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Review

Knee osteoarthritis: disease burden, available treatments, and emerging options

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***Abstract*:** Osteoarthritis (OA) is a prevalent condition that affects nearly 528 million people worldwide, including 23% of the global population aged ⩾40, and is characterized by progressive damage to articular cartilage, which often leads to substantial pain, stiffness, and reduced mobility for affected patients. Pain related to OA is a barrier to maintaining physical activity and a leading cause of disability, accounting for 2.4% of all years lived with disability globally, reducing the ability to work in 66% of US patients with OA and increasing absenteeism in 21% of US patients with OA. The joint most commonly involved in OA is the knee, which is affected in about 60%–85% of all OA cases. The aging population and longer life expectancy, coupled with earlier and younger diagnoses, translate into a growing cohort of symptomatic patients in need of alternatives to surgery. Despite the large number of patients with knee OA (OAK) worldwide, the high degree of variability in patient presentation can lead to challenges in diagnosis and treatment. Multiple society guidelines recommend therapies for OAK, but departures from guidelines by healthcare professionals in clinical settings reflect a discordance between evidence-based treatment algorithms and routine clinical practice. Furthermore, disease-modifying pharmacotherapies are limited, and treatment for OAK often focuses solely on symptom relief, rather than underlying causes. In this narrative review, we summarize the patient journey, analyze current disease burden and nonsurgical therapy recommendations for OAK, and highlight emerging and promising therapies—such as cryoneurolysis, long-acting corticosteroids, and gene therapies—for this debilitating condition.

Keywords: emerging therapies, guidelines, intraarticular injections, NSAIDs, osteoarthritis

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Introduction

Osteoarthritis (OA) is a degenerative disorder of synovial joints characterized by progressive articular cartilage damage; structural alterations of subchondral bone, menisci, ligaments, joint capsule, and periarticular muscles; and degrees of synovial proliferation, resulting in substantial joint pain, stiffness, and functional limitations.[1–3] Clinical presentation of knee OA (OAK) and etiologies can be highly variable,[3] with inflammatory, metabolic, mechanical, and environmental factors including mechanical stress, limb overuse, injury, age, genetic disorders, and metabolic syndromes contributing to disease onset and progression.[2–4] Direct costs of OA account for 1%–2.5% of gross national product in the United States, United Kingdom, Canada, and Australia; total direct medical costs in the United States are approximately $72 billion.[5] Rates of disability associated with OA will likely increase given an earlier onset of disease, an aging population with longer life expectancy, and growing obesity rates.[6,7]

Racial and social factors (e.g., socioeconomic status) can impact disease prevalence, radiographic features, healthcare resource accessibility, and disease severity.[8] Osteoarthritis Research Society International (OARSI) grading, based on cartilage histopathology, defines mild OA (grades 1–3) as lacking erosion of collagen matrix, while more severe disease (grades 4–6) is typified by partial to complete erosion of the cartilage matrix and deformation of joint surfaces.[9] Although

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objective findings (e.g., physical examination, X-ray analyses) are necessary for diagnosis, pain is the key presenting symptom and clinical measure of severity, which guides treatment.[10,11]

Currently, there are no office-based/nonsurgical curative or disease-modifying agents for OA.[3,12,13] Nonsurgical options are the first line of treatment for patients with OA,[14] yet there is often a disconnect between treatment guidelines and clinical practice.[15] As there is robust literature describing surgical management of OAK,[16–19] this narrative review will focus on nonsurgical management, providing an overview of disease burden, current guidelines, standard treatments, and evidence for emerging therapies. We end with suggested clinical scenarios for various treatment approaches.

Epidemiology of OAK

OA affects millions of people worldwide, with the highest prevalence observed in the United States (9961 per 100,000 people),[20] where the overall lifetime risk of symptomatic OA is between 41% and 45%.[21] The joint most commonly affected by OA is the knee, accounting for 60%–85% of total OA cases.[20,22,23] Incidence of OAK is 1.39 times higher in women than men (95% confidence interval (CI), 1.24–1.56; $p < 0.00$).[22] Prevalence of OAK in women is 1.69 times higher than it is among men (95% CI, 1.59–1.80; $p < 0.00$).[22] Prevalence of OAK in the United States has been increasing in tandem with an aging population and a growing obesity epidemic.[7,24,25] The incidence of OAK in the United States is approximately 240 people per 100,000 each year[1] and is highest among patients aged 55–64 years.[7] However, OA is also being diagnosed in an increasingly younger population.[7] As the face of OA becomes younger and life expectancy increases, patients are anticipated to be symptomatic for a greater proportion of their lives.

Risk factors vary across age and gender; they are often studied in older populations with accumulated OA symptoms.[26,27] Factors that increase OAK risk in adults aged ⩾50 years include overweight/obesity, previous knee injury, female sex, older age, presence of hand OA, family history of OA, and exposure to physical exertion at work.[26,28] Increased age and physical activity in men, and increased body mass index (BMI) and alcohol intake in women, are associated with an elevated risk of OA.[27] In addition, both bilateral thumb OA and upper limb disability increase the risk of OAK among women.[27] Studies have identified 90 genetic risk loci for OA.[29] Gene single-nucleotide polymorphisms linked to increased OA risk or increased disease progression are associated with proinflammatory mediators, including interleukin-1 (IL-1) family cytokines; factors in skeletal development, including tumor growth factor-beta; and collagen components, including *COL2*.[29–32]

OA patient journey

Diagnosis and presentation

Patients often avoid seeking healthcare until they experience burdensome symptoms; therefore, healthcare providers (HCPs) may not see patients with OA until they become symptomatic with severe pain, stiffness, and functional limitations—often with concomitant advanced joint degeneration.[1,33,34] A survey of HCPs and patients with OAK noted the absence of persistent pain, difficulty in scheduling medical appointments, slow progression of OA, and optimism about OA getting better without intervention as reasons for the delay in seeking treatment.[34] Furthermore, imaging modalities used to diagnose OAK may not correlate with physical signs and symptoms as the presence of cartilage defects is estimated at 43% in adults ⩾40 years old; this prevalence may be impacted by different magnetic resonance imaging (MRI) techniques, including field strength and the type of MRI sequences used.[35,36]

