
# Clinical Practice Guideline

## Osteoarthritis of the Knee

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# Abbreviations

| | |
|---|---|
| AAOS | American Academy of Orthopedic Surgeons |
| ACR | American College of Rheumatology |
| AP | Anteroposterior |
| BMI | Body mass index |
| COX-2 | Cyclooxygenase 2 |
| CV | Cardiovascular |
| 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 |
| OTC | Over the counter |
| PA | Posterior-anterior |
| QoL | Quality of life |
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| SNRI | Serotonin-norepinephrine reuptake inhibitor |
| 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] Annually, 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. Unfortunately, OA is incurable.

According to Symmons et al. (Page 1):[5]

> Osteoarthritis (OA) is a complex disease entity that is difficult to diagnose and define. The Subcommittee on Osteoarthritis of the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee defined osteoarthritis (OA) as "A heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins."[6] Clinically, the condition is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation.

The diagnosis of OA is often delayed, although articular cartilage loss and/or bony changes can 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 function. The primary risk factors for incident radiographic OA of the knee are body mass index (BMI) >30 kg/m$^2$, aging, prior knee trauma such as prior surgical intervention, occupational activities,[7] and female gender.[8]

Risk factors for progression of OA include but are not limited to the following:[9, 10]

- Age
- Comorbidities
- Inactive lifestyle
- Genetics
- Infrapatellar synovitis detected on magnetic resonance imaging (MRI)
- Joint effusion
- Knee injury
- Clinical and radiographic extent of OA at initial diagnosis
- Type 2 diabetes in men
- BMI >30kg/m$^2$ (obesity)—according to Leyland et al,[10] overweight patients with knee OA have a 40% increased risk of total knee as compared to those with normal weight. Obese patients have double the risk for total knee replacement (TKR) as patients with normal weight.

Under normal conditions, there is an equilibrium between cartilage destruction in joints and cartilage synthesis. When cartilage destruction exceeds synthesis, OA can develop.[11]

The pain associated with OA is usually described as chronic (low to moderate pain at all times), severe (occurring sporadically), or a combination of both.[12] Often the severe, sporadic pain has the most negative impact on quality of life (QoL), because it is unpredictable.

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 mechanisms, especially coping with pain. Often patients have difficulty walking and climbing stairs. All of these issues contribute to a decrease in QoL.[13]

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.[6, 11]

Secondary OA may be related to:[6, 11, 14]

- 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 prevalence of OA in the population is expected to increase over the next 20 years.[12] Caring for these patients is costly and contributes to the overall high cost of healthcare in the US.

Kotlarz et al.[15] estimated that annual healthcare costs for all types of OA were $185.5 billion in 2007 dollars, with $149.4 billion paid by insurers and $36.1 billion paid by patients.

Direct costs of caring for patients with OA include non-pharmacologic and pharmacologic treatment, physician visits, imaging, 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.[16] The estimated annual costs of caring for an individual with OA in year 2000 dollars were $5700.[17] In 2011, Berger et al.[18] 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 as compared to $5057 for those without OA. Indirect costs for those in the OA group were $5002 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[19] demonstrated that the cost of total joint replacements accounted for the greatest increase in direct costs for caring for patients with OA, which was attributed to the greater prevalence of the disease, rapidly rising surgical costs and costs of prostheses, and a failure to diagnose and treat younger patients with OA, which could decrease the need for joint replacement as these patients age.

## Diagnosis

The diagnosis of idiopathic OA of the knee is usually 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. The American Rheumatism Association (prior name of 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.

