



KNEE DISORDERS

Effective October 28, 2015

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IMPACT

Of the many knee disorders reviewed in this guideline, few have been comprehensively studied using high-quality methods. For example, while robust prevalence, incidence, and cost estimates are available for osteoarthritis and meniscal and cruciate ligament tears, robust data on the burden of other knee disorders is largely unavailable.

Meniscal and anterior cruciate ligament (ACL) injuries are the first and second most common knee injuries, respectively. There are as many as 250,000 ACL injuries per year in the U.S., (1, 2) amounting to 1 in 3,000 of the general population. (3) Of those 250,000 injured, at least one-third elect to have surgery (the actual number is estimated to be approximately 100,000 procedures per year). (4) With operative costs of \$11,768, and non-operative costs of \$2,333 per procedure, (5) the total annual costs of knee injuries is approximately \$1.4 billion per year. But unlike knee replacements, the prevalence of ACL surgery is resistant to the aging of the population. The highest incidence of those suffering from an ACL injury occurs in the 15 to 25 year old age group (2) and 70% of all ACL injuries occur in the context of sport. The incidence of meniscal injuries has been estimated at 61 per 100,000 persons in the U.S., and the prevalence is 12 to 14%, with a strong relationship to age. Meniscal surgical procedures are common, comprising 10 to 20% of all orthopaedic surgeries and an estimated total of 850,000 patients per year.

Osteoarthritis (OA) is common, increases in incidence with age, and is associated with significant morbidity and cost. OA affects 13.9% of adults aged 25 years and older and between 33.6 to 46% of adults over age 65. Nearly 66% of obese adults will develop painful knee OA over their lifetime.(6, 7) Of the arthritis-related procedures that require hospitalization, 35% are due to hip and knee replacements. Job-related costs for OA overall are \$3.4 to \$13.2 billion per year with an average patient out-of-pocket direct expense of \$2,600 per year. Twenty-five percent of those affected with OA cannot perform major activities of daily living.(7)

Non-fatal work-related knee injuries and diseases involving days away from work have been decreasing, but physician visits for knee complaints and the incidence of certain knee surgeries has been increasing. According to the U.S. Department of Labor Statistics, number of non-fatal work-related knee injuries decreased from a peak of 130,000 in 2000, to 95,000 in 2007. Yet, total physician visits for knee complaints increased from 10,790,000 in 1998, to 14,960,000 in 2006, and the number of emergency room visits for knee complaints increased from 1,039,000 in 1998, to 1,452,000 in 2006.(8) The rate of total knee replacements for persons aged 65 years and older has been increasing, with women having more surgeries than men. Data from the National Center for Health Statistics indicate that from the period of 1980 to 2002, knee replacements increased approximately 8.1 times, from 10 per 10,000 in women to just fewer than 80 per 10,000, with similar trends observed in men.

OVERVIEW OF MANAGEMENT OF KNEE DISORDERS

The following knee disorders are covered in detail in this guideline. Other disorders not reviewed in this guideline in depth should be considered in the differential diagnosis of knee pain and knee symptoms. These include lumbar radiculopathy and lumbar spinal stenosis, (see Low Back Disorders guideline), osteochondritis dissecans, vascular disease, avulsion fractures, femoral mononeuritis, tumor, cancer, crystal arthropathies (e.g., gout, pseudogout, hydroxyapatite), and infections, including septic arthritis (see Basic Principles and Definitions for normal anatomy). Several of these disorders have a tenuous relationship with work, but are included for purposes of completeness (see Work-Relatedness section).

AVASCULAR NECROSIS

See Osteonecrosis below.

ANSERINE, INFRA-PATELLAR AND PRE-PATELLAR BURSITIS

Bursitis occurs when the bursae become inflamed and irritated, although classic symptoms and signs of inflammation are not always present. Bursitis results in swelling and pain when muscles overlying the bursae are used. There are many bursae around the knee, and this discussion includes some of those more commonly affected. Infra-patellar bursitis involves the bursa between the patellar tendon and the skin. Pre-tibial bursitis involves the bursa between the tibial tuberosity below the knee and the overlying dermis. Pre-patellar bursitis involves the bursa between the patella and the overlying dermis. Anserine bursitis (also pes anserine bursitis) involves a deeper bursa located between the conjoined tendons of the sartorius, gracilis, semitendinosus, and the medial collateral ligaments. Treatment of bursitis has most commonly included avoidance of kneeling or other exposures, NSAIDs, glucocorticosteroid injections (with or without aspiration), and rehabilitation therapy.

FRACTURE OF THE KNEE

Knee fractures include frank fractures and dislocated, hairline, and “stress” fractures. All fractures involve an application of force that is beyond the strength of the bone. In the knee, fractures can occur in the tibia (commonly as the tibial plateau), fibula, or patella. These almost invariably require surgical fixation, but treatment can range from immobilization with a knee brace to casting immobilization to surgical fixation, depending on the severity of the fracture. Stress fractures typically involve repeated applications of unaccustomed force over a relatively short interval of hours to a few days. These are usually treated with elimination of the offending exposure and observation. Physical therapy assessment to address movement system impairments, such as muscle performance and motor patterns, may assist in developing management plans to reduce forces on the affected site.

GROIN STRAINS

See Hip and Groin Disorders guideline.

HAMSTRING, CALF, AND QUADRICEP STRAINS, AND TEARS

A strain usually consists of a disruption of a myotendinous junction. The lower extremity is particularly prone to muscle strains, and strains of certain structures are more common than others. A hamstring strain involves the hamstring muscles of the thigh and can be located either distally or proximally depending on the strained muscle-tendon units, usually in the long head of the biceps femoris muscle. Calf strains typically involve the gastrocnemius or soleus muscles in the upper calf. Quadricep strains involve one or more of the quadriceps muscles as they insert on the superior patella. Complete muscular tears usually occur in the same muscles prone to developing strains. Strains are most commonly treated by removal from high force activities, NSAIDs, and therapy for more severe cases. Immobilization is sometimes implemented. Complete tears/ruptures of the quadriceps tendon or patellar ligament commonly require surgical repair while other muscle-tendon units are usually managed non-operatively.

ILIOTIBIAL BAND SYNDROME

This entity is common in runners, cyclists and participants in endurance sports. Pain is in the lateral knee. Treatment is largely empiric, as quality evidence is sparse, and may consist of NSAIDs, active physical therapy, glucocorticosteroid injections, and deep friction massage.

LUMBAR RADICULOPATHY AND LUMBAR STENOSIS

These disorders may present as knee, thigh, and calf pain. Thus, they should be considered in the differential diagnosis of knee pain (see Low Back Disorders guideline).

MENISCAL TEARS

Menisci are prone to degenerative changes and tears with age. Meniscal tears frequently accompany degenerative joint disease. Younger patients tend to tear with high-force discrete trauma as a result of sporting activities such as football. Older patients tend to acquire tears over time, without any inciting event or with relatively mild trauma, during performance of usual activities (e.g., stair climbing). The type of tear may help determine whether it is more likely degenerative or traumatic in nature. The medial meniscus is 2.7-fold more likely to be torn than the lateral meniscus.(9) Pain tends to be focal – e.g., at the posteromedial joint line for a medial posterior horn meniscal tear. Joint effusions tend to occur if there is an acute, large tear. Small degenerative tears may produce no effusion. Treatment of large “bucket-handle” tears involves surgical removal. Treatment of degenerative and small tears involves NSAIDs, activity modifications to avoid aggravating activities, glucocorticoid infiltration, and therapeutic exercises. Surgery may be needed in cases where non-operative results are not satisfactory.

OSTEOARTHRITIS INCLUDING DEGENERATIVE JOINT DISEASE (“OSTEOARTHRITIS” AND “DEGENERATIVE ARTHRITIS”)

Degenerative joint disease (DJD) of the knee is most commonly caused by osteoarthritis (OA). While osteoarthritis is the more common name for this entity, osteoarthritis is more technically precise since there is no classic inflammation. Other types of arthritic disorders that cause DJD include inflammatory autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, and psoriasis) and crystal diseases (e.g., gout, pseudogout, apatites). These latter disorders are non-occupational and are not included in this discussion. Knee OA and inflammatory knee arthritis can result in destruction of the knee joint, and these conditions may therefore be indistinguishable on x-ray. Thus, a correct interpretation of an x-ray may include DJD, but not “osteoarthritis.”

Most joints in the body have a modest female preponderance of OA and the knee is no exception with an estimate of 84% higher risk in women than men for reasons that are unclear.(10) Patients who already have OA in one or two joints may be at higher risk for developing OA in other joint groups. This is sometimes referred to as “systemic osteoarthritis.” Systemic osteoarthritis likely reflects genetic or other systemic predispositions. Several genetic risk factors have been identified.(11)

OA is more common with age and is associated with thinning of cartilage on the articular surfaces of the knee joint. Thinning of the cartilage in the knee joint may lead to pain with movement and stiffness. OA is generally characterized by stiffness (and pain) after both long periods of inactivity or in association with unaccustomed increases in activity. Most cases of OA are symmetrical and appear to arise without obvious physical exposure(s). A minority of cases occur after discrete significant trauma, most commonly fractures. The disease tends to progress irrespective of physical exposures.

Osteoarthritis: Initial Interventions/Role of Rehabilitation Therapy and Other Non-pharmacologic or Non-Invasive Interventions

Many patients with knee osteoarthritis are able to control their pain adequately through avoidance of activities that significantly provoke symptoms and through the use of over-the-counter (OTC) medication. Topical agents, heat, and ice may be helpful self-treatments. Braces and orthotics/insoles are sometimes helpful. Patients may benefit from education about the natural history of knee OA. Regular participation in programs stressing aquatic or gentle aerobic

(e.g., walking programs), or strengthening exercise may also be of benefit, although these modalities should be individualized to the patient's diagnosis, prior activity levels, desired activity levels, and overall preferences. Weight loss also is thought to be strongly indicated for patients who are either overweight or obese.(12-33) A few recent trials have suggested that weight loss reduces pain and morbidity.(13, 24, 34-36)

Osteoarthritis: Pharmacologic Management

Non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly used for patients with OA. Chronic NSAID therapy may warrant ancillary use of proton pump inhibitors, H-2 histamine blocking agents, or misoprostol to provide prophylaxis against gastrointestinal adverse effects. The advantage of selective Cox-2 inhibitors is their lower risks of gastrointestinal side effects. Tricyclic antidepressants, dual reuptake inhibiting antidepressants (i.e., SSNRIs) and acetaminophen may be of benefit for some patients. Highly selected patients may be candidates for judicious use of low doses of opioids if this results in functional improvement. Providers should also take into consideration that many OA patients are older and have significant comorbidities, including renal impairment. Medications should therefore be carefully prescribed.

Osteoarthritis: Role of Invasive Procedures

Invasive procedures are not indicated in the management of most osteoarthritis patients unless the condition is unable to be satisfactorily controlled with other non-invasive treatments. In such cases, intraarticular injections with glucocorticosteroid and viscosupplementation are sometimes utilized. In advanced cases, joint replacements and other surgical procedures are often performed.

OSTEOCHONDRITIS DISSECANS

Osteochondritis dissecans most commonly affects the knee, although the elbow, hip, and ankle are sometimes affected.(37) It is manifested by articular cartilage that dislodges or dissects from the underlying bone. Osteochondritis dissecans most commonly occurs in teenagers, although it can occur in adults. The cause of osteochondritis dissecans is unclear. However, there appears to be important genetic risks.(37, 38) Although sports activities, particularly in teenage years, also appear to be an important risk factor, there are no quality epidemiological studies of the association of osteochondritis dissecans with work. Consequently, osteochondritis dissecans will not be addressed further in this guideline.(39-51)

OSTEONECROSIS (AVASCULAR NECROSIS)

Osteonecrosis occurs when the tenuous blood supply to the bone is interrupted. Osteonecrosis may result from traumatic or non-traumatic factors. The condition is painless at early stages, but when it advances, patients generally present with pain and limitation of motion. Pain most commonly localizes over the affected bone. This condition most commonly affects the head of the femur, but it can affect any bone. Pain in the lower extremity is usually exacerbated by weight bearing and relieved with rest. Management of knee osteonecrosis is extrapolated from quality evidence for treatment of osteonecrosis of the head of the femur (see Hip and Groin Disorders guideline).

PATELLAR DISLOCATION AND INSTABILITY

The patella is subject to instability from congenital or inherited tendencies to dislocate (52-55) as well as trauma. Pain from dislocation is usually severe and associated with an inability to use the limb. Individuals with a congenital or inherited tendency to dislocate have usually dislocated their patella prior to reaching an employable age. The patella may dislocate with lesser force or stress over time, and recurrences are quite common. Surgery to attempt to tighten the quadriceps mechanism is usually attempted. Other cases of patellar dislocation occur as a

result of significant trauma (e.g., motor vehicle accident or fall). The patella may then be prone to recurrent dislocation after the initial dislocation, and a subjective feeling of instability may result. Strengthening exercises may be helpful. In most cases, particularly if recurrent, surgical repair is attempted.

PATELLOFEMORAL JOINT SYNDROME AND PATELLOFEMORAL JOINT DEGENERATIVE ARTHROSIS (Including Chondromalacia Patellae)

Patellofemoral joint syndrome is a diagnostic category that includes patients with pain thought to be primarily from the patellofemoral joint or the anterior aspect of the knee. Some of these patients are thought to have degenerative joint disease that is focused on that aspect of the knee joint, although they may also have degenerative changes in other parts of the knee joint. Theoretical mechanisms are controversial. Some patients may have muscle weakness that is present in one part of the quadriceps (e.g., vastus medialis), or alternatively the whole quadriceps may be judged as demonstrating weakness. When pain arises from arthrosis in the patellofemoral joint then treatment is comparable to other arthrosis reviewed above. However, when there is evidence of quadriceps muscle weakness, specific strengthening exercises for that muscle are usually prescribed.

PATELLAR TENDINOPATHY

Patellar tendinosis, which affects the patellar tendon, is sometimes referred to as “jumper’s knee.” This usually arises from high-force activities on a stereotypical basis, direct trauma, and/or as a degenerative condition. Patellar tendinosis is usually treated with NSAIDs and exercises. Knee appliances (e.g., sleeve, strap) are also sometimes used as are heat, ice, and topical treatments. Severe cases may rupture (see Patellar Tendon Tears).

PATELLAR TENDON TEARS

Patellar tendon tears usually occur with either a high-force event or an accident, but can result from severe patellar tendinosis. They are treated with surgical repair and rehabilitation; partial tears may be treated non-operatively.

SPRAINS AND TEARS OF THE CRUCIATE LIGAMENT (ANTERIOR AND POSTERIOR)

Cruciate ligament sprains and tears are sprains or partial or complete tears of the ligaments connecting the femur to the tibial plateau that generally occur as the result of high-force injuries from sports, accidents, or falls. In some cases involving less trauma, rupture is believed to occur because of prior injury and weakness. Symptoms include pain and instability. A large effusion may occur with large ruptures. Partial tears are usually treated with NSAIDs, ice, and may involve physical or occupational therapy. Complete tears of the anterior cruciate ligament are usually surgically reconstructed, although non-surgical treatment with rehabilitation may be attempted. Complete tears of the posterior cruciate are usually treated with exercise, although sometimes they are treated surgically.

SPRAINS AND TEARS OF THE COLLATERAL LIGAMENTS (MEDIAL AND LATERAL)

Collateral ligament sprains and tears are sprains and partial or complete tears of the ligaments connecting the lateral femur to the tibia (lateral collateral ligament) or medial femur to the tibia (medial collateral ligament). By definition, these are high force injuries and may occur during sports, accidents, trips, slips or falls. Pain is localized to the affected ligament. The medial collateral ligament may be accompanied by a medial meniscal tear due to shared fibers in these two anatomical parts. Treatments usually consist of NSAIDs and ice or heat, knee support sleeves in the acute phase, and may involve physical or occupational therapy. Isolated complete tears of the medial collateral ligament are usually treated non-operatively.

SYNOVITIS

Synovitis refers to inflammation of a synovial membrane, although in most cases, there are no classic symptoms and signs of inflammation. Synovitis is usually painful, especially with motion. Fluctuating swelling may occur due to effusion within the synovial sac. Treatments usually consists of NSAIDs, elimination of physical exposures (especially direct pressure if thought to be problematic), and often ice or heat.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

All guidelines include analyses of numerous interventions, whether or not they are approved by the U.S. Food and Drug Administration (FDA). For non-FDA-approved interventions, recommendations are based on the available evidence. This is not an endorsement of their use. Many of the medications recommended are utilized off-label. The following is a general summary of the recommendations contained in this guideline:

Evaluation and Diagnostic Issues

- The knee should be carefully evaluated with a history, physical examination, and focused diagnostic testing. A complete physical exam is recommended, since pain can be referred, particularly from the back or hip to the knee joint.
- The initial knee examination or consultation should focus on the detection of conditions that are remediable and “red flags” (e.g., fractures, osteonecrosis, or septic arthritis).
- Initial evaluation of knee joint symptoms may require knee x-rays depending on the presentation. The threshold for additional x-rays, particularly of the back and hip, should be low and may be indicated in certain situations.
- Magnetic resonance imaging is helpful for soft tissue disorders, including meniscal and cruciate tears.