Upon presentation to a physician with symptoms consistent with OA, established guidelines may aid in OA diagnosis. The American College of Rheumatology (ACR) clinical classification criteria outline idiopathic OA as knee pain with ⩾3 of the following characteristics: age >50 years, morning stiffness <30 min in duration, crepitus, bony tenderness, bony enlargement, and no palpable warmth.[37] A heterogeneous condition, OAK can be further defined using patients' radiographic severity, comorbidity status (Charlson Comorbidity Index), pain, joint sensitivity, and psychological factors to give an overall OA phenotype.[38,39] Patient phenotypes can be broadly categorized into four groups: (1) age-related and systemic phenotypes driven by metabolic diseases, aging, and endocrine diseases; (2) extra-articular phenotypes involving ligament and tendon laxity, sarcopenia, and varus and valgus malalignment; (3) intraarticular (IA) phenotypes including alterations in articular cartilage,

OARSI	0	1	2	3	4	5	6
	Surface intact Normal cartilage morphology	Surface intact Superficial fibrillation Cell death/proliferation	Surface discontinuity Focal fibrillation through superficial zone Cell death/proliferation	Vertical fissures/clefts into the mid zone which may branch Cell death/proliferation proximate to fissures	Erosion of cartilage matrix	Complete loss of cartilage matrix Microfractures and reparative fibrocartilage	Deformation with microfractures and bone remodeling

K-L	0	1	2	3	4
	None Absence of X-ray changes	Not severe Doubtful narrowing of joint space and possible osteophytic lipping	Minimal severity Definite osteophytes and possible narrowing of joint space	Moderate severity Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends	Severe Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

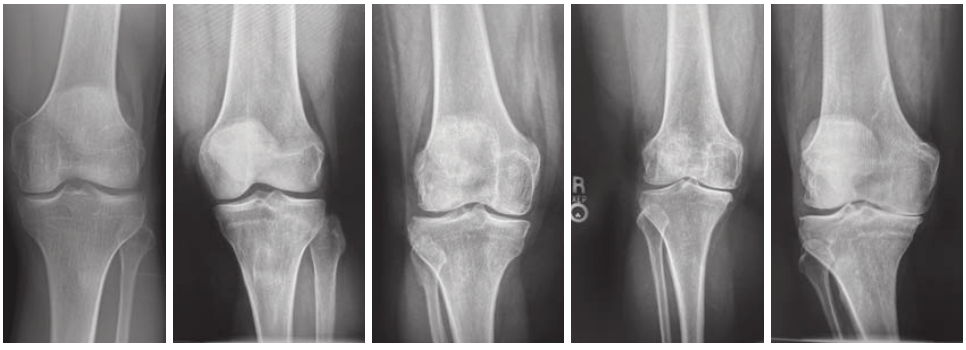

Figure 1. Disease Severity Ranking Scales for osteoarthritis.[9,50,52]
K–L, Kellgren–Lawrence scale; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

subchondral bone, and meniscus, as well as the presence of synovitis; and (4) secondary phenotypes capturing OA driven by development of crystals, traumatic injury, previous autoimmune arthritis, and occupational injuries.[40] However, the phenotype may neither predict symptoms nor inform specific treatment and management strategy,[40,41] and not all patient types fit neatly within these four phenotypes (e.g., a young athlete with a sports injury or a patient with generalized pain such as fibromyalgia). Pain at presentation can vary significantly and may be affected by neuroinflammation, joint inflammation (synovitis), OA-triggering joint trauma severity, compromised endogenous joint-repair processes, structural changes (bone marrow lesions, subchondral bone remodeling, and osteophyte formation), and peripheral and central sensitization.[41–43] In addition, patient symptoms may not align with structural changes observed on X-ray or MRI.[44,45] Structural changes precede disease development, diagnosis, and chronic pain,[33] and MRI imaging can often detect changes in soft tissues, such as meniscus changes or articular cartilage degeneration, better than radiographic imaging.[46] However, MRI is often not used if radiographic OA is present—unless mechanical symptoms or unusual pain suggestive of an alternative diagnosis are observed—given high cost, limited availability, generally long scanning times, and lack of standardization in MRI acquisition and interpretation.[46,47]

Disease progression and monitoring

Loss of articular cartilage, combined with cellular changes and biomechanical stress, can cause subchondral bone remodeling; osteophyte formation; development of bone marrow lesions; changes in the synovium, joint capsule, ligaments, and periarticular muscles; and meniscal tears and extrusion.[48] Disease progression is determined by assessing cartilage volume, thickness, and defects; presence and severity of bone marrow lesions via imaging; signs

of inflammation (i.e., synovitis); and presence of meniscal alterations.[49] Chondrocyte hypertrophy and endochondral ossification are key indicators of OA progression.[31] However, key factors in determining the clinical significance of disease progression are worsening pain and persistent symptoms.

Multiple methods have been used to assess OA severity. The Kellgren–Lawrence (K–L) scale, the most common, grades the radiographic extent of disease overall between 0 (no OA) and 4 (severe; Figure 1).[50] Risk for medical progression to surgical treatment increases considerably as the K–L grade increases.[51] In addition, the OARSI system grades changes to the subchondral bone and articular cartilage on a scale between grade 0 (normal cartilage) and grade 6 (articular cartilage and subchondral bone changes present).[9]

Biomarkers in bodily fluids that indicate type 2 collagen degradation may allow for further characterization of disease progression.[53] This disease's impact on patients and symptomatic treatments can be evaluated via patient-reported assessments, such as the Knee Injury and Osteoarthritis Outcomes Score and its multiple subscales, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and its subscales, and the Patient-Reported Outcomes Measurement Information System.[54,55] Minimum clinically important difference (MCID) thresholds have been characterized for OAK assessments, though a recent meta-analysis found that proposed MCID values differed across pain assessment publications.[55]

Ultimately, despite an improved understanding of diagnosis and patient phenotypes, responsiveness to treatment based on phenotypes, MRI, or other radiographic presentations, symptomatic classification systems remain unpredictable.

