Management of Knee Osteoarthritis

What Internists Need to Know

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KEYWORDS

• Osteoarthritis • Knee pain • Nerve growth factor • Placebo effect
• Platelet rich plasma

KEY POINTS

- Osteoarthritis (OA) is a clinical diagnosis, not a radiographic or laboratory diagnosis; as structural degeneration accompanies normal aging, clinical OA is defined by the presence of pain.
- As there is no therapy that alters the natural history of OA in people, therapy is focused on palliation of pain and retention of function.
- Therapy should include nonpharmacologic interventions such as self-efficacy, weight loss when appropriate, and exercise, preferably with the involvement of physical therapy.
- When pharmacotherapy is necessary to manage pain, nonsteroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of therapy when not contraindicated. Both topical and oral NSAIDs may be used. Intra-articular interventions, such as glucocorticoids, may be effective for short-term pain relief.
- OA pain is sensitive to the placebo effect. Widely marketed interventions, such as intraarticular stem cell therapy and platelet-rich plasma, are expensive and have not been demonstrated to be superior to the prominent placebo effect for knee OA pain.

Among musculoskeletal diseases, osteoarthritis (OA) is by far the most common form of arthritis and results in vast morbidity and societal costs. It is estimated that the overall costs to society represent more than 0.5% of the gross domestic product of industrialized countries[1]; in the United States, OA accounts for almost $200 billion annually in medical costs,[2] and symptomatically, it affects more than 25 million Americans, approximately 10% of the adult population.[2,3] Moreover, adults are estimated to have a 40% to 50% lifetime risk of developing clinically significant OA.[4] The dramatic advances in therapeutics for inflammatory arthritis in recent years have not been matched by comparable progress in OA. Hence, OA patients seen in routine

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Rheumatology care today have significantly worse clinical status than those with rheumatoid arthritis (RA),[5] and can expect to derive substantially less improvement with modern care.[6] However, careful examination of the status of patients with OA and RA revealed that even prior to the advent of the biologic therapies, those with OA had comparable pain and functional disability to those with RA.[7] Although OA can affect any diarthrodial joint, certain areas are more predisposed than others, and OA of the knees is among the most common and most debilitating sites. This article provides a narrative, evidence-based review of current management of OA of the knees, with emphasis on topical and injectable therapies.

DEFINITION

Historically, OA was considered a disease of degenerative cartilage, and hence therapeutic strategies throughout most of the 20th century were devoted to protecting and repairing articular cartilage. Fundamentally, however, that perspective failed to account for the widespread changes that occur throughout all joint tissues. In addition, as cartilage is not innervated, the source of OA-related pain in a cartilage-centric paradigm remained a mystery. It is now clear that OA is a degenerative process that involves all joint tissues, and therefore, to be effective, therapeutic strategies must deal with the entire joint. In addition, pain is now appreciated to be fundamental to the clinical condition of OA, and whereas structural degeneration of joints is a universal feature of normal aging, the disease of OA is not. By late middle age, virtually everyone has evidence of cartilage degeneration,[8] but clinical OA is present in only a minority of people, even among those with evidence of structural joint degeneration.[9] Although for large-scale epidemiologic studies, structural joint changes evident by radiography have been used to define the presence of OA, there is substantial discordance between radiographic OA and actual disease. Hence, a reasonable definition of OA is: "a joint disease that consists of painful degeneration affecting all joint tissues, and involves progressive deterioration of articular cartilage and alterations of subchondral bone and surrounding joint structures; local inflammation may be present but is not the primary source of joint dysfunction."[10]

CLINICAL PRESENTATION

The cardinal manifestation of knee OA is pain. Structural degeneration in a joint accompanies normal aging, is often asymptomatic, and may precede the development of clinical symptoms by years or decades. OA manifests as disease when the patient notices pain or dysfunction. OA pain is generally first noticed during loading of the involved joint; hence with knee OA, early symptoms occur while standing or walking. With disease progression, pain may become persistent even at rest. Knee pain may wax and wane during the disease course, and it is typical to have prolonged pain-free periods punctuated by painful flares that may last weeks or months. Other symptoms of knee OA include subjective joint instability and the gelling phenomenon, wherein the joint feels stiff transiently as the patient stands. Additionally, patients may notice decreased range of motion of the knee, and as the knees are superficial, they may notice prominent bony bumps cosmetically, which are caused by osteophytes. Physical examination of the OA knee often reveals crepitance, and frequently a cool effusion may be detected. It is important to note that the diagnosis of OA is a clinical diagnosis; there are no laboratory tests that are abnormal because of OA. Radiographically, the OA joint may have osteophytes, asymmetric joint space narrowing, subchondral sclerosis, and occasionally subchondral cysts. Nonetheless, radiographic abnormalities alone may be asymptomatic and thus do not imply clinical

