Clinical Practice Guideline

Osteoarthritis of the Knee

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Abbreviations

AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
AP	Anteroposterior
BMI	Body mass index
COX-2	Cyclooxygenase 2
CV	Cardiovascular
CVD	Cardiovascular disease
ESR	Erythrocyte sedimentation rate
FDA	US Food and Drug Administration
GI	Gastrointestinal
HA	Hyaluronic acid
IACS	Intra-articular corticosteroid
JAMA	Journal of the American Medical Association
KOOS	Knee Injury and Osteoarthritis Outcome Score
KOOS, JR.	Knee Injury and Osteoarthritis Outcome Score for Joint Replacement
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PA	Posterior-anterior
QoL	Quality of life
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SNRI	Serotonin-norepinephrine reuptake inhibitor
TENS	Transcutaneous electrical nerve stimulation
TKR	Total knee replacement
US	United States
WBC	White blood cell count
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Introduction

Osteoarthritis (OA) is the most prevalent type of arthritis in the United States (US). It is also one of the leading causes of disability, loss of productivity, and absenteeism from work.[1] Between 27 and 30.8 million adults in the US are believed to have OA.[2, 3] Approximately 14% of the US population over the age of 25 years, and 34% of those over the age of 65 years have one or more joints affected by OA.[4] Osteoarthritis of the knee was reported to account for 83% of the overall OA burden according to the Global Burden of Disease Study 2010.[5]

OA is incurable and progressive. Currently there is no medication that can stop the progression of the disease or reverse joint damage.[6] As will be discussed below, there are both nonpharmacologic and pharmacologic recommendations which have the potential of improving physical activity, decreasing pain, and slowing progression, but none that ultimately reduce the need for joint replacement in many patients.

According to Byers Kraus et al., the draft OARSI (Osteoarthritis Research Society International) definition of OA (Page 1237):[7]

> "*…is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."*

In 2011, OARSI, responded to a list of questions from the United States Food and Drug Administration (FDA). The answers to these questions were to be used to assist manufacturers and researchers in the development and evaluation of treatments and/or devices for the management of OA.[8] The members of the working group for this project did not think that the terms disease and illness should be used interchangeably when referring to OA. Instead they recommended that manufacturers and researchers look at potential treatments as either 1) treatments for the "disease" OA (those that impact the structural and antomic changes at the joint level); or 2) treatment for the illness of OA (those that improve the patient's symptoms or complaints). It was suggested that this differentiation may be helpful in clinical trials. Under normal conditions, there is an equilibrium between cartilage destruction in joints and cartilage synthesis. When cartilage destruction exceeds synthesis, OA can develop.[9] The pathology of OA includes inflammation of the synovial lining of the joint, degeneration of the menisci and articular cartilage, remodeling of bone and osteophyte formation.[10] Changes of the ligaments and tendons are also seen.

The most common patient complaints related to OA are joint pain, swelling, stiffness and limited mobility, all of which progress over time leading to a more sedentary life style than their peers

without OA. The pain associated with OA is usually described as chronic (low to moderate pain with weight bearing), severe (occurring sporadically), or a combination of both.[11] Often the severe, sporadic pain has the most negative impact on quality of life (QoL), because it is unpredictable. The development of constant pain in OA has been linked to the onset of central pain sensitization which occurs in a subset on OA patients.[12-14]

In addition to pain, patients may experience difficulty sleeping, fatigue, loss of independence, frustration about their inability to perform simple everyday tasks, and a general decrease in coping with lifestyle challenges leading to depression and/or anxiety.[15]

The diagnosis of OA is often delayed, although articular cartilage loss and/or bony changes may be seen on X-rays. Patients may be asymptomatic despite these changes and only seek medical attention when they develop joint pain and/or stiffness or decreased mobility. The primary risk factors for incident radiographic OA of the knee are body mass index (BMI) >30 kg/m^2; aging; prior knee trauma, including prior surgical intervention; occupational activities;[15] and female gender.[16]

Other risk factors for progression of OA include but are not limited to the following:[17, 18]

- Age
- Comorbidities
- Sedentary lifestyle
- Genetics
- Infrapatellar synovitis detected on magnetic resonance imaging (MRI)
- Joint effusion
- Knee injury
- Meniscal tear and/or meniscectomy
- Clinical and radiographic extent of OA at initial diagnosis
- Type 2 diabetes
- BMI >30 kg/m^2 (obesity)

According to Leyland et al,[11] overweight patients with knee OA have a 40% increased risk of total knee replacement (TKR) when compared to those with normal weight. Obese patients have double the risk for TKR as patients with normal weight. Some studies have indicated poorer outcomes from TKR in the setting of obesity, although this association has not been uniform across studies.[19-21]

Osteoarthritis is either primary (idiopathic) or secondary. The etiology of idiopathic OA, which is the most common form, is not fully understood; however, a combination of genetic, biochemical, and biomechanical factors are likely involved. Some of the biomechanical factors thought to be important include an occupation that requires working in a kneeling or squatting position, obesity, muscle weakness, or neurologic problems.[9, 22]

Secondary OA may be related to:[9, 22, 23]

- Trauma, including but not limited to anterior cruciate ligament or meniscal injury

- Congenital or developmental diseases
  - Bone dysplasias
  - Hypermobility syndromes
  - Gaucher's disease
  - Ehlers-Danlos syndrome
- Joint surgery
- Metabolic problems, including but not limited to:
  - Rickets
  - Hemochromatosis
  - Chondrocalcinosis (and calcium pyrophosphate deposition disease)
  - Ochronosis
- Acromegaly
- Gout
- Hyperparathyroidism
- Rheumatoid arthritis (RA)
- Neuropathic joint
- Septic arthritis
- Aseptic necrosis
- Paget's disease

The comparative differences in long-term outcome between the primary and secondary forms of OA remain to be elucidated, likely because of the considerable phenotypic heterogeneity resulting from the wide variety of underlying causes of secondary OA.

The prevalence of OA in the population is expected to increase over the next 20 years.[11] Caring for these patients is costly and contributes to the overall high cost of healthcare in the US. Kotlarz et al.[24] estimated that annual healthcare costs for all types of OA were $185.5 billion in 2007, with $149.4 billion paid by insurers and $36.1 billion paid by patients. In 2013, inpatient costs for OA were $16.5 billion, representing 4.3% of all inpatient hospitalization costs, second only to septicemia for hospital stays. Osteoarthritis accounted for 46% of all inpatient hospital costs in Medicare patients and for 25% of inpatient costs for private insurers.[25]

Direct costs of caring for patients with OA include nonpharmacologic and pharmacologic treatment, physician visits, imaging, hospitalizations, and joint-replacement surgery. Other direct costs are long-term care and the management of treatment complications. The indirect costs include absenteeism from work, reduced work hours, decreased productivity, homecare services, and the cost of other caregivers such as family and friends.[5] The estimated annual cost of caring for an individual with OA in year-2000 dollars was $5700.[26] In 2011, Berger et al.[27] estimated the annual direct costs of caring for 2399 employees in the private-sector. For those with OA, the direct costs of care were approximately $17,751 per patient as compared to $5057 for those without OA. Indirect costs for those in the OA group were $5002 per patient as compared to $2120 for those

without OA. In addition, employees with OA were absent from work approximately 62.9 days per year as compared to 36.7 days per year for those without OA.

