Osteoarthritis: An Overview with diagnostic criteria

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Review Article

ABSTRACT

The prior view of OA as a "bland" disease related to aging and "wear and tear" of the joint has given way to views of a dynamic condition with multiple pathogenic contributors.[1,2] Traditional views of articular cartilage failure have centered on various genetic, metabolic, and biochemical factors. Recent data have elucidated the importance of local factors, as well as crystals and inflammation, in contributing to disease progression. The new pattern of OA considers the condition a heterogeneous disease with numerous factors leading to its pathologic hallmark of cartilage loss and the clinical manifestations of joint pain with movement.[3] This new and innovative concept of OA as phenotypic subsets associated with a primary abnormality has opened the door for more targeted investigation into disease pathophysiology and treatment strategies.[4,5]Ironically, despite its growing prevalence, OA remains a condition that is poorly understood. For example, recent concerns about the safety of several medications that are commonly prescribed for the treatment of OA have highlighted the deficiencies in its management. Historically, only symptom-relieving therapy has been available for OA. As pain is the most common complaint, the perennial focus of therapy has been on pain control. Our advances in the understanding of OA have led to treatment strategies that emphasize reduction of joint vulnerability and load, however. [6]Pharmacologic therapy in the 21st century has added cyclooxygenase (COX)-2 specific inhibitors, glucosamine and chondroitin, as well as viscosupplementation to the standard armamentarium. Clinical trials are currently under way for several potential disease-modifying agents that may significantly change the treatment approach for OA.[7,8]Within this review, the epidemiology and burden of OA will be explored, along with newer insights into the pathophysiology and evidence surrounding innovative pharmacologic and nonpharmacologic approaches for the management of this disabling condition.

Key words: *Rheumatism, Osteoarthritis, NSAIDS, Cartilage*

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INTRODUCTION

OA is the most common form of arthritis and the leading cause of disability in older adults. In fact, the condition disables approximately 13% of those 60 years of age and older and compromises the quality life of more than 20 million Americans.[9] As the American population ages and the epidemic of obesity increases, the prevalence of OA is also expected to rise significantly. It has been estimated that by 2020, the number of those individuals with OA will double.[8] Economic analyses have suggested that the impact of OA in the United States is greater than $60 billion per year. Based on a 2004 US National Inpatient Sample, knee OA, the most frequent form of lower extremity OA, was the primary diagnosis for 430,000 hospital discharges and $14 billion of hospital charges.[10] In fact, a landmark government study suggests nearly 1 in 2 Americans (46%) will develop painful knee OA in their lifetime, particularly among those who are obese.[11] Today, OA is second only to ischemic heart disease as a cause of work disability in men over the age of 50 years.

OA is a slowly progressive musculoskeletal disorder that can occur in any joint but is most common in selected joints of the hand, spine, and the lower limb weight-bearing joints-the hips, knees, and feet (Figure 1).[7] The prevalence of OA in all joints increases with age.12 In some populations, more than 75% of adults aged 65 years and older have OA involving one or more joints. Epidemiologic studies further suggest that clear sex-specific differences exist[13,14] Before 50 years of age, the prevalence of OA in most joints is higher in men than in women. After 50, however, women are more often affected with hand, foot, and knee OA than men.[7,12]

REVIEW OF JOINT ANATOMY AND PHYSIOLOGY

The structural classification of joints is based on the presence or absence of a synovial joint cavity, which is the space between the articulating bones and the type of connective tissue binding the bones. Structurally, joints may be classified in 3 types-(1) *fibrous*, in which no synovial cavity exists, and the bones are bound by fibrous connective tissue; (2) *cartilaginous*, in which no synovial cavity exists, and the bones are held together by cartilage; and (3) *synovial*, in which a synovial cavity exists, and the bones forming the joint are united by a surrounding articular capsule and frequently by accessory ligaments. In the case of OA, the primary joints affected are cartilaginous and synovial. Two types of cartilaginous joints exist: *synchondrosis*, in which the connecting material is hyaline cartilage found along the ribs and the costal cartilages of the rib cage; and *symphysis*, in which the connecting material is a broad flat disc of fibrocartilage and can be found in the pubis and the joints formed by the intervertebral discs.[15] Synovial joints are also characterized by the presence of articular cartilage, which covers the surfaces of the articulating bones but does not bind the bones together. These joints are surrounded by a sleeve-like articular or joint capsule that encloses the cavity and unites the articulating bones. The joint capsule itself is made up of the fibrous capsule consisting of dense

collagenous tissue, which provides structural integrity and an inner lining layer called the *synovial membrane*. The synovial membrane secretes synovial fluid, which consists of hyaluronic acid and interstitial fluid formed from blood plasma, and provides lubrication within the joint itself [7]. As seen in Figure 1, the synovial joint is a very well engineered structure. Frictionless motion is provided by the combination of the smooth articular cartilage surface as well as lubrication of both the articular cartilage and the synovial membrane together, which make up the entire surface area of the inside of the joint. Shock absorption to the joint is provided by a combination of structures, including articular cartilage, subchondral bone (the bone beneath the cartilage), and the soft tissue structures (joint capsule and ligaments). Because of its resilient nature and ability to compress, articular cartilage is an excellent shock absorber, but its thickness and overall volume are far less than bone or soft tissues [7].

