Mobility as a Framework for Managing Osteoarthritis in a Holistic Chronic Disease Model

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Abstract

Currently, over 30 million Americans have osteoarthritis (OA), and the prevalence is increasing. Coordinated effort on the part of physicians, allied health professionals, pharmacists, payors, employers, patient advocacy groups, and community organizations is needed to address this growing public health crisis. We propose that OA prevention and treatment follow a chronic disease model. We propose specific prescriptions for change that emphasize patient education and self-management, prevention, early intervention, and evidence-based best practices. Preventive strategies in at-risk individuals and conservative care, introduced early in the course of the disease, are key components of this model. Long term drug safety is a major concern; opioids are not recommended as OA therapy, and intra-articular injections of hyaluron should be considered for treatment of knee OA. Patients should receive coordinated care by primary care providers, specialists, physical therapists, weight loss specialists, nutritionists, and pharmacists. Metrics used by researchers, clinicians, and payors should emphasize functional improvement rather than radiologic findings. Benefit plans need to be modified to encourage evidence-based best practices, including both nonpharmacologic and pharmacologic approaches.

Introduction

Approximately 30 million Americans have osteoarthritis (OA), a painful joint disease that is a prominent cause of disability, diminished quality of life, and workplace absenteeism both in the US and worldwide. [CDCb p1A, Cross 2014 p1327AB] Arthritis and other rheumatic

diseases are the leading cause of disability among US adults, and osteoarthritis is the most common of these conditions. [CDCa p1A,2A] OA can affect any joint in the body; the knee is the largest joint most commonly affected, followed by the hip. [Cross 2014 p1326A,1327A] Disease prevalence increases markedly with age, and most individuals develop OA after the age of 55. [Losina 2013 p707A, Harris 2015 2A] Women are more likely to develop knee OA than men. And obesity is a major factor in the development of knee OA. [Losina 2013 p707A, Harris 2015 3A] The prevalence of knee OA at different ages, for US men and women, with or without obesity, is presented in Figure 1. [Losina 2013 p707A] As the population ages, and if rates of obesity continue to increase, the prevalence of OA is predicted to rise, as well.

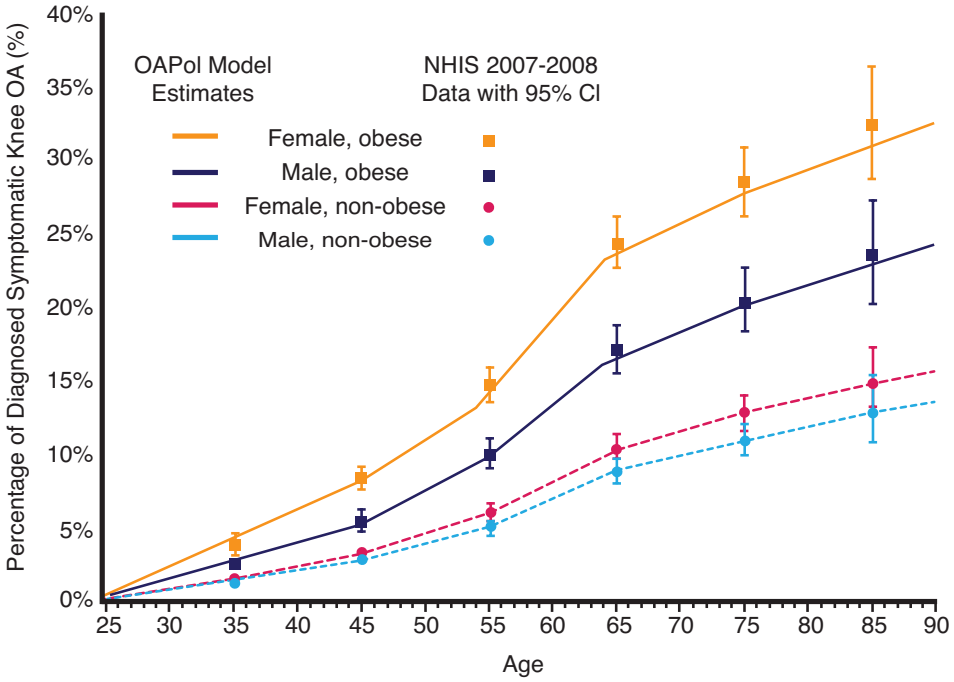

Figure 1. Estimated prevalence of diagnosed symptomatic knee osteoarthritis (OA) by age in the US (internal validation of Osteoarthritis Policy [OAPol] Model estimates using 2007-2008 national Health Interview Survey NHIS). Broken curves show the prevalence among non-obese persons and solid curves show the prevalence among obese persons. Female prevalence is in black: Male prevalence is in gray. Prevalence from the NHIS is depicted by squares for obese persons and diamonds for non-obese persons and is accompanied by 95% confidence intervals.

OA results from a loss of cartilage, the tissue that protects the bone ends within the joints. Instead of having smooth cartilage where the bones connect, the rough edges of bone rub against

each other, causing pain (Figure 2). Loose fragments of cartilage or other tissue may cause additional pain, and limit the joint's range of motion. [AAOS 2007 p1A,2A] Symptoms of OA include joint pain, swelling, stiffness, and limited range of motion. [White 2012 pS20A; Langworthy 2010 p134BC; Wittenhauer 2013 p5A] Although inflammation is not a cause of OA, the joint may become swollen in response to the tissue damage. Synovitis, or inflammation of the fluid-filled space known as the synovium, is a major cause of OA pain. [Langworthy 2010 p134A,B] Currently, no treatment is available to reverse the loss of cartilage; the goal of nonsurgical treatment is to reduce pain and prevent or delay further damage.

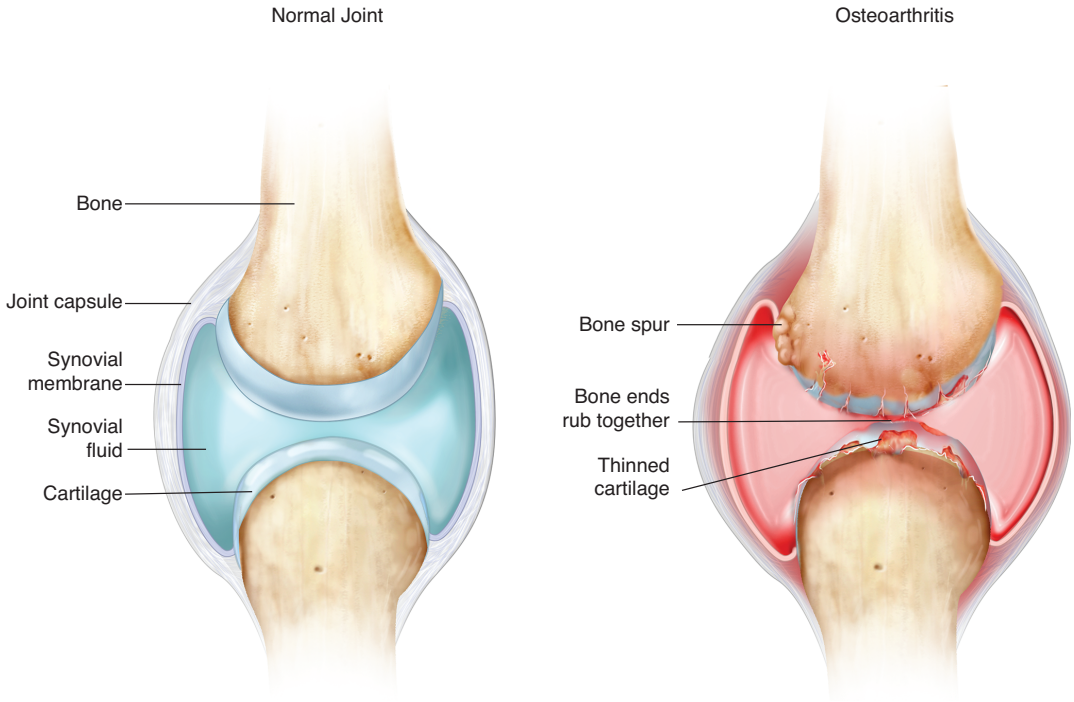

Figure 2. Comparison of normal and osteoarthritic joints.