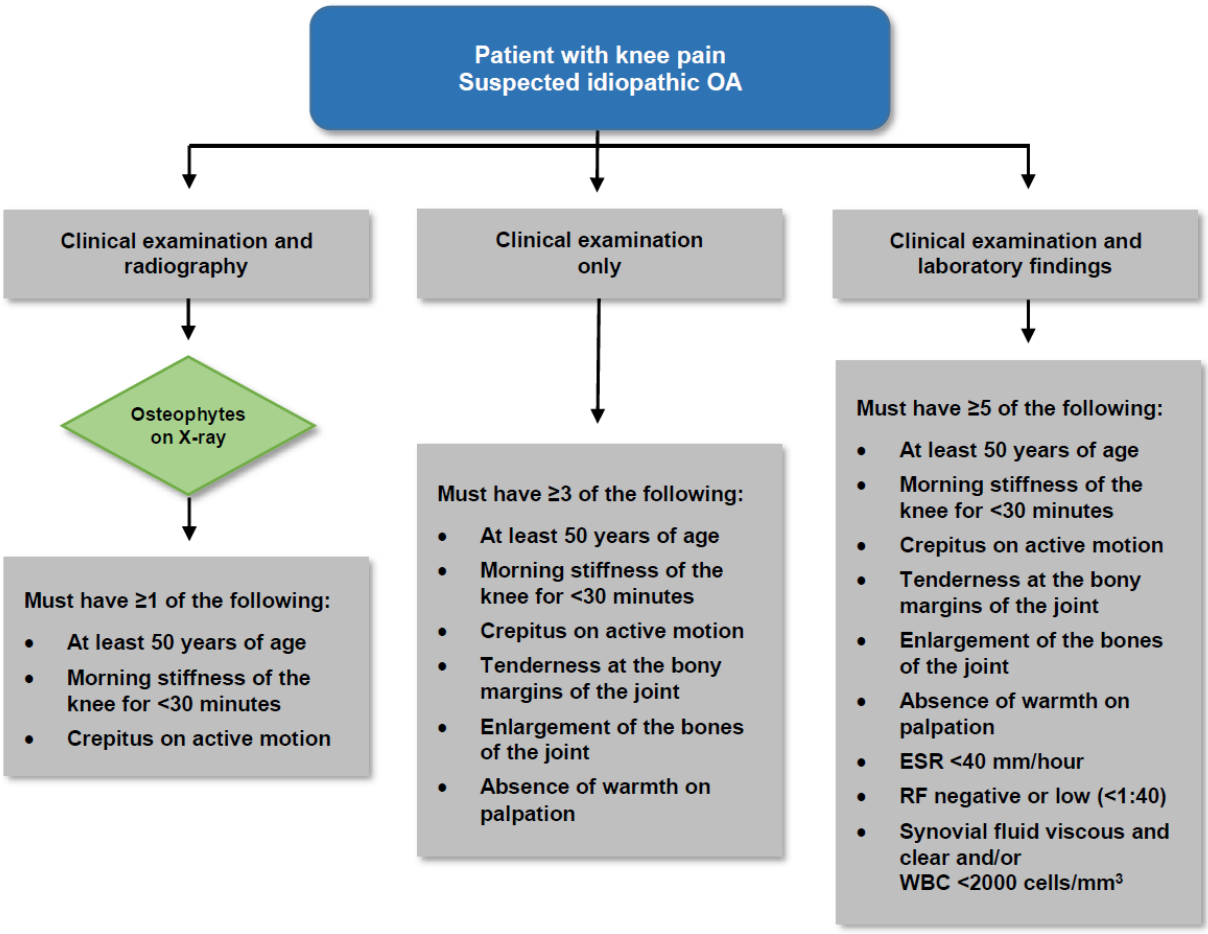


***Figure 1. Establishing the diagnosis of primary (idiopathic) OA of the knee.***

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 the patient's 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.[20]

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 tool 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 the supine position or weight bearing.

X-ray imaging of the knee must include at least one standing AP view and one semi-flexed PA view, whenever possible, as well as one lateral view, and one sunrise view. Additional imaging should be performed as needed:

- **Standing AP view** may include one or both knees.
- **Lateral view** is usually taken in the supine position with the knee flexed at 45 degrees for evaluation of the patellofemoral joint.
- **Sunrise view** (also referred to as skyline or sunset view) is used for the evaluation of the patellofemoral joint.
- **Standing flexed PA view** (also called the Rosenberg view) is performed standing with the knee flexed at 45 degrees with the patella touching the image receptor and the X-ray tube at a distance of 40 inches from the receptor and angled at 10 degrees caudad.

Attention to details of patient positioning, tube distance from the receptor, and tube angulation are essential for the meaningful comparison with subsequent X-rays.[21, 22]

## Magnetic Resonance Imaging (MRI)

Narrowing of the joint space, which is often the result of thinning articular cartilage, can be suspected on X-rays. It is sometimes accompanied by osteophytes, subchondral sclerosis, and/or subchondral cysts. However, early in the course of the disease, X-rays can 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. In these very 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[23] 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[24] 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.[25, 26]

Bone marrow edema, with normal X-rays and knee pain can also be seen on MRI of patients with OA.[27] 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.[28]

MRI should always be performed on a 1.5 or higher Tesla scanner using a knee surface coil. Three imaging planes (axial, coronal, and sagittal) should be obtained using a field of view of 12 cm to 14 cm.[27]

## 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
  - Rate intensity of pain on 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 rheumatological 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 least include the following assessments:

