Osteoarthritis (OA), also known as degenerative joint disease, is one of the most common chronic medical conditions worldwide and is the most common form of arthritis in the United States.1 Approximately 80% of people in Western countries age 75 or older have radiographic evidence of OA, and about 11% of people older than age 64 have symptomatic OA of the knee.2 Risk factors for OA include obesity and activities or occupations where overuse of a joint is common. Those at risk include baseball pitchers, dancers, dock workers, and marathon runners. Osteoarthritis may also be the result of trauma, such as a motor vehicle accident.

Clinical studies show these agents are very well tolerated and may be beneficial for osteoarthritis symptoms. The clinical features of OA include morning joint stiffness, joint pain that is usually worsened by movement and improved by rest, limited range of motion, gait instability, joint tenderness, bony crepitus (crackling noise with movement) and soft tissue swelling.3 Inflammation, if present, is usually mild and localized to the affected joint. Osteoarthritis commonly affects the knee, hip, hands, feet and spine. The disease generally presents with unilateral or asymmetrical involvement of an affected joint, although bilateral or symmetrical presentations may be observed in more advanced stages. The treatment of OA involves a combination of supportive treatment and pharmacologic therapy. Additionally, nutraceutical alternatives, such as glucosamine and chondroitin, are widely promoted and available to the general public as a treatment for OA. Since pharmacists are recognized as drug experts and are highly accessible to the public, they are likely to receive questions concerning the effectiveness and safety of these agents. Thus, the purpose of this article is to equip pharmacists with updated information concerning the safety and efficacy of glucosamine and chondroitin, alone and in combination, for the management of OA.

OVERVIEW OF OSTEOARTHRITIS MANAGEMENT
The treatment of OA involves a combination of supportive therapy and pharmacotherapy. Nonpharmacologic measures include patient education, self-management programs, weight loss (if overweight), aerobic exercise programs, physical therapy, range-of-motion exercises,
muscle-strengthening exercises, assistive devices for ambulation, and occupational therapy. The American College of Rheumatology recommends acetaminophen as initial treatment of early OA. However, nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen and diclofenac, are perhaps the most widely prescribed class of medications for OA. Approximately 73 million NSAID prescriptions are written for an estimated 17 million Americans, and over 30 billion over-the-counter tablets are sold annually in this country alone. NSAIDs, when used properly, are generally safe and well-tolerated by most patients. However, some users have experienced serious, life-threatening adverse events with these medications, particularly dangerous gastrointestinal (GI) events. Using the definition of a 3-mm or greater break in the gastric mucosa, about 25% of chronic NSAID users will have endoscopically detected gastric ulcers, and up to 50% will have either a gastric or duodenal ulcer. The majority of these gastric mucosal injuries are superficial, asymptomatic, and often self-limited. However, some patients develop severe erosions, or even peptic ulcers leading to GI hemorrhage, perforation, and death. The mortality rate for NSAID-induced GI bleeding is 5%–10%, with 107,000 hospitalizations per year, at an estimated cost of $15,000,000 per event; however, total direct costs may exceed $2 billion annually. Additionally, NSAIDs have adverse renal effects, which is a major concern in elderly individuals, those who are volume-depleted, and patients with underlying renal insufficiency.

A new class of compounds, the cyclooxygenase-2 (COX-II) inhibitors (e.g., celecoxib, rofecoxib), are at least as effective as NSAIDs for OA, but have significantly less adverse GI toxicity. However, COX-II inhibitors are not completely devoid of adverse renal effects and, like the NSAIDs, are associated with other systemic side effects. Local therapies, such as capsaicin cream and topical salicylates, are only of limited value, especially in more severe cases of OA. Patients with OA may need to be treated with a more potent analgesic, such as tramadol and opiates. These therapies carry additional risks, such as adverse central nervous system effects (e.g., sedation), and have the potential for addiction or abuse. Intra-articular injections of steroids and hyaluronate are also of limited value and cannot be used chronically. Furthermore, even when the aforementioned medications are prescribed with great diligence, many patients do not experience adequate relief of symptoms. Thus, the quest for compounds that are both highly efficacious and completely safe for OA remains elusive.