Patient burden

As OA is the leading cause of disability among US adults,[56] and OA-related pain is a barrier to physical activity,[57] OAK symptoms can cause considerable functional limitations.[1,57–59] Disability can range from minimal to severe, with severe disability involving chronic pain and reduced function.[57] Patients with OAK lost an average of 0.55 quality-adjusted life-years (QALYs) per person because of inactivity, with Black Hispanic women having the highest per-person QALY loss of 0.76.[60] Factors influencing the degree of disability and loss of function include female sex, lower education levels, and social disadvantages.[57] Disability associated with OA most substantially impacts patients whose careers or daily activities require weight-bearing exercise or positions that involve walking or knee bending.[57] Specific changes in physical abilities, such as gait alterations, can alter load distribution at the knee and have been associated with the risk of OAK, disease severity, and progression.[58,59]

Patients with OA reported significant pain interference with activities outside the home, including work, relative to those without OA ($p < 0.0001$).[61] Those with OA missed more work days and had higher odds of experiencing OA-related limitations than those without (3.68; $p = 0.000$).[62] Workers employed as manual laborers may be more affected by OA-related disability because of the activity level their jobs require.[63] Patients with higher disease severity are more likely to be unemployed and, if employed, are more likely to experience impairment while working.[61,64] The economic burden of OA can be summarized in annual per-patient costs (primarily indirect costs due to lost productivity) ranging from $9801 for mild disease to $22,111 for severe disease,[61,64] which is comparable to heart failure ($17,000–$30,000) and cancer ($2160–$31,176).[65,66]

Pain and functional limitations vary in intensity and over time.[1,57–59,67,68] In a study of 719 participants, 23%–32% reported substantial pain variability over time.[67] Another study reported significant variation in pain intensity by age, particularly between age groups of 20–39 and 40–59 years (mean difference, −3.68; $p = 0.01$) and 60–79 years (mean difference, −3.23; $p = 0.04$), with higher pain intensity in the 40–59 years group.[68] In addition, significant variation in physical function was observed between age groups of 60–79 and 20–39 years (mean difference, −20.85; $p = 0.02$) and 40–59 years (mean difference, −10.70; $p = 0.03$), with greater function in the 20–39 years group. Increased pain and decreased function in the 40–59 age group could reduce employment capacity and increase the economic burden of OAK.

Decreased ability to participate in physical exercise can increase obesity among patients with OA.[57] In the United States, adults with obesity and OA were 44% more likely to be physically inactive than adults with obesity who did not have OA.[69] Comorbidities with common risk factors (i.e., age and obesity), such as diabetes mellitus

(DM) and hypertension, are increased in patients with OA.[57] The prevalence of diabetes among patients with knee or hip OA is between 9.7% and 33%, and patients with OA have a relative risk of 1.32 of developing diabetes over 12 years.[57] Approximately 52% of patients with DM also suffer from some form of arthritis.[70] Furthermore, US patients with OA and diabetes experience more inactivity (29.8%) than those with OA or diabetes alone (17.3% and 21.0%, respectively). This is a particularly difficult cohort of patients to treat, as some effective treatment modalities, such as IA corticosteroid injections, may adversely impact glucose control.[71] Between 32% and 81% of patients with OA also have hypertension, and the combination of OA and hypertension is the most common combination of comorbidities, impacting more than 24% of adults over 65 years.[57] Metabolic syndrome—the combination of obesity, diabetes, hypertension, and dyslipidemia—affects 59% of patients with OA compared with 23% of those without; physical and mental burdens of OA may limit the ability to self-manage comorbidities.[57] Overall, comorbidities associated with OA and their consequences may worsen the clinical impact of OA, and OA may contribute to the development and/or exacerbation of comorbidities, which creates a negative feedback loop, impacting physical function and treatment decisions.

The cumulative impact of all these associations may explain why OA is also an independent risk factor for all-cause mortality. Patients with symptomatic or radiographic OAK have greater mortality (15.7 or 14.1 deaths per 1000 person-years, respectively) than patients with neither OAK nor knee pain (9.4 deaths per 1000 person-years), mediated in part by the impact of OA on either disability or physical component scores of quality of life assessments.[72] Of particular importance are activity restrictions; increases in physical activity, such as brisk walking, are associated with decreased all-cause mortality, but symptomatic OAK may preclude any vigorous activity.[73] As OA is prevalent among older patients, additional comorbidities increase the likelihood of polypharmacy, increasing the risk for frailty, falls, hospitalizations, and cognitive and physical impairment.[74–76]

Treatment selection

As noted previously, patients with symptomatic OAK present with different phenotypes, and with variable symptom severity. Therefore, therapeutic decisions must be individualized, focused on reducing pain and improving function, slowing disease progression, improving patient mobility and well-being, and ultimately reducing healthcare resource utilization.[77] Parameters such as patient age, comorbidities, presence of inflammation, disease severity, and patient preferences and expectations should be considered when determining patient-specific treatment plans.[78,79] Initiation of both nonpharmacological and pharmacological interventions is standard, and therapies progress from noninvasive treatment to more advanced, potent pharmaceuticals.[77] Total knee arthroplasty (TKA) may be required if a patient does not respond to interventions or is experiencing severe symptoms and poor quality of life.[77]

The decision to move forward with surgical intervention in the form of knee replacement when nonsurgical management has failed is almost entirely subjective. In addition, TKA outcomes are not always predictable and can be impacted by patient age, gender, activity level, expectations, comorbidities, surgeon and institutional volume and expertise, and many other patient- and surgeon-specific determinants.[80–82] In addition, some patients are either unready or cannot medically tolerate the intervention of knee replacement and rehabilitation that follows; conversely, some surgical practices delay or deny TKA procedures for patients who are above a certain BMI or who have other modifiable risk factors such as diabetes control and smoking.[83–85] Other individuals may be at risk for catastrophic complications, including fracture, infection, and poor functional outcomes.[86] Recent data suggest that roughly 10%–20% of patients are not fully satisfied with their pain and functional outcomes,[87,88] and 31%–54% of patients have residual symptoms.[89] Finally, although the longevity and durability of TKA are outstanding, with 82.3% of TKAs lasting 25 years,[90] need for revision due to aseptic loosening, infection, or other mechanical complications increases over time[91]; furthermore, revision knee arthroplasty is typically less durable than the primary procedure.[92] Younger patients with symptomatic OA, particularly those under 55 years, are at increased risk for revision,[93–95] primarily because of surface wear and biological responses to wear debris; new implant designs are not effectively reducing residual symptoms or revision risks among this population.[96,97] In addition, patients under 50 who undergo a knee revision are more likely to require