Microscopically, the articular cartilage consists of a dense network of collagenous and elastic fibers embedded in a matrix of chondroitin sulfate and proteoglycans, as well as mature cartilage cells or chondrocytes. These fibers provide the cartilage its tensile strength, whereas the matrix provides its resilience. Both the collagen and proteoglycans are extremely important for normal function of articular cartilage. Each proteoglycan aggregate contains the backbone of a glycoprotein with side chains of glycosaminoglycans. The glycosaminoglycans are highly ionized, long, unbranched polysaccharides consisting of repeating disaccharide units. Because of the repulsion of the side chains, as well as the attraction of water to the molecule related to its negative charge, the proteoglycans provide the stiffness to the cartilage and resist compression. Regarding the chondrocyte, this is the only cell type residing in the adult cartilage matrix and has a low metabolic activity, surviving under relatively hypoxic conditions and in the absence of a vascular supply. Ultimately, this cell is responsible for remodeling and maintaining the structural and functional integrity of the cartilage matrix yet possesses little regenerative capacity.[3-5]

PATHOPHYSIOLOGY OF OA

The pathophysiology of OA is more complex and intricate than just a disease of wear and tear on the joints and cartilage. In fact, the disease can be viewed as the clinical and pathologic outcome of a range of disorders that cause structural and functional failure of the synovial joints with loss and erosion of articular cartilage; subchondral bone alternations; synovial inflammatory responses; and bone and cartilage overgrowth. As discussed earlier, OA can occur in any of the synovial joints; however, the most common target joint affected is the knee joint, whereas hip, shoulder, spine, and toe are less frequently afflicted. Unlike rheumatoid arthritis (RA), OA mostly affects only one or a few joints. The global risk factors for OA are advanced age (older than 65 years), obesity, and any form of joint trauma (see Figure 2). In some families, OA may be inherited, in which genetic factors may cause disruption of chondrocyte differentiation and function. Specifically for OA in the hip, physical workload, high-intensity sporting activities,

and obesity appear to be major risk factors. Ultimately, destruction of cartilage in OA is considered to be a chondrocyte-mediated process. The etiological risk factors listed in Figure 2 cause biomechanical modulation of chondrocyte function, either through abnormal loading on normal cartilage or normal loading on abnormal cartilage. For example, high-intensity sporting activities may place extreme mechanical loading on normal cartilage, whereas aging may contribute to the abnormal state of cartilage. Nonetheless, once initiated, a vicious pathophysiologic process ensues, in which OA may slowly and insidiously progress from early-to late-stage disease, ultimately leading to poor health outcomes (Figure 2). As seen in Figure 3, during the initiation phase, the normally quiescent chondrocytes, as well as the synovial cells, respond to repetitive excess mechanical loading via stress-induced intracellular signals that mediate the production of cytokines, chemokines, other inflammatory mediators (eg, prostaglandin E2, bradykinin, interleukin [IL], tumor necrosis factora nitric oxide), free oxygen radicals, substance P, and cartilage-degrading proteinases—all of which are extremely toxic and destructive to cartilage. As the disease moves from early to late stages, cartilage matrix is broken into degradation products, which further upregulate these processes. In an attempt to repair damaged cartilage, chondrocytes undergo proliferation and cloning, which in turn overproduce numerous catabolic (eg, matrix metalloproteinases, cathepsin K, and ADAMTS proteinases) and anabolic (eg, bone morphogenetic protein and tissue growth factor-ß) substances. As cartilage breaks down, it begins to undergo calcification known as *tidemark duplication*. At the bone–cartilage interface, changes occur in the underlying bone, which thickens with the formation of bony outgrowths (osteophytes) along with the presence of microfactures as a result of invading blood vessels from the subchondral bone. With these blood vessels, sensory nerves also penetrate the area, thus leading to chemical and mechanical stimulation of the nerve endings in these vascular walls. In total, this vicious cycle ends with joint destruction and significant pain burden.

GOALS OF OA MANAGEMENT

When considering the overall management goals for patients with OA, care plans should be individualized to address findings on clinical examination, which include obesity, misalignment, and muscle weakness, in addition to joint pain. Pharmacists need to elicit accurate medical histories regarding medications and comorbidities. Comprehensive management strategies should always include a combination of treatment options directed toward the common goal of alleviating pain and increasing tolerance for functional activity. Treatment, both pharmacologic (Table 1) and nonpharmacologic, should be extremely flexible for the patient so that it can be altered according to functional and symptomatic responses.

PHARMACOLOGIC THERAPY

Nonnarcotic Analgesics

Acetaminophen

Acetaminophen is considered to be the first-line pharmacologic agent recommended

by the American College of Rheumatology, the European League Against Rheumatism, and the OA Research Society International Treatment Guideline Committee for mild-to-moderate OA.[16-18] In a meta-analysis of 10 randomized controlled trials, acetaminophen was associated with pain relief (effect size: 0.21, 95% confidence intervals: 0.02- 0.41) but showed no improvement in overall functional scores.[19] Based on these data, acetaminophen appears to be effective for pain relief and should not be expected to impact stiffness or function.