Patient Education Issues

- Patients should be reassured that knee pain is common. Knee arthroplasty is a major surgical procedure, but has a good prognosis. However, most knee arthrosis patients, particularly those without severe disease, do not require arthroplasty.
- Osteonecrosis often requires surgery, although bisphosphonates may substantially reduce the need for surgery.
- Rest and disuse of body parts are not recommended for the management of knee conditions other than fractures, as they usually cause further disability and prolong treatment and recovery.
- Patients should be encouraged to maintain a high level of function, although activity modifications may be helpful in reducing stresses on the knee.

Occupational Issues

- Aside from knee fracture patients in whom prolonged time away from work is often required, or stress fracture patients in whom significant restrictions to limit forceful activity and weight bearing may be recommended, patients should be encouraged to return to normal activity or work as soon as possible. Some situations might require modified duty. However, the more these activities are reduced, the greater the time generally required to rehabilitate the patient.
- If knee pain is present, reduced activity may be necessary if the job physical requirements exceed the patient’s capabilities.
- A functional capacity evaluation (FCE) can establish appropriate physical capacity for work. However, results should be interpreted with caution, as patients’ efforts might be submaximal because of pain. Testing is therefore preferably conducted by someone experienced in

dealing with these types of patients. Nonphysical factors, return to work programs and participatory ergonomics should be addressed as needed. Patients should be empowered to accept responsibility for managing their recovery.

Adaptive Equipment/Assistive Devices and Other Physical Methods

- Ambulatory assistive devices (e.g., canes and crutches) are often mandatory for severely affected patients until they can ambulate.ⁱ However, physicians should balance use against risks of accelerated muscle weakness, particularly in mildly affected patients.
- Ice should be considered as a part of self-care at home, particularly in the acute pain setting, and heat or ice in the chronic setting. They can provide temporary relief of symptoms, but can also reinforce pain and illness behaviors in persons with chronic pain. Many providers believe heat is not indicated in the acute phase of strains, sprains, and some other injuries, although acute low back pain has been demonstrated to be successfully treated with heat. Quality evidence for heat and ice in knee pain is lacking.
- Ice, heat, ultrasound, and other similar modalities are rarely indicated for treatment of knee pain outside the self-care setting. However, they may be considered for certain cases of patellar tendinopathy and anserine bursitis.
- Insoles and knee braces are modestly helpful for patients with osteoarthritis who are compliant with their use and can be considered if other therapeutic options are limited.
- There is no evidence to support prolonged and repetitive use of allied health therapies (massage, electrical therapies, manipulation, and acupuncture). Long-term and repetitive treatment, particularly if there is no documentation of functional improvement, is not indicated in managing patients with chronic pain, including knee pain from DJD.

Exercise Issues

- Graded exercises to assist in achieving a return to normal function are indicated.
- Gentle exercises are useful to regain normal range of motion (ROM) in the acute pain and post-operative settings. Aggressive stretching may be contraindicated if symptoms (e.g., pain and/or swelling) are substantially aggravated. It is also important for patients to understand that, while exercises after surgery may cause some discomfort, they should not cause significant increases in pain or new onset of increased swelling.
- Aerobic and strengthening exercises appear most helpful for the rehabilitation of most chronic knee pain conditions. Consultation with a physical therapist to determine the most appropriate exercises for the patient is recommended.

Medications

- Initial management of most knee pain conditions should be with NSAIDs and acetaminophen.
- Opioids should be avoided for most patients. Opioids may be considered for the management of selected patients with confirmed moderate to severe knee DJD.
- Glucocorticoid injections are indicated for treatment of bursitis, osteoarthritis, chondromalacia patella, and as initial therapy in degenerative meniscal tears.

Other Issues

ⁱSome patients require coaching to not limp, as some continue to limp as a pain behavior.

- Knee replacement surgery, osteotomy and other procedures are selectively recommended for symptoms of severe knee DJD that cannot be managed with other non-operative treatments (e.g. medications, injections).
- Surgery is indicated for knee meniscal tears that are unresponsive to non-operative treatment.
- Surgical treatment is generally recommended for anterior cruciate ligament tears, although non-operative treatment may be attempted particularly in older patients and in patients without clinically unstable knees.
- Intra-articular fragments, such as cartilage, in the knee joint may require arthroscopic exploration and removal.

BASIC PRINCIPLES AND DEFINITIONS

Acute, Subacute, and Chronic Pain: For the purposes of identifying interventions at different stages of diseases, acute pain is defined as pain of up to 1 month, subacute is pain from 1 to 3 months, and chronic is pain of more than 3 months duration (see Chronic Pain guideline for additional information).

Active Therapy: The term “active therapy” is commonly used to describe treatment that requires the patient to assume an active role in rehabilitative treatment. Although there is no one specific treatment defined by this term, it most commonly includes therapeutic exercises, particularly aerobic activities and muscle reconditioning (weight lifting or resistance training).(56) Some authors include active stretching and treatment with psychological, social and/or educational components requiring active participation from the patient.(57)

Active Exercise Therapy: Therapy that typically consists of cardiovascular training and muscle strengthening,(58, 59) though it may also include progressive or occasionally even active stretching, especially in those with substantially reduced ranges of motion. Active exercise therapy is used as a primary treatment for chronic pain, is frequently initiated in the course of treating subacute pain, and is a primary treatment after various surgeries. The goal of active exercise therapy is to improve function.(58) The word “active” is used to differentiate individualized exercise programs designed to address and rehabilitate specific functional, anatomic or physiologic deficits from passive treatment modalities or from forms of “exercise” that require very little effort or investment on the part of the patient or provider.

Bursae: Fluid-filled sacs within the body which provide lubrication in areas where muscles move over bony projections. Inflammation of the bursae may occur and is referred to as bursitis (see Bursitis). Commonly affected bursae include the infra-patellar, pre-patellar, suprapatellar and anserine bursae. These bursae lie in front of the tibial tuberosity, anterior to the patella, above the patella, and between the bone and adductor tendons along the medial knee, respectively.

Collateral Ligament: Ligaments connecting the lateral femur to the fibula (lateral collateral ligament) or the medial femur to the tibia (medial collateral ligament).

Cruciate Ligament: Ligament connecting the center of the distal femur to the center of the tibial plateau. There are two cruciate ligaments per knee – the anterior and posterior.

Delayed Recovery: Defined as an increase in the period of time between the onset of the injury and/or illness and the patient’s return to work or usual activities relative to the expected recovery time. Expected recovery takes into account reasonable expectations, disorder severity, age, and treatments provided.

Enthesopathy: Disorder of the muscular or tendinous attachment to bone.

Functional Capacity Evaluation (FCE): A comprehensive battery of performance-based tests used to attempt to assess an individual's ability for work and do activities of daily living.(60) An FCE may be done to identify an evaluatee's ability to perform specific job tasks associated with a job (job-specific FCE) or his or her ability to perform physical activities associated with any job (general FCE).

Functional Improvement: Entails tracking and recording evidence that the patient is making progress towards increasing his or her functional state. Use of validated tool(s) to track functional improvement is preferable.

Functional Restoration: A term initially used for a variant of interdisciplinary pain alleviation, or at least amelioration, characterized by objective physical function measures, intensive graded exercise and multi-modal pain/disability management with both psychological and case management features.(61-67) The term has become popular as a philosophy and an approach to medical care and rehabilitation. In that sense, functional restoration refers to a blend of various techniques (physical and psychosocial) for evaluating and treating the chronic non-malignant pain patient, particularly in the workers' compensation setting (see Chronic Pain guideline).

Iliotibial Band: Fibrous connection between the ilium of the pelvis to the tibia. The iliotibial band syndrome involves pain mostly in the lateral knee joint.

Knee Joint: The knee joint is a synovial hinge type joint based on the articulation of the distal femur and the tibia of the calf. Four ligaments hold the femur to the tibia – the medial and lateral collateral ligaments and the anterior and posterior cruciate ligaments.

Knee Pain: Pain originating from the knee is usually focally felt in the knee joint. However, some cases are experienced with pain primarily in the hip region. Anterior knee pain is commonly due to patellofemoral joint pain, patellar tendinopathy, and quadriceps strains. Medial joint pain is often caused by medial collateral ligament (MCL) sprains, medial meniscal tears, medial compartment OA, groin strains, and anserine bursitis. Lateral joint pain is frequently due to lateral collateral ligament (LCL) sprains, lateral meniscal tears, lateral joint OA, and iliotibial band syndrome. Posterior knee joint pain is commonly due to hamstring strains, calf strains, Baker's cysts, hyperextension injuries, and popliteal arterial disorders. Other patients have proximally or distally radiating pain. Pain in the knee may also be due to referred pain from cardiovascular or metastatic processes, lumbar disc herniation with nerve impingement, lumbar spinal stenosis, or arterial insufficiency.

Meniscus: A semilunar ("C-shaped") fibrocartilaginous structure which covers approximately 60% of the surface of the tibial plateau and helps distribute weight from the respective femoral condyle evenly. Each joint has a medial and lateral meniscus.

Pain Behavior: Verbal and non-verbal actions (e.g., grimacing, groaning, limping, using pain relieving or support devices, requesting pain medications, etc.) which communicate the concept of pain to others.

Passive Modality: Various types of provider-administered treatments in which the patient is passive. These treatments include medication, injection, surgery, allied health therapies (e.g., massage, acupuncture, and manipulation), and various physical modalities such as

hydrotherapy (e.g., whirlpools, hot tubs, spas, etc.), ultrasound, TENS, other electrical therapies, heat and cryotherapies.

Primary Prevention: Primary prevention involves preventing the condition or risk factor from developing (e.g., physical activity programs to prevent obesity).

Rehabilitation: Rehabilitation is used in these guidelines to mean physical medicine, therapeutic and rehabilitative evaluations, and procedures. Rehabilitation services are delivered under the direction of trained and licensed individuals such as physicians, occupational therapists, and physical therapists. Sometimes mental health professionals are incorporated into the treatment team, particularly for select chronic pain patients. Jurisdictions may differ on qualifications for licensure to perform rehabilitative evaluations and interventions.

Secondary Prevention: Secondary prevention involves reduction in the exposure or risk factor after the risk factor has already developed, but before the disease has manifested (e.g., use of fall protection equipment to prevent hip fractures).

Sprain: Disruption of a joint's ligaments. Examples in the knee include sprains of the medial or lateral collateral ligaments or anterior or posterior cruciate ligaments (see Cruciate and Collateral Sprain).

Strain: Disruption of a muscle or myotendinous junction, usually from a high force or unaccustomed exertion(s). It may also occur during an accident. This term is occasionally used to describe non-specific muscle pain in the absence of knowledge of an anatomic pathophysiological correlate. In the knee region, examples include hamstring, calf, and quadriceps strains (see Hamstring, Calf, Quadriceps Strain).

Stress Fracture: Fractures that occur mainly due to unaccustomed, forceful use. Treatment is generally activity modification to preclude high force use.

Synovial Membrane: The membrane surrounding the entire knee, including the medial, lateral, and patellofemoral joints. The synovial membrane may become inflamed, leading to synovitis (see Synovitis).

Synovial Plicae: Remnants of the divisions of the knee compartments. These are thought to be involved in inflammation and irritation, termed "plicae syndrome."

Tenosynovitis: Tenosynovitis refers to inflammation of a tendon sheath, although in most cases, there are not classic symptoms and signs of inflammation. Classic inflammation may occur with arthropathies or infectious agents.

Tertiary Prevention: The amelioration of the condition after it has already developed. For example, after a patient has osteonecrosis, precluding them from diving, which may be associated with dysbaric osteonecrosis, is a method of tertiary prevention.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): Most common knee outcome measure for osteoarthritis of the knee, other than standard and VAS pain ratings. It combines subjective ratings of pain with measures of activity levels, stiffness, physical function, social function and emotional function.(68)

INITIAL ASSESSMENT

The physician performing an initial evaluation of a patient with knee symptoms should aim to develop an appropriate differential diagnosis. A careful, thorough history and focused physical

examination is required (see General Approach to Initial Assessment and Documentation). A review that not only focuses on the knee, but also addresses the hip, foot, spine, abdomen, and genitourinary tract, is necessary. The examination of the patient with knee symptoms should focus on the knee joint and relevant neighboring structures. Findings of the medical history and physical examination can alert the physician to other non knee-related pathology. Certain findings, referred to as “red flags,” raise suspicion of serious underlying medical conditions (see Table 1). Potentially serious disorders include infections, tumors, and systemic rheumatological disorders.

Knee disorders may be classified into one of four somewhat arbitrary and overlapping categories (examples):

- **Potentially serious knee conditions:** fractures, dislocation, infection, neurovascular compromise, tumors.
- **Mechanical disorders:** derangements of the knee more commonly related to acute trauma, such as ligament sprains and tears, myotendinous strain, and some meniscus tears.
- **Degenerative disorders:** mostly consequences of aging, including osteoarthritis, tendinosis, and most meniscal tears.
- **Nonspecific disorders:** occurring in the knee and suggesting neither internal derangement nor referred pain.

Table 1. Red Flags for Potentially Serious Conditions Associated with Knee Pain*

Disorder	Medical History	Physical Examination
Tumor and Neoplasia	Severe localized pain, often deep-seated, unrelenting bony pain History of cancer (at any point in lifetime) Age >50 years Symptom consistent with disease in a specific organ system (e.g., cough, change in bowel habit, epigastric pain, early satiety) Constitutional symptoms, such as recent unexplained weight loss, fatigue Pain that continues at night or at rest	Pallor, reduced blood pressure, diffuse weakness New mass or tenderness, including tenderness over bony landmarks New findings at a distant site relative to the original complaints, including abnormal pulmonary examination (crackles, wheezes, rhonchi, decreased breath sounds)
Infection	Constitutional symptoms, such as recent fever, chills, or unexplained weight loss Recent bacterial infection (e.g., urinary tract infection); IV drug abuse; diabetes mellitus; or immunosuppression (due to corticosteroids, transplant, or HIV) History of recurring infections treated with antibiotics (e.g., repeated urinary tract infections) Foreign travel with potential exposure to infectious agents	Fever, tachycardia, tachypnea, hypotension Elevated white blood cell count (may be decreased in elderly or immunocompromised) Shift in the WBC differential towards immature cells (“left shift”) Abnormal urinalysis Abnormal body part examination (e.g., pulmonary) Tenderness over bony landmarks Joint effusion, tenderness and difficulty moving knee joint (if knee septic arthritis)
Significant or Progressive Neurologic Deficit	Severe spine or extremity pain Progressive numbness or weakness Complaints of new gait difficulty	Significant or progressive dermatomal and/or myotomal (motor) involvement Evidence of cauda equina syndrome, including urinary retention or bowel incontinence Hyper-reflexia, or other evidence of myelopathy

Compartment Syndrome	History of fracture, crush wound or other major trauma Very painful muscular compartment History of peripheral vascular disease	Tense compartment Exquisitely tender Distal neurovascular compromise (e.g., absent or decreased pulses or pale/cold extremity) if severe and/or prolonged
Rheumatologic Disease	Diffuse arthralgias Prior arthropathies, autoimmune diseases Skin changes, lesions, or ulcers Fatigue, malaise	Polyarticular joint effusions (usually with warmth) X-ray abnormalities consistent with erosive pathology Elevated sedimentation rate (ESR) or C-reactive protein (CRP) Hematuria, proteinuria Other specific abnormalities, as appropriate (e.g., ANA, RF, anti-DNA, C3, anti-Ro, anti-La, oral ulcers, pulmonary abnormalities, ophthalmological involvement, dermal abnormalities)

*The above list is not meant to be comprehensive but rather reviews many common historical and examination findings.

MEDICAL HISTORY AND PHYSICAL EXAMINATION

MEDICAL HISTORY

The initial evaluation of patients with knee pain should include a thorough medical history. Although knee symptoms are generally more accurately attributed to the knee joint than the hip joint, some cases of knee joint pathology may present with hip pain (see Hip and Groin Disorders guideline).ⁱⁱ A complete occupational history is also necessary to assist the patient with successful accommodation and rehabilitation, as well as to determine work-relatedness. Asking the patient open-ended questions, such as those listed below, allows the clinician to gauge the need for further discussion or specific inquiries to obtain more detailed information (see also General Approach to Initial Assessment and Documentation guideline):

1. "What may I do for you today?" (This question helps focus the discussion on what the patient feels is the main purpose of the visit. It also helps ensure that the physician is able to eventually address the main purpose of the visit, which is important for patient satisfaction.)
2. What are your symptoms? (Observing how the worker acts when describing symptoms may provide insight into the diagnosis and help the physician understand the impact of symptoms on the patient.)