Table 1. Pharmacologic treatment guidelines for osteoarthritis.[1,41,78,99–101]

Treatment	AAOS	ACR	NICE	OARSI[a]	EULAR[b]	ASPN
Topical NSAID	Strong recommendation	Strongly recommender	Recommended	Level 1A recommendation	Level A recommendation	Strong recommendation
Oral NSAID	Strong recommendation	Strongly recommender	Recommended	Level 1B recommendation	Level A recommendation	Strong recommendation
Oral acetaminophen	Strong recommendation	Conditionally recommender	Recommended	Conditionally not recommended	Level 1B recommendation	No recommendation
Oral narcotics	Strong recommendation	No recommendation	Recommended	No recommendation	No recommendation	Strongly against
Hyaluronic acid	Moderate recommendation	Conditionally against	Not recommended	Level 1B recommendation	Level B recommendation	Strong recommendation
Intraarticular corticosteroids	Moderate recommendation	Strongly recommender	Recommended	Level 1B recommendation	Level A recommendation	Moderate recommendation
Platelet-rich plasma	Limited recommendation	Strongly against	No recommendation	Strongly against	No recommendation	Strong recommendation

[a]Level 1A: ⩾75% of panelists in favor of recommendation and >50% in favor of strong recommendation; Level 1B: ⩾75% of panelists in favor of recommendation and >50% in favor of conditional recommendation.
[b]Level A: directly based on category 1 evidence (meta-analysis of randomized controlled trials or ⩾1 randomized controlled trial); Level B: directly based on category 2 evidence (⩾1 controlled study without randomization or ⩾1 type of quasi-experimental study) or extrapolated from category 1 evidence.
AAOS, American Academy of Orthopaedic Surgeons; ACR, American College of Rheumatology; ASPN, American Society of Pain and Neuroscience; EULAR, European Alliance of Associations for Rheumatology; NICE, National Institute for Health and Care Excellence; NSAID, nonsteroidal anti-inflammatory drug; OARSI, Osteoarthritis Research Society International.

re-revision than older patients.[98] Given the challenges with TKA in younger patients, it is crucial to understand and incorporate nonsurgical management options into the management paradigm of symptomatic OAK for patients who want to or for whom it is medically advisable to delay TKA. The remainder of this manuscript is devoted to reviewing current therapeutic guidelines established to support clinicians in identifying current and emerging nonsurgical therapies for patients with OA.

Nonsurgical treatment options for OA

Several guidelines for nonsurgical OAK treatment recommend weight loss, exercise, and pharmacologic interventions (Table 1).[1,41,78,99–101] Treatment selection should be based on patient-specific factors, such as disease duration, pain intensity, and presence of comorbid conditions.[78,102] Current OA therapies generally focus on reducing pain and improving function, and many therapies and technologies are under investigation to further improve disease outcomes. As of May 2023, there are 109 active interventional phase II or phase III studies for OAK (including 42 phase III studies).[103,104]

Nonpharmacologic interventions

The AAOS guidelines for OAK recommend manual therapy delivered by a therapist in conjunction with an exercise program.[1] Supervised or unsupervised exercise (land or aquatic) to strengthen muscles is recommended by AAOS, NICE, OARSI, and ACR.[1,41,99,101] To reduce the burden on and increase the function of the affected joint, guidelines also recommend self-management (i.e., patient-driven therapy and exercise programs), mobility aids, braces, heat and cold therapies, neuromuscular training, and weight loss.[1,105] Weight loss reduces joint loads, decreases joint pain, and has been associated with improved long-term prognoses and adherence to subsequent therapies.[106] Despite known health benefits, weight loss is difficult to achieve and has a high recidivism rate[106] because of dietary habits, sedentary behaviors, and difficulties with exercise—including temporary soreness or increase in knee pain.[106] In addition, dyslipidemia in patients with obesity, specifically elevations in proinflammatory adipokines and reduced high-density lipoproteins, is associated with bone lesions and increased inflammation, both systemically and within the joint.[107,108] Recent advances in treatment for type 2 diabetes, including glucagon-like

peptide-1 receptor agonists (GLP-1RAs) like semaglutide, liraglutide, and dulaglutide, are potentially disease-modifying therapies for OAK.[109] An observational study of 1807 patients with OAK showed clinically relevant (>5%) weight reductions in 57.9% of patients treated with GLP-1RA (135/233).[109] Significant differences from baseline were observed in WOMAC total scores ($p = 0.038$) and pain subscores ($p = 0.007$) for patients treated with GLP-1RA compared with those who were not, as well as lower incidence of TKA ($p = 0.014$) and IA steroid use ($p < 0.001$).[109] Cartilage-loss velocity was significantly lower in patients with predominantly lateral OA who were treated with GLP-1RA compared with those who were not ($p = 0.026$).[109] Importantly, changes were not consistently found to be mediated by weight reduction and HbA1c change,[109] so further research is needed to understand the impact of GLP-1RAs on OAK.

Topical therapies

For OA-related pain, guidelines recommend topical nonsteroidal anti-inflammatory drugs (NSAIDs) and topical capsaicin.[1,100,110] A meta-analysis evaluated topical NSAIDs—including diclofenac, ketoprofen, piroxicam, eltenac, felbinac, flurbiprofen, piketoprofen, nimesulide, flufenamate, indomethacin, and ibuprofen—applied as solutions, gels, or patches, and found topical NSAIDs, particularly diclofenac, to be as effective as oral NSAIDs in OAK.[111] In addition, topical NSAID therapy was well tolerated in patients ⩾65 years of age and patients with multiple comorbidities, including hypertension, type 2 DM, and cardiovascular disease.[112] While studies on long-term use of topical NSAIDs are scarce, consistent improvement was seen in pain, stiffness, and physical function after 12 months of consistent treatment with topical diclofenac sodium 1% gel.[113] In addition, the most common adverse events (AEs) reported with long-term use of topical NSAIDs were headache, arthralgia, back pain, and application-site dry skin or dermatitis.[113,114] Topical capsaicin provides comparable pain control to topical NSAIDs but has limited evidence in OA.[115] Though topical treatments limit the amount of medication absorbed systemically,[116] a comprehensive evaluation found topical NSAIDs not clinically important for the treatment of OAK.[117] Furthermore, topical treatments can cause skin reactions, including dry skin, rash, and dermatitis,[118] but reactions are generally mild and transient.[111]

