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## Viscosupplementation: Managed Care Issues for Osteoarthritis of the Knee

William Arnold, MD; Dwight S. "Pete" Fullerton, PhD, PRh;  
Sharon Holder, MSN, APRN, NP-C; and Coral S. May, RN, BSN, CME, MP

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### **S20** Continuing Education Posttest, Posttest Answers, Program Evaluation, and Verification of Completion Forms

#### **Purpose**

Provide the latest information on therapeutic options for OA of the knee, including viscosupplementation

#### **Target Audience**

Physicians, nurses, pharmacists, and case managers who treat patients with osteoarthritis

#### **Learning Objectives**

Upon completion of this activity, participants will be better able to

1. explain the pathophysiologic factors involved in osteoarthritis (OA) of the knee,
2. describe appropriate treatment for patients with OA of the knee, and
3. discuss benefits of viscosupplementation for management of OA of the knee as they pertain to the managed care environment.

This supplement was funded through an educational grant from Genzyme Biosurgery and is based on the proceedings of a series of meetings that took place in a managed care setting. It is jointly sponsored by Postgraduate Institute for Medicine (PIM) and Excellence in Medical Education (XME).

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## Viscosupplementation: Managed Care Issues for Osteoarthritis of the Knee

### Method of Participation

There are no fees for participating and receiving CE or CME credit for this activity. During the period from May 1, 2007 (release date), through May 31, 2008 (expiration date), participants must (1) read the learning objectives and faculty disclosures, (2) study the educational activity, (3) complete the posttest by recording the best answer to each question in the answer section of the Posttest Answers form, (4) complete the Program Evaluation form, and (5) mail or fax the Posttest Answers and Program Evaluation forms to Postgraduate Institute for Medicine (PIM). To complete this activity online, please see page S20.

The estimated time to complete this activity is 1 hour and 25 minutes. A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Your statement of credit will be mailed to you within 3 weeks.

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Sharon Holder, MSN, APRN, NP-C; and Coral S. May, RN, BSN, CME, MP

## ABSTRACT

**BACKGROUND:** Osteoarthritis (OA) affects an estimated 49 million adults in North America, or nearly 1 of every 6 adults. More than 8 million North Americans have limited mobility to some extent because of OA. By 2030, an estimated 71 million North Americans will be diagnosed with OA, an increase of 45% over current figures. For one group-model health maintenance organization (HMO), the average cost of care for patients with OA was \$543 per member, a total annual cost to the HMO of \$4,728,425. Of this total amount, 46% was for inpatient care, 32% was for medication, and 22% was for ambulatory care.

**OBJECTIVE:** To determine the impact of OA on managed care and discuss treatment options available to those with OA, particularly of the knee.

**SUMMARY:** OA represents an advanced stage of an active, progressive disease process. We know from medical research that OA is the endpoint of a progression in tissue degradation that results in loss of cartilage structure and function. Relief of pain and preservation of joint tissue must evolve to encompass treatments that interfere with cartilage-degrading mechanisms that follow acute or chronic injury, restore normal cartilage and joint homeostasis, and arrest the progression of disease. Optimal future treatments will also reverse existing damage and restore normal cartilage structure and function.

Viscosupplementation with an elastoviscous fluid containing polymers of hylan derivatives of the natural glycosaminoglycan hyaluronan is indicated for treating pain of OA of the knee that has not responded to or is contraindicated for conservative nonpharmacologic therapy and traditional analgesics. These analgesics include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors.

Clinicians in the managed care setting may consider using viscosupplementation in patients (1) who have persistent pain despite their use of conservative nonpharmacologic and pharmacologic therapy (e.g., exercise, weight loss, physician therapy, bracing/orthotics, NSAIDs, COX-2 inhibitors, and intra-articular glucocorticoids); (2) who have compromised gastrointestinal (GI) function or who are at risk for GI bleeding due to the adverse events of NSAIDs; (3) who are taking concomitant anticoagulant therapy for any condition; (4) who have cardiovascular or renal risk factors that preclude use of COX-2 inhibitors; and (5) for whom surgery is not appropriate.

Further study should be conducted with larger numbers of patients to help identify a subgroup of patients with OA in whom viscosupplementation may have even greater effects. Additional research should also concentrate on assessing the risks and benefits of extended treatments, because limited data are available concerning the effectiveness of multiple courses of therapy.

**CONCLUSION:** OA is an important public health issue as the leading cause of disability in North America. As populations age, socioeconomic costs of OA will dramatically increase. Among available treatment options, viscosupplementation is a valuable alternative to more conservative therapy and has the benefit of circumventing the possible side effects of systemically administered pharmacologic agents. Viscosupplementation demonstrated efficacy in OA of the knee, and its use in the managed care arena may generate savings in hospitalizations and other costs.

**KEYWORDS:** Cartilage-degrading mechanisms, Cost-effectiveness, Hyaluronan, Haluronate, Hylan, Managed care, Osteoarthritis, Viscosupplementation

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Osteoarthritis (OA) of the knee is a prevalent and often incapacitating condition that can be treated in a variety of ways, resulting in a range of clinical outcomes. This article will provide a brief overview of OA and specifically of OA of the knee. A concise review of the epidemiology, pathophysiology, and diagnostic tools associated with these conditions follows. Treatment options approved by the U.S. Food and Drug Administration (FDA) will be reviewed, with a focus on viscosupplementation. Pertinent cost-effectiveness data on treatment options for OA of the knee also will be presented.

## General Overview of Osteoarthritis

OA, the most common joint disorder, is a chronic arthropathy of 1 or more joints characterized by degeneration and loss of joint cartilage, along with other joint changes, including bone hypertrophy.<sup>1</sup> A progressive disease that occurs mainly in the latter half of life, OA can be progressively disabling. Patients mainly seek medical care because of the intractable pain caused by OA.<sup>2</sup> It often becomes symptomatic in the fifth and sixth decades of life and is almost universal by age 80.<sup>1</sup> In individuals younger than 40 years, OA occurs more frequently in men and is primarily a result of trauma. Occurrence predominates in women from age 40 to 70 years, after which men and women are equally affected.

## Impact

The estimated total cost associated with OA, including medical care and lost productivity costs, exceeds \$86.2 billion.<sup>3</sup> OA is the leading cause of lost time from work.<sup>3</sup> In addition, patients incur higher age-adjusted medical costs than do those without OA, not only for arthritis care but also for the care of comorbidities in the neurologic, gastrointestinal (GI), cardiovascular, and respiratory systems, to which patients may be more susceptible because of

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**TABLE 1** Demographics of Osteoarthritis (OA) of the Knee in the United States

- Prevalence: >13.5 million American adults report having knee joint pain, swelling, and stiffness<sup>50</sup>
- Age and duration: mean age of patients is 66 years, and mean symptom duration is 8 years<sup>25</sup>
- Race/ethnicity: the prevalence of knee OA among white persons is approximately twice that of black persons<sup>25</sup>
- Medical visits:
  - Patients make >5.5 million visits to physician offices and >271,000 outpatient visits<sup>50</sup>
  - In 1999, >400,000 inpatient hospital stays were reported for persons with OA of the knee<sup>49</sup>
    - Average duration of stay: almost 5 days
    - Average charge per hospital stay: \$23,746
    - Upon release, about 20% of patients with knee OA enter a skilled nursing facility or nursing home
    - In 1999, about 25% of patients with knee OA underwent surgery, most often total knee replacement
- Patient self-report of general health: >40% of people with knee OA rate their health as “fair” or “poor”<sup>50</sup>
- Impact on function: Approximately 50% of patients with knee OA have difficulty crouching, stooping, or kneeling<sup>11</sup>

overall decline in health.<sup>3</sup> Because of the high prevalence of OA and the associated medical costs, OA greatly impacts managed care. For one group-model health maintenance organization (HMO), the average cost of care for patients with OA was \$543 per member per year, at a total annual cost to the HMO of \$4,728,425. Of this total amount, 46% was for inpatient care, 32% was for medication, and 22% was for ambulatory care.<sup>4</sup>

### Pathophysiology and Pathogenesis

The pathogenesis and pathophysiology of OA is complex and affects several systems, beginning with the articular cartilage, which is a complex material synthesized and maintained by its living component, the chondrocyte.<sup>5</sup> Water makes up 65% to 85% of cartilage and interacts with matrix proteoglycans, matrix collagens, hyaluronic acid, and other components. Healthy cartilage is balanced between matrix synthesis and matrix degradation. In OA, regardless of the involved joint, matrix degradation overtakes matrix synthesis.

Articular cartilage degradation is associated with abnormal joint stresses over time. Stresses include obesity, which can place an abnormal load on the knee joint, microfractures in the subchondral bone, and trauma. Concurrent factors, including normal aging, metabolic diseases, inflammation, and immune system malfunctions, lead to biochemical changes that also result in cartilage degradation. These work synergistically to compromise cartilage, which results in (1) biophysical changes, such as collagen network fracture and proteoglycan unraveling, and (2) biochemical changes, such as a reduction in inhibitors

of degradative enzymes and an increase in proteolytic enzymes. OA is the endpoint of this series of events.<sup>5</sup>

All joint tissues become involved in OA. Subchondral bone stiffens and then undergoes infarction, becomes osteoporotic, and develops subchondral cysts.<sup>1</sup> Attempts at bony repair produce subchondral sclerosis; efforts to stabilize the joint produce osteophytes at the joint margins. Inflammation and thickening of the synovium ensues, producing more copious synovium. Periarticular tendons and ligaments become strained, resulting in tendonitis and contractures. As the joint becomes less mobile, surrounding muscles thin and become less supportive.