OA.[11] Moreover, the focus of therapy ought to be directed at symptom palliation and retention of function rather than structural degeneration. This is especially important with regards to the decision to proceed with surgical intervention for OA, which should be made strictly on the basis of clinical severity and not determined by the radiographic severity of OA. It is important to distinguish OA from the inflammatory arthritides, which are discussed in the rest of this issue. Rather than presenting with systemic symptoms, OA is not associated with diffuse synovitis or symptoms characteristic of systemic inflammatory disease (**Table 1**). Whereas patients with inflammatory arthritis such as RA experience prolonged stiffness in the morning, OA specifically presents with no or transient stiffness, such as the brief gelling phenomenon felt after a period of inactivity. In addition, OA joints tend to have palpable bony enlargements (osteophytes) and are either not inflamed or have a mild inflammatory response, with less than 2000 leukocytes/μL upon arthrocentesis. Meanwhile, rheumatoid joints are highly inflamed, erythematous, with boggy synovium, and effusions with greater than 2000 leukocytes/μL. It is equally important to distinguish OA from common extra-articular sources of knee pain, such as anserine bursitis, which presents as significant medial knee pain exacerbated by climbing stairs or rising from a chair; this is diagnosed by point tenderness over the anserine bursa at the proximal medial tibia. Although anserine bursitis may accompany knee OA, it is distinguished from OA pain by its focal localization which is extra-articular and sensitive to palpation.

APPROACH TO THERAPY

To date, there are no therapies that have been shown to alter the natural history of OA in people. The prevention of structural progression remains purely aspirational. Hence, the main goals of contemporary OA therapy are to palliate pain and to retain function. Recently, the American College of Rheumatology (ACR) and the Osteoarthritis Research Society International (OARSI) have published updated guidelines for the nonoperative management of knee OA.[12,13] These are largely concordant, and stress both nonpharmacological and pharmacologic modalities (**Table 2**).

NONPHARMACOLOGICAL APPROACHES TO OSTEOARTHRITIS

There is consensus that patients benefit from education and programs aimed at self-efficacy and self-management techniques, as part of a holistic approach to knee OA. These help patients to set realistic expectations and have been shown to be beneficial to patients' quality of life.[14] As knee OA is a chronic lifelong condition, and most patients become mildly symptomatic years before they develop severe daily pain, it is important for physicians to educate all such patients about the importance of noninvasive physical measures. Most will benefit from physical therapy, where they are taught exercise regimens, and undergo supervised range-of-motion and functional training. Additional adjunctive relief can be obtained by icing painful joints, especially before and after activity; some people prefer local heat to ice.

Weight Loss

Obesity is a significant risk factor both for incident knee OA and for progression of disease. Although sustained weight loss is impractical for a large number of patients, there is evidence that those who are able to lose weight derive substantial clinical benefit.[15] There appears to be a dose response between the magnitude of clinical benefit and the amount of sustained weight loss in knee OA, such that significant effects are noted at a loss of 5% of body mass, and benefit increases dramatically as the amount of weight loss increases, up to at least 20% in very overweight individuals.[16]

Table 1
The typical clinical features of osteoarthritis compared and contrasted with those of the inflammatory arthritides

	Osteoarthritis	Inflammatory Arthritides
History	• Worse with prolonged use or loading • Morning stiffness <30 min • Gelling phenomenon • Subjective joint instability	• Often improved with prolonged use • Morning stiffness >30 min
Physical examination	• Cool effusion • Varus/valgus deformity • Bony hypertrophy • Crepitance with damage	• Warm effusion • Skin erythema • Boggy swelling • Significant tenderness to palpation • Crepitance with damage
Laboratory findings	• No specific abnormalities	• Elevated ESR/CRP • Hypoalbuminemia • Anemia of chronic disease • Thrombocytosis • Positive autoimmune serologies
Synovial fluid	• <2000 leukocytes/μL, lymphocytic predominance • Incident CPPD crystals possible	• 2000- >50,000 leukocytes/μL, neutrophil predominance
Imaging	• Asymmetric joint space narrowing • Subchondral sclerosis and cysts • Osteophytosis • Meniscal or ligamentous damage with progression	• Dependent on subtype

The diagnosis of OA is a clinical decision not dependent on laboratory or radiographic features, and OA is distinct from the inflammatory arthritides, as it is not associated with systemic symptoms or with systemic inflammation.

