Upon successful completion of this continuing education lesson, the pharmacist should be able to:

1. Describe the epidemiology, socioeconomic burden, and clinical features of osteoarthritis (OA).
2. List conventional pharmacologic and supportive treatment modalities for OA.
3. Explain the rationale behind using glucosamine as supportive treatment for OA.
4. Discuss the safety and efficacy of glucosamine for OA based on evidence from recent controlled clinical trials.
5. List key pharmacist-to-patient counseling points related to the use of glucosamine for OA.

Overview of Osteoarthritis

Osteoarthritis (OA), also known as degenerative joint disease, is the most common type of arthritis in the United States. Approximately 26.9 million adults 25 and older have OA involving at least one joint, based on 2005 population estimates. Multiple risk factors associated with OA include advanced age, obesity, occupation, sports activities, previous joint injury, muscle weakness, and genetic factors, among others. Women are more likely than men to be diagnosed with arthritis, and advanced age is most closely associated with arthritis diagnosis and the presence of chronic joint symptoms. The overall risk for developing symptomatic OA in at least one knee by age 85 is 46 percent. During 2006, approximately 30 percent of adults 18 years and older reported experiencing some type of joint pain in the previous 30 days, and $18 billion was spent on hospital costs associated with total knee replacements.

As will be discussed, conventional treatments for OA may be unsatisfactory for patients. Dietary supplements, such as glucosamine, are widely promoted and available to the public as an alternative treatment for OA. (See Table 1 for a listing of commercially available glucosamine-only preparations.) Being medication experts and easily accessible to the public, pharmacists are likely to receive questions from patients concerning the safety and efficacy of glucosamine. Thus, the purpose of this article is to equip pharmacists with the tools to counsel patients on the use of glucosamine for managing OA. (See Table 2 for recommendations on pharmacist-to-patient counseling.)

Clinical Presentation

Osteoarthritis most commonly presents in patients over 40 years old. It predominantly affects the knees, hips, fingers, and spine, and rarely affects the elbows, wrists, ankles, and shoulders. OA is usually diagnosed by both clinical symptoms and radiographic changes. Patients with OA will usually complain of these symptoms: pain that typically worsens with weight-bearing activity and resolves with rest, morning stiffness and stiffness after prolonged periods of inactivity, crepitus (crackling noise with joint movement), tenderness or palpation, and/or limited joint motion. OA is not typically associated with inflammation, but if present, is usually mild and localized to the affected joint. Major radiographic features of OA include asymmetric joint space narrowing, subchondral sclerosis, osteophytes, and subchondral cysts. Radiographic changes may not correlate directly with severity of symptoms.

Pathophysiology

Osteoarthritis is also known as Degenerative Joint Disease (DJD) because degenerative changes predominately contribute to disability in patients with the condition. In healthy cartilage, chondrocytes replace macromolecules lost through degradation. In OA, this process
is disrupted, leading to increased degenerative changes, destruction or decrease in synovial fluid, and abnormal tissue repair. As the disease progresses, the abnormal repair process leads to the formation of osteophytes (bony projections that form along the joint) and subchondral cysts (fluid-filled sacs consisting of thickened joint material in the layer of bone just below the cartilage). Use of joints helps to stimulate remodeling, while prolonged decreased joint use leads to changes in the matrix composition and loss of tissue function.

CONVENTIONAL TREATMENT OVERVIEW
Because there is no known cure for OA, treatment is aimed at reducing pain, improving joint mobility, and limiting functional impairment. Patient education is necessary for the successful management of OA. Nonpharmacologic therapy for patients with OA may include weight loss (if overweight), aerobic exercise programs, range of motion and muscle strengthening exercises, joint protection, appropriate footwear, and assistive devices for ambulation and activities of daily living.

Pharmacologic therapy for pain management is most effective when combined with the previously mentioned nonpharmacologic measures. Acetaminophen, non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2)-selective NSAIDs, tramadol, topical capsaicin or methylsalicylate, and intra-articular corticosteroids or hyaluronic acid have all shown some benefit in patients with OA. When deciding which product to use, individual patient characteristics must be taken into consideration. Acetaminophen is one of the safest analgesics, and often produces adequate pain relief in patients with mild to moderate pain. However, it can be associated with hepatotoxicity in doses ≥ 4 grams/day, and should be avoided in patients with liver disease or chronic alcohol abuse due to increased risk.