These mechanisms are gradual, and the patient most often describes a deep aching pain as the earliest symptom. Therefore, OA begins as a disease of a single tissue with a single etiology and eventually becomes a disease of an organ (synovial joint), in which cartilage is primarily affected but which ultimately involves all tissues: bone, synovium, muscle, capsule, ligaments, and cartilage.<sup>1</sup>

The pathways that contribute to the pain of OA can be complex. Pain can be classified as (1) nociceptive, which occurs as a result of tissue damage activating nociceptors in either peripheral or deep tissues and is considered protective; (2) inflammatory, which can follow an inflammatory response to tissue damage and is a component of nociceptive pain; (3) neuropathic, which results from direct injury to nerves; and/or (4) functional, which is associated with an absence of neurologic deficit or peripheral abnormality.<sup>6</sup> In most cases of chronic pain, several pain pathways tend to coexist.

### The Role of Hyaluronic Acid

Normal articular cartilage is composed of an extracellular matrix and chondrocytes, the cells that produce and maintain the cartilage.<sup>7</sup> Within the matrix, water, collagen fibers, and proteoglycan macromolecules—large molecules containing protein and a type of polysaccharide—are cross-linked into an integrated network. The backbone of each proteoglycan network is a large molecule of hyaluronic acid, also called hyaluronan or sodium hyaluronate.<sup>5</sup> The interaction of these molecules forms the structural network providing cartilage with its most important biomechanical properties, compressibility and elasticity.<sup>5</sup>

High concentrations of hyaluronic acid are also found in the synovial fluid.<sup>8</sup> In healthy joints, this highly viscous, shock-absorbing lubricant is contained within the joint capsule and helps enable articulation of the joint.<sup>8</sup> The synovial fluid in osteoarthritic joints contains a decreased concentration and molecular weight of hyaluronic acid compared with those found in healthy joints.<sup>8</sup> The synovial fluid in osteoarthritic joints does not have the same elastic and viscous qualities as those of a healthy joint.

### Osteoarthritis of the Knee

According to data from the Third National Health and Nutrition

Examination Survey (NHANES, 1991-1993), 37.4% of U.S. adults aged 60 years and older have radiographic OA of the knee, and 12.1%—more than 4.3 million people—have symptomatic OA of the knee.<sup>9</sup>

### Demographics and Prevalence

The demographics of OA of the knee are shown in Table 1.<sup>2,10</sup> Data published in 2006 from the Third NHANES showed that patients who had greater body mass index (BMI  $\geq 30$  kg/m<sup>2</sup>), were older, were of non-Latino black heritage, and were male with manual labor occupations had higher odds of having both radiographic and symptomatic OA of the knee.<sup>9</sup> Only symptomatic OA of the knee was significantly associated with self-reported activity limitations: difficulty walking, stooping, standing from a seated position, and stair climbing. Adults with symptomatic OA of the knee used significantly more assistive walking devices, had slower measured gait velocities, and used significantly more prescription nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, and over-the-counter acetaminophen.<sup>9</sup> Prevalence data for OA of the knee among U.S. adults are presented in Table 2.<sup>9</sup>

### Pathophysiology

Of all the large weight-bearing joints, the knee is where OA occurs most frequently.<sup>11</sup> Although OA of the knee was once thought of as naturally occurring from the wear and tear of aging, more recent research shows important differences between aging knees and knees with OA:<sup>11</sup>

1. Degenerative changes are seen in non-weight-bearing surfaces and in weight-bearing joints.
2. Water content in cartilage of the aging joint does not change significantly, whereas the water content of cartilage in joints affected by OA increases early in the process.
3. Subchondral bone changes associated with OA are not seen in the aging joint.

### Risk Factors

The primary risk factors for OA of the knee can differ across patient populations but generally include the following:

1. Genetic predisposition—Gene mutations may be a factor in predisposing individuals to development of OA, although such information warrants further confirmation.<sup>12</sup>
2. Obesity—Recent analysis showed that obesity is linked to OA of the knee in women aged 50 years and older.<sup>13</sup> Jinks et al. found that obese women (BMI  $>30$  kg/m<sup>2</sup>) and overweight women (BMI 25-30 kg/m<sup>2</sup>) with no knee pain at baseline had a 2.8-fold and 1.3-fold increased risk, respectively, for onset of severe knee pain at 3 years than did those with normal BMI ( $<25$  kg/m<sup>2</sup>). This study also suggested that 19% of cases of new-onset severe knee pain could be avoided by a 1-category downward shift in BMI (e.g., from obese to overweight or from overweight to

**TABLE 2** Prevalence of Osteoarthritis (OA) of the Knee in the United States Among Adults<sup>9</sup>

Radiographic OA of the Knee	
All adults	37.4%
Symptomatic—all adults*	12.1%
Women	42.1%
Men	31.2%
Severe† OA of the Knee	
Women	12.9%
Men	6.5%
Adults who have undergone total knee replacement	1.6%

\* Prevalence of symptomatic radiographic OA of the knee did not differ by sex.

† Kellgren-Lawrence grade 3-4 changes.





OA = osteoarthritis.

normal). However, although unburdening weight-bearing joints could reduce the incidence of OA of the knee in overweight and obese people, Zhang et al., in a study of Chinese patients, demonstrated that OA could also progress in patients with low body weight.<sup>14</sup> Compared with American women in the Framingham Osteoarthritis Study,<sup>15</sup> Chinese women, a population with overall low BMI, had a higher prevalence of radiographic OA of the knee (43% vs. 34%) and a higher prevalence of symptomatic disease (15% vs. 11%). The prevalence of OA of the knee in American and Chinese men was comparable. Speculative reasons for the higher prevalence of OA in Chinese women than in American women despite lower BMI include greater physical activity among the Chinese women and genetic factors.

3. Aging—Cartilage repairs itself at a slower rate over time.<sup>11</sup> OA of the knee affects older people; peak incidence occurs in women older than 75 years.<sup>11</sup>
4. Estrogen therapy—Postmenopausal women tend to have more OA of the knee than do men of similar age.<sup>16</sup> The relationship between estrogen and OA in women is not clear. Although estrogen may provide joint protection,<sup>17</sup> studies have reported a higher incidence of OA in the hips and knees of women undergoing short-term (fewer than 5 years) hormone therapy, a situation possibly due to more frequent medical care and diagnosis.<sup>18</sup> Estrogen may be involved indirectly in the pathogenesis of OA by maintaining bone stiffness and directly by influencing collagen synthesis, including its suppression. Estrogen may also be linked to OA when a substantial inflammatory component or an immune response is present, rather than when a simple mechanical abnormality exists.<sup>19</sup>

OA of the knee is not always age dependent. The incidence of this disease is also related to occupation and sports involvement in relatively young adults. For example, employment in building

**TABLE 3** Kellgren and Lawrence Radiographic Criteria for Assessment of Osteoarthritis<sup>22</sup>

					
Radiographic grade	0	1	2	3	4
Classification	Normal	Doubtful	Mild	Moderate	Severe
Description	No features of osteoarthritis	Minute osteophyte; doubtful significance	Definite osteophyte; normal joint space	Moderate joint-space reduction	Joint space greatly reduced; subchondral sclerosis

**TABLE 4** American College of Rheumatology Criteria for Classification of Idiopathic Osteoarthritis (OA) of the Knee<sup>24</sup>

Clinical and Laboratory	Clinical and Radiographic	Clinical
Knee pain + ≥5 of 9: <ul style="list-style-type: none"> <li>• Age older than 50 years</li> <li>• Stiffness &lt;30 minutes</li> <li>• Crepitus</li> <li>• Bony tenderness</li> <li>• Bony enlargement</li> <li>• No palpable warmth</li> <li>• ESR &lt;40 mm/h</li> <li>• Rheumatoid factor &lt;1:40</li> <li>• SF OA</li> </ul>	Knee pain + ≥1 of 3: <ul style="list-style-type: none"> <li>• Age older than 50 years</li> <li>• Stiffness &lt;30 minutes</li> <li>• Crepitus</li> <li>• + Osteophytes</li> </ul>	Knee pain + ≥3 of 6: <ul style="list-style-type: none"> <li>• Age older than 50 years</li> <li>• Stiffness &lt;30 minutes</li> <li>• Crepitus</li> <li>• Bony tenderness</li> <li>• Bony enlargement</li> <li>• No palpable warmth</li> </ul>
92% sensitive	91% sensitive	95% sensitive
75% specific	86% specific	69% specific

ESR=erythrocyte sedimentation rate (Westergren); SF OA=synovial fluid signs of osteoarthritis (clear, viscous, or white blood cell count <2,000/mm<sup>3</sup>).

