Clinical Practice Guideline

Osteoarthritis of the Knee

Version 1.2 2021

April 2021

Table of Contents

List of Tables

List of Figures

Abbreviations

AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
AP	Anteroposterior
BMI	Body mass index
COX-1 (inhibitor)	Cyclooxygenase 1 (inhibitor)
COX-2 (inhibitor)	Cyclooxygenase 2 (inhibitor)
CVD	Cardiovascular disease
ESR	Erythrocyte sedimentation rate
FDA	US Food and Drug Administration
GI	Gastrointestinal
HA	Hyaluronic acid
IACS	Intra-articular corticosteroid
IAHA	Intra-articular hyaluronic acid
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
MCID	Minimal clinically important difference
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PA	Posterior-anterior
PASS	Patient acceptable symptom state
PPI	Proton pump inhibitor
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SCD	Substantial clinical difference
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

Approximately 500 million people worldwide have osteoarthritis (OA). This is an increase of 48% from 1990.[1] In the United States (US), OA is the most common type of arthritis. In 2013, it was estimated that 27 million US adults had OA.[2] Currently, the Centers for Disease Control and Prevention estimate that 32.5 million adults have OA.[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.[3] The knee is the most common joint to be affected by OA, accounting for slightly over half of all cases.[4, 5] Women, especially those over 50 years of age, develop OA more frequently than men.[6] The prevalence of OA in the population is expected to increase over the next 20 years[7] as the population ages and the rate of obesity increases.[8]

OA is one of the leading causes of disability, loss of productivity, and absenteeism from work.[3, 9, 10] This finding reflects the impact of pain, limited mobility, fatigue, anxiety, and depression on a patient's ability to perform work that requires prolonged weight bearing, bending, kneeling, pushing or pulling large objects, alone or in any combination.[11-13]

Caring for patients with OA is costly and contributes to the overall high cost of healthcare in the US. Kotlarz et al.[14] 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. OA accounted for 46% of all inpatient hospital costs in Medicare patients and for 25% of inpatient costs for private insurers.[15]

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.[16] The estimated annual cost of caring for an individual with OA in year-2000 dollars was $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 per patient as compared with $5057 for those without OA. Indirect costs for those in the OA group were $5002 per patient as compared with $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. In knee OA, the cost of total joint replacements are dramatically greater than any other cost driver. In a recent Canadian study,[19] the cost of knee replacements also accounted for the greatest increase in direct costs of caring for patients with OA over time. 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.

OA usually develops slowly. It may be related to past or recent trauma, overuse, and/or obesity. It may also be idiopathic. There is a genetic component that is currently poorly understood but individuals with a family history of OA are at an increased risk of developing the disease. In addition, individuals who have OA of the hand have an increased risk of developing OA of the knee.[3]

Although age is a potent risk factor for OA, it is important to distinguish OA from normal aging. The etiology of OA is thought to be multifactorial and involves a combination of genetic factors, loss of articular cartilage, subchondral bone remodeling and inflammation of the synovium.[20, 21] Articular cartilage is avascular and aneural. It is mostly made up of chondroid matrix with comparatively low density of a single cell type, the chondrocyte, which is responsible for the manufacture of the extracellular matrix and repair of the cartilage. Traditionally, the early changes of OA have been thought to start with damage to the articular cartilage, although some have theorized that changes begin in the subchondral bone. Regardless, as there is no nerve supply to articular cartilage, this damage does not elicit any pain. The loss of articular cartilage also results in loss of some of the chondrocytes. Cytokines, such as, but not limited to, interleukin-1, interleukin-6, and tumor necrosis factor, are produced by the remaining chondrocytes, osteoblasts, and the synovium, which result in further cartilage damage.[20]

Once the cycle of cartilage destruction starts, cartilage debris is found in the joint space, contributing to inflammation of the synovium, which then produces proteases and proinflammatory cytokines. This, in turn, results in further cartilage damage and debris in the joint, leading to the production of more proinflammatory cytokines that cause additional damage to the cartilage.

Further details about the pathophysiology of OA are beyond the scope of this guideline. The process is well summarized by Kraus et al.,[22] (Page 1237) OA:

> "*…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."*

Inflammation of the synovium and the subchondral bone does cause pain. 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 leading to depression and/or anxiety.[23]

The diagnosis of OA is often delayed, although structural damage in the form of 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, swelling, or

decreased mobility. The reason for the absence of pain early in the disease process is explained above.

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 (including kneeling, squatting, using a pneumatic drill, construction work, heavy labor),[23] and female gender.[24-26]

Other risk factors for progression of OA include, but are not limited to, the following:[27, 28]

- Comorbidities such as diabetes, hypertension, cardiovascular disease (CVD), and depression
- 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

According to Leyland et al.,[28] 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.[29-31]

OA is either primary (idiopathic) or secondary. The etiology of idiopathic OA, which is the most common form, is not fully understood; however, as described above, there are many contributing factors (loss of articular cartilage, inflammatory changes in the subchondral bone and synovium) thought to be involved.

Secondary OA may be related to:[25, 26, 32]

- 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 determined, likely because of the considerable phenotypic heterogeneity resulting from the wide variety of underlying causes of secondary OA.

In 2011, Osteoarthritis Research Society International (OARSI) responded to a list of questions from the US 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.[33] 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 anatomic 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 cartilage repair, OA can develop.[26] 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.[34] Changes of the ligaments and tendons are also seen.

Osteoarthritis is a Serious Disease

In 2016, OARSI published a white paper in support of classifying OA as a ***serious disease***.[35] The purpose of this paper was to demonstrate to providers and the FDA that because OA is a serious disease, treatments for it should be given priority by manufacturers of medical devices and pharmaceutical companies. 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."[36]

By providing evidence-based data demonstrating that OA fits this 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).[35]

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 negative impact of OA on several common comorbidities, such as CVD, type 2 diabetes, hypertension, and depression.[13] Two-thirds of those with hip or knee OA suffer from at least one comorbid condition and a greater number of comorbidities is associated with worsened Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and poorer quality of life.[37] Furthermore, OA and its comorbidities may follow a downward spiral as patients with limited mobility due to OA pain may become progressively more obese, hypertensive, and insulin resistant (See Figure 1). Often the pain on walking leads to a progressively more sedentary lifestyle that results in further weight gain, progression of CVD, and 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, the negative relationship between OA and its common comorbidities is bidirectional as progressive obesity, inactivity and weakness (caused by comorbid conditions such as coronary artery disease-related limitation in exercise tolerance) often leads to worsened OA symptoms and functional ability.

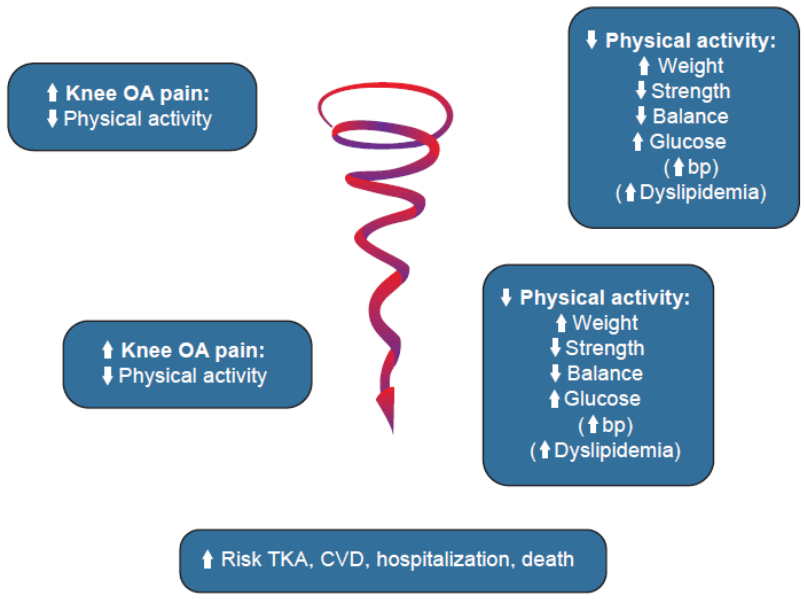

Figure 1. OA and comorbidities: a downward spiral

bp, blood pressure; OA, osteoarthritis; TKA, total knee arthroplasty; CVD, cardiovascular disease.

A 2011 study[38] of "all cause and disease specific mortality in patients with OA 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 issue.[39]

It is important for patients and providers to understand the importance of the relationship of the pain of OA in conjunction with a patient's concomitant obesity, hypertension, diabetes and CVD. Appropriate nonpharmacologic and pharmacologic modalities described below should always be used together.[40] 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.[35] See Figure 1.