- BMI
- Swelling and/or 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 gets better with rest. There may be a history of trauma, prior surgery of the knee such as anterior cruciate ligament injury and/or reconstruction, meniscectomy, or patellar tendon dislocation. Morning joint stiffness that lasts for less than 30 minutes is also a common complaint. Joint stiffness 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 knee (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.[6, 27-31]

Synovial fluid aspiration should be obtained, if there is a monoarticular effusion in the absence of another explanation.[31]

Findings on examination that suggest a diagnosis other than OA include but are not limited to:[30]

- Fever or chills
- Redness
- Warmth

# 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. Most patients require a combination of non-pharmacologic and pharmacologic therapy. 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

## Non-pharmacologic Recommendations

All patients with OA of the knee should be encouraged to participate in low-impact aerobics and/or resistance exercises that may reduce pain and disability and improve physical fitness, stability,and range of motion; water-based exercises are also recommended.[32-34] In addition, patients should participate in physical therapy programs. These programs should be designed to improve the patient's symptoms and may decrease the need for medication and repeated physician office visits.[33-35]

For those who are overweight (BMI >25), weight loss is also strongly recommended.[11, 29, 32, 34, 35] Even modest weight loss of more than 5% improves function, physical disability, and pain.[36] Conversely, overweight patients are 40% more likely, and obese patients more than twice as likely, to require knee replacement surgery than patients with normal weight.[10]

A recent meta-regression analysis of exercise programs for knee OA has revealed the attributes of activity programs that are most effective.[37] Exercises for knee OA are more effective if they are:

- Focused on a single goal—either improvement of aerobic fitness or lower-extremity function, but not a combination of both
- Conducted three times per week
- Performed under supervision

Other non-pharmacologic recommendations that should be considered include the following:

- Physical therapy to maintain/improve strength and range of motion
- Use of walking aids as needed (including but not limited corrective footwear)
- 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.[32, 38]
- Social support
- Self-management and education

## Pharmacologic Management

When non-pharmacologic 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 a drug for at least 2 to 4 weeks before switching to a different medication. 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.

Most published guidelines recommend acetaminophen as the initial drug of choice for the management of painful OA of the knee.[39] However, often by the time patients see a rheumatologist, many have already failed to improve with acetaminophen. In March 2016, the *Lancet* published an article by da Costa et al.[39] in which the authors state that, "we see no role for single agent paracetamol [acetaminophen] for the treatment of patients with osteoarthritis irrespective of dose" (Page 1). The article also reports that diclofenac 150 mg/day is the most effective nonsteroidal anti-inflammatory drug (NSAID) for improving both pain and function. However, the researchers caution about the potential adverse effects associated with the long-term use of oral NSAIDS, which is often required for patients with OA of the knee. Adverse events associated with NSAIDs range from GI complications such as bleeding, gastric ulcers, and bowel perforation to CV events, including death. Oral NSAIDs should be prescribed at the lowest possible dose. A more recent systematic review published by the Cochrane Library[40] reported that most likely paracetamol provided no signicant or clinically important benefit in the management of hip or knee OA.

***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

United Rheumatology prefers the use of topical rather than oral NSAIDs, especially for patients with significant comorbidities or a contraindication to oral NSAIDs. 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 US Food and Drug Administration (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 to be 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.[39] In addition, the NSAID concentration in the underlying synovium is equal to that seen with oral NSAIDs.[41] The use of topical NSAIDs is supported by both the Osteoarthritis Research Society International (OARSI) and the American Academy of Orthopaedic Surgeons (AAOS).

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 uncommon.[41]

If a patient takes low-dose aspirin, the physician should be aware that an NSAID may interfere with the aspirin. Nonsteroidal anti-inflammatory drugs should be prescribed at the lowest possible dose and for the shortest duration that is clinically appropriate to avoid the well-known GI and CV complications of these medications.

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)[42] documented an increased mortality when patients took tramadol as the first prescription drug to treat OA when compared to NSAIDs. There was no difference in mortality rate with tramadol when compared to codeine, when used as the initial treatment of OA of the knee. In patients who have a history of depression, risk for addiction, or are taking antidepressants; tramadol should be prescribed with caution. Because of these concerns, United Rheumatology recommends that the use of tramadol should be severely restricted.

Although 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. These 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.[43] Duloxetine can be given to patients with multiple-joint OA and comorbidities.[32, 33]

Narcotic analgesics and tramadol should be limited to patients who are not surgical candidates or do not want surgery and for whom all other measures have failed.