Table 2
A summary of the recently updated treatment guidelines for knee osteoarthritis, as published by the Osteoarthritis Research Society International and by the American College of Rheumatology

Treatment Modality	OARSI	ACR
Nonpharmacological		
Exercise	Yes, for all patients	Yes, for all patients
Physical therapy	Yes, for all patients	Yes, for all patients
Eastern disciplines (yoga, tai chi)	Yes, for all patients, preference for tai chi	Yes, for all patients, preference for tai chi
Weight reduction, if overweight	Yes, for all patients	Yes, for all patients
Self-management and education	Yes, for all patients	Yes, for all patients
Biomechanical (cane)	Recommended	Recommended
Unloading knee braces	Not recommended	Recommended
Heat/therapeutic cooling	Conditionally recommended	Conditionally recommended
Balance training	Conditionally recommended	Conditionally recommended
Cognitive behavioral therapy	Conditionally recommended	Conditionally recommended
Pharmacologic		
Topical NSAIDs	Strongly recommended	Strongly recommended
Topical capsaicin	Not recommended	Conditionally recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended: short-term use
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	Conditionally recommended	Strongly recommended when not medically contraindicated
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	Conditionally recommended	Recommended
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
PRP	Strongly recommended against	Strongly recommended against
Mesenchymal stem cell therapy	Strongly recommended against	Strongly recommended against
Anti-NGF therapy	Not addressed	Not addressed
Complementary		

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Table 2
(continued)

Treatment Modality	OARSI	ACR
Acupuncture	Uncertain	In appropriate circumstances
Glucosamine and/or chondroitin sulfate	Strongly recommended against	Strongly recommended against
TENS	Strongly recommended against	Strongly recommended against
Therapeutic Ultrasonography	No recommendation	Conditionally recommended
Kinesiotaping	Not recommended	Conditionally recommended

Abbreviations: COX-2, cytotoxygenase-2; OARSI, osteoarthritis research society international; TENS, transcutaneous electrical nerve stimulation.

[a]This table summarizes the major recommendations of each organization shown and is not intended to represent a complete listing of their guidelines. There is overall concordance regarding recommendations, although some variation exists.

Adapted from Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol 2020;72(2):220-233; and Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27(11):1578-1589; with permission.

Exercise and Muscle Strengthening

Patients who exercise regularly have reduced knee OA pain, and formal exercise training regimens supervised by physical therapists provide significant pain relief.[17,18] The original intention of such regimens for knee OA was to provide biomechanical unloading by strengthening the periarticular musculature. Although the mechanical benefit of such programs has not been borne out and there is no evidence that these programs alter structural progression, the pain advantage is unambiguous. There is insufficient evidence to support a particular modality of exercise over others[12]; rather, it appears that aerobic conditioning of all types provides pain relief. The most common exercise is walking, which should be encouraged among knee OA patients. Swimming and cycling are considered lower-impact activities, and are often preferred as the reduced loading of arthritic knees may perhaps be better tolerated. In addition, neuromuscular training and balance training are often advocated, although without a full database to support them in OA. Nonetheless, neuromuscular training may assist in reducing falls and knee injuries.[19]

In addition to standard exercise regimens, there has been attention to Eastern practices as potential adjuncts for palliating knee OA. Tai Chi is the modality that has the most supportive information in OA, and is now strongly recommended by the recent ACR[12] and OARSI[13] guidelines. Yoga is also popular, may be beneficial, and is also recommended by the updated guidelines.

Mechanical Unloading

It has been accepted for years that progression of knee OA is mediated by aberrant biomechanical loading,[20] and it has been expected that amelioration of the abnormal loading would provide salutary effects both on structural progression and on pain. Various noninvasive mechanically active strategies have been identified, which have been shown to have beneficial effects on knee loading, although none have been

demonstrated to affect disease progression. Importantly, the simple use of a cane while walking can yield substantial unloading effects across the knee[21] and provides stability for patients who feel subjective knee buckling or for those who may have unsteady gait. Additional unloading can be accomplished by using bilateral walking sticks.[22] However, despite the mechanical benefits of cane use, there is no evidence that it has a beneficial structural effect on the disease.[23] Valgus unloading knee braces have been approved by the US Food and Drug Administration (FDA) for many years for the pain of medial knee OA, and they do provide mechanical benefit by reducing loads across the arthritic knee. For people who tolerate them, they may provide an important option for noninvasive care, and they are recommended by the updated ACR guidelines.[12] Thus, it may be worthwhile to try braces, generally facilitated by referral to Physical Medicine and Rehabilitation. Nonetheless, many patients find them cumbersome, unsightly, and uncomfortable, and there is insufficient evidence for their actual efficacy to expect that they will be helpful in most patients.[24]

PHARMACOLOGIC APPROACH TO OSTEOARTHRITIS

As knee OA is a chronic, progressive, lifelong disease, most patients will eventually require more than adjunctive measures to control their pain. This implies pharmacologic intervention. As there are no strategies that have been shown to delay disease progression or to modify the course of the disease over time, pharmacologic approaches focus on control of pain and maintenance of function while limiting adverse reactions.