Systemic therapies

Systemic, oral therapies recommended for OA pain management include oral NSAIDs (nonselective and COX-2 selective, with/without proton pump inhibitor), oral acetaminophen, and oral tramadol,[1,100,110] but chronic treatment with systemic therapies includes substantial risks. For example, acetaminophen is an adjunctive therapy that should be used with caution given risks of liver toxicity with excessive dosing,[1,119] and NSAIDs are contraindicated in patients taking some antihypertensives or with a history of hypertension.[120] In addition, narcotics should be avoided except in extreme cases given the high risk of AEs.[1]

In 2007, the Food and Drug Administration released a medication guide for oral NSAIDs.[121] This guide details associated AEs, including serious AEs (e.g., heart attack, stroke, intestinal bleeding, and kidney failure) and less-threatening AEs (e.g., stomach pain, constipation, and heartburn).[121] The guide specifies that NSAIDs should be taken at the lowest dose possible for the shortest time needed.[121] However, >111 million prescriptions for NSAIDs are written in the United States annually.[122] Chronic use of NSAIDs increases with age, so even low percentages of AEs can add up to a large number of affected patients. Most NSAIDs are used as needed, and whereas NSAIDs such as ibuprofen have a short half-life and are absorbed quickly for immediate relief, NSAIDs with a longer half-life—such as naproxen or celecoxib—may be more beneficial for the persistent chronic OAK-associated pain.[122] Compared with the efficacy of opioids for musculoskeletal conditions such as OA, NSAIDs have been shown to comparably reduce pain intensity, with some studies showing significantly lower rates of AEs.[123] Similarly, compared with acetaminophen, NSAIDs are associated with improved pain control and a better safety profile.[124] Though a recent meta-analysis of symptom relief and AEs with oral NSAIDs for treatment of OA found that all NSAIDs were associated with an increased probability of gastrointestinal (GI) AEs and minor cardiovascular events relative to placebo, this cardiovascular risk was lower with increased COX-2 selectivity.[125] Furthermore, the absolute risk of serious GI and cardiovascular complications such as GI bleeding and heart failure-related mortality increases with age among patients taking nonselective NSAIDs, particularly those with prior bleeding complications, hospitalizations for heart failure, and concomitant use of anticoagulants.[126]

These collective safety issues with NSAIDs suggest alternatives should be explored for long-term OA pain management.

Novel systemic treatments under investigation to target specific pain-signaling channels may improve OA-related pain treatment by avoiding off-target effects that may lead to AEs (PF05089771 for $Na_v1.7$ sodium channels, capsaicin for transient receptor potential cation channel subfamily V member 1).[127,128] In addition, treatments developed for osteoporosis, including strontium ranelate and denosumab, have shown potential as disease-modifying therapies in OA, with significant improvements in radiological changes, as well as function and pain.[129,130] For example, in patients with OAK, daily treatment with 2 g strontium ranelate significantly improved versus placebo in joint space width (−0.27 vs −0.37 mm, respectively; $p=0.018$), WOMAC total score (−51.9/300 vs −40.7/300 mm; $p=0.045$), and WOMAC pain subscore (−19.1/100 vs −14.7/100 mm; $p=0.028$).[129]

Local injection therapies

Locally delivered therapies, such as IA injections, can more directly address OA symptoms. In general, guidelines recommend IA-CS injections and do not recommend other IA injections, although AAOS gives IA platelet-rich plasma (IA-PRP) a limited recommendation (discussed in "Emerging Treatments").[1] Injections of IA-CS can provide effective relief of OAK pain for up to 3 months.[131] While IA-CS injections are recommended for short-term OAK relief,[1] a comparison of short-acting IA-CS with other injectables found no difference in pain level for all injections; however, other injectables led to greater improvements in function than IA-CS injectables at and beyond 3 months following treatment.[132] In addition, a review of nonoperative treatments for OAK found that IA injections of hyaluronic acid (IA-HA) demonstrated clinical efficacy at molecular weights between $\geqslant$1500 to $<$6000 and $\geqslant$6000 kDa,[117] though they are not generally recommended by guidelines.[1,41,78,99–101] In 54 trials that used IA-HA injections to treat OAK pain, function, and stiffness, IA-HA was efficacious at 4 weeks, reached peak effectiveness at 8 weeks, and had a residual effect at 24 weeks after treatment.[133] Across 74 trials, IA-HA products were well tolerated, with AE rates similar to those of placebo.[134] In a systematic review and meta-analysis of 50 years of data regarding viscosupplementation with IA-HA—which reviewed 24 placebo-controlled trials ($N=8997$) for pain outcomes, 19 placebo-controlled trials ($N=6307$) for function, and 15 placebo-controlled trials ($N=6462$) for serious AEs—viscosupplementation demonstrated greater reductions in pain intensity than those of placebo, but the incidence of serious AEs was higher in the treatment group and pain reductions were below the MCID.[135] Many randomized controlled trials of viscosupplementation with IA-HA exhibited similar or worse treatment outcomes compared with placebo, though these results were never published.[135] The implications of these findings for ongoing and future use of viscosupplementation are yet to be determined.

The AAOS cautions that short-acting IA injections carry a potential risk of accelerating OA,[1] yet some evidence for this is based on populations not representative of typical OA patients and derived from studies with notable limitations. Two observational studies published in 2019 investigated OA progression to TKA following IA-CS.[136] One found an increased risk of TKA with IA-CS treatment compared with those treated without IA-CS (22.3% vs 5.4%), but the authors also acknowledged that only one patient in the IA-CS group had TKA due to worsening K/L assessment.[136,137] The other study found no increased 5-year risk in patients treated with IA-CS compared with patients treated with IA-HA.[136,138] Another questionnaire-based study identified a possible increase in risk for TKA in professional soccer players; results for this study were limited to survey respondents, and information gathered from professional athletes is not directly translatable to the general arthritic patient.[136,139] Despite these concerns, a trial of 140 patients with OAK injected with IA triamcinolone or placebo every 3 months found that cartilage thickness loss was not statistically different between groups ($p=0.14$) among study completers.[140] The reported worst-case scenario of cartilage loss with IA triamcinolone (~0.055 mm/year over 2 years)[140] is unlikely to be clinically meaningful, particularly if the steroid provides symptomatic relief.