United Rheumatology recommends against the use of glucosamine, chondroitin, and topical capsaicin.[32, 34, 36] United Rheumatology also recommends against the use of stem cell and plasma rich protein injections.[44, 45]

Intra-articular corticosteroid (IACS) injections may be considered a first-line treatment for some patients with OA of the knee,[33] although long-term benefits have not been demonstrated. These injections typically provide short-term pain relief for 3 to 4 weeks[46] and, as a general rule, should not be administered more frequently than once every 3 months except for Zilretta®, which is recommended to be given one time only.[30, 47, 48] Steroid injections are not disease modifying but are applied for symptom relief. This intervention is 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.[47] Group one (34 patients) received IACS injections into the same knee every 3 months for up to 2 years. The second group of 34 patients had saline injected 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-injections 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.[47]

The Osteoarthritis Initiative[49] recently published a study online in which patients were asked about IACS injections at 12-month intervals for 4 years. All patients had radiographs at the start of the study and annually for 4 years. The X-rays were evaluated for either joint space narrowing or Kellegren and Lawrence grade worsening. It was not a randomly matched study and, although the study concluded that there was more radiographic progression in the IACS-injection group, it is not clear if this group was more symptomatic than the patients who did not receive injection therapy; therefore, these conclusions are not well-founded. Additional, better controlled studies are needed before any recommendation can be made with respect to treatment with IACS injections.

A recent publication in the *JAMA* also questioned the benefit of IACS.[50] 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 had the IACS injections was found to have more cartilage loss than the saline group. At the end of 3 months, there was no significant difference in pain between the two groups. However, pain was not evaluated at any other interval between visits. The efficacy and timing of IACS are not clearified by this report, and further study is indicated.

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

Osteoarthritis causes a decrease in both, the concentration and molecular weight, of the 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 respone of immune cells to inflammation. In addition, it may decrease cartilage loss and possibly promote cartilage regeneration.[8, 51]

The use of intra-articular HA injections for OA of the knee has recently become the subject of debate, with the most recent ACR Guidelines[33] initially giving it a conditional recommendation for patients who have failed to respond adequately to non-pharmacologic therapy and analgesics, and the 2013 AAOS Guidelines[34] considering it "inappropriate." The ACR subsequently issued a Position Statement to clarify their recommendation on the use of intra-articular HA injections in which they explain that (Page 1):[52]

1. The American College of Rheumatology recommends the use of intra-articular hyaluronic acid injection for the treatment of osteoarthritis of the knee in adults, in accordance with the ACR 2012 OA guidelines.
2. Hyaluronic acid injection is clinically indicated for management of osteoarthritis in patients who are not good candidates or who do not respond to other treatment options.

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,[8] 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.[53, 54]

Patients with OA are candidates for injections of HA when they have persistent pain, despite an adequate trial of a combination of non-pharmacologic and pharmacologic therapy (including NSAIDs). Intra-articular HA is also appropriate for those who have a contraindication to NSAIDs.[55] 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.[52]

When intra-articular HA is used, injections are given weekly for 1 to 5 weeks, depending upon the product.[55] 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.[56, 57] Many patients have adequate pain relief up to 26 weeks after the injection.[58] Treatment may be repeated at 6-month intervals.

Contraindications to the intra-articular injection of HA include:[55]

- Protein/avian allergies (except with Euflexxa®)
- Pregnancy
- Nursing
- Pediatric patients
- Local overlying skin disease
- Joint infection
- Bacteremia

United Rheumatology recommends the stepwise management of patients with OA (Figure 2), starting with the recommendations for non-pharmacologic treatment described above and, if there is insufficient response, adding pharmacologic management starting with either acetaminophen or topical NSAIDs if there is no contraindication (different drugs may be tried), or intra-articular injections of steroids or HA.

If a patient fails the standard treatments described above, the next step may 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).[59] 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. Only 19% of the patients required TKR.[59]

Altman et al.[60] 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.