GLUCOSAMINE AND CHONDROITIN AS DIETARY SUPPLEMENTS

Recently, with the release of the book entitled The Arthritis Cure, describing glucosamine and chondroitin sulfate as effective agents for OA treatment, consumer interest in these compounds soared, especially in the U.S. Another factor that prompted increases in sales of these nutraceuticals was the passage of the Dietary Supplement Health and Education Act in 1994. This legislation permits the marketing of products claiming to affect the structure or function of the body as a dietary supplement without requiring FDA approval. Glucosamine and chondroitin are marketed as dietary supplements, and as such must contain a disclaimer stating that they are not intended to diagnose or treat any specific medical condition.

The use of glucosamine and chondroitin for OA is not without controversy. To provide some clarification, a special subcommittee of the American College of Rheumatology released the following statement last year concerning use of these agents for OA:

While a number of studies support the efficacy of both glucosamine and chondroitin sulfate for palliation of joint pain in patients with knee OA, the subcommittee believes that it is premature.
to make specific recommendations about their use at this time because of methodologic considerations, including lack of standardized case definitions and standardized outcome assessments, as well as insufficient information about study design in a number of these published reports. A pivotal clinical trial being planned by the NIH should help define the role of these agents, singly and in combination, in the treatment of patients with knee OA.

Thus, it seems prudent and timely to review the evidence from clinical trials to assist in providing recommendations to patients and healthcare professionals for these compounds.

**PATHOPHYSIOLOGY**

To better understand the potential for glucosamine and chondroitin to treat OA, a brief overview of pathophysiology is necessary. Osteoarthritis is a degenerative disease affecting the articular cartilage, leading to acute periodic inflammation. Cartilage is made up of two components. The first are the chondrocytes, the cellular component, which are distributed in and actually produce the second component, the matrix. The matrix is amorphous and made up of collagen and elastic fibers in a chondromucoid substance of proteoglycans and glycoproteins. A protein backbone is formed from complex proteoglycans with sulfated mucopolysaccharides, specifically chondroitin sulfates A and C, and keratin sulfate, branching off laterally.

The presence of these sulfate groups allows binding that can result in a strongly electronnegative structure with high water retention. This ensures the elasticity and resistance of the cartilage. During load bearing, the proteoglycans act as shock absorbers by slowly releasing this water. The pathophysiologic mechanism of cartilage degeneration appears to be linked to metabolic changes in the chondrocytes that disrupt the components and reduce the water content, leading to tissue damage by the leukocyte proteolytic enzyme elastase. The proteoglycan content is depleted in the matrix, which results in a loss of shock absorption and compressibility. Bone responds to this with hypertrophic repair, increasing the subcondral bone thickness.

**PROPOSED MECHANISMS OF ACTION FOR GLUCOSAMINE AND CHONDROITIN**

Glucosamine is an aminomonosaccharide that is part of almost all tissues in the human body, including cartilage. Furthermore, it is the principal component of O- and N-linked glycosaminoglycans, which form the connective tissue matrix. Glucosamine sulfate, a salt of the natural aminomonosaccharide, has a relatively low molecular weight. Following oral administration, it is 90% absorbed, with about 8%-2% retained in the tissues. The chondrocytes incorporate glucosamine into the proteoglycans, which are then excreted into the matrix. The sulfate moiety specifically plays an important role in proteoglycan synthesis because the glycosaminoglycans are highly sulfated and may contribute to its therapeutic effect. Glucosamine bioavailability after oral administration is about five times lower than after intravenous administration, likely due to the extensive first-pass effect in the liver. Glucosamine is a slow-acting drug for OA treatment; it may have a chondroprotective role in OA. The chondroprotective effect includes an increase in proteoglycan synthesis that may be dose-dependent, along with effects on chondrocyte gene expression, thereby increasing levels of mRNA and collagen synthesis. Glucosamine may also have an anti-inflammatory effect, although it is 50-00 times lower than that of indomethacin. It may also be related to reducing the formation of superoxide radicals by macrophages or inhibiting lysosomal enzymes.