Early in the management of OA, nonsteroidal anti-inflammatory drugs (NSAIDs) may be prescribed to treat joint pain. NSAIDs should be prescribed at the lowest possible dose and used on an as needed basis for as short a period of time as possible while controlling symptoms to prevent recognized side effects, which increase in frequency after 2 weeks of continuous use.[41] For many patients without contraindications, comorbidities, or generalized OA involving multiple joints, regularly scheduled NSAIDs with careful monitoring may be the best available option. Long term use of NSAIDs may contribute to premature death among patients with concurrent CVD.[42] NSAIDs can also result in adverse events in the gastrointestinal (GI) tract and kidneys. These drugs may cause gastritis, and/or peptic ulcers which may be limited or controlled by using a gastroprotective agent with oral NSAIDs. Increased risk of acute myocardial infarction, heart failure and acute renal failure have also been reported with NSAIDs. Hemorrhagic stroke has been associated with the use of diclofenac and meloxicam.[43, 44] Topical NSAIDs may have a reduced risk of adverse events as compared to oral NSAIDs and are preferred. For more detail of the adverse effects of NSAIDs in patients with OA please see Cooper et al.[45]

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 when the diagnosis is in question, although some findings are rare, with only 0.5% of radiographs revealing pathology altering the treatment plan (osteonecrosis, osteochondral lesion, fracture, and subluxation).[46]

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 2). These criteria are not designed to be used if secondary OA of the knee is suspected.

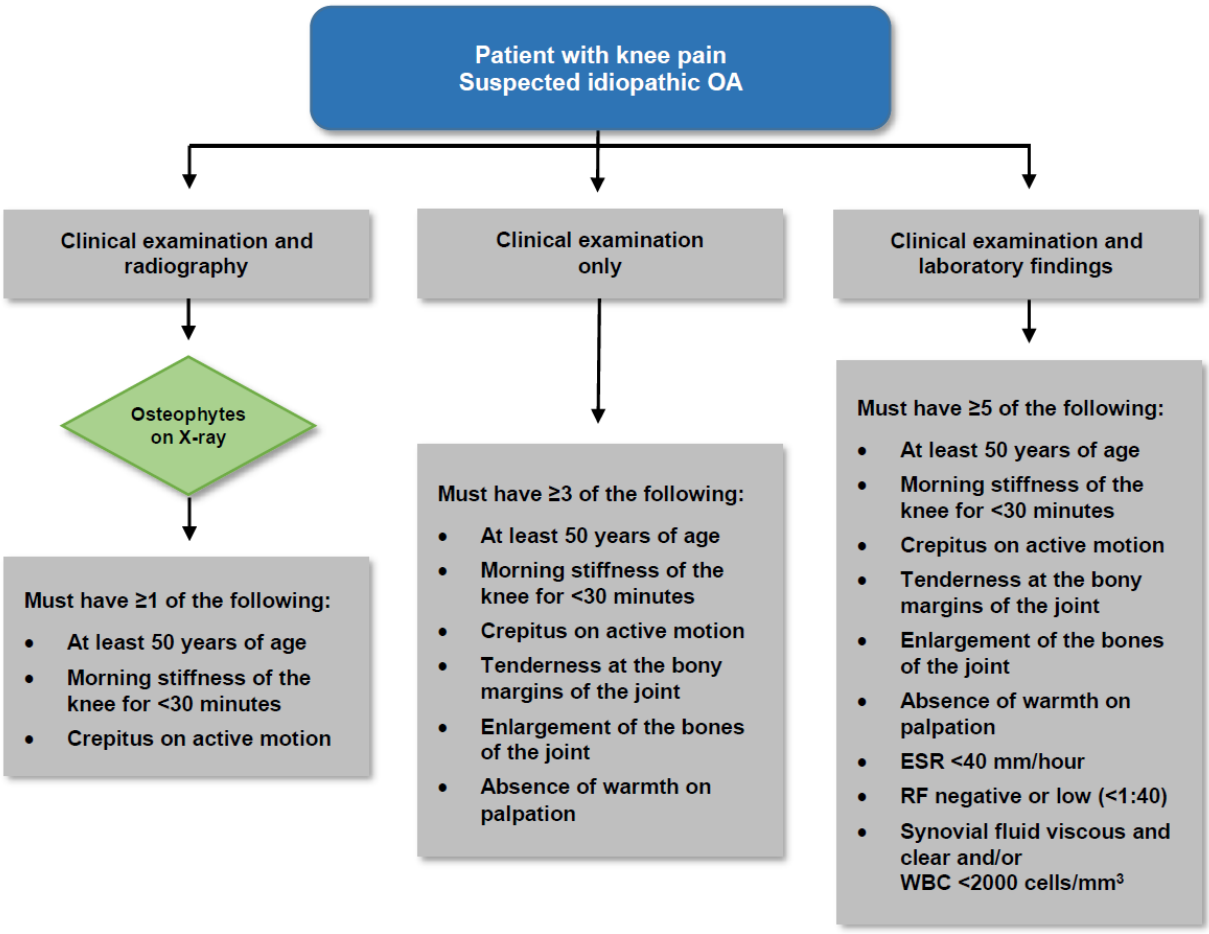

Figure 2. Establishing the diagnosis of primary (idiopathic) OA of the knee.

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

Imaging

The diagnosis of OA is a clinical one and does not require the use of any imaging except for unusual cases where the diagnosis is unclear.

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.[47] X-ray can be of value in determining the relative severity of the radiographic impact of the disease. This is important for communicating severity and prognosis to patients, as well as in the selection of appropriate treatment options. When considering referral for surgical evaluation, X-rays are useful in identifying whether or not a patient has end-stage cartilage loss, as those without such severe damage are not typically considered appropriate candidates for total joint replacement. However,

radiographic severity does not predict the response of patients with knee OA to non-operative interventions including physical therapy.[48] Radiographic findings that support the diagnosis of OA include:

- Asymmetric joint space narrowing involving the medial or lateral femorotibial, and/or patellofemoral compartments
- Subchondral sclerosis
- Marginal osteophytes, including the tibial spines
- Subluxation
- Subchondral cysts

If imaging is utilized, the initial technique 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, whenever possible. Non-weight-bearing films may overestimate cartilage thickness and underestimate the extent of disease. Lateral views may be taken either supine 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 the result of a combination of articular cartilage loss and, in the femorotibial area, meniscal damage and/or extrusion. 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[49] 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[50] 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 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.[51, 52]

Bone marrow lesions, with normal X-rays and knee pain can also be seen on MRI of patients with OA.[53] Recent studies have shown that the severity of bone marrow lesions is associated with greater risk for progressive cartilage loss. There is a positive association with the need for knee arthroplasty within 4 years in patients with significant or progressive bone marrow lesions.[54]

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.[53]

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
- History of trauma, recent or remote
- Duration of morning stiffness (typically less than 30 minutes in OA)
- Additional knee complaints, such as swelling, giving way, or locking
- Evidence of mood changes, depression, or poor quality of sleep

- Other medical illness/comorbidity that may affect treatment choices, including, but not limited to, the following:
  - Diabetes
  - Hypertension
  - CVD, especially coronary artery disease
  - Renal disease
  - 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
- Medication allergies

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

- BMI
- Synovitis/effusion
- 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 abnormalities
- Gait (including evaluation for varus thrust)

The most common patient complaints are joint pain (which increases with activity or weight bearing), swelling, stiffness, and limited mobility, all of which progress over time leading to a more sedentary lifestyle than their peers without OA. The pain associated with OA is usually described as either chronic (low to moderate pain with weight bearing), severe (occurring sporadically but compromising patient movement); or a combination of both.[7] Often the severe, sporadic pain has the most substantial negative impact on quality of life because it is unpredictable. The development of constant pain in OA has been linked to the onset of central pain sensitization that occurs in a subset of OA patients[55-57] who may require specific treatment to address this pain source. Initially,

pain is intermittent, but over time pain may progress to a constant low level persistent pain with intermittent exacerbations of severe pain that, at late stage, become more frequent. There may be a history of remote joint trauma affecting the anterior cruciate ligament or menisci or patellar dislocation or other parts of the joint. Morning joint stiffness, typically less than 30 minutes' duration, may be reported.

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. A varus thrust is identifiable during simple observation of gait[58] as a rapid, varus deviation in knee alignment visible during the weight bearing phase of gait that reverses during the non-weight bearing phase. The presence of a varus thrust is evidence of dynamic, frontal-plane instability that correlates with pain, particularly during weight bearing activity,[59] and is a poor prognostic factor with four times the risk of progressive cartilage damage in the medial femorotibial compartment over 18 months.[60]

Crepitus with active motion, joint line tenderness, deformity, limitation of motion, and effusions support the diagnosis of OA of the knee.[25, 53, 54, 61-63]

If there is a monoarticular effusion in the absence of another explanation, synovial fluid aspiration should be obtained.[61]

Findings on examination that suggest a diagnosis other than OA include but are not limited to:[63]

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

Treatment

OA of the knee is irreversible, incurable and often progressive.[35]

Currently there are no disease-modifying drugs available for OA. The goal of treatment is to control pain and improve physical function. According to Hunter and Bowden,[64] management of OA patients must be individualized according to the needs of each patient, including consideration of comorbidities. Collaboration with the appropriate medical specialists is helpful. In order to achieve the goals above, both nonpharmacologic therapy and pharmacologic therapy are necessary. When used together these treatments can improve physical activity and function, slow the progression of disease, and decrease pain. Lifestyle changes as described below are also essential for the successful management of OA[34, 65-67] with the current tools available.