ⁱⁱThe clinical phenomena of primary hip and pelvic region pathology referring pain to the knee is well documented.⁶⁹ Leshner JM, Dreyfuss P, Hager N, Kaplan M, Furman M. Hip joint pain referral patterns: a descriptive study. *Pain Med.* 2008;9(1):22-5. and appears to be particularly prevalent in the pediatric population. This may include delayed diagnoses of serious pelvic region pathology such as osteogenic sarcoma in younger soldiers. Disorders such as Legg-Calve-Perthes and slipped capital femoral epiphysis may be associated with primary complaints of knee pain. These conditions might be seen in younger workers.⁷⁰ Rahme D, Comley A, Foster B, Cundy P. Consequences of diagnostic delays in slipped capital femoral epiphysis. *J Pediatr Orthop B.* 2006;15(2):93-7, 71. Flatman JG. Hip diseases with referred pain to the knee. *JAMA.* 1975;234(9):967-8. Similarly many patients with a chief complaint of hip pain actually have a knee disorder that is usually osteoarthritis. Clues to the origin of symptoms can be determined with a careful patient history as primary hip pathology typically is perceived in the buttocks, anterior inguinal region, thigh and occasionally in the foot and ankle.⁶⁹ Leshner JM, Dreyfuss P, Hager N, Kaplan M, Furman M. Hip joint pain referral patterns: a descriptive study. *Pain Med.* 2008;9(1):22-5. Hip pathology presents as difficulty crossing legs, laying on the hip and restricted internal rotation, while knee pathology presents as difficulty climbing stairs, kneeling onto the knee, and bending the knee to get in and out of the car. Consequently, the hip, pelvic region and lumbar spine should be examined thoroughly in any instance of thigh or knee pain that is not clearly an isolated acute knee injury. (Flatman JG. Hip diseases with referred pain to the knee. *JAMA.* 1975;234:967-968; Leshner JM, Dreyfuss P, Hager N, Kaplan M, Furman M. Hip joint pain referral patterns: a descriptive study. *Pain Med.* 2008;9:22-25; Rahme D, Comley A, Foster B, Cundy P. Consequences of diagnostic delays in slipped capital femoral epiphysis. *J Pediatr Orthop B.* 2006;15:93-97.)

- What are your symptoms?
- When did your symptoms begin?
- Where are the symptoms located?
- Do you have pain or stiffness?
- Do you have swelling, locking, or giving way? If swollen, how long after the injury did your knee become swollen? What is the pattern to your symptoms? Are they better when first getting out of bed in the morning, during the morning, mid-day, evening or while asleep? When is it worst?
- Do you have fever, night sweats, or weight loss?
- Do you have pain or other symptoms elsewhere?
 - Do you have numbness, tingling, or weakness? Have you lost control of your bowel or bladder? Are your symptoms worse when climbing or going down stairs or hills? (These questions are particularly important if knee pain is felt to be associated with radicular spine pain or spinal stenosis).
 - Since these symptoms began, have your symptoms changed? How?
 - How do your symptoms affect your life?
 - Can you walk on your leg?
 - Do you have difficulty sleeping? What position is most comfortable?

3. How did the condition develop?

Past:

- Have you had similar episodes previously?
- Have you had previous testing or treatment? What treatment? What were the results? With whom? How long did it take to get back to work? To light duty?
- Did you receive a disability or impairment rating?
- Was recovery complete? (Did you get a disability award?)

Cause:

- What do you think caused the problem? When?
- Do you think it is related to work?
- Did your symptoms begin suddenly or gradually? (It is important to distinguish between symptoms associated with a specific traumatic injury and those that represent cumulative trauma over time).
- What were you doing at the time when your symptoms began? Did you have a slip, trip, fall, or twist or strike an object? (It is important to document the circumstances surrounding the injury and any biomechanical risk factors).
- For traumatic injuries: Was the area deformed? Did you lose any blood or have an open wound? When after the injury did your symptoms begin?
- For degenerative conditions: Is there a history in your family of this problem? Does anyone else have arthritis in your family?

Job:

- What are your specific job duties?
- What are your work hours, and what is your break schedule?
- Do you rotate duties?
- How long do you spend performing each duty on a daily basis?
- How much do you lift, push, or pull at work as a maximum? Usual lift, push, or pull?
- Do you have assistance of other people or assistive (e.g. lifting) devices?
- What previous jobs have you held, and what were your job duties?
- What is the hardest part of the job for you to do with your injury? Why?
- Is modified duty available at your workplace? What type of modified duty is available?

Non-Occupational Activities:

- What other activities (e.g. hobbies, sports) do you engage in at home or elsewhere? What prior activities did you engage in?
 - Describe your current daily activities. Do you do any heavy lifting, pushing, or pulling? How often?
 - Could these activities have contributed to the development of your symptoms?
4. Assess treatments and determine whether responses differ from expected outcomes.
- What treatments have you had?
 - Did anything help decrease your symptoms? What, and for how long?
 - Are you doing any exercises at home? Which ones? How often?
 - Are you taking any non-prescription medications and supplements?
5. Discuss symptom limitations.
- Do you expect to recover? How soon?
 - How do your symptoms limit you?
 - Can you perform activities of daily living (e.g., dressing, bathing, grooming, etc.) or instrumental activities of daily living (e.g., shopping, food preparation, housekeeping, etc.)?
 - How long can you sit, stand, walk, and bend?
 - How much weight can you lift (use items such as gallons of milk, groceries, etc. as examples)?
 - How much can you push or pull?
 - If these symptoms limit you, how long have your activities been limited?
6. Do you have other medical problems? For example:
- Osteoarthritis, rheumatoid arthritis, gout, pseudogout, or other arthritides?
 - Fractures or lower extremity surgeries?
 - Cardiovascular disease?
 - Pulmonary disease?
 - Gastrointestinal disease?
 - Diabetes mellitus?
 - Neurological disorders (including radiculopathies, headaches)?
 - Psychophysiologic disorders (e.g. irritable bowel syndrome, chronic fatigue syndrome, or fibromyalgia)?
7. Do you have a history of mental health disorders or alcohol, tobacco, or other substance use?
- Have you ever had a substance use problem? Have you ever been charged with driving under the influence (DUI)? Have you ever been in a detoxification program? Have you ever had an alcohol problem? (CAGE or MAST screening should be performed in the case of suspected osteonecrosis, as alcohol use is associated with a higher risk of osteonecrosis)
 - Do you or have you ever used tobacco (assess pack-years)?
 - Do you or have you ever used any other drugs?
8. What do you think about your job (psychosocial context)?
- Do you like your job?
 - Do you have control over your job? Partial control?
 - Do you feel your job demands are reasonable?
 - What is your relationship with your co-workers and supervisor? How do they treat you?

9. What do you think about Assess whether there are problems at home or in the social life? Is there support?
- How do you get along with your family members? Do they help and support you?
 - Does your family treat you differently now that you are in pain? Have your roles at home changed because of your injury? Do your friends treat you differently?
 - Are your symptoms worse when you are dealing with problems with your family and friends?
10. Are there advocagenic (litigious) influences?
- Do you have a workers' compensation claim for this injury?
 - Do you have a lawsuit or other legal action involving this problem?

PHYSICAL EXAMINATION

Objectives of the physical examination of the knee include defining physical abnormalities, narrowing diagnostic considerations, and developing and focusing an effective, specific treatment plan. In order to align an intervention strategy with deficits such as impaired strength, or movement balance, the examination should first reveal the impairments. Examination of knee includes active and passive ranges of motion and accessory movements. Muscle strength and flexibility should be revealed through valid testing. Coordination, balance, and fall risk should also be assessed. Special tests for specific pathologies are often only a small aspect of the examination and may be overall less important to nonsurgical management of the knee disorder. Special tests are more helpful when there is clear evidence that the pathology revealed is better managed by a process other than restoring normal movement, strength, flexibility, and coordination to the knee.

Physical examination data, including vital signs, should be reviewed for potential inferences about infectious or neoplastic etiologies of knee symptoms. The physical examination should begin the moment the physician sees the patient. Observing how the patient sits, walks, and moves is extremely important. It is also helpful to have the patient demonstrate what positions caused or seem to provoke the symptoms.

Guided by the medical history, the physical examination includes:

- general observation of the patient, including stance and gait, and how the patient changes positions (monitoring for pain behavior during range of motion (ROM) and posture changes often offers a clue to the origin of the problem);
- regional examination of the knee and testing for specific knee disorders;
- examination of organ systems related to appropriate differential diagnoses, including a neurological examination.

Much of the knee examination is not purely objective. There is an element of patient cooperation when determining strength or active range of motion, and most maneuvers require a subjective statement of pain to be considered positive. It is often helpful to assess patients' capabilities in the clinic to follow in subsequent clinic visits. These may include:

- walking distance and ability to climb stairs (observe, if possible, and inquire about any progress);
- repeated toe raises (number able to perform), heel walking (distance), and squats (number);
- sensory examination findings (e.g. pin prick, using monofilaments).

The use of validated functional assessment tools is recommended, if possible, to assess capabilities. Active involvement of the provider in evaluating patients' function is believed to be helpful in facilitating patients' recoveries.(72) (Henningsen 07)

PHYSICAL EXAMINATION FOR SPECIFIC DIAGNOSES

Physical examination findings vary based on the acuity and severity of the disorder. In general, conditions that arise acutely present with more pronounced physical examination findings. Patients with long-standing conditions may have less prominent physical examination findings. The most commonly used physical examination maneuvers are described below. In addition, there are other examination maneuvers and techniques, including performance of maneuvers under anesthesia.(73-91) It is suggested that the examiner become familiar with a specific set of maneuvers rather than an entire battery.

Pes Anserine Bursitis

Tenderness over the pes anserine bursa is usually present.(92, 93) In contrast with other bursidities, there is usually no palpable swelling or warmth.(92, 94, 95)

Bursitis (Infrapatellar, Prepatellar, Suprapatellar)

Swelling in the affected bursa(e) is present.(96-98) The affected bursa may be slightly warm, but is generally minimally tender or non-tender. Moderate or severe pain or tenderness, overlying warmth, and erythema raise the probability of septic bursitis.(98, 99) Crystal arthropathies may affect the bursae, but are rare, particularly in the infrapatellar or prepatellar bursae.

Collateral Ligament Sprains and Tears (MCL and LCL)

Collateral ligament sprains present with focal tenderness over the specific ligament.(100, 101) Increased pain with stressing the ligament (i.e., valgus stressing for the medial collateral ligament and varus stressing for the lateral collateral ligament) is consistent with a ligamentous sprain.(102, 103) Patients with complete tears have tenderness over the normal location of the ligament, and valgus or varus stressing reveals widening of the joint line.(100, 102-104)

Cruciate Ligament Tears and Sprains

Cruciate ligament tears generally have effusions that may be sizable, particularly if acute.(105-108) Joint tenderness may be present. Joint laxity is the major clinical finding and may be detected with Lachman's maneuver which is performed recumbent, with the knee flexed 20° and the examiner pulling the shin forward. If an ACL tear is present, there is greater movement than normal and compared with the other knee and with a soft endpoint.(85, 102, 109-112) The anterior drawer sign is performed with the knee flexed 90° and shin pulled forward, with greater movement than normal and compared with the other knee indicating an anterior cruciate ligament tear. The posterior drawer sign is performed with the knee flexed 90° and shin pushed backwards, with greater movement than normal indicating a posterior cruciate ligament tear.(111, 113, 114) Sprains without complete tears may present with some laxity in the drawer signs, but generally with hard endpoints. There is conflicting evidence on the utility of the most commonly used physical examination signs (see Table 2). For example, there is disagreement about the utility of the pivot shift test.(73, 83) This test may only be adequately performed under anesthesia.(115) However, there is general consensus that the Lachman's test is the most sensitive physical examination maneuver for detecting ACL tears.(84, 111, 115-122)

Table 2. Operant Characteristics of Physical Examination Signs of Anterior Cruciate Ligament Tears*

	Sensitivity (%)	Specificity (%)
Lachman	82-100	43-100

Anterior Drawer	22-80	74-100
Pivot shift	71-90	4-98

*Data compiled from Sandberg, Kim, Liu, Torg, Jonsson, Donaldson, Zarins, Gelb, Lee, and Katz.(84, 111, 115-122)

Hamstring, Calf, and Quadricep Strains and Tears

Complete ruptures are accompanied by an inability to use the knee, including an inability to walk.(123, 124) Moderate to severe strains also produce considerable difficulty using the limb and bearing weight. Moderate to severe strains and tears generally cause swelling and ecchymosis. Development of hematoma in the area of the strain or rupture is common.(123) Mild strains may present with some difficulty with knee use and focal tenderness.(123-125)

Iliotibial (IT) Band Syndrome

Patients with IT Band Syndrome have pain in the distal lateral thigh, which is typically worse with provocative activities, including running, cycling and other endurance sports.(126-130) Tenderness may be present along the lateral fascia from the lower thigh to the knee, particularly the lateral femoral condyle,(131) and pain may be worse at 30° of flexion,(132) otherwise, the knee joint is usually normal.

Knee Fracture

Patients with knee fractures are often unable to bear weight or walk,(133) and bony deformity and crepitus may be present. Patients with stress fractures may be able to bear weight normally but usually have focal tenderness over the fibular head, patella, or tibia.(133, 134)

Knee Dislocation

Patellofemoral dislocations are the most common knee dislocation and may be congenital or trauma associated.(135) Patients with tibiofemoral knee dislocations tend to have a history of high-impact trauma(135) which do not spontaneously reduce are unable to bear weight or walk, have deformity, and may have signs of fractures. Tears of multiple ligaments are usually present and tenderness over sprained and/or torn ligaments is present. Effusions are usually present.

Meniscal Tears

The extent of the meniscal tear usually determines the degree of physical examination abnormalities, which can range from marked findings to a normal examination. Patients with large, acute tears tend to have swelling, focal tenderness, difficulty walking, difficulty using the knee, locking, and giving out or buckling. Patients with mild, chronic degenerative tears that are symptomatic frequently have no effusion, but may have focal tenderness. Specific physical signs include joint line tenderness, McMurray's test (painful palpable click when moving knee from full flexion to 90°), Ege's test (audible and painful palpable click with squatting; feet turned outwards for medial meniscus and inwards for lateral), and Apley's test (pain on axial compression of the tibia with external rotation while patient prone and knee flexed).(75, 102, 114, 136-141) The sensitivity of these tests is generally higher for medial than lateral meniscal tears,(142, 143) and it has been suggested that the tests should be combined for increased accuracy.(144) However, there is conflicting data on the value of these physical examination signs (see Table 3), and they may not have the same operant characteristics depending on the anatomic location, e.g., with anterior tears less likely to be captured by McMurray's. Acutely locked knees have been reported to reflect meniscal tears (47.9%), ACL tears (14.6%), meniscal and ACL tears (22.9%), a loose body (4.2%), or an unidentifiable mechanical cause (10.4%).(145)

Table 3. Operant Characteristics of Physical Examination Signs of Meniscal Tears*

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Joint Line Tenderness	55-92	31-97	57-96
McMurray	20-67	69-96	45-82
Apley (distraction or compression)	6-16	90	28
Ege	64-67	81-90	71-84
History of mechanical symptoms	20	94	--

*Data compiled from Kurosaka, Konan, Corea, Wadey, Fowler, Lowery, Akseki, Anderson, and Benjaminse.(74, 75, 83, 139, 142-144, 146, 147)

Osteoarthritis

Patients with osteoarthroses usually have an antalgic or slow gait. Those with more severe disease commonly are slow to stand and initiate gait. Bony enlargement (osteophytes) develops.(148) Alignment may become abnormal. If medial joint disease is disproportionate, varus deformities can develop. Other physical signs of osteoarthritis include crepitus on range of motion. Tenderness is usually present but poorly localized, and effusions may or may not be present. Warmth and erythema are normally absent.(149, 150)

Patellar Dislocation

Patients with a dislocated patella cannot walk or bear weight on the knee.(135) Deformity with displacement of the patella is apparent. Testing for instability can include variants of a patellar apprehension test (putting a lateral force on the patella, causing a sensation that the patella may dislocate).(52, 151) The sensitivity and specificity of apprehension testing has been reported to be 39 to 100%, and 88.4%, respectively.(52, 152)

Patellar Tendinopathy

The main finding of patellar tendinosis on physical examination is tenderness over the patellar tendon. The tendon is often affected at the junction with the patella, but the quadriceps insertion on the patella may also be affected. This condition is often seen in athletes and others with high loading of the tendon (“jumper’s knee”).(153-156) Unless the patellar tendon is ruptured, other associated anatomic abnormalities are infrequent.

