

Consensus Guidelines on Interventional Therapies for Knee Pain (STEP Guidelines) from the American Society of Pain and Neuroscience

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Abstract: Knee pain is second only to the back as the most commonly reported area of pain in the human body. With an overall prevalence of 46.2%, its impact on disability, lost productivity, and cost on healthcare cannot be overlooked. Due to the pervasiveness of knee pain in the general population, there are no shortages of treatment options available for addressing the symptoms. Ranging from physical therapy and pharmacologic agents to interventional pain procedures to surgical options, practitioners have a wide array of options to choose from – unfortunately, there is no consensus on which treatments are “better” and when they should be offered in comparison to others. While it is generally accepted that less invasive treatments should be offered before more invasive ones, there is a lack of agreement on the order in which the less invasive are to be presented. In an effort to standardize the treatment of this extremely prevalent pathology, the authors present an all-encompassing set of guidelines on the treatment of knee pain based on an extensive literature search and data grading for each of the available alternative that will allow practitioners the ability to compare and contrast each option.

Keywords: knee, knee pain, genicular nerve, ablation, regenerative medicine, platelet-rich plasma, dorsal root ganglion, peripheral nerve stimulation

Introduction Background

Knee pain affects tens of millions of people in the United States annually – the pain can be disabling and often negatively impacts the patient's quality of life, function and can even prevent one's ability to simply ambulate across a room. While osteoarthritis is the most common cause of knee pain,¹ there are numerous other lesser known causes that can present in a variety of ways with significant overlap between the various diagnoses. As one would expect from a condition with such a large incidence, there are a wide variety of treatments available to treat knee pain; however, there is no consensus on which treatments should be offered over others and in what order. The purpose of these guidelines is to consolidate the data into one document on the various modalities available, ranging from medication and physical therapy to interventional treatments and joint arthroplasty, thus offering practitioners a sing

These clinical guidelines are based on a systematic review of published studies examining the conservative, interventional, and surgical treatment options for the most common sources of knee pain in adults: knee osteoarthritis, post-surgical knee pain, soft tissue injury to the knee, and complex regional pain syndrome (CRPS) involving the knee joint. The intent and purpose of these guidelines is to help practitioners integrate the current evidence into clinical practice. Given the broad nature of the topic, effort was placed on reviewing recent meta-analyses and systematic reviews to summarize key findings and recommendations.

Incidence

Knee pain is a common reason for patients to present to primary care physicians and pain medicine specialists alike. An estimated 25% of Americans over the age of 55 have constant knee pain,² and the most common underlying etiology is osteoarthritis.³ Knee osteoarthritis is more common in the geriatric population with increasing incidence with age.⁴ Up to one in five people over the age of 50 reports severe difficulty with physical function due to knee pain even without a formal diagnosis of osteoarthritis.⁴ Extrapolating this to the United States population reveals that up to 21 million Americans are suffering with reduced ability to function due to knee pain.⁵

As we see a rise in the aging population and obesity rates, the incidence and prevalence of knee pain is expected to rise. For the most common culprit of knee pain, knee osteoarthritis, the incidence and prevalence are difficult to accurately define, given knee osteoarthritis can exist radiographically without symptoms or clinically due to symptomatic pathology. The pooled global incidence of knee OA was 203 per 10,000 person-years in individuals aged 20 and over.⁶ Not all patients with knee pain suffer from symptomatic osteoarthritis, however. With the rise in access to healthcare and surgery, the incidence of persistent post-surgical knee pain after total knee arthroplasty is also a source of chronic knee pain. Despite good outcomes for most patients who undergo total knee arthroplasties, approximately 20% of the patients experience chronic pain after total knee arthroplasty (TKA).⁷ Among the post-arthroplasty population, the incidence of neuropathic post-surgical pain, concerning for CRPS, can be as high as 34%.⁸ Ultimately, the rising prevalence of chronic knee pain will present challenges within our healthcare systems as well as economic costs associated with them. These guidelines hope to provide evidenced-based decision support to physicians and other healthcare providers to improve the quality and efficiency of care.

Economic Burden of Knee Pain

Osteoarthritis is a prevalent and disabling condition currently affecting 40 to 50 million Americans, with approximately 10–30% of those afflicted having significant pain, impaired function, and decreased quality of life.^{1,9,10}

The pain and loss of function can be debilitating; in developed countries the resultant socioeconomic burden is large, costing between 1% and 2.5% of gross domestic product.¹¹ The socioeconomic burden of knee and hip OA alone averages more than \$12,000 per patient annually in both direct and indirect costs of disease.¹² In 2015, the average cost of TKA was approximately \$16,000 per discharge, summing up to almost \$10 billion in inpatient costs alone.¹³ Time lost from employment and leisure by participants and their unpaid caregivers accounted for 80% of the total cost.¹² A 2017 study found that, when compared to healthy controls, knee OA patients had significantly more per-patient-per-year outpatient and pharmacy claims and costs. Knee OA patients incurred \$7707 more per-patient-per-year total healthcare costs than controls.¹⁴

In a national, cross-sectional, population-based study, it was found that about one-third of the population aged 50–64 had OA and more than half were out of paid work. Only knee OA was associated with early exit from work. The estimated annual cost of early exit from work attributable to OA was €384 per capita, €1294 per OA patient and €2095 per OA patient out-of-work.¹⁵ In another study, it was estimated that mean health losses due to knee OA over people's lifetimes are 3.44 quality-adjusted life years (QALYs) per person.¹⁶

Opioids

The United States accounts for 5% of the worldwide population yet consumes roughly 80% of opioids worldwide.¹⁷ As a nation, we have a obvious proclivity for choosing opioids to treat pain, even in cases where other treatments have been shown to be more effective and safer long term – as is the case when it comes to treating knee pain. From 2004 to 2014,

16% of the patients presenting with knee pain and osteoarthritis were prescribed opioid medications for treatment.¹⁸ Despite this, there are no data supporting the effectiveness of chronic opioids for either pain or functional improvement in patients with osteoarthritis.¹⁹ In fact, only about 35% of the patients who take opioids for osteoarthritis report pain improvement.²⁰ This is compared to 31% of the patients who were given placebo for similar pain.²⁰ Similar numbers are revealed when we evaluate physical functional improvements in response to opioids or placebo.²⁰ While opioids have not demonstrated benefits, they definitely have their risks. Opioid-naïve patients who are prescribed an 8-day supply of opioids have a 13.5% probability of continuing opioid therapy at 1-year.²¹ If this is increased to >30 days, the probability increases to 29.9%.²¹ With the Centers for Disease Control (CDC) reporting 46,802 opioid overdose deaths in 2018,²² the risk of opioid therapy in this population is felt to be greater than any potential benefit, with the exception of high-risk patients with limited alternative therapies.

Despite the presence of a plethora of suitable alternatives (most of which possess high levels of evidence to support their utility), practitioners continue to recommend opioids for the treatment of knee pain – even though there is little-to-no evidence to support their use in this particular setting. One of the principal goals of these guidelines is to illustrate just how many evidence-based treatment options that are available for knee pain that go beyond a seemingly innocuous prescription for opioid pain medication.

Methods

The Consensus Guidelines on Interventional Therapies for Knee Pain (STEP) panel is composed of participants considered experts in the field and was selected by the American Society for Pain and Neuroscience (ASPN) executive board after receiving nominations. The board's approach ensured diversity across practice locations and panelist demographics. Consideration was given to research experience, clinical experience, prior publications, work in the field, professional specialty, and speaking engagements. Invitations were sent, and upon acceptance, writing assignments were made. Database searches used replicable methods and are presented with outcomes, in each of the recommendations sections below. Multiple panelists contributed to the same topic in order to ensure consensus across experts. Panel members recused themselves from any section with actual or perceived conflict of interest. A third party was employed to edit the overall documents once panel members drafted their sections.

Literature search and summary methods were in accordance with the US Preventive Services Task Force (USPSTF) criteria for evidence level and degree of recommendation.²³ In treatment areas with early or incomplete literature the expert opinion of the panel contributors was presented, expert consensus was sought to fill gaps in knowledge. USPSTF criteria for evidence levels, meaning of recommendation degrees, and strength of consensus, assuming a quorum of 80% of the participants available for vote, appear in [Tables 1–3](#).²³

Evidence was quality ranked according to the following methods:

- Evidence Level 1 evidence is as a score of 39 or greater on the randomized controlled trial (RCT) and observation study score sheet (out of 48) on the Interventional Pain Management—Quality Appraisal of Reliability and Risk of Bias Assessment (IPM) score sheet²⁴ and 10–12 on QAREL score sheet²⁵ and 10–13 on Cochrane.²⁶

Table I USPSTF Hierarchy of Studies by the Type of Design

Evidence Level	Study Type
I	At least one controlled and randomized clinical trial, properly designed
II-I	Well-designed, controlled, nonrandomized clinical trials
II-2	Cohort or case studies and well-designed controls, preferably multicenter
II-3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experiences
III	Clinical experience-based opinions, descriptive studies, clinical observations, or reports of expert committees

Table 2 USPSTF Meaning of Recommendation Degrees

Degree of Recommendation	Meaning
A	Extremely recommendable (good evidence that the measure is effective and that benefits outweigh the harms)
B	Recommendable (at least moderate evidence that the measure is effective and that benefits exceed harms)
C	Neither recommendable nor inadvisable (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low-quality, or contradictory evidence; the balance between benefit and harms cannot be determined

Table 3 USPSTF Strength of Consensus

Strength of Consensus	Definition
Strong	>80% consensus
Moderate	50–79% consensus
Weak	<49% consensus

- Level 2 evidence is a score between 29 and 38 on the RCT and observational study score sheet (out of 48) on IPM procedure scores sheet²⁴ and 8–9 on QAREL²⁵ and 8–9 on Cochrane.²⁶
- Level 3 is a score between 16 and 28 on IPM procedures score sheet²⁴ and 6–7 on QAREL²⁵ and 6–7 on Cochrane.²⁶
- Is a score <16 on IPM score sheet²⁴ and <6 on QAREL²⁵ and Cochrane score sheet.²⁶

Additionally, a qualitative modified approach to grading of evidence is in [Table 4](#), modified from Manchikanti et al²⁷

Lastly, a guide for strength of recommendations is also available via the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (see [Table 5](#)).²⁸

Table 4 Level I–V Definitions

Level	Descriptor	Definition
Level I	Strong	Evidence obtained from 2 or more relevant high-quality randomized controlled trials for effectiveness. or Evidence obtained from 4 or more relevant high-quality observational studies or large case series for assessment of preventive measures, adverse consequences, effectiveness of other measures.
Level II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials. or Evidence obtained from at least 2 high-quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level III	Fair	Evidence obtained from at least one relevant high-quality nonrandomized trial or observational study with multiple moderate or low-quality observational studies. or At least one high-quality relevant observational study or large case series for assessment of preventive measures, adverse consequences, effectiveness of other measures.
Level IV	Limited	Evidence obtained from multiple moderate or low-quality relevant observational studies. or Evidence obtained from moderate-quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level V	Consensus based	Opinion or consensus of a large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures.

Table 5 NEATS Recommendations

Rating for Strength of Recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (eg, benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (eg, benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (eg, benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Patient Evaluation and Imaging

Physical Exam

As in all areas of medicine, a thorough physical exam is a crucial step in the work-up and diagnosis of knee pain. While imaging can provide a clear answer as to what pathology may or may not present within the knee joint, it may not be able to definitively diagnose what the pain generator is. An examination of the knee should start with basic inspection to assess for swelling or skin changes. There are a number of pathologies in the knee that may cause swelling or edema in or around the joint (ie, osteoarthritis, Baker's cyst, infection, soft tissue injury, etc) and would likely require further work up. Skin changes, such as erythema, shiny appearance, or loss of hair, may suggest CRPS or infection depending on the precipitating factors leading up to the symptoms.

Next, the provider should perform a cursory exam on the joint that includes

- Muscle strength: extension (quadriceps femoris, L3, femoral nerve); flexion (hamstrings, S2, sciatic nerve)
- Range of motion: 0° to 135°
- Sensation: L3 – medial aspect, L4 – anterior aspect, L5 – lateral aspect, S1 – posterior-lateral aspect, S2 – posteriod-medial aspect
- Palpation: posterior tenderness is common with Baker's cysts; medial or lateral tenderness may indicate a soft tissue injury (ie, meniscus, collateral ligament, etc)

The final, and perhaps most important, part of the exam involves performing a series of “special” maneuvers – these are a series of standardized examination techniques that specifically stress certain parts of the knee to reveal if a particular part or aspect has been injured (Table 6).^{29–31}

X-ray, MRI, CT, Bone Scan

- X-ray: According to the American College of Radiology (ACR) Appropriateness Criteria, radiographs should be the initial imaging modality utilized for the evaluation of knee pain. Radiographs provide adequate evaluation of the joint space, osteophyte and subchondral cyst formation, displaced or chronic stress fractures, joint effusions, and sclerosis in the subarticular region.^{32,33}
- Magnetic resonance imaging (MRI): If radiographs are normal, or demonstrate a joint effusion, the ACR recommends an MRI without intravenous (IV) contrast as the next most appropriate study. MRI accurately demonstrates the soft tissues of the knee, without the use of ionizing radiation, and depicts tendon and ligamentous damage, tears and other abnormalities of the meniscus, the presence of synovitis, the extent of effusions, the presence and/or

Table 6 “Special” Maneuvers for Examining the Knee

Test	Positive Test Indication
McMurray's test	Medial or lateral meniscus injury/tear
Lachman's test	Anterior cruciate ligament (ACL) injury/tear
Pivot shift test	ACL deficiency/acute vs chronic injury
Reverse pivot shift test	Torn posterior collateral ligament (PCL), lateral collateral ligament (LCL), arcuate complex and popliteal fibular ligament (PFL)
Anterior drawer test	ACL injury/tear
Posterior drawer test	PCL injury/tear (most accurate test to diagnose this issue)
Dial test	Combined posterolateral corner injury and PCL injury
Valgus stress test	Medial collateral ligament (MCL) injury/tear
Varus stress test	LCL injury/tear
Patellar grind test	Patellofemoral chondromalacia
Apley's distraction test	Ligamentous injury/tear
Apley's compression test	Meniscus injury/tear
Noble test	IT band syndrome
Ober test	IT band syndrome

rupture of a popliteal cyst, the extent of cartilage loss, bone marrow lesions, subchondral insufficiency fractures, tibial stress fractures, and osteonecrosis.^{32,34}

- MRI with and without IV contrast is not usually indicated when initial radiograph is negative or a joint effusion is detected. However, the utilization of IV contrast may be beneficial to help more accurately diagnose such causes of chronic knee pain as infrapatellar bursitis, adhesive capsulitis, patellofemoral friction syndrome (“runner’s knee”), pigmented villonodular synovitis (PVNS), and Hoffa’s fat pad syndrome.^{32,35}
- Computed tomography (CT): While not a first-line imaging modality for the evaluation of knee pain, according to the ACR, under certain circumstances, a CT without IV contrast may be indicated for the evaluation of knee pain, especially in settings where MRI may be contraindicated (ie, in a patient with a non-MRI compatible pacemaker, spinal column stimulator, or deep brain stimulator). CT offers enhanced bony detail and may be useful to confirm a prior osseous injury such as a subtle acute non-displaced fracture or chronic stress fracture. In the setting of chronic knee pain related to patellofemoral syndrome, CT may be helpful in evaluating the patellofemoral anatomy.^{32,35} CT with IV contrast is not usually indicated but may be used to evaluate the menisci, articular cartilage, and the presence of loose bodies.³²
- Bone scan: Bone scan is not usually indicated to evaluate patients with knee pain. Bone scan has low specificity and decreased anatomic resolution when compared to CT or MRI. However, bone scan may help to distinguish between bone and soft-tissue origins for pain.^{32,33,35}
- Ultrasound: Ultrasound is not often useful as a diagnostic tool for the comprehensive examination of the knee. It may be appropriate to use ultrasound to confirm a suspected effusion or popliteal cyst, and can be utilized to guide in aspiration of synovial fluid which can be evaluated for crystal disease or infection.³² It also may be utilized to evaluate for synovial pathology, where the use of power Doppler ultrasound can demonstrate increased synovial blood flow that is associated with knee pain.^{32,36,37} Ultrasound is also useful for following patients with iliotibial (IT) band syndrome and in evaluating medial plicae.^{32,34} Ultrasound can also demonstrate an extrusion of the

meniscus (with is suggestive of an underlying meniscal tear) and, on occasion, can detect peripheral meniscus tears, and chondrocalcinosis.^{32,34}

Kellgren–Lawrence Scale

The Kellgren and Lawrence system is a widely used method by which osteoarthritis (OA) is graded radiographically. Originally published in 1957, and still in use today, the method classifies OA by five grades:

- Grade 0 (none): nothing on X-ray
- Grade 1 (doubtful): suspect OA
- Grade 2 (minimal): OA definitely present, yet minimal
- Grade 3 (moderate) moderate osteophytes, joint space narrowing, may be some sclerosis or bony deformations
- Grade 4 (severe) severe joint space narrowing, large osteophytes, severe sclerosis and bony deformity.³⁸

The scale has both interobserver and intra-observer validation for reliability and with diagnostic accuracy.³⁹ The Kellgren–Lawrence scale is limited by its ability to comment on disease progression and detect changes as it assumes linear disease progression starting with osteophytes and then to joint space narrowing, ending in joint deformation, the latter not being able to be measured without the former being present.³⁹

Common Conditions Causing Knee Pain

Sprains

- Background: Knee sprains include injury to any of the ligamentous structures within the knee joint. Major ligaments include the anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), and lateral collateral ligament (LCL) and will be discussed here. Additionally, there are the anterolateral ligament (ALL), transverse meniscal ligament, posterior meniscomfemoral ligament, oblique popliteal ligament, arcuate ligament, popliteofibular ligament, and the ligaments that form the joint capsule.
- Etiology: Ligamentous knee sprains are due to trauma or sports injury, both with contact and non-contact forces. The ACL is commonly injured during plant and cut maneuvers due to increased knee abduction during hip adduction and knee valgus during hip internal rotation.⁴⁰ Additionally, internal rotation of the tibia increases risk of ACL strain. These three movements are combined in landing from jump with hip extended and internally rotated, knee extended and valgus, tibia internally rotated, and foot planted.⁴⁰ Hewett et al evaluated ACL injury mechanics in female athletes and found that abduction angle was 8° greater in ACL injury and those with ACL injury had 2.5 times greater abduction moments.⁴¹ PCL injuries are usually concomitant with injury to other ligaments particularly when varus or valgus stress or rotational force is involved. The PCL is injured with posterior translation of the tibia in relation to the femur. Force is required and a PCL tear is commonly known as a “dashboard injury” which occurs when the flexed knee hits a motor vehicle dashboard during a collision and is translated posteriorly, or during hyperflexion of the knee with the foot in plantar flexion, such as falling onto the flexed knee.⁴²
- MCL injuries can occur in isolation or in combination with the ACL or PCL. The MCL originates at the medial epicondyle of the tibia deep to the pes anserine and inserts 5–7 cm below the joint line. It functions as the primary medial knee stabilizer and resists valgus stress, anterior tibial translation, and internal rotation. The most common mechanism of injury to the MCL is direct lateral force to the knee or maneuvers that induce severe valgus stress to the knee, and injury most often occurs at the femoral insertion.⁴³ The LCL is the primary stabilizer of the lateral knee, originates at the lateral epicondyle of the femur and inserts on the medial fibular head. It resists varus stress, external rotation and posterior displacement of the fibula; therefore, it can be injured by contact and non-contact forces in these planes. Common mechanism of injury is direct varus force to the medial knee or hyperextension stress across the knee.⁴⁴
- Diagnostic Criteria: Sprains are graded based on severity: Grade 1 – mild, painful stretching or minimal tearing of fibers, Grade 2 – moderate, painful, partial tearing of fibers, Grade 3 – severe, painful or sometimes not painful, complete rupture of ligament and may demonstrate instability. Clinical physical exam findings: ACL – knee line pain, positive

Lachman's test. PCL – dimple sign, posterior drawer test, posterior sag test, quadriceps active test, external rotation recurvatum test.⁴² MCL – medial joint line pain and tenderness, positive valgus stress test. LCL – lateral joint line pain and tenderness, lateral joint edema, positive varus stress test, lateral compartment laxity with figure 4 position. History and physical exam support the clinical diagnosis, and imaging should include weight-bearing knee series and stress radiographs; however, the gold standard for diagnosis of ligament injury in the knee is MRI.