TOPICAL THERAPIES

Topically administered medications have relatively limited systemic absorption, and have been shown to be effective for OA pain, at least in superficial joints. As many OA patients are elderly and have comorbid conditions that may preclude long-term NSAID use, a trial of topical therapy may be preferred. Some authorities recommend topical capsaicin, which is available without prescription in the United States and has been approved for use in knee OA for many years. It is thought to act by depletion of Substance P and to reduce the sensitivity of peripheral nociceptors,[25] and has been shown to have pain-palliating effects in OA if used 4 times daily. It must be applied cautiously, and the hands washed thoroughly after application, because exposure to mucous membranes causes significant burning pain, as capsaicin is the active ingredient in hot peppers. The aggregate experience, however, suggests that topical capsaicin may provide only minor pain relief in OA, and a Cochrane Collaboration systematic review, which found short-term pain advantages, concluded that only some patients will feel substantial relief long term.[26] In addition, there appear to be adverse events in 80% of the cases, for the reasons noted previously.[27]

An important option is topical NSAIDs. In the United States, diclofenac gel is now available both by prescription and over the counter; in other countries, additional NSAIDs are topical options, including ibuprofen and ketoprofen. These tend to be well tolerated and may be used in many situations where systemic NSAIDs are contraindicated. Topical salicylates have also been an option in combination preparations over the counter. Diclofenac gel has been approved by the FDA for the treatment of knee OA and has been shown to be more effective than placebo in short-term (less than 6 weeks) and longer-term (12 weeks) studies in clinical trials.[28] An over-the-counter preparation is now available without prescription.

ORAL THERAPIES

Eventually, most OA patients will require more than topical therapy to control their pain. Although various options exist, OA pain remains incompletely treated in many patients, and is widely recognized as a major unmet medical need.

Acetaminophen

For many years, acetaminophen was recommended by most societies' guidelines for the initial treatment of knee OA. This was on the basis of perceived safety and an early study suggesting equivalence to oral ibuprofen in a short 4-week trial.[29] However, when acetaminophen was tested against placebo as well as against an NSAID positive control in a 12-week trial, which is more relevant to the chronic pain of OA, it was found to lose its efficacy after 4 weeks and to be indistinguishable from placebo by 12 weeks.[30] This was eventually confirmed by multiple other trials, which suggested the lack of a clinically relevant benefit.[31] In addition, acetaminophen has been implicated in a large number of accidental cases of fulminant hepatic failure because of accidental overdose. As such, it may still be useful for short-term painful flares in OA, but ought not be used in the chronic care of OA, and it has now been removed as a recommendation by OARSI.[13]

Nonsteroidal Anti-inflammatory Drugs

As a category, nonsteroidal anti-inflammatory drugs (NSAIDs) represent the most effective and widely available oral therapy for knee OA, and they remain the mainstay of OA therapy. For analgesia, they have been shown to be superior to placebo and pure analgesics, and to retain their activity during long-term use.[32,33] There are many NSAID preparations that are available, both by prescription and over the counter, and all are largely equi-efficacious at full doses.[34] A recent network meta-analysis that had suggested some benefit of diclofenac over naproxen or ibuprofen was subsequently retracted (Lancet, DOI:https://doi.org/10.1016/S0140-6736(16)30002-2). Despite their efficacy, chronic use of NSAIDs entails some risk, especially among many patients with OA. They must be used with caution in patients with cardiac disease, renal impairment, or who are at risk of gastrointestinal (GI) bleeding. Generally, those who are middle-aged or older, or who are at increased risk of gastritis are treated concomitantly with gastric-neutralizing therapy, such as proton pump inhibitors or misoprostol; alternatively, the use of cyclooxygenase-2 inhibitors such as celecoxib may be safer for the GI tract and for patients who take anticoagulation therapy. Regular monitoring of renal function and of blood counts is important for all patients who are taking NSAIDs chronically. With such measures, however, NSAIDs may be safely used in a large number of OA patients, many of whom cannot attain similar levels of relief with other classes of therapeutics.

Neuroactive Medications

When OA was considered to be an isolated disease of degenerative cartilage, therapy was directed at ameliorating the local pain and inflammation caused by such processes. As a result, the primary strategy involved use of anti-inflammatories, such as NSAIDs and intra-articular glucocorticoids, as well as analgesics. However, it is now appreciated that OA pain has a complex pathophysiology, and in addition to the nociceptive component, which conventional analgesics target, there may also be components of inflammatory, neuropathic, and dysfunctional pain that require different strategies for relief.[35] Neuroactive agents may be helpful with both the neuropathic components and the chronic pain components of OA pain. Duloxetine, a

serotonin and norepinephrine reuptake inhibitor (SNRI), has been shown to be superior to placebo for OA pain.[36] It has been approved by the FDA for use in OA and musculoskeletal pain since 2010, and it may be used to relieve the complex pain of knee OA. Other agents that are widely used to treat neuropathic pain and depression have not been formally approved for the OA indication by the FDA; nonetheless, many, such as gabapentin, pregabalin, and other selective serotonin reuptake inhibitors (SSRIs) and SNRIs, are used clinically by many physicians to treat chronic pain, including chronic OA pain.