Patellar Tendon Tears

Patellar tendon tears are relatively uncommon and present with an inability to walk.(157, 158) Deformity of the anterior knee, with clinical findings of a ruptured patellar tendon, is present. Tenderness is also present, and there is usually some proximal patellar retraction proximally, also known as patella alta.

Patellofemoral Syndrome

Patients with patellofemoral syndrome have anterior knee pain, usually with a normal gait.(159, 160) Patellar alignment may be normal, but is often lateral. Some measure the Q-angle), formed by a line drawn from the anterior superior iliac spine through the center of the patella and a line drawn from the center of the patella to the center of the tibial tubercle, is too large, although the clinical applicability of this angle appears weak.(161-163) Crepitus on range of motion (ROM) of the patella and with squatting is common. Pain with patellofemoral compression during ROM constitutes a positive grind test and may be helpful in the diagnosis of patellofemoral joint syndrome.(164) Tenderness along the edges of the patella has been reported to be 78% sensitive, 37% specific, and 58% accurate for the diagnosis of patellofemoral joint syndrome,(74) although the positive likelihood ratio for this sign is under 2.5.(165)

WORK-RELATEDNESS

Acute occupational knee injuries are related to a specific acute traumatic event. The location of that event determines work-relatedness, and work-relatedness in this case is usually non-controversial. Most jurisdictions also request an opinion from the physician as to whether a disease or disorder should be considered as work-related for the purpose of a workers' compensation claim. Physicians need to remember that their role is to supply opinion, and that the "medical/scientific answer" and the "legal answer," as determined by the regulations and case law precedents in a particular jurisdiction (workers' compensation system), are different (see Work-relatedness guideline). However, there have been few quality epidemiological studies that address work-related knee disorders. Thus, aside from these specific circumstances (e.g., occupational fractures and other acute trauma, meniscal tears from acute trauma, osteonecrosis from barotrauma, prepatellar bursitis in a roofer), most opinions are speculative.

Pes Anserine Bursitis

Anserine bursitis appears to occur both in the presence and absence of trauma. There are no quality studies of occupational factors, and one study reported the only associated factor found was a valgus knee deformity.(95) In settings where significant trauma has occurred to precipitate the bursitis, work-relatedness is not controversial. In the absence of trauma, a theory may be constructed whereby physical factors such as unaccustomed forceful use of the knee may cause the condition; however, this is speculative.

Bursitis (Infrapatellar, Prepatellar, Suprapatellar)

Infrapatellar bursitis appears to occur most commonly in the setting of kneeling activities, often in workers who are unaccustomed to kneeling.(166) This diagnosis in this context is considered work-related and is not usually controversial. Similarly, prepatellar bursitis in the context of discrete trauma or kneeling is considered work-related.(167-170) However, for other cases of bursitis, including where there is no discrete trauma, there are no quality studies of occupational factors. However, a theory may be constructed whereby physical factors such as unaccustomed forceful use of the knee may cause the condition.

Collateral Ligament Sprains and Tears (MCL and LCL)

Collateral ligament sprains are thought to be consequences of significant trauma. The mechanism of the trauma determines whether the condition is work-related.

Cruciate Ligament Tears and Sprains

Cruciate tears and sprains are largely attributed to the consequences of significant trauma.(171-174) The mechanism of the trauma determines whether the condition is work-related.

Hamstring, Calf and Quadriceps Strains and Tears

Hamstring, calf, and quadriceps strains involve myotendinous strains in the respective muscle-tendon unit. Symptoms are usually acute in onset and these injuries are considered more analogous to acute injuries than diseases, although repeated, unaccustomed use may have precipitated the event. Thus, the nature of the forceful unaccustomed use determines whether the condition is work-related.

Iliotibial Band Syndrome

This entity is considered a disease, rather than an acute injury. Most case series occur in athletes, particularly in runners, weight lifters, bicyclists, and downhill skiers, and among military recruits.(127, 129, 175-197) However, quality epidemiological studies are absent and risk factors are unclear. As there are no quality epidemiological studies, the condition has not been documented as occupational.

Knee Fracture

Knee fractures are consequences of significant trauma. The mechanism of the trauma determines whether the condition is work-related.

Meniscal Tears

Meniscal tears are highly prevalent.(198-208) The mechanism of injury will determine whether the meniscal tear is considered work-related. Acute, large meniscal tears occurring with a discrete traumatic event are usually considered as being consequences of that trauma.(208) The mechanism of the trauma normally determines whether the condition is work-related. On the other end of the spectrum, there are cases of degenerative-appearing meniscal tears without a discrete traumatic event. In such cases, these tears are diseases. There is little quality epidemiological evidence that they are work-related, although some have theorized a relationship.(208-212) There are many cases occurring between the two extremes noted above, and work-relatedness is often unclear.

Osteoarthritis

A minority of cases of osteoarthritis appear to arise in a knee after either fracture, removal of a meniscus,(213-219) torn meniscus,(29, 220, 221) ACL surgery,(222-224) other surgery, or major trauma or injury.(220, 225-228) The mechanism of that trauma is usually believed to be responsible for the osteoarthritis particularly as the magnitude or risk is generally considerable,ⁱⁱⁱ and this often determines work-relatedness. However, the majority of cases have no significant traumatic history and thus causation is often unclear. Yet, while some aspects are poorly understood or controversial, there are some aspects of the epidemiology of knee osteoarthritis that are robust. The condition has been traditionally labeled non-inflammatory in contrast with rheumatoid arthritis and other inflammatory arthritides. Yet there are many different inflammatory mediators that are detectable in joints or systemically in affected individuals, including collagenase, tissue inhibitor of metalloproteinases, proteoglycan fragments, aggrecan, stromelysin-1, decorin, biglycan, lumican, keratocan,(229-239) and hyaluronic acid, which has predicted earlier progression of OA.(240) Weight loss has been shown to reduce those same inflammatory markers among knee osteoarthritis patients.(25)

Age is a well documented risk factor for knee osteoarthritis.(10, 241-255) Obesity has been shown to be an unusually robust risk factor for osteoarthritis of the knee,(10, 31, 225, 244, 246, 250, 256-274) as it is for other joints throughout the body(244, 275-277) (see Hip and Groin Disorders and Hand, Wrist, and Forearm Disorders guidelines). That obesity is associated with osteoarthritis of the upper extremity suggests the mechanism is at least partially unrelated to weight bearing. Additionally, weight loss appears to result in lower risk for osteoarthritis,(258) reduces biomarkers,(25) and improves prognoses of patients with osteoarthritis.(25, 278, 279)

Genetic factors have been reportedly strong,(260, 280-282) and the knee joint is frequently involved in generalized osteoarthritis.(201, 203, 251, 274, 283-288) Generalized OA as well as signs of active disease including effusions predicts faster progression of OA.(289) Heberden's nodes reportedly increase risk of knee degenerative changes by 6-fold over a 12-year period,(274) hand osteoarthritis conveys a 50% increased risk for knee OA,(10) and a specific hand-knee OA subset has been proposed.(290, 291)

ⁱⁱⁱPooled odds ratio estimated at 3.86, 95% CI 2.61-5.70.10. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2010;18(1):24-33. (Blagojevic 10)

Muscle weakness is thought to increase risk of knee OA(292-299) and forms a basis for one of the interventions for which there is some quality evidence of efficacy (see exercise section). Leg length discrepancy is also an apparently risk factor(300) as is knee malalignment.(274) Bone marrow edema is another reported risk.(301)

Job physical factors have not been studied in a quality epidemiological study reported to date. The proper study designs have yet to be reported, particularly either cohort studies or at least a well done case-control study with measured job physical factors and adjustments for the non-occupational factors.

Purported associated factors have included kneeling, squatting and lifting. However, results are inconsistent,(256, 257, 302) concerns about biases have been noted,(303) risks are nearly always low magnitude when positive, and nearly completely based on retrospective methods without measured job factors.(170, 220, 270, 304-313) However, some studies reported interactions of risk factors, and this suggests further need for study.(223, 270) Of all risks, kneeling appears to be most consistently associated with knee OA.(170, 210, 270, 306) A registry study from Sweden has suggested increased risk among farmers, construction workers, and firefighters, while risks were not elevated among numerous other occupational groups.(309, 310) Others have suggested no increased risk of knee OA among farmers.(314)

Numerous studies of runners have been performed with a basic presumption of risk due to high force use of the knees; however, nearly all studies including long duration cohort and other studies have been negative.(315-320) There also is suggestive evidence of thicker cartilage among runners(321) and in some animal models.(322) Mixed sports and power sports have reportedly led to earlier knee OA, but not endurance sports.(318) Another study found increased risks among women with high levels of physical activity, but not among men.(323)

A few other studies may also be of interest including a lack of differences in injuries between artificial turf and natural grass in a prospective cohort study of soccer players.(324) A comparative study of cartilage from the apparently unaffected side in unicompartmental OA patients found the cartilage was inferior to the cadaveric controls,(325) suggesting the cartilage of affected patients is inherently defective.

Patellar Dislocation

Patellar dislocations are, absent congenital abnormalities, consequences of significant trauma. The mechanism of the trauma determines whether the condition is work-related. In those with recurrent dislocations, there is frequently an inherited or congenital abnormality with a propensity towards recurrences. In situations where there is a congenital abnormality, dislocation may occur in the context of an “event at work” and produce a controversy regarding work-relatedness that likely will be determined largely based on the specific statutory definition of work-relatedness in the setting of pre-existing, non-occupational conditions.

Patellar Tendon Tendinosis and Tears

These are believed to be degenerative tendon conditions and tears, similar to those in the rotator cuff and are considered more analogous to diseases. However, discrete accidents may contribute to these tears. It is theorized that forceful use may contribute to the condition; thus, it is possible that they may be occupational in some circumstance(s), likely involving high-force quadriceps contraction. However, there currently are no quality epidemiological studies to identify occupational risk factors. Repeated, high force stereotypical use is believed to be a risk (i.e., “jumper’s knee”).

Patellofemoral Joint Syndrome

This is a disease for which there is not quality evidence of work-relatedness. There are reports that the condition is most common in those with high knee demands including military recruits(326) and among those kneeling.(327, 328) Chondromalacia patellae was previously thought to be a distinct entity,(329) although increasingly the term anterior knee pain has been used.

ERGONOMIC INTERVENTIONS

The physician may recommend ergonomic redesign of the workplace to facilitate recovery and prevent recurrence of knee disorders.(330) Ergonomic evaluations of the workplace can be conducted on-site by a qualified professional such as an ergonomist, occupational or physical therapist, or other health safety specialist. There are no quality studies regarding ergonomic interventions to prevent knee conditions, nor are there quality studies regarding return to work and secondary prevention. Thus, suggested changes to the work environment are empiric. Knee protection for kneeling activities is recommended. Falls result in considerable knee morbidity (including fractures), and fall protection equipment has resulted in far fewer fatalities in industry over the past few decades.(331)

1. *Recommendation: Knee Pads for Kneeling Activities*

Knee pads are recommended for activities which require kneeling.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. *Recommendation: Fall Protection*

Measures to prevent falls are recommended.

Strength of Evidence – Recommended, Insufficient Evidence (I)

3. *Recommendation: Ergonomic Interventions for Knee MSDs*

There is no recommendation for or against the use ergonomic interventions for knee MSDs.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

Ergonomic interventions for spine and upper extremity disorders have been attempted in numerous occupational settings,(332) and RCTs of ergonomic interventions in these settings have been reported. However, there are no quality studies of ergonomic interventions for the lower extremity. In the upper extremity, some interventions that had been thought to be beneficial were found to be unhelpful. Thus, without quality evidence, there is no recommendation for or against ergonomic interventions for knee MSDs. Although there is no quality evidence for fall protection in preventing knee disorders, falls from heights continue to cause morbidity and deaths, and fall protection is therefore recommended.

SPECIAL STUDIES, DIAGNOSTIC AND TREATMENT CONSIDERATIONS

Special studies are not needed to evaluate most knee symptoms (see Table 4), unless a period of conservative care and observation has failed to lead to resolution or improvement of symptoms. The American College of Radiology (ACR), in its most recent appropriateness criteria, lists the following clinical parameters as predicting the absence of significant fracture. These parameters may be used to support the decision *not* to obtain a radiograph following knee trauma, although the decision rests with the primary treating physician who has completed a history and physical exam:

- patient is able to walk without a limp;

- patient had a twisting injury and there is no effusion.

The clinical parameters for ordering knee radiographs following trauma, as recommended by the ACR, are:

- joint effusion within 24 hours of direct blow or fall;
- palpable tenderness over fibular head or patella;
- inability to walk (4 steps) or bear weight immediately or within a week of the trauma;
- inability to flex knee to 90°.

Table 4. Ability of Various Techniques to Identify and Define Knee Pathology

Technique	Meniscus Tear	Ligament Sprain	Ligament Tear	Patello-femoral Syndrome	Tendinopathy	Prepatellar Bursitis	Regional Pain
History	++	++	++	++++	+++	++	++
Physical examination	++++	++++	++++	++	++++	++++	++
Laboratory studies	0	0	0	0	0	0	0
Electromyography/nerve conduction velocity (EMG/NCV) studies	0	0	0	0	0	0	0
Imaging studies							
Radiography [†]	0	0	0	+	0	0	0
Bone scan [†]	0	0	0	+	0	0	0
Arthrography [†]	+++	0	+	0	0	0	0
Computed tomography (CT) [†]	0	0	0	0	0	0	0
Magnetic resonance imaging (MRI) [†]	++++	+++	++++	+++	+++	+++	0

[†]Risk of complications (e.g., infection, radiation) highest for arthrography, less for radiography and computer tomography (CT), and lowest for bone scan and MRI.

DIAGNOSTIC CRITERIA

The criteria presented in Table 5 follow the clinical thought process, from the type of illness or injury, to symptoms and signs of a particular disorder to, finally, test results (if any tests are indicated).

Table 5. Diagnostic Criteria for Non-red-flag Knee Disorders

Probable Diagnosis or Injury	Symptoms	Signs	Tests and Results
Knee Osteoarthritis	Non-radiating knee pain. Morning stiffness or stiffness upon standing or after prolonged sitting. Sleep disturbance sometimes present as a result of pain, but mood disturbance usually not present. Other joints are often affected.	ROM generally reduced, especially knee flexion. May be normal when mild.	X-rays usually ordered to help secure diagnosis. Other diagnostic tests only if there is a potential for meaningful intervention
Patellofemoral Joint Syndrome (chondromalacia patella)	Anterior knee pain. Pain with stair climbing, other activities involving knee flexion, or sitting for a prolonged period of time.	Anterior knee tenderness. Crepitus on range of motion. Pain with patellofemoral compression	X-rays often ordered. Sunrise patella view particularly helpful. Other testing usually not necessary.
Patellar Dislocation and Instability	Inability to bear weight. Acute onset associated with forceful event or accident. Congenital or inherited variants tend to be recurrent. Instability if feeling of impending recurrence of	Unable to bear weight. Patella visibly displaced. Difficulty extending the knee.	Knee x-rays usually ordered. Other testing usually not necessary.

	subluxation with specific activities.		
Patellar Tendinopathy	Focal patellar tendon pain. Pain increases with use including stair use and jumping.	Focal tenderness over patella. Resisted knee extension may reproduce pain.	X-rays may demonstrate calcification and osteophytes at inferior patellar pole (which also may be non-specific). Ultrasound may show small tears.
Fractures	Fall, motor vehicle accident, or other significant trauma. Severe pain.	Unable to bear weight. Angulation, deformity, point tenderness, and bony crepitus.	X-rays required. Other testing usually not necessary in the acute treatment setting.
Meniscal Tears	Non-radiating knee pain. Typically provoked with specific, predictable activities in specific position(s). May have symptoms of joint effusion, buckling, clicking, catching or locking. Pain may be worse with pivoting and walking or stair-climbing.	Variable findings depending on extent of tear(s). May have joint effusion and modest warmth. Knee pain often worse with ROM and extent of ROM may be restricted. Pain reproduced with knee rotation and flexion. Click and/or crepitus may be present on exam.	X-rays often ordered. MRI is sometimes ordered, and MR arthrography may be helpful.
Osteonecrosis	Non-radiating bony pain. History of systemic factors (e.g., diabetes mellitus, alcohol). Pain generally increases with weight-bearing.	Reduced ROM and pain with passive ROM usually present. May have pain with weight bearing. May be unable to bear weight if osseous collapse has occurred.	X-rays required. MRI and CT may be ordered for further evaluation of the necrotic region. Bone scans sometimes ordered.
Infrapatellar, Prepatellar, Suprapatellar, and Anserine Bursitis	Anserine bursitis may be painful, but without clear effusion or exertional component. Other types of bursitis frequently not painful, but do have effusion/swelling.	Tender over anserine bursa. Other bursitis often minimally or not tender. ROM usually normal.	X-rays usually not needed. X-rays sometimes ordered if questions of usual settings, including concerns for infection, osteomyelitis, and foreign body. Other testing usually not required.
Collateral Ligament Sprains and Tears (lateral and medial)	Focal knee joint line pain. Medial more prone to be accompanied by meniscal tear. If complete tear, will typically have instability.	May have antalgic gait, especially if moderate to severe sprain. Focal tenderness over collateral ligament. Usually no effusion.	X-rays usually ordered in acute setting to rule out fracture, particularly for moderate to severe injuries. MRI may be helpful in chronic setting to rule out associated meniscal tear. Other testing usually not required.
Iliotibial Band Syndrome	Non-radiating lateral knee pain.	Lateral knee pain with use, especially running, cycling. Tender over lateral fascia.	X-ray generally not necessary, but may be indicated if concerns of unusual diagnostic concerns, such as accompanying arthrosis.
Cruciate Ligament Sprains, Tears and Ruptures. (anterior, Posterior)	Sudden pain with accident or other traumatic event. May have giving out and immediate swelling after event. May be asymptomatic. Event usually involved exaggerated adduction	Effusion if acute tear. Joint laxity with complete tears, including positive posterior or anterior drawer signs.	X-ray usually ordered in acute setting to rule out fractures. MRI may be helpful.

	and external rotation or abduction.		
Non-specific Knee Pain	Non-specific. No acute trauma	None	None
Non-specific Effusion	None. No acute trauma.	Effusion. No signs of infection or other abnormality.	X-ray often ordered, but by definition, normal other than effusion. Need evaluation for rheumatological disorder.