and construction trades for as few as 11 years is associated with an almost 4-fold increased risk of OA of the knee.<sup>19</sup> Interestingly, while men who work in farming do not have a higher risk for OA of the knee, women who have worked in agriculture for more than a single decade have more than a 2-fold increased risk of knee arthritis.<sup>20</sup> Increased risk of OA of the knee has also been found among athletes active in various sports, including soccer (1.6-fold increased risk), ice hockey (1.9-fold increased risk), and tennis (2-fold increased risk).<sup>21</sup>

Additional risk factors include trauma; repetitive stress injuries (walking, lifting weights); rheumatoid arthritis; other forms of inflammatory arthritis, such as repeated episodes of gout or septic arthritis; and metabolic abnormalities (hypothyroidism,

hyperparathyroidism, bone dysplasias).<sup>11</sup> Evidence shows that regular, moderate use of healthy joints does not increase the risk for OA and can help maintain overall health, muscle strength, and range of motion.<sup>11</sup>

### Diagnosis

The major symptoms of OA of the knee are use-related pain, stiffness, and loss of movement. Major signs include bony swelling, crepitus (a grinding noise or sensation within a joint), joint-margin tenderness, cool effusion, decreased range of movement, and instability.<sup>22</sup> Typically, patients initially come to clinicians because of pain. At first presentation, no radiologic evidence of the disease may be present, making diagnosis

difficult.<sup>22</sup>

The Kellgren and Lawrence system for the classification of OA assigns a severity grade (0–4) at various joint sites—knee, hip, hand, and spine—according to joint site and x-ray findings (Table 3).<sup>22</sup> However, the prominence of changes in radiographic osteophytes at all joint sites is controversial, and no single global system is suitable for the assessment of OA at all sites. The criteria for increasing severity relate to the assumed sequential appearance of osteophytes, joint-space loss, subchondral sclerosis, and formation of cysts. Grading is performed by comparing the index radiograph against reproductions in a radiographic atlas, although it is important to note that radiographic grade does not reliably correlate with symptoms.<sup>23</sup> As the disease progresses, joint space decreases, and formation of osteophytes and thickening of the synovial membrane occur. At the end stage of the disease, full-thickness loss of articular cartilage is seen, as well as thickening of the subchondral bone, cysts, obvious osteophytes, and stiffness/immobility of the joint.<sup>22</sup>

According to the American College of Rheumatology (ACR), a diagnosis of OA of the knee can be established by using any of 3 methods (Table 4).<sup>24</sup> The selected method depends on the types of data available to the clinician. As shown in Table 4, the ACR analysis demonstrates that a combination of clinical and radiographic criteria yields the best combination of sensitivity and specificity and is the most common method of diagnosis in clinical practice. The number of radiographic changes of OA of the knee can be visualized, particularly in the elderly. Unfortunately, a poor correlation exists between radiographic findings and severity of clinical symptoms<sup>23</sup>; therefore, attributing knee pain to OA based on radiographic evidence alone can lead to diagnostic and therapeutic errors.

### Treatment

Because no curative treatment exists, the goals for treating OA of the knee are to relieve pain, slow disease progression, improve joint biomechanics, improve muscle strength and conditioning, delay total knee replacement (TKR), and preserve functional independence, mobility, and quality of life.<sup>25</sup> Treatment of OA of the knee should be individualized. Before initiating treatment, practitioners must exclude other causes of musculoskeletal pain, including referred pain, bursitis, and inflammatory rheumatic diseases.

### Nonpharmacologic Therapy

Exercise, weight loss, and education are the cornerstones of nonpharmacologic treatment.<sup>26</sup> Only a small number of randomized, controlled clinical trials have evaluated nonpharmacologic interventions in OA. However, practical management strategies have evolved from clinical observations and controlled trials. These strategies include patient education and support, unloading and protection of involved joints,

**TABLE 5** Pharmacologic Therapy for Patients With Osteoarthritis\*<sup>26</sup>

- **Oral**
  - Acetaminophen
  - Cyclooxygenase-2–specific inhibitor (celecoxib)
  - Nonselective nonsteroidal anti-inflammatory drug (misoprostol or a proton pump inhibitor should be added in patients at high risk of upper gastrointestinal adverse events)
  - Nonacetylated salicylate (choline magnesium trisalicylate, salsalate)
  - Weak  $\mu$  ( $\mu$ ) opioid agonist (tramadol)
  - Strong  $\mu$  ( $\mu$ ) opioid agonist (e.g., codeine)
  - Chondroitin/glucosamine
- **Intra-articular**
  - Glucocorticoids
  - Hyaluronan
- **Topical**
  - Capsaicin
  - Methylsalicylate

\* The choice of agent should be individualized on a per-patient basis.

strengthening of the muscles around joints, and local pain relief measures, including application of heat and cold.

Patient education is an integral part of the treatment plan. Patients should be encouraged to participate in self-management programs. Social support via routine telephone contact may also be a cost-effective intervention.<sup>26</sup>

The ACR has recommended a number of nonpharmacologic therapies that can help the patient meet some or all of his or her treatment goals.<sup>26</sup> For overweight patients, a weight loss program should be instituted. A cane or splint may also be used to reduce the load on weight-bearing joints. Joints may be protected by avoiding activities that cause unwarranted stress (such as kneeling and squatting). A variety of exercises, including aerobics and motion and strength training, may be used to strengthen the appropriate muscles, either under the supervision of a physical therapist or at home. Other treatment methods can be used, including using patellar taping, wearing medial- or lateral-wedged insoles, and/or using an unloader brace designed to decrease the load supported by a single side of the knee joint.

### Pharmacologic Therapy

Pain relief is the primary indication for systemic drug therapy in patients with OA of the knee. Drug therapy for pain management is most effective when coupled with nonpharmacologic strategies.<sup>26</sup> No pharmacologic agents are available that reverse the structural or biochemical abnormalities of the disease. Table 5 presents many of the medications used to treat OA of the knee.<sup>26</sup> The standards of therapy are acetaminophen and NSAIDs, and opioids, topical analgesics, and intra-articular glucocorticoids.<sup>26,27</sup>

Guidelines recommend acetaminophen as the initial drug of

choice, followed by NSAIDs and then opioid analgesics.<sup>26</sup> Opioid analgesics, such as propoxyphene, codeine, or oxycodone, are not well suited for long-term use, due to the development of tolerance, dependence, and side effects.<sup>26</sup> However, short-term use of these agents may be helpful in treating acute pain. In patients with OA of the knee who have mild to moderate pain, who do not respond to acetaminophen, and who opt not to undergo systemic therapy, the use of topical analgesics is recommended as either adjunctive treatment or as monotherapy.<sup>26</sup> In a few short-term trials, significant reduction of pain measures was observed with topical 0.025% capsaicin<sup>28</sup>; with topical 5% lidocaine patch, significant reduction of pain and improvement of stiffness and physical function was observed.<sup>29,30</sup>

### **Acetaminophen**

Acetaminophen, at doses up to 4 g per day, is the recommended initial drug of choice for systemic treatment of symptomatic OA of the knee.<sup>26</sup> In some randomized, placebo-controlled trials, acetaminophen 2-4 g per day significantly reduced pain associated with OA; in meta-analyses, acetaminophen was found to relieve pain due to OA by 79% to 87%.<sup>31,32</sup> At therapeutic doses, acetaminophen provides symptom relief equivalent to that obtained with NSAIDs but with fewer gastric adverse effects. However, 2 studies of patients with OA demonstrated a greater preference for NSAIDs than for acetaminophen, although many patients continued to take acetaminophen.<sup>33,34</sup> Although acetaminophen is the most commonly used analgesic in the United States, it should be used with caution because of the risk of hepatotoxicity.

Acute acetaminophen ingestion and toxicity are rare; the observed incidence in one local study was 21.4 and 4.8 cases per 100,000/year, respectively.<sup>35</sup> However, acetaminophen is the most common cause of acute liver failure.<sup>36</sup> A recent study showed that 42% (275/662) of cases of acute liver failure were caused by the use of acetaminophen, and unintentional acetaminophen overdose accounted for almost 50% of these cases.<sup>36</sup> Most patients with acetaminophen-induced acute liver failure (79%) reported taking the products specifically for pain. Clinical pictures and outcomes were similar for the intentional and unintentional overdoses, with a mortality rate of 29% and liver transplantation in 7% and 9% of cases, respectively. Patients with liver failure from unintentional overdose were more likely to be taking several products containing acetaminophen (38%) and were more likely to be using prescription products containing a combination of acetaminophen and narcotics (63%). The most popular of these combinations was acetaminophen with hydrocodone. The investigators found that individuals were taking more than the maximum dose of 4 g per day recommended on product package inserts; the mean daily dose in this group was 7.5 g (1.0-7.8 g).<sup>36</sup>

When taken as directed, acetaminophen is safe, although there is evidence that regular, daily intake of 4 g of acetaminophen in

healthy adults is associated with a higher rate of elevated alanine aminotransferase level, compared with placebo: up to 44% vs. 0% incidence of levels 3 times the normal limit.<sup>37</sup> It should be stressed that, if a patient has elevated liver enzymes, recent acetaminophen use should be investigated as a possible cause. In addition, acetaminophen can prolong the half-life of warfarin sodium; therefore, careful monitoring of the prothrombin time is recommended in patients taking warfarin who subsequently begin high-dose acetaminophen treatment.<sup>38</sup>

Recent evidence shows that, with physician supervision, 4 g per day of acetaminophen is generally well tolerated and does not result in extremely high hepatic enzyme levels in patients with OA of the knee when taken for up to 12 months.<sup>39</sup> Regardless, education of patients, physicians, and pharmacists should be aimed at monitoring, if not limiting, the use of this drug in high-risk patients, and patients should be cautioned about the increased risk of liver damage, especially if they chronically consume alcohol.