Capsaicin

Topical capsaicin contains a lipophilic alkaloid extract from chili peppers, which not only depletes substance P from neurons but activates and sensitizes peripheral c-nocioreceptors. The agent can be considered as an alternative to systemic pharmacotherapy or as an adjunct when response to conservative therapy is suboptimal. In a doubleblind study of patients with knee OA, Deal and colleagues found that capsaicin cream 0.025% relieved pain in 80% of patients after 2 weeks, compared with those receiving placebo.[20]

Tramadol

For decades, tramadol has demonstrated long-term safety and efficacy for the treatment of moderate-to-severe pain and has demonstrated fewer adverse events, compared with narcotic analgesics.[21,22] Tramadol exhibits a unique mechanism of action as it binds supraspinally to μ-opioid receptors and also weakly inhibits spinal reuptake of norepinephrine and serotonin. The agent can be used alone for moderate-to-severe pain or in combination with conventional pharmacotherapy when additional pain relief is warranted.[22] Tramadol is formulated as an immediate-release (IR) tablet, a combination product with acetaminophen, and a sustained-release (SR) formulation. In patients with knee OA, IR tramadol significantly reduced naproxen dose (P = .021) and maintained similar analgesic efficacy in patients who achieved pain relief with naproxen.23 Compared with placebo, the SR formulation has been shown to significantly improve physical function, joint stiffness, sleep quality, and pain reduction (P <.05) for patients with knee or hip OA.[24,25]

Non-acetylated salicylates

The nonacetylated salicylates such as salsalate and choline magnesium trisalicylate inhibit prostaglandin synthesis but to a lesser extent than other nonsteroidal anti-inflammatory drugs (NSAIDs). Thus, whereas these agents can be considered in patients with mild renal impairment or those at risk for gastrointestinal (GI) bleeding, their effects on pain may not be as substantial. **NSAIDs**

NSAIDs are often added or substituted for the treatment of mild-to-moderate pain associated with OA in patients who do not adequately respond to acetaminophen.16-18 Of note, many providers will turn to an NSAID first for pharmacologic management of OA based on greater efficacy and patient preference.[26-28] NSAIDs can be characterized as either nonselective (eg, aspirin, naproxen, ketoprofen, and ibuprofen) or selective (COX-2 inhibitors).29 The principal mechanism of action for the

nonselective NSAIDs is the inhibition of both COX-1 and COX-2 pathways, which inhibit the production of prostaglandins and other mediators that cause pain and inflammation. As a review, COX-1 acts more to produce "housekeeping" prostaglandins that mediate normal platelet function and renal blood flow and protect the GI mucosa. COX-2 mediates inflammation as well as pain and fever, however.[29] The COX-2 inhibitors such as celecoxib, rofecoxib, and valdecoxib have been shown to demonstrate analgesic efficacy comparable with that of traditional NSAIDs but with a more favorable GI side-effect profile.[30-32] Unfortunately, despite their advantages, the routine use of NSAIDs in patients with OA has many disadvantages. For example, NSAIDs are attributed to over 16,500 deaths and over 103,000 hospitalizations per year in the United States, predominantly for their GI toxicity but also for their renal and cardiovascular side effects. It is extremely important to note, however, that all NSAIDs, both selective and nonselective, have been associated with an increased risk of myocardial infarction and stroke. Both types of NSAIDs are also associated with fluid retention, hyperkalemia, and acute renal failure and should be avoided in patients with renal and/or heart failure. Because of this increased risk for cardiovascular events, rofecoxib and valdecoxib were withdrawn from the US market in 2005. Only celecoxib can presently be found in US pharmacies. Product labeling for all NSAIDs now contains black box warnings stating these concerns.[33] In 2007, the American Heart Association (AHA) published an advisory statement regarding the use of NSAIDs in patients with underlying cardiovascular disease or underlying risk factors for heart disease.[33]

They suggested a step-wise approach be taken when considering pharmacotherapy in this population. Per the recommendations, acetaminophen, aspirin, tramadol, or short-term use of narcotic analgesics should be considered first-line, followed by nonacetylated salicylates. The next steps consist of consideration of NSAID therapy, but in the following order: nonselective COX-2 inhibitors, NSAIDs with some COX-2 activity, and finally, COX-2 selective agents. The AHA warrants that before adding an NSAID, consideration should be given to patients with a low risk for thrombotic events and that the lowest possible NSAID dose should be initiated. Once an NSAID is started in a patient with cardiovascular disease, pharmacists should keep a close eye on worsening blood pressure, edema, renal function, or possible GI bleeding. If any of these adverse events should arise, the offending agent should be immediately discontinued; the dose of the medication reduced; and/or an alternative agent considered for pain control [33]. So, what are the best strategies for avoiding drug toxicities for patients who require NSAIDs? First, pharmacists need to stratify patients who are at high risk for peptic ulcer disease or GI toxicity, which include those older than 65 years of age, those taking anticoagulants, and those with comorbid medical conditions or a history of peptic ulcer disease or GI bleeding.[30] For these patients, a nonselective NSAID plus a gastroprotective agent (eg, a proton pump inhibitor [PPI] or misoprostol) or a selective COX-2 inhibitor