The use of lifestyle changes, including education about OA self-management techniques, exercise, physical therapy, prevention of knee injuries, mood, sleep management, walking aids, and weight management must be included in every patient's treatment plan. These nonpharmacologic

interventions comprise the anchor treatment for OA. As such, each of these changes must be emphasized at each re-evaluation and patient adherence must be monitored and encouraged. Walking aids may be helpful in decreasing progression of disease. Modifiable lifestyle interventions, when used together, have the potential to improve or stabilize physical function and decrease pain.[68] Providers should always be encouraging and positive with their patients, as well as help them to understand OA and the lifestyle changes required to improve physical function and pain.[66]

An individualized exercise program for each patient should be designed based on the patient's needs and abilities at baseline and adjusted according to the patient's response at subsequent visits. Mood changes should also be evaluated and the patient should be encouraged to participate in group activities including, but not limited to, group exercise classes and behavioral therapy, when needed.

Non-operative treatment regimens that include more than one treatment modality have been demonstrated to be more effective.[48] Accordingly, United Rheumatology recommends establishing an individualized treatment plan for patients with knee OA, which considers the patient's medical status and comorbidities, while generating a dynamic treatment program that specifically addresses each of the following six core treatment domains:

- **Pain control** (see below for more detail)
    - Topical NSAIDs
    - If the above is not effective, advance to oral selective NSAIDs such as the cyclooxeganase-2 (COX-2) inhibitor celecoxib (preferred) or non-selective NSAIDs with or without proton pump inhibitors (PPIs)
    - Intra-articular injection of corticosteroids
    - Intra-articular hyaluronic acid (IAHA) injections
    - Duloxetine
- **Exercise** should be included in every treatment plan and should account for the patient's baseline level of exercise tolerance and physical fitness. The exercise program should be modified as needed based on the patient's progress
    - Increased activity
    - Home exercises
    - Physical therapy (water-based, "pool" therapy may be substituted for land-based therapy at initial stages when necessary)
    - Repeat, short-course of physical therapy to update home exercise program
    - Return to sport/activity
- **Inflammation control**
    - Icing post-activity
    - Topical NSAID
    - Oral NSAID
    - Steroid injection
    - Colchicine (if calcium pyrophosphate dihydrate crystal deposition disease is present)

- **Knee stability**
  - Knee sleeve
  - Patellar stabilization brace when applicable for patellofemoral pain/damage
  - Medial compartment “unloader brace” (off the shelf unless significant varus or valgus deformity that may require a custom-fit brace)
  - Cane
  - Walker
- **Nutrition**
  - Nutrition consult
  - Anti-inflammatory diet
  - Restricted calorie diet
  - Weight loss medications
  - Referral for bariatric surgery
- **Behavioral health**
  - Self-care
  - Web/app resources
  - Psychology referral
  - Psychiatry referral
  - Psychoactive medication(s) prescription

At every visit, each domain should be assessed and a treatment recommendation made within each domain. That recommendation may accelerate, decelerate or persist compared to the treatment in that domain from the prior visit. See Figure 3 and Figure 4 for two examples of how this is used: early OA with inflammation; late OA with chronic synovitis/effusion, obesity, depression, and GI comorbidity.

Nonpharmacologic Recommendations

Patients with OA of the knee should participate in either a land- or water-based exercise program, as appropriate. The program ideally should consist of aerobic exercise and resistance, strength, flexibility, and balance training. Given the challenges inherent to learning to exercise with OA of the knee (fear of falling, pain, injury, etc.), an initial course of physical therapy is often useful to teach patients how to safely exercise without exacerbating their OA symptoms. This may be provided in a step-wise program to slowly increase a patient’s exercise effort and activity, an approach that was recently demonstrated to be beneficial in a randomized clinical trial.[69] Exercise is a safe and effective intervention for patients with knee OA regardless of the severity of disease.[70] Additional exercises, such as tai chi and yoga are also recommended.

Early on in the treatment of OA of the knee, it should be stressed to patients that exercise can contribute to improving symptoms but also help control some of the common OA comorbidities, such as diabetes, CVD, and obesity. Patient preferences should be considered through a shared decision-making dialogue when designing an exercise program. The program should be monitored

and modified as the patient's condition changes. At every visit, the patient should be encouraged to continue the program.[71] The patient should be taught to monitor and describe any changes in exercise capability or adherence from one visit to the next. Keeping an exercise log may be useful in this context.

Rheumatologists are challenged to find an easy-to-use and convenient educational self-management program and an exercise program in which patients can participate. A randomized clinical trial that compared an internet-based, smart phone delivered education and exercise program to the usual self-management and exercise programs, was published in 2021.[72] This approach is potentially very valuable to both the patient and the provider. It allows the patient to access it at home at any convenient time. The program consists of exercises designed for individual patients and lessons about OA as well as "an asynchronous dialogue with a physiotherapist and outcome monitoring" (Page 2/15). The exercise program includes lower extremity strength training, balance training, and core strengthening. The exercises can be adjusted based on the patient's evaluation at baseline and can be stepped up or down. The educational lessons were followed by a short quiz to document how much the patient understood of the lesson. Patient adherence was encouraged by digital communication with the participant via e-mail, smartphone notifications, texts, or telephone. At the end of 6 weeks, the internet-based program group had a significant improvement in pain and WOMAC scores as compared to the control group who were given the customary approach to education and exercise. This type of internet-based approach should be considered by rheumatologists as a way to improve patient adherence to both an educational program and exercise. Continual reminders and follow-up contacts may be important to the success of an internet-based program. Further information about this technique can be found at these websites https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776721 and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7056265/pdf/pone.0229783.pdf.

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 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 OA in the exercise groups as compared to the control groups. Education and self-management programs are even 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.[73]

In 2009, another analysis of randomized controlled studies compared land based exercise to no exercise.[74] 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 in the exercise group. 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 because classes are usually supervised.

A randomized controlled study of 150 patients was reported in 2004.[75] Approximately half the patients were in the control group and half in the intervention group. 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: https://academic.oup.com/gerontologist/article/44/2/217/876634). 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 improved 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 often decreased and function improved. Thorlund et al.[76] 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 (0–100 mm) 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. 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. Supervised individual exercise sessions may be the most effective but they are not always available to all patients. The greater the supervision, the better the results. A home-based program combined with supervised sessions is a good alternative to all supervised exercise sessions and is less costly. Group exercise combined with a home-based program is also a good alternative. Whatever type of program is agreed upon, it should be continued without a planned endpoint. Patients should be as physically active as their condition permits. Patients should report any severe pain during exercise to their supervisor or provider, especially if it does not go away after a few hours. Increased swelling, night pain, or pain the day after exercise should also be reported.[71]

Unfortunately, according to Bennell et al.,[71] exercise is not prescribed for patients with OA as frequently as it should be, despite the fact that it is recommended by most clinical guidelines. It is critical that exercise be included in the treatment plan for every patient with OA.

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.[26, 62, 77-79] Even modest weight loss ≥5% of body weight improves function, physical disability, and pain.[80] 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.[28] Weight loss programs often start with basic nutritional education and/or referral to a nutritionist or dietician for a more in-depth understanding of how to lose weight on a healthy diet. Weight loss medications can be tried if the patient fails to lose weight with the help of a dietician. Finally, for morbidly obese patients the possibility of bariatric surgery can be considered, but this should be the last choice. Weight loss progress should be re-evaluated at every visit.[81] The patient should maintain a weight management log.

Other nonpharmacologic management includes the following:[34]

- **Use of walking aids** as needed, including the use of a cane.[65] It is important for providers to recognize that many patients are hesitant to use these devices because they have a negative view of them. Providers should be sure that the patient understands to use the device in the hand contralateral to the affected knee. At each encounter, patients should be encouraged to regularly use the device(s).[82] Even the use of a simple, sleeve-type brace has been demonstrated to improve symptoms[83] and walking mechanics.[84]
- The use of **a customized walking stick** may also be helpful. The patient should be instructed as to how to use it.[85]
- **Knee braces** are a useful treatment for all patients with knee OA who do not have a contraindication, such as a history of deep venous thrombosis. The use of a simple knee sleeve has been demonstrated to reduce pain, activity limitation, and self-reported knee instability, among those with knee OA in one study,[86] as well as pain and pathologic joint loading in another.[84] Valgus bracing for medial-compartment OA has been effective in some patients for decreasing pain, improving function, decreasing joint stiffness and decreasing medication use.[79, 87] Challenges in the use of valgus bracing include obtaining proper fit, developing patient facility with properly putting the brace on and understanding when it has migrated out of position, as well as patient nonadherence. In order to mitigate the effect of these limitations, clinicians should specifically address them as part of a shared decision-making dialogue when considering prescribing valgus braces.