Adapted from AMA Guides to Impairment Rating – 6th edition and Sanders S, et al. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients. *Pain Prac.* 2005;5(4):303-15.

DIAGNOSTIC TESTING AND OTHER TESTING

ANTIBODIES

There are numerous antibodies that are markers for specific rheumatic diseases (e.g., rheumatoid factor, anti-nuclear antibodies, anti-Sm, anti-Ro, anti-La for rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s, mixed connective tissue disorder, etc.). Patients with rheumatic disorders are at increased risk for degenerative joint disease of the knee.(283, 333-339)

1. *Recommendation: Antibodies for Diagnosing Knee Pain with Suspicion of Chronic or Recurrent Rheumatological Disorder*

Antibody levels are recommended to evaluate and diagnose patients with knee pain who have reasonable suspicion of rheumatological disorder. However, ordering of a large, diverse array of antibody levels without targeting a few specific disorders is not recommended.

Indications – Knee pain with suspicion of rheumatological disorder.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. *Recommendation: Antibodies to Confirm Specific Disorders*

Antibody levels are strongly recommended to confirm specific disorders (e.g., rheumatoid arthritis).

Indications – Knee pain and presumptive diagnosis of a rheumatological disorder.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

Rationale for Recommendations

Elevated antibody levels are useful for confirmation of clinical impressions of rheumatic diseases. However, routine use of these tests in knee pain patients, especially as wide-ranging, non-focused test batteries are likely to result in inaccurate diagnoses due to false positives and low pre-test probabilities. Providers should also be aware that false negative results occur. Measurement of antibody levels is recommended for focused testing of a limited number of diagnostic considerations for which there is clinical suspicion. Measuring antibody levels is minimally invasive, unlikely to have substantial adverse effects and low to moderately costly, depending on the specific test ordered.

ARTHROGRAPHY

This diagnostic procedure has been replaced by MRI, which is both more sensitive and specific.

KNEE ARTHROSCOPY

Arthroscopy of the knee has been increasingly utilized for treatment of knee disorders.(9, 137, 340-367) It has become the gold standard for measuring the utility of the clinical examination as well as the comparative standard for other treatments.(368) Disorders commonly treated arthroscopically include meniscal tears, cruciate tears, and chondral fractures.(353, 369-374) However, there are few high quality studies from which to determine indications for either diagnostic or therapeutic arthroscopic knee procedures.

1. *Recommendation: Knee Arthroscopy for Diagnosing and Treating Knee Pain with Suspicion of Meniscal Tear, Intraarticular Body, or Other Subacute or Chronic Mechanical Symptoms*
Arthroscopy is only recommended to evaluate and diagnose patients with knee pain if there is suspicion of a clinically significant meniscal tear, intraarticular body, or other subacute or chronic mechanical symptoms and an equivocal or inconclusive MRI.

Indications – Knee pain with suspicion of meniscal tear, intraarticular body, or other subacute or chronic mechanical symptoms treatable by arthroscopy.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. *Recommendation: Knee Arthroscopy for Diagnosing Acute Knee Pain*
Arthroscopy for diagnosing acute knee pain, other than large meniscal tears, cruciate tears or intraarticular bodies, is not recommended.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

3. *Recommendation: Knee Arthroscopy for Staging a Surgical Procedure*
Arthroscopy is recommended for staging a surgical procedure.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

4. *Recommendation: Knee Arthroscopy for Diagnosis or Treatment in Acute, Subacute, or Chronic Osteoarthritis without Mechanical Symptoms and Other Remediable Mechanical Defect*
Arthroscopy is not recommended for diagnosis or treatment in patients with acute, subacute, or chronic osteoarthritis in the absence of a remediable mechanical defect such as clinically significant symptomatic meniscal tear.(375)

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

Arthroscopy of the knee is widely utilized for treatment of several knee disorders, especially meniscal tears. Complications usually occur with more serious injuries and include nerve retraction, neuropraxias, infection, and complex regional pain syndrome.(376-385) Adverse effects are minimal when small-bore arthroscopes are used. Osteoarthritis was previously thought to be treatable by arthroscopy.(369) However, arthroscopy is currently not believed to be helpful, and arthroscopy with chondroplasty has been shown not to be helpful, in the absence of remediable mechanical symptoms suggesting a clinically significant meniscal tear or intraarticular body.(375) Arthroscopy is invasive and expensive, but it is recommended for selected patients, particularly those with remediable mechanical defects such as meniscal tears.

Evidence for the Use of Arthroscopy

There is 1 low-quality RCT in Appendix 1.(386)

BONE SCANS

Bone scans involve intravenous administration of a radioactive tracer medication that is preferentially concentrated in areas of metabolic activity in bone.(387, 388) The radioactivity is

then detected by a large sensor and converted into images of the skeleton. There are many causes of abnormal radioactive uptake, including metastases, infection, inflammatory arthropathies, fracture or other significant bone trauma. Thus, positive bone scans are not highly specific. Bone scans have been used for the diagnosis of early osteonecrosis, which is often not apparent on x-ray.(389-392)

1. *Recommendation: Bone Scanning for Select Use in Acute, Subacute, or Chronic Knee Pain*
Bone scanning is recommended for select use in patients with acute, subacute, or chronic knee pain to assist in diagnosing osteonecrosis, neoplasms, or other conditions with increased polyostotic bone metabolism, particularly if more than one joint is to be evaluated.

Indications – Knee pain with suspicion of osteonecrosis, Paget’s disease, neoplasm, or other increased polyostotic bone metabolism.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. *Recommendation: Routine Use of Bone Scanning for Knee Joint Evaluations*
Bone scanning is not recommended for routine use in knee joint evaluations as it is generally thought to be inferior to MRI.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

Bone scanning may be a helpful diagnostic test to evaluate suspected metastases, primary bone tumors, infected bone (osteomyelitis), inflammatory arthropathies, and trauma (e.g., occult fractures). It may be helpful in those with suspected early AVN without x-ray changes. There is no indication for bone scanning in cases where the diagnosis is felt to be secure, as bone scanning does not alter management. Bone scanning is minimally invasive, has minimal potential for adverse effects (essentially equivalent to a blood test), but is costly.

Evidence for the Use of Bone Scans

There are no quality studies evaluating the use of bone scans for the evaluation of knee pain.

COMPUTERIZED TOMOGRAPHY (CT)

Computerized tomography is a useful imaging procedure for bony anatomy, whereas MRI is superior for soft tissue abnormalities.(393, 394) CT may be useful for certain knee joint abnormalities, including complex fractures, in which advanced imaging of the bones is required. CT may be helpful for the evaluation of AVN. CT may also be useful for evaluation of the spine in patients with contraindications for MRI, including implanted metallic-ferrous device.(394)

1. *Recommendation: Routine CT for Evaluating Acute, Subacute, or Chronic Knee Pain*
Routine CT is not recommended for evaluating acute, subacute, or chronic knee pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

2. *Recommendation: CT for Evaluating Patients with Osteonecrosis (AVN)*
CT is recommended for evaluating patients with osteonecrosis or for those who need advanced imaging, but have contraindications for MRI.

Indications – Knee pain from osteonecrosis with suspicion of subchondral fracture(s), or increased polyostotic bone metabolism.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

3. *Recommendation: CT for Evaluating Patients with Periprosthetic Osteolysis after Total Knee Arthroplasty*

CT is recommended for evaluation of total knee arthroplasty patients with potential periprosthetic osteolysis.

Indications – Arthroplasty thought to have periprosthetic osteolysis.(395)

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

Computerized tomography is considered superior to MRI for imaging of most knee abnormalities where advanced imaging of calcified structures is required. CT has been used to evaluate periprosthetic osteolysis.(395) A contrast CT study is minimally invasive, has few adverse effects, but is costly. It is recommended for select use. Helical CT scan is thought to be superior to MRI for evaluating subchondral fractures; however, a large, high-quality study comparing these modalities has not yet been published.(396)

Evidence for the Use of CT

There are no quality studies evaluating the use of CT for the evaluation of knee pain.

C-REACTIVE PROTEIN, ERYTHROCYTE SEDIMENTATION RATE, AND OTHER NON-SPECIFIC INFLAMMATORY MARKERS

There are many markers of inflammation that may be measured serologically. These include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, and a total protein-albumin gap.(397-400)

Recommendation: Non-specific Inflammatory Markers for Screening for Inflammatory Disorders in Subacute or Chronic Knee Pain Patients

Erythrocyte sedimentation rate and other inflammatory markers are recommended to evaluate for inflammatory disorders or prosthetic sepsis when there is a reasonable suspicion of an inflammatory disorder in subacute or chronic knee pain patients. However, ordering a large, diverse array of inflammatory markers without targeting specific disorders for which there is clinical suspicion is not recommended.

Indications – Knee pain with suspicion of inflammatory disorder, including infection.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

Erythrocyte sedimentation rate is the most commonly used systemic marker for non-specific inflammation. The ESR is elevated in numerous inflammatory conditions, including rheumatological disorders, as well as with infectious diseases. C-reactive protein is a marker of systemic inflammation that has been reported to be associated with an increased risk of coronary artery disease. However, it is also a non-specific inflammatory marker. Other non-specific markers of inflammation include an elevated ferritin and protein-albumin gap. CRP and ESR measurements are minimally invasive, have low risk of adverse effects, and are relatively inexpensive. They are recommended as a reasonable component of the evaluation when there is suspicion of a systemic inflammatory condition.

Evidence for the Use of C-Reactive Protein, Erythrocyte Sedimentation Rate, and Other Non-specific Inflammatory Markers

There are no quality studies evaluating the use of C-reactive protein, erythrocyte sedimentation rate, and other non-specific inflammatory markers for knee pain.

CYTOKINES

See Chronic Pain guideline.

LOCAL ANESTHETIC INJECTIONS AND EPIDURALS

Local anesthetic injections are sometimes used for diagnostic confirmation of knee conditions (see Injections). These injections are also sometimes used to differentiate pain from a distant site, such as the hip or spine. Diagnostic injections include intraarticular injections (knee, hip, or sacroiliac), ilioinguinal, genitofemoral, and saphenous nerve blocks, and lumbar epidurals. (401-404)

Recommendation: Local Anesthetic Injections to Diagnose Subacute or Chronic Knee Pain

Local anesthetic injections are recommended to assist in the diagnosis of subacute or chronic knee pain.

Indications – Subacute or chronic knee pain from an unclear source; immediate and delayed results of injection(s) should be recorded.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

Local anesthetic injections may be helpful for confirming diagnostic impressions, although there are no quality studies evaluating the use of injections for these purposes. Intraarticular knee injections are often performed with anesthetic agents and glucocorticosteroids, as this generally accomplishes both diagnostic and therapeutic purposes simultaneously. These injections are minimally invasive, have minimal potential for adverse effects, and are moderately costly.

Evidence for the Use of Local Anesthetic Diagnostic Injections

There are no quality studies evaluating the use of local anesthetic diagnostic injections for knee pain.

ELECTROMYOGRAPHY (including Nerve Conduction Studies)

See the Low Back Disorders guideline for discussion regarding the use of electrodiagnostic studies for evaluation of back-related disorders that may present as knee pain. Electrodiagnostic studies have also been used to confirm diagnostic impressions of other peripheral nerve entrapments, including of the lateral cutaneous nerve of the thigh (meralgia paresthetica). (405-417)

Recommendation: Electromyography for Diagnosing Subacute or Chronic Peripheral Nerve Entrapments

Electrodiagnostic studies are recommended to assist in the diagnosis of subacute or chronic peripheral nerve entrapments.

Indications – Subacute or chronic paresthesias with or without pain, particularly with an unclear diagnosis.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

Electrodiagnostic studies may assist in confirming peripheral nerve entrapments. These studies are minimally invasive, have minimal potential for adverse effects (essentially equivalent to a blood test), and are moderately costly.

Evidence for the Use of Electromyography

There are no quality studies evaluating the use of electrodiagnostic studies for diagnosing peripheral nerve entrapments relevant to the knee.

FUNCTIONAL CAPACITY EVALUATIONS

See Chronic Pain guideline.

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging (MRI) has been widely used for diagnostic purposes in patients with knee pain, particularly for evaluating the menisci and cruciate ligaments.(137, 340, 341, 343, 344, 346-352, 354-358, 360-362, 365-367, 418-420) MRI is considered the gold standard for evaluating AVN.(421-429)

1. *Recommendation: MRI for Knee Joint Pathology, Including Diagnosing Meniscal Tears, Cruciate Ligament Tears, Hamstring and other Muscular Tears, and for Select Patients with Post-arthroplasty Chronic Pain or Periarticular Masses*

MRI is recommended for select patients with subacute or chronic knee symptoms in which mechanically disruptive internal derangement or similar soft tissue pathology is a concern. It is generally not indicated for patients with acute knee pain.

Indications – Subacute or chronic knee pain in which imaging of surrounding or intraarticular soft tissues is needed (including menisci); evaluation of moderately severe and severe cruciate ligament sprains and tears to evaluate the extent of the injury and help determine whether surgery is indicated.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. *Recommendation: MRI for Diagnosing Osteonecrosis (AVN)*

MRI is recommended for diagnosing osteonecrosis.

Indications – Subacute or chronic knee pain thought to be related to osteonecrosis (AVN), particularly if the diagnosis is unclear or if additional diagnostic evaluation and staging is needed.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

3. *Recommendation: MRI for Routine Evaluation of Acute, Subacute, or Chronic Knee Joint Pathology*

MRI is not recommended for routine evaluation of acute, subacute, or chronic knee joint pathology, including degenerative joint disease.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

MRI has not been evaluated in quality studies for knee joint pathology, although studies have reported accuracy estimates ranging from 82 to 96% for cruciate ligament and meniscal tears.(84, 121, 348, 356, 357, 367, 430-434) False-negative MRI interpretations are particularly likely in posterior horn meniscal tears.(368) There is concern that MRI is overutilized, particularly in cases where clinical examination is sufficient.(84, 102, 116, 435) However, most physicians believe that MRI should be performed prior to arthroscopy for meniscal or ACL tears(436) or in patients with non-specific knee pain.(437)

MRI may play a role in staging osteoarthritis,(438) although there is no quality evidence that this practice affects prognosis or treatment. MRI can detect osteophytes(439) and is better than x-ray for identifying cartilage loss and subchondral cysts, but it is relatively poor at detecting early subchondral sclerosis.(439, 440) There are no quality studies evaluating the use of MRI for osteonecrosis of the knee joint. There is low-quality evidence that MRI may be less sensitive for detection of subchondral fractures than helical CT or plain x-rays in patients with osteonecrosis.(396) MRI is not invasive, has no adverse effects, although there may be issues related to claustrophobia or complications of concomitantly administered medications, but it is costly. MRI is not recommended for routine knee imaging, but it is recommended for selected knee joint pathology, particularly suspected soft tissue pathology.

Evidence for the Use of MRI

There are no quality studies evaluating the use of MRI for diagnosing knee pain.

MR ARTHROGRAM

Magnetic resonance imaging with arthrography (MR arthrography) has been performed to evaluate meniscal and chondral lesions,(441, 442) for example following chondrocyte and meniscus implants.(442, 443)

Recommendation: MR Arthrogram for Evaluation of Select Patients Needing Advanced Meniscal and Cartilage Imaging and Following Chondrocyte Implantation

MR arthrograms are recommended for select patients who require advanced imaging of the menisci and articular cartilage or following procedures such as chondrocyte implantation.