### **NSAIDs and Cyclooxygenase-2 Inhibitors**

If pain is not resolved with use of acetaminophen, NSAIDs are the agents of choice.<sup>26</sup> NSAIDs have demonstrated efficacy in treating pain associated with OA of the knee. In a meta-analysis of 23 randomized placebo-controlled trials, 2 to 13 weeks of treatment with NSAIDs, compared with placebo, was found to be 15.6% more effective in treating pain, as assessed using a visual analog scale (VAS).<sup>40</sup> The choice to prescribe an NSAID should be made after evaluating risk factors for serious upper GI conditions and renal toxicity. Specifically, in older adults, NSAIDs have become a leading cause of GI-related hospitalization and may increase the risk of death from ulceration more than 4-fold.<sup>41</sup> Risk factors for upper GI bleeding in patients treated with NSAIDs include age of 65 years and older, history of peptic ulcer disease or upper GI bleeding, concomitant use of oral glucocorticoids or anticoagulants, comorbidity, and, possibly, smoking or alcohol consumption.<sup>26</sup>

NSAIDs are associated with an increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.<sup>26</sup> These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk of serious GI events. Patients who are at higher risk of GI adverse reactions should be prescribed misoprostol or a proton pump inhibitor in conjunction with the NSAID.<sup>25</sup>

Cyclooxygenase-2 (COX-2) inhibitors have been demonstrated to be effective in the treatment of patients with OA; for example, in a randomized trial in patients with OA of the knee, treatment with 12.5 mg or 25 mg per day of rofecoxib or 200 mg per day of celecoxib resulted in significant relief of pain on walking, pain at rest, night pain, and morning stiffness. At 6 weeks of treatment, up to 60% reported good or excellent response in global assessment, compared with 39% taking 4 g

per day of acetaminophen.<sup>42</sup> Furthermore, endoscopic evidence shows that COX-2 inhibitors produce a lower incidence of gastroduodenal ulcers than do traditional NSAID treatment.<sup>43</sup>

However, COX-2 inhibitors have been associated with a low but significantly increased cardiovascular risk, warranting consideration of baseline cardiovascular risk. Long-term use in patients at risk for recurrent colon polyps is associated with a 2- to 3-fold increased risk of serious adverse cardiovascular events, and a 2-fold increased cardiovascular risk is observed when COX-2 inhibitors are used immediately after coronary artery bypass surgery.<sup>44</sup> A thorough review of COX-2 inhibitor data by the FDA resulted in the following conclusions<sup>44</sup>:

1. COX-2 inhibitors, as a class, are associated with an increased risk of serious cardiovascular adverse events, including stroke and myocardial infarction.
2. Available data do not permit a rank ordering of COX-2 medications according to cardiovascular risk.
3. Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as consistent with a class effect of increased risk with the use of COX-2 selective and nonselective NSAIDs.
4. Short-term use to relieve acute pain, particularly at low doses, does not appear to confer increased risk.

### **Tramadol**

Tramadol, a centrally acting oral analgesic, is a weak  $\mu$  ( $\mu$ ) opioid agonist that also inhibits reuptake of norepinephrine and serotonin.<sup>26</sup> The agent has been approved by the FDA for the treatment of moderate to severe pain and might be used in patients who have contraindications, including impaired renal function, to COX-2-specific inhibitors and nonselective NSAIDs, or in patients who have not responded to previous oral therapy. Although numerous study results assessing the use of tramadol in general pain have been published, few controlled studies have evaluated its use in OA. However, the efficacy of tramadol is comparable with that of ibuprofen in patients with OA of the hip and of the knee.<sup>45</sup>

### **Glucosamine and Chondroitin**

Glucosamine and chondroitin sulfate are used to treat OA. Both are naturally occurring substances found in and around the cells of cartilage.<sup>46</sup> Glucosamine is an amino sugar that the body produces and distributes in cartilage and other connective tissue; chondroitin sulfate is a complex carbohydrate that helps cartilage retain water. In the United States, glucosamine and chondroitin sulfate are sold as dietary supplements, which are regulated as foods rather than drugs.

The multicenter, double-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial evaluated their efficacy and safety as a treatment for OA of the knee.<sup>46</sup> The mean age of patients was 59 years, and 64% were women. More than 1,500 people enrolled in the study. All

were aged 40 years or older and had OA of the knee, mild or moderate to severe knee pain, and a loss of cartilage in the affected knee. Patients were randomly assigned to receive glucosamine alone, chondroitin sulfate alone, glucosamine and chondroitin sulfate combined, celecoxib, or a placebo for 24 weeks.

Overall, glucosamine and chondroitin sulfate were not significantly better than placebo in reducing knee pain by 20% (the primary outcome measure). For participants with mild pain, relief was not significantly better with glucosamine ( $P = 0.30$ ), chondroitin ( $P = 0.17$ ), or both ( $P = 0.09$ ) than with placebo. For a small group of participants with moderate to severe pain, glucosamine combined with chondroitin provided significant pain relief compared with placebo ( $P = 0.002$ ). However, because of the small size of the group, the researchers noted that this finding is preliminary and must be confirmed in additional studies. Participants taking celecoxib, compared with placebo ( $P = 0.008$ ), experienced significant pain relief, as expected. The researchers concluded that recent positive study results do not change the cornerstones of OA management—education, exercise, physical therapy, weight reduction, and simple analgesics—even though glucosamine and chondroitin may be another effective therapeutic option for managing pain in selected patients with OA.<sup>46</sup>

### **Glucocorticoid Injections**

Intra-articular injections of glucocorticoids can relieve acute knee pain, particularly in patients who have signs of local inflammation with joint effusion.<sup>26</sup> A large meta-analysis of 28 randomized controlled trials in patients with OA of the knee demonstrates that treatment with intra-articular glucocorticoids has short-term efficacy, persisting for about 4 weeks for pain reduction and about 1 week for global endpoints.<sup>47</sup>

In comparisons of corticosteroids and HA products, no statistically significant differences were, in general, detected at 1 to 4 weeks postinjection. Between 5 and 13 weeks postinjection, HA products were more effective than corticosteroids for 1 or more of the following variables: WOMAC OA Index, Lequesne Index, pain, range of motion (flexion), and number of responders.<sup>47</sup>

In the painful and swollen joint, the procedure is to aspirate fluid and then intra-articularly inject a glucocorticoid preparation, such as triamcinolone hexacetonide 10-40 mg or prednisone acetate 10-25 mg.<sup>48</sup> Glucocorticoid injection can be used as monotherapy or as an adjunct to systemic therapy with an analgesic, an NSAID, or a COX-2 inhibitor.<sup>25</sup> Joints should be aspirated/injected using aseptic technique, and the fluid should be evaluated for a cell count. Some patients may experience a mild flare of synovitis due to a reaction to the crystalline steroid suspensions; however, these flares are transient and can be relieved with analgesics and cold compresses. If standard aseptic technique is used, the risk of introducing infection into a joint with OA is extremely low. A gram stain and culture should be performed if infection is suspected.

**TABLE 6** Definitions and Characteristics of Hyaluronic Acid and Hylans<sup>8</sup>

Intra-articular Hyaluronans	Characteristics
Hyaluronic acid	<ul style="list-style-type: none"> <li>• Naturally occurring</li> <li>• Also known as sodium hyaluronate</li> <li>• Long, nonsulfated, straight chains of variable length</li> <li>• Repeating disaccharide unit of N-acetylglucosamine and glucuronic acid</li> <li>• Forms a randomized coil in physiological solvents</li> <li>• Average molecular weight 4-5 million d</li> </ul>
Hylans	<ul style="list-style-type: none"> <li>• Synthetic</li> <li>• Cross-linked hyaluronan chains in which the carboxylic and N-acetyl groups are unaffected</li> <li>• Average molecular weight 6 million d</li> <li>• Can be water-soluble as a gel (e.g., hylan B) or membrane bound</li> </ul>

Contraindications to intra-articular glucocorticoid injection include infection in or around the joint, bacteremia or sepsis, significant skin breakdown at the injection site, osteochondral or other intra-articular fracture at the joint to be injected, and severe joint destruction (e.g., Charcot's joint).<sup>48</sup> Other, uncommon potential side effects of intra-articular glucocorticoid treatment include tendon weakening and rupture, fat atrophy, and muscle wasting precipitated by misdirected injections; nerve and blood vessel damage, due to misdirected injections; steroid arthropathy; and systemic effects caused by high doses and multiple simultaneous injections.<sup>48</sup>

**Total Knee Replacement**

TKR is a last resort for treating OA-associated knee pain and is not always preferred by patients. Yet the procedure is becoming more commonplace. The prevalence of primary knee arthroplasty (TKR) has tripled in the United States, from 129,000 in 1990 to 381,000 in 2002.<sup>49</sup> By 2030, the number of primary TKRs is expected to jump by more than 9 times to 3.5 million.