- Treatment: Symptomatic pain emanating from knee sprains is typically managed conservatively with topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) in those without contraindications as well as alternating ice and heat. From an orthopedic perspective, grade I and II sprains are treated with progressive weight bearing as tolerated, bracing, gentle active assisted range of motion, and strengthening of surrounding supportive musculature and are specific to each ligament involved. Some isolated Grade 3 sprains are treated with a longer period of immobilization and bracing, toe touch weight bearing, followed by aggressive range of motion (ROM); however, combined injury or severe Grade 3 sprains with complete ligament rupture can be treated surgically, particularly if the ACL is involved.⁴³

Meniscal Injuries

- Background: The menisci function to absorb shock and transmit load forces across the femorotibial joint and protect the articular cartilage. The medial and lateral menisci are composed of layers of collagen fibers. The superficial layer is finely woven, the surface layer comprises randomly oriented fibers, and the deepest layer is a combination of circumferential and radial fibers. The menisci are located between the medial and lateral femorotibial joints. The medial meniscus is attached to the tibial plateau by the coronary ligaments and is C-shaped. The lateral meniscus is circular and more mobile with loose attachments. The outermost 3 mm is the “red zone”, is well vascularized from the peri-meniscal plexus off the genicular arteries. Most tears in the red zone will heal. Within 3–5mm from the capsular junction is the “white zone”, with reduced perfusion, some tears will heal. The remaining meniscus >5mm from the capsular junction makes up the inner two-thirds, is avascular, receives nutrients from the synovial fluid, and most tears will not heal. Meniscus tears cause knee pain by direct effect on the nociceptors in the meniscus tissue and synovium, as well as by elevated levels of intra-articular cytokines.⁴⁵
- Types of traumatic tears:
 - Longitudinal vertical tear: if lesion stable then conservative management. Surgical debridement vs repair for unstable lesions.
 - Radial tear: debridement vs surgical repair.
 - Root tear: often associated with ACL tear, debridement vs surgical repair.
- Types of degenerative tears:
 - Horizontal cleavage in young athletes: rare, due to overuse, if cessation of the activity fails then proceed to surgical intervention.
 - Degenerative meniscal lesions in the elderly: prevalence increases with age, 60% asymptomatic, associated with osteoarthritis, conservative management.⁴⁵
- Diagnostic criteria: Clinical presentation includes joint line pain, knee locking, and positive special tests including McMurray, Ege, and Thessaly due to their high sensitivity and specificity.⁴⁵ Radiologic evaluation with weightbearing AP, lateral, and Schuss views are first-line evaluation to assess for alternative sources of pain such as osteoarthritis. If pain persists despite conservative therapy, MRI is obtained to evaluate the menisci.
- Treatment: Similar to sprains, pain secondary to meniscal injuries is managed symptomatically (ie, PT and NSAIDs). If the pain fails to respond to conservative care and/or persists beyond the acute phase, intra-articular injections should be considered.
- Intra articular platelet-rich-plasma injection has not been identified to improve meniscus healing. If the joint is unstable and/or non-invasive treatment modalities fail, surgical intervention is usually indicated, depending on the type and severity of the tear.⁴⁶

Tendinopathy

- **Background:** Tendinopathy is characterized by pain and dysfunction in a tendon, commonly due to excessive load or strain. In active patients and athletes, overuse can lead to chronicity.⁴⁷ The most common tendinopathy in the knee is of the patellar tendon, is colloquially known as “jumper’s knee” since it is commonly seen in jumping athletes, and can lead to microtears at the tendon insertion at the distal pole.
- **Diagnostic criteria:** Diagnosis is based on history and physical exam. Patients with patellar tendinopathy present with anterior knee pain that is worse with activity, tenderness to palpation at the inferior pole of the patella. Other tendinopathies present with tenderness to palpation and pain at the tendon insertion site with activation of the muscle. Radiologic imaging will be normal. Ultrasound can assist in confirming diagnosis and will show loss of the normal fibrillar pattern, increased spacing between fibrillar lines, and generally reduced echogenicity.⁴⁸ MRI will show increased signal at the tendon insertion.
- **Treatment:** Pain secondary to tendinopathy is treated symptomatically in the acute phase – this includes NSAIDs and physical therapy with a progressive loading program. Additional adjuncts for pain control such as cryotherapy, peritendinous injection with corticosteroids or platelet-rich plasma (PRP), and extracorporeal shockwave therapy can be considered if the pain fails to respond to NSAIDs and PT and/or the pain persists beyond the acute phase.⁴⁹ Ultrasound-guided needle tenotomy, percutaneous needle scraping, and high volume injection, and stem cells are at the forefront of regenerative medicine for tendinopathy and are currently being evaluated.⁵⁰ If non-invasive management fails, surgical intervention would be the next step.⁴⁹

Bursitis

- **Background:** A bursa is a sac filled with synovial fluid that acts as a friction cushion between structures. There are 10 bursa within and around the knee, and the 4 major bursa are the prepatellar, suprapatellar, infrapatellar, and pes anserine bursa. When friction or trauma irritates a bursa, it can become inflamed and be a significant source of knee pain. Bursitis is clinically recognized by localized pain, point tenderness, and edema at the site of the bursa. Septic bursitis may also present with erythema, warmth, and systemic symptoms such as fevers and leukocytosis.
- **Etiology:** Superficial to the patella is the subcutaneous prepatellar bursa, which can become inflamed with kneeling activities, and is colloquially called “housemaid’s knee or carpenter’s knee”. Inferior to the patella are two bursae, subcutaneous infrapatellar bursa which lies superficial to the patellar ligament, and the deep (subtendinous) infrapatellar bursa which lies deep to the patellar ligament. Inferomedial knee pain may be caused by anserine bursitis. The anserine bursa lies deep to the pes anserinus comprising the tendinous attachments of the semitendinosus, gracilis, and sartorius. Proximal to the anserine bursa and deep to the semimembranosus tendon is the semimembranosus bursa. There are three lateral bursae: the bursa deep to the iliotibial tract, bursa deep to the lateral collateral ligament, and the inferior subtendinous bursa deep to the biceps femoris tendon. Posteriorly, there are two subtendinous bursa, one deep to the medial and lateral heads of the gastrocnemius. A bursa can become inflamed by overuse leading to increased friction across the bursa. Septic bursitis requires bacteria to enter the bursa and is associated with trauma.
- **Diagnostic criteria:** Physical exam is significant for pain and point tenderness overlying the affected bursa and may be associated with swelling. Prepatellar bursitis will present with egg-shaped swelling superficial to the patella. Septic bursitis may present with erythema and warmth. Radiologic knee series are usually normal. Evaluation with ultrasound will show a hypoechoic fluid filled sac or discrete fluid collection at the site of pain indicating bursitis.^{51,52}
- **Treatment:** The treatment of bursitis-related knee pain is typically focused on reducing the inflammation of the bursa, itself – this includes ice, NSAIDs, activity modifications (such as knee pads for prepatellar bursitis), injections of corticosteroid, and therapeutic aspiration. For patients with active lifestyle or occupational demands and non-septic bursitis, intrabursal injection of corticosteroids provides acute pain relief. If septic bursitis is suspected, infectious workup includes blood sampling for evaluation of leukocytosis and aspiration of bursal fluid with gram stain and cell count. Treat septic bursitis with antibiotics. Recurrent or persistent severe bursitis may benefit from surgical interventions such as bursectomy.^{53,54}

Osteoarthritis

- **Background:** Osteoarthritis of the knee is a common source of knee pain, increases with advancing age, and is more prevalent in women than in men.
- **Etiology:** It is a disorder that develops after macro and micro-trauma leads to maladaptive repair response, activation of the pro-inflammatory immune response, and is characterized by cell stress and extracellular matrix degradation.⁵⁵ Mechanical stress, varus and valgus malalignment lead to excessive loading of bone and subsequent development of bone marrow lesions, abnormal focal remodeling, and loss of articular cartilage. Osteoarthritis can involve one or both knees and can occur in any of the three compartments of the knee, most commonly in the medial compartment. Symptom onset is gradual, can be localized or generalized joint pain that is worse with weight bearing and joint motion, and relieved with rest. Morning stiffness resolves in less than 30 minutes and the joint may stiffen briefly after inactivity. Clinical exam findings include bony enlargement, small effusions that are body temperature, and crepitus with joint motion.⁵⁶
- **Diagnostic criteria:** Diagnosis can be made based on history and physical exam. Standing radiographs may not show pathology in early OA so normal radiological findings do not exclude OA. Radiologic findings include osteophytes, subchondral cysts, subchondral sclerosis, and joint space narrowing which is graded using the Kellgren–Lawrence grading system (discussed previously).^{56,57} MRI is used to assess soft tissue if associated injury is suspected; however, it is rarely indicated for diagnosis of osteoarthritis. Ultrasound is an inexpensive and portable way to visualize the knee joint and assess for effusions and osteophytes; however, it is not accurate when assessing degree of joint space narrowing.⁵⁶
- **Treatment:** With the exception of joint arthroplasty and regenerative therapies, most treatments for knee pain secondary to OA are palliative in nature. Treatments are tiered depending on the stage and level of disability of the patient. Conservative management includes activity modifications, weight loss if appropriate, exercise, physical therapy, and education. NSAIDs should be considered first line for “as-needed” symptomatic pain control.^{19,20,58,59} Opioids have minimal benefit in OA and are associated with undesirable side effect profile and safety risks, therefore use is discouraged.⁶⁰ Intra-articular injections with corticosteroid or hyaluronic acid (HA) are well-accepted treatments for temporary symptomatic relief. Biologics such as PRP or mesenchymal stem cells have been proposed to attenuate the pro-inflammatory degradation in OA and potentially remodel the joint.⁶¹ Several adjunct medications such as cathepsin K inhibitors, Wnt inhibitors, anabolic growth factors, nerve growth factor inhibitors are being studied as a means of not only reducing the pain from knee OA but potentially stopping the progression of structural damage. For patients with advanced knee osteoarthritis who failed conservative therapy and who are candidates, total joint replacement is definitive treatment.⁵⁶

CRPS

- **Background:** CRPS is a chronic neurologic pain condition caused by trauma and is characterized by the presence of autonomic dysfunction, persistent regional inflammatory changes, lack of dermatomal distribution. Clinical presentation often includes allodynia, hyperalgesia, and skin temperature changes. It is formally known as “causalgia” or “reflex sympathetic dystrophy”. CRPS is divided into Type I (formerly reflex sympathetic dystrophy) due to trauma with no associated major nerve injury, and Type II (formerly causalgia) due to trauma or surgical insult in the presence of major nerve injury.⁶² CRPS occurs in the peripheral limbs and therefore is a source of knee pain.
- **Etiology:** CRPS is a combination of nervous system sensitization, autonomic dysfunction, and inflammatory changes in response to injury. Shortly after injury, inflammatory factors (tumor-necrosis factor alpha and prostaglandin E2) are released which leads to peripheral nociceptive sensitization and subsequent hyperalgesia. It is thought that persistent firing of A δ and C afferent neurons fire persistently leading to engagement of the autonomic nervous system and the distinct CRPS symptomatology. Peripheral nociceptors become sensitive to catecholamines after injury. There is probable chronologic change in the peripheral nervous system leading to degradation of large somatomotor A α neurons and preservation of A δ fibers.
- **Continuous firing of peripheral nerves** also leads to increased synaptic firing in the dorsal horn. This process is mediated by neuropeptides including glutamate and Substance P, leading to allodynia and hyperpathia. Over time, the central nervous system responds by central reorganization of motor and sensation pathways.

- Autonomic dysregulation is thought to be due to coupling of adrenergic and nociceptive pathways. During the acute phase, studies have shown circulating catecholamines and norepinephrine, which explains vasodilation, edema, and change in limb temperature. Over time, this leads to catecholamine sensitivity, which explains the vasoconstriction, cold temperature, and clammy skin seen in chronic CRPS.
- The innate immune system also plays a role. Mast cells release cytokines and neuropeptide levels increase (substance P and gene-related-peptide) leading to elevated inflammatory factors (TNF, IL-1b, IL-6, nerve growth factor) and subsequent peripheral sensitization to noxious stimuli.⁶²
- Diagnostic criteria: The Budapest criteria state that patients must meet all four criteria for diagnosis of CRPS (Table 7).⁶³
- Nerve damage can be diagnosed by electromyography (EMG).⁶⁴ Sudeck atrophy is a radiologic finding consistent with CRPS and includes diffuse osteopenia with juxtacortical demineralization, and subchondral cystic changes.⁶⁵ Stellate ganglion block causing sympathetic blockade with associated reduction in symptoms has been shown to be efficacious for treatment and confirmation of CRPS Type 1 diagnosis.⁶⁶
- Treatment: As is the case for the treatment of CRPS in any body part, a proactive, multidisciplinary approach that includes pain management, psychiatric, physical therapy, primary care, and case worker/social work at time of diagnosis is important. Treatment is divided into acute and chronic phases. Acute treatment focuses on pain control with local nerve blocks and rehabilitative modalities to alleviate pain, manage edema, and prevent contractures. Pain management includes systemic steroids, tramadol, gabapentin, antidepressants, ketamine, calcium channel blockers, bisphosphonates, and baclofen. Therapeutic modalities include edema control, range of motion, mirror therapy, graded motor imagery, acupuncture, biofeedback, stress loading, and aerobic conditioning. Chronic pain that is refractory to acute treatment is managed by progressing to spinal cord stimulator, dorsal root ganglion stimulator, or botulinum toxin (Botox) injection. Palliative surgical treatment includes nerve decompression, resection of neuromas, joint contracture release, and amputation.^{62,64,65,67}

Chondromalacia

- Background: Patellar chondromalacia is softening of the patellar articular cartilage and is a common source of anterior knee pain. Patellar chondromalacia is a precursor to patellar osteoarthritis.

Table 7 Budapest Criteria for CRPS Diagnosis

1. Continuing pain that is disproportionate to the inciting event		
2. At least one sign in 3 of 4 categories by history	Sensory:	Hyperesthesia, allodynia
	Vasomotor:	Temperature abnormalities/asymmetry, skin color changes/asymmetry
	Sudomotor:	Edema, sweating changes/asymmetry
	Motor/trophic:	Decreased range of motion, weakness, dystonia, hair, nail, or skin changes
3. At least one sign in 2 of 4 categories by exam	Sensory:	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch, temperature sensation, deep somatic pressure, and/or joint movement)
	Vasomotor:	Evidence of temperature asymmetry > 1°C, skin color changes/asymmetry
	Sudomotor:	Evidence of edema, sweating changes, asymmetry
	Motor/trophic:	Evidence of decreased range of motion, weakness, tremor, dystonia, hair, nail, skin changes
4. There is no other diagnosis that better explains the symptoms		

- Etiology: The patella is in the trochlear groove and friction during knee flexion causes breakdown of the patellar cartilage. Malalignment of patellar tracking within the trochlear groove can increase this friction and is often due to vastus medialis oblique (VMO) weakness. The exact etiology is unclear; however, it is proposed that friction trauma to superficial chondrocytes results in a proteolytic enzymic breakdown of cartilage matrix.⁶⁸
- Diagnostic criteria: Anterior knee pain that may be exacerbated by squatting, jumping, rising from sitting, or ascending/descending stairs. Retro-patellar crepitus may be present during knee range of motion, joint effusion, and >2 cm quadriceps wasting support chondromalacia. Tenderness over the medial or lateral patellar facets suggests progression to osteoarthritis. Special tests include patellar grind and patellar apprehension. Radiologic imaging with Merchant or skyline view is useful for evaluating the patellofemoral compartment.⁶⁹ Sagittal-patellar tilt should be taken into consideration during evaluation if MRI is obtained. Aksahin et al⁷⁰ evaluated patellar chondromalacia with MRI and found that sagittal plane malpositioning and chondral lesions might be related to chondromalacia. Tuna et al⁷¹ found that patellar tilt and trochlear dysplasia were related to the presence of chondromalacia.
- Treatment: Pain control for mild cases of chondromalacia is typically managed with NSAIDs, bracing, weight loss (if appropriate), activity modification, and a physical therapy regimen that focuses on stretching the VMO and strengthening the lower extremity kinetic chain.⁶⁹ In a systematic review of outcomes, faster VMO reflex time was associated with improvement after exercise intervention.⁷² Moderate cases of chondromalacia may require intra-articular injections of corticosteroid or hyaluronic acid. If conservative management fails after 3–6 months, surgical intervention may be warranted.⁶⁹ Biologic treatments including PRP and stem cell therapy are of particular interest due to their ability to potentially slow or even reverse progression of cartilage degradation. A study of autologous chondrocyte implantation (ACI) to patellar cartilage defects resulted in significant functional improvement at minimum 2 years and lasted up to 15 years.⁷³ Surgical modalities include tubercle osteotomy to correct lateral maltracking, realignment, patellectomy, patellofemoral replacement, and total knee replacement.⁶⁹

Post-Surgical Knee Pain (PSKP)

- Background: PSKP can be a difficult condition to diagnose, especially in the acute phase, as reports of pain after surgery are to be expected – it is not until several weeks, or even months, into the postoperative period that a practitioner will begin to suspect something is “wrong.” Even then, once any complications with the surgery (ie, infection, prosthesis malfunction, fracture, etc) have been ruled out, the usual assumptions are either malingering or drug seeking. For these reasons, PSKP tends to be underdiagnosed and its true incidence is difficult to measure as many patients reporting symptoms of PSKP are simply taken back to the operating room for subsequent surgeries. For example, many patients who undergo arthroscopic knee surgeries for knee OA eventually undergo total knee arthroplasty (TKA). A systematic review reports the overall incidence of TKA after knee arthroscopy is 2.62% and increases to 3.98% when selecting for older patients. The mean and median time from arthroscopy to TKA was 3.4 and 2.0 years, respectively.⁷⁴ Annual revision rates of TKA are 0.49%, compared to revision rates of medial unicompartmental arthroscopy (1.07%), lateral unicompartmental arthroscopy (1.13%), and patellofemoral arthroscopy (1.75%).⁷⁵ Nearly 20% of the patients experience suboptimal results following TKA, and residual post-TKA pain is a common complaint.⁷⁶ Predictors of increased residual post-TKA pain include other pain sites, catastrophizing, and depression.⁷⁷
- Etiology: Post-TKA pain can be caused by intrinsic or extrinsic etiologies. Table 8 outlines the possible causes.
- Diagnostic criteria: Assessment of residual post-TKA pain includes detailed history, review of surgical reports, and physical exam. Acuity, onset, nature, exacerbating factors can help distinguish between intrinsic and extrinsic causes. Physical exam includes visual inspection including joint alignment, palpation, range of motion, patellar tracking and stability in coronal/sagittal planes during range of motion, gait, and exam of the hip and spine. Preoperative and postoperative radiologic images should be reviewed. Obtain weight bearing anterior-posterior, lateral, and merchant views of the knee. Additionally, weightbearing films of the entire leg, hip, and ankle will assess varus or valgus abnormalities. Diagnostic intra-articular local anesthetic injection will support diagnosis of intra-articular source if pain is relieved within a few minutes of injection.⁷⁶

Table 8 Intrinsic or Extrinsic Etiologies of Post-TKA Pain

Intrinsic Causes	Extrinsic Causes	Rare Causes
Infection	Hip pathology	Synovitis
Implant mal-positioning, loosening, failure	Spine pathology	Recurrent hemarthrosis
Knee instability	Vascular pathology	Nerve related (cutaneous neuroma, CRPS, fibromyalgia, Tourniquet palsy)
Extensor mechanism disorders (quadriceps/patellar tendon rupture)	Tendinitis, bursitis	Worker's compensation
Arthrofibrosis	Metal sensitivity	Heterotopic ossification
	Minimal preoperative knee OA	Psychiatric disorder

- Treatment: Treating knee pain secondary to surgery can be extremely complicate given the fact that it may not be readily apparent what the pain is consequential to. Is it merely postsurgical discomfort that is taking longer than expected to heal, is it the result of a nerve injury (ie, CRPS Type II), a new pathology created by the surgery itself, or something else entirely? An unfortunate confounding factor that negatively impacts these situations is the presence of opioids as these patients will all inevitably be taking due to their having just had a surgical procedure. As such, multimodal analgesia is the optimal perioperative pain control regimen and reduces long-term opioid use with improved patient outcomes. This includes a combination of preemptive analgesia, neuraxial anesthesia, peripheral nerve blockade, patient controlled analgesia, local infiltration analgesia, and oral opioid/non-opioid medications.⁷⁸ Yu et al report discontinuing patient-controlled analgesia and femoral nerve blocks from the multimodal regimen and replacing them with liposomal bupivacaine resulted in less overall opioid consumption, with no difference in functional recovery or reported pain control.⁷⁹ In patients with centrally sensitized knee pain prior to TKA, duloxetine should be considered to minimize post-TKA pain.⁸⁰ For patients with persistent post-TKA pain, physical therapy, range of motion, and transcutaneous electrical nerve stimulation (TENS) are conservative measures that are effective.⁸¹ Interventional therapies to consider include nerve blockade, peripheral nerve neuromodulation, and dorsal root ganglion neuromodulation.

Recommendations Regarding Conservative Care

Medication

NSAIDs

Twenty-one randomized control trials were included in this systematic review of oral NSAIDs for knee pain. Overall, three separate knee pain diagnostic groups had sufficient evidence to warrant inclusion. Twelve studies were included on knee osteoarthritis;^{82–93} eight studies were included on pain following total knee arthroplasty,^{82–85,94–101} and one study was included on patellofemoral pain syndrome.¹⁰² Of the studies regarding knee OA, five studies reported level 1 evidence in support of NSAID use, four studies reported level 2 evidence in support of NSAID use, and two presented level 3 evidence in support of NSAID use. Each of the supporting studies reported at least 30% reduction in knee pain with NSAID use. Of note, one study reported non-superiority of naproxen over placebo.⁸⁵ Of considerable interest, cyclooxygenase-2 (COX-2) inhibitors were as effective as non-selective NSAIDs across studies, with several reporting enhanced analgesia and all describing a decreased incidence of adverse side effects, primarily GI upset, with COX-2 inhibitors. One RCT even described superiority of celecoxib 20 mg qd over tramadol 300 mg extended release, with each superior to placebo.⁸⁹

Regarding pain following total knee arthroplasty, each of the eight included studies supported the use of NSAIDs, with seven reporting level 1 evidence and one study reporting level 2 evidence. Consistent with the bulk of evidence for COX-2 inhibitors in knee osteoarthritis, COX-2 inhibitors were also supported across all studies, with sustained analgesic benefit noted after from COX-2 inhibitor use in the first weeks following arthroplasty.

Lastly, one study described a significant analgesic benefit of acute NSAID use in patellofemoral syndrome versus placebo, with a 5-point reduction in visual analog scale (VAS) score in comparison to 2 point with placebo¹⁰² (see Table 9).

In summary, oral NSAIDs are moderately effective in controlling pain in patients with moderate-to-severe pain due to knee osteoarthritis and pain s/p total knee arthroplasty. COX-2 selective NSAIDs are similarly effective to non-selective NSAIDs in controlling pain with the advantage of a considerably improved safety profile, especially regarding gastrointestinal upset. While all NSAIDs are associated with an increased risk of acute kidney injury, patients with a history of hypertension, heart failure, or diabetes have higher chance of developing these complications.