Indications – Patients with negative or equivocal MRI imaging with ongoing suspicion of clinically significant intraarticular pathology such as meniscal tears or articular cartilage defects or following selected procedures such as chondrocyte implantation.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

MR arthrograms have not been evaluated in quality studies, but appear helpful in evaluating patients with ongoing intraarticular mechanical symptoms despite negative or inconclusive MRIs. These studies are also likely to be helpful for those with certain post-operative indications, including after chondrocyte implantation. MR arthrography is minimally invasive, has no adverse effects, although there may be issues related to claustrophobia or complications of concomitantly administered medications, but it is costly. However, it is likely the best imaging procedure available for certain select patients.

Evidence for the Use of MR Arthrogram

There are no quality studies evaluating the use of MR arthrogram.

ROENTGENOGRAMS (X-RAYS)

X-ray is the initial test for evaluation of most cases of knee pain.(283, 342, 438, 444-449) X-rays are considered the initial test of choice for evaluating patients with suspected knee osteoarthritis. Two or three supine views are generally performed. There are no quality studies of x-ray in the evaluation of knee pain. It should be noted that the threshold for x-ray of the lumbosacral spine and/or hip joint should be low, particularly if the findings on knee x-ray are either normal or do not readily explain the degree of clinical findings. Stress radiography (x-ray taken while a stress is applied to the joint and used to demonstrate instability) has been described for evaluation of ACL tears, but is not usually necessary to establish a diagnosis.(110) In the case of osteonecrosis, plain x-ray results differ by stage of disease. Early x-rays are usually normal or have less distinct trabecular patterns, but as the disease progresses, x-rays begin to show osteoporotic areas progressing to sclerotic areas and flattening and bony collapse.(450) X-rays are also used to evaluate post-arthroplasty knees.

1. *Recommendation: X-ray for Evaluating Acute, Subacute, or Chronic Knee Pain*
X-ray is recommended for evaluating acute, subacute, or chronic knee pain.

Indications – In the absence of red flags, knee pain of moderate to severe intensity lasting at least a few weeks, and/or limited range of motion.

Frequency/Duration – Obtaining x-rays once is generally sufficient. For patients with chronic or progressive knee pain, it may be reasonable to obtain a second set of x-rays, months to years after the baseline x-rays to re-evaluate the patient’s condition, particularly if symptoms change.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. *Recommendation: X-ray for Diagnosing Fracture*
X-ray is recommended for diagnosing fracture.

Indications – Patients thought to have fracture, particularly those with an inability to bear weight, effusion, or ecchymosis.(451)

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

3. *Recommendation: X-ray for Diagnosing Osteonecrosis (aka Avascular Necrosis, AVN)*
X-ray is recommended for diagnosing osteonecrosis.

Indications – Patients thought to have osteonecrosis (ON).

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

X-ray is helpful in evaluating most knee pain, both to diagnose and to assist with narrowing the differential diagnosis. A clinical algorithm was constructed to evaluate the need for x-ray to rule out fracture, and the presence of at least one sign of fracture was deemed to be highly sensitive for fracture.(451) There are no quality studies of the use of x-ray to evaluate knee pain. There is one low-quality study suggesting x-ray has higher sensitivity than MRI for detection of subchondral fractures in patients with osteonecrosis.(396) However, x-ray has long been used to stage osteoarthritis(283, 342, 438, 452-456) and evaluate for post-arthroplasty osteolysis.(457) X-ray is non-invasive, low to moderately costly, and has little risk of adverse effects.

Evidence for the Use of X-rays

There are no quality studies evaluating the use of x-rays for knee pain, including for diagnosing osteonecrosis.

SALINE LOAD TEST

The saline load test has been used when there is a knee laceration to determine whether there has been penetration of the joint capsule.(458-460) The test involves injection of saline into the joint to ascertain whether the solution flows through the joint capsule and out of the trauma site.(461)

Recommendation: Saline Load Test for Select Knee Lacerations

A saline load test is recommended for select patients with knee lacerations that may have penetrated the joint.

Indications – Lacerations in the knee region that may have penetrated the knee joint but have not clearly done so.

Dose – At least 150 to 200mL of saline injected with an 18-g needle. Volume required varies based on size of potential laceration (more saline required for smaller lacerations) and may differ based on location of laceration. The lateral suprapatellar instillation site has been utilized.(460) Superomedial and inferomedial locations have been compared; more volume required for the superomedial location (mean 95.2 vs. 64.0mL).(459)

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

There are no quality studies of the saline load test in the evaluation of joint capsule penetration. A study in 30 arthroscopy patients suggested that more than 194mL was required for the saline load test to be at least 95% sensitive.(460) Another study of knee arthroscopy patients found at least 155mL of saline must be injected to detect 95% of 1-cm inferolateral arthrotomies.(459) This procedure is minimally invasive, has minimal potential for adverse effects, is relatively inexpensive, and is recommended for select patients.

Evidence for the Use of Saline Load Test

There are no quality studies evaluating the use of saline load test for the evaluation of knee pain.

ULTRASOUND

Many of the usual causes of knee pain are better imaged with modalities other than ultrasound. Diagnostic ultrasound has been used for evaluating the patellar ligament, including for “jumper’s knee” and partial ruptures,(156, 462-468) effusions,(469) dysplasia,(470, 471) labral tears,(472) and occult fractures.(473) Ultrasound for cruciate ligament tears has been described as technically difficult.(78) Ultrasound has also been used to guide injections in deep body structures, although the knee joint is relatively accessible. The diagnostic accuracy of ultrasound for patellar partial ligament ruptures has been reported as 100% in a modest sized case series.(462)

1. *Recommendation: Ultrasound for Evaluating Patellar Tendinopathy, Pes Anserine Bursitis, Hamstring Strains, Quadriceps Strains or Post-arthroplasty Chronic Pain When Peri-Articular Masses Are Suspected*

Ultrasound is recommended for evaluating patients with patellar tendinopathy, pes anserine bursitis, hamstring strains, quadriceps strains, or post-arthroplasty chronic pain, when peri-articular masses are suspected.

Indications – Patients with knee pain thought to be from these disorders.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. *Recommendation: Ultrasound for Evaluating Other Knee Disorders including Osteonecrosis, Osteoarthritis, Dysplasia, or Fractures*

There is no recommendation for or against the use of ultrasound for evaluating other knee disorders, including osteonecrosis, osteoarthritis, dysplasia, or fractures.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Rationale for Recommendations

Ultrasound has been found to be helpful in evaluating tendinopathy and myotendinous strains. There is no clear indication for use of ultrasound for the evaluation of osteoarthritis. Ultrasound is not invasive, has no adverse effects, is moderately costly, and is recommended for select use.

Evidence for the Use of Diagnostic Ultrasound

There are no quality studies evaluating the use of diagnostic ultrasound.

INITIAL CARE

Although comfort is often a patient’s first concern, the treating physician must first evaluate for remediable conditions or red flags. Nonprescription analgesics may provide sufficient pain relief for most patients with acute or subacute knee pain. If treatment response is inadequate (i.e., if symptoms and activity limitations continue) or the physician judges the condition limitations to

be more significant, prescribed pharmaceuticals or physical methods can be added. Co-morbid conditions, invasiveness, adverse effects, cost, and physician and patient preferences guide the choice of recommendations. Initial care, including comfort items, may consist of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, cryotherapy, heat, exercises, or education and advice on activities. Education about knee pain should begin at the first visit.

This section addresses the evidence for efficacy of many knee interventions. Interventions with quality evidence of proven efficacy are recommended in this guideline. Complication rates and safety profiles, if available, were considered in developing these guidelines. Interventions not supported by moderate- to high-quality studies are not recommended and are indicated as **Not Recommended, Insufficient Evidence (I)**.

ACTIVITIES AND ACTIVITY MODIFICATION

Activities and activity alterations are typically managed differently in patients with acute and chronic knee pain. Acute knee pain patients may benefit from activity limitations, while chronic knee pain patients almost never improve with activity limitations. Acute knee pain often improves with avoidance of occupational and non-occupational activities that result in *substantial* increases in pain. However, even in the acute pain setting, appropriate activity alterations are difficult to identify. For example, prolonged inactivity of any musculoskeletal pain usually results in increased pain upon movement. It is easy to erroneously conclude the activity aggravated the pain. Even in the acute setting, however, some activity is usually desirable. In general, activities causing a *significant* increase in knee symptoms should be reviewed with the patient and modifications advised when appropriate. These activities may include stair climbing, walking, lifting, and frequency of postural changes.

Chronic knee pain is managed differently. Almost invariably, rehabilitation of chronic knee pain involves gradually performing the occupational and non-occupational activities that result in increased pain in order to improve function. The same types of limitations may be reasonable, but progressive increases in activity frequency, intensity and/or durations is generally necessary to rehabilitate these problems.

Work limitations should take into account four main factors: 1) the job physical requirements; 2) the severity of the problem; 3) work organizational issues (e.g. ability to control job or tasks, overtime, work allocation, wage incentives); and 4) the patient's understanding of his or her condition. Sometimes it is necessary to write limitations or prescribe activity levels that are above what the patient feels he or she can do, particularly for patients who believe they should remain sedentary. Progressively increased activity is important, and restrictions that state "sedentary work" are *not* appropriate for most knee patients. Physicians should recognize that a patient's expectations regarding return-to-work status are often set prior to the first appointment,⁽⁴⁷⁴⁾ (Kapoor 06) and therefore education may be necessary to set realistic expectations and goals. It is best to communicate early in the treatment that limitations will be progressively reduced as the patient progresses. This should be reiterated at each successive visit so that the patient is well advised in advance of the treatment plan.

There are no quality studies of restrictions, so determining appropriate restrictions is often left to clinical judgment. Assessment of work activities and potential for modifications may be facilitated by a worksite visit and analysis by a healthcare provider with appropriate training (e.g., occupational therapist, physical therapist, physician, or ergonomist). Common limitations involve stair climbing and modifying the weight of objects lifted, frequency of lifts, and posture while taking into account the patient's capabilities. For severe cases of acute knee pain, initial modification of occupational and non-occupational activities often includes:

- frequent alternation of sitting and standing;
- no lifting more than 10 pounds;
- no prolonged or repeated knee bending (flexion);
- no prolonged or repeated crouching and squatting;
- avoidance of ambulation on slippery surfaces or uneven ground; and
- avoidance of frequent stairs.

These work and home activity guidelines are generally reassessed every week in the acute phase. Gradual increases in activity levels are recommended with a goal of returning to full duty in 6 to 12 weeks. The amount of weight handled can be progressively increased. Alternatively, patients can be returned to 1 to 2 hours a day of prior full duty work, with the remainder of the day spent at modified duty. The numbers of hours of full duty work can be increased every 1 to 2 weeks. Individualization of management plans is often necessary. For example, if prior job physical tasks involved frequent lifting of more than 100 pounds, then restricted work guidance may be substantially greater (e.g., 25 pounds of lifting and carrying at first). For workers who have control over their job tasks, assistance from someone else and alternating between sitting and standing as needed, may be included in the management plan.

It should be noted that some workplaces provide healthcare or rehabilitation therapy on-site, so brief periods of recumbent time during the day and on-site physical or occupational therapy may be possible. The physician should make it clear to patients and employers that:

- prolonged walking and/or stair climbing may aggravate symptoms;
- moderately heavy lifting, carrying, or working in awkward positions may aggravate symptoms; and
- any restrictions are intended to allow for recovery and time to build activity tolerance through structured exercise.

It is in the patient's best interest for the short- and long-term to maintain maximal levels of activity, including work activity. Written guidance on activity limitations, when applicable, communicates the status of the patient to the employer and gives the patient information on what he or she should or should not do both at work and at home.

KNEE PAIN AND OSTEOARTHRISIS

Physicians should develop individualized patient treatment and follow-up plans based on the severity of the condition, co-morbidities, occupational demands, psychosocial factors, and patient motivation and need for encouragement. The ability to return to work should be considered when determining the frequency of follow-up. More frequent appointments are generally required for patients whose limitations have not been accommodated. The patient should be transitioned to work, or from modified work to full work, at the earliest date possible, and should be supported during that transition and counseled about the likelihood of increased symptoms while being reassured that pain does not equate to injury.

ACTIVITY MODIFICATION

Recommendation: Activity Modification for Acute, Subacute, or Chronic Knee Pain

Activities that do not substantially aggravate symptoms are recommended for most patients with acute, subacute, or chronic knee pain.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendation

There are no quality studies evaluating modification of activity for treatment of knee pain. Common post-arthroplasty limitations have included no lifting over a weight limit, no running, and no jumping. Lifting limits may commonly be 50 pounds, but are frequently based on prior weight-lifting capabilities and anticipated future abilities. While modification of activity is not invasive, it may result in increased disability through disuse, or increased cardiovascular morbidity through lack of exercise. It also may result in high costs through lost productivity. Thus, implementation of activity modifications should be carefully balanced against increased longer term morbidity and other costs. In cases where activity does not aggravate the symptoms or disease, activity modifications are not recommended – rather, activity is recommended.

Evidence for the Use of Activity Modification

There are no quality studies evaluating the use of activity modification for treatment of knee pain.

BED REST AND NON-WEIGHT-BEARING

1. *Recommendation: Bed Rest and Non-weight Bearing for Patients with Acute, Subacute, or Chronic Knee Pain*

Bed rest and non-weight bearing are not recommended for patients with acute, subacute, or chronic knee pain.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

2. *Recommendation: Bed Rest and/or Non-weight Bearing for Unstable Fractures*

Bed rest and/or non-weight bearing activities are recommended for patients with clear contraindications to weight-bearing, such as an unstable fracture.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendations

Bed rest and/or non-weight bearing are unlikely to be beneficial and generally should be avoided for all patients other than for those with clear contraindications to weight-bearing, such as evidence of an unstable fracture.

Evidence for the Use of Bed Rest and Non-Weight Bearing

There are no quality studies evaluating the use of bed rest for treatment of knee pain.

EXERCISE

Exercises have been utilized for the prevention and treatment of osteoarthritis, including aerobic exercise, strengthening exercise, and flexibility.(475-491) Exercise is also thought to be effective for rehabilitation after knee arthroplasty.(492) Educational programs have also been used to treat knee osteoarthritis, often in combination with an exercise program.(6, 481, 493-499)

Arthritic patients tend not to engage in high levels of physical activity.(500) Some believe that exercise is an effective primary and secondary preventive intervention.(12) Opinions on the relative importance of aerobic versus strengthening versus flexibility conflict,(482, 484, 491, 501-512) and some endorse the belief that “exercise may be the most effective, malleable, and inexpensive modality available to achieve optimal outcomes for people with osteoarthritis.”(483)

Available research addressing exercise for knee OA consists of mostly low- to moderate-quality trials with few high-quality studies. In these recommendations, the entire body of exercise-related articles has been included, program.(279, 513-519) since several studies have included both inflammatory conditions,(501, 520-540) as well as osteoarthritis. Most studies have combined different exercises into programs that at least partially obscure effects of a specific

exercise prescription (e.g., flexibility versus aerobic versus strengthening). However, some patterns do appear. While specific to knee or hip osteoarthritis, these recommendations also appear to apply to rheumatoid arthritis patients as well,(520, 541-543) as materially different results were not found in that population (see exercise evidence table and Hip and Groin Disorders guideline).

1. *Recommendation: Aerobic Exercise for Treatment of Knee Osteoarthritis*

Aerobic exercise is strongly recommended for the treatment of knee osteoarthritis.

Indications – All patients with knee osteoarthritis. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises (follow ACSM *Guidelines for Exercise Testing and Prescription*, 7th ed.).(544)

Frequency/Dose/Duration – Dose is somewhat unclear. A self-directed program is recommended for all patients. Supervised programs may be particularly indicated for those who require supervision to initiate a program or otherwise need assistance with motivation or concomitant fear avoidant belief training. Supervision may be for a few appointments to help initiate the program. The highest quality trial prescribed walking 40 minutes per session, 3 times a week.(508, 545-547) Another common regimen is walking at least 4 times a week at 60% of predicted maximum heart rate ($220 - \text{age} = \text{maximum heart rate}$). Both regimens are comparable and either is recommended.(548, 549) Nearly all patients should be encouraged to continue aerobic exercises on a long-term basis for fitness purposes, including maintaining lower extremity muscle strength.

Indications for Discontinuation – Intolerance (rarely occurs), development of other disorders.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

2. *Recommendation: Stretching Exercises for Treatment of Knee Osteoarthritis*

Stretching exercises are recommended for select patients with knee osteoarthritis who have significant reductions in range of motion that are not thought to be fixed deficits.

Indications – Patients with significant reductions in range of motion that are thought to be non-fixed deficits (e.g., limitations based on stiffness or disuse rather than osteophytes).