In a Wisconsin study of TKR costs from 1990 to 2000, total charges for TKR ballooned from \$69 million to \$148 million—a 107% inflation-adjusted increase.<sup>50</sup> Kurtz estimated that a 1% reduction in TKR revision surgeries alone could save between \$53.5 million and \$98.4 million per year in the United States.<sup>49</sup>

As the number of primary procedures increases, and these procedures are performed on younger patients, it is expected that revision surgeries will increase as well. An examination of U.S. TKR data from 1990 to 2002 found a TKR revision rate of 8.2%.<sup>49</sup> Between 1990 and 2002, the rate of TKR revision increased by 146%—from approximately 12,000 revision surgeries in 1990 to 35,000 in 2002. Currently, the average

total charge for TKR revision surgery is more than \$73,000, with substantially higher costs for patients undergoing surgery because of deep joint infection or for those receiving more complex implants.<sup>49</sup> The number of revision procedures is expected to increase 62% to almost 57,000 in 2030. Projected costs to the hospital alone for these procedures may exceed \$2 billion by 2030. Reimbursement rates will not cover hospital costs for this procedure, despite recent increases in Medicare payments for revision arthroplasty.<sup>49</sup>

**Viscosupplementation Using Hyaluronic Acid**

Another approach in the palliation of joint pain is viscosupplementation using intra-articular hyaluronan preparations (Table 6).<sup>8</sup> Hyaluronan and hylan products (HAs) provide an opportunity to treat OA pain in knee joints.

**Rationale for Using Viscosupplementation**

Viscosupplementation with HA products helps to improve the physiologic environment in an osteoarthritic joint by supplementing the shock absorption and lubrication properties of osteoarthritic synovial fluid.<sup>51,52</sup> The rationale for using viscosupplementation is to restore the protective viscoelasticity of synovial hyaluronan, decrease pain, and improve mobility. The immediate benefits of viscosupplementation are the relief of pain. Longer-term benefits are believed to include the return of joint mobility by the restoration of transsynovial flow and, ultimately, the metabolic and rheologic homeostasis of the joint.<sup>51</sup>

**Types of HA Available in the United States**

Two types of HAs are available in the United States—naturally occurring hyaluronan (low molecular weight [0.5-3.6 million d] and hylan G-F 20 (high molecular weight [6 million d]),<sup>53,54</sup> which are derived from rooster combs or bacterial cultures, purified, and then isolated in noninflammatory form.<sup>55</sup> Although the indications for these products are the same—the treatment of pain associated with OA of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics such as acetaminophen—they differ with respect to physical properties, number of injections per treatment course, and duration of effect.<sup>54-58</sup> Direct comparisons of duration of effect have not been performed.

Table 7 lists the products approved for use in patients with OA of the knee, as well as these physical properties.<sup>54-58</sup> The ACR added viscosupplementation to its OA treatment algorithm in 2000, making this therapy a viable option along with NSAIDs, COX-2 inhibitors, and glucocorticoid injections (Figure 1).<sup>26</sup>

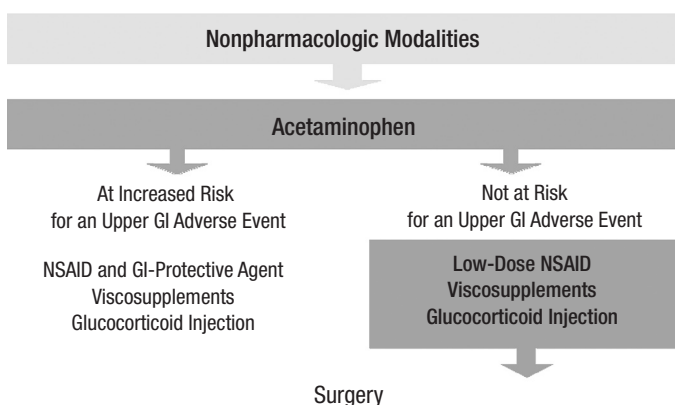
Hylans are cross-linked HAs, which give them a higher molecular weight and increased elastoviscous properties.<sup>53,59</sup> The higher molecular weight of hylan may make it more efficacious than naturally occurring HA because of its enhanced elastoviscous properties and its longer period of residence in the

**TABLE 7** Comparison of Hyaluronate Products<sup>54-58</sup>

Product	Euflexxa (1% Sodium Hyaluronate)	Hyalgan (Sodium Hyaluronate)	Orthovisc (High-Molecular-Weight Hyaluronan)	Supartz (Sodium Hyaluronate)	Synvisc (Hylan G-F 20)
Dose per injection (mg)	20	20	30	25	16
Number of injections per treatment course	3	3-5	3 or 4	5	3
Duration of pain relief	3 months	3 injections: 2 months 5 injections: 6 months	6 months	6 months	6 months
Molecular weight* (× 10 <sup>6</sup> d)	2.4-3.6	0.5-0.7	1.0-2.9	0.6-1.2	6.0

\* Molecular weight of human hyaluronic acid is ~6 million d.

**FIGURE 1** Treatment Summary for Osteoarthritis of the Knee



Adapted with permission from the American College of Rheumatology.<sup>26</sup>  
GI=gastrointestinal; NSAID=nonsteroidal anti-inflammatory drug.

joint space because of slower resorption.<sup>52</sup> Studies have shown that the higher-molecular-weight, more elastoviscous hylan G-F 20 has a large treatment effect compared with placebo.<sup>60</sup> The actual period that the injected HA product stays within the joint space is hours (naturally occurring HA) to weeks (hylan B), but the time of clinical efficacy is usually months,<sup>55-59</sup> suggesting additional mechanisms of action.

For example, relief of knee pain in OA using HA supplementation may be at least partially due to direct effects on nerve impulses and nerve sensitivity. Knee joint inflammation excites the nociceptors of articular nerves, making them

exquisitely sensitive.<sup>61</sup> Administration of HA significantly decreases ongoing and movement-evoked nerve activity.<sup>61,62</sup> HA also has a range of effects at the cellular level:

1. It can enhance the synthesis of proteoglycans and of extracellular matrix proteins, including chondroitin.<sup>8</sup>
2. It can alter the profile of inflammatory mediators and expression/activity of matrix-degrading enzymes in such a way that the balance is tipped away from cell matrix degradation to cell matrix synthesis.
3. It acts as an antioxidant by enhancing the scavenging effect of synovial fluid, reducing reactive oxygen species and thereby protecting articular tissues from oxidative damage.<sup>63</sup>
4. It affects immune cells. HA supplementation can modulate leukocyte function, including macrophage phagocytosis, a process that is more pronounced in higher-molecular-weight HA.<sup>64</sup> It can also inhibit neutrophil-induced cartilage destruction, again, in a dose- and molecular-weight-dependent manner, with higher-molecular-weight hylans providing greater protection.<sup>65</sup>

### Advantages and Disadvantages of HA

Results from several clinical studies, preclinical experiments, and meta-analyses indicate that viscosupplementation with different HA products has several advantages, particularly for some subpopulations of patients. A meta-analysis of 20 randomized controlled trials showed that overall, HA viscosupplementation therapy significantly decreases symptoms of OA of the knee.<sup>60</sup> In clinical trials of HA preparations, pain relief among patients was comparable with that of oral NSAIDs.<sup>51,60,66</sup> One randomized controlled trial showed that for resting pain relief, HA is as effective as NSAIDs and is superior to NSAIDs alone in relieving pain associated with physical activity and functional performance.<sup>67</sup> Compared with intra-articular glucocorticoid injections, pain relief is achieved more slowly with HA injections,

but their effect may last considerably longer.<sup>51,68,69</sup>

In the meta-analysis, HA viscosupplementation was less likely to be beneficial for patients aged 65 years and older as well as those with the most advanced radiographic stage of OA.<sup>60</sup> A study of 4,253 patients with OA of the knee found that with short-term treatment with intra-articular hylan G-F 20, potential predictors of efficacy in pain reduction included being underweight, being male, having severe baseline pain, and having a recent diagnosis (<1 year and 1-5 years vs. 10 years).<sup>70</sup> Two other studies also demonstrate lesser efficacy with more severe symptoms: patients with more advanced radiographic grades were less likely to respond to HA therapy.<sup>67,71</sup>

Intra-articular hyaluronans are well tolerated in clinical trials and practice.<sup>51</sup> The most common adverse event associated with intra-articular hyaluronans is mild, short-lasting injection site pain and inflammation. Major adverse events associated with intra-articular hyaluronans are rare: in the trials included in the meta-analysis, the overall incidence of serious events, including severe swelling, vasculitis, hypersensitivity reaction, and painful acute local reaction, was 0.36% (4/1,141).<sup>60</sup> The pooled relative risk of transient mild increase in local pain or swelling was 1.19 (95% confidence interval [CI], 1.01 to 1.41). In addition to these potential adverse effects, another drawback for some patients is the need for a series of 3 to 5 weekly HA injections.<sup>72</sup> It is therefore recommended that this approach be reserved for patients with symptoms and a significant need for surgery and for patients with mild OA in whom more conservative approaches—physical therapy, weight loss, NSAID, and intra-articular glucocorticoids—have failed.<sup>66</sup>