NSAIDs, such as ibuprofen, naproxen, and diclofenac, provide comparable relief for patients with mild to moderate pain, but may be more effective in patients with severe pain due to OA. This class of drugs comes with risk of serious gastrointestinal (GI) side effects and renal toxicity. Risk factors for upper GI adverse events include patients 65 or older, comorbid medical conditions, oral glucocorticoid use, history of peptic ulcer disease, history of upper GI bleeding, and anticoagulant use. In patients with increased risk for GI adverse events, NSAIDs should be administered with a proton pump inhibitor (PPI) or misoprostol. Long-term use of NSAIDs should be avoided, if possible.

COX-2-selective NSAIDs have been found to be more effective than placebo and come with a lower risk for GI adverse events when compared to NSAIDs. However, they may cause renal toxicity; thus, caution should be used in patients with renal insufficiency. Addi-tionally, consensus guidelines from multiple organizations rec-

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<td><strong>Brand</strong></td>
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* There are a number of other products containing glucosamine with chondroitin and MSM, as well as liquid and topical preparations. (Chart based on information from www.drugstore.com, January 2009.)

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ommend using extreme caution when COX-2-selective NSAIDs are used in patients who have or are at risk for cardiovascular disease. Currently, celecoxib is the only available COX-2-specific inhibitor available in the United States. Other COX-2 inhibitors have been removed from the U.S. market amidst cardiovascular safety concerns, including rofecoxib and valdecoxib.

Tramadol is a non-narcotic opioid analgesic that has been approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe pain. It is a useful alternative for patients who have contraindications to COX-2 inhibitors or NSAIDs, or patients who have not responded to previous oral therapy. Caution must be exercised when using tramadol in elderly patients, patients with seizure disorders, and patients taking monoamine oxidase inhibitors or selective serotonin reuptake inhibitors.

Topical agents are becoming more popular due to decreased systemic effects and toxicity when compared to oral medications. Diclofenac gel and lidocaine patches are prescription-only products, while topical salicylates and capsaicin creams are available over the counter in the United States. These products have demonstrated a reduction in pain in patients with OA. However, they have only been studied in short duration trials, so benefits of long-term use is unknown.

Intra-articular injections of corticosteroids have been used for pain relief, though OA is thought not to have a predominant inflammatory component. Some patients have seen an improvement in symptoms with intra-articular corticosteroids. However, studies have not shown a long-term benefit. Physicians should inform patients that corticosteroids may only have a short-term benefit (only one week) in osteoarthritis.

Another agent used in OA is hyaluronic acid, a product thought to be a potential disease-modifying drug. However, studies have not demonstrated a change in the rate of progression of the disease. Some studies have shown statistically significant improvements in pain and function, but the response was variable between studies. Neither intra-articular corticosteroids nor hyaluronic acid injections are recommended for routine, chronic use in OA.

GLUCOSAMINE: AN OVERVIEW

Glucosamine is a natural compound found in healthy cartilage and synovial fluid and is important for maintaining elasticity and strength of cartilage in movable joints. It is a key substrate used in the synthesis of macromolecules that comprise connective tissue, including glycolipids, glycoproteins, hyaluronic acid, proteoglycans, and glycosaminoglycans. Glucosamine is about 90 percent absorbed when administered orally as glucosamine sulfate, but glucosamine can be found in other forms, including hydrochloride, N-acetyl-glucosamine, and chlorohydrate salt.

Glucosamine is a dietary supplement; thus its regulation falls under the Dietary Supplement Health and Education Act (DSHEA). Relative to prescription drugs, the FDA does not as strictly regulate dietary supplements. Thus, there is little guarantee of efficacy, but clinical trials have shown glucosamine supplements to be somewhat effective for OA of the knee and relatively safe with minimal side effects. The most common adverse effects in clinical trials were epigastric pain or tenderness, heartburn, nausea, and diarrhea. Until recently, the use of glucosamine in the treatment of OA has been generally supported. However, more recent evidence has challenged the notion that glucosamine has analgesic efficacy and disease-modifying properties in OA.

GLUCOSAMINE: EVIDENCE FOR CLINICAL TRIALS IN OA

A study in 2002 (Pavelká) examined the long-term effects of glucosamine sulfate on the progression of knee OA structural modifica-

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tions and symptoms. Patients were included in the trial if they met the American College of Rheumatology clinical and radiological criteria for knee OA. Exclusion criteria included a history of joint diseases other than OA, a history of trauma to the knee joint, a body mass index greater than 27, or systemic or intra-articular corticosteroid therapy in the last three months. A total of 202 patients were randomized to three years of treatment with packets of powder for oral solution containing either glucosamine sulfate 1,500 mg or placebo to be taken once daily. Acetaminophen 500 mg tablets were provided for additional pain relief if needed. Radiographs were taken at enrollment and after one, two, and three years of treatment.