Other nonpharmacologic treatments which are *conditionally* recommended for patients with OA include:[34]

- 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[34] recommends against transcutaneous electrical nerve stimulation 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. Management of comorbidities should be a collaborative effort by rheumatologists and the appropriate medical specialists. The introduction of an exercise program may help the patient to stabilize or improve CVD, hypertension, renal disease, and inflammatory bowel disease.

According to Swain et al, approximately 67% of patients with OA have at least one comorbidity.[88] Patients with more than one comorbidity may require individualized treatment and in general have worse outcomes from their OA than those with no or one comorbidity.[89] A study published in 2020 reported that patients with OA had an increased risk for both diabetes and CVD. In patients with knee OA, pain severity was found to be more severe among those who also suffered from diabetes. Interestingly, patients with diabetes were also found to have an increased risk for OA. In addition, patients with both OA and CVD had an increased risk of mortality.[90]

Pharmacologic Management

Patients should be cautioned that neither nonpharmacologic nor pharmacologic therapy alone will provide the best result. Multimodal, nonoperative care has been demonstrated to be more effective than unimodal care.[48] It is important that patients understand the rationale for combining both types of treatment.

While previously, acetaminophen had been recommended as the initial drug for the treatment of OA, more recent research suggests that this drug should not play a role in the management of OA of the knee, primarily because it is typically ineffective.[91, 92] Among the medications that should be used are topical or oral NSAIDs, intra-articular injection of glucocorticoids, or viscosupplementation (intra-articular injection of hyaluronic acid [HA] derivatives). Tramadol (Ultram®) and opioids, and any other medication that is potentially addictive, should not be used if at all possible. These drugs provide no clinically relevant pain relief in chronic OA according to a recent meta-analysis,[93] and are associated with significant unnecessary societal costs that have been estimated at $14 billion per year in a recent study.[94]

Assessment of the need for pharmacologic therapy should occur concurrently with lifestyle changes, including exercise, and should be re-addressed at each subsequent visit. To determine if a particular drug regimen is effective, the patient should take it for at least 2 to 4 weeks, unless side effects are noted, before switching to a different medication. Generics should be used when available. Table 1 provides an overview of the medications (with generic and brand names) used in the management of OA.

For those with pain in a single, or predominantly in a single, osteoarthritic joint, pharmacologic treatment should begin with a topical NSAID or an intra-articular steroid injection. The drugs that should be tried initially for those with generalized OA affecting multiple joints are oral NSAIDs (see Table 1), provided there is no contraindication to doing so.[34, 66] United Rheumatology recommends the use of topical NSAIDs before oral NSAIDs for all patients with one or two joints involved because of the favorable safety profile of this route of administration; especially for those with significant comorbidities or contraindications to oral NSAIDs. Adverse events from topical NSAIDs are minimal and, most commonly, local skin reactions, which are transitory.[66] The systemic complications of NSAIDs are related to the serum concentration of the drug and topical preparations are considered safer because the serum concentration is lower than that seen with oral NSAIDs. In addition, 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.[91] The NSAID concentration in the underlying synovium is equal to that seen with oral NSAIDs.[95]

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®). Voltaren has recently obtained FDA approval for nonprescription, over-the-counter use.[96] Oral NSAIDs are divided into selective and non-selective COX-2 inhibitors. Both selective and non-selective NSAIDs interfere with the function of COX-2, which is a cytokine-induced iso-enzyme. It is responsible for the production of prostaglandins associated with pain and inflammation. The non-selective NSAIDs also interfere with the synthesis of cyclooxygenase-1 or COX-1. This iso-enzyme is needed to produce the prostaglandins that help to maintain GI tract mucosa integrity and platelet aggregation. Drugs such as non-selective NSAIDs, which inhibit COX-1, are associated with an increased incidence of gastric ulcers, gastritis, and bleeding. NSAIDs such as aspirin, ibuprofen, naproxen, indomethacin, oxaprozin, piroxicam, diclofenac, sulindac, etodolac, and meloxicam are non-selective NSAIDs. Multiple clinical studies have demonstrated that selective NSAIDs have fewer GI adverse events than non-selective NSAIDs.[97, 98]

The only selective NSAID approved for use in the US is celecoxib. It is considered to be safer than the non-selective NSAIDs because it does not affect the function of COX-1.[99] Providers should note that the package insert for celecoxib states that this drug is contraindicated in patients with a history of coronary bypass graft.[100]

When an oral NSAID is needed, United Rheumatology supports the use of celecoxib as the initial drug of choice unless contraindicated.

If oral NSAIDs are necessary, physicians should be aware of the potential adverse effects associated with the long-term use of these drugs (especially the non-selective NSAIDs). Complications associated with oral 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, when non-selective NSAIDs are used, a PPI could be considered for gastric protection.

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.[95]

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.

Figure 3 and Figure 4 demonstrate how a multi-modal, domain-driven approach to the treatment of OA can be used clinically.

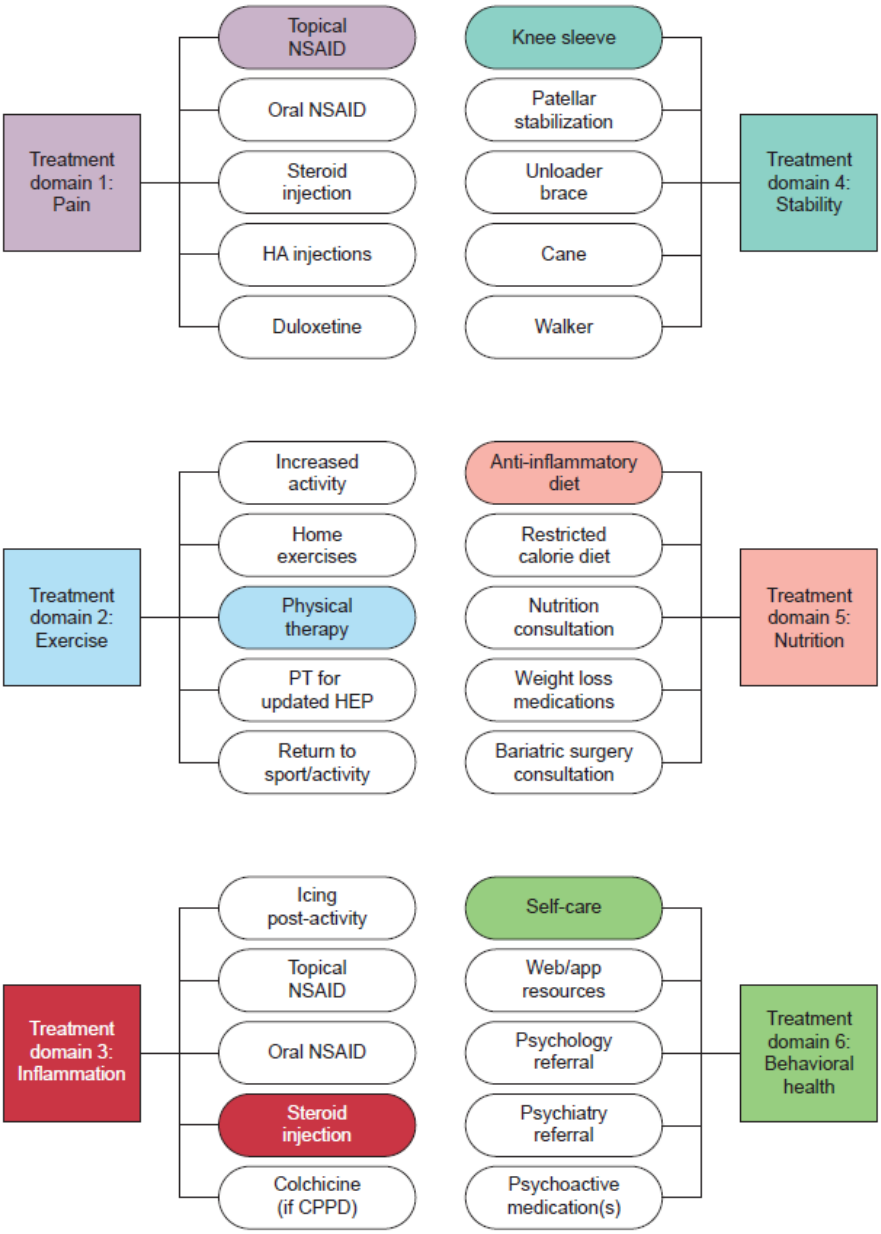

Figure 3. Example of an individualized, multimodal, domain-driven (M2D2) treatment for a patient presenting with early OA and an inflammatory flare

This figure demonstrates one of many possible individualized treatment programs that may be generated to treat a patient with OA. Note that one therapeutic intervention is selected from each of the six treatment domains to create an individualized treatment program in response to the patient's clinical presentation, which is assessed at each visit. The intervention selected within each domain may be independently accelerated, decelerated, or maintained at subsequent visits in response to improvement or regression in clinical response, as well as patient preference(s) and feedback.