### ■ Studies Involving Viscosupplementation

#### Meta-analyses

Recent meta-analyses have concluded that viscosupplementation using HA and HA products is (1) efficacious and safe and (2) lasts longer than intra-articular glucocorticoids. In 2004, a meta-analysis was conducted by Wang et al. to evaluate the therapeutic efficacy and safety of the procedure. Twenty blinded, randomized, placebo-controlled trial results published between 1966 and 2001 met the inclusion criteria.<sup>60</sup> The outcome measure of safety was relative risk for adverse events and the outcome measure for efficacy was scores of pain with activity, pain without activity, and function. This study includes data on 1,647 randomly assigned knees: 818 treated with HA and 829 with placebo. This meta-analysis confirmed that intra-articular injection of cross-linked and non-cross-linked HA, compared with placebo, decreases symptoms of OA of the knee and revealed significant improvements in pain with activity, pain at rest, and function, with few adverse events reported. The relative risk of minor adverse events with HA was 1.19 (95% CI, 1.01 to 1.41). Trials that involved cross-linked HA showed much greater pooled estimates of efficacy than did the trials involving non-cross-linked HA. However, among trials using non-cross-linked HA,

there was significant between-study heterogeneity in estimates of efficacy and, therefore, relative efficacy is inconclusive.

Bellamy et al. conducted a systematic review using Cochrane methodology to evaluate the safety and efficacy of HA products.<sup>51</sup> The *Cochrane Review* concluded that, overall, the analyses showed positive results for the HA class. Results were particularly positive for some products with respect to certain variables and time points, such as pain on weight bearing at 5 to 13 weeks postinjection. Forty trials included comparisons of HA preparations and placebo; 10 trials included comparisons of intra-articular glucocorticoids; 6 trials of NSAIDs; 3 trials of physical therapy; 2 trials of exercise; 2 trials of arthroscopy; 2 trials of conventional treatment; and 15 trials of other hyaluronans/hylan. The pooled analyses of the effects of viscosupplementation against placebo controls supported the efficacy of this type of intervention in OA of the knee. In these same analyses, varied efficacy was observed for different HA products on different variables and at different time points. Notably, the 5- to 13-week postinjection period showed an improvement from baseline of 28% to 54% for pain and 9% to 32% for function. In general, efficacy was comparable with the NSAIDs, and longer-term benefits were seen in comparison with intra-articular glucocorticoids.

#### Notable Individual Studies—Comparative Effectiveness

The few head-to-head human clinical trials that have been published have not consistently demonstrated a clear advantage in efficacy for one product over another. However, some study results suggest that higher-molecular-weight HA is more efficacious. A recent prospective, randomized clinical trial compared hylan G-F 20 (3 injections) (n = 181) with sodium hyaluronate (5 injections) (n = 167) in 392 patients with predominantly grade 3 OA of the knee. Pain was measured on a 10-cm VAS of 0 (no pain) to 10 (worst pain). By 6 weeks, knee pain on the VAS improved from 6.7 to 3.2 ( $P = 0.02$ ), with an intergroup difference of  $P = 0.001$ , and was sustained until 12 months (VAS of 3.7 [ $P = 0.04$ ]) with hylan G-F 20, with an intergroup difference of  $P = 0.01$  (intergroup differences in favor of the hylan G-F 20 group). Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores were significantly superior for hylan G-F 20 at 3 months ( $P = 0.02$ ), 6 months ( $P = 0.01$ ), and 12 months ( $P = 0.02$ ).<sup>73</sup> Several studies of HA products for OA of the knee have demonstrated no benefit compared with controls; possibly, at least in some cases, because of the age and OA severity of the patient population assessed.<sup>51,74</sup>

In the hyaluronate group, pain improved from 6.6 to 5.7 at 6 weeks ( $P > 0.05$ ) and to 4.1 at 3 months ( $P = 0.04$ ) but was sustained only until 6 months (VAS, 5.9;  $P > 0.05$ ).

General patient satisfaction was better in the hylan group at all times, although it was only statistically significant at 3 months ( $P = 0.01$ ) and 6 months ( $P = 0.02$ ). Patient adherence

was 99.2% in the hylan group versus 92.2% in the hyaluronate group with regard to the number of injections. This finding, however, may be confounded by differences in the number of injections required for the 2 treatment groups: 3 in the hylan group and 5 in the hyaluronate group.

The cost of the agents was comparable, but the total treatment cost was 23% more in the hyaluronate group because of 2 additional visits to complete the 5-injection treatment course. Thus, although both treatments relieved pain significantly, treatment with hylan G-F 20 relieved pain earlier and the effect was sustained longer.

Pain relief with a low incidence of adverse events using viscosupplementation with hylan has been reported for up to 18 months.<sup>75</sup> Repeat treatment may extend pain relief in patients who experienced beneficial results with an initial course of therapy. Although only limited information is available, an analysis of 255 patients with OA of the knee suggests that these agents are effective and safe when given repeatedly.<sup>76</sup> Karatosun et al. performed a randomized controlled trial comparing 1 series of HA injections with progressive knee exercises in 105 patients.<sup>77</sup> The investigators followed up with the patients for 18 months. No significant differences were observed between the study arms in terms of pain and function scores following treatment at 18 months. However, the HA injections also increased the levels of satisfaction of the patients with OA, an important consideration in patients who may not be able or willing to adhere to a steady exercise regimen.

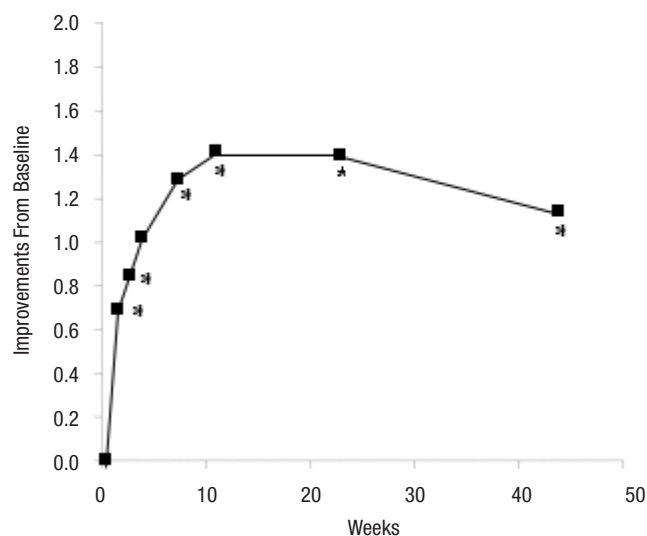
A prospective open-label study by Waddell et al. evaluated the efficacy and tolerability of a second course of hylan G-F 20 for the treatment of OA-associated knee pain over a 12-month period in patients who had previously experienced a beneficial initial course of therapy.<sup>50</sup> The main efficacy measure was the WOMAC index question A1, which assessed the patient's pain while he or she walked on a flat surface. All efficacy parameters significantly improved ( $P < 0.001$ ) from baseline at weeks 1, 2, 4, 8, 12, 26, and 52. Improvements from baseline to weeks 26 and 52 for WOMAC index question A1 were 1.4 and 1.1 (1-category shifts), respectively (Figure 2).

While the study design undermines conclusions—patients may have improved without viscosupplementation and results may be confounded by investigator and patient biases—the authors argue that the beneficial effects were likely due to viscosupplementation. Before the study, patients had achieved similar degrees of improvement with viscosupplementation and then worsening of symptoms after completing the course of treatment.

### Possible Delay of TKR With HA

A few studies suggest that the use of HA products could delay the need for TKRs and generate savings in the managed care setting. In a retrospective analysis of patients with advanced OA of the knee awaiting TKR, hylan G-F 20 effectively managed

**FIGURE 2** Improvements in WOMAC Index Up to 52 Weeks



Improvements from baseline (week 0) in scores for the WOMAC index question A1 (pain while walking on a flat surface) with hylan G-F 20 at weeks 1, 2, 4, and 8 (n = 70), 12 (n = 67), 26 (n = 66), and 52 (n = 51). Asterisks indicate significant improvements from baseline ( $P < .001$ ).