A significant challenge of IA-CS, which contributes to its short-term clinical impact, is that small-molecule drugs such as triamcinolone acetonide (TA) are not retained in the joint space, leading to rapid egress from the joint into plasma circulation and waning analgesic effects.[141] Formulation of these drugs with compounds that allow longer

joint residence should enable longer treatment periods without increased toxicity.[142] An extended-release formulation of TA (TA-ER) has been developed that embeds TA within poly(lactic-co-glycolic acid) microspheres.[141] These microspheres reside within the synovium of the joint and slowly degrade to release bioactive TA.[143] The microspheres, which degrade to carbon dioxide and water, reside in the joint for at least 3 months—this corresponds with clinically relevant detectable levels of TA within the joint at 3 months in contrast to standard TA, which is gone from the joint by 6 weeks.[143,144] The low IA concentration leads to a low diffusion gradient and an 18 times lower peak plasma concentration of TA.[144] This lower plasma concentration has demonstrated no adrenal suppression and minimal impact on blood glucose in diabetic patients.[144–147] Initial phase II studies demonstrated significant pain reduction with TA-ER relative to saline placebo.[141,148] A subsequent three-arm, phase III study comparing placebo, crystalline-suspension formulation of TA (TA-CS), and TA-ER demonstrated an approximately 50% reduction in pain from baseline with TA-ER at 12 weeks (average daily pain (ADP) intensity scores from baseline to week 12 of −3.12 compared with −2.86 with TA-CS ($p = 0.2964$) and −2.14 with placebo ($p < 0.0001$)), with a statistically and clinically meaningful reduction in pain compared with placebo (least squares mean (LSM) difference −0.37; $p < 0.0001$) and TA-CS (LSM difference −0.17; $p = 0.0475$) at 12 weeks, and rescue medication use was also significantly reduced with TA-ER versus placebo (LSM difference −0.50; $p = 0.0006$).[149] Subsequent post hoc analysis of these same data also demonstrated statistically significant improvement using TA-ER versus TA-CS in ADP intensity scores from weeks 4 to 21 ($p < 0.05$) and WOMAC-A scores at weeks 4, 8, 12, and 24 ($p < 0.05$) in patients with unilateral OAK and those who at baseline had consistent concordant pain reporting utilizing both ADP and WOMAC-A.[150,151] Furthermore, in a phase IIIb real-world study, 92% of participants opted for a repeat injection based on efficacy of the first injection.[152] The clinical response of the second injection was comparable in duration and magnitude to the first injection, with a median time for redosing of 16.6 weeks.[152] At 52 weeks, there were no radiographic signals to suggest progression of disease with no change in joint space narrowing, subchondral bone changes, insufficiency fracture, and osteonecrosis.[152] Other than a slight increase in arthralgia, the second dose of TA-ER did not increase incidence of AEs, and the increase in arthralgia was attributed to disease pathology or progression of OA.[152] Extended-release intraarticular corticosteroids (IA-CS) are included in the AAOS guidelines with a moderate recommendation to improve patient outcomes over immediate-release corticosteroids.[1]

Other liposomal or extended-release formulations of corticosteroids have been investigated for OAK. In a preliminary phase I study, extended-release fluticasone propionate (FP-ER) was well tolerated with a trend toward improved pain relative to placebo between 8 and 12 weeks, although significance was not reached.[153] In addition, TLC599, a liposome-delivered extended-release formulation of dexamethasone sodium phosphate, was evaluated in a phase IIa study in 75 patients with OAK.[154] One 12-mg dose significantly improved patient pain compared with placebo ($p = 0.0027$) and showed sustained pain control through week 24.[154] A phase III trial of TLC599 has been completed, but results have not yet been released [ClinicalTrials.gov identifier: NCT04123561]. In addition, nano products—such as micelles, exosomes, and cell-based nanotherapies—for targeted and sustained delivery of therapies are under investigation.[155] Emerging treatments also include potential disease-modifying therapies that would prevent further joint destruction and improve function (e.g., IL-1 receptor antagonist IA injection, gene therapy such as PCRX201, cell-based therapies including ELIXCYTE and TissueGene-C, and inhibitors of Wnt signaling pathway (lorecivivint)).[142,156–159]

PRP products concentrate platelets, white blood cells, and platelet-derived growth factors from a patient's centrifuged blood.[160] IA-PRP receives a limited recommendation in the AAOS guidelines[1] but is not recommended in the ACR guidelines.[101] In a meta-analysis of randomized clinical trials of IA-PRP compared with IA-HA, ozone, and IA-CS, significant differences for IA-PRP over the control group were demonstrated in total WOMAC scores and WOMAC physical function subscores at 3, 6, and 12 months.[161] Similarly, significant improvements in total WOMAC scores and International Knee Documentation Committee Subjective Knee Evaluation Form scores at 24 weeks were noted in a systematic review and analyses of four randomized clinical trials and two prospective cohort studies comparing IA-PRP with IA-HA or placebo.[162] Significant improvement in radiographic parameters, including patellofemoral cartilage volume and synovitis,

was observed 8 months after IA-PRP treatment compared with placebo ($p = 0.001$ and $p = 0.026$, respectively) in a 2020 randomized clinical trial.[163] Hypertension and proteinuria have been noted by AAOS as treatment-related AEs for IA-PRP,[1] but a meta-analysis found that all AEs—including pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia—were neither specific nor severe and resolved within days.[161] Although the European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) consensus group found enough evidence to support the use of PRP in OAK,[164] AAOS guidelines note that additional evidence over a 2-to-5-year period is needed to determine whether IA-PRP is cartilage sparing compared with IA-CS.[1] Given the heterogeneity of preparation and variable concentrations of blood products (e.g., platelets, leukocytes), investigators have also called for increased consistency in reporting PRP preparation steps and composition of the PRP delivered in clinical studies,[165] as available data lack sufficient detail to interpret results or enable trial replication.[166] Furthermore, current studies lack knee function or structural change data, limiting analysis of long-term efficacy.[167]