The cause of OA is unknown. Individuals with a family history of OA are at greater risk, and many potential genetic markers for OA have been identified, but the genetic regulation of OA is poorly understood. [Sawitzke p72A] Advanced age, a history of joint injury, and high body mass are all strong predictors for the development of OA, suggesting that OA is at least in

part the result of excessive wear and tear on the joints. [Sawitzke p70A,72A] Some researchers view the mechanism as an imbalance between the rates of joint destruction and repair. [Kielly 2017 p156A]

Quality of Life and Economic Burden

Osteoarthritis causes both pain and functional disability. Approximately 43% of patients with arthritis reported arthritis-related limitations of daily living, and 25% of arthritis patients who work reported work-related limitations. [CDCa p2A] Among the elderly, knee and hip OA are the greatest independent risk factors for walking difficulty, and the risk increases if more than one joint is affected. [King 2017 p11A,12A] Patients with OA have low short form 36 (SF-36) scores in the areas of pain, functional capacity, functional limitations, social and emotional aspects, vitality, and general health. [Kawano 2015 p309A]

In addition to the impact on patient's quality of life, OA is associated with a large economic burden, with costs borne by the patient, family, payor, and employer. The estimated lifetime cost of OA-related medical care for US patients with knee OA is $12,400. That is expected to rise as knee replacement surgery becomes more routine. [Losina 2015 p204A,p209A] Recent studies indicate that total knee arthroplasty (TKA) is over-utilized, with 30% of TKAs occurring in patients considered inappropriate for the surgery, and these patients show relatively little functional benefit following surgery than appropriate patients. [Riddle 2015 p2A,4A,5A]

Direct OA-related medical costs are only a small part of the economic burden; indirect medical costs and lost productivity have a much larger impact. As one would expect in an elderly population, patients with OA generally have multiple comorbidities, with resulting high medical

expenditures. Yet, certain comorbidities occur even more frequently in patients with OA than in an age-, gender-, and geographically matched cohort (Figure 3). [Gore 2011 p498A,501A] Some of these comorbidities are likely to be directly related to OA. For example, Figure 3 shows that the odds ratios for other musculoskeletal disorders are particularly high, suggesting the possibility of a shared mechanism or a causal relationship. Depression, anxiety, and sleep disturbance are all commonly associated with chronic pain conditions. [Gore 2011 p500B] Limited mobility may put OA patients at greater cardiovascular risk. Each patient with OA spends, on average $8,000 more on annual medical costs than matched controls; [Gore 2011 p503A] this figure represents the direct and indirect medical costs of OA.

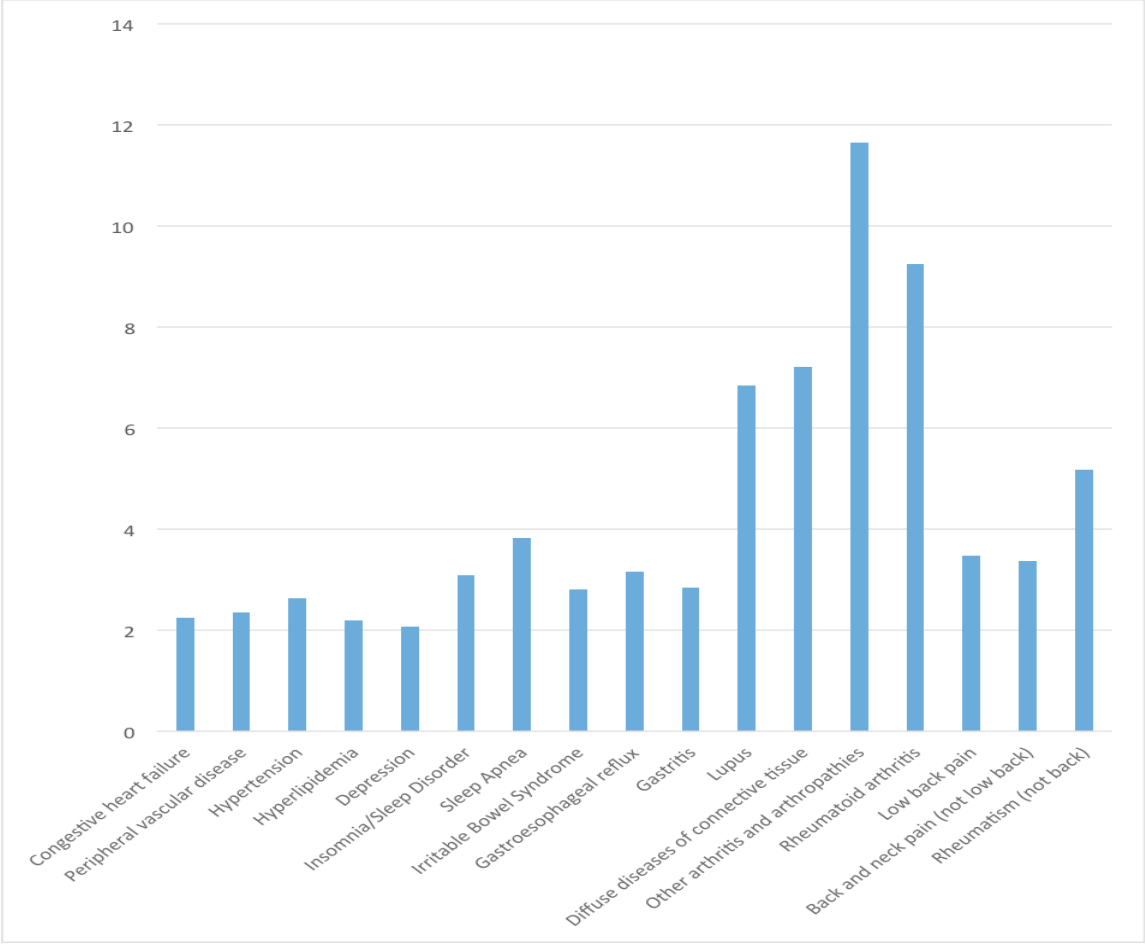

Figure 3. Comorbidities more than twice as likely for patients with osteoarthritis than age, gender, and geographically matched controls. [Gore 2011 498A,501A]

Lost productivity is the major source of the economic burden of OA. It can take the form of absenteeism, in which the worker has missed time from work, or presenteeism, in which the worker has reduced productivity while at work. If job reassignment is required, there are added training costs for both the reassigned and the replacement worker. A cross-sectional analysis of data from a large-scale, internet–based representative survey found that individuals in the workforce with moderate and severe OA had significantly more lost hours of productivity than matched controls (Figure 4). [DiBonaventura 2012 p2AB,5A,7A] Those with moderate to severe OA had significantly more absenteeism, presenteeism, and work and activity impairment. Overall, patients with OA spent 30% less time in productive work. Presenteeism accounted for 3-4 times as many lost hours as absenteeism, even among those with no OA. [DiBonaventura 2012 p5A] If a monetary cost is estimated for those lost hours, it accounts for the greatest share of the economic cost of OA: $10,968 and $15,596 per patient with moderate or severe OA, respectively (Figure 5). [DiBonaventura 2012 p9A]