The primary outcome was change in joint space width in the narrowest medial compartment of the tibio-femoral joint after three years, and secondary measurements of joint structure modification were presence of marginal osteophytes and subchondral sclerosis. Investigators assessed symptoms of knee OA at each clinic visit using the Lequesne index for functional limitation and maximum distance walked. The Western Ontario and McMaster Universities (WOMAC) index was also used to measure severity of joint pain, stiffness, and limitation of physical function in the 48 hours prior to clinical assessment. Results of the study showed there was progressive joint space narrowing after each year of treatment in patients randomized to placebo, versus no average loss in joint space width in patients treated with glucosamine. When the two groups were compared, a significant difference was apparent during the first year of treatment, and maintained during the following two years. No significant difference was noted between the groups with respect to acetaminophen use. Frequency and pattern of adverse events did not differ between the two groups. This trial concluded that long term oral glucosamine sulfate may delay the natural progression of knee OA, while improving pain and functionality.

One trial published in 2004 set out to evaluate the effect of continuing or withdrawing glucosamine in patients with knee OA. Patients were included in the six month, randomized, double blind, placebo-controlled trial if they had clinical and radiographic evidence of OA, daily use of glucosamine for at least one month, and at least moderate improvement in pain since starting on glucosamine. Patients were excluded if they used chondroitin sulfate within the last two months, had hyaluronic injections in the previous six months, received corticosteroid injections in the previous three months, used narcotic analgesics, or had an uncontrolled medical condition or planned surgery that could interfere with evaluations. One hundred thirty seven patients were randomized to either receive placebo or continue glucosamine sulfate at the same dosage as prior to the study (maximum dose of 1,500 mg/day). Acetaminophen and NSAIDs were allowed for additional pain relief, if needed. The primary endpoint was the proportion of patients with disease flare, defined as either the patient’s view of worsening symptoms or a worsening in the physician’s global assessment of the patient. Secondary outcomes included time to disease flare; change from baseline to flare in WOMAC pain, stiffness, function, and total scores; change from baseline to flare in Visual Analog Scale (VAS); and use of acetaminophen and/or NSAIDs.

The difference between the two groups was not statistically significant for the primary endpoint of disease flare, time to disease flare, use of acetaminophen and NSAIDs, or WOMAC pain, stiffness, and function scores. There was no difference in adverse events between the glucosamine and placebo groups. Researchers concluded that for patients with knee OA and moderate improvement with previous glucosamine use, there is no benefit from continued use of glucosamine sulfate on OA symptoms.

The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) published in 2006 was a 24-week, randomized, double blind, placebo- and celecoxib-controlled multicenter trial sponsored by the National Institutes of Health. The study’s purpose was to evaluate the efficacy and safety of glucosamine, chondroitin sulfate and the two in combination in the treatment of pain due to OA.
of the knee. Patients were eligible for the trial if they were at least 40 years old and had clinical and radiographic evidence of OA. Patients were excluded if they had concurrent medical conditions that could confound evaluation of the knee, a history of trauma or surgery to the joint, or comorbid disease that could interfere with successful completion of the trial. A total of 1,583 patients, a majority of whom were women, were randomized to one of five treatment groups: 500 mg of glucosamine hydrochloride three times daily, 400 mg of sodium chondroitin sulfate three times daily, 500 mg of glucosamine plus 400 mg of chondroitin sulfate three times daily, 200 mg of celecoxib daily, or placebo. Patients were allowed to take up to 4,000 mg of acetaminophen daily except during the 24 hours before a clinical evaluation; use of narcotics and NSAIDs was not permitted.

Primary outcome measure was response to treatment, defined as a 20 percent decrease in the summed score for the WOMAC index over 24 weeks. Secondary outcome measures included scores for stiffness and function, the patient’s global assessments of disease status and response to therapy, the investigator’s global assessment of disease status, the presence or absence of swelling or effusion in the knee, physical function scores, and acetaminophen use. Adverse events were generally mild and the evaluated products can be deemed as relatively safe. Patients in the celecoxib group had a faster time to pain relief, while the other groups had a more gradual onset of improvement. Evaluation of the primary outcome measure did not show that glucosamine, chondroitin, or the combination of the two, was effective, and no significant benefit was identified for using either product alone [under mild degree of pain]. The authors noted that the study had several limitations, including a high rate of response to placebo and mild degree of pain from OA among study participants. They concluded that the combination of glucosamine and chondroitin sulfate may be effective in patients with moderate-to-severe OA, but this must be confirmed by a future trial.