Opioids

Opioids have long been used effectively to control acute pain; however, their role in chronic nonmalignant pain has been controversial. There is abundant evidence that opiates effectively palliate OA pain.[37] However, there is substantially less evidence that they retain efficacy over long periods, and, importantly, they are associated with greatly increased risk of adverse effects.[38] Some of these, such as falling,[39] may be life-threatening in the elderly. As a result, opioids are no longer recommended in the ACR[12] and OARSI[13] guidelines for use in OA pain, and are not widely used by OA authorities.

Tramadol is a weak opiate agonist that has been shown to have efficacy in pain modification and is approved for use in OA. Earlier data suggested that a clinically significant pain reduction would be achieved by a substantial minority of patients, although at the cost of high prevalence of adverse events, principally GI upset.[40] With greater experience and large numbers treated, it has appeared that the efficacy of tramadol may be less significant than previously reported,[41] and guidance regarding the cost-benefit analysis remains uncertain. Nevertheless, tramadol remains in widespread use clinically in the United States, as there is a paucity of alternatives to NSAIDs for refractory OA pain.

INTRA-ARTICULAR THERAPIES

Glucocorticoids

Glucocorticoids have been delivered intraarticularly for several decades to treat the pain of OA. It is widely acknowledged that they may provide short-term relief, but there remains controversy regarding the magnitude of the benefit, and the severity of associated risks. In addition, there is little evidence to suggest that the relief from such therapy is prolonged.[42] A recent clinical trial evaluated intra-articular injections of solumedrol every 3 months and reported that after 2 years, there was no benefit to pain or function over placebo injections, but there was some evidence of more rapid degradation of articular cartilage in the treated group,[43] suggesting that there may be some risk to prolonged glucocorticoid exposure of the articular cartilage, and providing evidence for the long-held belief that any joint should not be injected more than a few times each year. There does not appear to be compelling evidence that any particular form of glucocorticoid is substantially superior to the others for intra-articular use. Of interest, a novel preparation of long-acting triamcinolone (triamcinolone acetonide extended-release injectable suspension) has recently been approved for intraarticular use in OA; it may provide a pain advantage over conventional triamcinolone in the first few weeks, but appears to be equivalent by 12 weeks.[44]

Hyaluronan

Hyaluronan, formerly called hyaluronic acid (HA), is an unsulfated glycosaminoglycan that is present throughout the extracellular matrix in many tissues and has diverse

functions in growth, development, and in maintaining structural integrity. In articular cartilage, it forms enormous aggregates with the large aggregating proteoglycan aggrecan; these aggregates, which have very high negative charge densities, are trapped in a collagen network and provide the mechanical stiffness that permits cartilage to cushion the bones during loading. Hyaluronan is also present in synovial fluid and augments nonboundary lubrication during articulation. Hyaluronan was originally developed therapeutically as a viscosupplement in an effort to improve joint function in OA, and to thereby retard disease progression. However, after injection, it is cleared rapidly from the joint, and any biomechanical advantage is lost within several hours. Nonetheless, it was observed that some people had significant pain relief after hyaluronan injections, and that pain relief at times was durable. On the basis of those observations, several preparations of hyaluronan have been developed and approved for use by the FDA for intra-articular use in knee OA.[45] There remains controversy regarding the magnitude of benefit above the placebo effect, and professional societies disagree on its utility. Whereas OARSI conditionally recommends its use,[13] the ACR conditionally does not recommend it.[12] Nonetheless, there is evidence that for people who obtain a salutary response from HA, the response may last for several months,[46] and when incorporating the placebo response, the total benefit (of the active agent added to the placebo response) may be substantial.[45] The cost of HA is high relative to the limited increment above placebo, the average wholesale acquisition cost being between $750 and $1400 for each dosing cycle, and hence most authorities use it sparingly.

BIOLOGIC THERAPIES

In light of the vast societal costs and morbidity resulting from knee OA, and the fact that conventional medical therapy cannot fully alleviate the pain and dysfunction caused by the disease, there is an enormous market for more effective therapeutics that would at least relieve the pain, and preferably would delay OA structural progression. As a result, the pharmaceutical industry has invested vast resources in discovery, and there is a pipeline of potential agents. Many of these targets have been revealed by new knowledge regarding the pathophysiology and neurobiology of OA pain.[47,48] Currently, there are no biologic agents that have been approved for use in OA; however, at least 1 group of monoclonal antibodies is far along in development.

Antinerve Growth Factor

The target that is most advanced in clinical trials of knee OA therapeutics is antinerve growth factor (anti-NGF). NGF was originally described by Rita Levi-Montalcini and Stanley Cohen in 1951 for its role promoting neuronal growth and survival in check embryos.[49] In the 1990s, while under investigation as a potential therapeutic for peripheral neuropathies, it was found to result in rapid-onset hyperalgesia that prevented further development, and in fact was potently pronociceptive.[47] This observation led to the development of neutralizing antibodies directed against NGF, and for trials in various painful conditions. The first large-scale phase 2 trial for knee OA was published in 2010[50] and reported substantial relief of knee OA pain. Shortly thereafter, however, the FDA imposed a halt on clinical testing in OA because of the occurrence of rapidly progressive OA, including in otherwise uninvolved joints, and a concern of avascular necrosis. After extensive testing and evaluation, the clinical hold was lifted in 2015, and trials were permitted to resume, subject to stringent mitigation strategies and lower doses. Although there are 2 antibodies that continue in clinical development, tanezumab and fasinumab, phase 3 trials have recently been published using