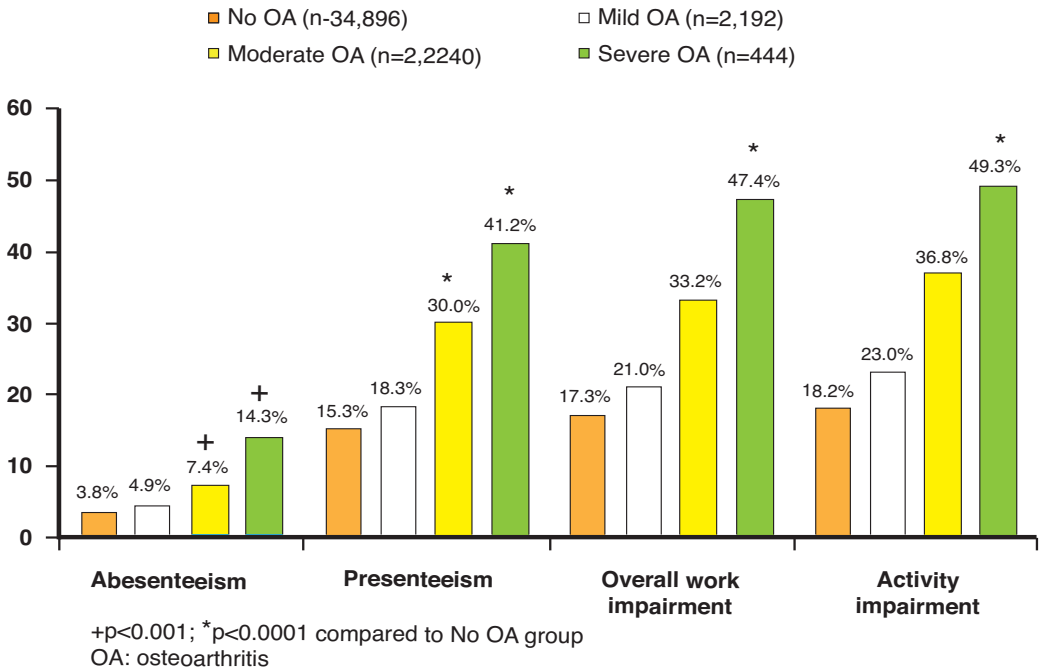

Figure 4. Lost time at work increases with osteoarthritis severity. [DiBonaventure 2012 p7A]

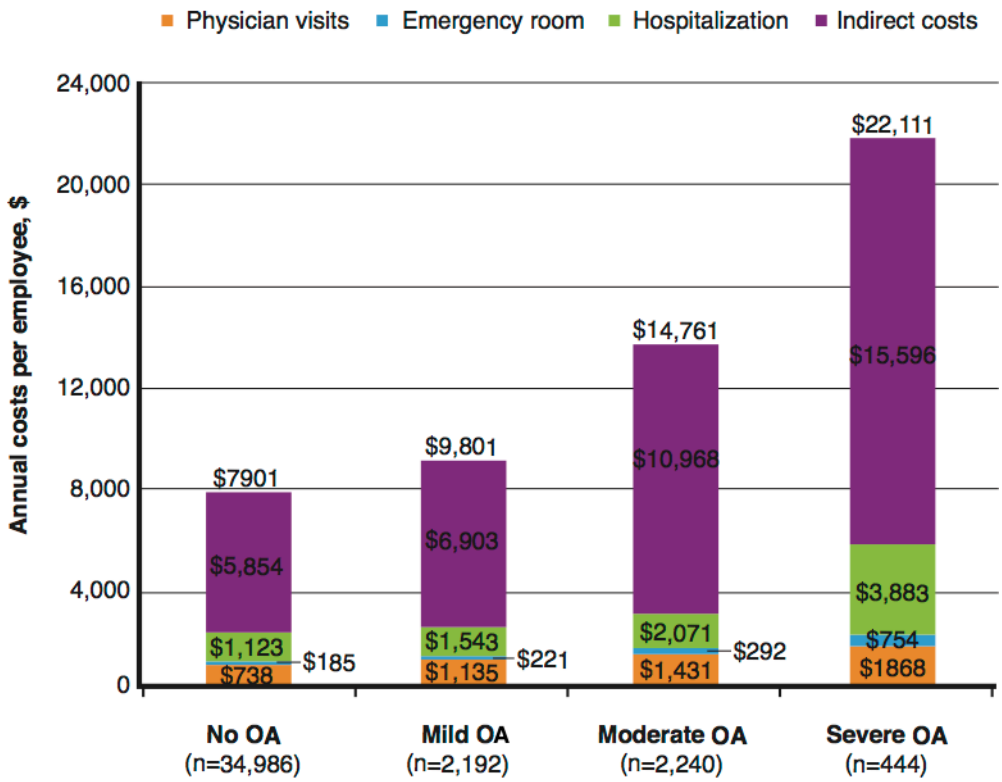

Figure 5. Annual unadjusted costs per individual among workers with osteoarthritis (OA) by self-rated OA severity and workers without OA [DiBonaventura 2012 p9A]

Public Health Imperative and the Epic Summit

The prevalence of OA is predicted to rise over the next decades, making it a public health priority. [White 2012 pS20B,S22A] Several public health initiatives of the past decade are working to address this need. In 2009, the Arthritis Foundation and the US Centers for Disease Control (CDC), along with 75 other partner organizations, adopted the National Public Health Agenda for Osteoarthritis, with specific recommendations for ways that healthcare providers, patient advocacy groups, government agencies, business and industry, and community organizations could improve awareness and management of OA. A diverse set of stakeholders must become involved in order to create systemic change. Certain steps have already been taken, such as a large-scale public education campaign targeted to adults ≥55 years. The Arthritis Foundation and CDC advocate for change at a variety of levels, promoting projects such as

employee wellness programs, training of park and fitness professionals, and increased research spending. [White 2012 S24B,S25A]

To further the goals of current public health measures, representatives from medical practice, hospital administration, industry, insurance, employer benefits, physical therapy, and pharmacy met in Philadelphia in June, 2017, to discuss the current state of OA management, barriers to care, and effective strategies for improved outcomes. This was part of a series of Employer-Provider Interface Council (EPIC) Summits, and was entitled *"Evidence-Based Decision Making in the Treatment of Osteoarthritis and Impacts on Outcomes and Employer Metrics."* The EPIC Task Force on Osteoarthritis focuses on conservative treatment, promoting strategies that will reduce the pain and functional limitation of OA without surgery. This paper summarizes the EPIC Task Force on OA findings and prescriptions for change.

Chronic Disease Model

Improved outcomes in OA management rest, to a large extent, on a paradigm shift in the minds of clinicians, patients, payors, and other stakeholders, from viewing OA as a disease that can be "cured" with joint replacement to a chronic disease model. OA is a progressive, long-term disease. Although OA occurs primarily in the aged, the earliest signs can occur at a much younger age. [Losina 2013 p707A] Early symptoms may be dismissed by the patient or physician as just normal signs of aging. However, identifying early symptoms is critical to preventing or delaying disease from progressing to the point where surgery is required.