Improvements from baseline (week 0) in scores for the Western Ontario and McMaster Universities Osteoarthritis index question A1 (pain while walking on a flat surface) at various time points in a prospective, open-label study to assess a second course of hylan G-F 20 in patients with osteoarthritis of the knee. Adapted with permission from Waddell et al.<sup>50</sup>

pain. Sixty-nine percent (64/93) of knees treated with hylan G-F 20, including 74% (14/19) of knees with severe OA, did not require TKR during the 2.5-year average follow-up.<sup>78</sup> In a separate study, 59% (19/46) of knees treated with hylan G-F 20 did not progress to TKR during the 30-month follow-up.<sup>79</sup>

Waddell and Bricker performed a 6-year retrospective data review of 1,187 knees treated with intra-articular hylan G-F 20 in 863 TKR candidates (100% grade IV OA of the knee) who underwent 3 weekly intra-articular hylan G-F 20 injections.<sup>80</sup> Of the knees treated with hylan G-F 20, 45% and 14% received 2 and 3 courses of therapy, respectively; fewer patients received 4 (4%) and 5 (1.1%) courses of therapy. The mean age was 67.5 years for patients who did not undergo TKR and 66.8 years for those who underwent TKR. The overall incidence of TKR in this population was 19.0% (n=225). The incidence of TKR was highest in patients aged 60 to 69 years (35.7%); the lowest incidence of TKR was in patients younger than 50 years (7.1%) and older than 80 years (8.4%). Age was the only significant covariate influencing the odds of TKR ( $P = 0.0002$ ).

**TABLE 8** Most Frequently Reported Adverse Events Associated With Visco-supplementation in 4,235 Patients<sup>70</sup>

Adverse Event	Local Treatment Related, n (%)
Joint effusion	91 (2.14)
Joint swelling	48 (1.13)
Arthralgia	42 (0.99)
Joint warmth	23 (0.54)
Injection site erythema	13 (0.31)
All injection site reactions	217 (5.12)

These adverse events in aggregate may be quite high as many are related to the same injection-site reaction.

**TABLE 9** Age-Dependent Distribution of Osteoarthritis of the Knee Disease Severity in a Pharmaco-economic Model of Patients in a Managed Care Setting

Disease Severity (%)	Age (Years)	
	35-64	Older Than 64
Mild*	40	20
Moderate†	40	50
Severe‡	20	30

\* Discomfort but rare function limitation; episodic flares.

† Some functional limitation and reduced mobility; regular flares requiring constant analgesic or nonsteroidal anti-inflammatory drug use.

‡ Poor mobility and nearly constant pain; frequent or perpetual flares requiring treatment.

Adapted with permission from Waddell et al.<sup>83</sup>

The time to TKR was 638 days, or 1.8 years per survival analysis. Therefore, in TKR candidates, symptomatic relief from hylan G-F 20 therapy for OA of the knee can delay the need for surgery. No data are available on the effect of other HA products on TKR.

The ability to delay TKR would be advantageous for patients in whom TKR is not medically appropriate or for patients who fear or do not prefer surgical intervention. Delay of TKR would also decrease the need for revision arthroplasties, which are associated with greater risk of complications than index procedures. Because TKRs are costly, can carry serious risks, and may need revision in younger patients, treatment that would delay last-resort surgery would be valuable.

### Tolerability of Viscosupplementation

Local adverse events with viscosupplementation are typical of those observed with other intra-articular injections, including

corticosteroids and saline. In a large study of hylan G-F 20, local treatment-related adverse events occurred in 4.2% of 4,253 patients and 2.4% of 12,600 injections.<sup>70</sup> Results of the analysis of synovial fluid obtained from reactive knees after viscosupplementation showed that local adverse events were noninfectious, inflammatory, noncrystalline induced, and nonallergic. Most adverse events were mild to moderate and included joint effusion and swelling, arthralgia, joint warmth, and injection site erythema (Table 8).<sup>70</sup> A higher, statistically significant incidence of injection-site pain was reported in an earlier, smaller, randomized controlled study of intra-articular hyaluronate in patients with OA: 23% versus 13% with placebo ( $P < 0.01$ ).<sup>81</sup> Rare incidences of gout, anaphylactoid reactions, and severe acute inflammatory reactions have been reported with viscosupplementation.<sup>81</sup>

### Cost Implications of Viscosupplementation in the Managed Care Setting

The cost-effectiveness and cost utility of viscosupplementation via HA injections (hylan G-F 20) were measured using prospective data from a 1-year randomized, controlled, open-label Canadian trial by Torrance et al.<sup>82</sup> In this trial, 225 patients were randomly assigned to “appropriate care with hylan G-F 20” (AC+H) or “appropriate care without hylan G-F 20” (AC), which included intra-articular glucocorticoids, and completed a number of outcomes questionnaires, including the WOMAC and the Health Utilities Index Mark 3. Over the year, the AC+H group incurred higher costs (Canadian \$2,125 vs. \$1,415;  $P < 0.05$ ), improved more significantly (69% vs. 40%;  $P = 0.001$ ), and experienced increased quality-adjusted life-years (QALYs, which means years of perfect health; 0.071;  $P < 0.05$ ) than the AC group. The incremental cost-effectiveness ratio (the ratio of change in costs) was \$2,505 per patient improved. The incremental cost-utility ratio (a function of the incremental cumulative costs divided by incremental cumulative effects over the year of the study) was Canadian \$10,000 per QALY gained. Since the cost-utility ratio is below the suggested Canadian adoption threshold, the investigators stated that their results provide strong evidence for HA treatment in patients with OA of the knee and in settings similar to those studied in the trial.

To illustrate the current cost of treating OA of the knee and to demonstrate potential savings associated with viscosupplementation in a managed care setting, Waddell et al. developed a pharmacoeconomic model with inputs obtained from peer-reviewed medical literature, clinical trial data, clinical expert opinion, and claims data.<sup>83</sup> A hypothetical cohort of subjects (mild, moderate, severe OA of the knee; Table 9) was followed up over a 3-year period. Analysis was conducted from the perspective of a managed care plan with a large Medicare population.

The 3-year savings to the plan associated with adding 1 or more courses of hylan G-F 20 therapy to the standard treatment

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**TABLE 10** Cost Savings in a Pharmacoeconomic Model of Patients With Osteoarthritis of the Knee in a Managed Care Setting

Description	Year 1	Year 2	Year 3	Overall
Base-case treatment costs (\$)	15,455,330	16,569,839	23,834,031	55,859,200
Osteoarthritis of the knee treatment costs with G-F 20 added (\$)	10,414,476	14,927,606	21,706,346	47,048,428
Annual savings (\$)	5,040,854	1,642,232	2,127,685	8,810,771
Decreases (%)	33	10	9	16
Average annual savings over 3 years (\$)				2,936,924
Total average savings per patient with osteoarthritis receiving G-F 20 over 3 years (\$)				4,706

Adapted with permission from Waddell et al.<sup>83</sup>

**TABLE 11** TKRs Avoided in a Pharmacoeconomic Model of Patients With Osteoarthritis of the Knee in a Managed Care Setting

Description	Year 1	Year 2	Year 3	Overall
Cases without HA: number of TKRs	290	409	808	1507
Cases with HA: number of TKRs	0	290	408	699
Total number of TKRs avoided with G-F 20	290	119	399	808

Adapted with permission from Waddell et al.<sup>83</sup> HA=hyaluronic acid; TKR=total knee replacement.

pathway for OA of the knee was \$8,810,771 (Table 10). The total savings per patient with OA receiving hylan G-F 20 was \$4,706. These savings were based on the assumption that 808 TKRs were avoided (Table 11). This estimate presumed that patients would not opt for arthroplasty as long as their knee pain was being relieved satisfactorily by nonsurgical means (a presumption supported by the 3 studies cited above). The model was therefore highly sensitive to the durability of the analgesic effect of hylan G-F 20; increasing and decreasing durability within a reasonable range resulted in 3-year savings of \$9,131,879 and \$2,012,082, respectively.<sup>83</sup>

This same study also looked at managed care plans with no or few Medicare-aged enrollees. When the analysis was rerun to determine cost savings in a younger (i.e., younger than 65 years) population, the population of patients with OA of the knee dropped 66% to 1,297. The number of patients receiving hylan G-F 20 also dropped 76% from 1,872 to 441. Using this

model, the total savings decreased 80%—from \$8.8 million to \$1.7 million. However, the savings per patient with OA of the knee receiving G-F 20 therapy did not decline to the same level (from \$4,706 to \$3,920, down 16%). These results show that managed care plans with no or few Medicare-aged enrollees still can achieve considerable savings on a per-patient basis. While the removal of aged enrollees reduced the overall savings, the savings that were achieved remained positive and considerable among patients treated with hylan G-F 20.<sup>83</sup>

Figure 3 highlights some significant differences among the hyaluronic products that are of interest to those in the managed care field. For example, these injections are administered in a course of 3 or 5 weekly injections costing \$100 to \$200 per injection, not including the cost of the physician office visit. Also, because the numbers of injections required for a course of treatment are different—and therefore the number of office visits vary accordingly—the total cost of HA therapies varies

**FIGURE 3** U.S. Food and Drug Administration Labels Indicate Different Treatment Regimens

	Months of Clinical Benefit						Total Cost 2006 for 6 Months of Benefit (Including Injections)
	1	2	3	4	5	6	
Synvisc	XXX →						\$852
Hyalgan 3 injections	XXX →		XXX →		XXX →		\$1,840
Hyalgan 5 injections	XXXXX →						\$987
Supartz 3 injections	XXX →			XXX →			\$1,222
Supartz 5 injections	XXXXX →						\$983
Orthovisc 4 injections	XXX →					XXX →	\$1,169
Euflexxa	XXX →		XXX →			XXX →	\$1,226

Assumptions: Wholesale acquisition costs for viscosupplementation products as published in November 2006 Red Book, \$70/arthrocentesis, \$53/office visit.