Consensus Points for NSAIDs

1. NSAIDs are an effective treatment for mild-to-moderate pain secondary to osteoarthritis knee pain; Level 1, Grade A, Consensus Strong
2. Topical NSAIDs are recommended before oral treatments because of their lower systemic exposure/toxicity; Level 1, Grade A, Consensus Strong
3. Topical diclofenac 70–81 mg/day should be considered as first-line pharmacological treatment for knee OA - can be effective and generally safer than oral NSAIDs due to reduced systemic exposure and lower dose; Level 1, Grade A, Consensus Strong
4. NSAIDs should not be used for patients with comorbidities due to risk of adverse events; Level 1, Grade A, Consensus Strong
5. NSAIDs should not be used on a long-term basis (>3 months) due to side effect profile (cardiovascular and gastrointestinal) and lack safety data; Level 1, Grade A, Consensus Strong
6. Celecoxib and non-selective NSAIDs are as effective as opioid for knee OA; Level 1, Grade A, Consensus Strong
7. Due to low effect on pain and physical function, regardless of dose, the potential clinical benefit of opioids does not outweigh the potential harm in patients with knee OA; Level 1, Grade A, Consensus Strong

Topicals

Out of the 17 studies included in this study, 6 reported level 1 evidence in support of the use of topical NSAIDs for knee osteoarthritis.^{103–108} 9 studies reported level 2 evidence in support of topical NSAIDs^{109–117} one reported level 3 evidence in support of topical NSAIDs;¹¹⁸ and one study reported level 2 evidence not in favor of topical NSAID therapy.¹¹⁹ Adverse events were rare in all included studies, primarily limited to minor skin irritation at the site of application. The clinical effect of topical NSAIDs was modest at best in comparison to placebo, but all studies did report statistically significant improvements in pain reduction. There was insufficient evidence to support recommendations for

Table 9 Evidence Table Regarding NSAIDs

Study	Details	Results	USPSTF Rating
Adatia et al, 2012 ³⁴⁵	Systematic review on ibuprofen for knee and hip OA: 10 RCTs, n=1777	Ibuprofen effective and relatively safe at low doses for mild-to-moderate OA of knee	Level I
Smith et al, 2016 ³⁴⁶	Systematic review on celecoxib/non-selective NSAIDs, less potent opioids, and more potent opioids for knee OA: 9 RCTs on celecoxib, n=2937; 4 RCTs on non-selective NSAIDs, n=587	No statistical significance in WOMAC reduction between Celebrex/non-selective NSAIDs and opioids	Level I
Da Costa et al, 2021 ⁵⁸	Systematic review on NSAIDs and opioids for knee OA: 192 RCTs, n=102,829	NSAIDs are clinically effective for improving pain and function with knee OA; safe when used for intermittent short- to midterm periods of time; Etoricoxib 60 mg/day and diclofenac 150 mg/day most effective	Level I

other topical medications (eg, capsaicin, copper). Osteoarthritis of the knee was the only diagnosis with sufficient literature to support recommendations regarding topical NSAID therapy.

Importantly, five separate studies demonstrated non-inferiority to oral NSAID therapy. Of note, one study reported inferiority of topical NSAID therapy in comparison to placebo. Indeed, the placebo effect was readily apparent in each study, which is a well-known phenomenon found in trials of topical medications (see [Table 10](#)).

To sum, topical NSAIDs have established efficacy comparable to oral NSAID therapy in the treatment of knee osteoarthritis, with a vastly improved adverse side effect profile and decreased cost. Topical NSAIDs may be preferable for patients with knee osteoarthritis older than 75, those with comorbidities or at an increased risk of renal, cardiovascular, or gastrointestinal adverse events.

Consensus Points for Topicals

1. Topical NSAIDs are an effective treatment for symptomatic knee osteoarthritis and can be utilized as part of an adjuvant analgesic treatment plan; Level 1, Grade A, Consensus Strong
2. Topical NSAIDs should be utilized before oral NSAID therapy for the treatment of knee osteoarthritis; Level 1, Grade A, Consensus Strong

Opioids

Due to the US opioid crisis, the use of chronic opioids for osteoarthritic, neuropathic, and non-surgical pain syndromes is currently under scrutiny.¹²⁰ Prior to 2013, 15.9% of the patients with knee osteoarthritis were prescribed an opioid.¹⁸ While opioid prescribing for this condition has not been directly studied since, opioid prescribing has declined or all comers since 2013. Despite this, opioid prescribing for chronic knee pain continues to be routinely practiced.

Welch and colleagues performed a systematic review of 22 double blinded trials (8942 participants) which compared opioids for chronic osteoarthritic knee pain versus placebo.¹²⁰ These authors found based on low-quality evidence that opioids provided no clinical relevant improvement in disability and no clinically relevant pain relief of 50% or greater.¹²⁰ While there was no difference in serious adverse events compared to placebo, there was a relevant dropout rate for the opioid group due to side effects.¹²⁰

Krebs et al conducted a randomized controlled trial comparing acetaminophen and non-steroidal anti-inflammatory medications in patients with osteoarthritis of the back, knee, and hip.¹²¹ While this study did not directly isolate knee patients, they found that there was no difference between the two groups in pain-related function and brief pain inventory interference.¹²¹ There was significant improvement in pain intensity in the non-opioid group when compared to opioids. Lastly, the opioid group had greater medication-related side effects and adverse events.¹²¹

There is limited peer-reviewed literature evaluating the benefits of opioids for chronic post-surgical knee pain specifically, but we do know that chronic opioid use has risks of opioid use disorder and overdose. Others have also detailed that chronic opioid use prior to total knee arthroscopy is an independent risk factor for persistent opioid use after surgery.^{122,123}

There is also little peer-reviewed literature evaluating the benefits of opioids for neuropathic knee pain. Busse et al in a systematic review of opioids for non-cancer pain found that opioids, compared to placebo, were associated with small but significant improvements in pain and physical functioning in patients with neuropathic pain but also associated with side effects.¹²⁴ Vergne-Salle specifically discussed opioids for neuropathic pain of the knee in an expert review and stated that opioids should only be used when other available treatments have failed.¹²⁵ This is because high doses are often needed to provide the desired effect and these are associated with high morbidity and mortality.¹²⁵

Consensus Points for Opioids

1. Due to low effect on pain and physical function, regardless of dose, the potential clinical benefit of opioids does not outweigh the potential harm in patients with knee OA; Level 1, Grade A, Consensus Strong
2. There is no evidence to support the use of opioids over NSAIDs for the treatment of knee osteoarthritis; Level 1, Grade A, Consensus Strong
3. For the treatment of knee pain, opioids should be limited to the acute postoperative post-injury/trauma period; Level 2, Grade B, Consensus Strong

Table 10 Evidence Table Regarding Topicals

Study	Study Type	Details	Systematic Literature Review Grading	USPSTF Rating
Barthel et al, 2009 ¹⁰⁸	RCT	N=492; Diclofenac gel versus vehicle with follow-up at 3 months, Outcome measures: VAS and WOMAC	Level 1 study based on all criteria	Level I
Rother et al, 2007 ¹¹⁰	RCT	N=324; Epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo with follow-up at 6 weeks, Outcome measures: WOMAC and patient global assessment (PGA)	Level 2 based on strong quality scoring for Cochrane and moderate scoring for QAREL and IPM	Level I
Conaghan et al, 2013 ¹⁰⁹	RCT	N=1395; Topical ketoprofen in Transfersome gel (IDEA-033) versus ketoprofen-free vehicle (TDT 064) and oral celecoxib with follow-up at 12 weeks, Outcome measures: WOMAC	Level 2 based on strong quality scoring for Cochrane and moderate scoring for QAREL and IPM	Level I
Bruhlmann and Michel 2003 ¹¹¹	RCT	N=103; Diclofenac hydroxyethylpyrrolidine (DHEP) patch versus placebo with follow-up at 2 weeks, Outcome measures: spontaneous pain and Lequesne's Index	Level 2 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Underwood et al, 2008 ¹⁰³	RCT and observational	N=282 (RCT) and 303 (observational) with follow-up at 1 year, Outcome measures: WOMAC and SF-36	Level 1 study based on all criteria	Level II-I
Rother and Conaghan, 2013 ¹¹⁹	RCT	N=555; Topical ketoprofen gel versus ketoprofen-free gel with follow-up at 12 weeks, Outcome measures: WOMAC	Level 2 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Yataba et al, 2016 ¹¹²	RCT	N=633; S-flurbiprofen plaster versus flurbiprofen patch with follow-up at follow-up at 2 weeks, Outcome measures: VAS	Level 2 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Tiso et al, 2010 ¹¹⁸	RCT	N=20; Oral versus topical ibuprofen with follow-up at 2 weeks, Outcome measures: WOMAC and SF-12	Level 3 study based on all criteria	Level II-I
Baraf et al, 2011 ¹⁰⁴	RCT	N=976; Topical diclofenac sodium 1% gel versus vehicle with follow-up at 12 weeks, Outcome measures: WOMAC, VAS, and pain on movement	Level 1 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Baraf et al, 2010 ¹¹⁷	RCT	N=420; Topical diclofenac sodium 1% gel versus vehicle with follow-up at 6 months, Outcome measures: WOMAC, spontaneous pain, and global rating of benefit	Level 1 study based on all criteria	Level I
Roth et al, 2004 ¹⁰⁵	RCT	N=326; Topical pensaid versus vehicle with follow-up at 12 weeks, Outcome measures: WOMAC, physical function subscales and a patient global assessment	Level 1 study based on all criteria	Level I

Bookman et al, 2004 ¹⁰⁷	RCT	N=248; Topical diclofenac gel versus vehicle with follow-up at 4 weeks, Outcome measures: WOMAC and PGA	Level 1 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level 1
Baer et al, 2005 ¹¹³	RCT	N=216; Topical diclofenac versus vehicle with follow-up at 6 weeks, Outcome measures: WOMAC and PGA	Level 2 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level 1
Kneer et al, 2013 ¹¹⁴	RCT	N=866; Ketoprofen in Transfersome® gel (IDEA-033) compared with the ketoprofen-free vehicle (TDT 064) with follow-up at 12 weeks, Outcome measures: WOMAC, PGA and Outcome Measures in Rheumatology (OMERACT)-Osteoarthritis Research Society International (OARSI) responder rates	Level 2 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level 1
Niethard et al, 2005 ¹⁰⁶	RCT	N=238; topical diclofenac diethylamine gel 1.16% versus placebo with follow-up at 3 weeks, Outcome measures: WOMAC and PGA	Level 1 study based on all criteria	Level 1
Varadi et al, 2013 ¹¹⁵	RCT	N=64; Transdermal ibuprofen formulation (VALE®-ibuprofen) containing 10% ibuprofen versus placebo with follow-up at 2 weeks, Outcome measures: WOMAC and VAS	Level 2 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level 1
Wadsworth et al, 2016 ¹¹⁶	RCT	N=260; Diclofenac sodium 2% topical solution versus vehicle with follow-up at 4 weeks, Outcome measures: WOMAC and PGA	Level 2 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level 1

Tricyclic Antidepressants and Neuroleptics

While opioids and non-steroidals are the most prescribed oral medications for chronic knee pain, utility can be limited due to risk factors, side effects, and other causes of morbidity. In these situations, some have turned to adjuvant medications including both tricyclic antidepressants (TCA) and neuroleptic medications. Unfortunately, there is little evidence of their efficacy. A group in New Zealand studied the effectiveness of nortriptyline in lowering WOMAC scores in 205 patients with painful knee osteoarthritis.¹²⁶ In this double-blind, prospective study, patients were randomized to a maximum dose of nortriptyline 100 mg daily or placebo. Both placebo and nortriptyline decreased WOMAC, but the difference between the decrease in WOMAC between the groups (6 points) was insignificant. Also, the nortriptyline group had significantly more side effects including dry mouth, constipation, and sweating. In an older study (1993) published in *Pain*, 50 mg amitriptyline was shown to have no benefit for patients after on post-operative days 1–3 when used as an adjuvant to opioids.¹²⁷ Actually, patients randomized to TCA had a higher mean VAS score.

While ramosetron has demonstrated efficacy in decreasing post-operative nausea and vomiting, there is little evidence about its pain efficacy.¹²⁸ It has been used in some large postoperative pain protocols, which have shown efficacy, but it has not been isolated as the beneficial component.¹²⁹ While there is another large-scale trial to study the efficacy of amitriptyline for chronic knee OA, based on the current evidence, the authors do not believe that neuroleptics or tricyclic antidepressants currently have a place in the algorithm for the treatment of knee pain.¹³⁰ However, TCAs may have a place in the treatment of neuropathic knee pain (ie, PSKP, CRPS, etc) as an adjuvant treatment, or potentially even as a standalone, whereas neuroleptics have not been found to be effective – more evidence is needed.

Consensus Points for Tricyclic Antidepressants and Neuroleptics

1. TCA may be effective in the treatment of neuropathic knee pain, PSKP and/or CRPS when used as adjuvants and should be utilized as a first-line therapy; Level II-3, Grade C, Consensus Strong.

Antihypertensives

Hypertension and OA have a number of shared risks (ie, aging, obesity, chronic inflammation, etc) and often coexist with one and other as comorbidities. Given the significant overlap between these patient populations, antihypertensive medications have been routinely administered to patients with OA (particularly knee OA); however, it remains unclear as to whether or not they have an impact aside from their intended value on the cardiovascular system. The five medication classes of interest for knee OA include beta-blockers, ACE inhibitors, angiotensin receptor blockers, CCBs, and thiazide diuretics. Beta-blockers have been shown to be associated with lower WOMAC scores and statistically significantly lower risk of joint pain, whereas other authors detected no evidence of analgesic effect.^{131,132} Calcium channel blockers, on the other hand, have been associated with higher pain scores and a higher prevalence of joint replacement.^{132–134} What is more concerning is the idea that calcium channel blockers may accelerate the process of OA by impairing the proliferation of chondrocytes.¹³⁵ The evidence is extremely limited on the use of these classes of medication for knee pain, and recommendations cannot be made for or against their use.

Consensus Points for Antihypertensives

There is insufficient evidence to make any recommendations on the use of these medications for knee pain – more data is required.

Physical Therapy

Osteoarthritis (OA)

Conservative measures for the treatment of OA include physical therapy (PT) with the focus placed on improving aerobic capacity, quadriceps muscle strength and/or lower extremity performance. These treatment modalities have proven to be effective when performed under supervision at least three times per week for 4 weeks. These types of programs yield similar outcomes regardless of patient attributes to include the degree of severity of the OA.¹³⁶

The 2014 meta-regression analysis of RCTs titled “Impact of exercise type and dose on pain and disability in knee osteoarthritis” reviewed 48 RCTs. Over the more than 4000 patients studied, it was determined that therapy programs focusing on one single modality were more efficacious in pain reduction for patient-reported disabilities than those mixing several types of exercise with different goals within the same session.¹³⁶

There is ample evidence to support focusing on one type of exercise when instituting a PT program for OA of the knee. The amount of exercise should be at least three times per week over a 4-week period to relieve pain and reduce disability.

Post-Surgical Knee Pain (PSKP)

Each surgery requires the specific surgeon who performed it to carefully balance the patient’s individual risks and benefits throughout the rehabilitation process to secure the best outcome.

This topic is so broad and the post-operative treatment modalities for individual therapy are so unique that this decision should be deferred to the surgeon who performed the procedure to generate a consensus point.

CRPS

Two authors evaluated 18 RCTs with 739 participants to test the efficacy of physiotherapy-based interventions between 1992 and 2015. There are only two studies specifically discussing CRPS Type 1 of the lower extremities (inclusive of the knee). Unfortunately, only one study is available as the other was removed from the site.¹³⁷

While physiotherapy and rehabilitation remain to be first-line treatments for people with CRPS, the review could find no evidence to support or dismiss its efficacy.¹³⁷

There is low-quality evidence due to the fact that most of the included trials were unclear or at high risk for bias. The trials were too broad with regard to interventions and did not allow for ample opportunity to pool data. This led to imprecision and inconsistency in the trials.

Soft Tissue Injuries

A systematic review and search was conducted from January 1, 1990 to April 8, 2015. A total of 9494 citations were screened and 11 RCTs were found of which 8 were discarded due to critical appraisal. Of the remaining 3 included, only 2 pertained to knee pain.¹³⁸

The first RCT used found statistically significant improvements in pain and function illustrating the benefits of progressive combined exercises over watchful waiting for patellofemoral pain syndrome (PFPS). The second suggested supervised closed kinetic chain exercise can lead to greater symptom improvements than open chain exercises for PFPS.¹³⁸

While the study found limited high-quality evidence supporting the use of PT to manage soft tissue injuries of the knee, there was anecdotal evidence that facility-based PT programs can potentially benefit patients with PFPS. Further high-quality research on this topic is needed.

Consensus Points for Physical Therapy

1. PT is an effective treatment for OA of the knee; Level I, Grade A, Consensus Strong
2. PT can be utilized for the treatment of CRPS of the knee; Level III, Grade C, Consensus Weak
3. PT is an effective treatment for soft tissue injuries of the knee (excluding PFPS); Level II-2, Grade B, Consensus Strong
4. PT can be utilized for the treatment of PFPS; Level III, Grade C, Consensus Weak

Durable Medical Equipment (DME)

As a part of the treatment of common musculoskeletal disorders, durable medical equipment (DME) refers to the medical equipment that assists in the treatment of musculoskeletal disorders, injury, illness. DME is further defined as reusable and nondisposable. Overall, the term DME refers to a wide range of equipment including devices for mobility such as bracing, orthotics, wheelchairs and canes as well as devices for activities of daily living (ADLS) such as shower chairs and even hospital bed.¹³⁹ For the purpose of this paper, the following discussion will focus on DME indicated for the

treatment of knee pain. DME is generally indicated for the knee used prophylactic, functional, postoperatively and for rehabilitative applications. Selecting the appropriate DME for knee pain starts with a proper diagnosis. The following discussion will focus on various types and indications for bracing and assistive devices (AD).¹³⁹

For a clinician to effectively prescribe the proper DME for a patient, they must know the correct diagnosis, patient goals and the patient's ability to comply with the DME prescription.¹³⁹ In order to prescribe a brace, a clinician only needs to know generalities and it is recommended that the clinician has access to an orthotist who specializes in custom-made and off-the-shelf products.¹³⁹

Bracing

The goal of functional braces is to provide stability and enhance function, while prophylactic braces prevent injury or decrease the severity of a possible injury and rehabilitative or postoperative braces allow controlled range of motion and help limit swelling.¹³⁹

It is common practice for knee braces to be prescribed by physicians for OA pain, post surgically in total knee replacements (TKRs) and after ACL repairs as well as in the case of soft tissue or ligamentous injury. Types of knee braces include soft, hinge, medial and lateral offloading, hinged, compression, wrap around, band straps, open or closed patella and open or closed popliteal.¹⁴⁰

Practitioners often prescribe bracing to relieve pain from osteoarthritis, a degenerative disease that occurs often later in life. Most commonly found in adults, OA is increasing to epidemic proportions in the US with 50 million Americans diagnosed and counting.^{139,141} Knee pain generated from OA is treated with medications, physical therapy, exercise, weight loss bracing and surgery. DME can assist in the management of OA pain oral medications fall out of favor, and non-medication options are gaining popularity.

The medial knee joint is more susceptible to mechanical stress which leads to overloading of the articular cartilage and can cause early degeneration.¹⁴¹ Unloader or offloading braces work to remove some of the medial or lateral compartment stress on the knee joint as well as improve bone alignment. These braces may in fact provide significant improvement in pain and function. In medial compartment OA, the varus deformity that develops can be offset by the valgus force against the joint from a brace; unloading the medial joint which has become compressed. Valgus offloading or unloader braces may be used. One study failed to show a difference both radiographically and clinically between the N=50 Bledsoe Thruster brace and the N=50 SofTec OA brace at 2 and 12 weeks follow-up, showing that both braces are effective in treating of varus medial knee OA (Level 1, Grade C).¹⁴² One paper concludes with a low quality of evidence that wearing a knee brace past 12 months as compared to not wearing one does not provide a difference in pain reduction or increased joint function and there is evidence that wearers may discontinue use due to this lack of effect.¹⁴³ A Cochrane review showed bracing to be effective in treating unicompartmental OA, especially medial compartment allowing for improved function, which improved activity levels, thus allowing more opportunity for strengthening and weight loss.¹³⁹ The European League Against Rheumatism (EULAR), the OsteoArthritis Research Society International (OARSI), and the American College of Rheumatology (ACR) recently put forth that knee OA management suggests the use of medications, exercise, strength training. There is however a lack of consensus regarding knee offloader braces.¹⁴¹ The OARSI did not recommend offloading braces citing "inconclusive evidence" of their symptomatic benefit, yet were "strongly recommended" in the new ACR guidelines.¹⁴¹

In the treatment of OA, the VER-brace, which is a medial compartment unloader brace that works by applying valgus force combined with and external rotation, was found by one randomized crossover trial to be more comfortable and decrease pain as compared to a valgus three-point bending system brace V3P-brace or a standard stabilizing brace using post-injury (ACL). These findings were suggestive of increasing compliance in bracing treatment (Level 1, Grade B).¹⁴⁴

One observational study showed a decrease in pain and improved function with a multidisciplinary non-operative approach in the setting of patellofemoral OA or tibiofemoral OA, yet donning a patellofemoral or a tibiofemoral knee brace did not seem to give additional benefits (observational study Level II-3).¹⁴⁵ When comparing a standard knee offloading brace to new knee OA ankle brace (ankle foot orthotic; AFO), one study found newer AFO clinically as effective in treating medial knee OA (multicenter randomized control) (Level II-1, Grade C).¹⁴⁶

- Soft knee braces: Knee braces made from soft flexible material work by reducing dynamic instability found in OA.¹⁴⁷ Thus, wearing a soft knee brace has been shown to provide increased leeway in activity in patients with OA at the knee (Level II-3 Grade B).¹⁴⁸ Whether the brace fit tightly made no difference in outcome.¹⁴⁷ Soft braces are thought to work by improving proprioception at the knee (Level II-3 Grade B).¹⁴⁸ One meta-analysis of both randomized and nonrandomized controlled trials showed moderate effects of soft braces on pain mild-to-moderate changes to subjective reports of physical function in knee OA. However, the authors cited low-quality level of evidence due to some lack of blinding (Level I, Grade C).¹⁴⁹
- PFPS: One study showed that the use of bracing for PFPS provided immediate reduction of pain and quadriceps activation. Variability in pain symptoms was seen in individuals, so they were grouped into two groups, one group more and one with less pain. Some study participants felt uncomfortable pressure on the patella from the design of the knee brace, no hole present, thought by the researchers to be from a silicone ring within the front of the brace. They suggest prescribers of this brace for PFPS should instruct patient to only wear during pain-provoking activities. No adverse reactions. They cite that they do not fully understand why these braces reduce pain in PFPS remains unclear and cite that it could be due to the increase in contact area and change in the abnormal joint movement which may be reducing stress on the joint.¹⁵⁰
- Hole cut-out: One study reported knee bracing without a patella hole cut-out as superior citing the thought that the cut-out gives the wearer more dynamic somatosensory stimulation and control (Level 1 Grade B or C).¹⁵¹ For anterior knee pain in the case of PFPS and tendinitis, the knee sleeve, either elastic or neoprene, compresses the knee, and patellar strap can be used to control pain. The patella cut-out in the knee sleeve provides comfort and not function.