tanezumab.[51,52] There appears to be a significant pain benefit to anti-NGF, stronger at 5.0 mg subcutaneously than at 2.5 mg. However, even at the lower doses used after restarting trials, there was a clear dose-response relationship to rapidly progressive OA and to progression to joint replacement. In addition, although these agents are efficacious, they may not provide a dramatic benefit over current OA therapy; in the earlier trials, even at the higher doses of 10 mg of tanezumab, the actual effect sizes[53] were not greatly superior to conventional OA treatments.[54] Nonetheless, on the basis of the positive phase 3 trial results, Pfizer has announced that it has submitted an application to the FDA for approval of tanezumab 2.5 mg for the treatment of knee OA (https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_accepts_regulatory_submission_for_tanezumab_a_potential_first_in_class_treatment_for_patients_with_chronic_pain_due_to_moderate_to_severe_osteoarthritis).

POPULAR AND HEAVILY MARKETED UNCONVENTIONAL STRATEGIES

As conventional treatments for OA pain have not fully relieved patients' pain, a large commercial market has developed that offers various biologically plausible approaches. This market is largely unregulated, but many of the approaches are marketed with promises of dramatic relief without surgery. Before considering individual treatments, it is essential to understand the role of the placebo effect in OA pain.

Contextual Effect

To fully appreciate the results of OA pain trials in general, it is essential to understand the role that the contextual effect plays in this disease. The contextual effect is the sum of all of the factors that comprise a response to a treatment except for the direct effect of that therapy itself. Thus, additional extraneous therapies, the natural history of the disease, and the social context of the patient may each contribute to the outcome. Importantly, this also includes the placebo effect, which is the benefit obtained from an inactive placebo agent. It has been known for years that OA pain is sensitive to placebos. Hence, in blinded placebo-controlled trials, the subjects receiving placebo routinely obtain clinically significant pain improvement. The magnitude of this improvement can be substantial, typically greater than a 40% reduction in pain.[55] Moreover, there is evidence that intra-articular placebo treatments may have significantly greater placebo effects than orally administered placebo.[56] The role that the placebo effect plays in OA therapeutics was evaluated systematically by Zou and colleagues, who reported that across 215 OA trials, approximately 75% of the pain reduction in the treatment groups was attributable to the placebo response.[57] Similar findings have been described when treatment options are limited to nonpharmacological approaches.[58] In light of the dramatic efficacy of placebos, the utility of novel OA therapies must be evaluated with clear reference to whether they are superior to the already high level of pain relief provided by placebos.

The placebo effect is particularly important in understanding the popularity of some alternative modalities. For example, glucosamine and chondroitin sulfate have been popular dietary supplements for decades, with many OA patients deriving symptomatic relief. These have good safety profiles, assuming that they are manufactured using good manufacturing practice. However, there is compelling evidence that they do not provide substantial benefit beyond the placebo effect, although as previously noted, the placebo effect is potent in OA. There was great interest in these agents in the late 20th century (**Fig. 1**, top panel), and early literature was enthusiastic; however, the studies suffered from high levels of design and publication bias. Subsequently, independently funded studies have consistently failed to demonstrate clinically

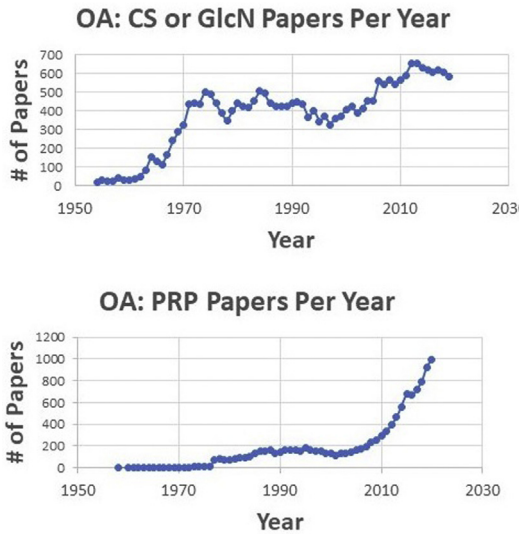

Fig. 1. The total number of publications related to glucosamine (GlcN) and chondroitin sulfate (CS) in OA, Top Panel, and to PRP in OA, as indexed by PubMed, by year. Top Panel: For GlcN/CS, there was great interest in the later years of the 20th century, which started to decline as large controlled studies failed to demonstrate substantial benefit. Interest in these agents recovered, however, as they remain in popular use, although it has been difficult to demonstrate clinically significant benefit beyond the contextual effects, as described in the text. Lower Panel: Interest in PRP for treating OA had an exponential increase, as measured by total PubMed-indexed publications, in the early 21st century, which appears to be coincident with the availability of devices that prepare the PRP in the United States, after initial clearance by the FDA.

significant benefit beyond placebo,[59,60] and these agents are not recommended by current OARSI or ACR guidelines.[12,13] Nonetheless, these agents remain widely used, and in light of the substantial placebo effect, they appear to provide substantial relief to many individuals.