Chondroitin sulfate is an important component of the cartilaginous matrix. Chondroitin sulfate may be able to increase the synthesis of RNA by chondrocytes, thereby leading to an increase also in proteoglycan concentration and collagen synthesis. Furthermore, chondroitin
sulfate may have some inhibitory activity on the degradation of elastase. The activity of chondroitin sulfate has been postulated to decrease the inflammatory response in arthritis as well. Marketed chondroitin sulfate extracts contain mostly chondroitin-4 sulfate and chondroitin-6 sulfate, both of which are large molecules and absorbed minimally, only about 10%, from the GI tract.\textsuperscript{18} Although chondroitin is sold as an oral dietary supplement, the compound was usually administered by injection in clinical trials.

**CLINICAL EVIDENCE FOR GLUCOSAMINE**

A double-blind, placebo-controlled study conducted by Drovanti et al. compared 1.5 g/day of glucosamine sulfate in three divided doses with placebo in 80 patients with OA for one month.\textsuperscript{19} The results of this study showed that symptom scores decreased more in the glucosamine sulfate group compared to the placebo group, 72% and 36%, respectively, with symptoms continuing to improve at 30 days. Improvement was measured by assessing decreases in swelling and tenderness, and increases in range of motion. Tissue was also examined under an electron microscope. This study showed an improvement in pain after seven days, improvements in tenderness, swelling, and active range of motion after 14 days, and passive range of motion improving in 21 days. Electron microscopy of cartilage also yielded favorable results in the glucosamine sulfate group, relative to placebo. Limitations to this study include the small sample size, short study duration, and the fact that cartilage samples were obtained from only four subjects, two from each study group.

Another double-blind study evaluating 54 outpatients to determine the efficacy and tolerance of intra-articular glucosamine versus placebo was conducted in Thailand. After baseline measurements of pain, swelling, range of motion and other symptoms were documented, patients were injected with either a commercial dosage form of glucosamine salts or 0.9% NaCl. Results showed significant improvement in pain for the glucosamine group as well as improved range of motion compared to the placebo.\textsuperscript{20} All the patients were diagnosed with gonarthritis, a common problem in Thailand due to their typical sitting position, which requires acute flexion of the knee. The investigator concluded that the metabolic action of glucosamine partially succeeded in restoring the articular function of cartilage and relieving pain. A small number of patients with very specific OA in a limited area were selected for this study. As a result, the outcomes of this test may not be applicable to the population as a whole. Furthermore, parenteral glucosamine is generally not used or available in the U.S.

In a study from Portugal, 40 patients diagnosed with unilateral knee OA were treated with glucosamine 1.5 g daily or ibuprofen 1.2 g daily to compare the efficacy and tolerance of oral treatment.\textsuperscript{21} In this double-blind trial, pain scores improved in both groups, with a more rapid result seen in the ibuprofen group. However, continual improvement was noted throughout the eight weeks with the glucosamine group. Differences observed in swelling and other parameters were not noted to be significant in this trial, suggesting that glucosamine has less anti-inflammatory action and more effect on normalizing the cartilage metabolism through stimulation of proteoglycan synthesis and inhibition of degradation, allowing partially restored articular function. The results showed better tolerability with glucosamine, which was also the case in the overall evaluation by the physician, compared to ibuprofen. The investigator concluded that outcomes may be optimal if the patient is started on glucosamine and NSAID treatment initially to ensure rapid reduction of pain, and then continued on glucosamine alone for a longer period depending on patient needs.

A study done by Rindone et al. was conducted in 98 patients to determine the efficacy of glucosamine in reducing pain from OA of the knee.\textsuperscript{22} This double-blind, randomized, parallel...
trial of 500 mg of glucosamine sulfate, given three times a day, compared to a placebo, showed no statistical benefit with glucosamine over the two-month period. Mean scores on both visual analog scales for resting and walking were taken at 30 and 60 days with no statistical differences noted when compared to the baseline in either group. Side effects were mild and self-limiting in both groups. One suggested reason for this negative result was that the patients in this study were older, heavier, and had arthritis longer than many patients evaluated in other studies. This may suggest that more pronounced arthritis does not respond as well to glucosamine due to more extensively damaged cartilage. Further, this study was only conducted for two months, which may not be long enough to produce beneficial results, especially in more severe cases.