A Canadian study[28] demonstrated that the cost of total joint replacements accounted for the greatest increase in direct costs of caring for patients with OA.These increased costs were attributed to the greater prevalence of the disease, rapidly rising surgical and prosthesis costs and a failure to diagnose and treat younger patients with OA. A truly disease modifying agent could decrease the need for joint replacement as these patients age.

Osteoarthritis is a Serious Disease

In 2016, OARSI published a white paper in support of classifying OA as a ***serious disease***.[6] The purpose of this paper was to demonstrate to providers and the FDA that OA meets the definition of a serious disease and that treatments for OA should be given priority by manufacturers of medical devices and pharmaceuticals. According to the FDA:

> "Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."[29]

By providing evidence based data demonstrating that OA fits the definition of a serious disease, OARSI argued that there is currently an "*urgent need for clinical studies of new and existing agents that might intervene in the pathophysiology and progression of OA"* (Page 2).[6]

Using the FDA definition above, OARSI categorizes OA as a serious disease associated with progressive disability and premature death. This association likely is caused by the bidirectional negative impact of OA on several of common comorbidities, notably concomitant CVD, type 2 diabetes and hypertension. Patients with limited mobility due to OA pain may become progressively more obese, hypertensive and insulin resistant. Often the pain on walking leads to a a progressively sedentary lifestyle which then results in further weight gain and progression of CVD which, in turn, increases the risk of diabetic complications such as hospitalization for poor blood sugar control, infection (often pneumonia), peripheral vascular disease resulting in amputation, retinopathy and renal dialysis. To complicate matters further, progressive obesity, inactivity and weakness, caused by comorbid conditions such as coronary artery disease-related limitation in exercise tolerance, may worsen OA symptoms.

A 2011 study[30] of "all cause and disease specific mortality in patients with osteoarthritis of the knee and hip" (Page 1) demonstrated that premature death in patients with OA was associated with CVD, dementia, diabetes and cancer. The strongest relationship between premature death and OA was

found in patients with difficulty walking and CVD (independent of traditional CVD risk factors). These findings were confirmed in a 2014 publication that studied the same problem.[31]

It is important for patients and providers to understand the importance of the relationship of the pain of OA in conjunction with the patient's obesity, hypertension, diabetes and CVD. Appropriate nonpharmacologic and pharmacologic modalities described below should be used.[32] If patients develop increased exercise tolerance, they might be able to gradually expand the time and distance that they exercise which may in turn help to improve the management of their comorbidities.[6]

Early in the management of OA, nonsteroidal anti-inflammatory drugs (NSAIDs) may be prescribed to treat joint pain. Long term use of NSAIDs may contribute to the premature death of the patients who have concurrent CVD.[33] NSAIDs can also result in adverse events in the gastrointestinal tract and kidneys. These drugs may cause gastritis, and/or peptic ulcers which can managed by using a gastroprotective agent with NSAIDs. Increased risk of acute myocardial infarction, heart failure and acute renal failure have also been reported with these drugs. Hemorrhagic stroke has been associated with the use of diclofenac and meloxicam.[34, 35] Topical NSAIDs may have a reduced risk of adverse events as compared to oral NSAIDs. For more detail of the adverse effects of NSAIDs in patients with osteoarthritis please see Cooper et al.[36]

Diagnosis

The diagnosis of idiopathic OA of the knee is established by clinical history and physical examination. Radiographs are commonly obtained but are not required to establish the diagnosis. X-rays are helpful in eliminating other problems such as fracture, osteonecrosis, or tumors, which can present with a complaint of knee pain and to evaluate the severity of articular damage. The American College of Rheumatology (ACR) described three different sets of criteria for the classification of idiopathic OA of the knee in patients with knee pain (Figure 1). These criteria are not designed to be used if secondary OA of the knee is suspected.