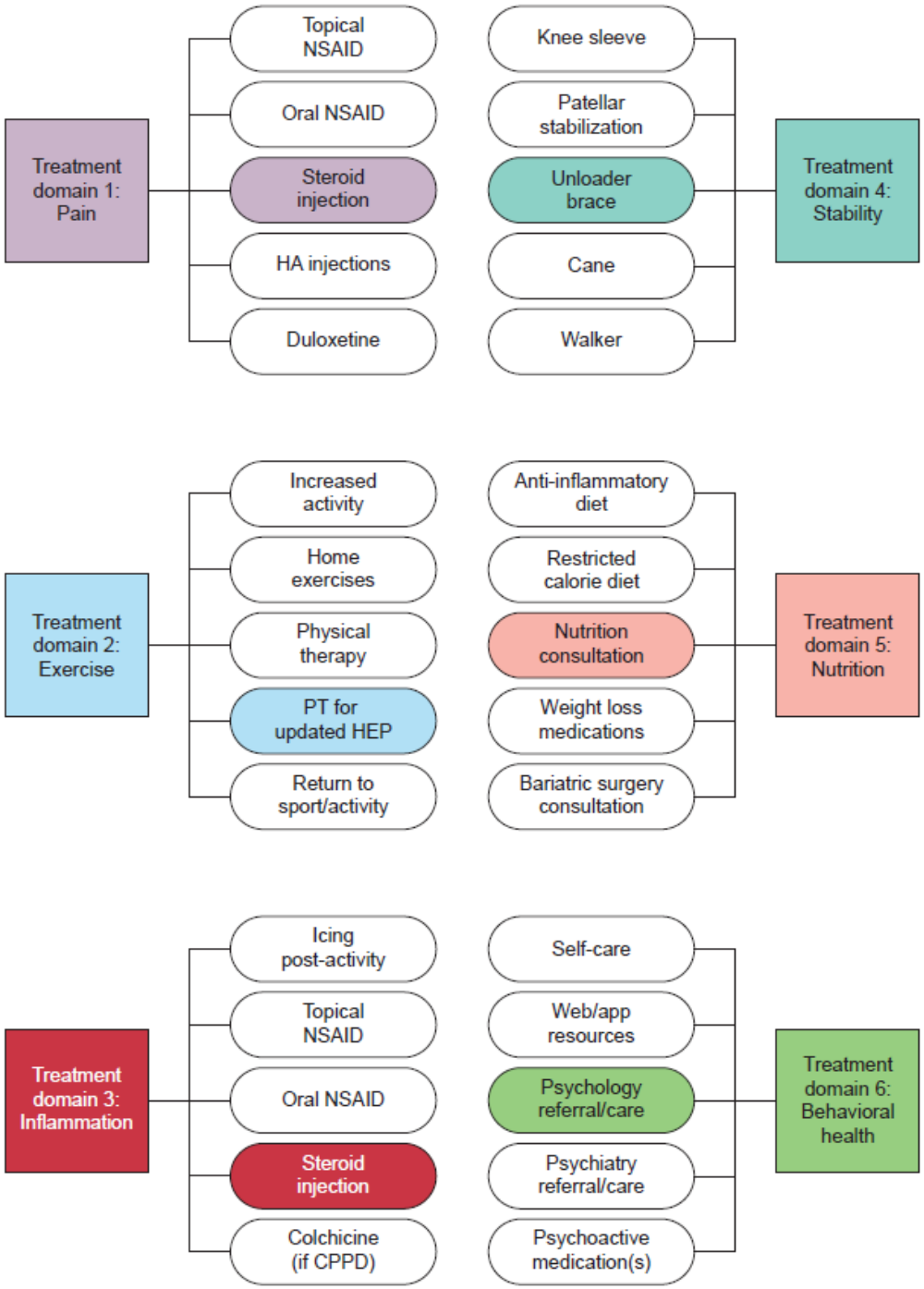

Figure 4. Example of individualized, multimodal, domain-driven (M2D2) treatment for a patient presenting with late OA with chronic synovitis/effusion, obesity, depression, and a GI comorbidity

This figure demonstrates an alternative among the many possible treatment programs that can be generated for a patient with OA following an M2D2 treatment paradigm that addresses the six different treatment domains.

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

Drug Classification	Generic Name	Brand Name
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®

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

The use of tramadol is discouraged because it can become addictive. In some cases, however, it may be unavoidable for those who have not responded to oral or topical NSAIDs, to intra-articular injections of steroids (see below) or HA. A recent article in the *Journal of the American Medical*

Association (JAMA)[101] documented an increased mortality when patients took tramadol as the first prescription drug to treat OA when compared to NSAIDs. 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 discouraged and only used for patients who are not surgical candidates or who do not want surgery and for whom all other measures have failed. Patients must understand that these drugs are potentially addictive and have not been judged to be effective in OA according to a systematic review of the literature.[93] In general, United Rheumatology recommends that the use of tramadol and opioids should be severely restricted, because they are not particularly effective, often associated with side effects, and can be addictive.[66]

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. Duloxetine may be particularly effective among those with knee OA and with neuropathic pain or central pain sensitization. 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.[102] Duloxetine should be given only to patients with multiple-joint OA and comorbidities for whom topical or oral NSAIDs have failed to relieve their pain.[79, 103] This drug is conditionally recommended by the ACR.[34]

Intra-articular corticosteroid (IACS), triamcinolone acetonide, injections could be considered as a first-line treatment for some patients with OA of the knee,[103] although long-term benefits have not been demonstrated. These injections typically provide short-term pain relief for 3 to 4 weeks[104] and, as a general rule, should not be administered more frequently than once every 3 months. Triamcinolone acetonide extended-release injectable suspension (Zilretta®), initially approved by the FDA in 2017, may provide longer duration of symptomatic relief than traditional corticosteroid injections, an attribute which may be of particular benefit by presenting a longer pain-controlled window of opportunity for solidifying desired lifestyle changes and exercise interventions. In 2019 and 2020 the package insert was modified to state that "*efficiency and safety of repeat administration of Zilretta have not been demonstrated"* (Pages 1,2[105]).[63, 106, 107]

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.[106] 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.[34, 66, 106]

A recent publication in the *JAMA* also questioned the benefit of IACS.[108] 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 osteoarthritic knee with triamcinolone every 12 weeks; the other group had intra-articular injections of saline every 12 weeks regardless of the presence or severity of symptoms. 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, the magnitude of the changes found in the trial are of dubious clinical significance and the methodology employed in the trial, including repeat injections every 3 months regardless of symptomatology, does not reflect real-world care.

United Rheumatology recommends the use of IACS injections for the management of patients not responding to a combination of nonpharmacologic and/or oral or topical pharmacologic management, or in patients whose performance of exercises may be compromised by the severity of their pain.

OA causes a decrease in both, the concentration and molecular weight of naturally occurring HA in the knee. As a result, the synovial fluid of the knee becomes less viscous. Currently, the mechanism of action of IAHA 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.[24, 109]

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,[24] in which they concluded that no information was currently available to determine whether or not the use of IAHA 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 IAHA injections 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 IAHA.

In addition, recently various scenarios have been proposed to identify specific patients with OA of the knee who would likely benefit from IAHA injections.[110, 111]

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). IAHA is also appropriate for those who have a contraindication to NSAIDs.[112] 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 IAHA is used, injections are given weekly for 1 to 5 weeks, depending upon the product.[112] 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.[113, 114] Many patients have adequate pain relief up to 26 weeks after the injection.[115] Treatment may be repeated at 6-month intervals.

Contraindications to the intra-articular injection of HA include:[116-127]

- 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 supports the use of IAHA injections for patients who fail to sufficiently improve after an adequate trial of either topical and/or oral NSAIDs or intra-articular injections of glucocorticoids.