Orthovisc is now approved for a series of 3 injections. Costs associated with 6 months of benefit are not yet available.

Note:

Synvisc (hylan G-F 20) is a registered trademark of Genzyme Biosurgery.

Hyalgan (sodium hyaluronate) is a registered trademark of Fidia Farmaceutici S.p.A.

Supartz (sodium hyaluronate) is a registered trademark of Seikagaku Corporation.

Orthovisc (high molecular weight hyaluronan) is a registered trademark of Anika Therapeutics, Inc.

Euflexxa (1% sodium hyaluronate) is a trademark of Ferring Pharmaceuticals Inc.

Source:

Federal Register. Vol 70, No. 223, Monday, November 21, 2005.

among the different agents. Proven FDA-approved durations vary among the different products. For example, 3 injections of sodium hyaluronate are an option. However, since the duration of effect is shorter than with 5 injections, a patient may require more total injections in a fixed period for symptom relief. Therefore, the total cost for 6 months of benefit, which may require multiple courses of therapy, can range from \$852 to \$1,840, depending on which product is used. Such costs were calculated using the wholesale acquisition costs for the products, the cost of arthrocentesis, and the cost of office visits.

### Conclusions

OA represents an advanced stage of an active, progressive disease process. Medical research has led to the understanding that OA

is the endpoint of a continued progression in tissue degradation resulting in loss of cartilage structure and function. Relief of pain and preservation of joint tissue must evolve to encompass treatments that interfere with the induction of cartilage-degrading mechanisms that follow acute or chronic injury, restore normal cartilage and joint homeostasis, and arrest the progression of disease.<sup>84</sup> Optimal treatments of the future should also reverse, whenever possible, existing damage and restore normal cartilage structure and function.

HA preparations are indicated for the treatment of pain in patients with OA of the knee whose condition has failed to adequately respond to conservative nonpharmacologic therapy and to traditional analgesics and in those for whom NSAIDs, COX-2 inhibitors, and intra-articular glucocorticoids are either contraindicated or ineffective. Clinicians in the managed care

setting should consider using viscosupplementation in patients (1) who have persistent pain despite the use of conservative therapy, (2) who have compromised GI function or at risk of GI bleeding due to the adverse events of NSAIDs, (3) who are taking concomitant anticoagulant therapy for any condition, (4) who have cardiovascular or renal risk factors precluding use of COX-2 inhibitors, and (5) for whom surgery is not appropriate.

Results of studies are published or studies are under way to test the theory that HA therapy will improve symptoms and function in other joints, such as the shoulder, hand, hip, temporomandibular joint, spine, and ankle.<sup>85</sup> Further study should be conducted with larger numbers of patients to help identify a subgroup of patients with OA in whom HA treatments may have even greater effects.<sup>11</sup> Additional research should also concentrate on assessing the risks and benefits of extended treatments, because limited data are available concerning the effectiveness of multiple courses of therapy.

Considering its prevalence and economic effect, OA is an important public health issue. OA is the leading cause of disability in our country. As the population ages, the socioeconomic costs of this disease will dramatically increase. In light of systemic side effects of therapies for OA of the knee, patients may prefer local therapy for their local joint disease. Viscosupplementation is one treatment with proven efficacy in OA of the knee. Its use in the managed care arena may improve patients' symptoms and thereby reduce hospitalizations and improve efficient use of clinical resources.

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## Viscosupplementation: Managed Care Issues for Osteoarthritis of the Knee

This activity may be completed online\* or by indicating the correct answer on the Posttest Answers form and faxing or mailing that and the Program Evaluation form to Postgraduate Institute for Medicine (see page S21 for instructions).

1. In persons younger than 40 years of age, most osteoarthritis
  - a. is in men and results from obesity.
  - b. is in men and results from trauma.
  - c. is in women and relates to menopause.
  - d. is in women and relates to genetic predisposition.
2. Cartilage is made up mostly of
  - a. hyaluronic acid.
  - b. matrix proteoglycans.
  - c. collagen.
  - d. water.
3. Which statement about the pathophysiology of osteoarthritis is not true?
  - a. It is a disease that is strictly caused by the wear and tear of aging.
  - b. Degenerative changes are seen in non-weight-bearing surfaces as well as in weight-bearing joints.
  - c. The water content in cartilage of an aging joint does not change significantly.
  - d. The subchondral bone changes associated with osteoarthritis are not seen in an aging joint.
4. Evidence shows that regular, moderate use of healthy joints does not increase the risk for osteoarthritis.
  - a. True
  - b. False
5. Which statement about acetaminophen is true?
  - a. It is the most common cause of renal failure.
  - b. It is the most common cause of liver failure.
  - c. Studies show that patients with OA prefer acetaminophen over the nonsteroidal anti-inflammatory drugs.
  - d. It should be used with misoprostol.
6. Which is not true of the hylans?
  - a. They are synthetic.
  - b. They are cross-linked hyaluronan chains.
  - c. Their average molecular weight is 6 million d.
  - d. They form a randomized coil in physiologic solvents.
7. Hyaluronic acid supplementation can modulate leukocyte function, including macrophage phagocytosis, a process that is more pronounced in
  - a. higher-molecular-weight hyaluronic acid preparations.
  - b. more severe osteoarthritis.
  - c. older patients.
  - d. All of the above
8. Patients with a complete collapse of joint space or bone loss with intra-articular hyaluronic acid may benefit the most from viscosupplementation.
  - a. True
  - b. False
9. Which of the following hyaluronates has the highest molecular weight?
  - a. Sodium hyaluronate
  - b. Hylan G-F 20
  - c. Hyaluronic acid found in human synovial fluid
  - d. High-molecular-weight hyaluronan
10. In a recent prospective, randomized trial comparing hylan G-F 20 and sodium hyaluronate in patients with osteoarthritis of the knee, the cost of the agents was comparable, but the total treatment cost was 23% more in the hyaluronate group because of
  - a. poor efficacy.
  - b. increased number of side effects.
  - c. more visits to complete the necessary number of injections.
  - d. All of the above

\*To complete this activity ("Viscosupplementation: Managed Care Issues for Osteoarthritis of the Knee") online, go to [www.amcp.org](http://www.amcp.org) (Learning Center/Online CE), where you will access the posttest and evaluation form.

## Viscosupplementation: Managed Care Issues for Osteoarthritis of the Knee

If you wish to receive acknowledgment for completing this activity, please complete the posttest and Program Evaluation form (and Verification of Participation form, if applicable) and fax to (303) 790-4876 or mail to Postgraduate Institute for Medicine, 367 Inverness Pkwy., Suite 215, Attention: Records Dept., Englewood, CO 80112.

### Posttest Answers

1	2	3	4	5	6	7	8	9	10

### Request for Credit

Name \_\_\_\_\_ Degree \_\_\_\_\_

Organization \_\_\_\_\_ Specialty \_\_\_\_\_

Address \_\_\_\_\_

City, State, ZIP \_\_\_\_\_

Telephone \_\_\_\_\_ Fax \_\_\_\_\_ E-mail \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

### Physicians

- I participated in the entire activity and claim 1.25 credits.
- I participated in only part of the activity and claim \_\_\_\_\_ credits.

### Pharmacists

- I participated in the entire activity and claim full contact hours.

### Nurses

- I participated in the entire activity and claim full contact hours.

### Case Managers

- I participated in the entire activity and claim full contact hours.

Please submit Verification of Completion form on page S23.

## Viscosupplementation: Managed Care Issues for Osteoarthritis of the Knee

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment of participation for this activity. (PIM ID #4581 ES 29)

**Please answer the following questions by circling the appropriate rating:**

1 = Strongly Disagree

2 = Disagree

3 = Neutral

4 = Agree

5 = Strongly Agree

### Extent to Which Program Activities Met the Identified Purpose

Provide the latest information on therapeutic options for osteoarthritis of the knee, including viscosupplementation. 1 2 3 4 5

### Extent to Which Program Activities Met the Identified Objectives

*After completing this activity, I am now better able to:*

- explain the pathophysiologic factors involved in osteoarthritis (OA) of the knee 1 2 3 4 5
- describe appropriate treatment for patients with OA of the knee 1 2 3 4 5
- discuss benefits of viscosupplementation for management of OA of the knee as they pertain to the managed care environment 1 2 3 4 5

### Overall Effectiveness of the Activity

*The content presented:*

- Was timely and will influence how I practice 1 2 3 4 5
- Enhanced my current knowledge base 1 2 3 4 5
- Addressed my most pressing questions 1 2 3 4 5
- Provided new ideas or information I expect to use 1 2 3 4 5
- Addressed competencies identified by my specialty 1 2 3 4 5
- Avoided commercial bias or influence 1 2 3 4 5

### Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity:

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Please list any topics you would like to see addressed in future educational activities:

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### Additional Comments About This Activity:

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### Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

- Yes, I would be interested in participating in a follow-up survey.
- No, I'm not interested in participating in a follow-up survey.









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