.L. is a 36-year-old woman who has aggravated right knee OA that developed during her career as a tennis professional. The knee is not swollen but is extremely painful on walking. She was not taking anything before aggravating the knee but she has responded fairly well to acetaminophen in the past. Her medical history is otherwise unremarkable but she is presently 8 months pregnant with her second child.

12. Which one of the following options is best?
- Rofecoxib 25 mg/day.
 - Acetaminophen 1 g 4 times/day.
 - Naproxen 500 mg 2 times/day.
 - Triamcinolone hexacetonide injection into the knee given once.
13. A year later, M.L. returns to the clinic with another exacerbation of knee pain. She has been using nabumetone 1 g/day for the past 3 months without much relief. Currently, her pain is 7 on a scale of 1 to 10. Her

physician decides that a local knee injection of some type should be used. Which one of the following treatments should you suggest?

- A. Intra-articular hylan G-F 20 for three weekly injections.
 - B. Triamcinolone hexacetonide injection given once.
 - C. Intra-articular sodium hyaluronate for five weekly injections.
 - D. Methylprednisolone injection given once.
14. A 67-year-old man presents to the family practice clinic with a 5-year history of episodic stiffness and pain of the right hip that radiates to the groin. The pain has become worse in the past 3 weeks due to strenuous exercise. Pain occurs after the patient walks half a mile or climbs two flights of stairs. Over-the-counter acetaminophen (less than or equal to 2600 mg/day) had worked to control the pain until the past few weeks. Medical history includes peptic ulcer disease diagnosed radiologically and successfully treated 10 years ago. Current drugs are hydrochlorothiazide 25 mg/day for hypertension and glyburide 5 mg 2 times/day for diabetes. Findings on physical examination include restricted range of motion of the right hip and pain on abduction. Which one of the following should be prescribed now?
- A. Acetaminophen increased to 4 g/day.
 - B. Naproxen 500 mg 2 times/day.
 - C. Naproxen 500 mg 2 times/day plus misoprostol 200 µg 4 times/day.
 - D. Celecoxib 200 mg 1 time/day.
15. A 58-year-old woman presents to the clinic with a 3-week history of intermittent mid-epigastric pain that is gnawing in character, not related to meals, and sometimes precipitated by stress. She has had no nausea, vomiting, or black stools. The patient had a similar problem 3 years ago that was diagnosed and treated as anxiety. She has a 3-year history of left hip pain that was radiographically diagnosed as OA 6 months ago. Naproxen 500 mg 2 times/day was prescribed at that time. The patient used naproxen occasionally until a month ago when she started taking the full dose plus OTC ketoprofen. Medical history is otherwise negative. She does not smoke or drink and lives alone. Findings on physical examination include left hip pain on rotation, and mid-epigastric tenderness with no rebound tenderness or radiation. Which one of the following is the optimal prescription for this patient?
- A. Continue NSAID therapy and prescribe omeprazole 20 mg/day.
 - B. Discontinue ketoprofen and prescribe misoprostol 200 µg 4 times/day.
 - C. Discontinue both NSAIDs and prescribe rofecoxib 25 mg/day.
 - D. Discontinue both NSAIDs and prescribe acetaminophen up to 4 g/day.

Questions 16 and 17 pertain to the following case.

A 60-year-old woman who works as a janitor at the local university presents today with a painful right knee (described

as 5 on a scale of 1 to 10) that has bothered her for about 1 month. She has not taken any drug treatment for it but puts ice on the knee when she gets home from work, which helps. She has been in excellent health until now and has not seen a physician in 23 years. On physical examination, crepitus is heard on motion, the knee is swollen and has a moderately large effusion. She does not smoke or drink and lives with her husband. Radiographic study of the affected knee shows advanced loss of joint space.

16. Which one of the following is the best drug therapy now?
- A. Acetaminophen 1 g 4 times/day.
 - B. Ibuprofen 400 mg 3 times/day.
 - C. An injection of intra-articular methylprednisolone.
 - D. Sustained-release oxycodone 10 mg 2 times/day.
17. The physician chooses to treat with intra-articular methylprednisolone and recommendations for exercises to strengthen the quadriceps muscle. The patient responds well. Three months later she returns with the same symptoms and again responds to a steroid injection but this time relief only lasts for 2 weeks before she is back with significant pain in the knee. The physician requests your advice. Which one of the following is the best therapy now?
- A. One injection of triamcinolone hexacetonide.
 - B. A 3-week course of intra-articular hylan G-F 20.
 - C. Tramadol 50 mg 4 times/day.
 - D. Ibuprofen 600 mg 4 times/day.
18. A 55-year-old, 175-pound school teacher developed a tender swelling in her right knee 4 months ago. Since then she has experienced intermittent pain in her right knee and hip. Currently, she has moderate stiffness in the hip and knee after inactivity, and experiences mild pain (3 out of 10 on a VAS) on ambulation. Examination of her hands reveals Heberden's nodes in her fingers, limitation of flexion in the right hip to 90 degrees, patellar crepitus, and moderate tenderness and swelling of the right knee. She has used no drug therapy up to now except glucosamine which was given to her by her friend, but that did not seem to help. Which one of the following is the best drug therapy for this patient?
- A. Ibuprofen 400 mg 3 times/day as needed.
 - B. Ibuprofen 800 mg 3 times/day.
 - C. Tramadol 50 mg 4 times/day.
 - D. Acetaminophen 600 mg 4 times/day.