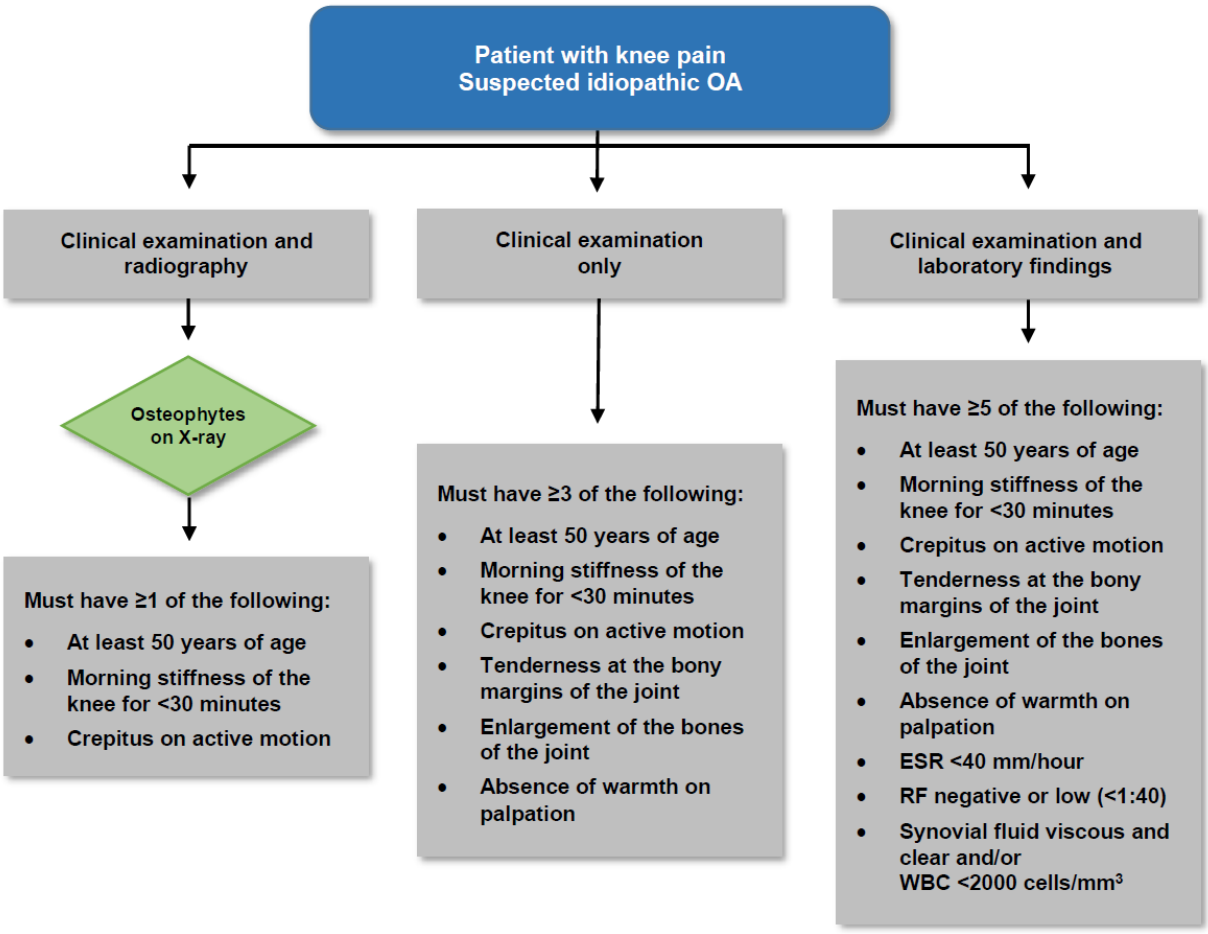

Figure 1. Establishing the diagnosis of primary (idiopathic) OA of the knee.

ESR, erythrocyte sedimentation rate; OA, osteoarthritis; RF, rheumatoid factor; WBC, white blood cell count

Imaging

Use of X-ray

In patients with OA, there is frequently a discrepancy between the radiographic changes in the knee and symptoms. A study designed to explain the marked increase in knee replacement surgery in the US found that only half of patients with radiographic findings of OA complained of knee pain.[37]

Radiographic findings that support the diagnosis of OA include:

- Asymmetric joint space narrowing, with the medial compartment more commonly affected than the lateral or patellofemoral compartments
- Subchondral sclerosis
- Marginal osteophytes, including the tibial spines
- Subluxation
- Subchondral cysts

The initial imaging for patients with known or suspected OA should be plain films. Careful attention to patient position and radiographic technique is important. All anteroposterior (AP) or posterior-anterior (PA) films should be weight bearing, if possible. Non-weight-bearing films may overestimate cartilage thickness and underestimate the extent of disease. Lateral views may be taken in either the supine position or weight bearing.

- X-ray imaging of the knee must include at least one standing AP view; a Rosenberg view (PA view with the knee flexed at 45°, and the patella touching the image receptor with the X-ray tube at a distance of 40 inches from the receptor and angled at 10 degrees caudad); a lateral view (usually taken in the supine position with the knee flexed at 45° for evaluation of the patellofemoral joint; and a sunrise view (also referred to as skyline or sunset view) for the evaluation of the patellofemoral joint. Attention to details of patient positioning, tube distance from the receptor, and tube angulation are essential for the meaningful comparison with subsequent X-rays.

Magnetic Resonance Imaging (MRI)

Structural articular damage from OA may be identifiable on X-rays as narrowing of the joint space, which is often the result of loss of articular cartilage. Other characteristic radiographic changes of OA include osteophytes, subchondral sclerosis, and/or subchondral cysts. However, early in the course of the disease, X-rays may be normal despite the clinical complaint of knee pain and the presence of risk factors. In these cases, additional imaging may be needed to better categorize the source of pain and establish a treatment plan. The diagnosis might be early OA without radiographic changes; however, the pain could also be related to a fracture not visible on X-ray, or ligamentous or meniscal injuries. In addition, at times, radiographic changes may be discordant with the clinical findings. Finally, just because X-rays reveal changes consistent with OA, this does not rule-out other pathologic entities, including for example joint infection, which may be suggested by clinical features that are not typical for OA. In these limited circumstances, MRI could help to explain the cause of the knee pain. However, **MRI should not be routinely performed for the diagnosis of OA.**

A study published in 2013[38] found MRI results were not well correlated with clinical findings in OA of the knee and contributed little to treatment decisions. Another study published in 2015[39] reported that, in patients with suspected degenerative or nonspecific knee pain, knee MRI had a

low likelihood of providing information that led to a correct diagnosis or information that was valuable in determining treatment plans.

Patients with significant trauma and knee pain with or without known OA should have an MRI examination of the knee; which may document an acute problem such as a meniscal or ligamentous injury, or even a fracture superimposed on chronic knee pain, or OA.

In individuals with a short duration of knee pain and a high suspicion of OA but negative X-rays, contrast-enhanced MRI may demonstrate very early cartilage loss consistent with OA.[40, 41]

Bone marrow lesions, with normal X-rays and knee pain can also be seen on MRI of patients with OA.[42] Recent studies have shown that the severity of bone marrow lesions is associated with increased cartilage loss. There is a positive association with the risk of knee arthroplasty within 4 years in patients with significant or progressive bone marrow edema.[43]

Magnetic resonance imaging should always be performed on a 1.5 or 3 Tesla scanner using a knee surface coil. Three imaging planes (axial, coronal, and sagittal) should be obtained using a field of view of 12 to 14 centimeters.[42]

Patient Assessment

A complete medical history with special attention to the knee should be obtained, including but not limited to the following:

- Pain
  - Age of onset
  - Continuous or sporadic
  - Sudden or slow onset
  - Description: sharp, dull, tight, pinching
  - Intensity of pain on a scale of 0 to 10
  - The activity that reproduces the pain or makes it resolve
  - Location of pain
  - Previous treatment/surgery/diagnostic studies
  - Exercise regimen
  - Type of work
- Duration of morning stiffness for less than 30 minutes
- Additional knee complaints such as swelling, giving way, or locking
- Other medical illness, including but not limited to the following:
  - Diabetes
  - Hypertension
  - Cardiovascular (CV) disease, especially coronary artery disease
  - Renal disease
  - Gastrointestinal (GI) problems, especially a past history of GI bleeding

    - Obesity
    - Pulmonary disease
    - Neurological disease
    - Physical problems that limit activities
    - History of deep venous thrombosis
    - History of psoriasis or gout
    - Other rheumatologic diseases, including but not limited to RA and psoriatic arthritis
    - Liver disease
    - Calcium pyrophosphate deposition disease
- Allergies

Physical examination of the knee in a patient with OA should at a minimum include the following assessments:

- BMI
- Inspection of the knee for synovial thickening and associated erythema or warmth
- Muscle strength and evidence of muscle atrophy
- Degree of active and passive range of motion and any associated pain
- Crepitus
- Joint swelling, erythema, discoloration, and/or tenderness
- Joint deformity and/or enlargement
- Point tenderness at the medial/lateral joint lines, quadriceps tendon, infrapatellar tendon, tibial tubercle, femoral condyles, and pes anserine bursa
- Foot and ankle abormalities
- Gait
- Effusion

Often patients with OA complain of knee pain that increases with activity or weight bearing and improves with rest. There may be a history of remote joint trauma with or without subsequent surgery to the knee, particularly those affecting the anterior cruciate ligament or meniscal tears, or patellar dislocation. Morning joint stiffness that lasts for less than 30 minutes is also a common complaint. Joint stiffness and pain may get worse as the disease progresses, and the knee may become enlarged.