Over the past several decades, research suggests that structural changes in how healthcare is delivered to patients with chronic illness leads to improved outcomes and lower healthcare costs. This chronic care model (CCM) includes features such as promoting patient self-management,

mobilization of community resources, decision support and access to clinical information for healthcare providers, use of evidence-based protocols, and reorganization of healthcare delivery. [Wagner 1997 p706A,707A,708AB,709A; Davey 2015 p3A] This model has been applied with success to a variety of chronic illnesses, including diabetes, cardiovascular disease, depression, respiratory disease, and renal disease. [Davy 2015 p4A] A systematic review of the literature found that most studies incorporating at least one aspect of the CCM showed improved clinical outcomes. However, these studies generally did not include all aspects of the CCM; support of patient self-management was the most frequently incorporated element. [Davy 2015 p4B, 7A] Overall, the demonstrated clinical benefits of the CCM in other disease states lead us to advocate for a CCM in the management of osteoarthritis, with particular emphasis on patient education and self-management, prevention, early intervention, and promoting evidence-based best practices.

Disease Management

Prevention

Ideally, widespread preventive methods could stop the development of OA before it even begins. Patient and community education efforts should focus on those at greatest risk for developing OA, and they should focus on risk factors that can be modified with lifestyle changes, such as diet and exercise. Individuals who are obese or overweight are approximately 3 times more likely to develop OA than those of normal weight, indicating that weight is an important modifiable risk factor in preventing the development of OA. [Neogi 2011 p2A] Occupations involving kneeling, squatting, and heavy lifting are associated with increased risk for developing OA; [Klussman 2010 p6A,7A,9A] Avoiding injury, through routine safe,

strengthening exercise, is another key preventive step; individuals who develop a meniscal tear are 30 times more likely to develop knee OA. [Neogi 2011 p2B]

Healthcare providers, employers, and payors can all take steps to support lifestyle changes that reduce the risk of developing OA. Physicians and other healthcare professionals and community health organizations can provide education to patients at risk, regarding the importance of nutrition, weight loss, and exercises that strengthen, rather than injure, joints. Employers can provide wellness programs that include injury prevention, weight management, and counseling for healthy eating. Wellness programs should promote an active lifestyle that includes strength and flexibility exercises to help support the joints and their movements. Employers can also take steps to reduce workplace injuries by cross-training in various job tasks and providing ongoing ergonomics training, focusing on proper posture and using good body mechanics. Insurers can provide discounts and reimbursements for health activities, including health club memberships, group fitness classes such as yoga, or tai chi, and nutritional counseling. These activities can reduce the risk of developing OA and a wide variety of other chronic illness.

Diagnosis

A key tenet of the chronic care model is that early detection of progressive diseases leads to early intervention, which can prevent the development of more advanced, debilitating disease. This improves patients' lives and reduces the overall cost of treatment. There is currently a need for improved screening for OA, so that the disease can be detected in the early stages. Most patients with persistent knee pain do not seek medical care, [Marra 2007 p1239AB] possibly attributing the pain to normal aging. This issue can be addressed with routine screening for OA in primary care practice. However, the screening does not need to be limited to a medical office.

For example, a series of studies in Canadian pharmacies showed the benefits of pharmacist-initiated screening for OA. Patients who reported undiagnosed knee pain completed a screening questionnaire. Those with likely OA were assigned to receive either a pamphlet on OA self-management or a more intense intervention. The intervention consisted of individual counseling that incorporated education, medication review, referral to a physiotherapist, and notifying the primary care physician. [Marra 2012 p1838C,1839A] Three quarters of those who entered the study were considered to have undiagnosed OA. [Marra 2012 p1839B] Furthermore, those receiving pharmacist-counseling and physiotherapy showed significant gains in function, pain, and quality of life scores than the control group. [Marra 2012 p1842AB]

Osteoarthritis is diagnosed based on a combination of history, physical exam, laboratory findings, and x-ray. Patients usually report sore or stiff joints, either no morning stiffness or stiffness that lasts for less than 30 minutes, and pain after activity. [Kielley 2017 p157A] The physical exam is the key component for a diagnosis of OA. Symptoms that should prompt the clinician to consider OA include joint swelling, limited range of movement, pain during normal movement, and tenderness when the joints are pressed. Also, osteoarthritic joints may make a grating sound during movement, known as crepitation. [Wittenauer 2013 p12A] A plain radiograph that shows joint space narrowing can confirm the diagnosis and can be used to eliminate other possible diagnoses. However, radiographs are often misused by clinicians to indicate disease severity; in fact, the radiographic findings do not correlate with the amount of pain or functional limitations that the patient experiences. [Bedson 2008 p2A,8A] Clinicians frequently order knee MRIs, although MRIs are expensive and have little to no value in diagnosing OA, [Menashe 2012 p6AB] and MRI abnormalities frequently occur in asymptomatic individuals. [LaPrade 1994; Beattie 2005]

After the initial diagnosis of OA is made, it is important to have a functional assessment of the joint. Biomechanical evaluations, by specially trained physical therapists or other professionals, help identify which patients will benefit most from certain exercises. Specifically, physical therapists can determine whether the joint has a "directional preference," which means that repeated movement in a specific direction leads to improved function in certain tasks of daily living. A recent study compared exercise intervention to usual care in patients with knee OA. The patients in the exercise group were assessed to determine whether they have a directional preference (either flexion or extension). Those with a preference received focused therapy in that direction, while those without directional preference received strength training and recommendations for aerobic exercise. Those diagnosed with directional preferences, who received customized therapy, had improved pain scores and function scores for up to 3 months, compared to those with no directional preference or to controls. [Rosedale 2014 p174A,175A-E,178A]

Non-pharmacological, non-surgical treatment

The first treatment step following diagnosis is education regarding the disease state, the chronic nature of the disease, and the important role of patient self-management. [AAOS 2013 p31A] Unless patients understand the progressive nature of OA, they are unlikely to adopt lifestyle changes that may slow that progression. Furthermore, educating patients may result in fewer TKAs performed in individuals who are not appropriate candidates for surgery.

Providing patient education is critical, but learning from the patient is necessary, as well. Patients bring their own values and healthcare expectations with them. For example, they may be willing to trade a measure of pain control and choose a medication with fewer side effects, or the opposite may be true. [Papandony p1015AB,1016A] Patients may avoid an appropriate exercise

regimen because cost, time constraints, or other barriers are too great. Alternative medicine, including acupuncture and dietary supplements, may be preferred because it offers a holistic, more natural approach to care. [Papandony p1012A,1015A,1016BC] Ideal patient education involves effective, two-way communication. The clinician needs to communicate the rationale for treatment and self-management, but also needs to tailor the treatment plan in response to patient input. The Patient Advocate Foundation recently published a roadmap for increasing patient involvement in healthcare, which provides numerous case studies illustrating how to achieve person-centered healthcare. "Designing a person-centered system is neither exclusively a clinical activity, nor a primary burden for the patient. The ultimate goal is to have patients and their providers co-create health care plans that meet clinical objectives while honoring individual values." [PAF 2017 p4A]

When tissue degradation is in its early state, lifestyle modifications play an important role in slowing disease progression. For overweight and obese patients, weight management is an important goal, yielding improved OA outcomes, as well as other health benefits. [AAOS 2013 p138AB] Recommended exercises include strengthening and low-impact aerobic exercise, such as walking, biking, aquatic exercise, weights, tai-chi, and yoga. [Gecht-Silver 2017 p2B,3AB] All physical activities and exercise programs should accommodate a patient's current fitness status, with a goal of gradually increasing intensity and variety over time.