The patella strap attaches underneath the patella and gives it a slight push up in efforts to lower traction across the patellar tendon. Limited evidence, citing a Cochrane review; unable to make concrete recommendations on their use. They may have some use as a second-line treatment in pain reduction as they are inexpensive and without contraindication. Patients can simply stop using them if no benefit is found.

Knee braces may improve post-surgical kinesiophobia, or fear of movement, in short-term follow-up (2 and 6 weeks) with PFP compared with minimal intervention (single-blind randomized controlled trial (1:1)).¹⁵² Practitioners may consider prescribing knee bracing when clinically relevant for rehabilitation of PFP (single-blind randomized controlled trial (1:1)).¹⁵² One literary review found strong evidence that the higher the level of kinesiophobia, the higher the pain intensity and disability levels (Level 1 Grade B).¹⁵³

- Prophylactic braces: These aim to prevent injury to medial collateral ligament (MCL) due to excessive valgus force as literature claims these braces may provide more than 10% to 30% resistance to this force as compared to a braceless knee. They are most commonly used in American football leagues; however, both the American Academy of Orthopedic Surgeons and the American Academy of Pediatrics claim there is insufficient evidence to support their use. Some studies do show benefits in high-risk conditions; however, these braces are not shown to prevent MCL injury.¹³⁹
- Functional braces: These help stabilize the joint after a meniscus or ligamentous injury with the use of sturdy material, with a goal to prevent more injury. There is little difference between custom versus off-the-shelf and functional braces.¹³⁹

In the case of a PCL injury, strength evidence has shown favorable outcomes in the use of newly developed dynamic bracing when integrated into a conservative management plan.¹⁵⁴ These braces work by applying an anterior counterforce to the posterior tibial translation proximally.¹⁵⁴

In bracing after ACL reconstruction, meta-analysis of seven studies with a total number of 440 participants, there was no significant difference between the bracing and not bracing group. Thus, researchers concluded that knee bracing post repair likely does not provide clinical improvements and they recommend against routinely prescribing bracing for these patients. However, the same meta-analysis found adverse effects of bracing, noting this was subjectively scored. Adverse

effects may include thigh atrophy, soft tissue compression and a loss of flexion (Level I, meta-analysis. Grade D).¹⁴⁹ One study cited that up to 87% of the orthopedic surgeons prescribed functional knee bracing post ACL repair and that these braces, which may lead to thigh muscle atrophy and decrease strength, do not significantly impact the laxity in the knee joint nor have a significant impact on pain reduction or an effect on joint laxity, pain, or satisfaction. Can add support but not replace rehabilitative therapies.¹³⁹

- Orthotics and shoe inserts: Shoe orthotic inserts may be prescribed by practitioners for OA knee pain.¹³⁹ One paper showed, with low quality of evidence, little to no difference in pain reduction when using a lateral wedge shoe insert on knee OA pain as compared to a no insole and probably little to no pain reduction or improvement of function or quality of life compared to the use of a neutral insole more than 12 months.¹⁴³ Additionally, lateral wedges compared to valgus knee braces showed the possibility of little to no difference in pain reduction and increased function after 6 months of wear.¹⁴³ One paper showed, with a low quality of evidence, that people with OA who use knee braces experience little to no pain relief or increase in function.¹⁴³ There is moderate quality of evidence to suggest lateral wedged and neutral insoles give little to no pain relief or increase in function.¹⁴³ One meta-analysis did not find clinical significance between the use of lateral wedge insoles and neutral insoles in pain reduction in the treatment of medial compartment knee OA pain (meta-analysis Level 1, Grade C).¹⁵⁵
- Taping: Kinesiology tape or “kinesio taping” has been shown in meta-analysis to be effective in relieving pain and increasing function in patients suffering from knee OA; however, the results should be interpreted cautiously due to the low quality of evidence as there was a small sample size in most of the RCTs and lack of good comparison to drug standards (Level I, Grade C).¹⁵⁶
- Bracing complications and noncompliance: Multiple studies cite noncompliance as an ongoing issue with bracing to relieve knee pain and in particular varus bracing (Level I, Grade C).^{139,142} Adverse effects of knee bracing have been reported to include pain in the posterior knee, low back, leg and plantar aspect of the foot, skin irritation and bruising; poor fit may worsen these symptoms.^{139,143} While comparing an AFO brace for OA to a standard knee offloading brace one study noted significantly lower side effects in the AFO group. However, this study was limited in that those in the AFO group, less knee contacting brace, used more bandaging and more therapy, which begs the question of whether these factors contributed to the perception of less side effects or actually prevented some of the side effects on their own (multicenter randomized control) (Level II-1 Grade C).¹⁴⁶ Need for scoring side effects, which impact compliance. Braces are cumbersome and uncomfortable, shoe inserts require bigger bulkier and less stylish shoes. Long-term study are needed to look at braces and orthoses against conservative care.¹⁴³

Assistive Devices

Practitioners often prescribe assistive walking devices (eg, cane, crutch, walker), to relieve pain from OA.¹³⁹ Our search did not find any studies showing a superior device when comparing cane to walker to crutches.

- Canes: The cane has been shown to reduce the intra-articular loading forces by more than 10% and are most effective for medial and lateral compartment disease with less efficacy in patellofemoral disease.¹³⁹ When a person starts using a cane, the energy expenditure is increased for about the first month and then diminishes as the user habituates to its daily use.¹⁵⁷ There is about 1 month of decreased efficacy where the user gets used to using the cane; in month 2, energy expenditure decrease as well as pain.¹⁵⁷ In knee OA prescribers should ensure proper cane height and instruct patients to utilize the cane on the contralateral side, having the cane advance with the affected leg while the patient is walking.¹³⁹ Canes have been shown to reduce pain and improve function as well as some quality of life (QOL) aspects. One single blinded study showed the use of a cane to decrease pain with ambulation and decrease the use of NSAIDs (Level I Grade),¹⁵⁷ with diminished returns over 3 months.¹⁵⁸
- Walkers and crutches: Walkers provide stability and are safer for patients with danger of falls. Long-term use of a walker has a high association with older age and poorer prognosis. Crutches are generally better suited for patients with post of knee pain or knee injury that demonstrate good safety awareness and upper body strength (“crutch muscles”).

Thus, in summary, the optimal choice for an orthosis remains unclear, and long-term implications are still to be determined.¹⁴³ One study cites the quality of evidence, and studies are poor and need to be improved focusing on randomization and blinding, and prior to increasing lengths of studies, short-term efficacy should be shown to justify long-term efficacy. A period of 5 years, in the case of knee pain from OA, is likely necessary because of the chronicity of the disease. Additionally, this study suggests a standardized knee score when pooling data (such as WOMAC).¹⁴³

Consensus Points for Durable Medical Equipment (DME)

1. DME is an effective treatment modality for knee pain; Level II-2, Grade B, Consensus Strong
2. The choice DME to be utilized for knee pain should be based on the individual diagnosis and takes into account comfort and compliance; Level I, Grade C, Consensus Weak
3. Unicompartamental unloading bracing: medial compartment unloading braces are an effective treatment for knee OA and superior to other bracing options; Level II-1, Grade B, Consensus Strong
4. Lateral shoe wedge is an effective treatment for OA knee pain as compared to a neutral insole. The patients may benefit from the feeling of protection which could decrease their likelihood of kinesiophobia and improve recovery as motion is liberalized; Level II-3, Grade C, Consensus Weak
5. Patella strap, neoprene sleeve and taping should be utilized for knee pain; Level II-3, Grade C, Consensus Weak
6. A cane is an appropriate treatment for OA knee pain, with the proper training size selection and guidance by the prescriber; Level II-1, Grade B, Consensus Strong
7. A walker can be used for chronic pain secondary to knee OA and in the elderly to improve gait stability in those patients with higher risk of falls, as well as for ambulation in short distances; Level II-1, Grade B, Consensus Strong
8. Crutches should be utilized post knee injury in younger patients with good balance and upper body strength; Level II-2, Grade C, Consensus Strong

Recommendations Regarding Injection-Based Therapies

Corticosteroid Injections

Intra-articular corticosteroid (IAC or IACS) injections were pioneered by Dr Jollander in 1953.¹⁵⁹ The first trial for IAC injections was performed by White and Norton in 1958.¹⁶⁰ IAC injections have become standard therapy for patients with knee osteoarthritis (OA). However, there is still debate on the efficacy of IAC injections for knee OA. A Cochrane review in 2015 evaluated 27 trials with a total of 1767 participants comparing IAC injections with a sham injection or no treatment for patients with knee OA.¹⁶¹ The quality of evidence was “low” due to a high or unclear risk of bias in many studies. There was also a significant amount of inconsistencies regarding the dosage of corticosteroid and the type of corticosteroid used. The review did find IAC injections reduced pain and improved function more effectively than control interventions. The authors reported an improvement of pain after IAC injection was moderate at 1–2 weeks post-injection, mild to moderate at 4–6 weeks, and minor at 13 weeks. There was no statistically significant evidence of treatment effect at 26 weeks. The Cochrane review concluded, given the poor quality and variability in the studies, it is uncertain if there is a significant advantage of IAC injections for knee OA after 6 weeks post-injection.

Conversely, a more recent systematic review and meta-analysis evaluating the magnitude and duration of the effect of IAC for knee OA found moderate evidence for IAC injections to reduce pain related to knee OA.¹⁶² The treatment effect was up to 3 months after the injection in the meta-analysis. The number needed to treat was 10. Unfortunately, as was such the case in the Cochrane review, there is significant heterogeneity between studies evaluating IAC for knee OA. The inconsistency between the Cochrane review and the meta-analysis underscores the need for RCTs with specific corticosteroids used and a fixed-dose to consider further the efficacy of pain relief and duration of effect (see Table 11).

In summary, IAC may provide short-term mild-to-moderate pain relief for patients with knee osteoarthritis.

Consensus Points for Intra-Articular Corticosteroid Injections

1. Intra-articular corticosteroids (IACS) may provide short-term pain relief for patients with symptomatic OA of the knee refractory to conservative medical management; Level 1, Grade B, Consensus Moderate
2. IACS is superior to intra-articular hyaluronic acid only in the short-term (2–4 weeks), and is more effective in patients with severe knee pain secondary to OA; Level 1, Grade B, Consensus Moderate
3. IACS is associated with an increase in cartilage volume loss. Caution should be exercised with repeat injection to prevent progression of disease; Level II, Grade B, Consensus Moderate

Hyaluronic Acid

HA, also known as hyaluronan, is a large glycosaminoglycan that is one of the natural components of cartilage. This is not to be confused with hylan, which is the modified form of hyaluronic acid. Hylan has a higher viscosity to theoretically increase the time in the joint and therefore increase the efficacy of treatment.¹⁶³ Studies have shown that HA can stimulate the synthesis of cartilage and reduce inflammation.¹⁶⁴ Broadly, these injections are referred to as viscosupplementation. There has been debate over both the cost-effectiveness and efficacy of HA injections to treat knee osteoarthritis. There also is a lack of consensus about the number of injections needed and the type of viscosupplementation utilized.

A meta-analysis published in *JAMA* in 2003 reviewed a total of 22 trials with a review of a total of 2927 patients. Overall, there was a small noticeable effect of HA injections when compared to placebo. Furthermore, the authors found a publication bias which confounds the reported benefit of HA injections.¹⁶⁵ A systematic review and meta-analysis of randomized trials, which included a total of 831 patients, showed that HA injections had statistically significant improvement in knee pain but without clinically meaningful outcomes when compared to oral NSAID use. The long-term side effect profile of HA is better than with oral NSAID use which could support its use over NSAIDs, particularly in the elderly population.¹⁶⁶ A meta-analysis of randomized controlled trials published in 2018 compared HA injections to methylprednisolone injections for knee osteoarthritis. Five studies with a total of 1004 patients showed that both HA and methylprednisolone injection therapies were safe interventions that were effective in pain and physical function and stiffness at multiple time points (4 weeks, 12 weeks, and 26 weeks).¹⁶⁴ In addition, Dai et al compared the efficacy and safety of HA versus hylan. Their meta-analysis showed that there was no clinically significant difference between either treatment. However, due to the higher cost of hylan, it was recommended that its use be discouraged from treating knee osteoarthritis pain.¹⁶³

Another area of debate is the number of injections that are needed for HA therapy. A meta-analysis of single-injection products utilizing a post hoc placebo comparison showed that a single injection could produce results similar to multi-injections. One of the limitations is that the study was funded by LCA Pharmaceuticals, and the author is an employee and shareholder of the company that makes a single injection HA product.¹⁶⁷ Another systematic review compared the effectiveness of different dosing regimens of HA. This study identified 11 studies and found no difference in outcomes between a series of three and five injections. The authors' conclusion based on their results suggested that there appears to be a similar efficacy with single injections with greater cost-effectiveness.¹⁶⁸ A review of the effectiveness and safety of Supartz (sodium hyaluronate) from pooled clinical trials showed that single 5-week injections could provide reductions in pain and improve function without any significant side effects. A total of 1155 patients were included in the analysis, and the intervention was compared to placebo¹⁶⁹ (see Table 12).

Unfortunately, there are many conflicting conclusions from systematic reviews and meta-analyses on viscosupplementation for the treatment of knee osteoarthritis. Overall, viscosupplementation is a safe, well-tolerated procedure that has been shown to have an improvement in pain and function. However, there is no evidence to suggest that one type of viscosupplementation product is superior to another, and also no evidence to suggest that a series of injections are better than a single injection.

Table 11 Evidence Table Regarding Intra-Articular Corticosteroid Injections

Study	Study Type	Details	Systematic Literature Review Grading	USPSTF Rating
Arroll et al 2004 ³⁴⁷	Meta Analysis	10 studies; IACS vs placebo with follow-up at 24 weeks, Outcome measures: VAS	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I
McAlindon et al, 2017 ¹⁸⁶	RCT	N=140; IACS q4 months vs placebo with 2-year follow-up, Outcome measures: WOMAC, cartilage volume	Level I study based on all criteria	Level I
Jüni et al, 2015 ¹⁶¹	Systematic review	27 included studies, N=1767; IACS vs placebo with follow-up to 26 weeks; Outcome measures: WOMAC, joint space narrowing, quality of life and function	Level I study based on all criteria	Level I
van Middelkoop et al, 2016 ³⁴⁸	Meta analysis	7 studies, N=620; IACS vs placebo with follow-up 4 weeks to 1 year, Outcome measures: VAS, WOMAC	Level I study based on all criteria	Level I
Concoff et al, 2017 ³⁴⁹	Systematic review	30 studies, N=5848; single vs multiple intra-articular hyaluronic acid (IAHA) injections with follow-up at 13–26 weeks, Outcome measures: WOMAC, VAS, Knee Osteoarthritis Outcome Score (KOOS), Musculoskeletal Outcomes Data Evaluation and Management System (MODEMS), Index of Severity for Osteoarthritis for the Knee (ISK)	Level I study based on all criteria	Level I
Richette et al, 2015 ³⁵⁰	Meta analysis	8 studies, N=2199; IAHA vs placebo with follow-up at 3 months, Outcome measures: pain intensity, WOMAC	Level I study based on all criteria	Level I
van der Weegen et al, 2015 ³⁵¹	RCT	N=196; IAHA vs placebo with follow-up at 1, 3, and 6 months, Outcome measures: ROM, VAS, and WOMAC	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I
Bannuru et al, 2009 ³⁵²	Meta analysis	7 studies, N=606; IACS vs IAHA with follow-up at 2, 4, 8, 12, and 26 weeks, Outcome measures: pain change from baseline	Level I study based on all criteria	Level I
Yilmaz et al, 2019 ³⁵³	RCT	N=90; IACS vs IA-NSAIDs with follow-up at 1, 3, and 6 months, Outcome measures: VAS and WOMAC	Level 2 study based on all criteria	Level I
Riis et al, 2017 ³⁵⁴	RCT	N=100; IACS vs placebo with follow-up at 14 and 26 weeks, Outcome measures: KOOS-Pain	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I
Bodick et al, 2014 ³⁵⁵	RCT	N=228; a immediate release vs extended release IACS with follow-up at 8, 10, and 12 weeks, Outcome measures: numeric rating scale (NRS), WOMAC	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I

Table 12 Evidence Table Regarding Hyaluronic Acid

Study	Study Type	Details	Systematic Literature Review Grading	USPTF Rating
Petrella et al, 2002 ³⁵⁶	RCT	N=120; IAHA vs NSAIDs vs placebo with follow-up at 4 and 12 weeks, Outcome measures: VAS, WOMAC, function	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I
Miller et al, 2020 ¹⁶⁶	Meta analysis	N=831; IAHA vs NSAIDs with 4–26 weeks follow-up, Outcome measures: pain and function	Level I study based on all criteria	Level I
Bellamy et al, 2006 ³⁵⁷	Systematic review	76 included studies; IAHA vs placebo, CS, NSAIDs, PT, exercise, arthroscopy, CAM, with follow-up to 18 months; Outcome measures: pain and function	Level I study based on all criteria	Level I
Stitik et al, 2017 ³⁵⁸	Meta analysis	24 studies, N=2168; IAHA vs placebo, PRP, 3 vs 5 HA injections, NSAIDs, arthroscopy, CS, with follow-up 12–52 weeks, Outcome measures: VAS, WOMAC	Level I study based on all criteria	Level I
Concoff et al, 2017 ³⁴⁹	Systematic review	3 studies, N=5848; single vs multiple IAHA injections with follow-up at 13–26 weeks, Outcome measures: WOMAC, VAS, KOOS, MODEMS, ISK	Level I study based on all criteria	Level I
Campbell et al, 2015 ³⁵⁹	Systematic review	14 studies, N=20,049; PRFA: IAHA vs placebo, NSAIDs, or CS with follow-up to 6 months, Outcome measures: VAS, pain, function, range of motion, activity-related knee pain, pooled effect size, Lequesne score, WOMAC	Level I study based on all criteria	Level I
Richette et al, 2015 ³⁵⁰	Meta analysis	8 studies, N=2199; IAHA vs placebo with follow-up at 3 months, Outcome measures: pain intensity, WOMAC	Level I study based on all criteria	Level I
van der Weegen et al, 2015 ³⁵¹	RCT	N=196; IAHA vs placebo with follow-up at 1, 3, and 6 months, Outcome measures: range of motion (ROM), VAS, and WOMAC	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I
Navarro-Sarabia et al, 2011 ³⁶⁰	RCT	N=306; 4 cycles of 5 IAHA vs placebo with follow-up at 6, 12, 24 and 36 months, Outcome measures: VAS and OARSI criteria	Level I study based on all criteria	Level I
Strand et al, 2012 ³⁶¹	RCT	N=379; a single IAHA vs placebo with follow-up at 13 weeks, Outcome measures: VAS and WOMAC	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I
Berenbaum et al, 2012 ³⁶²	RCT	N=426; IAHA vs IAHA with follow-up at 6, 14, 20 and 26 weeks, Outcome measures: VAS, WOMAC, intermittent and constant osteoarthritis pain index (ICOAP), Lequesne, OMERACT	Level 2 study based on strong criteria for QAREL and Cochrane and moderate quality for IPM	Level I
Arden et al, 2013 ³⁶³	RCT	N=218; a single IAHA vs placebo with follow-up at 2, 4, and 6 weeks, Outcome measures: WOMAC	Level 3 study based on intermediate criteria for QAREL and Cochrane and fair quality for IPM	Level I

Consensus Points for Hyaluronic Acid

1. Intra-articular hyaluronic acid (IAHA) is a safe and effective therapeutic option for patients with symptomatic OA of the knee refractory to conservative medical management; Level 1, Grade A, Consensus Strong
2. IAHA demonstrates superior, longer-lasting efficacy post-injection in comparison to intra-articular corticosteroids in patients with knee pain secondary to OA; Level 1, Grade A, Consensus Strong
3. Current evidence suggests there is no difference between the reduction in knee pain secondary to OA following a 3-week course of IAHA versus a 5-week course; Level II, Grade B, Consensus Moderate
 - (a) HA formulation differences including molecular weight and cross-linkage have been proposed as more or less effective; Level III, Grade C, Consensus Weak

Recommendations Regarding Genicular Nerve Ablations

Genicular nerve ablation (GNA) is a percutaneous, needle-based therapy option designed to palliatively treat knee pain. Analogous to an intra-articular injection with corticosteroid, GNA is not intended to remedy the root cause of pain or structurally alter the joint in any way; rather, the goal is to block/interrupt the transmission of pain signals from the knee, itself, thus eliminating the perception of pain by the brain. Like facet rhizotomy, GNA utilizes radiofrequency energy (aka radiofrequency ablation or RFA) focused on the active tip of a needle or cannula to create a focal energy field that will coagulate targeted sensory nerves caught in its path, thus preventing their ability to communicate with the central nervous system – in the case of the knee, the targeted nerves, for the most part, are the genicular nerves.