On examination, there may be progressive development of a bow-legged (genu varum) appearance secondary to involvement of the medial compartment of the knee. If the lateral compartment is involved, the patient may develop a knock kneed (genu valgum) appearance. The patient may also have an antalgic gait and favor the involved knee.

Crepitus with active motion, joint line tenderness, deformity, limitation of motion, and effusions support the diagnosis of OA of the knee.[22, 42-46]

If there is a monoarticular effusion in the absence of another explanation, synovial fluid aspiration should be obtained.[44]

Findings on examination that suggest a diagnosis other than OA include but are not limited to:[46]

- Fever or chills
- Redness of the affected joint
- Warmth of the affected joint

Treatment

Osteoarthritis of the knee is irreversible and incurable. There are no disease-modifying drugs available for OA at this time. The goal of treatment is to control pain and improve physical function. Nonpharmacologic therapy should be provided to all patients with OA. Pharmacologic therapy may be considered if the patient does not adequately respond to such lifestyle-directed management. However, nonpharmacologic treatments, as described below, must be maintained for at least 6 to 12 weeks to determine their impact.

Some of the challenges in caring for these patients are:

- Inability to maintain a response
- Need for multiple therapies
- Lack of adherence
- Comorbidities
- Safety of some of the long-term therapies
- Concomitant medications and possible drug interactions
- Coordination with other healthcare providers
- Cost of long-term treatment

Nonpharmacologic Recommendations

Initial management of OA of the knee should include an exercise prescription along with patient education and self management, as well as weight-reduction strategies (when appropriate). These "lifestyle interventions" are the anchor therapy in the management for OA.[10, 47-49] The assessment of adherence to prescribed dietary and exercise programs is a critical component of each knee OA follow-up visit.

United Rheumatology believes that all patients with OA of the knee should participate in either a land or water based exercise program as appropriate. The program should consist of aerobic exercise and resistance, strength, flexibility, and balance training. Such a program has the potential to reduce pain and disability; improve balance and range of motion; and improve overall physical fitness[50-52] as well as slow the progression of disease. Given the challeges inherent to learning to exercise with OA of a weight bearing joint, a course of physical therapy is often prescribed to teach

patients how to safely exercise without exacerbating the symptoms related to their arthritis. This may be provided in a step-wise acceleration of efforts to activate a patient's lifestyle, an approach that was recently demonstrated to be beneifical in a randomized clinical trial.[53] Additional exercises, such as Tai Chi and yoga are also recommended and should be considered.

Clinical studies of the value of exercise and education (or self management) for OA patients are difficult to compare because of the many variations in study design. There are however, many systematic reviews and meta analyses of these studies which are helpful in understanding the value of these programs. A few of them are commented on below.

One analysis looked at 16 studies which ranged in size from 20 to 786 participants. Overall, exercise was found to have a positive impact on the disease in the exercise groups as compared to the control groups. Education and self management programs are more difficult to evaluate and very variable. However it is generally believed that this is an important component of a conservative management plan for OA.[54]

In 2009, another analysis of randomized controlled studies compared land based exercise to no exercise.[55] Exercise programs included individual exercise, exercise classes, and home exercise programs. The supervision of the exercise sessions varied from none to more than 36 sessions. Sessions also varied from 30 to 90 minutes. The included trials lasted from 1 month to 2 years. When the studies were combined, a small but significant improvement of knee pain and physical function was found with exercise. The more supervised sessions the greater the improvement in pain and physical function. The authors also stress that "long-term adherence to exercise, or increased leisure-time physical activity is required to maintain the benefits of exercise" (Page 115). They also indicate that this usually requires supervision or monitoring of some kind. In addition, patients must have the resources to permit access to appropriate exercise facilities which can be problematic. For many individuals a home based program may be the only option which is better than no exercise. In-person, group-based exercise classes at a community center or gym may be another possibility especially since classes are supervised.

A randomized controlled study of 150 patients was reported in 2004.[56] Approximately half the patients were in the control group and half in the intervention cohort. A small number dropped out of each group. The participants were evaluated at baseline, 2 months and 6 months after the intervention. (Details of the design of the study can be found at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.576.628&rep=rep1&type=pdf). The intervention group participated in a 6 month program of exercise and an education and problem solving program which was aimed at developing self-efficacy for both exercise and adherence to an exercise program. Participants then developed individual exercise plans for themselves which were to be performed at home after the 6 month follow-up. At 6 months the exercise group had a 48.5% increase in adherence to the program and 13.3% increase in distance walked at the end of 6 minutes compared to baseline. In comparison, at 6 months the individuals in the control group decreased their adherence to exercise and distance walked during 6 minutes. At the end of 6 months, the exercise group were provided with logs to record their at-home exercise sessions which was found

to improve compliance. Research staff also called the participants in the exercise trial every quarter to check up on the number of exercise sessions per week and the length of those sessions. The authors concluded that the "benefits of strength and aerobic exercise can be maintained only among persons who adhere to exercise routines over time, it is essential that interventions include educational components that help motivate older adults with OA to embrace and adhere to exercise behaviors over time" (Page 226).

When education is combined with an exercise program, pain is decreased and function improved. Thorlund et al.[57] reported that in patients with either hip or knee OA who participated in an 8-week trial of both exercise and disease education, pain was reduced by 12.8 to 13.6 mm on the visual analogue scale (0–100mm) and the use of analgesics was reduced from 62.2% before the program to 44.1% after intervention. In addition, about half the patients using analgesics before the program either stopped them completely or changed to a lower risk drug. The use of opioids also decreased. Reducing the use of drugs and increasing the use of exercise is important in the development of a treatment algorithm for OA of the knee.

For those individuals who are overweight (BMI >25 kg/m^2), weight loss is strongly recommended as a core component of the treatment of OA of the knee.[9, 45, 50, 52, 58] Even modest weight loss ≥5% of body weight improves function, physical disability, and pain.[59] Conversely, overweight patients are 40% more likely, and obese patients more than twice as likely, to require knee replacement surgery than patients with normal body weight.[18]

Other nonpharmacologic recommendations that should be considered include the following:[10]

- Use of walking aids as needed, including the use of a cane
- Valgus bracing for medial-compartment OA has been effective in some patients for decreasing pain and improving function, and for decreasing joint stiffness and drug use.[50, 60] Even the use of a simple, sleeve-type brace has been demonstrated to improve symptoms[61] and walking mechanics[62]
- Social support
- Self-management and education

Other nonpharmacologic treatments which are *conditionally* recommended for patients with OA include:[10]

- Heat or cold applied to the joint
- Acupuncture
- Cognitive behavioral therapy

The 2019 ACR/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee[10] recommends against transcutaneous electrical nerve stimulation (TENS) and *conditionally* recommends against massage therapy, iontophoresis, pulsed vibration therapy, and footwear modifications.