Despite often requiring a physician referral for reimbursement, patients with limited motion or pain while exercising should consult a physical or occupational therapist, who may modify the exercise based on the patient's individual condition. [Gecht-Silver 2017 p2A] Ongoing physical therapy may also be recommended. Joint malalignment is strongly correlated with radiographic disease progression, providing further support for the benefit of training with a

physical therapist. [Bastick 2015 p2973A,2977A] The EPIC Task Force recommends consulting a physical or occupational therapist trained in conducting biomechanical evaluations. As discussed in the "Diagnosis" section above, identifying a joint directional preference leads to the design of individualized, highly effective therapy. [Rosedale 2014 p174A,178A] Unfortunately, Medicare and other payors frequently cap physical therapy reimbursement.

Other nonpharmacological interventions may include shoe insoles, patellar taping, a knee brace, walking aids, and heat or cold therapy. [Hochberg 2012 p469B,471C] These should only be used following a careful evaluation to determine the appropriate therapy for each individual patient.

Pharmacological treatment

Pharmacological treatment should occur together with nonpharmacological strategies, rather than replacing them. Because of the high rates of adverse events and variable efficacy among the many treatment options available, designing optimal therapy can be difficult to align for clinicians, patients, and payors alike. Treatment guidelines are created to assist clinicians in this task. However, current treatment guidelines for OA often conflict with one another on many key strategies. Rather than present a comprehensive description of all available treatment options, we will review the recommendations from professional societies, and discuss the issues of greatest controversy.

When recommending pharmacological therapy for the pain of OA, clinical guidelines suggest treatment options with the greatest safety profiles as first-line care. The recommendations for oral and topical analgesic agents for 3 different professional societies – the American College of Rheumatology (ACR), the American Academy of Orthopaedic Surgery

(AAOS), and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) vary among the 3 societies and are summarized in Table 1. . Acetaminophen (or paracetamol) is a first line treatment in the ACR and ESCEO guidelines, [Bruyere 2016 pS5A, Hochberg 2012 p470A,471A] due to its relatively strong safety profile. However, the AAOS makes no recommendation for or against the use of acetaminophen, due to the lack of placebo-controlled trials in OA. The AAOS systematic review identified only one placebo-controlled trial, which found no significant benefit for acetaminophen. [AAOS 2013 p343A] The EPIC Task Force recommends the use of acetaminophen, due to its positive safety profile when compared with other oral analgesics. However, long term use should be recommended with caution, and, although the maximum dosage by prescription is 4,000 mg/day, we agree with current recommendations to limit the dosage to 3,000 mg/day. [AAOS p343A]

All three guidelines recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for appropriate patients, while avoiding this class of drugs in patients with high risk for gastric bleeding, cardiovascular events, or renal impairment. [Bruyere pS6A,7CD, Hochberg p470B, AAOS 2013 p3A] Topical NSAIDs have comparable efficacy and fewer gastrointestinal adverse events than oral NSAIDs. [Bruyere 2016 pS6b] ESCEO guidelines recommend that a trial of topical NSAIDs be attempted in all patients prior to initiating oral NSAID [Bruyere 2016 pS5]; the ACR guidelines recommend topical NSAIDs, but not oral NSAIDs, for patients ≥75 years old. [Hochberg 2012 p470B] Clinicians can reduce the risk for gastric bleeding by prescribing a COX-2 selective inhibitor, and/or prescribing a proton pump inhibitor as co-therapy. [Bruyere 2016 pS6A; Hochberg 2013 470C] NSAIDs should be used intermittently or in limited cycles, rather than continuously, and at the lowest possible dose. [Bruyere 2016 p7A]

This rapidly evolving concern around use of such therapies in a sequence or step therapy is questioned today from an outcomes-based purchaser and payer perspective, as well.

The use of opioids is controversial with opioid abuse being a serious public health problem. In 2014, almost 2 million Americans abused or were dependent on prescription opioids, resulting in approximately 400,000 emergency care visits and 15,000 deaths. [CDCc 2017] The rate of deaths due to drug overdose has risen precipitously in the past several decades; there was an estimated 19% increase from 2015 to 2016, and preliminary data suggest an even greater increase in 2017 (Figure 6). [Katz 2017 p1B] Although opioid treatment may be efficacious in managing OA pain, a meta-analysis found no significant difference in clinical response to any of three opioid therapies (tramadol, hydromorphone, or oxycodone) compared to NSAIDs. [Smith 2016 p8A] Furthermore, although the efficacy of short term opioid use is well studied, the benefits and safety of long term use have not been established. [Dowell 2016 p2A] Because of the high risk of opioid abuse, the ESCEO guidelines state that most opioids should not be prescribed for treatment of osteoarthritis pain. [Bruyere 2016 pS8B] The guidelines recommend the short-term use of tramadol, a weak opioid active at the mu opioid receptor, as the last choice of pharmacological options. [Bruyere 2016 pS8B] The ACR guidelines recommends that opioid therapy not be used for patients with hand OA, and, for patients with knee or hip OA, it should be limited to patients who failed to respond to other pharmacological and nonpharmacological modalities and refused or are not candidates for arthroplasty. [Hochberg 2012 p469A,470E,471B] However, both the ACR and AAOS recommend tramadol therapy as strongly as NSAIDs. [Hochberg 2012 p469A,470A,471A; AAOS 2013 p3A] Because of the high risk of abuse, and lack of clinical benefit over other treatment options, The EPIC Task Force agrees with the ESCEO guidelines that opioids should not be used for the management of OA

pain. If opioids are prescribed, the clinician should follow CDC guidelines, prescribe in combination with nonpharmacologic and nonopioid therapies, and create a treatment plan, which includes a strategy for opioid discontinuation, that is shared with the entire healthcare team. [Dowell 2016 p16A,19B]

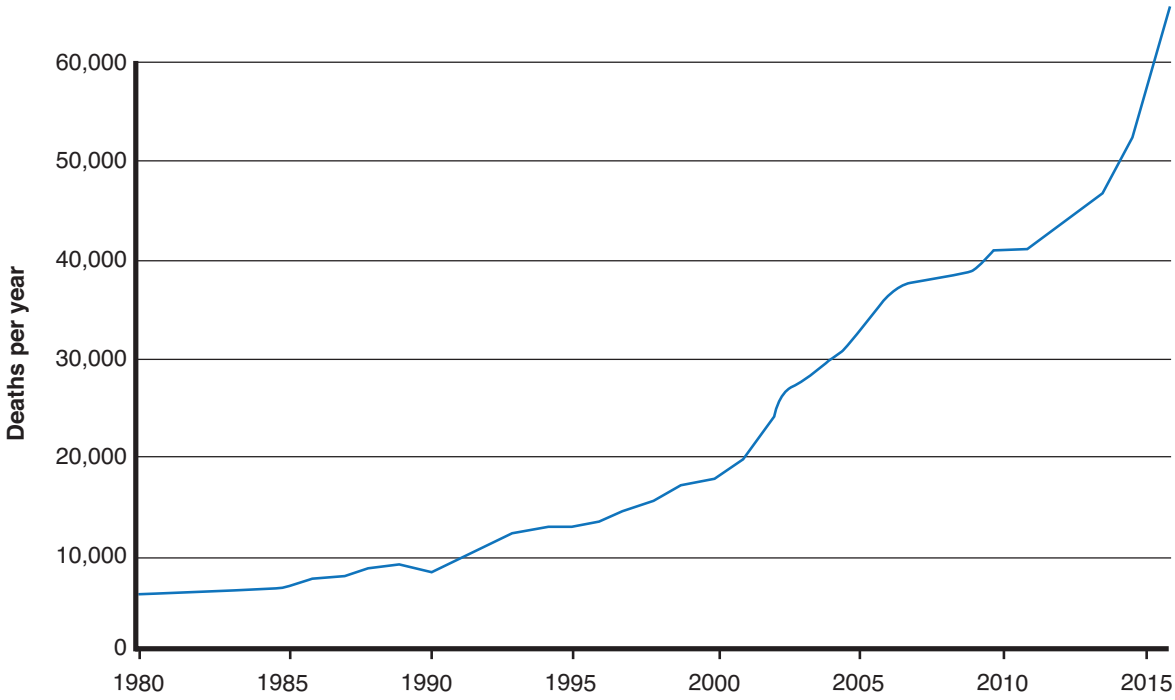

Figure 6. US drug deaths from prescription opioids 1980-2017 (projected). [Katz 2017]