If a patient fails the 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).[128] 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 IAHA 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.[128]

Altman et al.[129] 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.[130] reviewed multiple meta-analyses assessing the value of HA in the management of OA of the knee. According to this review, IAHA 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 IAHA injections delayed TKR by 2.67 years.[131]

United Rheumatology recommends against the use of glucosamine, chondroitin, bisphosphonates, hydroxychloroquine, and topical capsaicin.[78-80] United Rheumatology also strongly recommends against the use of prolotherapy, as well as stem cell and platelet rich plasma injections.[34, 66, 132, 133]

Monitoring

All patients with OA should complete a Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS-JR) survey (see Appendix A) and a Global Assessment survey at every visit to establish a baseline and track the results of therapy. Longitudinal capture of the KOOS-JR at each clinic visit allows serial assessment of improvement or worsening. In addition, the KOOS-JR also allows the provider to determine if the patient has reached Patient Acceptable Symptom State (PASS). Furthermore, such serial assessments also provide a useful context for evaluating the magnitude of improvement imparted by changes in management by determining whether estimates of the minimal clinically important difference (MCID) or the substantial clinical difference (SCD) have been achieved. These measures vary according to the specific clinical context, even when the same outcome instrument is utilized. However, they are valuable in that they present an interpretive context that can be used to evaluate the meaning of the magnitude of change in an individual developed from serial application of an outcome measure. That is, in a given clinical context, by standardizing the magnitude of change over time in an individual in comparison to responses of others, these categories of response provide "touchstones of meaning" with which such changes can be contextualized.[134-136]

The MCID is calculated by subtracting the current KOOS-JR interval score at baseline from the current visit score. A KOOS-JR interval score difference of +10 to 15 is the range that patients typically associate with the impression that their knee is "better", or has achieved the MCID. If the calculated difference in the interval score is +16 to 20 or more, then the patient may be considered "a lot better", or as having achieved the SCD. If the calculated KOOS-JR raw sum is >68 then the patient may have achieved the PASS, or "good enough". This can be directly queried by asking the patient if the knee(s) functioning is "good enough, as is" or not.

If the difference in scores is negative or <10, a change in management should be considered (See Appendix A).

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:[137]

- 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
- 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).[138]

The KOOS-JR is an abridged version of the original KOOS. It is a simple, quick questionnaire that can be used to evaluate whether or not the patient is improving on the current treatment. 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. This form can be filled in by the patient online prior to a visit, or in the waiting room, on paper or using an electronic device such as an iPad. Of note, the KOOS-JR is subject to ceiling effects that may limit its utility in more highly functional individuals with OA. A patient and physician global assessment should also be obtained at every visit.

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**.[78, 139] 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.[140-142]

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.[140] An earlier study published in the same journal, also had found no improvement in symptoms after arthroscopic lavage, debridement, or sham surgery.[141]

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.[143]

Arthroscopic partial meniscectomy is also a commonly performed procedure. In 2013, Sihvonen et al.[144] 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[78] 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:[142]

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.[142] Another recent study identified a past history of knee surgery as an independent risk factor for rapid progression to knee arthroplasty.[145] 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.[146] published the results of a seven-institution randomized controlled trial of patients aged 45 years or older with mild to moderate OA and a meniscal tear on imaging. 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.[147] From 1996 to 2006, the number of knee arthroscopies increased by 49%, with a slight decrease in the numbers performed for OA.[148] 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.[149] This is encouraging given the results reported by Katz et al. described above.[146]

TKR 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.[150] 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,[3] 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.[151] 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.[152] According to Losina et al.,[152] 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.[153]

United Rheumatology recommends against the use of arthroscopy with or without debridement for the management of painful OA of the knee regardless of whether an associated meniscal tear is suspected by physical exam or identified by MRI.

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”) in the painful compartment(s) of the knee by X-ray and 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		

MCID (“Better”): + 10-15

SCD (“A lot better”): + 16-20

PASS (“Good enough): > 68

References

1. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. *Lancet* 2020;396:1711-1712.

2. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1145-1153.

3. Centers for Disease Control and Prevention (CDC). Osteoarthritis. http://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed February 2021.

4. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1545-1602.

5. Turkiewicz A, Petersson IF, Björk J, Hawker G, Dahlberg LE, et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. *Osteoarthritis Cartilage* 2014;22:1826-1832.

6. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115-2126.

7. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014;10:437-441.

8. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis* 2014;73:1659-1664.

9. Hochberg M, Cisternas MG, Watkins-Castillo S. Bone and Joint Initiative, the burden of musculoskeltal diseases in the United States: Osteoarthritis; https://www.boneandjointburden.org/fourth-edition/iiib10/osteoarthritis. Accessed February 2021.

10. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2197-2223.

11. Osteoarthritis Alliance. OA prevalence and burden; https://oaaction.unc.edu/wp-content/uploads/sites/623/2019/08/FINAL-OA-Prevalence-and-Burden-final.pdf. Accessed February 2021.

12. Hawker GA, Gignac MA, Badley E, Davis AM, French MR, et al. A

longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res (Hoboken)* 2011;63:1382-1390.

13. Caughey GE, Vitry AI, Gilbert AL, Roughead EE. Prevalence of comorbidity of chronic diseases in Australia. *BMC Public Health* 2008;8:221.

14. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: evidence from national survey data. *Arthritis Rheum* 2009;60:3546-3553.

15. Torio CM, Moore BJ. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013: Statistical Brief #204. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs.* Rockville (MD); 2006. Accessed February 10, 2020.

16. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2163-2196.

17. Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C, et al. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study. *Ann Rheum Dis* 2004;63:395-401.

18. Berger A, Hartrick C, Edelsberg J, Sadosky A, Oster G. Direct and indirect economic costs among private-sector employees with osteoarthritis. *J Occup Environ Med* 2011;53:1228-1235.

19. Sharif B, Kopec J, Bansback N, Rahman MM, Flanagan WM, et al. Projecting the direct cost burden of osteoarthritis in Canada using a microsimulation model. *Osteoarthritis Cartilage* 2015;23:1654-1663.

20. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011;7:33-42.

21. Martel-Pelletier J. Pathophysiology of osteoarthritis. *Osteoarthritis Cartilage* 2004;12 Suppl A:S31-33.

22. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis Cartilage* 2015;23:1233-1241.

23. Richmond SA, Fukuchi RK, Ezzat A, Schneider K, Schneider G, Emery CA. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. *J Orthop Sports Phys Ther* 2013;43:515-B519.

24. Newberry SJ, Fitzgerald MD, Maglione MA, O'Hanlon CE, Booth M, et al. Systematic review for effectiveness of hyaluronic acid in the treatment of severe degenerative joint disease (DJD) of the knee. https://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id101TA.pdf. Accessed September 8, 2017.

25. Altman R, Asch E, Bloch D, Bole G, Borenstein D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29:1039-1049.

26. Michael JW, Schluter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Dtsch Arztebl Int* 2010;107:152-162.

27. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, et al. Diabetes is a risk factor for knee osteoarthritis progression. *Osteoarthritis Cartilage* 2015;23:851-859.

28. Leyland KM, Judge A, Javaid MK, Diez-Perez A, Carr A, et al. Obesity and the relative risk of knee replacement surgery in patients with knee osteoarthritis: a prospective cohort study. *Arthritis Rheumatol* 2016;68:817-825.

29. Foran JR, Mont MA, Etienne G, Jones LC, Hungerford DS. The outcome of total knee arthroplasty in obese patients. *J Bone Joint Surg Am* 2004;86:1609-1615.

30. Burke DT, Bell RB, Al-Adawi S, Burke DP. The effect of body mass index on the functional prognosis of traumatic brain injury patients. *PM R* 2019;11:1045-1049.

31. Yoo JH, Oh HC, Park SH, Kim JK, Kim SH. Does obesity affect clinical and radiological outcomes in minimally invasive total knee arthroplasty? Minimum 5-year follow-up of minimally invasive TKA in obese patients. *Clin Orthop Surg* 2018;10:315-321.

32. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. *Clin Orthop Relat Res* 2004;S6-15.

33. Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. *Osteoarthritis Cartilage* 2011;19:478-482.

34. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res (Hoboken)* 2020;72:149-162.

35. Osteoarthritis Research Society International (OARSI). Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration. https://oarsi.org/sites/default/files/library/2018/pdf/oarsi_white_paper_oa_serious_disease121416_1.pdf. Accessed December 23, 2020.

36. Food and Drug Administration. Expanded Access | Keywords, Definitions, and Resources. https://www.fda.gov/news-events/expanded-access/expanded-access-keywords-definitions-and-resources#:~:text=in%20the%20LOA.-,Serious%20disease%20or%20condition,day%2Dto%2Dday%20functioning. Accessed December 22, 2020.

37. Wesseling J, Welsing PM, Bierma-Zeinstra SM, Dekker J, Gorter KJ, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip and Cohort Knee) study. *Rheumatology (Oxford)* 2013;52:180-188.

38. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ* 2011;342:d1165.

39. Hawker GA, Croxford R, Bierman AS, Harvey PJ, Ravi B, et al. All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. *PLoS One* 2014;9:e91286.

40. Hawker GA, Croxford R, Bierman AS, Harvey P, Ravi B, et al. Osteoarthritis-related difficulty walking and risk for diabetes complications. *Osteoarthritis Cartilage* 2017;25:67-75.

41. Osani MC, Vaysbrot EE, Zhou M, McAlindon TE, Bannuru RR. Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)* 2020;72:641-651.

42. Rahman MM, Kopec JA, Cibere J, Goldsmith CH, Anis AH. The relationship between osteoarthritis and cardiovascular disease in a population health survey: a cross-sectional study. *BMJ Open* 2013;3.

43. Zhang W, Robertson WB, Zhao J, Chen W, Xu J. Emerging trend in the pharmacotherapy of osteoarthritis. *Front Endocrinol (Lausanne)* 2019;10:431.

44. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol* 2020;17:574-584.

45. Cooper C, Chapurlat R, Al-Daghri N, Herrero-Beaumont G, Bruyere O, et al. Safety of oral non-selective non-steroidal anti-inflammatory drugs in

osteoarthritis: what does the literature say? *Drugs Aging* 2019;36:15-24.

46. Skou ST, Thomsen H, Simonsen OH. The value of routine radiography in patients with knee osteoarthritis consulting primary health care: a study of agreement. *Eur J Gen Pract* 2014;20:10-16.

47. Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Ann Intern Med* 2011;155:725-732.

48. Skou ST, Derosche CA, Andersen MM, Rathleff MS, Simonsen O. Nonoperative treatment improves pain irrespective of radiographic severity. A cohort study of 1,414 patients with knee osteoarthritis. *Acta Orthop* 2015;86:599-604.

49. Baert IA, Mahmoudian A, Nieuwenhuys A, Jonkers I, Staes F, et al. Proprioceptive accuracy in women with early and established knee osteoarthritis and its relation to functional ability, postural control, and muscle strength. *Clin Rheumatol* 2013;32:1365-1374.

50. Song YD, Jain NP, Kim SJ, Kwon SK, Chang MJ, et al. Is Knee Magnetic Resonance Imaging Overutilized in Current Practice? *Knee Surg Relat Res* 2015;27:95-100.

51. Multanen J, Rauvala E, Lammentausta E, Ojala R, Kiviranta I, et al. Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 Tesla. *Osteoarthritis Cartilage* 2009;17:559-564.

52. Tiderius CJ, Olsson LE, Leander P, Ekberg O, Dahlberg L. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) in early knee osteoarthritis. *Magn Reson Med* 2003;49:488-492.

53. Hayes CW, Jamadar DA, Welch GW, Jannausch ML, Lachance LL, et al. Osteoarthritis of the knee: comparison of MR imaging findings with radiographic severity measurements and pain in middle-aged women. *Radiology* 2005;237:998-1007.

54. Tanamas SK, Wluka AE, Pelletier JP, Pelletier JM, Abram F, et al. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. *Rheumatology (Oxford)* 2010;49:2413-2419.

55. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23:1043-1056.

56. Arendt-Nielsen L. Pain sensitisation in osteoarthritis. *Clin Exp Rheumatol* 2017;35 Suppl 107:68-74.

57. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. *Eur J Pain* 2014;18:1367-1375.

58. Sharma L, Chang AH, Jackson RD, Nevitt M, Moisio KC, et al. Varus Thrust and Incident and Progressive Knee Osteoarthritis. *Arthritis Rheumatol* 2017;69:2136-2143.

59. Lo GH, Harvey WF, McAlindon TE. Associations of varus thrust and alignment with pain in knee osteoarthritis. *Arthritis Rheum* 2012;64:2252-2259.

60. Chang A, Hayes K, Dunlop D, Hurwitz D, Song J, et al. Thrust during ambulation and the progression of knee osteoarthritis. *Arthritis Rheum* 2004;50:3897-3903.

61. Abhishek A, Doherty M. Diagnosis and clinical presentation of osteoarthritis. *Rheum Dis Clin North Am* 2013;39:45-66.

62. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for the Non-surgical Management of Hip & Knee Osteoarthritis. http://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPGFINAL090214.pdf. Accessed September 8, 2017.

63. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. *Arthritis Rheum* 1995;38:1541-1546.

64. Hunter DJ, Bowden JL. Therapy: Are you managing osteoarthritis appropriately? *Nat Rev Rheumatol* 2017;13:703-704.

65. Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72:1125-1135.

66. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578-1589.

67. National Institute for Health and Care Clinical Excellence (NICE). Osteoarthritis: care and management. https://www.nice.org.uk/guidance/cg177/resources/osteoarthritis-care-and-management-pdf-35109757272517. Accessed August 30, 2020.

68. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol* 2014;28:5-15.

69. Allen KD, Woolson S, Hoenig HM, Bongiorni D, Byrd J, et al. Stepped exercise program for patients with knee osteoarthritis : a randomized controlled trial. *Ann Intern Med* 2020.

70. Skou ST, Roos EM. Physical therapy for patients with knee and hip osteoarthritis: supervised, active treatment is current best practice. *Clin Exp Rheumatol* 2019;37 Suppl 120:112-117.

71. Bennell KL, Dobson F, Hinman RS. Exercise in osteoarthritis: moving from prescription to adherence. *Best Pract Res Clin Rheumatol* 2014;28:93-117.

72. Gohir SA, Eek F, Kelly A, Abhishek A, Valdes AM. Effectiveness of Internet-Based Exercises Aimed at Treating Knee Osteoarthritis: The iBEAT-OA Randomized Clinical Trial. *JAMA Netw Open* 2021;4:e210012.

73. Devos-Comby L, Cronan T, Roesch SC. Do exercise and self-management interventions benefit patients with osteoarthritis of the knee? A metaanalytic review. *J Rheumatol* 2006;33:744-756.

74. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. *J Rheumatol* 2009;36:1109-1117.

75. Hughes SL, Seymour RB, Campbell R, Pollak N, Huber G, Sharma L. Impact of the fit and strong intervention on older adults with osteoarthritis. *Gerontologist* 2004;44:217-228.

76. Thorlund JB, Roos EM, Goro P, Ljungcrantz EG, Gronne DT, Skou ST. Patients use fewer analgesics following supervised exercise therapy and patient education: an observational study of 16 499 patients with knee or hip osteoarthritis. *Br J Sports Med* 2020;online ahead of print; DOI: 10.1136/bjsports-2019-101265.

77. Ettinger WH, Jr., Burns R, Messier SP, Applegate W, Rejeski WJ, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). *JAMA* 1997;277:25-31.

78. American Academy of Orthopaedic Surgeons (AAOS). Treatment of Osteoarthritis of the Knee. Evidence-based Guideline. https://aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/osteoarthritis-of-the-knee-2nd-editiion-clinical-practice-guideline.pdf. Accessed July 26, 2021.

79. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:363-388.

80. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2007;66:433-439.

81. Vincent HK, Heywood K, Connelly J, Hurley RW. Obesity and weight loss in the treatment and prevention of osteoarthritis. *PM R* 2012;4:S59-67.

82. Conaghan PG, Birrell F, Porcheret M, al. e. Osteoarthritis care and management in adults. Clinical guideline CG177. Methods, evidence and recommendations,; 2014. https://www.nice.org.uk/guidance/cg177/evidence/full-guideline-pdf-191761311. Accessed March 2021.

83. Cudejko T, van der Esch M, van der Leeden M, Roorda LD, Pallari J, et al. Effect of soft braces on pain and physical function in patients with knee osteoarthritis: systematic review with meta-analyses. *Arch Phys Med Rehabil* 2018;99:153-163.

84. Mohd Sharif NA, Usman J, Wan Safwani WKZ, Siew Li G, Abdul Karim S, et al. Effects of simple knee sleeves on pain and knee adduction moment in early unilateral knee osteoarthritis. *Proc Inst Mech Eng H* 2019;233:1132-1140.

85. Liow Y, Wang W, Loh VW. Outpatient management of knee osteoarthritis. *Singapore Med J* 2017;58:580-584.

86. Cudejko T, van der Esch M, van der Leeden M, van den Noort JC, Roorda LD, et al. The immediate effect of a soft knee brace on pain, activity limitations, self-reported knee instability, and self-reported knee confidence in patients with knee osteoarthritis. *Arthritis Res Ther* 2017;19:260.

87. Moyer RF, Birmingham TB, Bryant DM, Giffin JR, Marriott KA, Leitch KM. Valgus bracing for knee osteoarthritis: a meta-analysis of randomized trials. *Arthritis Care Res (Hoboken)* 2015;67:493-501.

88. Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies. *Arthritis Care Res (Hoboken)* 2020;72:991-1000.

89. Muckelt PE, Roos EM, Stokes M, McDonough S, Grønne DT, et al. Comorbidities and their link with individual health status: A cross-sectional analysis of 23,892 people with knee and hip osteoarthritis from primary care. *J Comorb* 2020;10:2235042x20920456.

90. Constantino de Campos G, Mundi R, Whittington C, Toutounji MJ, Ngai W, Sheehan B. Osteoarthritis, mobility-related comorbidities and mortality: an overview of meta-analyses. *Ther Adv Musculoskelet Dis* 2020;12:1759720x20981219.

91. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, et al.

Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017;390:e21-e33.

92. Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, et al. Paracetamol versus placebo for knee and hip osteoarthritis. *Cochrane Database Syst Rev* 2019;2:CD013273.

93. Welsch P, Petzke F, Klose P, Häuser W. Opioids for chronic osteoarthritis pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. *Eur J Pain* 2020;24:685-703.

94. Huizinga JL, Stanley EE, Sullivan JK, Song S, Hunter DJ, et al. Societal Cost of Opioid Use in Symptomatic Knee Osteoarthritis Patients in the United States. *Arthritis Care Res (Hoboken)* 2021.

95. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs* 2000;60:555-574.

96. Food and Drug Administration Newsroom. FDA approves three drugs for nonprescritpion use through Rx-to-OTC switch process [FDA news release]. February 14, 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-three-drugs-nonprescription-use-through-rx-otc-switch-process. Accessed February 22, 2020.

97. Laine L, Harper S, Simon T, Bath R, Johanson J, et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. *Gastroenterology* 1999;117:776-783.

98. Laine L, Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology* 2003;124:288-292.

99. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247-1255.

100. Highlights of prescribing information, Celebrex-celecoxib, 2021; http://labeling.pfizer.com/showlabeling.aspx?id=793. Accessed June 20, 2021.

101. Zeng C, Dubreuil M, LaRochelle MR, Lu N, Wei J, et al. Association of tramadol with all-cause mortality

among patients with osteoarthritis. *JAMA* 2019;321:969-982.

102. Wang ZY, Shi SY, Li SJ, Chen F, Chen H, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: a meta-analysis of randomized controlled trials. *Pain Med* 2015;16:1373-1385.

103. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64:465-474.

104. Juni P, Hari R, Rutjes AW, Fischer R, Silletta MG, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015;CD005328.

105. Food and Drug Administration. Highlights of Prescribing Information, Zilretta; 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208845s011lbl.pdf. Accessed April 24, 2021.

106. Raynauld JP, Buckland-Wright C, Ward R, Choquette D, Haraoui B, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2003;48:370-377.

107. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010;18:476-499.

108. McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA* 2017;317:1967-1975.

109. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther* 2003;5:54-67.

110. Cooper C, Rannou F, Richette P, Bruyere O, Al-Daghri N, et al. Use of intraarticular hyaluronic acid in the management of knee osteoarthritis in clinical practice. *Arthritis Care Res (Hoboken)* 2017;69:1287-1296.

111. Bhadra AK, Altman R, Dasa V, Myrick K, Rosen J, et al. Appropriate use criteria for hyaluronic acid in the treatment of knee osteoarthritis in the United States. *Cartilage* 2017;8:234-254.

112. Strauss EJ, Hart JA, Miller MD, Altman RD, Rosen JE. Hyaluronic acid viscosupplementation and

osteoarthritis: current uses and future directions. *Am J Sports Med* 2009;37:1636-1644.

113. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2005;CD005321.

114. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)* 1999;38:602-607.

115. Miller LE, Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. *Clin Med Insights Arthritis Musculoskelet Disord* 2013;6:57-63.

116. Rudwaleit M, Jurik AG, Hermann KG, Landewe R, van der Heijde D, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-1527.

117. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1-44.

118. Synvisc One® [prescribing information]. 2014. Ridgefield, NJ: Genzyme Biosurgery https://www.synviscone.com/?_ga=2.168728289.1138047301.1585778065-355030593.1585778065. Accessed April 1, 2020.

119. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-783.

120. Rudwaleit M, Claudepierre P, Wordsworth P, Cortina EL, Sieper J, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol* 2009;36:801-808.

121. Monovisc™ [prescribing information]. 2013. Bedford, MA: Anika Therapeutics, Inc https://www.accessdata.fda.gov/cdrh_docs/pdf9/P090031c.pdf. Accessed April 2, 2020.

122. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009;60:717-727.

123. Sieper J, van der Heijde D, Landewe R, Brandt J, Burgos-Vagas R, et al.

New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis* 2009;68:784-788.

124. Song IH, Rudwaleit M, Listing J, Sieper J. Comparison of the Bath Ankylosing Spondylitis Disease Activity Index and a modified version of the index in assessing disease activity in patients with ankylosing spondylitis without peripheral manifestations. *Ann Rheum Dis* 2009;68:1701-1707.

125. Rudwaleit M, Rodevand E, Holck P, Vanhoof J, Kron M, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. *Ann Rheum Dis* 2009;68:696-701.

126. Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770-776.

127. Triluiron™ [product information]. 2019. Florham Park, NJ: Fidia Pharma USA Inc https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180040C.pdf. Accessed April 2, 2020.

128. Waddell DD, Bricker DC. Total knee replacement delayed with Hylan G-F 20 use in patients with grade IV osteoarthritis. *J Manag Care Pharm* 2007;13:113-121.

129. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database. *PLoS One* 2015;10:e0145776.

130. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Semin Arthritis Rheum* 2016;45:S28-33.

131. Mar J, Romero Jurado M, Arrospide A, Enrique Fidalgo A, Soler López B. [Cost-analysis of viscosupplementation treatment with hyaluronic acid in candidate knee replacement patients with osteoarthritis]. *Rev Esp Cir Ortop Traumatol* 2013;57:6-14.

132. Goldberg A, Mitchell K, Soans J, Kim L, Zaidi R. The use of mesenchymal stem cells for cartilage repair and regeneration: a systematic review. *J Orthop Surg Res* 2017;12:39.

133. Food and Drug Administration. Considerations in Demonstrating

Interchangeability with a Reference Product: Guidance for Industry. Draft Guidance. January 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-guidance-industry. Accessed February 6, 2020.

134. Hung M, Bounsanga J, Voss MW, Saltzman CL. Establishing minimum clinically important difference values for the Patient-Reported Outcomes Measurement Information System Physical Function, hip disability and osteoarthritis outcome score for joint reconstruction, and knee injury and osteoarthritis outcome score for joint reconstruction in orthopaedics. *World J Orthop* 2018;9:41-49.

135. Lyman S, Lee YY, McLawhorn AS, Islam W, MacLean CH. What Are the Minimal and Substantial Improvements in the HOOS and KOOS and JR Versions After Total Joint Replacement? *Clin Orthop Relat Res* 2018;476:2432-2441.

136. Gowd AK, Lalehzarian SP, Liu JN, Agarwalla A, Christian DR, et al. Factors Associated With Clinically Significant Patient-Reported Outcomes After Primary Arthroscopic Partial Meniscectomy. *Arthroscopy* 2019;35:1567-1575.e1563.

137. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S208-228.

138. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003;1:64.

139. American Association of the Hip and Knee Surgeons (AAHKS). Surgical Option for Knee Arthritis. https://hipknee.aahks.org/surgical-options-for-knee-arthritis/. Accessed July 26, 2021.

140. Kirkley A, Birmingham TB, Litchfield RB, Giffin JR, Willits KR, et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2008;359:1097-1107.

141. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81-88.

142. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *Br J Sports Med* 2015;49:1229-1235.

143. Dhawan A, Mather RC, 3rd, Karas V, Ellman MB, Young BB, et al. An epidemiologic analysis of clinical practice guidelines for non-arthroplasty treatment of osteoarthritis of the knee. *Arthroscopy* 2014;30:65-71.

144. Sihvonen R, Paavola M, Malmivaara A, Itala A, Joukainen A, et al. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med* 2013;369:2515-2524.

145. Riddle DL, Kong X, Jiranek WA. Factors associated with rapid progression to knee arthroplasty: complete analysis of three-year data from the osteoarthritis initiative. *Joint Bone Spine* 2012;79:298-303.

146. Katz JN, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med* 2013;368:1675-1684.

147. Owings MF, Kozak LJ. Ambulatory and inpatient procedures in the United States, 1996. DHHS Publication No. (PHS) 99-1710, 1998. National Center for Health Statistics

148. Kim S, Bosque J, Meehan JP, Jamali A, Marder R. Increase in outpatient knee arthroscopy in the United States: a comparison of National Surveys of Ambulatory Surgery, 1996 and 2006. *J Bone Joint Surg Am* 2011;93:994-1000.

149. Essilfie A, Kang HP, Mayer EN, Trasolini NA, Alluri RK, Weber AE. Are orthopaedic surgeons performing fewer arthroscopic partial meniscectomies in patients greater than 50 years old? A National Database Study. *Arthroscopy* 2019.

150. Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR. Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991-2010. *JAMA* 2012;308:1227-1236.

151. Helmick CG, Watkins-Castillo S. Arthritis and Related Conditions. *In: The Burden of Musculoskeletal Diseases in the United States Arthritis.* http://www.boneandjointburden.org/2013-report/iv-arthritis/iv. Accessed September 8, 2017

152. Losina E, Thornhill TS, Rome BN, Wright J, Katz JN. The dramatic increase in total knee replacement utilization rates in the United States cannot be fully explained by growth in population size and the obesity epidemic. *J Bone Joint Surg Am* 2012;94:201-207.

153. Riddle DL, Jiranek WA, Hayes CW. Use of a validated algorithm to judge the appropriateness of total knee arthroplasty in the United States: a multicenter longitudinal cohort study. *Arthritis Rheumatol* 2014;66:2134-2143.

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
1.1.2019	2019 annual review	Apr 2019
1.1.2020	2020 annual review	Aug 2020
1.1.2021	2021 annual review	Apr 2021