Comorbidities such as high blood pressure, CVD, kidney disease, and GI problems should be taken into consideration when recommending either nonpharmacologic or pharmacologic treatment. Managememt of comorbidities should be a collaborative effort by rheumatologists and the appropriate medical specialists.

Pharmacologic Management

Patients should be cautioned that neither nonpharmacologic nor pharmacologic therapy alone will provide the best result.

When nonpharmacologic interventions do not provide adequate pain relief or maintain and/or improve function, pharmacologic therapy should be added. To determine if a particular drug regimen is effective, the patient should take it for at least 2 to 4 weeks before switching to a different medication providing no side effects are noted. Generics should be used if available. Table 1 provides an overview of the medications (with generic and brand names) used in the management of OA.

In the past, acetominophen was recommended as the initial drug for the treatment of OA. However, research suggests that this drug probably does not play a role in the management of OA of the knee, primarily as a consequence of a lack of effectiveness.[63, 64]

Currently, the initial drug that should be tried is either a topical or an oral NSAID as listed in Table 1.[10, 48] United Rheumatology prefers the use of topical rather than oral NSAIDs for all patients, especially for those with significant comorbidities or contraindication to oral NSAIDs. Adverse events from topical NSAIDs are minimal and, most commonly, local skin reactions, which are transitory.[48] Currently, there are two brand-name topical NSAID preparations available in the US for the treatment of OA—diclofenac sodium topical gel 1% (Voltaren®) and diclofenac sodium topical solution 1.5% w/w (Pennsaid®). In addition, the FDA has approved generic formulations of both Voltaren and Pennsaid.

Because the systemic complications of NSAIDs are related to the serum concentration of the drugs, topical preparations are considered safer. In fact, the local concentration of topical NSAIDs has been reported to be higher than that seen with the oral preparations in about half of the patients.[63] In addition, the NSAID concentration in the underlying synovium is equal to that seen with oral NSAIDs.[65] Voltaren has recently obtained FDA-approval for nonprescription, over-the-counter use.[66]

If oral NSAIDs are used, physicians should be aware of the potential adverse effects associated with the long-term use of of these drugs. Adverse events associated with NSAIDs range from GI complications such as bleeding, gastric ulcers, and bowel perforation to CVD events, including death. Oral NSAIDs should be prescribed at the lowest possible dose and should not be prescribed as needed but rather as continuous dosing. In some cases, a proton-pump inhibitor could be considered for gastric protection. In weighing the risk-benefit ratio of prescribing oral NSAIDs to patients with OA, it should be recognized that patients with OA are at greater risk for NSAID-related side effects than those without OA.

Patients with renal disease and a glomerular filtration rate of ≤30 should not be given oral NSAIDs; however, topical NSAIDs may be used in this population, if renal function is monitored closely. The most common adverse effects of transdermal NSAIDs are seen at the site of application; GI complications are very uncommon.[65]

If a patient takes aspirin for cardioprotection, the physician should be aware that an oral NSAID may interfere with the aspirin-related benefit to platelet inhibition. It should also be noted that the risk of peptic ulcer disease increases with the combination of aspirin and an oral NSAID.

Table 1. Generic and brand-name drugs for the treatment of OA of the knee

Drug Classification	Generic Name	Brand Name
Analgesic	Acetaminophen	Tylenol®
Oral NSAIDs	Ibuprofen	Motrin®, Advil®
	Naproxen	Aleve®, Anaprox®, Naprosyn®, Naprelan®
	Indomethacin	Indocin®
	Oxaprozin	Daypro®
	Piroxicam	Feldene®
	Celecoxib	Celebrex®
	Diclofenac	Cataflam®, Cambia®, Zipsor®, Voltaren®, Voltaren®-XR, Zorvolex®
	Diclofenac + Misoprostol	Arthrotec®
	Salsalate	Amigesic®, Salflex®, Argesic®-SA, Artha®-G, Salsitab®, Marthritic®
	Sulindac	Clinoril®
	Etodolac	Lodine®, Lodine® XL
	Naproxen + Esomeprazole	Vimovo®
	Meloxicam	Mobic®
Topical NSAIDs	Diclofenac gel 1%	Voltaren® gel
	Diclofenac sodium topical solution 1.5%	Pennsaid®
Centrally acting analgesic	Tramadol	Ultram®
SNRI	Duloxetine	Cymbalta®
Viscosupplements	Hyaluronics (visco supplementation)	Euflexxa®, Hyalgan®, Orthovisc®, Monovisc®, Supartz®, Synvisc®, Synvisc®-One, Hymovis®, Gel-Syn 3™(3 injections), Durolane®
	Cross-linked hyaluronate	Gel-One® (one injection)
Intra-articular steroids	Betamethasone	Celestone® Soluspan®
	Methylprednisolone	Depo-Medrol®, Solu-Medrol®, A-methaPred®
	Triamcinolone	Aristospan®, Kenalog®-10, Kenalog®-40
	Triamcinolone acetonide extended release injectable suspension	Zilretta® (not intended for repeat administration)

NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; SNRI, serotonin-norepinephrine reuptake inhibitor

Tramadol (Ultram®) can be tried in patients who have not responded to oral or topical NSAIDs or to intra-articular injections of steroids (see below). A recent article in the *Journal of the American Medical Association* (JAMA)[67] documented an increased mortality when patients took tramadol as the first prescription drug to treat OA when compared to NSAIDs. When used as the initial treatment of OA of the knee, there was no difference in mortality rate between tramadol and codeine. In patients who have a history of depression, risk for addiction, or are taking antidepressants; tramadol could be prescribed, but with caution. Narcotic analgesics and tramadol should be limited to patients who are not surgical candidates or who do not want surgery and for whom all other measures have failed. Patients must understand that this drug is potentially addictive and has not been adequately studied for the management of OA.[10] In general, United Rheumatology recommends that the use of tramadol and other opiods should be restricted, because they are not particularly effective and can be addictive.[48]

Duloxetine (Cymbalta®) is FDA-approved for the treatment of chronic musculoskeletal pain, including OA, and a 2015 meta-analysis of three placebo-controlled studies of patients with OA of the knee treated with duloxetine demonstrated that the duloxetine group had statistically significant improvement in pain when compared to the placebo group. The study reported more adverse events in the duloxetine group than seen with other agents; which included myalgia, arthralgia, cough, nausea, increased sweating, nausea, constipation, insomnia, dry mouth, fatigue, sleepiness, and palpitations. In addition, more patients discontinued the use of duloxetine than placebo.[68] Duloxetine could be given to patients with multiple-joint OA and comorbidities for whom topical and oral NSAIDs have failed to relieve their pain.[50, 51] This drug is conditionally recommended by the ACR[10] because it has not been adequately studied for use in OA.