The nutritional supplements chondroitin sulfate and glucosamine are widely used and have been extensively studied. Both are available in both over-the-counter and prescription formulations. Long term use of either agent is associated with joint space narrowing, suggesting a potential disease-modifying role, rather than providing symptomatic relief alone. [Bruyere pS5B,S6A] Yet, meta-analyses of clinical trials have shown little benefit for either agent, alone or in combination. [Hochberg p472A; AAOS p262ABC] Both the ACR and AAOS recommend against the use of chondroitin sulfate and glucosamine due to lack of efficacy. [Hochberg p469A,470A,471A; AAOS p260B] In contrast, the ESCEO recommends these supplements as

first-line agents in OA management, although its endorsement is limited to the patented crystalline formulation of glucosamine. [Bruyere p4A,5A] The ESCEO guidelines are the most recent of the three; however, the clinical trials they cite were mostly published prior to 2012, so this cannot account for the difference in treatment recommendations. Despite the endorsement of the ESCEO, The EPIC Task Force recommends against the use of the nutrient supplements glucosamine and chondroitin sulfate, or any supplements for which strong efficacy and safety data are not available.

In addition to oral and topical treatments, two drug therapies involving intra-articular injection are available for the treatment of knee OA: corticosteroids and hyaluronic acid (HA). Corticosteroids have strong anti-inflammatory properties. A Cochrane review of trials comparing intra-articular corticosteroids to placebo or no treatment found that patients receiving corticosteroids had a moderate improvement in pain scores and a small increase in function compared to the control group. This benefit was greatly reduced by 3 months, and there were no between group differences at 6 months. [Juni 2015 p2AB,3A,4A]

HA is a normal component of synovial fluid, and viscosupplementation with injectable HA reduces joint pain directly by binding to receptors on nerve endings. It also has anti-inflammatory effects. [Altman 2015b p4B,5A] HA is not a cure for OA; however, its mechanisms of action suggest that it may provide clinical benefit beyond symptomatic relief. It acts in multiple ways to block the progression of OA, and potentially reverses some of the pathology. Preclinical studies indicate that HA both reduces apoptosis and increases proliferation of cartilage cells. [Altman 2015b p3A] It stimulates the synthesis of and reduces the degradation of proteoglycans, components of cartilage that decrease in OA. [Altman 2015b p4A] HA also blocks certain intracellular pathways that contribute to bone degradation. [Altman 2015b p4D]

Furthermore, HA increases the viscosity of the fluid in the joint, providing mechanical protection. [Altman 2015b p4B] .

A recent meta-analysis of clinical trials found similar efficacy between intra-articular injections of HA and corticosteroids, with corticosteroids more effective in the first month and HA more effective in the long term – up to six months from the time of injection. [He 2017 p98A] HA has also been shown to delay time to surgery. A retrospective claims analysis of 182,000 patients undergoing total knee arthroplasty found that those who had received a single injection of HA had delayed the time to surgery by an average of 1.4 years compared with those who received no HA treatment; patients who received 5 or more courses of treatment had a mean delay of 3.6 years. [Altman 2015a 2A,3A,5A] This study was limited to patients undergoing arthroplasty; in practice, however, some patients may avoid surgery altogether. [Altman 2015a 9A]

Despite the clinical benefits of HA, with a mechanism of action that inhibits tissue damage as well as alleviating pain, both corticosteroid and HA therapy remain controversial. Table 2 provides a summary of consensus guidelines for these intra-articular therapies. The ACR recommends the use of intra-articular corticosteroids, and recommends it as strongly as acetaminophen, NSAIDs, and tramadol. [Hochberg 2012 p470AC,471A] These guidelines do not recommend for or against HA. The AAOS does not recommend for or against the use of injectable corticosteroids, citing studies in which it was inferior to HA and needle lavage. [AAOS 2013 p747AB] However, even though HA was superior to corticosteroid in the study cited, the AAOS recommends against the use of HA, because the clinical benefit did not reach its standard of a "meaningfully important difference." [AAOS 2013 p770AB] In contrast to this lack of endorsement, the ESCEO recommends both HA and corticosteroids; they are placed in the

treatment algorithm after oral NSAIDs due to the inconvenience of delivery, not because of efficacy or safety. [Bruyere pS3A,S8A] The American Medical Society for Sports Medicine (AMSSM) recommends the use of HA in appropriate patients. It bases its scientific statement on a meta-analysis of trials that indicate the proportion of patients achieving clinically significant improvement, rather than a mean change from baseline across subjects. Clinical benefit was defined by criteria established by two international arthritis research organizations – the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and the Osteoarthritis Research Society International (OARSI) – known as the OMERACT-OARSI criteria. [Trojian 2016 p2A] Significantly more patients showed a clinically meaningful response to HA on this scale than to corticosteroids or placebo, and the response to corticosteroids was not significantly greater than to placebo. [Trojian 2016 p3A,4A] Therefore, the AMSSM recommends the use of HA therapy in appropriate patients with knee OA. The EPIC Task Force agrees with the position of the ESCEO and the AMSSM. Because of its clinical benefit, long-lasting effect, positive safety profile, and potential to delay or reverse disease progression, HA is an important component in managing knee OA as a chronic disease.

Treatment providers

Most patients receive clinical care for osteoarthritis from their primary care provider (PCP). Patients who do not respond well to treatment, or for whom injectable therapy is recommended, will often be referred to sports medicine specialists, rheumatologists, or orthopedic surgeons. The chronic disease model of OA indicates a need to move beyond the primary care/specialist model to include other care providers, such as weight loss specialists, physical therapists, and pharmacists. Pharmacists are uniquely positioned to provide counseling, assessment, and follow-up, since many patients see their pharmacists more frequently than their primary care physicians,

in a less formal setting, and, as was discussed earlier in this paper, pharmacist interventions have been proven to have clinical benefits. [Kielly 2017 p156C]

Metrics

A challenge in interpreting clinical trial results and applying them to clinical practice is the lack of a standard metric for determining disease severity. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, validated scale developed over 20 years ago. It is a 24-item scale assessing pain, stiffness, and physical function. [McConell 2001 453AB] More recently, several additional scales incorporate the WOMAC items, but add additional questions. For example, the Knee injury Osteoarthritis Outcomes Score (KOOS), incorporates many WOMAC items, but also includes quality of life and function questions that are specific for patients with knee pain. There are also versions for hip (HOOS) and foot and ankle (FAOS) OA. [Roos 2003 p1A,3AC] The proportion of patients achieving OMERACT-OARSI criteria is another valuable metric for evaluating change in clinical trials. [Trojian 2016 p5A,8A]

Radiographic metrics are often used to categorize OA severity in clinical research and to influence treatment decisions, especially surgery eligibility. A common radiographic metric is measuring joint space narrowing over time. The Kellgren-Lawrence grading scale, another common radiographic metric, incorporates data on joint space narrowing and osteophyte formation. [Emrani 2008 p1AN,2A] Other clinical trials use general health metrics, such as the SF-36, to assess pain and functioning, rather than instruments specific to OA, in order to capture more information regarding emotional and social health. [Kawano 2015 p307A, Marra 2007 1239C] This lists only a few of the more common scales used to measure OA severity; however,

it is enough to convey the complexity and lack of uniformity with which OA is assessed in clinical research and clinical practice.