Frequency/Duration – Generally taught as home exercises over 1 to 3 appointments.

Indications for Discontinuation – Worsening of symptoms, identification that the deficits are fixed, or achievement of exercise program goals.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

3. *Recommendation: Strengthening Exercises for Treatment of Knee Osteoarthritis*

Strengthening exercises are moderately recommended for treatment of knee osteoarthritis.

Indications – Knee osteoarthritis.

Frequency/Duration – Home program at least 2 to 3 times a week. Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. There is moderate-quality evidence that isometric exercises are least successful.(550) May be added with aerobic exercises to an exercise program. In limited circumstances where range-of-motion deficits are considerable, but thought to not be fixed, strengthening is sometimes added after beginning flexibility exercises. One moderate-quality trial suggests strengthening exercises are more effective for neutrally aligned knees.(551)

Indications for Discontinuation – Development of a strain or failure to improve.

Strength of Evidence – Moderately Recommended, Evidence (B)

4. *Recommendation: Educational Sessions for Treatment of Knee Osteoarthritis*
Educational sessions are recommended to help facilitate treatment of knee osteoarthritis.

Indications – Knee osteoarthritis.

Frequency/Duration – One to 3 sessions over 6 weeks, primarily to facilitate an active exercise program and compliance. Content is suggested to be focused on active exercises rather than passive interventions or disease pathophysiology as this may be helpful, particularly in addition to an active exercise program when compliance is challenging or periodic encouragement and facilitation to overcome incapacity in patients with severe osteoarthritis.

Indications for Discontinuation – Noncompliance, failure to improve.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendations

There are multiple RCTs addressing hip knee and/or hip osteoarthritis patients. Studies compare exercise to non-exercise controls,(476, 494-496, 508, 545-547, 552-566) exercise to exercise,(567-574) and exercise to other treatments(575-579) (see Exercise evidence table). As there is not a strong rationale for believing that there are major differences in efficacy for hip versus knee OA (see Hip and Groin Disorders guideline),(563) and analysis of the available evidence fails to suggest major differences, this summary assumes the outcomes are similar in both sets of patients. Most of the studies considered here combined different exercises. Some exercise programs were unstructured and some studies did not clearly describe the interventions. These limitations preclude drawing strong evidence-based conclusions regarding any single intervention. Yet, there are quality studies comparing exercise to non-exercise controls (580) that allow evidence-based conclusions to be made on the relative value of aerobic, stretching, and strengthening exercises. There also is experimental evidence that the glycosaminoglycan content in the post-meniscectomized knee is superior if exercised.

A high-quality trial of knee osteoarthritis suggests that while both aerobic and resistance training are helpful, aerobic exercises are modestly superior to resistance training and far superior to education.(508, 545-547) A moderate-quality trial using a comparable exercise regimen also suggests that walking is beneficial.(548) These studies support the idea that weight bearing is beneficial,(581) raise questions about which specific exercises are most beneficial, and suggest that aerobic exercise may be superior for knee osteoarthritis patients.

All quality studies which included a major component of documented compliance with increased aerobic exercise found benefits of aerobic exercise.(548, 560, 565) Strengthening exercise results appear similar. There is not clear superiority of aerobic or strengthening exercises or vice versa. The available quality evidence suggests aerobic and strengthening exercises are superior to flexibility or range-of-motion exercises.(476, 548) Some, but not all data, suggest increased exercise intensity results in superior outcomes. Some, but not all studies that have assessed inflammatory markers and joint scores among those with OA or RA have found reductions in erythrocyte sedimentation rates and lower joint scores among those exercising. Pool-based programs have been evaluated and evidence of superiority of water-based programs is lacking (see Aquatic Therapy). A Cochrane review of exercise for knee OA found platinum (highest) level evidence of modest beneficial effects on knee pain and disability, but

unclear evidence on the rate of disease progression.(582) A second Cochrane review found equal efficacy for both high- and low-intensity exercise.(583)

Problems with compliance and persistence with exercise programs after discharge are considerable. Evidence is mixed regarding whether supervised exercise programs are necessary or whether home-based programs are sufficient. Providers need to encourage ongoing compliance with these programs. Exercise programs are not invasive, have low adverse effects, and are low to moderate cost depending on numbers of supervised appointments. Programs emphasizing aerobic and strengthening exercises are recommended, as is stretching for those with considerable reductions in range of motion that do not appear fixed.

Educational programs are largely ineffective compared to exercise or other active treatments.(508, 545-547, 584) Trials have sometimes employed educational programs as a sham or control treatment. However, a few educational visits to emphasize need for exercise and to tailor exercise and other activities are recommended in concert with an exercise prescription, as educational interventions have low adverse effects and are not costly. There is moderate quality evidence a combination of exercise and weight loss is effective for osteoarthritis, providing additional rationale for educational interventions targeted at weight loss.(24, 585, 586)

Evidence for the Use of Exercise for Knee Osteoarthritis and Rheumatoid Arthritis

There are 5 high- and 78 moderate-quality RCTs incorporated into this analysis. There are 21 low-quality RCTs(504, 507, 511, 512, 516, 587-602) (one with two reports(603, 604)) in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Exercise for Post-surgery Patients						
Ebert 2008 RCT	4.5	N = 62 who underwent MACI (matrix induced autologous chondrocyte implantation) to localized, full thickness medial or later femoral condylar defects to knee	Traditional (5 weeks WB at 20% (toe-touch) BW, followed by progressive increase to full WB 11 weeks post-op vs. accelerated rehab (progressively increased WB immediately with full WB attained at 8 weeks post-op) patients had knee braced and used single crutch in both groups.	KOOS subscales for pain significantly improved in accelerated patients over time, p = 0.033; 6 minute walk test and activity levels at 3 months after surgery significantly greater in accelerated group, p <0.05; 6 minute walk test at 3 months: accelerated 515.8±19.1 vs. traditional 464.1±19.1, p = 0.041. Activity at 3 months: accelerated 101115±462 vs. traditional 8551±430, p = 0.016. Traditional group reported more knee pain at gait analysis.	“The ‘accelerated’ load bearing approach that reduced the length of time spent ambulating on crutches resulted in reduced knee pain, improved function, no graft complications and may speed up the recovery of normal gait function. Patient follow-up to at least 24 months would be required to observe longer-term graft outcomes.”	Data suggest early weight bearing is beneficial for pain and better function.
Exercise Advice for Osteoarthritis						
Ettinger 1997 Rejeski 1997	8.0	See Exercise vs. Exercise Controls for Osteoarthritis table below.				

Rejeski 1998 Mangani 2006						
Maurer 1999 RCT	4.5	N = 113 knee OA (ACR), mild to moderate knee pain for at least previous 3 months and a score of 1-3 on KL scale	Isokinetic knee extensor dynamometer strength training (3 sets of 3 reps each at 90, 120 and 150°/s) 3 times a week vs. 4 classes on OA education and self- management (OA disease education, self- management, diet, psychologist for coping) over 8 weeks; 12 weeks follow-up.	Isometric extension torque (Nm/kg) change at 8 weeks from baseline for exercise 6.06 vs. education 6.30. Extension torque at 90°/sec (Nm/kg) change at 8 weeks from baseline for exercise 4.22 vs. education 3.51. Extension torque at 120°/sec (Nm/kg) change at 8 weeks from baseline for exercise 3.25 vs. education 1.97, NS. WOMAC section A (mm) change at 8 weeks from baseline for exercise -43.54, and change from Week 8 to Week 12 for education -18.07; 50' moderate walk pain change at 8 weeks from baseline for exercise -0.63. Stair pain change at Week 8 from baseline for exercise -1.50, p <0.001. MOS pain change at 8 weeks from baseline for education 5.87. "ADL" change at 8 weeks from baseline for exercise -0.53 vs. for education -0.38. WOMAC section C (mm) change at 8 weeks from baseline for exercise -88.3 vs. education -106.9. AIMS mobility change at 8 week from baseline for exercise - 0.59 and change from Week 8 to week 12 for education 0.32. AIMS walk and bend change at Week 8 from baseline for education -1.14.	"Isokinetic exercise is an effective and well tolerated treatment for knee osteoarthritis, but a much less costly education program also showed some benefits."	Percent improved in pain 65% exercise vs. 36% education (p = 0.007). Stair pain also favored exercise (p = 0.02). Most data suggest exercise more effective than educational control.
Veenhof 2006 RCT	4.0	N = 200 hip or knee OA	Behavioral graded activity program vs. usual care for 12	VAS pain (baseline/change at 13 weeks/65 weeks): BGA 4.3±2.8/-0.61/-	"Because both interventions resulted in beneficial long-term	Cluster randomization by physical therapist.

			weeks and a maximum 18 sessions, then up to 5 booster sessions.	1.01 vs. UC 3.7±2.5/-0.47/-0.58. WOMAC pain scores and WOMAC physical function subscales not different between groups. Patient global assessments % improved (13 weeks/65 weeks): BGA 41/56 vs. UC 36/49 (NS).	effects, the superiority of (behavioral graded activity program) over (usual care) has not been demonstrated. Therefore, BGA seems to be an acceptable method to treat patients with hip and/or knee OA, with equivalent results compared with UC.”	Baseline data somewhat worse disease in usual care group. Many protocol deviations. Data suggest behavioral graded exercise program ineffective compared with usual care.
Exercise vs. non-Exercise Control for Osteoarthritis						
Ettinger 1997 RCT	8.0	N = 439 knee OA, x-rays of knee OA, pain most days/month, self reported difficulty with ADLs	Aerobic exercise program (3-month facility-based, 15 month home walking, 1 hour with 40 minutes walking a session, 3 sessions a week) vs. resistance exercise program (2 sets of 12 reps, 1 hour class with 40-minute resistance exercise, 3 days a week for 18 months) vs. health education program (monthly 1.5 hour education session for 3 months, included exercise topics).	Six-minute walk test: aerobic 1507 vs. resistance 1406 vs. education 1349 feet, p <0.02 vs. with education. Stair climb: 12.7 vs. 13.2 vs. 13.9s. Disease activity intensity score 2.14 vs. 2.21 vs. 2.40 (p = 0.001, p = 0.02). Peak VO2 18.3 vs. 17.9 vs. 17.5mL/kg/minute. Knee extension strength 89.0 vs. 90.2 vs. 87.0 Nm at 30°. Overall self-reported disability scores: 1.72 vs. 1.74 vs. 1.90. Pain intensity scores 2.14 vs. 2.21 vs. 2.46. Self-reported disability by compliance with aerobic exercise (0-39%/40-79%/80-100%): 2.08/1.88/1.70 vs. resistance: 1.96/1.95/1.87.	“Older disabled persons with osteoarthritis of the knee had modest improvements in measures of disability, physical performance, and pain from participating in either an aerobic or a resistance exercise program. These data suggest that exercise should be prescribed as part of the treatment for knee osteoarthritis.”	Exercise superior to education. Data also suggest weight bearing/walking may be modestly preferable to resistance training for knee OA. Compliance was approximately 69% and results were better with more compliance, especially with aerobic training.
Rejeski 1997 RCT	8.0	N = 439 as above	Health education control vs. aerobic exercise vs. resistance exercise (see above).	Knee pain in resistance training group not different from controls. Prior behavior best predictor of adherence.	“[I]t was possible to explain more variance for time spent exercising ([almost equal to] 40%) during the first 3 months than for attendance ([almost equal to] 10%). Furthermore, once participants completed the first 3 months of their training, prior behavior was the strongest predictor of exercise compliance.”	Report from FAST trial. Suggests prior behavior important predictor.

Rejeski 1998 RCT	8.0	N = 439 as above	Health education control vs. aerobic exercise vs. resistance exercise (see above).	Stair climbing self-efficacy at 18-months higher for both training groups vs., mean (SD) for aerobic group 66.06±3.11, resistance group 67.38±3.26, controls 58.06±2.99, p <0.05. Aerobic and resistance groups had better health perceptions vs. controls, p <0.001.	"The findings suggest that control beliefs and changes in physical symptoms such as knee pain are important outcomes in physical activity programs with patients who have OA of the knee. Moreover, these variables mediate the effects that such programs have on disability and health perception."	Report from FAST. Data suggest beliefs and knee pain are important predictors of outcomes.
Mangani 2006 RCT	8.0	N = 439 in FAST trial	Health Education program (HE) vs. aerobic exercise program (AE) vs. weight training program (WT). Described in Ettinger 97 (FAST trial).	Knee score changes occurred with and without comorbidity for AE, WT, and HE.	"AE and WT interventions improve physical function in individual with comorbidity. AE improves physical function and knee pain independently of the presences of comorbidity."	FAST trial report. Improvements shown with comorbidities.
Van Baar 1998 RCT	7.5	N = 201 hip or knee OA	Individual exercise therapy with PT (strength, ROM, ADLs) 1 to 3 times a week vs. no exercise for 12 weeks treatment and 24 weeks follow-up. Both groups treated with education and medication.	Most patients reported adherence. Baseline paracetamol use higher in exercise group (52% vs. 38%). Pain in past week reduced after treatment: exercise - 22.8 vs. controls -5.7 (p <0.01). NSAID medication use 42% vs. 36%, p = 0.38. Paracetamol use 35% vs. 51%, p = 0.02. Observed disability - 0.21 vs. -0.02, p = 0.04. No significant effectiveness differences between hip and knee.	"[E]xercise therapy reduces pain and disability in patients with OA of the hip or knee. The size of the effects is medium to small, respectively."	PT exercise groups not structured, precluding assessment of value of specific treatments. PT program as described had modest effect over home exercise education when used with regular care. Pain and disability assessments improved, but no difference in NSAIDs consumed.
Jan 2008 RCT	7.0	N = 102 bilateral knee OA (ACR), Grade ≤3 KL and knee pain >6 months	High-resistance exercise (HR, 60% of MVC, approx 45-50kg, 3 sets of 8 reps) vs. low-resistance exercise (LR, 10% of MVC, 10 sets of 15 reps) vs. no exercise for bilateral knee pain. All given health education. All had 3 sessions a week	WOMAC pain subscale pre/post significant training (pre 8.5±3.8/post 4.8±3.5, p <0.05) and LR training (pre 7.8±3.3/post 4.8±2.7, p <0.05) and vs. controls (pre 8.3±4.6/7.1±3.4, p <0.008). WOMAC physical function subscale significant within group for HR training (pre 26.4±9.0/post 14.7±8.5, p <0.05) and LR	"Both high-resistance and low-resistance strength training reduced pain and improved function in patients with knee OA. Although high resistance strength training demonstrated effect sizes that consistently were slightly greater than those achieved with low-resistance strength training, the	HR group required 30 vs. 50 minutes for LR. Data suggest exercise superior to control.

			for 8 weeks. 8 weeks follow-up.	training (pre 26.1±8.1/ post 14.8±9.2, p <0.05) and vs. controls (pre 25.4±11.3/ post 22.5±10.9, p<0.008). Walking time for level ground, stairs, figure-8 pattern, and spongy surface superior for HR (p <0.05) and LR (p <0.05); figure-8 pattern and spongy surface significant vs. control for both groups (p <0.008). Extensor for 60°/s, 120°/s, 180°/s and flexion at same degrees significant within groups for HR and LR training and vs. controls.	differences in improvement between the HR and LR groups were not significant.”	
Baker 2001 RCT	6.5	N = 46 knee OA, age>55 years, BMI≤40, pain >50% of days in past month following physical activities, and x-ray knee OA evidence	Home-based progressive strength training: squats, step-ups, use body weight for resistance, isotonic ankle weights for knee extension/flexion, hip extension/abduction/adduction, 2 sets of 12 reps, 3 times a week vs. nutritional education control group (increase fruits and vegetables, food logs, 7 home visits over 4 months); 4 month program.	WOMAC pain scale decreased 36% for exercise vs. 11% for controls, p = 0.013. Clinical knee exam improvement for exercise (37%, 95% CI 27-62%) vs. control (17%, 95% CI -7.2-40%), p = 0.049. Time to ascend stairs decreased for exercise vs. control, p = 0.03-0.04. Four of 8 SF-36 scales improved significantly for exercise vs. controls, p = 0.0001-0.01.	“[A] home-based progressive strength training program substantially improves muscle strength, physical function, and pain in individuals with knee OA. The improvements in some of the quality of life and self-efficacy scales are of interest and should be explored in future larger studies. The larger effect on physical function we observed compared to other strength training studies is probably due to the greater improvements in dynamic muscle strength in the study.”	Study claims blinding to intervention (presumably attempted sham deception); however this seems at best incomplete. Higher noncompliance in nutritional educational controls (35% vs. 16%). Data suggest strength training superior.
Lin 2009 RCT	6.5	N = 108 OA, KL Grade≤3, knee pain >6 months and over age 50	Proprioception training (PrT, computer game foot-stepping exercise, 20min each lower extremity) vs. strength training (ST, baseline resistance at 50% MVC, 4 sets and 6 reps/set, with progressive increments of	“Both PrT and ST significantly improved WOMAC-pain and -function score after intervention (P<.008). The improvement secondary to ST in the WOMAC-function scores (17.2 points) and for knee extension strength (10.3-14.9 Nm) was greater than the minimally clinically important difference	“[N]on-weight-bearing PrT and ST exercises interventions were effective in improving pain, function, walking speed on different terrains, and knee strength in patients with knee OA. PrT was found to be superior to enhance neuromuscular function, most	Data suggest functional outcomes including WOMAC function and stair climbing superior with strength training. Pain better in both exercise groups.