Intra-articular corticosteroid (IACS) injections could be considered as a first-line treatment for some patients with OA of the knee,[51] although long-term benefits have not been demonstrated. These injections typically provide short-term pain relief for 3 to 4 weeks[69] and, as a general rule, should not be administered more frequently than once every 3 months. Triamcinolone acetonide extended-release injectable suspension (Zilretta®), was initially approved by the FDA in 2017. In 2019 the package insert was modified to state that "*efficiency and safety of repeat administration of Zilretta have not been demonstrated"* (Page 1[70]).[46, 71, 72]

Steroid injections are not disease modifying but are used for symptom relief; they are commonly used by rheumatologists for the management of patients with OA of the knee. Recently, there have been several articles questioning whether IACS injections may result in progression of cartilage damage. In one study, 64 patients with OA were randomly divided into two groups.[71] In one group, 34 patients received IACS injections into the same knee every 3 months for up to 2 years. The second group of 34 patients received saline injections into the same knee every 3 months. Radiographically, there was no difference in progression of joint space narrowing between the two groups at 1 and 2 years. However, the group that received IACS injections had some improvement in symptoms that was not seen in the saline-injection group. The findings support the use of IACS injections in the management of patients with OA of the knee who do not respond to other forms of treatment.[10, 48, 71]

A recent publication in the *JAMA* also questioned the benefit of IACS.[73] One hundred and forty patients started the study, and 119 completed it. All patients were at least 45 years of age and had met the ACR classification criteria for OA of the knee. The participants were randomized into two groups—one group had injections of an osteoarthric knee with triamcinolone every 12 weeks; the other group had intra-articular injections of saline every 12 weeks. The study was conducted over 2 years, and MRIs were obtained annually. At the end of 2 years, the group that received the IACS injections was found to have statistically greater cartilage loss than the saline group. However, several additional findings of the study have raised questions about the study and its conclusions including uncertainty regarding the clinical significance of the small differences in cartilage loss relative to the natural progression of the disease, the lack of significant differences when a completers analysis was applied, the non-real-world application of time- rather than symptom-directed injections, the lack of other structural correlates of OA disease progression, and the lack of significant difference in symptoms reflective of progressive cartilage damage between the two groups.

At this time, United Rheumatology recommends the use of IACS injections for the management of patients not responding to nonpharmacologic and/or oral or topical pharmacologic management.

Osteoarthritis causes a decrease in both, the concentration and molecular weight of naturally occurring intra-articular hyaluronic acid (HA) in the knee. As a result, the synovial fluid of the knee becomes less viscous. Currently, the mechanism of action of intra-articular HA is unknown. It may decrease the production of substances that increase inflammation and change the response of immune cells to inflammation. In addition, it may decrease cartilage loss and possibly promote cartilage regeneration.[16, 74]

In their 2019 Guidelines regarding the management for OA of the knee,[10] the ACR considers the injections of HA into the knee to be *conditionally* not recommended.

In July 2015, the Agency for Healthcare Research and Quality published an evidence-based review prepared by the RAND Southern California Evidenced-Based Practice Center,[16] in which they concluded that no information was currently available to determine whether or not the use of intra-articular HA injections could delay or avoid a TKR. The report suggested that a large randomized study of treated and untreated patients was needed to determine if intra-articular injections of HA can bend the curve for knee replacement surgery. However, the report also stated that there was evidence to demonstrate a small, “statistically significant” improvement in function with older patients treated with intra-articular HA.

In addition, recently various scenarios have been proposed to identify specific patients with OA of the knee who would likely benefit from intra-articular HA injections.[75, 76]

Patients with OA are candidates for injections of HA when they have persistent pain, despite an adequate trial of a combination of nonpharmacologic and pharmacologic therapy (including NSAIDs). Intra-articular HA is also appropriate for those who have a contraindication to NSAIDs.[77]

This includes patients with common comorbidities such as heart disease, renal disease, or hypertension that, according to the ACR, may limit the option of using NSAIDs.

When intra-articular HA is used, injections are given weekly for 1 to 5 weeks, depending upon the product.[77] These injections may result in relief of pain for up to 6 months, but the most pronounced improvement is seen between 5 and 13 weeks after treatment.[78, 79] Many patients have adequate pain relief up to 26 weeks after the injection.[80] Treatment may be repeated at 6-month intervals.

Contraindications to the intra-articular injection of HA include:[81-92]

- History of allergy to sodium hyaluronate preparations
- Allergy to gram positive bacterial proteins (Orthovisc, Monovisc)
- Pregnancy—the safety of hyaluronan-based products has not been established in pregnant women
- Nursing—the safety of hyaluronan-based products has not been established in lactating women
- Pediatric patients—the safety of hyaluronan-based products has not been established in children under the age of 18 years
- Local overlying skin disease
- Joint infection

United Rheumatology recommends the stepwise management of patients with OA (Figure 2), starting with the recommendations for nonpharmacologic treatment. If there is insufficient response, adding pharmacologic management, starting with either topical or oral NSAIDs or intra-articular injections of glucocorticoids, is recommended. If these steps fail to reduce the patient's pain, then injection of HA could be considered.

If a patient fails the standard treatments described above, the next step could be referral for surgical evaluation. However, not all patients with OA of the knee who have failed standard therapy want to proceed with TKR. In addition, TKR may not be medically appropriate (e.g., for patients of older age or with comorbidities such as diabetes or heart or lung disease).[93] As described above, over the last decade, there have been a number of encouraging reports demonstrating that the use of HA injections may delay surgery.

A retrospective review of 1187 knees in 863 patients treated with an average of 1.6 courses (three injections per course) of intra-articular HA injections and followed for 6 years showed that the median time to either TKR or last observation was 2.1 years. But only 19% of the patients required TKR.[93]

Altman et al.[94] reviewed healthcare claims of 182,022 patients continuously enrolled in a single health plan for the 6 years of the study who had OA and a TKR. Of these patients, approximately 27.7% had been treated with HA. Half of the patients who were not treated with HA had a TKR within 114 days of diagnosis. Half of the HA users had a TKR within 484 days after diagnosis. Patients who had at least five courses of HA delayed TKR on average by 3.6 years.

A 2016 publication by Maheu et al.[95] reviewed multiple meta-analyses assessing the value of HA in the management of OA of the knee. According to this review, intra-articular HA injections can reduce pain and decrease the need for analgesics and, in some cases, actually improve function. In addition, although the improvement with HA injections was slower than that with steroid injections, it lasted longer than the pain improvement with steroids.