A recent three-year, double-blind study in 212 Belgian patients with OA randomized subjects to receive either oral glucosamine sulfate 1,500 mg QD or placebo. After three years, patients who received placebo had a mean joint space loss of 0.3 mm (tibiofemoral joint), whereas those receiving glucosamine had no significant loss of joint space. Standard, validated symptom scores for OA pain and disability were significantly improved in the glucosamine group and slightly worse in the placebo group at the end of the study. There were no significant differences between groups in the frequency or pattern of adverse events. This should be considered a landmark study since it demonstrates that glucosamine provides symptomatic improvement and is well-tolerated and safe for long-term use. This well-designed study also suggests that glucosamine may have disease-modifying properties in OA as well.

### CLINICAL EVIDENCE FOR CHONDROITIN AND COMBINATION THERAPY

Relative to glucosamine, there is even less compelling evidence to support chondroitin monotherapy as a primary treatment for OA. A study performed by Morreale et al. was designed to assess the clinical efficacy of chondroitin sulfate, when compared to the NSAID diclofenac sodium, in patients with knee OA. This was a randomized, double-blind, parallel group study that collected data from 126 patients and lasted six months. Patients were divided into two groups. For the first month, the chondroitin sulfate group received 400 mg of chondroitin sachet three times a day and a placebo (diclofenac dummy) three times a day. The diclofenac sodium group was given 50 mg of diclofenac three times a day and a placebo sachet (chondroitin dummy) three times a day. For months two and three, the chondroitin

### ROLE OF THE PHARMACIST AND PATIENT COUNSELING

Pharmacists are consulted regularly for information on dietary supplements; they are likely to receive questions about glucosamine and chondroitin. Patients should be encouraged to discuss their use of glucosamine and chondroitin with their physicians. Patients should be reminded that these therapies have a gradual onset of therapeutic effect; other agents such as NSAIDs will provide more immediate relief of acute symptoms. Generally, patients should use glucosamine or chondroitin for at least a continuous 8-2 week trial before discontinuing use, and should be counseled to remain compliant.

While these supplements are used predominantly in older patients with OA, pharmacists should advise against the use of these supplements during pregnancy or lactation since their effects on fetal development and breast milk excretion are unknown. Patients should also be advised to take the same dosage and frequency that has been studied in clinical trials, and not to exceed labeled amounts. Pharmacists should discourage the sale and use of glucosamine and chondroitin products that do not list the exact amount or dosage contained in the product. Finally, pharmacists should remind patients that glucosamine and chondroitin are not regulated by the FDA in the same manner as prescription products for OA. However, good scientific evidence now exists to support the use of glucosamine as a safer, effective alternative to NSAIDs or as an adjunct to a comprehensive OA management plan.
sulfate group received chondroitin sulfate sachets only while the diclofenac sodium group received placebo sachets only. During months four, five, and six, only placebo chondroitin sulfate sachets were given to both groups. Scores on the Lequesne Index (a series of questions that rates pain during activity) decreased sharply during the first month in both groups. This decrease was greater in the diclofenac sodium group; however, by the end of the first month, the score evened out in the diclofenac sodium group. This group was treated for the next five months with placebo and showed a continual increase in pain scores through the rest of the study. On the other hand, the chondroitin sulfate group showed a continual decrease in pain scores through the next two months of continued chondroitin sulfate treatment. At the end of the study, the scores were 64.4% lower overall compared to baseline in the chondroitin sulfate group, and 29.7% lower in the diclofenac sodium group. When spontaneous pain was measured, both groups showed a decrease progressively through the first two months; however, patients in the chondroitin sulfate group had a higher consumption of acetaminophen for breakthrough pain. The remainder of the study showed a progressive decrease in mean values for spontaneous pain in the chondroitin sulfate group and an increase in mean values for the diclofenac sodium group. This difference proved to be statistically significant during the last four months of the study. From the results of this study, the conclusion was made that chondroitin sulfate has slow but gradually increasing effectiveness in OA.