can be considered [34]. Data suggest that COX-2 inhibitors may have a GI safety profile similar to that of a nonselective NSAID with a PPI. Spiegel and colleagues found that, compared with the NSAID plus PPI, the number needed to treat to prevent dyspepsia was 27 for the COX-2 inhibitors and 11 for the NSAID–PPI combination [35]. Second, pharmacists could recommend another formulation of an NSAID for patients who are at high risk for possible GI toxicity. For example, topical NSAIDs have been reported to be just as effective as oral NSAIDs in controlling knee pain.[36-38] This method of delivery is attractive, as it maximizes local delivery while minimizing systemic toxicity. The drawbacks are more local side effects such as rash, itching, and burning.[38] Presently, diclofenac epolamine is the only NSAID marketed as a topical patch; however, pharmacists should expect the appearance of further prescription NSAID patches on the market by 2009. Finally, pharmacists also need to screen and educate patients regarding potential drug–drug interactions with NSAIDs and aspirin. Concomitant use of low-dose aspirin may partially abrogate the protective GI effect of the COX-2 inhibitors. Furthermore, evidence indicates that ibuprofen, but not rofecoxib (a COX-2 inhibitor), acetaminophen, or diclofenac, interferes with aspirin's ability to irreversibly acetylate the platelet COX-1 enzyme. Although not proven, the AHA suggests that the addition of ibuprofen to aspirin could reduce the protective effect of aspirin on risk for atherothrombotic events.[33] In 2007, the FDA released a warning addressing the concern and management for this interaction (see Table 2).[33]

Intra-articular Agents

Corticosteroids

Intra-articular corticosteroids (IACs) have been widely used for the treatment of OA for many years. Few long-term studies exist, however, regarding their efficacy in this population. In a meta-analysis of 26 studies, IACs were found to be more effective than placebo in controlling pain at 1 to 3 weeks after injection; however, these data were limited at 4 to 24 weeks after injection, and symptomatic improvement was neither clinically nor statistically significant.[39] Based on these data, IACs should be considered only in patients who present with acute exacerbations of pain and signs of local inflammation with joint effusion with no evidence of infection or inflammatory arthritis on synovial fluid analysis.

Hyaluronan

Hyaluronan (hyaluronic acid) is a high-molecular-weight polysaccharide found in the extracellular matrix of connective tissue and is available in 2 intra-articular preparations, hyaluronate and hylan G-G 20, which are approved only for knee OA.[40] Presently, limited head-to-head comparisons exist between products, and no data support the use of one preparation over another.[41-44] The efficacy of the hyaluronic acid products has been shown to be comparable with that of NSAIDs and IACs. When specifically compared with IACs, however, these products are more efficacious from 5 to 13 weeks in regard to pain, range of motion, as well as improvement in global pain and function scores. Whereas several meta-analyses evaluating the efficacy of hyaluronan have

been published, they are not in complete agreement, largely due to varied study selection methods and publication bias. Nonetheless, most suggest that the effects of hyaluronan in knee OA are moderate at best.[40]

Narcotic Analgesics

For patients with moderate-to-severe OA who do not respond to acetaminophen or NSAIDs or cannot tolerate the side effects of these agents, American and European guidelines recommend opioid analgesics, which inhibit pain pathways by binding to the opioid receptor in the central nervous system.[16-18] The selection of the opioid analgesic for patients with chronic pain is influenced by factors such as pain intensity, pharmacokinetics, pharmacodynamics, previous adverse effects, and comorbid conditions. In addition, clinicians must consider available dosage forms (eg, transdermal, extended-release, short-acting, injectable) and dosing interval.[45,46] In a meta-analysis of 18 randomized, placebo-controlled trials, opioids were found to reduce pain intensity and slightly improve physical functioning in patients with OA. Whereas adverse events were reversible and not life-threatening, the number needed to harm in patients receiving opioids compared with placebo was 5.[45] Nonetheless, the investigators highlighted that long-term efficacy and safety of these drugs for OA is still to be determined due to the short mean trial duration of the studies evaluated.

Nutraceuticals

Since 2000, more than 800 brand-name nutriceuticals targeting OA have appeared on the US market. Of these, methylsulfonylmethane, *Harpagophytum procumbens* (devil's claw), *Curcuma longa* (turmeric), *Zingiber officinale* (ginger), S-adenosylmethionine (SAMe), chondroitin, and glucosamine have been touted to treat the aches and pains associated with OA.[47] Only the latter 2 have sufficient evidence supporting their use, however.