The Glucosamine Unum In Die (once a day) Efficacy (GUIDE) trial published in 2007 was a prospective, randomized, placebo-controlled, double-blind study, with the purpose to evaluate the effects of glucosamine sulfate on the symptoms of knee OA over six months. Patients were included if they had been diagnosed with symptomatic knee OA according to the clinical and radiographic criteria of the American College of Rheumatology. Enrollment of patients with a body mass index of >30 kg/m² was discouraged. Symptomatic medications taken before the study were discontinued, and 325 patients were randomized to receive either 1,500 mg glucosamine sulfate powder for oral solution once daily, 1,000 mg of acetaminophen three times daily, or placebo. Primary efficacy outcome was the six-month change in the Lequesne index of severity of OA of the knee. Secondary outcome measures included changes in WOMAC scores for pain, function, and stiffness. When compared with placebo, the degree of improvement was statistically significant in the glucosamine group for both primary and secondary outcomes. The acetaminophen group did not reach statistical significance in primary or secondary outcome measures when compared with placebo. Overall, glucosamine was well-tolerated, and at the once daily dosage of 1,500 mg is an effective medication for knee OA symptoms.

Most recently, a study evaluated the effect of glucosamine on the progression of OA of the hip. Patients were eligible for the GOAL (Glucosamine in Osteoarthritis: Long term Effectiveness) study if they met the American College of Rheumatology clinical criteria for hip OA, but patients who had undergone or who were awaiting hip replacement surgery were not eligible. Patients were excluded if they had renal or liver disease, diabetes mellitus—a comorbid condition that would make visits to the research center impossible, or if they were already taking glucosamine. A total of 222 patients were randomly assigned to receive either 1,500 mg of oral glucosamine sulfate or placebo once daily. Primary outcome measures were WOMAC pain and function scores and joint space narrowing over two years. Secondary outcome measures were WOMAC pain, function, and stiffness scores after 3, 12, and 24 months; VAS to measure pain in the past week; and pain medication use. WOMAC and VAS
pain analyses were adjusted for factors that may have influenced symptoms, including body mass index, sex, and age. Investigators found that pain, functionality, and joint space narrowing did not differ between patients receiving glucosamine sulfate and the placebo group. Twenty patients had total hip replacement surgery during the study, which significantly limited the ability of the investigators to interpret the outcome measures in these patients. Another significant limitation of this study was the inclusion of a large number of patients who were in the relatively early stages of OA, when cartilage loss is slower, making it difficult to see the effect on joint space narrowing. The GOAL study concluded that receiving 1,500 mg of glucosamine sulfate daily for two years did not offer any benefit in patients with hip osteoarthritis.

CONCLUSION
The effects of glucosamine on relief of symptoms, preservation of function, and delay of joint damage are still unclear. This could be due to the lack of a standard preparation used in all studies, location of OA, enrollment of patients with relatively mild symptoms of OA, varying clinical presentation and progression of disease, and a large placebo effect. Conclusions of each respective trial can only be applied to the formulation of glucosamine used and the joint that was studied during the trial period. Most studies used a formulation of glucosamine sulfate in patients with knee OA. Some showed benefit in pain and function, while others did not. Because the recently published GOAL trial only enrolled patients with OA of the hip, results from that study can only be applied to that joint. A subgroup analysis compared hip-only versus generalized OA, and glucosamine sulfate showed a statistically significant reduction in WOMAC pain and function scores in the generalized OA group. Another factor that may affect the outcome of OA trials is the severity of the disease. Patients in the earlier stages of OA lose cartilage more slowly, while severe OA progresses rapidly, making it easier to see an improvement in symptoms, function, and joint space. In trials that found use of glucosamine to be beneficial, improvement was seen after 30 to 90 days of treatment.

Based on clinical trials, recommending a four to six week trial of glucosamine sulfate in selected patients with OA seems reasonable. Patients most suitable include those with contraindications, intolerance to, or lack of response with conventional therapy. Some patients may have an aversion to using prescription drugs because of side effects or cost, and wish to try a complementary or alternative agent may benefit from glucosamine, which is generally well tolerated. Pharmacists should inform patients that clinical trials have yielded conflicting results, but the balance of data seems to favor use of this supplement for mild to moderate OA of the knee. Patients should also be reminded that glucosamine is not intended to be used an analgesic for acute pain in OA.