Part of the difficulty in standardizing metrics is that different stakeholders value different outcomes. Clinicians need an easily administered tool that will track progression of disability and change in disease severity over time. Along with population health or macro trend metrics related to business, employers do use compounded annual growth rate (CAGR) and multidimensional productivity growth (MPG) measures for quarterly or annual comparisons versus competitor firms. Employers can also value patient/employee satisfaction and increased productivity. For patients, some outcomes may be more valuable than others; for example, pain reduction may be more of a priority than range of motion. Regaining the ability to take long walks may be an important outcome, reducing social isolation.

The EPIC Task Force does not recommend a particular metric for all clinical research. However, we do feel that efficacy measures in clinical trials should include the proportion of patients achieving a certain degree of improvement, rather than the mean change in the treatment group vs control. This is more valuable information to clinicians, who want to know "How likely is it that my patient will show meaningful improvement with this treatment?" [Trojian 2016 p5A,8A]

Call to Action

The EPIC Task Force concludes that considering OA management in the framework of a chronic disease model will yield numerous benefits, preventing the development of OA in some at-risk patients, and providing the opportunity for a greater proportion of patients to achieve satisfactory relief with conservative treatments. Treating patients earlier in the course of the

disease will also lower the overall cost of the disease and improve workplace productivity. We recommend the following specific actions on the part of clinicians, payors, employers, and community health organizations:

- Develop improved public and patient information materials
    - Promote early adoption of exercise, weight loss, and work and leisure modifications as preventive strategies in high-risk individuals
    - Encourage patient self-management
        - Co-create drug regimen with primary care provider
        - Adhere to appropriately designed exercise plan
        - Follow weight-loss regimen, if appropriate
        - Maintain copies of health records
- Develop informational materials for nonmedical stakeholders, such as employers and insurers
    - Emphasize importance of prevention and early intervention
    - Describe direct medical costs and indirect costs of OA at work, including absenteeism and presenteeism
- Design benefit plans to support and promote prevention and early intervention strategies
- Promote biomechanical joint evaluations by specifically trained physical therapists or other professionals
    - As soon after diagnosis as possible since outcome may determine subsequent treatment
    - Ideally, in clinicians office

- Adopt drug treatment algorithms that emphasize long-term safety
    - Opioids not appropriate therapy for OA
    - Oral NSAID uses with caution
    - Hyaluron intra-articular injections recommended for appropriate patients with knee OA
- Use functional outcomes as measurements of treatment efficacy
- Promote the use of more meaningful metrics in future clinical trials
    - Proportion of patients that achieve a clinically meaningful real-world outcome
        - Pain, functioning or functional status, and quality of life outcomes more meaningful than radiographic measurements
    - Adaptation or translating clinical metrics to meaningful business and benefit plan performance metrics
- Better information sharing among primary care, specialists, and other licensed health professionals
    - Patients should maintain their own copies of medical records, to share with new providers
    - Pharmacists monitor drug (use) information and provide feedback to one or more prescribers
- Expanded role for pharmacist in managing pharmacotherapy: screening, counseling, and medical care collaboration as part of coordinated patient centered chronic care model

Conclusions

Osteoarthritis is a progressive disease that significantly impairs quality of life and poses a major economic burden. As the population ages, the prevalence is increasing and OA is currently a

public health imperative. Adopting a chronic disease model for managing OA can lead to prevention and improved treatment outcomes. All stakeholders need to be involved to create this paradigm shift in disease management: patients need appropriate education and support in self-management, employers and insurers should modify benefit plans and workplace routines to support best practices, physicians must prioritize long-term drug safety when selecting a treatment plan, and all healthcare providers must work together to provide coordinated care.

References

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. Assassi S, ed. *PLoS ONE*. 2015a;10(12):e0145776..

Altman R, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. *BMC Musculoskeletal Disorders*. 2015b;16:321.

American Academy of Orthopaedic Surgeons (AAOS). *Treatment of Osteoarthritis of the Knee*. 2013. Downloaded on June 8, 2017 at https://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf

American Academy of Orthopaedic Surgeons (AAOS). Ortholink: Osteoarthritis. 2007. Downloaded June 22, 2017 http://orthoinfo.aaos.org/topic.cfm?topic=A00227

Bastick AN, Belo JN, Runhaar J, Bierma-Zeinstra SMA. What Are the Prognostic Factors for Radiographic Progression of Knee Osteoarthritis? A Meta-analysis. *Clinical Orthopaedics and Related Research*. 2015;473(9):2969-2989.

Beattie KA, Boulos P, Pui M, . Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. *Osteoarthritis Cartilage*. 2005;13(3):181-186.

Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskeletal Disorders*. 2008;9:116.

Bruyère O, Cooper C, Pelletier JP, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis—from evidence-based medicine to the real-life setting. *Seminars in Arthritis and Rheumatism*. 2016:45:S3–S11.

Center for Disease Control (CDC)a. Arthritis Related Statistics. Downloaded June 22, 2017 at https://www.cdc.gov/arthritis/data_statistics/arthritis-related-stats.htm

Center for Disease Control (CDC)b. Osteaorthritis Fact Sheet. Downloaded June 20, 2017 at https://www.cdc.gov/arthritis/basics/osteoarthritis.htm

Center for Disease Control (CDC)c. Prescription Opioid Overdose Data. Downloaded June 21 at https://www.cdc.gov/drugoverdose/data/overdose.html

Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1323–30.

Davy C, Bleasel J, Liu H, Tchan M, Ponniah S, Brown A. Effectiveness of chronic care models:

opportunities for improving healthcare practice and health outcomes: a systematic review. *BMC Health Services Research*. 2015;15:194

Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep* 2016;65(No. RR-1):1–49.

Emrani PS, Katz JN, Kessler CL, et al. Joint Space Narrowing and Kellgren-Lawrence Progression in Knee Osteoarthritis: An Analytic Literature Synthesis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2008;16(8):873-882.

Harris EC, Coggon D. Hip osteoarthritis and work. *Best practice & research Clinical rheumatology*. 2015;29(3):462-482.

He WW, Kuang MJ, Zhao J, et al. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: A meta-analysis. *Int J Surg*. 2017 Mar;39:95-103.

Hochberg MC, Altman RD, April KT 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*. 2012;64:465–474.

Jüni P, Hari R, Rutjes AWS, et al. Joint corticosteroid injection for knee osteoarthritis. *Cochrane Library*. 2015 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005328.pub3/abstract

Katz J. Drug deaths are rising faster than ever. *New York Times*. June 5, 2017. Downloaded June 5, 2017 at https://www.nytimes.com/interactive/2017/06/05/upshot/opioid-epidemic-drug-overdose-deaths-are-rising-faster-than-ever.html

Kawano MM, Araújo ILA, Castro MC, Matos MA. Assessment of quality of life in patients with knee osteoarthritis. *Acta Ortopedica Brasileira*. 2015;23(6):307-310. doi:10.1590/1413-785220152306150596.