Glucosamine

Glucosamine is an amino sugar, which is a constituent of cartilage proteoglycans that is derived from marine exoskeletons or is produced synthetically. The molecule is required for the synthesis of glycoproteins, glycolipids, and glycosaminoglycans (also known as mucopolysaccharides). These carbohydrate-containing compounds are found in tendons, ligaments, cartilage, synovial fluid, mucous membranes, and structures in the eye, blood vessels, and heart valves.[48] In OA, glucosamine stimulates metabolism of chondrocytes in the articular cartilage and of synovial cells in the synovial tissues.[49] Evidence suggests that glucosamine may exhibit a disease-modifying effect, either stopping or slowing OA progression. Preliminary research suggests that glucosamine inhibits protein N– glycosylation and cytokine-stimulated production of mediators of inflammation and cartilage degradation as well as IL-1ß, which stimulates the gene expression and protein synthesis COX-2.[50] Glucosamine does not appear to directly affect COX. The effect of glucosamine on glucose metabolism has raised

a lot of concern.[51] Preliminary evidence suggests glucosamine might decrease glucoseinduced insulin secretion by inhibiting pancreatic glucokinase in the beta cells of the islet of Langerhans.[52] Other preliminary research highlights that glucosamine may impair insulin-mediated glucose uptake and metabolism in skeletal muscle. Animal research suggests that glucosamine could increase glucose metabolism through the hexosamine pathway, a pattern of change in glucose metabolism similar to that seen in type 2 diabetes. Animals may handle glucosamine differently than humans, however. The majority of human research suggests that glucosamine does not affect the pharmacokinetics of glucose; however, caution is still warranted when using glucosamine in this population.[53,54]

Regarding published evidence, a recently updated Cochrane review of 20 pooled studies evaluating 2570 patients with OA found glucosamine sulfate administration to be associated with a significant reduction in pain and improvement in function, compared with placebo.[55] This updated review did not find an improvement in overall global pain and functional subscales, however. Consistent with these findings are the results of the highly publicized multicenter Glucosamine-chondroitin Arthritis Intervention Trial, which randomized 1583 patients with OA of the knee to placebo, celecoxib, glucosamine hydrochloride, chondroitin sulfate, or the combination of glucosamine/chondroitin for 6 months.[56] The investigators found that, when used alone or in combination with chondroitin, glucosamine hydrochloride did not reduce symptoms of knee OA; however, subgroup analysis suggested that the combination may reduce pain in patients with moderate-to-severe symptoms, compared with placebo (P = .002). In the overall study group, the only significant response was seen in pain reduction for those on celecoxib, compared with those on placebo (P = .002). It is important to note that glucosamine hydrochloride was used instead of the sulfate salt. Presently, it remains unclear whether the hydrochloride salt has the same potential clinical benefits as the glucosamine sulfate preparations, as most studies showing efficacy for glucosamine in OA have used the sulfate salt.

Chondroitin

Chondroitin sulfate belongs to a class of very large molecules called *glucosaminoglycans*, which consist of glucuronic acid and galactosamine. Chondroitin is manufactured from natural sources, such as shark and bovine cartilage. Pure chondroitin is a relatively large molecule, weighing about 16,900 daltons. The species or tissue of origin and the extraction method used can affect the size of the molecule.[57] Chondroitin has been used in OA, as it is endogenously found in cartilaginous tissues of most mammals and serves as a substrate for the formation of the joint matrix structure. Some limited evidence suggests that chondroitin sulfate may protect cartilage against degradation by inhibiting the action of the enzyme leukocyte elastase, by decreasing the migration of polymorphonuclear leukocytes and by increasing the synthesis of proteoglycans and hyaluronic acid [57,58]. Less research is available on chondroitin than

on glucosamine sulfate. Furthermore, research findings have been inconsistent.[59] Preliminary evidence suggested that long-term chondroitin use may slow joint space narrowing and disease progression.[60-62] One analysis demonstrates that when pooling all chondroitin studies, the supplement may improve symptoms of pain; however, when only higher quality studies are included in the analysis, no beneficial effect is seen [63].

NONPHARMACOLOGIC THERAPY

Education, exercise, and weight loss are the mainstays in the management of OA and the promotion of general health. Unfortunately, data have shown that exercise programs, such as those emphasizing strength training and aerobic exercise, are considerably underused by patients with OA.[64] Recent meta-analyses have suggested that strengthening exercises may be more effective in the short-term reduction of pain and tenderness, whereas low-impact aerobic exercise, such as walking, biking, or swimming, is more effective in improving function. The role of education, development of strategies to ensure compliance, and willingness of providers to tailor a fitness program to a patient's individual needs should be considered more important than the prescription of any specific regimen of exercise. As mentioned earlier, obesity plays a significant role in the development of OA. Therefore, it comes as no surprise that data support that weight loss may produce symptomatic improvement in OA, particularly for those suffering from OA of the knee.[65-67]

Furthermore, the benefits in pain reduction may persist up to 1 year if the weight loss is maintained. In fact, the combination of exercise and weight loss may actually be superior to either intervention alone.[67] For more information and resources regarding life-improvement programs, such as nutrition and exercise for patients with OA, the Arthritis Foundation has developed an excellent Web site (http://www.arthritis.org/programs.php), as well as Johns Hopkins (www.hopkins-arthritis.org/mngmnt/mngmnt.html) and Tufts University(www.nutrition.tufts.edu/research/growingstrong er).