The genicular nerves provide innervation to the majority knee via a network of different branches that collectively communicate pain from different locations around the joint (Figure 1):

- Superior medial (SM)

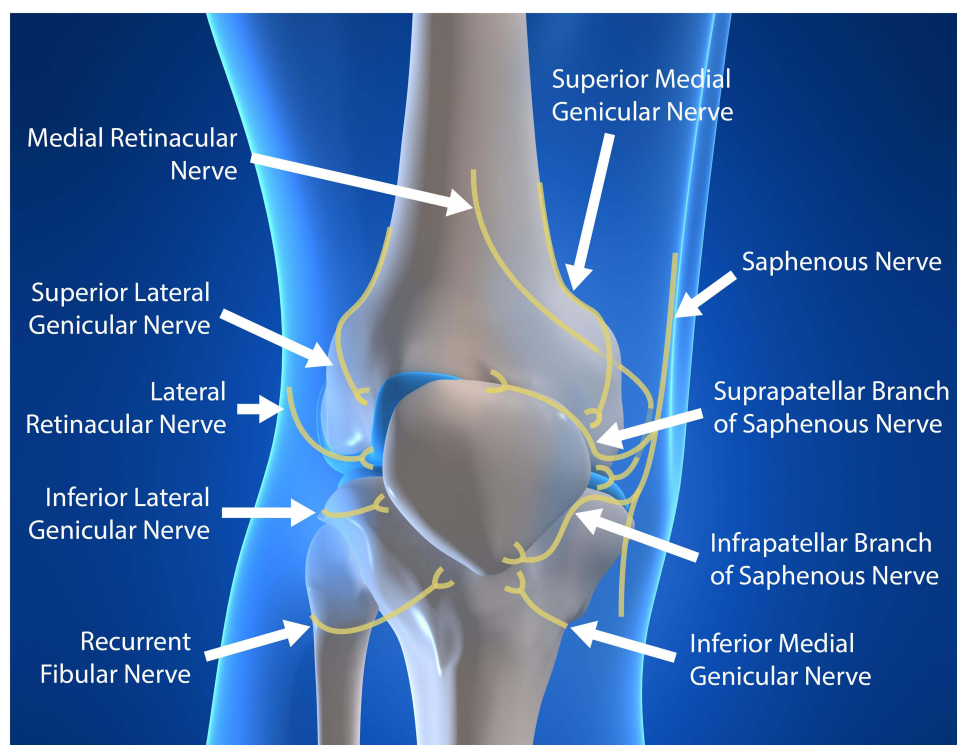


Figure 1 Illustration of the innervation of the knee.

- Superior lateral (SL)
- Inferior medial (IM)
- Inferior lateral (IL)

Additional innervation to the knee is provided by branches from the saphenous and the fibular nerves (Figure 1):

- Recurrent fibular nerve (RFN)
- Infrapatellar branch of the saphenous nerve (IPB)
- Suprapatellar branch of the saphenous nerve (SPB)
- Medial retinacular nerve (MR)
- Lateral retinacular nerve (LR)

Not all of these nerves need be ablated to provide significant relief as the majority of the evidence for GNA involves the ablation of only the SM, SL and IM genicular nerves. The initial publications on GNA were a number of case series demonstrating the efficacy of the therapy on pain after knee arthroplasty surgery.^{170–172} Over time, the procedure evolved in its application and began to be used prior to surgery. At the time of this manuscript, eight RCTs on GNA have been completed, all of which demonstrated efficacy in reducing pain and safety by ablating the SM, SL and IM genicular nerves.^{173–175} The first of these was published by Alcidi et al in 2007 on 40 patients treated with GNA and then followed for 1 month. The authors demonstrated significant improvements in pain and function as compared to control (TENS).¹⁷⁶

In 2011, Choi et al published the results of a double-blind RCT on 38 patients with knee OA receiving either GNA or sham.¹⁷⁷ The authors showed statistically significant improvements in VAS and function at 4 and 12 weeks, with no adverse events noted. The authors showed significant reductions in pain and improvements in quality-of-life scores. El-Hakeim et al published similar results in 2018 on 60 patients out to 6 months.¹⁷⁸ In 2017, Qudsi-Sinclair et al published the results of an RCT on 30 patients with knee pain refractory to total knee arthroplasty (TKA) by targeting the SM, SL and IM nerves. The authors showed significant improvements in pain and function out to 12 months in the treatment group.¹⁷⁹

In 2018, Davis et al published the results of the largest prospective RCT to date – 151 patients with knee osteoarthritis treated with cooled GNA or intra-articular steroid (IAS) injections.¹⁷⁴ The authors showed statistically significant improvements in pain and function out to 12 months in patients treated with GNA. In a follow-up study, Hunter et al published the 18- and 24-month data on this subject group showing sustained improvements in pain and function with no safety concerns identified.¹⁸⁰

While the bulk of the evidence on GNA demonstrates efficacy by ablating the “three main genicular nerves” (ie, SM, SL and IM), there remains some debate as to whether they are the most optimal targets, or if others should be done in conjunction with the main three to provide for a more complete denervation of the knee. In 2011, Ikeuchi et al published the results of a non-randomized, prospectively trial on 35 patients treated with ablation of the MR and IPB.¹⁸¹ The authors demonstrated significant improvements in knee pain and quality of life scores out to 6 months. In stark comparison to the studies published on GNA using the 3 main nerves, Ikeuchi’s study reported minor bleeding and prolonged hypoesthesia in 67% and 78% of the subjects, respectively, suggesting that while the improvements are comparable, targeting these nerves instead of SM, IM and SL may come with a higher incidence of adverse events. The prevalence of hypoesthesia is not surprising given that the MR is responsible for cutaneous innervation of the knee as a branch of the medial femoral cutaneous nerve. This complication could be potentially averted by using a pulsed ablation instead. The results published by Ikeuchi suggest that the MR and IPB should be considered as supplemental targets in those patients with refractory pain to ablation of SM, SL and IM nerves.

Of the 10 RCTs, 5 used thermal RFA (TRFA) (70° to 90°C; 90–270 seconds) 4 used cooled RFA (CRFA) (60°C for 150 seconds, and 1 used pulsed RFA (PRFA) (42°C for 10 minutes). At the time of this manuscript, there are no comparative studies suggesting which RFA modality provides better results for knee pain. As it pertains to pulsed RFA, aside from the one RCT by Gulec et al,¹⁸² which did not have a control arm and only compared bipolar to monopolar pulsed GNA, the remaining

Table 13 Evidence Table Regarding Genicular Nerve Ablations

Study	Study Type	Details	Systematic Literature Review Grading	USPSTF Rating
Alcidi et al, 2007 ¹⁷⁶	RCT	N=40; TRFA vs TENS with follow-up at 30 days, Outcome measures: VAS and Lequesne's index	Level 3 study based on all criteria	Level II-I
Choi et al, 2011 ¹⁷⁷	RCT	N=38; TRFA vs sham with follow-up at 4 and 12 weeks, Outcome measures: VAS and Oxford Knee Score (OKS)	Level 2 based upon moderate quality scoring for Cochrane and QAREL and intermediate study scoring for IPM	Level I
Ikeuchi et al, 2011 ¹⁸¹	n-RCT	N=35; RFA vs nerve block with follow-up at 1, 3 and 6 months; Outcome measures: VAS and WOMAC	Level 3 study based on all criteria	Level II-2
Shen et al, 2016 ³⁶⁴	RCT	N=54; TRFA w/ PRP+HA vs PRP+HA with follow-up 3 months, Outcome measures: VAS, American Knee Society Score (AKSS), Short-Form Health Survey 36-item (SF-36)	Level 2 based upon moderate quality scoring for Cochrane and intermediate study scoring for IPM and QAREL	Level II-I
Takahashi et al, 2016 ³⁶⁵	RCT	N=17; RFA vs microwave diathermy with follow-up at 1 and 3 weeks, Outcome measures: Japan Orthopaedic Association (JOA) scale, Lequesne Index	Level 3 based upon moderate quality scoring for QAREL and IPM and low study scoring for Cochrane	Level II-I
Gulec et al, 2017 ¹⁸²	Case Series	N=100; Percutaneous RFA: monopolar vs bipolar with follow-up at 12 weeks, Outcome measures: VAS	Level 3 study based on all criteria	Level II-2
Qudsi-Sinclair et al, 2018 ¹⁷⁹	RCT	N=28 post-TKA; TRFA vs sham with follow-up at 12 months, Outcome measures: VAS, OKS and KSS	Level 2 based upon moderate quality scoring for QAREL and IPM and intermediate study scoring for Cochrane	Level I
Sari et al, 2018 ¹⁷⁰	RCT	N=73; TRFA vs IAS + morphine with follow-up at 1 and 3 months, Outcome measures: VAS and WOMAC	Level 3 study based on all criteria	Level II-I
Davis et al, 2018 ¹⁷⁴	RCT	N=151; CRFA vs IAS with follow-up at 6 and 12 months, Outcome measures: NRS and OKS	Level 2 based upon intermediate quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
El-Hakeim et al, 2018 ¹⁷⁸	RCT	N=60; Conventional RFA vs oral analgesics with follow-up at 2 weeks, 3 and 6 months, Outcome measures: VAS and WOMAC	Level 3 based upon moderate quality scoring for QAREL and IPM and low study scoring for Cochrane	Level I
McCormick et al, 2018 ³⁶⁶	RCT	N=53; Conventional RFA with follow-up at 1, 3 and 6 months, Outcome measures: NRS and WOMAC	Level 3 based upon moderate quality scoring for QAREL and IPM and low study scoring for Cochrane	Level II-2

evidence is limited to prospective and retrospective case series and case reports¹⁷³ – therefore, there is no high-level evidence to support its use for knee pain (see Table 13).

Consensus Points for Genicular Nerve Ablation

1. RFA of the SM, SL and IM genicular nerves is a safe and effective therapeutic option for treating knee pain secondary to OA as well as pain refractory to TKA; Level 1, Grade A, Consensus Strong
2. RFA of the SM, SL and IM genicular nerves can significantly reduce knee pain and improve function in patients with knee OA and pain refractory to TKA; Level 1, Grade A, Consensus Strong
3. Thermal or cooled RFA should be utilized when performing GNA; Level 1, Grade A, Consensus Strong
4. In patients with persistent knee pain after GNA targeting the SM, SL and LM genicular nerves, one may consider targeting IL, MR and/or IPB for supplemental treatment; Level III, Grade B, Consensus Moderate

Recommendations Regarding Regenerative Therapies

Platelet-Rich Plasma

PRP was first introduced in the 1970s for wound and bone healing in the field of oral and maxillofacial surgery.¹⁸³ Recently, PRP shows promise for treating various orthopedic, musculoskeletal, and pain syndromes. PRP has varied components including platelets and other cell types, growth factors, and cytokines. The basic premise to foster an environment that promotes healing by directing cell proliferation, chemotaxis, and angiogenesis.¹⁸⁴ These changes are seen in intra-articular PRP injection for symptomatic knee osteoarthritis where studies demonstrate a significant decrease in protein concentration of immunoglobulins associated with inflammation, including apolipoprotein A-I, haptoglobin, immunoglobulin kappa chain, transferrin, and matrix metalloproteinase. Additionally, post PRP injection proteins associated with chelation and anti-aging physiological functions increase significantly, including matrilin, transthyretin, and complement 5. Moreover, these laboratory findings are complemented with clinical success, including improvements in knee symptoms of the index of osteoarthritis severity¹⁸⁵ and a decrease in synovial fluid volumes. This enhanced environment for healing can be an inherent advantage of PRP in comparison to other injectates. For instance, repeated intra-articular corticosteroids may have detrimental systemic and local effects, including greater cartilage volume loss. Although the clinical outcomes of such have not been fully demonstrated.^{186,187}

It is important to discern that all PRP is not equivalent. Factors at minimum that can affect the final PRP product include volume of blood aspirated, baseline platelet count, patient health status and comorbidities, patient medications, anticoagulant of choice, centrifugation parameters, and inclusion/exclusion of leukocytes. Not distinguishing for this variability, we have summarized below the gross evidence evaluating the use of PRP for knee-related pathology.

The combined data from the reviews discussed support PRP's excellent safety profile. A total of 26 studies (n=1051) that reported adverse events demonstrated non-significant differences between other conservative treatments and PRP injection.¹⁸⁸ The other reviews show agreement that PRP-treated patients did not display significant increased adverse events or additional side effects.^{189–191} PRP intra-articular knee injection is safe with comparable risk factors to other conservative treatment for knee osteoarthritis.

- Intra-articular PRP: Several systematic reviews have analyzed the available literature regarding PRP specifically focusing on symptomatic knee osteoarthritis. In 2017, Dai et al evaluated the efficacy of PRP for the treatment of knee osteoarthritis compared to saline control and hyaluronic acid. Meta-analysis of 10 RCTs (n=1069) revealed that at 6 months post injection, PRP and hyaluronic acid had similar effects with respect to pain relief and functional improvement. However, at 12 months, PRP was associated with significantly better pain relief and functional improvement as measured by the WOMAC that exceeded the minimal clinically important difference. When comparing PRP to saline, PRP intervention was more effective for pain relief and functional improvement at 6 and 12 months with scores that again exceeded the minimal clinically important difference.¹⁸⁹

Similarly, in 2020, Hohmann et al compared intra-articular knee injections of PRP primarily to hyaluronic acid. A pooled estimate of 12 RCTs (n=1248) supported superiority of PRP (n=636) compared to hyaluronic acid (n=612) for symptomatic knee pain at 6 and 12 months. There was significant difference in reported knee pain favoring PRP at both 6 months and 12 months. Although the data did not demonstrate significant difference in clinical outcomes utilizing the WOMAC and International Knee Documentation Committee (IKDC) scores. The authors present evidence in favor of PRP for treatment of symptomatic knee osteoarthritis pain.¹⁹²

A separate systematic review in 2020 investigated PRP versus hyaluronic acid in the treatment of knee osteoarthritis by including 14 RCTs (n=1350). Compared with hyaluronic acid, PRP had higher scores in long-term (>24 weeks) VAS, IKDC, WOMAC-Pain, WOMAC-stiffness, WOMAC-Physical Function, and WOMAC-Total. The authors conclude that PRP demonstrates more advantages over hyaluronic acid in the conservative treatment of knee osteoarthritis, including reduced long-term pain and improved knee function.¹⁹⁰

Moreover, in 2019 another systematic review found analogous evidence when comparing PRP to hyaluronic acid. Meta-analysis of RCTs (N=1314) revealed that PRP injections reduced pain and improved function more effectively than hyaluronic acid injections in patients with knee osteoarthritis. The VAS pain score showed a significant difference at 12 months. Furthermore, better functional improvement was observed in the PRP group, as measured by the WOMAC function score at 3, 6, and 12 months.¹⁹¹

A recent comprehensive systematic review and meta-analysis in 2020 largely supported the above findings and divided the meta-analysis by both reported pain score (VAS) and functional improvement (WOMAC). Trams et al included 22 studies (n=888) for meta-analysis, investigating reported pain via the VAS comparing PRP versus placebo (6 studies, n=190), corticosteroids (2 studies, n=53), or hyaluronic acid (15 studies, n=645). PRP showed significant improvements in VAS compared to both placebo and hyaluronic acid subgroups. The same review also analyzed functional outcomes measured by the WOMAC scale: 25 studies compared PRP versus control groups: 9 studies compared against placebo (n=264), 1 study compared against corticosteroids (n=19), and 15 studies compared against HA (n=730). The pooled estimates, as well as each subgroup, showed significant differences in favor of PRP.¹⁸⁸

While most studies have compared PRP to hyaluronic acid injections or placebo, we reviewed two RCTs that investigated PRP versus corticosteroid. In 2017, Jubert et al randomized patients to treatment either with single leukocyte-reduced PRP (n=34) or corticosteroid intra-articular injection (n=30). Quality of life differences at 3 and 6 months were significantly improved in the PRP group and so did general health perception differences at 6 months. The authors conclude that a single PRP intra-articular injection is effective for relieving pain and improving activities of daily living and quality of life in late-stage knee OA (Kellgren–Lawrence grade III to IV). Furthermore, for patients older than 67 years, a single intra-articular injection of PRP has similar results to a single injection of corticosteroid.¹⁹³

A second RCT by Guvendi et al included 50 patients diagnosed with grade III knee osteoarthritis. Patients were randomized to three groups: single corticosteroid injection group (n=17), single PRP injection group (n=19), and three PRP injection group with 1 week interval (n=14). WOMAC and Lequesne function scores at the 6-month follow-up were significantly improved in the PRP groups compared to the corticosteroid group. No significant differences were demonstrated in the single PRP treatment group compared to the three-injection group, which differs from previous studies that suggest superiority to multiple injections. The authors suggest this lack of improvement after multiple injections may be due to later-stage cartilage damage in the patients, or due to the short one-week interval between injections.¹⁹⁴

A systematic review pooled these two aforementioned studies (n=53) to conclude there were non-significant differences in pain score via VAS in favor of PRP versus corticosteroid ($p = 0.23$).¹⁸⁸ The same systematic review reported that PRP was significantly superior compared to corticosteroid in terms of functional outcomes. Compared to corticosteroid injection for symptomatic knee osteoarthritis, PRP intra-articular injection shows superior outcomes, including improved knee joint function and quality of life.

In 2021, Bennell et al published the results of an RCT comparing PRP to saline for the treatment of knee pain secondary to OA. While the results showed no statistically significant difference between PRP and placebo, the authors were not technically using PRP in the treatment arm.¹⁹⁵ PRP is defined as a concentration of platelets that is $\geq 2\times$ that of whole blood – the concentration utilized by the authors was only $1.6\times$, thus it cannot be considered PRP. This fact alone

largely explains why the results are contrary to those published in over three dozen other studies. As such, the results of this study are not reflective of PRP as a treatment for knee pain secondary to OA. In 2022, Chu et al published the results of the largest RCT on PRP to date (n=610) comparing PRP to sham, utilizing a concentration of roughly 4.3× that of whole blood. The PRP arm showed statistically significant improvements over sham in IKDC, WOMAC, and VAS out to 60 months.¹⁹⁶

Although there has been much variation in treatment protocols and specifically the total number of PRP injections, the optimal number of PRP injections for positive outcomes has been under investigation. In 2019, one systematic review studied the clinical effectiveness of single versus multiple (double or triple) PRP injections for knee osteoarthritis. Meta-analysis of five clinical trials (n=301) showed that, at 6 months after the intervention, there were no significant differences in pain improvement between the differing number of injection groups. However, at 6 months, there was a significant and clinically important difference in improvement in knee functionality in favor of multiple injections, with sub-analysis only evident for the results of single versus triple injections. However, the authors conclude that there is difficulty in generalizing data due to the lack of standardization between the multiple injection intervals.¹⁹⁷

A second meta-analysis of six studies (n=255) comparing single versus multiple [two (n=85) or three times (n=170)] injections of PRP assessed significant differences in reported VAS pain scores in favor of multiple injections. However, only three injections of PRP (n=170) showed significant differences compared to a single injection.¹⁸⁸ The same review reported functional outcomes were also analyzed in five studies (n=211) comparing single versus multiple injections and showed significant differences again in favor of multiple injections.¹⁸⁸ Further research is needed to create frequency protocols, although data suggest multiple PRP injections may provide superior relief relative to a single injection.

- **Intraosseous PRP:** The benefit of intraosseous PRP injections compared to intra-articular injection alone has also been investigated. Su et al randomized 86 patients with grade II to III knee osteoarthritis to one of three groups: intra-articular PRP combined with intraosseous injection of PRP, intra-articular PRP alone, or intra-articular hyaluronic acid. Patients that received both intraosseous and intra-articular PRP received both 2 weeks apart. The group that received both intraosseous and intra-articular PRP demonstrated significantly superior VAS and WOMAC scores than the other groups up to 18-month follow-up.¹⁹⁸

These findings support the pilot study by Sanchez et al where patients (n=13) diagnosed with severe knee osteoarthritis grade III and IV received one PRP intra-articular injection combined with two PRP intraosseous injections targeting the subchondral bone. There was a significant improvement in pain, symptoms, function, and quality of life measures from baseline at week 8 through the 24-week study period. Eight of the 13 patients who completed the study showed minimal clinically important improvement.¹⁹⁹

Further building on these positive findings, Sanchez et al studied 60 patients suffering from severe knee osteoarthritis (grade III and IV) who either received intra-articular PRP (weekly for 3 weeks) or a combination of intra-osseous and intra-articular PRP (intraosseous plus intra-articular injection week 1, followed by 2 weekly intra-articular injections). In this observational study, the combination of intraosseous with intra-articular injection group showed significant improvement in KOOS and WOMAC. Sixteen of the 30 patients in the intraosseous group reached minimal clinically important difference at 2 and 6 months, compared to 8 out of 30 in the intra-articular PRP alone group. When comparing the response of both groups, there was a statistically significant improvement in pain reduction and functional improvement at 6 and 12 months. Of note, there were no clinically superior differences at 2 months which the authors suggest relates to the delayed time course of PRP, and interestingly, intra-articular PRP alone in this study did not show statistical benefits in either pain or functional scores.²⁰⁰ Both of the above studies report no significant adverse effects post intraosseous PRP injection.