Darrell Hulisz, RPh, PharmD, is an associate professor of family medicine at the Case Western Reserve University School of Medicine in Cleveland, and is an associate clinical professor of pharmacy practice at Ohio Northern University College of Pharmacy in Ada, Ohio. Lauren Seibert, PharmD, is a pharmacist at Walgreens, Inc.

Editor’s Note: To obtain the complete list of references used in the article, contact Chris Linville at NCPA (703-838-2680) or at chris.linville@ncpanet.org.

CONTINUING EDUCATION QUIZ
Select the correct answer.

1. Which of the following risk factors are associated with osteoarthritis (OA)?
   a. Advanced age
   b. Obesity
   c. Previous joint injury
   d. All of the above

2. The overall risk for developing symptomatic OA in at least one knee by age 85 is:
   a. 16 percent
   b. 25 percent
   c. 46 percent
   d. 100 percent
3. Symptoms of OA include:
   a. Pain that typically worsens with weight-bearing activity and resolves with rest
   b. Morning stiffness and stiffness after prolonged periods of inactivity
   c. Crepitus
   d. All of the above

4. Asymmetric joint space narrowing is a common radiographic finding of OA.
   a. True
   b. False

5. Nonpharmacologic therapy for patients with OA include which of the following?
   a. Weight loss (if overweight)
   b. Range-of-motion and muscle strengthening exercises
   c. Assistive devices for ambulation and activities of daily living
   d. All of the above

6. Which of the following is true regarding the use of acetaminophen for OA?
   a. It often fails to produce adequate pain relief in patients with mild-to-moderate pain.
   b. It is associated with nephrotoxicity in doses $\geq$ 4 grams/day.
   c. It should be avoided in patients with liver disease or chronic alcohol abuse due to increased risk.
   d. None of the above

7. Risk factors for upper GI adverse events due to NSAIDs for OA include:
   a. Age of 65 or older
   b. Glucocorticoid use
   c. History of peptic ulcer disease
   d. All of the above

8. In patients with increased risk for GI adverse events, NSAIDs should be administered with a proton pump inhibitor or misoprostol.
   a. True
   b. False

9. Caution must be exercised when using tramadol in which of the following settings?
   a. Use in elderly patients
   b. Use in patients with seizure disorders
   c. Concurrent use of selective serotonin reuptake inhibitors
   d. All of the above

10. Which of the following topical agents used for OA are over the counter?
    a. Diclofenac gel
    b. Transdermal lidocaine
    c. Capsaicin cream
    d. None of the above

11. Intra-articular corticosteroids and hyaluronic acid injections are acceptable for routine, chronic use in OA.
    a. True
    b. False

12. Which of the following statements is true concerning natural glucosamine?
    a. It is found in healthy cartilage.
    b. It is found in synovial fluid.
    c. It is important for maintaining elasticity and strength of cartilage in movable joints.
    d. All of the above

13. What percent of glucosamine sulfate is orally absorbed:
    a. Less than 1 percent
    b. 10 percent
    c. 50 percent
    d. 90 percent

14. Glucosamine regulation falls under the DSHEA.
    a. True
    b. False

15. A common adverse effect seen in clinical trials with glucosamine include:
    a. Renal failure
    b. Epigastric pain or tenderness
    c. Hepatotoxicity
    d. All of the above
16. The 2002 study by Pavelká used glucosamine sulfate 1,500 mg once daily in which dosage form:
   a. Tablets
   b. Packets of powder for oral solution
   c. Subcutaneous
   d. None of the above

17. A major finding in the 2002 study by Pavelká, as compared to placebo, was that in the glucosamine group:
   a. There was no loss in average joint space narrowing.
   b. There were more side effects than placebo.
   c. Mortality was greater than in the placebo group.
   d. All of the above

18. In the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), the salt form of glucosamine used was:
   a. Sulfate
   b. Acetate
   c. Hydrochloride
   d. None of the above

19. In the Glucosamine Unum in Die Efficacy (GUIDE) trial, glucosamine sulfate powder 1,500 mg daily was shown to be ineffective for treatment of OA of the knee, and less effective than acetaminophen:
   a. True
   b. False

20. Studies using glucosamine for OA yielded conflicting results, in part because of which of the following:
   a. Lack of a standard preparation used in all studies
   b. Differences in the joint location of OA
   c. Enrollment of patients with relatively mild OA symptoms in some trials
   d. All of the above