Kielly J, Davis EM, Marra C. Practice guidelines for pharmacists: The management of osteoarthritis. *Canadian Pharmacists Journal : CPJ*. 2017;150(3):156-168.

King, L. K., Kendzerska, T., Waugh, E. J. and Hawker, G. A. (2017), The Impact of Osteoarthritis on Difficulty Walking: A Population-Based Study. *Arthritis Care & Research*. Accepted Author Manuscript

Klussmann A, Gebhardt H, Nübling M, et al. Individual and occupational risk factors for knee osteoarthritis: results of a case-control study in Germany. *Arthritis Research & Therapy*. 2010;12(3):R88. doi:10.1186/ar3015.

LaPrade RF, Burnett QM II, Veenstra MA, Hodgman CG. The prevalence of abnormal magnetic resonance imaging findings in asymptomatic knees: with correlation of magnetic resonance imaging to arthroscopic findings in symptomatic knees. *Am J Sports Med*. 1994; 22:739-745.

Marra C, Cibere J, Grubisic M, et al. Pharmacist-initiated intervention trial in osteoarthritis: a multidisciplinary intervention for knee osteoarthritis. *Arthritis Care & Research*. 2012:64(12): 1837–1845.

Marra C, Cibere J, Tsuyuki RT, et al. Improving osteoarthritis detection in the community: pharmacist identification of new, diagnostically confirmed osteoarthritis. *Arthritis & Rheumatism (Arthritis Care & Research)*. 2007:57(7):1238–1244.

McConnell, S., Kolopack, P. and Davis, A. M. (2001), The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis & Rheumatism, 45: 453–461.

Menashe L, Hirko K, Losina E, et al. The diagnostic performance of MRI in osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2012;20(1):13-21.

Neogi T, Zhang Y. Osteoarthritis prevention. *Current opinion in rheumatology*. 2011;23(2):185-191. doi:10.1097/BOR.0b013e32834307eb.

Patient Advocate Foundation. The roadmap to clarity in health care decision making: making person-centered care a reality. Downloaded June 15, 2017 at http://www.npaf.org/npaf/roadmap

Papandony MC, Chou L, Seneviwickrama M, et al. Patients' perceived health service needs for osteoarthritis (OA) care: a scoping systematic review. *Osteoarthritis Cartilage*. 2017 Jul;25(7):1010-1025.

Riddle DL, Perera RA, Jiranek WA, Dumenci L. Using Surgical Appropriateness Criteria to Examine Outcomes of Total Knee Arthroplasty in a United States Sample. *Arthritis care & research*. 2015;67(3):349-357.

Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health and Quality of Life Outcomes*. 2003;1:64. doi:10.1186/1477-7525-1-64.

Rosedale R, Rastogi R, May S, et al. Efficacy of exercise intervention as determined by the McKenzie System of Mechanical Diagnosis and Therapy for knee osteoarthritis:a randomized controlled trial. *J Orthop Sports Phys Therapy*. 2014:44(3):173-181.

Sawitzke AD. Personalized medicine for osteoarthritis: where are we now? *Therapeutic Advances in Musculoskeletal Disease*. 2013;5(2):67-75.

Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2016;24(6):962-972.

Wagner EH. Managed care and chronic illness: health services research needs. *Health Services Research*. 1997;32(5):702-714.

White PH, Waterman M. Making osteoarthritis a public health priority. *Am J Nurs*. 2012 Mar;112(3 Suppl 1):S20-25.

Wittenauer R, Smith L, Aden K. Update on 2004 Background Paper, BP 6.12 Osteoarthritis . Geneva: World Health Organization, 2013.

Table 1. Summary of Guidelines for Oral or Topical Pharmacological Treatment of Osteoarthritis. Guidelines from the American College of Rheumatology (ACR), the American Academy of Orthopaedic Surgeons (AAOS), and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

Drug Class	ACR (Hochberg 2012)	AAOS (AAOS 2013)	ESCEO (Bruyere 2016)
Acetaminophen	First-line treatment (p469A,470AC,471A)	No recommendation for or against (p4A)	First-line treatment, as short term rescue analgesia (pS5)
Oral Non-selective NSAIDS	Conditionally recommended for hand, knee, and hip OA (p469A,470A,471A)	Strongly recommended (p3A)	Third line agents, if glucosamine, chondroitin sulfate, or topical NSAIDs insufficient (pS5)
Selective Cox-2 Inhibitors	Conditionally recommended for hand, knee, and hip OA (p469A,470A,471A)	Strongly recommended (p3A)	Third line agents, if glucosamine, chondroitin sulfate, or topical NSAIDs insufficient (pS5)
Topical NSAIDs	Conditionally recommended for hand and knee OA; for patients ≥75 years old, preferred over oral NSAIDs (p469A,470AB)	Strongly recommended (p3A)	Second-line therapy, preferred over oral NSAIDs (pS5)
Tramadol	Conditionally recommended for hand, knee, and hip OA (p469A,470A,471A)	Strongly recommended (p3A)	Short-term use as last treatment option, following intra-auricular injections [pS8B]
Opioids (non-Tramadol)	No recommendation for or against for knee or hip OA. Conditionally recommended NOT to use for hand OA (p469A,470A,471A)	No recommendation for or against (p4A)	Should NOT be used (pS8)
Chondroitin sulfate	Should NOT use for knee or hip OA due to lack of efficacy (p470A,471A, 472A)	Not recommended, based on strong evidence showing minimal efficacy (p260B)	First-line treatment (pS5)
Glucosamine	Should NOT use for knee or hip OA due to lack of efficacy (p470A,471A, 472A)	Not recommended, based on strong evidence showing minimal efficacy (p260B)	First-line treatment (pS5)
Duloxetine	Conditionally recommended in patients for whom NSAIDs is contraindicated for knee OA (p470B). No recommendation for hip OA (p471A)	No mention	Short-term use as last treatment option, following intra-auricular injections [pS8B]

NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis

Note: The AAOS and ESCEO guidelines are specific to osteoarthritis of the knee; the ACR guidelines include osteoarthritis of the knee, hip, and hand.

Table 2. Summary of Guidelines for the Use of Intra-Auricular Injection of Hyaluronic Acid or Corticosteroids in the Treatment of Osteoarthritis of the Knee. Guidelines from the American College of Rheumatology (ACR), the American Academy of Orthopaedic Surgeons (AAOS), the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), and the American Medical Society for Sport Medicine (AMSSM)

Drug Class	ACR (Hochberg 2012)	AAOS (AAOS 2013)	ESCEO (Bruyere 2016)	AMSSM (Trojian 2016)
Hyaluronic Acid	No recommendations for or against. p469A,470AC,471A)	Recommends against; improved outcomes in controlled trials do not meet standard of a "meaningfully important difference" (p770A,B)	Effective and safe. Recommended after NSAIDs in algorithm because of inconvenience of injections. Different time course than corticosteroids, with greater efficacy after 8 weeks, for up to 6 months (pS7B, S8A)	Significantly more patients show clinically meaningful response than to corticosteroids or placebo (p3A)
Corticosteroids	Recommends as strongly as acetaminophen, NSAIDs, and tramadol p470AC,471A)	Do not recommend for or against; controlled trials found injected corticosteroids superior to placebo but inferior to injected hyaluronic acid or needle lavage (p747A,B)	Recommended after NSAIDs in algorithm. Different time course than hyaluronic acid, with greater efficacy in first 4 weeks.(p S3A, S7B)	Response not significantly different than placebo (p4A)

NSAID: nonsteroidal anti-inflammatory drug