- **Use in soft tissue**
 - **Chronic patellar tendinopathy:** PRP has been studied in chronic patellar tendinopathy. In 2014, Dragoo et al randomized 23 patients with patellar tendinopathy on examination and MRI who had failed nonoperative treatment to receive ultrasound-guided dry needling alone (n=13) or with injection of leukocyte-rich PRP

(n=10). Both groups received standardized eccentric exercises. The PRP group had improved significantly more than the dry needling group at 12 weeks, although by greater than 26 weeks there was no significant difference in the Victorian Institute of Sports Assessment score for patellar tendinopathy. The authors conclude that PRP treatment accelerates the recovery from patellar tendinopathy relative to exercise and ultrasound guided dry needling alone, although the benefits decrease over time.²⁰¹

- In 2015, Zayni et al further evaluated PRP to treat chronic patellar tendinopathy. Patients received either one or two PRP injections 2 weeks apart (n=40) under ultrasonography guidance within and around the hypoechogenic patellar tendon area; nine patients failed PRP treatment and needed surgery, the remaining patients significantly improved. Those receiving two PRP injections had better outcome measures in the Victorian Institute of Sport Assessment-Patella, VAS, and Tegner scale.²⁰² These studies suggest, PRP may improve outcomes in functionality in treatment of chronic patellar tendinopathy within the first 12 weeks, and two injections may provide additional benefit over one.
- Pes anserinus: One study evaluated PRP in the treatment of pes anserinus pain syndrome. In 2014, Rowicki et al investigated 33 patients with chronic pain in the pes anserinus who were treated with PRP into that region. And 84.8% of these patients demonstrated total or near-total pain relief within 6 months of treatment. However, this study lacks a control group and provides low-level evidence in favor of PRP for pes anserinus pain syndrome.²⁰³
- Medial collateral ligament sprains: Regarding medial collateral ligament sprains, 46 healthy athletes with high grade II or III medial collateral ligament sprains were randomly allocated to two equal groups: one group received a single PRP injection and both groups went on to participate in a 12-week functional rehabilitation program. In the PRP treatment group, only at the 4-week mark, pain was significantly reduced, while stability and Lysholm scores were noted to have no significant difference.²⁰⁴
- Meniscal tear: One case report describes a bucket handle meniscal tear treated with three separate PRP injections in and around the meniscus within 7 months of the diagnosis. Patient-reported resolution of pain 8 months post injury and MRI 10 months post injury and arthroscopy 47 months post injury showed complete resolution of the meniscal tear. Although promising reports for the treatment of ligaments, cartilage, and tendons further studies are required before appropriate recommendations may be made.²⁰⁵

In conclusion, PRP is an anabolic, safe, effective approach for knee osteoarthritis, as well as possible targeted treatments specifically for meniscus and ligament structures (see Table 14). Best practice approach is pending, but Level 1 evidence supports treatment of symptomatic knee osteoarthritis with PRP. Further research is needed for development of standardized treatment protocols demonstrating ultimately the ideal composition of injectate along with optimal dosing, timing interval, and frequency, as well as patient selection.

Consensus Points for Platelet-Rich Plasma

1. Intra-articular PRP is an effective and safe treatment for knee pain secondary to osteoarthritis with Kellgren–Lawrence Scale II–III; Level 1, Grade A, Consensus Strong
2. Intra-articular PRP is at least as effective as an entire series of viscosupplementation with hyaluronic acid; Level 1, Grade A, Consensus Strong
3. Intra-articular PRP can improve function in patients with knee pain secondary to osteoarthritis; Level 1, Grade A, Consensus Strong

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) have also been used in hopes of promoting an anabolic healing environment. MSCs have the ability to provide signals for tissue regeneration as well as the additional potential to differentiate into a variety of connective tissue-type cells. Animal studies suggest intra-articular and intraosseous injection of MSCs appear to result in regeneration of articular cartilage in osteoarthritic models.²⁰⁶ However, it is important to be cognizant given their inherent nature, not all MSCs are equivalent. MSCs are found in most tissues of the human body but primarily sourced

Table 14 Evidence Table Regarding Platelet-Rich Plasma

Study	Study Type	Details	Systematic Literature Review Grading	USPSTF Rating
Cerza et al, 2012 ³⁶⁷	RCT	N=120; PRP vs HA with follow-up at 24 weeks, Outcome measures: WOMAC	Level 3 study based on all criteria	Level I
Filardo et al, 2012 ³⁶⁸	RCT	N=109; PRP vs HA with follow-up at 12 months, Outcome measures: IKDC, EQ-VAS, Tegner, KOOS and ROM	Level I based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Spaková et al, 2012 ³⁶⁹	Observational, Prospective	N=120; PRP vs HA with follow-up at 6 months, Outcome measures: WOMAC and NRS	Level 3 based upon intermediate quality scoring for QAREL and Cochrane and low study scoring for IPM	Level II-2
Patel et al, 2013 ³⁷⁰	RCT	N=78; PRP vs PRP x2 vs saline with follow-up at 6 months, Outcome measures: WOMAC and VAS	Level 2 based upon moderate quality scoring for QAREL and Cochrane and intermediate study scoring for IPM	Level I
Cole et al, 2015 ³⁷¹	RCT	N=111; PRP vs HA with follow-up at 1 year, Outcome measures: WOMAC, IKDC, VAS, and Lysholm	Level I study based on all criteria	Level I
Filardo et al 2015 ³⁷²	RCT	N=443; PRP vs HA with follow-up at q2 months, Outcome measures: IKDC, Tegner, VAS, and EuroQol	Level I based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Raeissadat et al, 2015 ³⁷³	RCT	N=160; PRP vs HA with follow-up at 12 months, Outcome measures: WOMAC and SF-36	Level 3 study based on all criteria	Level I
Forogh et al, 2016 ³⁷⁴	RCT	N=41; PRP vs corticosteroid with follow-up at 6 months, Outcome measures: KOOS, 20MV, ROM, and VAS	Level I study based on all criteria	Level I
Lana et al, 2016 ³⁷⁵	RCT	N=105; PRP vs HA vs PRP and HA with follow-up at 12 months, Outcome measures: WOMAC and VAS	Level I based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Montañez-Heredia et al, 2016 ³⁷⁶	RCT	N=53; PRP vs HA with follow-up at 6 months, Outcome measures: VAS, KOOL and EuroQol	Level I based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Paterson et al, 2016 ³⁷⁷	RCT	N=37; photo-activated PRP vs HA with follow-up at 12 weeks, Outcome measures: VAS, KOOS, and KQoL	Level 2 based on moderate quality scoring for Cochrane and QAREL and intermediate study scoring for IPM	Level I
Simental-Mendía et al, 2016 ³⁷⁸	RCT	N=65; PRP vs oral acetaminophen with follow-up at 24 weeks, Outcome measures: VAS, WOMAC and SF-12	Level 3 study based on all criteria	Level-I
Smith et al, 2016 ³⁷⁹	RCT	N=30; PRP vs saline with follow-up 1 year, Outcome measures: WOMAC	Level I study based on all criteria	Level I
Duymus et al, 2017 ³⁸⁰	RCT	N=102; PRP vs HA vs Ozone with follow-up at 12 months, Outcome measures: WOMAC and VAS	Level 2 based on moderate quality scoring for Cochrane and intermediate scoring for QAREL and IPM	Level I

Görmeli et al, 2017 ³⁸¹	RCT	N=162; PRP vs HA with follow-up at 6 months, Outcome measures: VAS and IKDC	Level 1 study based on all criteria	Level I
Güvendi et al, 2017 ¹⁹⁴	Observational, Prospective	N=50; PRP x1 vs PRP x3 vs corticosteroid x1 with follow-up at 6 months, Outcome measures: WOMAC, VNS, Lequesne, and HADS	Level 3 study based on all criteria	Level II-2
Jubert et al, 2017 ¹⁹³	RCT	N=75, PRP vs corticosteroid with follow-up at 6 months, Outcome measures: KOOS and SF-36	Level 1 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Lisi et al 2017 ³⁸²	RCT	N=30; PRP vs HA with follow-up at 6 months, Outcome measures: WOMAC, Lysholm, Tegner, AKSS, Lequesne and VAS	Level 1 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Ahmad et al, 2018 ³⁸³	RCT	N=89; PRP vs HA with follow-up at 6 months, Outcome measures: VAS and synovium appearance	Level 2 based on moderate quality scoring for Cochrane and intermediate scoring for QAREL and IPM	Level I
Angoorani et al, 2018 ³⁸⁴	RCT	N=54; PRP vs PT/TENS with follow-up at 8 weeks, Outcome measures: VAS	Level 2 based on moderate quality scoring for Cochrane and QAREL fair study scoring for IPM	Level I
Buendía-López et al, 2018 ³⁸⁵	RCT	N=106; NSAIDs vs HA vs PRP with follow-up at 12 months; Outcome measures: WOMAC and VAS	Level 2 study based on all criteria	Level I
Di Martino et al, 2018 ³⁸⁶	RCT	N=167; PRP vs HA with follow-up at 24 months, Outcome measures: IKDC, EuroQol, Tegner	Level 1 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Gaballa et al, 2018 ³⁸⁷	RCT	N=200; PRP vs HA vs Plasma w/ growth factors vs Ozone with follow-up at 12 months, Outcome measures: VAS, WOMAC, and Lequesne	Level 3 study based on all criteria	Level I
Khan et al, 2018 ³⁸⁸	RCT	N=150; PRP vs corticosteroid with follow-up at 6 months, Outcome measures: WOMAC and VAS	Level 3 based upon intermediate quality scoring for QAREL and Cochrane and low study scoring for IPM	
Lin et al, 2018 ³⁸⁹	RCT	N=87; PRP vs HA vs saline with follow-up at 12 months, Outcome measures: WOMAC and IKDC	Level 1 study based on all criteria	Level I
Louis et al, 2018 ³⁹⁰	RCT	N=54; PRP vs HA with follow-up at 6 months, Outcome measures: WOMAC and VAS	Level 1 based on strong quality scoring for Cochrane and QAREL and moderate study scoring for IPM	Level I
Nabi et al, 2018 ³⁹¹	RCT	N=67; PRP vs Triamcinolone with follow-up at 6 months, Outcome measures: KOOS and VAS	Level 2 study based on all criteria	Level I
Rahimzadeh et al, 2018 ³⁹²	RCT	N=44; PRP vs Prolotherapy with follow-up at 6 months, Outcome measures: WOMAC	Level 1 study based on all criteria	Level I

(Continued)

Table 14 (Continued).

Study	Study Type	Details	Systematic Literature Review Grading	USPSTF Rating
Su et al, 2018 ¹⁹⁸	RCT	N=86; IO PRP vs IA PRP vs HA with follow-up at 18 months, Outcome measures: WOMAC and VAS.	Level 3 study based on all criteria	Level I
Wu et al, 2018 ³⁹³	RCT	N=20; PRP vs Saline with follow-up at 6 months, Outcome measures: WOMAC	Level 2 based on moderate quality scoring for Cochrane and QAREL and intermediate study scoring for IPM	Level I
Huang et al, 2019 ³⁹⁴	RCT	N=120; PRP vs HA vs corticosteroid with follow-up at 12 months, Outcome measures: WOMAC and VAS	Level 3 study based on all criteria	Level I
Anz et al, 2020 ³⁹⁵	RCT	N=90; PRP vs bone marrow aspirate concentrate (BMAC) with follow-up at 12 months, Outcome measures: WOMAC and IKDC	Level 2 based on moderate quality scoring for Cochrane and intermediate scoring for QAREL and IPM	Level I
Elksniņš-Finogejevs et al, 2020 ³⁹⁶	RCT	N=40; PRP vs Triamcinolone with follow-up at 1 year, Outcome measures: VAS, IKDC, and KSS	Level 2 based on moderate quality scoring for Cochrane and QAREL and intermediate study scoring for IPM	Level I
Kesiktaş et al, 2020 ³⁹⁷	RCT	N=54; PRP vs HA vs Prostralan with follow-up at 3 months, Outcome measures: WOMAC, VAS and HAC	Level 2 based on moderate quality scoring for Cochrane and QAREL and intermediate study scoring for IPM	Level I
Pishgahi et al, 2020 ³⁹⁸	RCT	N=92; PRP vs Prolotherapy vs autologous conditioned serum with follow-up at 6 months, Outcome measures: WOMAC and VAS	Level 3 study based on all criteria	Level I
Raeissadat et al, 2020 ³⁹⁹	RCT	N=102; PRP-derived growth factor vs HA with follow-up at 12 months, Outcome measures: WOMAC and Lequesne	Level 2 based on moderate quality scoring for Cochrane and QAREL and intermediate study scoring for IPM	Level I
Reyes-Sosa et al, 2020 ⁴⁰⁰	RCT	N=60; PRP vs oral Celecoxib with follow-up 12 months, Outcome measures: WOMAC	Level 3 based upon intermediate quality scoring for QAREL and Cochrane and low study scoring for IPM	Level I

for reimplantation from the bone marrow and adipose due to ease of access. Volume of aspirate, patient health status and comorbidities, patient medications, harvesting protocol parameters and technique can all affect the final MSC product. Not distinguishing this heterogeneity, we have summarized below the gross clinical evidence evaluating using MSCs for knee-related pathology.

In 2020, Prodromos et al investigated the use of autologous MSCs (stromal vascular fraction, culture-expanded adipose-derived stem cells, bone marrow aspirate, culture-expanded bone marrow, and minimally manipulated fat graft) for the treatment of knee osteoarthritis. This extensive systematic review utilized historical controls of placebo treated patients adapted from the placebo arms of other prior knee injection studies for treatment of osteoarthritis. In the 29 studies of 1063 treated knees included, VAS pain scores were statistically significant with improvements greater than the minimally important clinical difference at a post-treatment mean of 6 months. Those post MSC injection showed continuing functional improvements greater than 6 months and continued to improve up to 1 year, whereas the placebo scores were down trending by 6 months. There was no dose-response relationship shown regarding the number of cell dose and outcomes. Also, in comparing cell type among those with large enough cohorts, culture-expanded adipose-derived stem cells, bone marrow aspirate, and culture-expanded bone marrow all show similar outcomes. This review concludes that autologous MSCs are effective to improve both pain and function for those suffering from knee osteoarthritis.²⁰⁷

A second review in 2020 by Migliorini et al enrolled a total of 1069 osteoarthritic knees from 18 studies (of which 3 had controls), with mean age 57.39. Seventy-two percent of all studies harvested the stem cells from the iliac crest (bone marrow-derived MSCs), whereas 28% harvested from the adipose tissue (adipose-derived MSCs). The mean VAS improved from a baseline of 55.20 to 30.98 and 36.91 at 6- and 12-month follow-up, respectively. The mean WOMAC score improved from a baseline of 25.66 to 25.23 and 15.60 at 6- and 12-month follow-up, respectively. Mean walking distance also improved from a baseline of 71.90 m to 152.22 and 316.72 m at 6- and 12-month follow-up, respectively. No significant differences were seen in VAS, WOMAC, and walking distance scores concerning the donor source. Those treated with earlier stage Grade II and III osteoarthritis did show statistically significant better outcomes.²⁰⁸ The study reports there were 136 (12.7%) local complications detected. Mostly pain and swelling, and rare cases of skin reaction (n=1), allergic reaction (n=2), and hematoma (n=2). The authors agree that autologous MSCs are safe and show favorable results in improving both pain and function in treating knee osteoarthritis.

To control for the increased bias that may result from additional therapies at the time of MSC delivery, Tan et al formulated their systemic review in 2021 with the goal to pool the outcomes of treatment using intra-articular injections of MSCs alone without any adjuvant therapies for osteoarthritis. Nineteen Level I or Level II studies (n=440) were included of which 9 used bone marrow MSCs and 10 used adipose MSCs. The meta-analysis concluded intra-articular injections of MSCs without any adjuvant therapies significantly improves pain and function for knee osteoarthritis. Interestingly, differing from prior reviews, this review suggests significant better outcomes obtained with the use of bone marrow MSCs as compared with adipose MSCs. The authors also found favorability of cultured MSCs compared to uncultured MSCs. The authors suggest that due to their stringent inclusion criteria, this review provides greater homogeneity among the studies and thus fairer comparisons among the data.²⁰⁹

On the contrary, one systemic review by Dai et al in 2021 investigating intra-articular MSC injection for knee osteoarthritis formed an unfavorable conclusion compared to the previously discussed reviews that predominately support the use of MSCs. The authors suggest there was no significant difference found in the MSC treated osteoarthritic knee compared to a placebo control. This review included both autologous and allogeneic MSCs totaling 13 studies of which 6 were adipose-derived, 5 were bone-marrow-derived, 1 was placenta-derived, and 1 was umbilical cord-derived (MSC=250; total controls=111). In the subgroup analysis compared to placebo (n=66), MSC intra-articular injections (n=67) did not show significant differences in VAS for pain, WOMAC pain score, WOMAC function score, nor WOMAC stiffness score. However, compared to hyaluronic acid (n=77), MSC intra-articular injection (n=77) did show significantly better improvement in VAS for pain, WOMAC pain score, WOMAC total score, and WOMAC stiffness score. Although the minimum clinically important difference was not exceeded. Furthermore, in the pooled groups of controls including both placebo and hyaluronic acid (n=143), the authors did again find a statistically significant difference in favor of MSCs (n=144). In terms of function, including a total of 8 studies and pooling

hyaluronic acid and all placebo controls (n=121) compared to MSCs (n=118), there was also a statistical improvement in WOMAC which did exceed minimum clinically important difference only when compared to the hyaluronic group, but not the placebo group alone. Although this study shows MSCs did not statistically outperform placebo injections, the total number of subjects evaluated to make this comparison was low (n=66) and the majority of follow-up was relatively short-term at 6 months compared to 12 month outcomes for the majority of the hyaluronic acid controls.²¹⁰ In addition, pooling placebo and hyaluronic acid controls the MSCs did reach statistically significant levels of pain and function improvement.

Regarding potential cartilage repair several studies included radiological evaluations. In 2019, Kim et al published a meta-analysis of level II RCTs to investigate clinical outcomes and cartilage repair in osteoarthritis of the knee post treatment with intra-articular injections of MSCs at 12 or 24 months. Four of the studies utilized bone marrow-derived mesenchymal stem cells, while one study utilized adipose-derived stromal vascular fraction. Of note, two of these studies performed concomitant surgery (high tibial osteotomy), and three of the studies used additional injections including PRP or hyaluronic acid. Of the studies that reported VAS (4 studies: MSCs=56; controls=58), there was a significant decrease in VAS in MSC treated knees compared to controls. Additionally, in combined VAS and WOMAC pain scales (MSCs=91; controls=93) a significant decrease was also seen. Looking at functional outcomes reported in three studies (MSCs=35; controls=35), there was an improvement in WOMAC scores although this did not reach a level of statistical significance. However, two studies that reported Lysholm knee function scores (MSCs=49, controls=51) did demonstrate statistical improvement in those treated with MSCs. Moreover, the combined functional scores of both WOMAC and Lysholm (MSCs=69; controls=71) did reach statistical significance in favor of MSCs improving functional outcomes. Regarding improvements in imaging, three studies (n=96) reported MRI evaluation post treatment with a trend towards improvement; however, this did not reach a level of statistical significance. The authors conclude that MSCs did show improved pain and function in a period of 12–24 months. However, there was not clinical evidence to suggest improving cartilage repair in knee osteoarthritis.²¹¹

An additional systematic review in 2019 by Ha et al includes 17 studies (6 RCTs) focusing on intra-articular MSCs for osteoarthritis of the knee clinical outcomes and cartilage repair. Eight studies used bone marrow-derived MSCs, six used adipose tissue-derived stromal vasculature fraction, two used adipose tissue-derived MSCs, and one used umbilical cord blood-derived MSCs. Fifteen of the 17 studies reported improved clinical outcomes at final follow-up in the MSC group. Nine of 11 studies reported improvement of the cartilage state on MRI, and 6 of 7 studies reported repaired tissue on second-look arthroscopy, although some studies displayed mixed results. The authors conclude that intra-articular MSCs showed improvements in pain and function in many cases at follow-up less than 28 months.²¹²

Similarly, Jaibaji et al in 2021 published a systematic narrative review to analyze autologous MSCs for the treatment of cartilage defects of the knee. Seventeen studies (including 5 RCTs, of which 8 using bone marrow sourced, 3 using adipose-derived, 3 using synovial-derived, 2 using peripheral blood, and 1 using bone marrow and peripheral blood) were found with a mean age of 35.1 years (n=367). The authors conclude that all studies demonstrated significant improvements in function outcomes in their patients with osteochondral lesions, suggesting MSCs, whether derived from synovium, bone marrow, adipose tissue, or peripheral blood, may have clinical efficacy in cartilage regeneration. Of note the authors do acknowledge a high risk of bias in at least one category in each of the five RCTs. Four out of five had high risk for bias due to lack of appropriate blinding.²¹³

In 2020, Ma et al included 10 RCTs (n=335) to analyze the efficacy and safety of intra-articular injection of MSCs in the treatment of knee osteoarthritis. Five used autologous mesenchymal stem cells (adipose-derived MSC=3; bone marrow-MSC=2) and five used allogeneic mesenchymal stem cells (umbilical cord-derived=1; placenta-derived=1; bone marrow-derived MSC=2, adipose-derived MSC=1). The strength of this review includes the increased stringent exclusion criteria which included the exclusion of studies with concomitant treatment such as low/high tibial osteotomy, micro-fracture, and knee replacement. This meta-analysis showed significant improvement in MSC groups pain scores compared to control groups. In terms of function, all WOMAC scores also improved significantly. However, 2 of the 10 studies were not blinded. Regarding cartilage repair, there was no significant difference in the Whole-Organ Magnetic Resonance Imaging Score (WORMS), but the MSC group did show significant increase in cartilage volume (3 studies, MSC=46: control=42). There were also a significantly higher proportion of patients with adverse events reported in the

MSC treatment group. All 10 studies in their review evaluated adverse events, reporting mostly mild and moderate clinical symptoms including joint pain, swelling, pain at the injection site, and joint effusion. One study reported three severe adverse effects including dyslipidemia, anemia, and muscle hemorrhage although all had complete recovery. Another study reported one patient with development of severe prepatellar bursitis that ultimately resolved. Of the six studies that reported both numbers of patients in MSCs and control arms with adverse events, there was a significant higher rate of adverse events in the MSCs group. However, as discussed, the overwhelming majority of adverse events were rare and mild. The authors conclude that intra-articular injection of MSCs is an effective and safe modality to relieve pain and improve the function of patients with knee osteoarthritis. This review states the improved findings in both pain and function may be due to the addition of newly incorporated studies of adipose tissue and umbilical cord stem cell sources.²¹⁴ Furthermore, The overall good safety profile of MSCs was consistent among each of the systematic reviews we have previously discussed, suggesting MSCs are a safe treatment for knee osteoarthritis.