A Spanish study of 224 patients who were candidates for TKR reported that intra-articular HA injections delayed TKR by 2.67 years.[96]

United Rheumatology recommends against the use of glucosamine, chondroitin, bisphosphonates, hydroxychloroquine, tumor necrosis factor inhibitor agents, IL-1 inhibitors, and topical capsaicin.[50, 52, 59] United Rheumatology also strongly recommends against the use of prolotherapy, and stem cell and platelet rich protein injections.[10, 48, 97, 98]

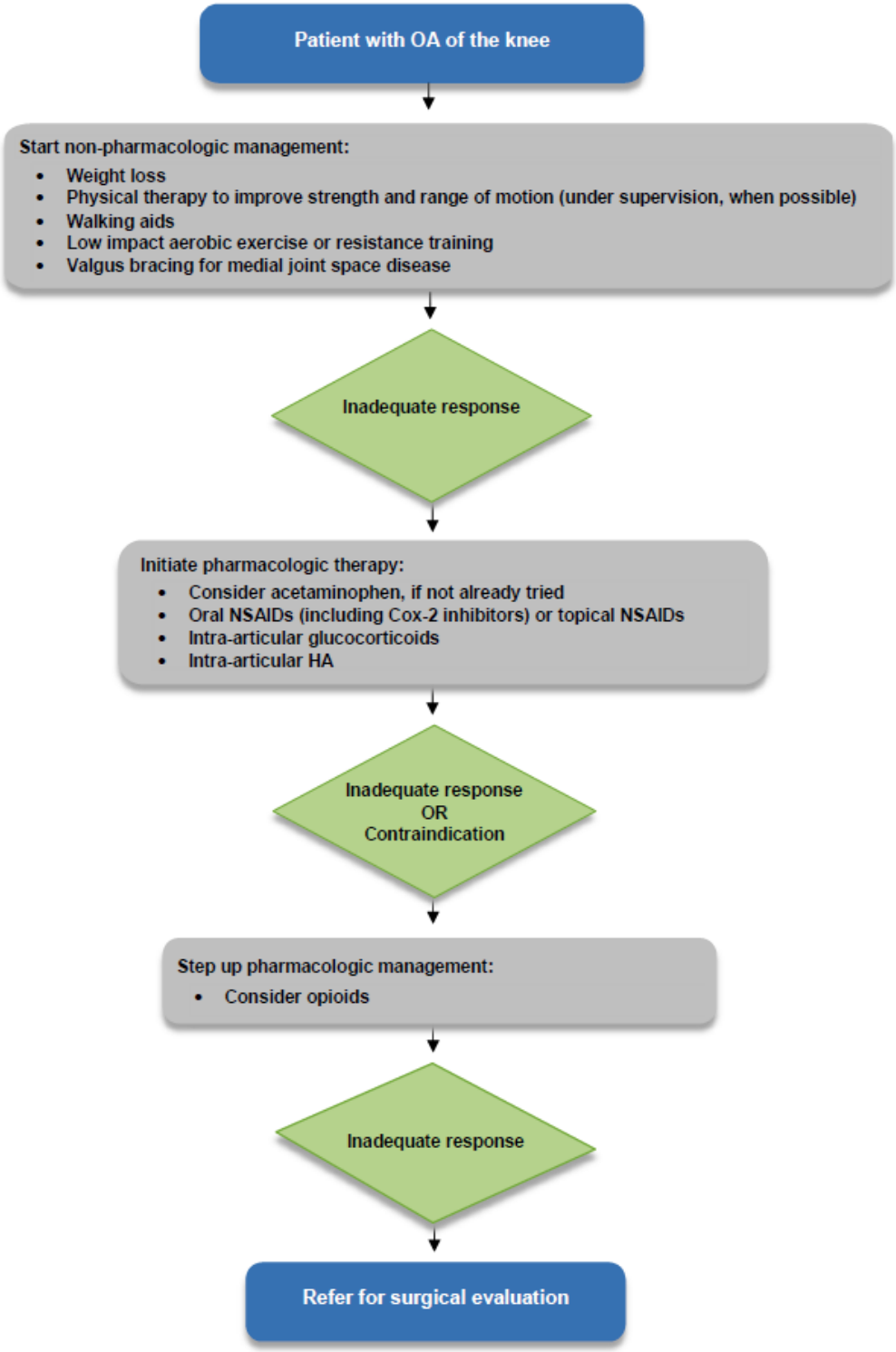

Figure 2. Stepwise management of OA of the knee

The drugs for initial pharmacologic management may be used in any order. If one fails to elicit the desired response, another medication or delivery mode should be tried. Generic drugs are preferred when available.

COX-2, cyclooxygenase; HA, hyaluronic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis

Monitoring

All patients with OA should complete a validated, patient outcome assessment at every visit to establish a baseline and track the results of therapy. There are many scoring systems or sets of criteria to measure the results of therapy for OA of the knee. In 2011, a comparison of the following patient assessment systems were published:[99]

- International Knee Documentation Committee Subjective Knee Evaluation Form
- Knee Injury and Osteoarthritis Outcome Score (KOOS)
- Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form
- Knee Outcome Survey Activities of Daily Living Scale
- Lysholm Knee Scoring Scale
- Oxford Knee Score
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
- Activity Rating Scale
- Tegner Activity Score

One of the best-known and widely used tools is the WOMAC. This index or scoring scale focuses on current pain, stiffness, and function of the knee. (Prior to using the WOMAC, clinicians must obtain permission from the developers.) The Lysholm scoring scale focuses on the short-term effects of injury and OA. The KOOS system focuses on both the long- and short-term effects of injury and OA. It "was developed as an extension of the WOMAC, with the purpose of evaluating short-term and long-term symptoms and function in subjects with knee injury and osteoarthritis" (Page 1).[100]

The Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS, JR.) is an abriged version of the original KOOS. It is a simple, quick questionnaire that can be used to score disease activity. United Rheumatology recommends using this system, because it is both patient and physician friendly, and it has been identified to meet the patient-reported outcome portion of the Medicare Comprehensive Care for Joint Replacement Model. The questions used and scoring for this system can be found in Appendix A. A patient and physician global assessment should also be obtained at every visit. Of note, the KOOS, JR. is subject to ceiling effects that may limit its utility in more highly functional individuals with OA.

Patients should be re-evaluated after starting a new therapy to determine its efficacy. (For patients treated with viscosupplementation, a KOOS, JR. score should be calculated at 8 to 12 weeks after injection. This can be done over the phone or by asking the patient to complete a paper version of the KOOS, JR. and send it to the rheumatologist). If necessary, treatment should be changed as indicated above until adequate control is achieved.

Surgical Evaluation

Surgical evaluation should be considered when the patient has proven refractory to all modalities previously mentioned in the Treatment section of this Guideline (including but not limited to

intra-articular injection of HA), and the patient is deemed to have an acceptable risk for the proposed surgery. Prior to surgery, the risks and benefits must be fully discussed with the patient. The range of surgical options includes:

- Arthroscopy with partial meniscectomy, in patients with both a torn meniscus and OA
- Osteotomy
- Partial knee replacement
- Total joint replacement

Both the American Academy of Orthopaedic Surgeons (AAOS) and the American Association of Hip and Knee Surgeons do not recommend arthroscopy with lavage and/or debridement for the treatment of OA.[52, 101] These recommendations are supported by multiple studies and systematic reviews which have demonstrated no greater efficacy of these approaches over nonoperative interventions as well as risk for destabilization of the meniscus and rapid OA progression in the case of meniscal debridement.[102-104]

In 2008, a randomized controlled study of arthroscopic surgery for OA of the knee was published in the *New England Journal of Medicine*. It demonstrated no benefit to arthroscopy when compared to optimized combined physical and pharmacologic therapy.[102] An earlier study published in the same journal, also had found no improvement in symptoms after arthroscopic lavage, debridement, or sham surgery.[103]

Despite the guidelines from national medical specialty societies and many studies demonstrating no benefit to arthroscopy with lavage and/or debridement, a large number of inappropriate arthroscopic procedures are still performed for OA in the US.[105]

Arthroscopic partial meniscectomy is also a commonly performed procedure. In 2013, Sihvonen et al.[106] published the results of a study with 146 patients between the ages of 35 and 65 years with symptoms of a degenerative medial meniscus tear and no OA. The patients were randomized into two groups: the first group had arthroscopic surgery and a partial meniscectomy; the second group had sham surgery. At 1 year, there was no difference between the two groups with respect to knee pain after exercise or the number of patients who required subsequent surgery.