ATTEMPTS AT DISEASE MODIFICATION

As noted previously, there are no treatments or strategies that have been shown to effectively retard the natural history of OA in people, despite several decades of investigation. Most of the modalities that have attracted attention as alternative approaches to OA pain were initiated as attempts to modify disease progression, especially through protection or repair of articular cartilage. Hence, most have underlying biological rationales that may well be plausible. However, whereas these modalities began as attempts to alter the structural progression or to repair cartilage, they are typically marketed as pain-palliating therapies.

Stem Cell Therapy

Adult articular cartilage is a nonreparative tissue, and once damaged, it tends to fibrillate and degenerate over time. When OA was considered to be merely a disease of degenerative cartilage, efforts were made to regenerate biomechanically functional cartilage. When it became clear that stem cells could be induced to differentiate along a chondrocytic lineage, there was hope that this might be a strategy to repair human

cartilage, and stem cells have been an attractive target for OA therapy since the late 20th century. There are numerous ongoing efforts to engineer functional cartilage using stem cell technology, but the clinical use of stem cells today depends on the injection of free stem cells rather than on inserting engineered neocartilage into defective joints. The hope is that by injecting these cells into the synovial cavity, they will adhere to the joint surface and begin to synthesize cartilage-like matrix and anti-inflammatory mediators that will palliate pain. Normally, if a specific product were to be marketed for such an indication, it would require FDA approval and be required to demonstrate that it is both safe and effective. However, as these are clinical procedures and do not utilize standardized products, the intra-articular injection of stem cells is not regulated. Nonetheless, this has been studied in translational animal models. A recent systematic review of structural benefit and pain palliation of stem cell injections in animals, which assessed gross morphology, histologic and immunohistological analyses, radiography, and behavior analyses, found that any evidence to support benefit was of low quality.[61] Evidence of efficacy is equally scarce in people. A PubMed search using the keywords "osteoarthritis" and "stem cells" and "humans" yielded 1382 hits, although only 32 were controlled trials. In addition, there were 28 systematic reviews (pubmed.ncbi.nlm.nih.gov, searched 06/25/2020). Sources of the stem cells included autologous and allogenic adipose tissue, bone marrow, placenta, and peripheral blood. The systematic reviews generally reported that there was a positive response to pain with stem cell therapy, although there was heterogeneity and lack of reproducibility in the methodology, and no clear structural advantage.[62] Importantly, there is a consensus that current evidence does not support the use of intraarticular stem cells,[63] nor are they recommended by either the OARSI or ACR guidelines.[12,13] Notwithstanding the lack of compelling evidence, stem cell injections are widely used in people; in the United States, the number of clinics offering stem cell injections almost doubled between 2016 and 2018, to more than 700 nationwide.[64] This procedure is not typically covered by insurance and is cash only. The costs have been estimated as averaging more than $5000 per procedure, and patients surveyed afterward appear overwhelmingly satisfied with their results.[65] The discordance between objective evidence of benefit and satisfaction with treatment may be best explained by the extremely potent placebo effect in OA pain, especially when used with intra-articular injections.

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is the name given to any preparation of autologous plasma whose platelet count is higher than that in the circulating blood (ie, it is enriched for platelets). This is typically prepared in a point-of-care process that involves centrifugation steps to separate plasma enriched with platelets. The resulting preparation is then injected intra-articularly in an attempt to palliate knee OA. Although marketing efforts frequently refer to this process as having FDA approval, in fact there is no approved indication for PRP; rather the devices that prepare the PRP are cleared by the FDA under a process known as 510(K) clearance, whereby the device itself is declared to be technically safe (ie, the resultant plasma product is not hazardous, and the performance has been shown to be technically similar to prior approved devices). In contrast to approval, which requires demonstration that the process is safe and effective, 510(K) clearance does not typically require demonstration of efficacy.[66] The FDA granted 510(K) clearance at least by 2011 for PRP processing,[67] and it is likely not a coincidence that interest in the literature had an exponential expansion at that time (see **Fig. 1**, lower panel). In addition to the absence of formal approval for the use of PRP in knee OA, there is no standardization regarding the volume of