The overwhelming majority of systematic reviews conclude that MSCs are favorable and safe in the treatment of knee osteoarthritis, particularly demonstrating improvements of pain and function. One out of the eight reviews in their subgroup analysis concludes that MSCs did not show improvement in pain or function compared to purely placebo controls; however, in the same review, the pooled placebo and hyaluronic acid controls groups did show statistical differences favoring MSCs. This contradiction may be due to a small sample size and a relatively short follow-up. Furthermore, several reviews were also able to demonstrate increases in cartilage volumes and at the minimum suggest MSCs may play a role to delay further progression of osteoarthritic changes. However, given the inherent heterogeneity of MSCs as well as the lack of RCTs, there is insufficient evidence for ideal treatment paradigms and generalizability at this time.

Consensus Points for Mesenchymal Stem Cells

1. Intra-articular MSCs are a safe treatment for knee OA; Level II-1, Grade B, Consensus Moderate
2. Intra-articular MSCs are effective for treating pain and improving function in patients OA; Level II-1, Grade B, Consensus Moderate

Amniotic Tissue

Human amniotic membrane (HAM) and human amniotic fluid-derived cells (HAFCs) contain properties that present potential for alleviation of OA disease progression. Amniotic tissues consist of anti-inflammatory factors that upregulate anti-inflammatory pathways, high hyaluronic acid and proteoglycan content, as well as regenerative chondrocyte differentiation properties.

A study by Vines et al examined single intra-articular injection of cryopreserved particulated human amnion and amniotic fluid cells in six patients (n=6) with Kellgren–Lawrence (KL) grades 3 or 4 knee OA. This prospective open-label pilot study was conducted to assess feasibility and safety for future placebo-controlled trials of intra-articular amniotic suspension allograft (ASA) injections. The ASA injection did not significantly affect blood cell counts, lymphocytes, or inflammatory markers; there were, however, small but statistically significant increases in IgG and IgE levels.

Two patients developed a temporary increase in pain which resolved within 2 weeks. None of the patients developed an infection or experienced an inflammatory reaction; there was no difficulty with injection and no immediate complication.

The authors conclude that a single intra-articular injection of ASA is feasible in patients suffering from knee OA. Observed improvements in KOOS, IDKC, and single assessment numeric evaluation (SANE) scores within the small study population suggest substantial improvement if reproducible in a placebo-controlled trial.²¹⁵

Another study conducted by Ramon Castellanos assessed the short-term safety and effectiveness of amniotic membrane/umbilical cord particulate (AMUC) as a treatment option for knee OA. The single-center, prospective, investigator-initiated pilot study enrolled a total of 20 subjects (n=20). Ultrasound-guided injection of 50 mg AMUC was injected, and patients were monitored at 6 weeks, 12 weeks, and 24 weeks. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to evaluate pain scale, with WOMAC-A evaluating pain with five questions, WOMAC-B evaluating stiffness with two questions, and WOMAC-C evaluating physical function with seven

questions. Patients who did not report a greater than 30% reduction in pain using the WOMAC-A questionnaire received a second injection at 6 weeks.

The average pain score was reduced significantly from 74.3 ± 17.2 mm at baseline to 45.0 ± 25.4 mm at 6 weeks (pain reduction of 37.6%), 35.4 ± 26.6 mm at 12 weeks (pain reduction of 55.1%), and 37.4 ± 26.7 mm at 24 weeks (pain reduction of 51.7%). Those patients reporting more than 50% relief included 25% (5/20) at 6 weeks, 45% (9/20) at 12 weeks, and 50% (10/20) at 24 weeks.

Patients' physical function scores were significantly reduced from 74.2 ± 18.0 mm at baseline to 51.4 ± 24.9 mm at 6 weeks (physical function improvement of 25.3%), 40.3 ± 26.8 mm at 12 weeks (physical function improvement of 42.3%), and 41.7 ± 27.3 mm at 24 weeks (physical function improvement of 44.5%).

A patient global assessment (PGA) was also performed. Seventeen of the 20 patients reported positive improvement at 6 and 12 weeks, and 14 patients reported improvement at 24 weeks. However, it is important to note that hypertension was a significant covariate.

A total of 11 patients received a second injection at the 6-week mark. Seven of the 8 (87.5%) patients with a body mass index (BMI) >30 kg/m² received a second injection; only 4 of the 12 (33.3%) patients with BMI <30 kg/m² qualified for a second injection. One subject received greater than 30% improvement from the first injection (38% improvement) but was still allowed the second injection per investigator discretion. Results showed significant improvement in non-obese patients at all time points, but only significant improvement for obese patients at 12 and 24 weeks. MRI evaluation of the total study population showed significant improvement in bone marrow lesions (BMLs) in seven patients.

This study suggests preliminary safety and effectiveness in pain relief and improvement in function in those with knee OA BML grades 0–3. The authors conclude that randomized placebo-controlled studies would provide more insight on AMUC as a potential treatment option for symptomatic knee OA.²¹⁶

Mead et al conducted a single-center retrospective study investigating intra-articular knee injection of 100 mg lyophilized and micronized AMUC in those suffering from KL Grade 3 or 4 moderate-to-severe knee OA. Data points included patient global impression of change (PGIC), which used a 7-point scale, and global perceived improvement (GPI), which used a percentage improvement compared to baseline. The investigators used the Outcome Measures in Rheumatology (OMERACT)-OARSI responder criteria to evaluate changes in pain, function, and patient's global assessment.

Forty-two patients were enrolled into the study, reporting an average pain score of 6.6 ± 0.5 out of 10, prior to injection. Twelve months post injection, 31 of the 42 (74%) patients reported clinically significant improvement of knee pain and function via PGIC. Pain function improved by $62 \pm 24\%$ at 1 month, $69 \pm 27\%$ at 3 months, $69 \pm 27\%$ at 6 months, and $64 \pm 31\%$ at 12 months on the GPI. This improvement lasted a mean duration of 12.1 ± 4.5 months. Treatment response was 81% (34/42) ascertained by the simplified OMERACT-OARSI criteria at the 12-month mark.

Of the KL grade 3 knee OA subjects, improvement in knee pain and function by PGIC was seen in 87% of the patients (13/15) at 12 months and lasted 13.4 ± 3.6 months; the OMERACT-OARSI treatment response rate was 93% (14/15) in these patients at 12 months. In the KL grade 4 group, 67% of the patients (18/27) reported clinically significant improvement of knee pain and function via PGIC for a duration of 11.5 ± 4.9 months. At 12 months, the OMERACT-OARSI treatment response rate was 74% (20/27).

One patient developed knee swelling within 36 hours of injection. However, s/he reported progressive improvement and, by week 6, showed significant pain relief and increased range of motion. No other adverse events were found.

The authors suggest that the intra-articular injection of AMUC particulate may be a valuable treatment option for those with moderate-to-severe knee OA and could possibly delay knee replacement; however, prospective randomized controlled trials are needed for further validation.²¹⁷

In a multicenter randomized single-blinded controlled trial conducted by Farr et al, ASA was injected in subjects with knee OA and compared to saline and HA. The study included 200 subjects with a 1:1:1 randomization to ASA (68 subjects), HA (64 subjects), or saline (68 subjects). Patient-reported outcomes (PROs) including ED-5D-5L, KOOS, VAS, Tegner, and SANE were obtained at baseline, 3 months, and 6 months post injection. Those who reported unacceptable pain relief at 3 months were withdrawn which included nine patients from the ASA group (13.2%), 44 patients from the HA group (68.8%), and 51 patients from the saline group (75%). Significant differences were found between ASA and HA at the 3-month mark in the EQ-5D-5L pain and anxiety subgroup, KOOS pain, symptoms and

ADLs subgroups, and VAS for pain during strenuous work, pain during normal daily living, and overall pain. At 6 months post injection, scores for EQ-5D-5L mobility, activities, pain, health subgroups, KOOS pain, symptoms, ADL, SANE scores, and VAS overall pain demonstrated superior improvement in the ASA group compared to both HA and saline groups. Moreover, there was a larger responder rate for ASA (69.1%) in comparison to HA (39.1%) and saline (42.6%) (see Table 15).

In conclusion, this Level 1 randomized controlled trial investigating ASA in symptomatic knee OA depicts greater statistically and clinically significant improvements when compared to the saline and HA control groups. ASA may be a useful option as a non-operative treatment for symptomatic knee OA.²¹⁸

Consensus Points for Amniotic Tissue

1. Intra-articular ASA is an effective treatment option for knee pain secondary to OA; Level I, Grade B, Consensus Moderate

Recommendations Regarding Neurostimulation Peripheral Nerve Stimulation (PNS)

PNS uses electrical currents to treat selected nerves. This can also be done with peripheral nerve field stimulation (PNfS), where instead of stimulating a specific nerve, the small nerve endings in the tissue are stimulated.²¹⁹ When selecting patients for PNS, the main complaint of the patient should be a burning paresthesia in the peripheral nerve distribution that supplies the knee. A diagnostic block of the infrapatellar branches of the saphenous and the articular branch of the peroneal nerve should be done prior to consideration of PNS. If the patient responds with transient relief, they may be a good candidate for PNS/PNfS.²²⁰ While there are a number of case reports or series supporting the use of PNS for knee pain, there is only one RCT with a small sample size addressing PNS for knee pain²²¹; therefore, there are limited data to support its use currently.²²² Prior to pursuing permanent implant, a trial should be performed demonstrating at least 50% reduction of the patient's pain. The placement of the leads for PNS/PNfS can be placed under fluoroscopic or ultrasound guidance.²²⁰ When placed under ultrasound guidance, the nerves can be visualized allowing for the safe placement of the PNS leads while avoiding neurovascular damage.²²³ The sensory innervation of the knee comes mainly from the femoral and sciatic nerves with a small portion of the posterior aspect of the knee being supplied by the posterior branch of the obturator nerve.^{224,225} Therefore, placement of the leads should be done under image guidance with the goal to place the leads in the area of the femoral and sciatic nerves.²²²

Consensus Points for Peripheral Nerve Stimulation (PNS)

1. PNS is an effective treatment option for chronic post-surgical and neuropathic knee pain; Level IV, Grade I, Consensus Moderate

Dorsal Root Ganglion Stimulation (DRG)

In contrast to PNS, in the short time since the introduction of DRG, there have been a number of studies supporting its use for chronic knee pain, specifically, postsurgical joint pain in the knee.²²⁶ In a single-center retrospective study of 14 patients implanted with DRG systems, 8 patients underwent a single L3 lead implanted, 1 patient had a single L4 lead implanted, and 3 patients had 2 leads implanted (L3 and L4). Twelve of the 14 had greater than 50% reduction of their pain.²²⁷ Similarly, in the FOCUS study, 12 patients with total knee replacements had successful treatment of their pain after DRG stimulation.²²⁸ The efficacy of DRG treatment for post-operative pain associated with TKA has additionally been supported by Morgella et al's outcomes, with 27 patients implanted with DRG systems demonstrating a reduction in VAS of approximately 69%.²²⁹ Localization of where to place the DRG stimulation leads was based on a proposed method of predicting target levels using sensory stimulation of the DRG with a radiofrequency cannula.²³⁰ In a sample size of 23 patients, the most impactful DRG stimulation occurred at L4 for the knee with optimal lead placements being at L3 and L4.²³¹ While the 2019 Neurostimulation Appropriateness Consensus Committee (NACC) guidelines suggest that two leads may be sufficient for the majority of patients, therapy should be individualized to each patient and may

Table 15 Evidence Table Regarding Amniotic Tissue

Study	Study Type	Details	Systematic Literature Review Grading	USPSTF Rating
Vines et al 2015 ²¹⁵	Open-label prospective feasibility study	N=6; Study demonstrates feasibility of one intra-articular injection with amniotic suspension allografts for treating knee osteoarthritis.	Level 4 based on limited quality scoring for Cochrane and QAREL	Level II-3
Castellanos et al 2019 ²¹⁶	Prospective, investigator-initiated, single-center pilot study	N=20; Intra-articular injection of amniotic membrane/umbilical cord particulate demonstrates preliminary safety, relief of pain, and improvement in function in patients with knee OA with severities varying from BML Grades 0–3. A second injection may be needed in obese individuals.	Level 4 based on limited quality scoring for Cochrane and QAREL	Level II-3
Mead et al 2020 ²¹⁷	Single center, investigator-initiated, retrospective study	N=42; An intra-articular knee injection of amniotic membrane/umbilical cord particulate may be helpful in relieving pain and improving function in those with Kellgren–Lawrence (KL) grade 3 or 4. This treatment may delay knee replacement for up to one year.	Level 4 based on limited quality scoring for Cochrane and QAREL	Level II-3
Farr et al 2019 ²¹⁸	RCT	N=200; ASA versus HA versus saline with follow-up at 6 months, Outcome measures: EQ-5D-5L, KOOS, VAS and SANE. ASA showed statistically significant improvements in knee OA compared to control groups	Level 2 based upon moderate quality scoring for QAREL and Cochrane and intermediate study scoring for IPM	Level I

require addition of more leads to depending on the patients' response to the trial. Overall, DRG is a safe, efficacious and proven therapy for treatment of chronic post-surgical pain, including knee pain.²³²

Consensus Points for Dorsal Root Ganglion Stimulation

1. DRG is a safe and effective treatment option for chronic post-surgical and focal neuropathic pain of the knee (ie, CRPS); Level I, Grade A, Consensus Strong

Recommendations Regarding Arthroscopy

Knee arthroscopy was presented to the scientific public in 1912 by Swedish Physician Dr Nordentoft at the 41st Congress of the German Society of Surgeons in Berlin.^{233,234} This early description involved applying the use of the laprothroscope in examining the internal workings of the knee primarily in the diagnosis of tubercular disease of the knee for early treatment. By 1925, early US surgeons had started to pioneer/advocate for use of fluid distended arthroscopy of the knee joint to aid in meniscal pathology diagnosis. Dr Phillip Kreuzer published his paper, "Semilunar cartilage disease – a plea for the early recognition by means of the arthroscope" in 1925 and despite early frustration with technical limitations, laid the foundations for expansive growth in use later in the 20th century.²³⁵

Arthroscopy was re-introduced in the 1960s to North America after Dr Masaki Watanabe returned from WWII to Japan and drastically improved the technology involved in arthroscopy.²³⁵ Widely considered the "Father of Modern Arthroscopy", his arthroscopic advancements helped usher in rapid adaptation of arthroscopic techniques culminating in 1982 with the formation of a separate Orthopedic Society (Arthroscopy Association of North America) aimed at advancing the scope and outcomes of this type of surgery. Currently, the advent of arthroscopy can be considered one of the three most significant advancements of orthopedic surgery in the last two centuries along with total joint replacement and internal fixation of fractures.^{235,236}

The indications for arthroscopy of the knee have grown tremendously since its first adaptations in the United States back in the early 1920s and 1930s.²³³ As technology has improved, techniques have followed suit allowing increased diagnosis and treatment options available arthroscopically with a focus on limiting procedural morbidity.^{233,237} Currently, arthroscopy has become the standard of care for diagnosis of acute internal derangement of the knee and as such is one of the most performed orthopedic surgeries worldwide.²³⁸ Despite success in treatment and minimizing morbidity, there are clear contraindications to arthroscopic management. Several randomized controlled trials and subsequent meta analyses have demonstrated that arthroscopic management of degenerative joint disease has limited midterm benefits and does not represent a significant benefit versus conservative management.^{239,240} Specifically in middle-aged or older individuals with symptomatic degenerative knee joint disease, arthroscopic management has been shown to have minimal pain improvement and physical function improvement up to 3 months with no difference at 2 years compared to conservative management.^{239,240}

Perioperative Interventions

As technology has increased and the indications for arthroscopic treatment of knee joint pathology have expanded, perioperative interventions aimed at decreasing morbidity have similarly expanded. In terms of specific interventions, deep venous thromboembolism (DVT) prophylaxis, antibiotic therapy, and choice of anesthesia are all considerations.^{241,242}

DVT is a known complication that can occur after knee arthroscopy. Estimated rates of DVT after arthroscopic intervention of the knee range from 0.5% to 41% in the reported literature.^{243,244} Level IV evidence demonstrates that rates of proximal DVT can be reduced with use of low-molecular-weight heparin (LMWH).²⁴³ Other literature has recommended routine chemical prophylaxis in patients with increased venous thrombotic risk including patients with a clotting disorder, history of venous thromboembolism or malignancy, or two or more classic risk factors.²⁴⁵ The 2020 Cochrane review recommendations state low certainty evidence for reduction of pulmonary embolism and symptomatic DVT risk in the healthy adult population with LMWH and no moderate-to-low certainty evidence of no difference in asymptomatic DVT rates with use of LMWH, aspirin, or rivaroxaban.²⁴⁶

In terms of antibiotic prophylaxis, preoperative administration of antibiotic therapy has been shown to drastically reduce rates of local and systemic postoperative infection across orthopedic procedures.²⁴⁷ Some recent literature has questioned the need for antibiotic prophylaxis in the setting of simple knee arthroscopy secondary to such low reported

local infection rates; however, consensus statements demonstrate decreased rates of septic arthritis and systemic infection and as such antibiotic prophylaxis is routinely used.^{247,248}

In terms of anesthetic considerations, options between general, epidural, spinal, and regional anesthetics have been considered in knee arthroscopy. Literature results in knee arthroscopy suggest that general anesthesia outperforms neuraxial anesthesia in terms of recovery and satisfaction with decreased rates of post-operative admission.^{249,250} While Level 1 data are sparse for administration of peripheral anesthetics in ambulatory knee arthroscopy, limited literature suggests no difference in pain reduction or decreased opioid consumption over placebo.²⁵¹ In contrast, robust literature exists documenting successful and safe use of local anesthesia with IV sedation in reducing recovery time, adequately controlling patients' pain, and reducing cost.^{252–256}

Surgical Considerations

Surgical considerations during all arthroscopic surgery of the knee currently include tourniquet use, and tranexamic acid use. Traditionally, tourniquet use has been debated as proponents have advocated better visualization during the procedure, but complications such as neurologic injuries, vascular injuries, increased pain, post-operative stiffness, and functional weakness have been reported.²⁵⁷ A large meta-analysis comparing tourniquet use for arthroscopic ACL reconstruction demonstrated that the tourniquet group experienced a fewer visualization difficulty events during the procedure; however, all other measured outcomes were no different.²⁵⁷ A more recent systematic review and meta-analysis suggested that the visualization benefit was more historic and that when directly compared, the use of a no tourniquet for simple knee arthroscopy resulted in decreased post-operative opioid requirement and less post-operative blood loss with no difference in operative time, post-operative pain score between groups, or post-operative functional strength.²⁵⁸

Tranexamic acid has been found to reduce post-operative swelling, hemarthrosis incidence, and improve early post-operative function in total joint arthroplasty.²⁵⁹ As such its use in knee arthroscopy has increased in use as a mechanism to both improve visualization and decrease symptomatic post-operative hemarthrosis. Recent literature suggests that routine use of tranexamic acid (TXA) for simple and complex knee arthroscopy can result not only in decreased rates of symptomatic post-operative hemarthrosis but also result in creased early patient-reported outcomes.²⁵⁹ The safety of systemic and local administration of TXA has been well documented²⁶⁰; however, some concerns regarding biologic injury to native adult human cartilage have been raised with routine TXA use for arthroscopic procedures based on in vitro toxicity.²⁶¹ However, studies have demonstrated no difference in decreased hemarthrosis and improved post-operative functional scores with local or systemic administration of TXA and as such increasingly surgeons are routinely using TXA in knee arthroscopy.²⁶²

Outcomes

When correctly indicated knee arthroscopy can be a highly successful operation with good patient-reported outcomes and a low rate (<5%) of clinical complications with decreased morbidity compared to equivalent open techniques.²⁶³ However, certain preoperative patient factors and post-operative interventions have demonstrated an effect on overall outcomes. Smoking, or specifically clinically relevant levels of nicotine, places patients at increased risk of post-operative complication.²⁶⁴

Historic literature has estimated that the majority of patients who undergo simple knee arthroscopy demonstrate no knee-related activity restrictions by 4 weeks.²⁶⁵ As such, the routine use of physical therapy after routine simple knee arthroscopy has been controversial with no clear consensus across the largest reviews.^{266,267} Data for the use of physical therapy in the setting of complex arthroscopic reconstructions are heterogeneous.

Cryotherapy has been shown to be of benefit in reducing post-operative pain after arthroscopic ACL reconstruction while not demonstrating a difference in range of motion.²⁶⁸ The data are less clear on the effect that cryotherapy has on patient-reported functional outcomes.²⁶⁹ For simple arthroscopic procedures, cryotherapy post-operatively has been shown to decrease 24-h opioid consumption and pain scores compared to placebo.²⁷⁰

Consensus Points for Knee Arthroscopy

1. Arthroscopic knee surgery is a safe and effective treatment option for repairing soft tissue injuries and minor bony pathologies that cannot be rectified via conservative measures; Level I, Grade A, Consensus Strong
2. Arthroscopic knee surgery is effective for the treatment of knee OA; Level II-2, Grade C, Consensus Weak

Recommendations Regarding Joint Preservation Techniques

With increased life expectancy, the concern surrounding articular cartilage damage continues to increase. Increasing obesity rates, changing lifestyles and an increasingly aging population have contributed to a double prevalence of OA over the 1999–2014 time period.²⁷¹ It is now estimated that 31 million, or roughly >13% of the United States adult population suffers symptomatic, painful, functionally limiting arthritis representing a significantly morbid clinical and economic burden for the healthcare system.^{271,272} This trend holds at a regional, national, and global analytical level as well.