The AAOS Guideline[52] also states that the data to support arthroscopy and meniscectomy for patients with OA and a torn meniscus is inconclusive. Yet both procedures are still commonly performed. A recent systematic review and meta-analysis found that:[104]

1. Benefit from arthroscopy for OA was short-lived and vanished by 2 years
2. Arthroscopy was not without risk of significant adverse events

Accordingly, the authors recommended against arthroscopic surgery for middle-aged or older patients with knee pain with or without signs of OA.[104] Another recent study identified a past history of knee surgery as an independent risk factor for rapid progression to knee arthroplasty.[107] In this

context, it is important to have an informed discussion about evidence showing the limited utility of minor surgery in the setting of OA of the knee in those considering arthroscopic surgery.

In 2013, Katz et al.[108] published the results of a seven-institution randomized controlled trial of patients aged 45 years or older with mild to moderate OA on imaging and a meniscal tear. The study included 351 patients who were assigned to either surgery and post-surgical physical therapy or standard physical therapy alone (patients in the latter group were allowed to select surgery during the study). Patients were re-evaluated at 6 and 12 months after the intervention. At the end of 6 and 12 months, no significant differences were identified between the two groups. Furthermore, only 30% of those assigned to physical therapy alone had elected to undergo surgery by 6 months after entering the study; approximately 6% of patients in the surgery group did not have it. The authors report no significant differences between the surgical and non-surgical groups with respect to pain and/or function at 6 and 12 months.In the US, more than 650,000 arthroscopic procedures were performed in 1996.[109] From 1996 to 2006, the number of knee arthroscopies increased by 49%, with a slight decrease in the numbers performed for OA.[110] This decrease probably reflects changing practices for the surgical management of OA; however, the large number of arthroscopic procedures performed is not consistent with the current medical evidence. A newer study based on analysis of the Humana database from 2007 to 2015 found that the rate of arthroscopy for patients with OA of the knee between 2007 and 2010 increased significantly (18.59%) but that the rate of arthroscopy and partial meniscectomy decreased by 71.68% between 2010 and 2015.[111] This is encouraging given the results reported by Katz et al. described above.[108]

Total knee replacement is one of the most common surgical procedures in the US. The major indication for this procedure is OA with intractable pain not responding to a combination of standard nonpharmacologic and pharmacologic therapies. In the Medicare population alone, TKR increased by 161.5% between 1991 and 2010, from 31.2 procedures per 10,000 to 62.1 procedures per 10,000.[112] At the same time, revision of TKR increased by 105.9%. The authors of the Medicare study believe that the increase in TKR is, in part, due to an aging population and obesity, but they also suggest that there may be a loosening in the indications for this surgery.

According to the Centers for Disease Control and Prevention,[4] TKRs for OA increased by 217% between 1992 and 2011 (from 203.6 TKRs to 645.1 TKRs per 100,000), with OA being the most common reason for knee replacement surgery.[113] In 2008, there were approximately 600,000 TKRs costing over $9 billion in the US. The greatest increase in utilization of TKR was in people under 65, but most of these procedures were still performed in older patients with severe OA refractory to treatment with a combination of nonpharmacologic and pharmacologic therapies. For the age group of 44- to 64-year-olds, TKR increased by 119% between 1999 and 2008, and for those aged 65 years and older by 97%. The number of people falling into this latter category will continue to increase as a result of the aging population but, to date, these demographic changes fail to explain the rate of rise in TKRs.[114] According to Losina et al.,[114] one reason for the increase in TKRs in the 44- to 64-year-old age group may be that this group has become more active in 2008 than they had been in 1999, resulting in an increase of secondary OA due to trauma. Regardless of the cause for

the increase in TKRs, a recent study indicated that 33% of the knee replacements performed in the US were inappropriate by international standards.[115]

United Rheumatology recommends against the use of arthroscopy with or without debridement for the management of painful OA of the knee.

United Rheumatology does not recommend TKR, unless the patient has failed all attempts at non-surgical management, including intra-articular injections of HA, and has both severe damage (bone on bone) by X-ray and persistent severe pain that limits everyday functioning.

Appendix A

(KOOS, JR.) KNEE SURVEY

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities.

Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Stiffness

The following question concerns the amount of joint stiffness you have experienced in your knee during the last week. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

1. How severe is your knee stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

What amount of knee pain have you experienced the **last week** during the following activities?

2. Twisting/pivoting on your knee.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

3. Straightening knee fully.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

4. Going up or down stairs.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

5. Standing upright.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

6. Rising from sitting.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

7. Bending to floor/pick up an object.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS, JR.) Scoring Instructions, English version 1.0

KOOS, JR. SCORING INSTRUCTIONS

The KOOS, JR. was developed from the original long version of the KOOS survey using Rasch analysis. The KOOS, JR. contains 7 items from the original KOOS survey. Items are coded from 0 to 4, none to extreme respectively.

KOOS, JR. is scored by summing the raw response (range 0 to 28) and then converting it to an interval score using the table provided below. The interval score ranges from 0 to 100 where 0 represents total knee disability and 100 represents perfect knee health.

Table for converting raw summed scores to interval level scores from 0 (total knee disability) to 100 (perfect knee health)

Raw summed score (0-28)	**Interval score (0 to 100 scale)**	**Raw summed score (0-28)**	**Interval score (0 to 100 scale)**
0	100.000	15	50.012
1	91.975	16	47.487
2	84.600	17	44.905
3	79.914	18	42.281
4	76.332	19	39.625
5	73.342	20	36.931
6	70.704	21	34.174
7	68.284	22	31.307
8	65.994	23	28.251
9	63.776	24	24.875
10	61.583	25	20.941
11	59.381	26	15.939
12	57.140	27	8.291
13	54.840	28	0.000
14	52.465		

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Document Updates

Document Version	Description of Changes	Approval Date
1.1.2016	Creation of first version	10 Jun 2016
1.1.2017	2017 annual review	Aug 2017
1.1.2018	2018 annual review	Apr 2018
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