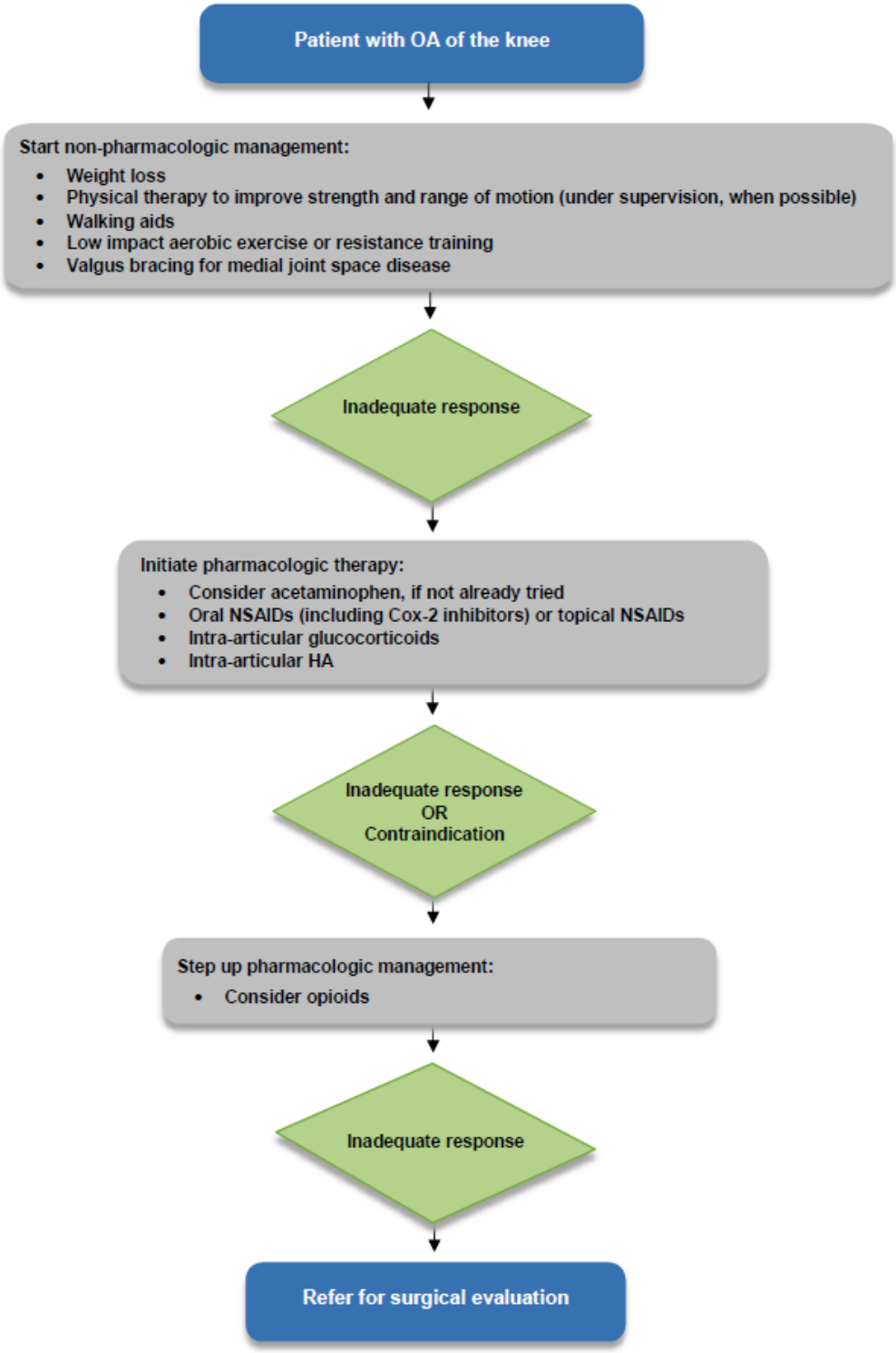


***Figure 2. Stepwise management of OA of the knee***

The drugs for initial pharmacologic management may be used in any order. If one fails to ilicit 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

A 2016 publication by Maheu et al.[61] 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.[62]

## Monitoring

All patients with OA should complete a patient assessment questionnaire 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:[63]

- 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).[64]

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 AAOS and the American Association of Hip and Knee Surgeons do not recommend arthroscopy with lavage and/or debridement for the treatment of OA.[34, 65] These recommendations are supported by multiple studies and systematic reviews.[66-68]

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.[66] An earlier study published in the same journal, also had found no improvement in symptoms after arthroscopic lavage, debridement, or sham surgery.[67]

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.[69]

Arthroscopic partial meniscectomy is also a commonly performed procedure. In 2013, Sihvonen et al.[70] 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[34] 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:[68]

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.[68] Another recent study identified a past history of knee surgery as an independent risk factor for rapid progression to knee arthroplasty.[71] 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.[72] 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.[73] From 1996 to 2006, the number of knee arthroscopies increased by 49%, with a slight decrease in the numbers performed for OA.[74] 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.[75] This is encouraging given the results reported by Katz et al. described above.[72]

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 non-pharmacologic 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.[76] 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.[77] 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 age of 65 years, but most of these procedures were still performed in older patients with severe OA refractory to treatment with a combination of non-pharmacologic 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.[78] According to Losina et al.,[78] 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.[79]

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 |
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| 1.1.2016 | Creation of first version | 10 Jun 2016 |
| 1.1.2017 | 2017 annual review | Aug 2017 |
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