plasma to be injected, the degree of platelet enrichment, or the frequency of injections. Despite the variability in regimens, evidence of actual efficacy in OA remains sparse. As noted, it was originally developed as a strategy to modify disease progression. However, there is little evidence to suggest that it has important structural effects on articular pathology, nor is there apparently much effort to assess the structural benefit of PRP. A Clinicaltrials.gov search using the search terms "osteoarthritis" and "platelet rich plasma" revealed a listing of 107 relevant trials, of which only 6 had sought structural outcomes (https://clinicaltrials.gov/ct2/results?term=platelet+rich+plasma&cond=Osteoarthritis&draw=2&rank=104#rowId103, searched 9 July 2020). In addition to there being a paucity of data suggesting structural benefit, there are few data of actual efficacy of PRP beyond the anticipated placebo effect for knee OA. A PubMed search using search terms "osteoarthritis" and "humans" and "platelet rich plasma" and "clinical trials" revealed 54 studies (PubMed searched 9 July 2020), of which only 18 were actually controlled trials of PRP for OA, including 1 trial for hip OA. An additional 5 trials were systematic or narrative reviews. Most studies reported that PRP was safe and that it provided comparable pain and functional relief to comparators, such as hyaluronan injection or glucocorticoid injection, although there was no compelling evidence that it was a superior modality. Systematic reviews and meta-analyses have been performed, and generally have described high risk of bias and heterogeneity among the clinical trials.[68] Importantly, even meta-analyses whose authors tried to impute significant effect to PRP were unable to demonstrate such effect statistically and were left to conclude that there was a great deal of uncertainty.[69] This is especially relevant to clinicians who choose to recommend the therapy, as it is not typically covered by medical insurance and involves substantial out-of-pocket costs; recent surveys suggest that a single injection averages $714 and may be as much as $1390.[70]

It is important to appreciate that the published literature includes a variety of protocols, with the PRP preparations including platelet concentrations between twofold and eightfold blood levels, variable volumes, and with the frequency of treatment varying between once and multiple injections. As noted previously, there is inadequate evidence to conclude that any particular regimen is superior to others, or in fact superior to other comparators. Hence, the choice of frequency of injections and platelet preparation styles becomes largely one of personal preference and appears to be arbitrary.

Arthroscopy

It is noteworthy that arthroscopic lavage and debridement continue to be used for knee OA. There have been several controlled clinical trials that have failed to demonstrate benefit from this modality, beginning with a landmark study published in 2002.[71] Nonetheless, arthroscopy remains extremely common as treatment for knee OA,[72] despite its demonstrated lack of efficacy. Patients appear to be satisfied with the results, and this can likely be attributed to the impact of the placebo effect.

SUMMARY

Knee OA is a common painful disease, especially among middle-aged and elderly patients, and results in enormous societal morbidity and costs. There are no modalities that have been shown to alter the progression of the disease in people, and the primary goal of therapy at present is to relieve pain and to preserve function. Notwithstanding enormous efforts over the past 50 years, OA pain remains inadequately controlled. Patient education and adjunctive measures are important, and exercise, physical therapy, and maintaining periarticular muscle strength relieve pain. Topical

agents, especially NSAIDs, are effective and well tolerated; however, oral NSAIDs remain the mainstays of therapy, despite the attendant risks of chronic use. Neuroactive agents, such as duloxetine, are important for the non-nociceptive components of OA pain, and intra-articular therapies, including glucocorticoids and hyaluronans, have been used to provide short-term relief. OA pain is extraordinarily susceptible to the placebo effect, and the efficacy of novel therapeutics needs to be assessed through an appreciation of the placebo effect. Biological-based therapeutics are under development; anti-NGF antibody therapy is under FDA consideration. It has been shown to be effective for OA pain; however, the effect size is not as great as desired, and there are attendant risks. Various commercially successful and expensive modalities are in widespread use, although without clear data of their superiority to placebo. These include intra-articular stem cell injections and PRP. The next few years will see multiple new targets for OA pain, but a likely successful approach to disease modification is not yet defined.

CLINICS CARE POINTS

- The focus of knee OA management is on relieving pain and preserving function, as there are no pharmacologic or nonpharmacologic therapies that have been shown to delay progression of knee OA.
- NSAID therapy (including topical application) remains the cornerstone of knee OA management in appropriate patients. Acetaminophen may be useful for short-term pain control but is not effective for the management of chronic OA pain.
- The placebo effect is potent for OA pain, and most of the effect of all currently used OA therapies may be ascribed to this effect. Hence, this must be considered when choosing therapeutic strategies.
- There is a lack of evidence demonstrating efficacy above the placebo effect for intra-articular PRP or stem cell therapy, and such interventions involve costly out-of-pocket expenditures.

DISCLOSURE

J.A. Block: In the last 12 months, J.A. Block has received royalties for intellectual property (human chondrosarcoma cell lines) from Daiichi-Sankyo, Agios, and Omeros, and has received clinical trial funds from Novartis, Pfizer, Jannsen, and TissueGene. He served as Chair of a DSMB for Discgenics and for the NIH/KAI Research Inc., and has consulted for Bioventus, GlaxoSmithKline, and Medivir. He receives compensation as editor in chief of *Osteoarthritis and Cartilage*. D. Cherny has no disclosures.

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