Other formulations of human plasma are under investigation for localized pain management. A combination of human plasma containing clonidine and HA, JTA-004, was designed for injectable pain control.[168] Although improvements were seen in the WOMAC pain subscale, physical function subscale, and total scores at all time points, the initial dosing study for JTA-004 did not show a significant difference from a reference treatment.[168]

Denervation therapies

Cryoneurolysis is a form of thermal neurolysis in which a cryoprobe cooled from −20°C to −100°C (−88°C with nitrous oxide as a coolant) is used to freeze peripheral sensory nerves at or near the source of pain.[169,170] The mechanism of action is to locally freeze the nerve, which results in Wallerian degeneration of the axon and myelin distal to the injury, but preservation of the nerve sheath. Over time, the nerve regenerates at 1–2 mm per day along the intact nerve sheath to its target innervation.[169,171] In a study including 180 patients with OAK, the application of cryoneurolysis to the infrapatellar branch of the saphenous nerve in patients with OA-related knee pain was well tolerated, with most commonly reported AEs (bruising, numbness, redness, tenderness upon palpation, and swelling) resolving within 30 days.[172] Cryoneurolysis significantly decreased knee pain (visual analog scale score) compared with sham treatment through 150 days (least-squares mean difference, −14.6; $p = 0.0010$).[172] A parallel-group randomized controlled trial currently recruiting in KOA [ClinicalTrials.gov identifier: NCT0377 4121] will allocate participants 1:1 to cryoneurolysis or sham treatment in combination with exercise and education[173].

Another form of thermal denervation is radiofrequency ablation (RFA).[174,175] In contrast to cryoneurolysis, cooled RFA delivers radiofrequency energy to degrade nerve structures through ionic heating at a high thermal temperature of 60°C to disrupt or destroy neurons.[176,177] The temperature is cooled locally during treatment, but high temperatures still may cause injury to surrounding tissues or permanent nerve injury.[176,178] In a randomized study of 38 patients with severe OAK pain lasting over 3 months, RFA ($n = 19$) significantly reduced visual analog scale (VAS) pain scores from baseline after 1 week compared with a sham-treated control group ($n = 19$).[179] Among patients treated with RFA, 59% achieved 50% pain reduction after 12 weeks, with no patients in the control group showing a similar reduction. In a direct comparison between RFA ($n = 37$) and IA-delivered analgesics (morphine and betamethasone; $n = 36$), patients treated with RFA saw significant reductions in VAS-pain, WOMAC total scores, and WOMAC-physical function after 1 month and VAS-pain and WOMAC stiffness after 3 months compared with those treated with IA.[180] Similar results were observed in comparisons of RFA with oral analgesics.[181] Patients treated with RFA showed sustained pain control, with a 67% improvement in pain from baseline at 3 months post-RFA and a 95% improvement at 6 months post-RFA,[182] and improvements in physical function and general health perceptions were seen post-RFA treatment.[161] Although AAOS guidelines suggest that denervation therapy may reduce pain and improve function, the number of studies is too limited for a full recommendation.[1] Data on long-term outcomes are limited for denervation therapies, and there is additional research, which is warranted regarding the potential complications of treating a neuropathic joint.

Framework to guide clinical decision-making

Although guidelines have been established for OAK treatment, real-world treatment decisions vary greatly based on patient phenotype and may

differ from guideline recommendations.[15] Although guidelines outline general recommendations for clinical management of OA, they are based on evidence from clinical trials and meta-analyses, which may not reflect patient outcomes in clinical practice.[183] In addition, clinical trials rarely include stacked therapy of multiple modalities, which is frequently utilized in clinical practice. For example, clinical trials have a limited duration of patient follow-up, whereas an HCP may see patients for a decade or more and thus develop a different perspective on safety and effectiveness, particularly for therapies continued over many years.[183] Likewise, efficacy thresholds set in clinical trials and incorporated into meta-analyses may not adequately reflect the chronicity of OA.[183] One study compared treatment effect sizes and thresholds of statistical significance and clinical importance to illustrate that 19 interventions, including commonplace treatments such as acetaminophen and topical NSAIDs, did not meet the standards of clinical importance.[117] Continuous ultrasound, lateral wedge insole, pulsed ultrasound, transcutaneous electrical nerve stimulation, and valgus bracing demonstrated possible clinical importance in this analysis.[117] To address the clinical complexity in the treatment of real-world OA patient populations, step-wise treatment algorithms have been utilized alongside published guidelines, as well as algorithms that monitor for suboptimal therapy and increased morbidity from AEs.[184]

With the development of technologies such as microspheres for targeted steroid release, denervation therapies, and gene therapy, it is appropriate to tailor treatment options to specific patients at specific times in their OA journey. To this end, the authors propose the following principles for consideration for treatment selection. Nonpharmacologic therapies, including bracing, therapy, and exercise, should be utilized throughout a patient's treatment plan. Depending on the level of pain at presentation, topical NSAIDs can be an initial choice for pain management to limit systemic exposure, followed by over-the-counter analgesics, such as oral NSAIDs and acetaminophen, if topical treatments are ineffective. These first-line anti-inflammatory adjuncts are important, but managing a 45-year-old male manual labor worker with severe bone-on-bone arthritis with ibuprofen for 10 years would not be an ideal treatment choice and could lead to a multitude of deleterious health consequences. In addition, a 50-year-old female account executive who wants to ski and ride horseback would likely be more amenable to targeted and local anti-inflammatory technologies versus oral medication that has significant systemic deleterious effects. For chronic treatment in patients with risk factors or comorbidities for AEs associated with systemic, pharmacologic agents, repeat treatment with TA-ER, cryoneurolysis, or emerging injectables may provide a local treatment option with minimal risk for systemic AEs.