FUTURE DIRECTIONS

Presently, a critical need exists to improve the options to treat OA. First, structure-modifying efficacy has not been demonstrated beyond a doubt for any of the existing medications on the market. Second, existing drug therapies for OA reduce symptoms (mainly pain) but are only moderately effective and often leave patients with a substantial pain burden. With this in mind, new strategies are considering the contributions of synovial inflammation and subchondral bone changes by key molecular drivers rather than just focusing on OA as disease of the cartilage. Because OA progression cannot be halted if early events are not prevented, the current challenge will be to understand further the mechanisms regulating chondrocyte responses, thus modifying disease and minimizing pain burden. Based on current knowledge, these potential therapeutic targets consist of the inflammatory mediators (eg, prostanoids, cytokines, and chemokines), cellular receptors (cannabinoid, kinin, adrenergic, and glutamate), and ion channels [5]. Presently,

several disease-modifying drugs are in early development. Pfizer, Procter and Gamble, and Shionogi each have a selective matrix metalloproteinase inhibitor within phase 1 and 2 studies; GlaxoSmithKline is investigating a cathepsin K inhibitor; and sanofi-aventis has an IL-1ß-converting enzyme inhibitor (eg, pralnacasan). Regarding emerging therapies for chronic pain, several selective COX-2 inhibitors are undergoing clinical development. Lumiracoxib (Prexige; Novartis) is the one selective COX-2 inhibitor furthest along in development. Based on the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), lumiracoxib exhibited a 3-4-fold reduction in ulcer complications when compared with ibuprofen and naproxen after 52 weeks. Licofelone is a competitive inhibitor of lipoxygenase as well as COX-1 and COX-2. The agent decreases the production of both leukotrienes and prostaglandins, thus minimizing inflammation and pain with low GI toxicity. Finally, several companies are evaluating the potential of coupling a nitric oxide–donating moiety with either a salicylate or an NSAID such as naproxen or diclofenac, which could reduce not only GI toxicity but cardiovascular risks as well.[1,5,7,68]

ROLE OF THE PHARMACIST

OA is an extremely painful and debilitating condition affecting millions of Americans. Unlike RA, no disease-modifying agents exist. Nonpharmacologic treatment strategies can play a substantial role in pain control, as well as in disease prevention, however. Due to their position in the community, pharmacists are the most accessible health care professionals, thus allowing them to provide detailed and essential education and resources to patients with or at risk for developing OA. With the assistance of a pharmacist, patients with OA can make informed decisions regarding their pharmacotherapy and lifestyle modifications.