Questions 19–21 pertain to the following case.

J.M., a 57-year-old woman, has had intermittent symptoms of pain in her hands for the past 12 months that make it difficult to perform her work as a secretary, as well as take care of her elderly mother at home. She has used acetaminophen for self-treatment but even "eating it like candy" has never helped at all. She has put off seeing a physician due to lack of health insurance, but was persuaded to come in today by her community pharmacist. Her physical examination is consistent with OA, showing both Heberden's nodes and Bouchard's nodes in her hands. She

also has some pain on abduction of the left hip. The rest of the physical examination is normal. Past medical history is important for a history of alcohol abuse (she has been sober for 10 years) and a 70 pack-year history of smoking (she is still an active smoker).

19. Her physician decides to use a NSAID. Which one of the following NSAIDs is best for her?
- Indomethacin 25 mg 3 times/day.
 - Ibuprofen 400 mg 3 times/day.
 - Rofecoxib 12.5 mg 1 time/day.
 - Nabumetone 1 g 2 times/day.
20. One month later, the patient returns claiming that her medication has been ineffective. She does not want to keep returning to the clinic to receive ineffective therapy. Which one of the following treatments is the best choice now?
- Naproxen 500 mg 2 times/day.
 - Celecoxib 200 mg 1 time/day.
 - Sustained release oxycodone 10 mg 2 times/day.
 - Glucosamine 500 mg 3 times/day plus chondroitin 400 mg 3 times/day.
21. Six months later the patient is doing well, with symptoms being mild and infrequent. She is able to perform her job and household duties without significant problems. In fact, she wants to stop her OA medication because she does not want to pay for it any more. How should you counsel this patient?
- Drugs must be continued for life to keep the symptoms under control and reduce progression of joint destruction.
 - She should reduce the dose of her drug so that she does not become tolerant to it.
 - She needs to see her physician about that decision because the physician will need to repeat her x-rays to see how the disease is progressing.
 - It is common for symptoms of OA to improve and as long as she is feeling fine she can stop the drug or use it as needed if she wants to.
22. One of the physicians at the family practice clinic is reading a new analysis of a homeopathic remedy for arthritis and finds the efficacy of the treatment described in terms of effect size. The effect size for the treatment is described as 0.22. You should explain that an effect size of this magnitude is generally considered to be of which one of the following?
- Small.
 - Moderate.
 - Large.
 - Uninterpretable without further information.
23. At your journal club you are describing a recent article on the effectiveness and safety of a new cyclooxygenase (COX)-2-selective drug. You are criticized for presenting this study because it is observational in design, even though it was well planned and reported,

and studied 8000 patients for 1 year. In debating the merits and weaknesses of this study, which one of the following statements should you include?

- Well-done, observational studies are weaker than randomized clinical trials and therefore usually provide incorrect information.
- Well-done, observational studies have greater external validity and therefore usually provide more valid information than randomized, clinical trials.
- Well-done, observational trials are flawed by so many confounding variables that they should not be used as a basis for evidence-based medicine.
- Well-done, observational studies often provide results that are similar in direction and magnitude as randomized, clinical trials.

Questions 24–26 pertain to the following case.

Mrs. Smith, a 67-year-old woman who has had OA for 10 years, is at the clinic complaining of severe pain in multiple joints, but especially her hips. The hip pain is described as being 9 on a 10-point scale. Her past medical history is notable for ischemic heart disease, hypertension, chronic renal impairment with a serum creatinine of 2.1, and long-standing type 2 diabetes with nephropathy. Her present drugs include naproxen 500 mg 2 times/day, lisinopril 10 mg 1 time/day, glyburide 5 mg 2 times/day, and amlodipine 10 mg 1 time/day. She does not smoke or drink and lives with her husband in her own home.

24. Which one of the following treatments should you recommend?
- Acetaminophen 1 g 4 times/day.
 - Celecoxib 200 mg 1 time/day.
 - Sustained-release oxycodone 10 mg 2 times/day.
 - Capsaicin 0.75% cream to affected joints.
25. On interviewing the patient she reveals that she has started taking four “health food” supplements. These are glucosamine 500 mg 3 times/day, chondroitin 400 mg 3 times/day, SAME, and fish oil capsules. Which one of the following supplements may need to be discontinued due to a possible adverse effect on her medical conditions?
- Glucosamine.
 - Chondroitin.
 - S-adenoyl-methionine.
 - Fish oil.
26. You are interested in knowing whether the treatments this patient is using have any effect on the underlying pathophysiology of the disease. To prove that any treatments have a disease-modifying effect in OA, which one of the following is the ideal monitoring parameter to follow?
- Lequesne OA index.
 - Magnetic resonance imaging of the knee.
 - Plain radiographs of the knee.
 - The Medical Outcomes Study Short Form-36 questionnaire.