As described previously, OAK is a chronic condition with significant negative effects on life and work, in addition to potential comorbid contributions from various treatment options. Newer technologies appear to be safer, more effective, and possibly more economically feasible in younger patients who are not candidates for joint arthroplasty. Though evidence for chondrotoxicity from IA injections is sparse and poor, in younger patients, consideration might be given to HA or biologic injections given their generally anecdotal improved safety profile over IA steroids; meanwhile, patients with diabetes may be good candidates for targeted IA technologies that are long-acting and slowly elute steroid to modulate IA inflammation with minimal systemic absorption. Emerging technologies may be even more beneficial in patients of advanced age who are no longer candidates for surgical replacement. Denervation therapy in conjunction with long-acting IA steroids has not only been shown to be effective and safe, but they have also demonstrated improved mobility and fall reduction in the authors' experience (e-mail, M.L., 25 March 2023). As patients approach the need for TKA, injections should be avoided within 3 months of planned surgery, and cryoneurolysis becomes an attractive extra-articular option without increasing perioperative risk or morbidity. Currently, there are no guidelines regarding which therapeutic interventions or treatment sequences are recommended for any given phenotype. Future expert consensus and additional studies will hopefully delineate this important clinical information; however, the current choice and sequence of therapeutic agents are empiric.

Areas for future research

Multiple therapies are under clinical development for OAK, with some highlighted in Table 2. Although research has been conducted into real-world treatment patterns in OAK, additional information on how extant and emerging therapies are used in clinical settings is needed. Expanded randomized clinical trials that distinguish between

Table 2. Select therapies in development for OAK[a].

Therapy	Current clinical development stage[b]	Mechanism of action	Route of administration
Ion channel targeting			
PF05089771[127]	Preclinical	Selective intracellular blockade of $Na_v1.7$ sodium channels	IA
Capsaicin[128]	Phase IIb TRIUMPH study (ClinicalTrials.gov identifier: NCT02558439)	Transient receptor potential cation channel subfamily V member 1 agonist	IA
OLP-1002[185]	Phase II [ClinicalTrials.gov identifier: NCT05216341]	PNA-based drug; inhibits expression of $Na_v1.7$ sodium channels	SC
RTX[186]	Phase II [ClinicalTrials.gov identifier: NCT04885972]	TRPV1 calcium channel agonist	IA
Cartilage formation promoter			
Strontium ranelate[129]	Phase III SEKOIA study (ISRCTN1323372)	Stimulates cartilage matrix formation and inhibits subchondral bone resorption	PO
Anti-inflammatories			
Denosumab[130]	Phase II (EUDRACT CT 2015-003223-53)	Receptor activator of NF-κB ligand inhibitor	NR
ER fluticasone propionate[153]	Phase I (ClinicalTrials.gov identifier: NCT02609126)	Corticosteroid; anti-inflammatory	IA
TLC599 (ER dexamethasone sodium phosphate)[154]	Phase IIa (ClinicalTrials.gov identifier: NCT03005873) and Phase III [ClinicalTrials.gov identifier: NCT04123561]	Glucocorticoid; anti-inflammatory	IA
JTA-004[168]	Phase II/III (ClinicalTrials.gov identifier: NCT02740231)	Antihypertensive and hyaluronic acid; anti-inflammatory and analgesic	IA
Gene therapies			
PCRX201[156]	Phase I (ClinicalTrials.gov identifier: NCT04119687)	Gene therapy; IL-1R antagonist triggered by an NF-κB promoter	IA
ICM-203[187]	Phase I/II [ClinicalTrials.gov identifiers: NCT05454566, NCT04875754]	Gene therapy; enhance NKx3.2 expression	IA
XT-150[188]	Phase II [ClinicalTrials.gov identifier: NCT04124042]	Gene therapy; induce IL-10 expression	IA
Cell-based therapies			
ELIXCYTE[157]	Phase I/II (ClinicalTrials.gov identifier: NCT02784964)	MSCs; immunomodulator, also targets chondrocytes and cartilage	IA
TissueGene-C[159]	Phase III (ClinicalTrials.gov identifier: NCT02072070)	Cell-based expression of TGF-β; cartilage restoration	IA
XSTEM	Phase I/II [ClinicalTrials.gov identifier: NCT05344157]	Allogenic MSCs selected for integrin α10β1	IA
SMUP-IA-01[189]	Phase II [ClinicalTrials.gov identifier: NCT05182034]	UBC-derived MSCs producing anti-inflammatory PTX-3	IA
Amnion-based therapy			
Amniotic suspension allograft[190]	Phase III [ClinicalTrials.gov identifier: NCT04636229]	Amniotic membrane particulate and amniotic fluid cells	IA

[a]This table includes representative therapies from each category and is not intended to be an exhaustive list.
[b]As of January 2024.
ER, extended release; IA, intraarticular; IL-1R, interleukin-1 receptor; IL-10, interleukin 10; MSC, mesenchymal stem cell; NF-κB, nuclear factor kappa B; NKx3.2, NK3 homeobox 2; NR, not reported; OAK, knee OA; PNA, peptide nucleic acid; PO, by mouth; PTX-3, pentraxin 3; RTX, Resiniferatoxin; TGF-β, tumor growth factor-beta; SC, subcutaneous; TRPV1, transient receptor potential cation channel subfamily V member 1; UBC, umbilical cord; Wnt, Wingless-related integration site.

patient phenotypes and incorporate more long-term data, along with additional information from registries and real-world studies, will give a more thorough picture of how novel therapies impact the heterogeneous population of patients with OA. In addition, standardized time points and measurement scales would allow for more direct comparisons between current and novel therapies. Further health economics and outcomes research is also needed to better understand the financial impact of OA on the community and individuals. One real-world registry for OA is the Innovations in Genicular Outcomes Registry, which is prospectively collecting real-world data from patients undergoing treatments for OAK [ClinicalTrials.gov identifier: NCT05495334]. Clinical effectiveness, safety, health-related quality of life, and economic burden are being assessed through patient-reported outcome measures and clinical, reimbursement, and healthcare resource utilization data [ClinicalTrials.gov identifier: NCT05495334].

Conclusion

OAK is a prevalent condition with variable disease presentation and trajectory that leads to a large humanistic and economic burden. While disease modification therapies have not yet been identified, several nonsurgical options have been characterized. Nevertheless, there is an unmet need for therapies that can meaningfully improve pain and functional outcomes. Recently emerging treatment options present opportunities to manage pain and increase mobility more effectively. While treatment guidelines provide a scaffold for determining the appropriate treatment path, each patient presents with a unique set of needs which, along with emerging treatment options, should be incorporated into an individualized approach to OAK management.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Michael Langworthy: Conceptualization; Writing – review & editing.

Vinod Dasa: Conceptualization; Writing – review & editing.

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