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Fig: 1

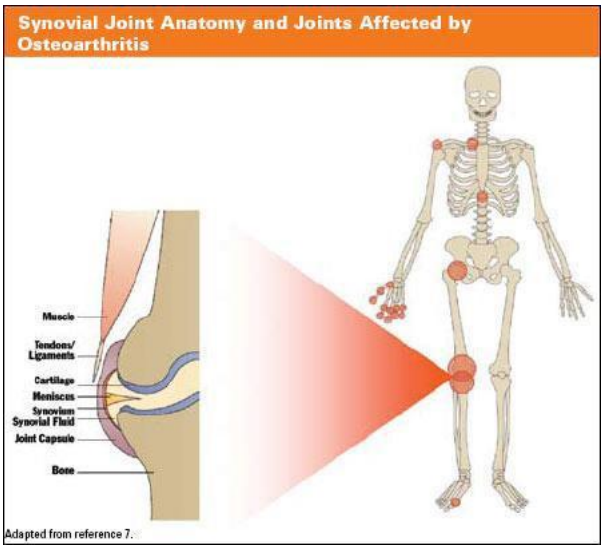
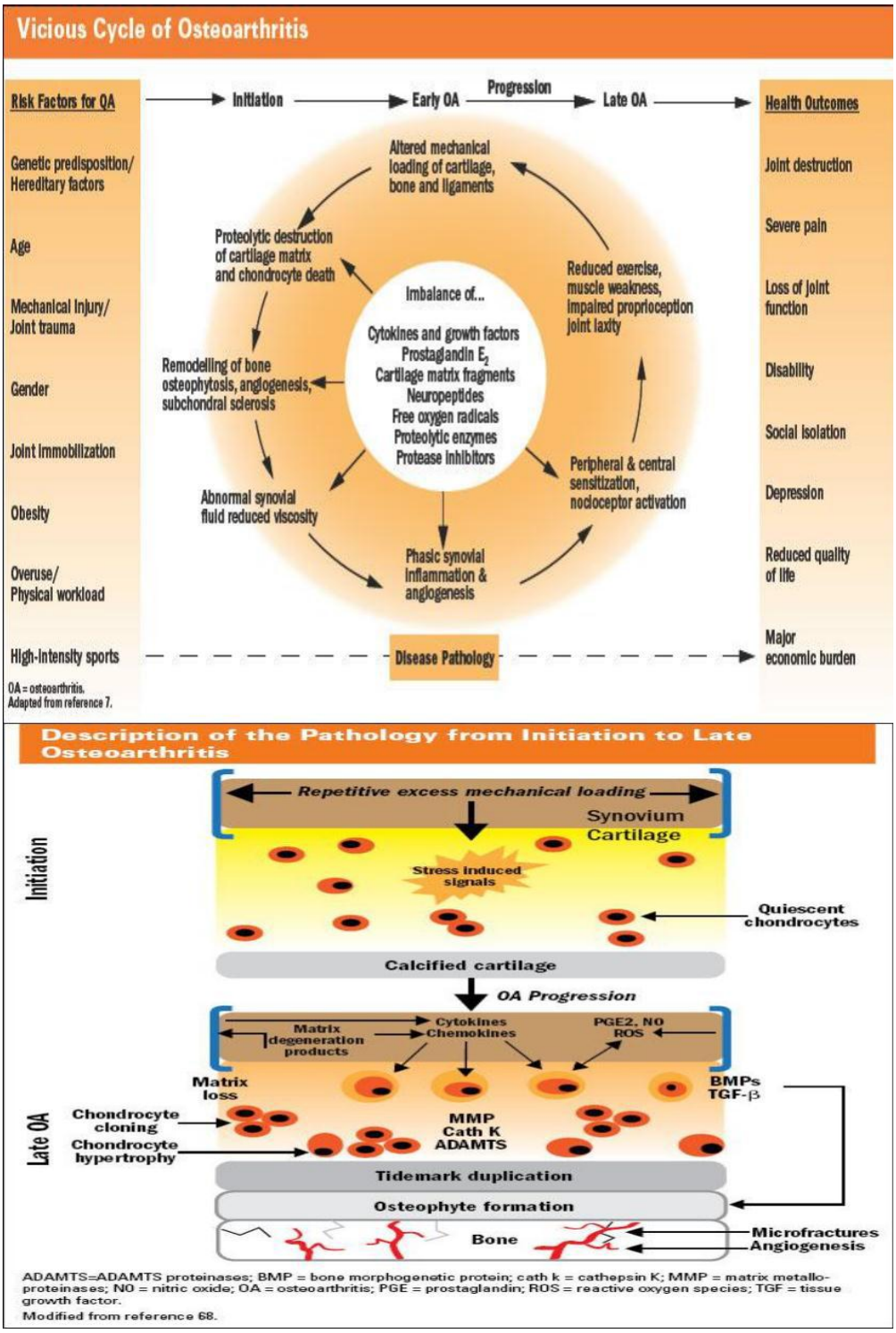


Fig: 2


Vicious Cycle of Osteoarthritis
Risk Factors for OA
Genetic predisposition/ Hereditary factors
Age
Mechanical injury/ Joint trauma
Gender
Joint immobilization
Obesity
Overuse/ Physical workload
High-intensity sports
Initiation
Early OA
Progression
Late OA
Health Outcomes
Joint destruction
Severe pain
Loss of joint function
Disability
Social isolation
Depression
Reduced quality of life
Major economic burden
Altered mechanical loading of cartilage, bone and ligaments
Proteolytic destruction of cartilage matrix and chondrocyte death
Reduced exercise, muscle weakness, impaired proprioception joint laxity
Imbalance of...
Cytokines and growth factors
Prostaglandin E2
Cartilage matrix fragments
Neuropeptides
Free oxygen radicals
Proteolytic enzymes
Protease inhibitors
Remodelling of bone osteophytosis, angiogenesis, subchondral sclerosis
Peripheral & central sensitization, nocioceptor activation
Abnormal synovial fluid reduced viscosity
Phasic synovial inflammation & angiogenesis
Disease Pathology
OA = osteoarthritis.
Adapted from reference 7.
Description of the Pathology from Initiation to Late Osteoarthritis
Initiation
Repetitive excess mechanical loading
Synovium
Cartilage
Stress induced signals
Quiescent chondrocytes
Calcified cartilage
OA Progression
Late OA
Matrix degeneration products
Cytokines Chemokines
PGE2, NO ROS
Matrix loss
BMPs TGF-β
Chondrocyte cloning
Chondrocyte hypertrophy
MMP Cath K ADAMTS
Tidemark duplication
Osteophyte formation
Bone
Microfractures
Angiogenesis
ADAMTS=ADAMTS proteinases; BMP = bone morphogenetic protein; cath k = cathepsin K; MMP = matrix metallo-proteinases; NO = nitric oxide; OA = osteoarthritis; PGE = prostaglandin; ROS = reactive oxygen species; TGF = tissue growth factor.
Modified from reference 68.