The intrinsic biomechanical property of cartilage itself makes it specifically at risk for progressive injury. Articular cartilage (type II hyaline cartilage) is on average 2–4 mm thick with a notable absence of blood vessels or innervation, relying on diffusion as a primary source of obtaining nutrients.²⁷³ As such, injury through this complex structure represents a significant challenge for healing and a compromise to the entire structure. Attempts at regeneration of type II cartilage are ongoing, but nevertheless, treatment of isolated articular lesions remains a clinical focus for improvement in the orthopedic community.²⁷⁴

Surgeons have struggled with developing techniques to combat the progression of symptomatic isolated cartilage lesions into arthritis since the advent of arthroscopy. Several reviews have estimated that the rate of Grade II of greater cartilage lesions in patients with symptomatic knee pain exceeds 60% based upon arthroscopic diagnosis.^{275,276} The techniques traditionally employed to treat these lesions have included marrow stimulation, autologous chondrocyte implantation, chondral transplantation (either autogenous or allograft), soft tissue procedures such as meniscal transplantation, and alignment surgeries such as osteotomies.²⁷⁴

Marrow Stimulation

Marrow stimulation which encompasses abrasive sub-chondroplasty, microfracture, or subchondral drilling aims at brining bleeding through the subchondral plate in the area of cartilage injury with the end goal of relocating mesenchymal stem cells into the area of injury.^{277–279} This migration coalesces with formation of a clot in the cartilage defect and eventual development of Type I fibrocartilage to replace the Type II hyaline defect.²⁷⁸ Historically microfracture has shown good short-to-midterm outcomes specifically for younger patients with smaller (~1 cm²) isolated lesions, but more recent reviews have called into question failure rates, arthritic progression, and return to sport rates.^{280,281} The biomechanical deterioration of fibrocartilage at 2 years when placed under the cyclic load experience at the joint surface is the impotence behind this concern.²⁷⁷

Autologous Chondrocyte Implantation

In an attempt to improve rates of Type II collagen in areas of traumatic cartilage loss, Brittberg et al in 1987 proposed the harvest and culture of autologous chondrocytes and reimplantation into the defect behind a periosteal membrane (matrix autologous chondrocyte implantation; MACI).^{274,282} In vivo animal studies in rabbit and equine models had previously been promising with second-look histological samples demonstrating >74% Type II collagen.^{274,282} Current indications for MACI include young active patients who have failed conservative management with isolated cartilage lesions ≥2 cm² with no subchondral bone involvement, BMI <36 kg/m², and no mechanical malalignment.^{283–285} The majority of failures happen early with this treatment (<24 months) and the overall complication rates are low with arthrofibrosis from open implantation the most commonly reported complication.²⁸³ Despite this, good short-to-midterm results have been reported with >70% of the grafts intact at long-term follow-up in some series.^{286,287}

Osteochondral Autograft Transplantation (Mosaicplasty)

In addition to a two-stage chondrocyte culture and re-implantation, bulk allograft or autograft osteochondral transplantation has been proposed as a mechanism of restoring type II hyaline cartilage to a focally painful defect.²⁷⁴ Osteochondral autograft transplantation is the concept of taking a plug(s) of articular cartilage and subchondral bone from a donor site of decreased utility and implanting this into the focally painful defect to restore motion arc and encourage Type II collagen ingrowth.²⁸⁸ The advantages include a single-stage procedure, ability to treat small to medium sized articular lesions with multiple “plugs” and restoration of Type II collagen at the joint surface. The disadvantages primarily include donor site

morbidity and contour matching.^{289,290} Good Level I evidence suggests that for medium sized defects, 2–5 cm² in patients 18–50 years old, osteochondral autograft transplantation results in better clinically relevant outcomes compared to microfracture at 2, 5, and 10 years.²⁹⁰ Despite these results, concern for donor site morbidity with ongoing pain rates from 5% to 13% have driven treating physicians to continue searching for optimal joint preservation techniques.^{289,291,292}

Osteochondral Allograft Transplantation

For larger lesions, autograft osteochondral harvesting carries to great of risk of morbidity and as such osteochondral allograft transplantation (OATs) has traditionally been used.²⁷⁴ Larger lesions, uncontained lesions, multiple lesions, and revision situations have traditionally been treated with OATs to allow restoration of joint architecture in addition to Type II cartilage ingrowth. The concerns for OATs have traditionally been the maintenance of chondrocyte viability from donor tissue and potential transmission of infectious diseases from the deceased host.²⁷⁴ Laboratory studies demonstrate superior chondrocyte viability with fresh allografts; however, good results and chondrocyte viability have still been demonstrated with frozen grafts implanted within 28 days from harvest.^{293,294} Additionally, results for OATs are difficult to standardize as satisfaction, survivorship, and functional scores are dependent upon patient factors and treatment area.²⁹⁵ In general, increasing age, obesity, malalignment, salvage use, bipolar cartilage lesions, or use in conjunction with meniscal transplant have portended worse outcomes.^{274,295} Added clinical caution is warranted as arthroplasty literature suggests that patients converted from OATs to a total knee arthroplasty represent an increased technical demand during the procedure and can expect higher rates of revision surgery.²⁹⁶

Meniscal Transplantation

Other procedures designed at joint preservation include restoration of joint contact pressures, lubrication, and stability with meniscal allograft transplantation.^{274,297} Since its first use in the 1980s, meniscal transplantation has gained in popularity for the correctly indicated patient.²⁹⁸ Typically, these patients are young (<50 years), with symptomatic meniscal deficiency, without arthritis, and with normal mechanical alignment and ligamentous stability.²⁹⁸ Technical considerations with meniscal transplantation revolve around graft incorporation to the native bone and joint capsule. While proponents of bone fixation will argue that bone-to-bone healing generates decreased rates of meniscal extrusion on MRI, recent reviews have demonstrated no difference in clinical outcomes with fixation method.²⁹⁹ Current experience suggests that meniscal allograft transplantation provides good pain relief and clinical results at short- and midterm follow-up but a high complication rate (up to 29%) and survivorship of 50% at 16 years.^{299,300} Longer term follow-up studies and higher-quality literature are still needed in this field.

Distal Femoral and Proximal Tibial Osteotomies

The final tool in the orthopedic armamentarium for joint preservation about the knee has been mechanical alignment procedures. Patients with greater than 5 degrees of mechanical malalignment have been shown to be at increased risk of progressive arthritic deformity in the overloaded knee compartment.²⁷⁴ This poses a difficult problem as younger patients with symptomatic unicompartmental arthritic changes are at increased risk of failure and dissatisfaction with arthroplasty procedures.³⁰¹ As such, distal femoral and proximal tibial osteotomies have been proposed to neutralize alignment and treat unicompartmental pain. For varus deformities, a closing wedge lateral tibial/femoral osteotomy or opening medial femoral/tibial osteotomy is typically performed. Conversely, for valgus deformities, an opening wedge lateral tibial/femoral osteotomy or closing wedge medial femoral/tibial osteotomy can be performed. Comparison of opening and closing wedge osteotomies is not definitive and advantages/risks exist with either treatment method. Closing wedge osteotomy proponents advocate stability of bone-on-bone apposition for healing, while opening wedge osteotomy proponents argue that correction is less reliant upon preoperative planning and there is greater ability to augment correction intraoperatively.³⁰² In addition, specific anatomic concerns with each approach make this surgeon dependent. Despite this, literature suggests that young patients (<60 years of age), with isolated unicompartmental arthritis, good preoperative range of motion and ligamentous stability benefit clinically from distal femoral osteotomy or high tibial osteotomy.^{274,301–304} There are concerns however as survivorship at 10 years is somewhere between 51% and 90%, and conversion from an osteotomy to an arthroplasty is technically demanding.³⁰⁵

Consensus Points for Joint Preservation Techniques

1. Marrow stimulation is an effective treatment for younger patients with small, isolated hyaline defects; Level II-2, Grade C, Consensus Moderate
2. Autologous chondrocyte implantation is an effective treatment for young patients with small, isolated cartilage lesions $\geq 2 \text{ cm}^2$ who have tried and failed conservative care; Level II-2, Grade C, Consensus Moderate
3. Mosaicplasty is an effective long-term treatment option for patients 18–50 years old with hyaline cartilage lesions $2\text{--}5 \text{ cm}^2$; Level I, Grade A, Consensus Moderate
4. OAT is an effective for knee joint preservation technique; Level II-2, Grade C, Consensus Weak
5. Meniscal transplantation is an effective treatment option for patients with symptomatic meniscal deficiency; Level II-2, Grade B, Consensus Moderate
6. Distal femoral and high tibial osteotomy are effective treatment options that can delay, or even prevent, the need for a partial or total knee replacement by preserving damaged joint tissue; Level I, Grade A, Consensus Strong

Knee Joint Arthroplasty

Total knee arthroplasty (TKA) is an incredibly popular solution for painful end-stage knee arthritis that has developed significantly over the last 50+ years. As early as the mid-19th century, physicians discussed soft tissue interposition grafting to alleviate knee pain but with little success.^{306–309} The idea of artificial replacement of the tibia and condyles came into focus in the 1950s, likely first attempted by Dr McKeever.³⁰⁶ The 1970s saw several biomechanical versions of knee replacement including condylar replacement, hinged replacement and resurfacing all with high component failure rates and high rates of infection.³¹⁰ Modern implant designs come from further focus on knee kinematics after replacement. Dr Insall proposed adding a cam-post to knee replacement to aid in femoral roll back and allow an increased degree of flexion.³¹⁰ Continued improvement of metallurgy, polyethylene wear rates, and kinematic designs have yielded high functioning prosthesis, and currently total knee arthroplasty is among the most performed orthopedic procedure worldwide.

Total knee arthroplasty is a well-described treatment for painful knee arthritis that has failed appropriate conservative therapy. The goal of arthroplasty is to alleviate pain and improve function secondary to pain alleviation.³¹¹ Correction of limb deformity secondary to structural progression of arthritis is also a relative indication for joint replacement surgery.^{311,312} Appropriate conservative therapy can include non-steroidal anti-inflammatories, weight loss, activity modification, bracing, physical therapy, walking aids, and intraarticular injections.³¹¹ Outside of the above indications, age, weight, or other medical cutoffs are debated across the literature.³¹² Contraindications include active sepsis, active local joint infection, or a medically unstable patient, while relative contraindications include neuropathic joint, morbid obesity, active smoking, or severe peripheral vascular disease.³¹²

Perioperative Interventions

In addition to implant design improvement, technical improvement, and enhanced recovery protocols, patient modifiable risk factors also play an important role in optimizing outcomes after total joint arthroplasty.³¹³ In the United States in particular, an increasingly aged population in combination with a longer lifespan is predicted to increase arthroplasty rates significantly over the next decades.³¹³ While non-modifiable risk factors include age, race, gender, and stable chronic disease, modifiable risk factors such as cardiovascular disease, morbid obesity, poorly controlled diabetes, opioid use, tobacco use, deconditioning, poor dentition, preoperative anemia and *Staphylococcus aureus* colonization have been areas of focus to reduce rates of complications and failure.³¹⁴

Specific focus has been on improving obesity rates as literature suggests that joint arthroplasty does not result in weight loss for patients, and in addition, obese patients have increased operative time, more frequent rates of infection, greater malpositioning of implants, and increased rates of early failure.^{314,315} This has led to a current work group recommendation to delay patients with BMI $>40 \text{ kg/m}^2$.³¹⁴ In terms of diabetic control, there is debate in the literature on optimal cut-off points for elective total joint surgery. However, the general consensus seems to be that with a hemoglobin A1c $>7.7\%$ patients are at an increased risk of periprosthetic joint infection.³¹⁶ Smoking, or smokeless tobacco use, has

also been reported as the single most important factor in wound healing problems and current smoking has been associated with increased risk of implant loosening, readmission, and mortality as well as wound complications.^{317,318} Current protocols for cessation or tobacco testing are also still debated, but literature does suggest that preoperative smoking cessation interventions may be effective and decrease the risk of these complications.³¹⁹

Literature has consistently demonstrated that the largest predictor of prolonged opioid use after surgery is opioid use prior to surgery and the amount of opioid use is correlated with increased length of stay, complications, and even 90-day mortality after elective total joint arthroplasty.^{320,321} Clear patient expectations for post-operative prescribing patterns are recommended, but exact cut-offs are varied. In terms of dentition, the current recommendation from the American Dental Association is to maintain oral hygiene prior to elective total joint replacement; however, recommendations on dental clearance are not uniformly recommended.³²² Anemia is another strong predictor of increased post-operative cardiovascular and infectious complications.³²³ Recommendations for screening and intervention are mixed, and some experts have recommended anemia work up for Hgb <11 g/dL, but the majority of literature has focused on minimizing perioperative blood loss as a means of preventing symptomatic post-operative acute surgical blood loss anemia.^{314,324}

In summary, modifiable risk factors exist in the arthroplasty population that warrant further work on evidence-based protocols for clearance for these elective procedures. It is estimated that >43% of the patients undergoing revision total knee surgery had at least one modifiable risk factor unoptimized at the time of index surgery.³²⁵ While cut-offs for denial of elective joint arthroplasty have demonstrated the ability to decrease complication and revision rates (HA1c <7%, Hgb >11 g/dL, BMI <35 kg/m², albumin >3.5 g/L) in some studies, specific recommendations are still group/patient/practitioner dependent.³²⁶

Surgical Considerations

As arthroplasty and patient selection have evolved, surgical technique and implant design have similarly improved. Specifically, varied approaches, metallurgy, and implant biomechanics have been compared with some consensus.

The standard extensile anterior medial parapatellar approach to the knee historically provides excellent access to the knee joint, ability to correctly position implants and correct deformity.³²⁷ In the 1990s minimally invasive or quadriceps sparing approaches to the knee joint including the sub/mid vastus approaches were reported to offer improved early post-operative pain and function compared to the standard paramedian approach.³²⁸ More recent literature suggests that objective differences between the approaches may not be as clinically relevant as earlier reported and the choice of approach should be based more upon patient-specific anatomy and surgeon familiarity.³²⁹

With the evolution of polyethylene components in total knee arthroplasty minimizing ultimate poly failure and wear rates, attention has turned to the metallurgy of the implants involved. Reports of metal hypersensitivity to nickel containing implant alloys remain a relevant controversy.³³⁰ While modern implants are made with significantly less nickel in their alloys, reports of hypersensitivity reactions range up to 10% in varying degrees.^{331,332} Standard metal allergy screening is not a consensus recommendation; however, nonmetal containing implants do exist for select use at the discretion of the treating surgeon and the patient.³³⁰

When selecting an implant design, total knee implants come on a spectrum of varying degrees of constraint ranging from a cruciate sacrificing implant all the way to a fully constrained hinge.³³³ Traditionally primary total knee arthroplasty has been divided into cruciate retaining implants (posterior cruciate retaining) and posterior stabilized designs. There are proponents of both designs as they have differing biomechanical mechanisms contributing to flexion and posterior femoral rollback.³³³ However, the majority of direct comparisons have not demonstrated a significant clinical difference in function, satisfaction, or revision-free survivorship.^{334,335}

After design has been selected, fixation strategy is another perioperative surgical consideration which has returned to controversy in the modern arthroplasty world. Traditional designs rely upon cement fixation to grout implants to the biologic bone surface. With the success of biologic bone ingrowth fixation in other joints, comparison between cemented and uncemented total knee arthroplasty has received increased interest. Currently, short- and midterm outcomes with modern implants demonstrate equivalent survivorship and functional outcomes.^{336–339}

Outcomes/Revision Surgery

Large database and population-based studies have demonstrated total knee arthroplasty is a safe and common procedure which results in marked improvements in quality of life, pain relief, and function.³⁴⁰ Factors that have been associated with improved patient outcome scores and implant survival outside of patient modifiable risk factors include age, sex, socioeconomic status and surgeon experience/volume.^{341–343}

However, even when these factors are controlled for, revision total knee arthroplasty surgeries historically have not demonstrated the same degree of improvements subjectively or objectively as their primary counterparts.³⁴¹ Despite an almost 9% decrease in patient-reported outcomes with revision TKA compared to primary TKA, good results are still obtainable with modern bone augmentation and fixation techniques.^{341,344}

Consensus Points for Knee Joint Arthroplasty

1. Knee joint arthroplasty is an effective surgical option for treating symptomatic knee OA that fails conservative treatment options; Level I, Grade A, Consensus Strong

Conclusion

The diagnosis and care of knee pain is an evolving area of medicine that is rife with innovation and emerging treatments. Considering the commonality of this malady in the aging and injured population, it is imperative to have a consistent treatment algorithm that is recognized and followed across the various specialties of medicine that encounter these patients. While the current paradigm still emphasizes palliative treatments as a means of prolonging or avoiding the need for surgical intervention, there is no consistency or clear agreement on which treatments should be provided at the various stages in the patient journey.

The guidance provided in this document is intended to delineate which treatments are proven to be the most efficacious and suggest the order in which they should be offered to a particular patient based on current peer reviewed evidence supplemented with expert opinion by a heterogeneous group of well-experienced clinicians. As newer modalities continue to enter the space, there will be an even greater need for guidance and grading of the evidence such that clinicians will be able to offer the right therapy to the right patient at the right time. These processes will change rapidly going forward and ASPN is committed to a living documented that is updated at regular intervals to guide best practices in the international community.

Abbreviations

ACL, Anterior cruciate ligament; ACR, American College of Radiology OR American College of Rheumatology; AD, Assistive device; ADLs, Activities of daily living; AEs, Adverse events; AFO, Ankle foot orthosis; AKSS, American Knee Society Score; AMUC, Amniotic membrane/umbilical cord particulate; ASA, Amniotic suspension allograft; ASPN, American Society for Pain and Neuroscience; BMAC, Bone marrow aspirate concentrate; BMI, Body mass index; BMLs, Bone marrow lesions; CDC, Centers for Disease Control; COX-2, Cyclooxygenase-2; CRPS, Complex regional pain syndrome; CT, Computed tomography; DHEP, Diclofenac hydroxyethylpyrrolidine; DME, Durable medical equipment; DRG, Dorsal root ganglion; DSG, Diclofenac sodium gel; DVT, Deep venous thromboembolism; EMG, Electromyography; EULAR, European League Against Rheumatism; GNA, Genicular nerve ablation; GPI, Global perceived improvement; HA, Hyaluronic acid; HAFCS, Human amniotic fluid-derived cells; HAM, Human amniotic membrane; IAC, IACS, Intra-articular corticosteroid; IAHA, Intra-articular hyaluronic acid; IAS, Intra-articular steroid; ICOAP, Intermittent and constant osteoarthritis pain index; IDEA-033, Ultra-deformable carrier loaded with ketoprofen for epicutaneous application; IKDC, International Knee Documentation Committee; IL, Inferior lateral; IM, Inferior medial; IPB, Infrapatellar branch of the saphenous nerve; IPM, Interventional Pain Management—Quality Appraisal of Reliability and Risk of Bias Assessment; ISK, Index of Severity for Osteoarthritis for the Knee; IT, Iliotibial; IV, Intravenous; JOA, Japan Orthopaedic Association; KOOS, Knee Osteoarthritis Outcome Score; LCL, Lateral collateral ligament; LMWH, Low-molecular-weight heparin; LR, Lateral retinacular nerve; MACI, Matrix autologous chondrocyte implantation; MCL, Medial collateral ligament; MODEMS, Musculoskeletal Outcomes Data Evaluation and Management System; MR, Medial retinacular

nerve; MRI, Magnetic resonance imaging; MSCs, Mesenchymal stem cells; NACC, Neurostimulation Appropriateness Consensus Committee; NEATS, National Guideline Clearinghouse Extent Adherence to Trustworthy Standards; NRS, Numeric rating scale; NSAIDs, Non-steroidal anti-inflammatory drugs; OA, Osteoarthritis; OARSI, OsteoArthritis Research Society International; OAT, Osteochondral allograft transplantation; OKS, Oxford Knee Score; OMERACT, Outcome Measures in Rheumatology; PCL, Posterior cruciate ligament OR Posterior collateral ligament; PFL, Popliteal fibular ligament; PFPS, Patellofemoral pain syndrome; PGA, Patient global assessment; PGA, Patient global assessment; PGIC, Patient global impression of change; PNfS, Peripheral nerve field stimulation; PNS, Peripheral nerve stimulation; PROs, Patient-reported outcomes; PRP, Platelet-rich-plasma; PT, Physical therapy; PVNS, Pigmented villonodular synovitis; QALYs, Quality-adjusted life years; QAREL, Quality Appraisal of Reliability Studies; QOL, Quality of life; QOL, Quality of life; RCT, Randomized controlled trial; RFA, Radiofrequency ablation; RFN, Recurrent fibular nerve; ROM, Range of motion; SANE, Single assessment numeric evaluation; SF-12, -36, Short-Form Health Survey 12- or 36-item; SL, Superior lateral; SM, Superior medial; SPB, Suprapatellar branch of the saphenous nerve; STEP, Consensus Guidelines on Interventional Therapies for Knee Pain; TCA, Tricyclic antidepressants; TENS, Transcutaneous electrical nerve stimulation; TKA, Total knee arthroplasty; TKR, Total knee replacement; TRFA, Thermal RFA; TXA, Tranexamic acid; USPSTF, US Preventive Services Task Force; VAS, Visual analog scale; VMO, Vastus medialis oblique; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index.

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