Combinations of chondroitin with glucosamine are advertised extensively in stores across the U.S. Only one controlled study has compared this combination with a placebo in patients with OA. This double-blind, placebo-controlled, crossover trial evaluated 21 males with chronic pain and OA of the knee or low back. The results of this trial showed that the combination of glucosamine sulfate and chondroitin sulfate was superior to the placebo in reducing pain scores in those with OA of the knee on the visual analog scale after eight weeks of treatment. However, it is unclear whether the addition of chondroitin contributed to this decrease or not. Changes from baseline measurements of pain along with functional questionnaires, physical exam scores, and running times were presented as a percentage of the average score of each patient. However, this same benefit was neither demonstrated nor excluded for degenerative joint disease of the spine. Also, running times were not significantly different.

A meta-analysis of 15 double-blind, randomized, placebo-controlled trials of oral or parenteral glucosamine sulfate or chondroitin sulfate for knee or hip osteoarthritis has recently been published. Studies were included in this analysis only if they were placebo-controlled and of at least four weeks in duration. This meta-analysis concluded that some degree of efficacy was likely, despite quality concerns, such as publication bias (manufacturers of glucosamine or chondroitin funded all but one trial).

A randomized, controlled trial was conducted in 95 patients with OA of the knee using a combination product (Cosamin DS) containing glucosamine HCl 1,000 mg, sodium chondroitin sulfate 800 mg, and manganese ascorbate 152 mg given BID, compared to placebo. Patients were evaluated at baseline and then every two months for six months using the Lesquene Index. Statistical improvement was seen in the active treatment group beginning at four months. The response rate to the combination product was 52%, versus 28% with placebo in 72 patients with mild to moderate OA. In the remaining 23 patients with severe OA there was no significant difference in efficacy between the two groups. The incidence of adverse reactions was comparable between the two groups. The investigators concluded that the combination of glucosamine HCl, sodium chondroitin sulfate, and manganese ascorbate was
effective in mild to moderate OA of the knee. A meta-analysis of seven double-blind, randomized, controlled trials using chondroitin sulfate for OA was recently published.\textsuperscript{26} When results of these studies were pooled, following patients to 120 or more days, chondroitin showed at least a 50\% improvement in pain scores compared to placebo. It should be noted, however, that in most of these trials chondroitin was given along with other analgesics and NSAIDs, confounding the exact magnitude of treatment effect due to chondroitin alone.

**ADVERSE EFFECTS**

It should be encouraging to pharmacists, other healthcare providers and patients that glucosamine and chondroitin have been very well-tolerated in research trials and in clinical practice.\textsuperscript{25} Chondroitin appears to be especially safe, with the incidence of adverse reactions being similar to placebo; no serious side effects have been reported. Similarly, glucosamine in clinical trials causes a less than 4\% incidence of GI effects, similar to placebo.\textsuperscript{26} Because glucosamine is an amino saccharide, some authorities recommend using this product with caution in diabetics; however, hyperglycemia has not been observed in patients using glucosamine.\textsuperscript{28} A reasonable recommendation is for diabetic patients receiving glucosamine products to increase the frequency of blood glucose monitoring, especially when first initiating glucosamine therapy.

**CONCLUSION**

The clinical trials of glucosamine and chondroitin in the use of OA treatment collectively demonstrate that their effects may be beneficial for OA symptoms. Based on available evidence, it appears that glucosamine monotherapy is preferable to chondroitin monotherapy. Combination therapy is promising, but clinical data is inconclusive. The National Institutes of Health has recently funded a randomized, double-blind, placebo-controlled trial comparing glucosamine sulfate 500 mg TID to chondroitin sulfate 400 mg TID, versus a combination of the two.\textsuperscript{29} Both treatments are being given orally, and the study results should be available later this year.

It is unknown whether these products are actually “disease-modifying,” and it is uncertain if combination products are superior to glucosamine alone. Using these agents appears to be relatively safe; however, drug interaction studies have not been carried out. Pharmacists should recommend these products only for confirmed cases of OA and suggest products that are marketed by reputable manufacturers. Glucosamine and chondroitin should not be recommended for acute pain or other inflammatory bone and joint diseases.

**Acknowledgment**
The author wishes to thank Gail Stitt for her contribution in preparing this manuscript.
REFERENCES