Therapeutic Agents Used to Treat Osteoarthritis

Drug	Mechanism of Action	Dosage	Benefit	Side Effects	Pharmacist Considerations
Nonnarcotic Analgesics					
Acetaminophen	Unknown, but may block pain-impulse generation in peripheral nervous system and to inhibit CNS prostaglandin synthesis	500-1000 mg 4 times daily	Reduces pain	Hepatoxicity if maximum daily dose exceeded or if used with alcohol	• Safe for elderly patients, patients with renal disease, and those with history of GI bleeding • Will not impact platelet function • Use with caution in patients with preexisting liver disease and those who drink ethanol (>2 drinks/day) regularly • Use with caution with high-dose warfarin, as it may increase INR
Capsaicin	Depletes substance P from neurons	Apply 0.025% cream 3 or 4 times daily		Local pain and redness	• Effective for hand and knee OA • 0.025% better tolerated than 0.075% • Assess efficacy after a 3- to 4-week trial
Tramadol	Weak μ-opioid receptor agonist, blocks reuptake of serotonin and norepinephrine	50-100 mg 4 times daily (IR)		Nausea, drowsiness, seizures (especially if history of seizures or administration with SSRIs, TCAs, and narcotic analgesics)	• May have abuse potential • Contraindicated in those with codeine allergies • Nausea can occur with higher doses • Must be renally dosed
Tramadol-Acetaminophen (37.5-mg/325-mg tablet)		2 tablets 4 times daily			
Choline magnesium, salsalate, trisalicylate	Decrease PMN aggregation, activation, and chemotaxis	1000-1500 mg twice daily	Reduces pain and inflammation	Tinnitus, CNS toxicity	• Nonacetylated salicylates • No effect on platelet aggregation • Effects on pain may be minimal
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)					
Ibuprofen	Inhibit COX-1 and COX-2	400 mg 3 or 4 times daily	Reduces pain and inflammation	Renal insufficiency, peripheral edema, bleeding, cardiovascular events, peptic ulcer disease; site reaction, dermatitis, pruritus, sensation of burning of skin (specifically for patch)	• Use lowest possible dose • Pain relief not dose-related • Use analgesic, not anti-inflammatory, doses • Higher doses = greater toxicity • Take with food • Use a GI protective agent with high-risk patients • Interaction with aspirin • Avoid in patients with renal disease or heart failure • For the patch, do not apply to damaged skin or wear during bathing or showering
Diclofenac		50 mg 2 or 3 times daily (orally); 1.3% patch (180 mg) to the most painful site twice daily			
Naproxen		250 mg twice daily			
Celecoxib	Selectively inhibits COX-2	200 mg daily	Reduces pain and inflammation	Edema; hypertension; renal insufficiency; skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis	• May increase risk for MI and stroke in high-risk patients • Contraindicated in those with sulfonamide allergies
Intra-articular Agents					
Methylprednisolone acetate	Multiple inhibitory effects on inflammatory cells and mediators	20-40 mg as a single local injection	Reduces pain and swelling quickly but only temporarily	Postinjection flare, transient flushing	• Reserved for patients with exacerbations of knee pain who also have effusions • Hips are not usually injected • Do not use more than once every 4 months due to possible cartilage and joint destruction • Only for short-term benefit (1 week)
Triamcinolone hexacetonide					
Triamcinolone acetonide					
Betamethasone sodium phosphate sodium acetate		6 mg as a single local injection			
Hylan G-F-20	Restores viscoelasticity of synovial fluid, augments flow of synovial fluid, and normalizes HA synthesis and/or inhibit hyaluronan degradation	Intra-articular injection for 3 or 5 consecutive weeks	Reduces pain and improves function	Injection site reaction	• Expensive • Symptom improvement may take several weeks • No data indicate which patients might best respond
Sodium hyaluronate					
Narcotic Analgesics					
Codeine-acetaminophen (30 mg/300 mg)	Opioid receptor agonist	1-2 tablets every 4-6 hours	Reduces pain	Nausea, sedation, dizziness, constipation, pruritus, respiratory depression, tolerance, dependence	• SR oxycodone has significant abuse potential • Dose should be titrated upward until pain is controlled • Maximum dose is limited by acetaminophen dose • Use with extreme caution in older adults due to susceptiblity to side effects
Hydrocodone-acetaminophen (5 mg/325 mg)					
Oxycodone-acetaminophen (5 mg/325 mg)					
Sustained-release oxycodone		10 mg 2 or 3 times daily			
Nutriceuticals					
Glucosamine	Stimulates metabolism of chondrocytes synovial cells; inhibits inflammation mediators and cartilage degradation	1500 mg daily or 500 mg 3 times daily	Reduces pain and may slow disease progression	Diarrhea, GI upset, flatulence	• Take with food • Sulfate salt preferred over hydrochloride salt • May take up to 4-6 weeks for symptom improvement
Chondroitin	Protects cartilage against degradation and is a substrate for cartilage matrix formation	200-400 mg 2 or 3 times daily		None	• Combination chondroitin–glucosamine is no better than glucosamine alone • Primarily derived from animal sources, raising questions regarding contamination from animal diseases

CNS = central nervous system; COX = cyclooxygenase; GI = gastrointestinal; INR = international normalized ratio; IR = immediate release; MI = myocardial infarction; OA = osteoarthritis; PMN = polymorphonuclear neutrophil; SR = sustained release; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.
Adapted from reference 8.