			5% of original MVC Q2 weeks without creating pain) vs. non-interventional control group; 3 sessions a week for 8 weeks; 8 weeks total follow-up.	for these measurements. The PrT group demonstrated greater improvement in walking time on a spongy surface and knee reposition error than the other 2 groups. No improvements were apparent in the control group.”	notably joint reposition sense and walking speed on a spongy surface. ST was demonstrated to be more effective to improve knee extension strength and functional performance, including going up and down stairs. Furthermore, the postintervention improvement in WOMAC-function score and in the strength of knee extension in the ST group is clinically meaningful.”	
Fransen 2001 RCT	6.5	N = 126 knee pain on most days, x-ray evidence of knee OA	Individualized exercise (choice, frequency, etc., at PT's discretion; not described) vs. group format exercise (stretches, stationary bicycle, non-weight bearing quadriceps mm strengthening, weight-bearing quad strengthening, quad/knee flexor concentric and eccentric exercises, weight bearing eccentric quads) for 1 hour, 2 times a week plus HEP vs. wait-listed controls for 8 weeks (WL controls then randomized to other 2 arms); 16 week follow-up.	Significant decrease in WOMAC pain mean change for combined exercise treatments (10.6, 95% CI 6.3-15.0) vs. controls (-1.5, 95% CI -5.5-2.4), p<0.01. WOMAC function mean change decreased with combined exercise treatments (7.7, 95% CI 4.2-11.2) vs. WL controls (-0.1, 95% CI -3.9-3.7), p <0.01. SF-36 PCS not different between treatment and control. Comparing individualized and group treatments, no clear differences.	“[S]tudy confirms the effectiveness of physical therapy for patients with knee OA seeking treatment in terms of self-reported pain, physical function, and HRQOL. Improvements revealed by self-report questionnaires were significantly associated with improvements in objective measures of physical performance, and treatment effectiveness was still apparent 2 months after formal treatment stopped.”	Individualized exercise arm not well described and precludes assessments of value of specific exercises or regimens. Wait-listed controls biases in favor of active treatment. Article does not provide baseline to 8 weeks differences among 3 groups. Data suggest both exercise groups superior to wait-listed controls.
Thomas 2002 RCT	6.5	N = 786 age ≥45 with self reported knee pain most days/month and over 1-year duration	Exercise (progressive resistance elastic bands, knee joint muscle strength, 4 home visits, 30 minutes over 2 months, 6 month follow-up) plus 2 minute phone calls to monitor symptoms and	Knee pain at 6, 12, 18, and 24 months lower with exercise vs. non-exercise, p = 0.003, 0.005, 0.003 and 0.001; telephone vs. non-telephone not significant at 24 months, p = 0.50. Physical function and stiffness at 24 months	“This study suggests that exercise therapy can provide significant health benefits for people with knee pain, but that the cost of delivering the exercise program is unlikely to be offset by any reduction in	Large sample size. Data suggest exercise program effective for pain and function compared to non-interventional or placebo controls. Data suggest exercise

			give advice vs. exercise, phone, placebo vs. exercise vs. phone vs. placebo vs. no intervention for knee OA.	significant, $p = 0.001$, 0.01.	medical resource use.”	effective despite overall relatively low compliance.
Thomas 2005 RCT 2nd report (Thomas 2002)	6.5	N = 600 with knee pain	Exercise plus telephone vs. exercise, telephone and placebo vs. exercise vs. phone vs. placebo vs. no intervention for knee osteoarthritis (see Thomas 2002 above); 2 years follow-up.	Exercise intervention cost statistically significant between exercise intervention (mean £145±32) and no-exercise control (mean £32±29), $p = 0.001$. “Bootstrapping cost data using 2000 resample estimates of the sample mean normalized the data and suggested that the exercise groups had significantly higher costs (mean change compared with nonexercise £225; 95% CI £232; $p < 0.001$).”	“Simple home based exercise programmes can produce significant reductions in knee pain over two years. Such programs are ideally suited for primary care.”	Total cost £112/ exercise therapy program participant and £61 for home contact. Exercise group incurred somewhat higher medical costs (£225 mean difference, 9% % CI £218-232, $p < 0.001$) that were widespread but more driven by higher NSAIDs, GP visits, surgical-related costs.
Hay 2006 RCT	6.5	N = 325 age ≥55 years with pain, stiffness, or both in one or both knees	Enhanced pharmacy review for 3 to 6 sessions of 20 minutes over 10 weeks vs. community physiotherapy for 3 to 6 sessions of 20 minutes over 10 week vs. standard advice and information by one phone call for osteoarthritis of knee.	At 3 months adjusted WOMAC mean (CI) pain score for pharmacy group 1.18 (0.3-2.0, $p = 0.006$), for physiotherapy 1.19 (0.3-2.1, $p = 0.008$) vs. control. WOMAC mean (CI) functional score for physiotherapy vs. control 3.65 (1.0-6.3, $p = 0.008$). Global assessment trends at 3 months improved for pharmacy ($p = 0.0002$) and physiotherapy ($p < 0.0001$) groups. Mean difference in knee pain and function: change in pain severity at 3 months for pharmacy -0.72 (-1.4 to -0.1, $p = 0.04$), physiotherapy -0.84 (-1.5 to -0.2, $p = 0.01$); change in severity of main problem for physiotherapy at 3 months -1.06 (-1.8 to -0.3, $p = 0.005$), at 6 months -1.22 (-2.0 to -0.4, $p = 0.002$).	“Evidence based care for older adults with knee pain, delivered by primary care physiotherapists and pharmacists, resulted in short term improvements in health outcomes, reduced use of non-steroidal anti-inflammatory drugs, and high patient satisfaction. Physiotherapy seemed to produce a shift in consultation behaviour away from the traditional general practitioner led model of care.”	Contact time much less in control group and controls appear essentially as “more of the same” thus study biased against controls. Data suggest no meaningful differences between active controls.
Nguyen 1997	6.5	N = 180 with lumbar	Spa therapy vs. “usual therapy” for 3 weeks. Spa	NSAID tablets consumed over 24-week follow-up	“This study suggests that spa therapy of 3 weeks	Treatments likely heterogeneous with multiple co-

RCT		spine, knee, and hip OA	included "journey, rest, balneotherapy, spring water and medical attention."	period: spa 144±192 vs. 216±240, p = 0.01. Graphic data suggest reduction in benefits over time. VAS pain scores (9 baseline/4 weeks/24 weeks): spa (50±20/-15±29/-9±28) vs. controls (47±22/1±22/3±24), p <0.0001.	duration has a prolonged, beneficial, symptomatic effect in osteoarthritis."	interventions, precluding conclusions. No long-term follow-up beyond 6 months; results not significantly different by months 4-6 by tablet count.
Petrella 2000 RCT	6.0	N = 179 with knee OA, age >65, Grade I-III tibial-femoral compartment OA, difficulties with ADLs	Progressive exercise (progressive ROM and resistance exercises) vs. Controls (non-weight bearing joint unloading and stretches) for 8 weeks.	Self-paced step test changed from baseline 11±5 vs. controls 4±3, p = 0.009. WOMAC pain scale: changed 18±9 vs. 11±7, p = 0.003. VAS pain also significant between groups, p = 0.02.	"Addition of a progressive exercise program to nonsteroidal anti-inflammatory therapy in patients with knee OA can improve measures of activity and activity related pain more than medication alone."	Randomization not well described. Compliance unclear. Timing of outcomes unclear. Claims of double blinding seem not plausible. Data are sparse, with data providing suggesting exercise effective.
Ravaud 2004 RCT	6.0	N = 867 physicians and 2,957 patients (2,216 with knee OA and 741 with hip OA)	Standardized tools (adjusted medications) vs. booklet with exercises and videotape (ROM and strength) for HEP 4 times a week for 6 months vs. standardized tools and exercise vs. usual medical care by rheumatologists. All patients given rofecoxib 12.5mg QD 1st month and 25mg QD after if needed.	VAS pain ST vs. exercise vs. ST+EX vs. usual care. WOMAC function and global assessments not different as improved in all 4 arms. Diaries completed by <50%. Patients in EX and ST+EX groups more likely to agree that rheumatologists provided advice about muscular strengthening and that "the rheumatologist has done his best to preserve their muscular function and their physical activities."	"Although patients' assessments favoured the exercise programme, results from this study failed to demonstrate a short term symptomatic effect of the two non-pharmacological treatments (weekly recording of condition and exercise) in patients with OA concurrently receiving nonsteroidal anti-inflammatory drugs."	Cluster randomized controlled study with randomization at physician level may result in relative lack of homogeneity of interventions. Study data do not clearly support exercise program, but implementation of rofecoxib as a co-intervention may have confounded results.
Thorstensson 2005 RCT	5.5	N = 61 knee OA, KL Grade III or more, 36-65 years old	Exercise (1 hour supervised exercise session, weight bearing, 60% HR maximum, 2 times a week for 6 weeks) vs. control; 26 weeks follow-up.	KOOS subscale for quality of life at 6 months favored exercise (5.1 vs. control -2.3, p = 0.02). SF-36 Mental Component Summary Score improved for exercise (2.1) vs. controls (-1.6), p = 0.04. Pain score trended in favor of exercise group.	"A six-week high intensive exercise program had no effect on pain or function in middle-aged patients with moderate to severe radiographic knee OA. Some effect was seen on quality of life in the exercise group compared to the control group."	Data suggest underpowered for effects as most effects trended in favor of exercise group.
Tak 2005	5.5	N = 109 hip OA	Hop with the Hip exercise	VAS pain (baseline/post/ follow-	"The exercise program had	Non-interventional

RCT			program (strengthening, treadmill, weight control, assistive devices) weekly 1-hour appointments for 8 weeks vs. no intervention.	up): exercise (3.8±2.1/3.6±2.5/3.5±2.1) vs. control (4.2±2.2/ 4.1±2.1/ 5.1±2.3) (p = 0.38 and p = 0.02 at follow-up). Harris Hip Score: exercise (71.1±12.9/77.0±11.6/75.4±14.6) vs. control (71.0±13.3/71.2±13.2/71.1±15.1) (p = 0.031, p = 0.081). Lower level of restrictions in exercise group NS. Physical subscale of SIP improved in exercise group at follow-up.	positive effects on pain and hip function, which are important mediators of disability. This study fulfilled a need for older adults with hip OA and provides evidence of the benefit of exercise in the management of hip OA.”	control group may bias in favor of intervention. Dropouts had worse disease measures. Data suggest exercise benefits hip OA patients.
Rogind 1998 RCT	5.5	N = 25 with knee OA; mean age 71.2; 90% female	Physiotherapy twice a week for 3 months vs. no training for knee osteoarthritis.	Baseline to 3 months, isokinetic quadriceps strength (30°/sec) improved 20% in least affected leg; isometric strength improved 21%. By 1 year, AFI had decreased 3.8 points, pain had decreased 2.0 points, and walking speed increased 13%.	“The patients had a high compliance to the program. During training muscle strength increased, but this effect was not sustained at the end of the observation period. However, the [intervention group] was characterized by a lasting increase in functional level and decrease in pain at night. The training program may be accompanied by adverse effects such as knee effusions.”	Small sample. Multiple co-interventions. Study suggests physical training is superior for severe OA.
Péloquin 1999 RCT	4.5	N = 137 aged ≥50 with mild to moderate knee(s) OA, no contradiction to exercise, no intra-articular steroid or viscoelastic injections in past 2 months	Experimental group 3 times 1 hour of supervised exercises sessions, per week for 3 months (aerobic exercises progressing to 16 minute duration and 60% HR max target, muscle strengthening, and stretching) vs. control group instructed to continue usual activities plus 1 hour education sessions 2 times a month. At least	After 3 months, significantly greater improvements in experimental group than control: arthritis pain (p = 0.02), ability to walk and bend (p = 0.03), aerobic capacity (p < 0.0001), hamstring and low back flexibility (p = 0.003), quadriceps and hamstring strength (p < 0.01). No significant differences between groups in isokinetic strength of quadriceps, joint tenderness (p = 0.18), and health perception (p = 0.7).	“[T]his program is effective for older persons with osteoarthritis of the knee and that it could contribute to maintaining their independence and improving their quality of life.”	Pre/post design with unclear follow-up timing. Co-interventions do not appear well controlled. Data suggest exercise program superior to education sessions.

			3 months follow-up.			
Roos 2005 RCT	4.5	N = 45 partial meniscectomy 3-5 years previously, between ages of 35-50	Supervised exercise (3 sessions per week for 4 months) vs. no intervention on GAG content of the knee cartilage.	Mean changes in BMI exercise group: -0.3±0.8 vs. control group: 0.2±0.6; p = 0.2. dGEMRIC results: 15±54 vs. -15±32; p = 0.036. One leg jump change: 17±10 vs. 7±8; p = 0.009.	“This in vivo cartilage monitoring study in patients at risk of knee OA who begin exercising indicates that adult human articular cartilage has a potential to adapt to loading change. Moderate exercise may be a good treatment not only to improve joint symptoms and function, but also to improve the knee cartilage GAC content in patients at high risk of developing OA.”	Data suggest adult cartilage responds to beginning exercise by increasing glycosaminoglycan content.
Halbert 2001 RCT	4.5	N = 69 with hip or knee OA symptoms	Individualized physical activity advice (at 0, 3, 6 months; emphasis on aerobic 3 sessions a week for ≥20minutes) vs. nutritional pamphlet.	More intervention moved up category or 2 to intend to exercise (p = 0.013). Somewhat more exercise in intervention group. OA symptoms unchanged and not different between groups. Well-being did not change between groups.	“An offer of primary care-based physical activity advice, with an emphasis on the benefits for general health (rather than “treatment” for OA), will attract individuals with OA symptoms. Although the present study was unable to demonstrate intervention-control group differences for the majority of outcomes, intention to exercise did appear to be positively influenced.”	Differences in exercising between groups minimal, suggesting advice had minimal influence.
Topp 2002 RCT	4.0	N = 102 with knee OA, ≥5 WOMAC pain subscale	Dynamic group with Thera-Band: exercises across a functional ROM vs. isometric: exercises at discrete joint angles vs. no intervention (control). Strength exercises for legs (knee flex/extend, hip flex/extend, plantar/dorsiflexion; 3 sets of 12 reps), 3 times a week for 16 weeks; 16 weeks total follow-up.	Mean self-reported measures of pain (WOMAC) comparing control vs. dynamic vs. isometric at pretest/ posttest: 10.75/ 10.77 vs. 12.40/10.71 vs. 11.75/ 10.38; p <0.05 pre/post, but NS between groups.	“Dynamic or isometric resistance training improves functional ability and reduces knee joint pain of patients with knee OA.”	Compliance unclear. Many details sparse. Data suggest equal efficacy of dynamic and isometric exercise.
Hopman-Rock 2000	4.0	N = 105 with hip or knee OA	Two hour weekly exercise sessions (“Living	IRGL pain scale (baseline/post/follow-up): exercise	“[T]his self-management program was	Non-interventional control group may

RCT			with osteoarthritis of the hip or knee”) (1.25 hour education, 45-minute exercises with HEP at least 3 times a week for 6 weeks vs. non-interventional controls.	(14.0±4.0/13.6±3.6/14.2±4.0) vs. controls (13.7±3.5/14.9±3.8/14.3±4.0), p = 0.045. Pain intolerance also favored exercise (p = 0.011) as did quality of life (p = 0.039).	reasonably effective in terms of the educational and exercise components. However, future interventions should pay more attention to proactive follow up interventions such as telephone follow up.”	bias in favor of intervention. Exercises appear unstructured and not well described. Stratification by hip or knee OA not performed. Most results negative; those positive were mild. Data support exercises, but results did not persist at follow-up.
Exercise vs. Other Exercises for Osteoarthritis						
Ettinger 1997 Rejeski 1997 Rejeski 1998 Mangani 2006	8.0	See Exercise vs. Exercise Controls for Osteoarthritis table above.				
Hoeksma 2004 RCT	8.0	N = 109 with hip OA	Manual therapy (stretching, manipulation and mobilization of hip joint) vs. exercise program (tailored to patients needs). Both 2 times a week for 9 treatments.	Percent improved after 5 weeks 81% manual therapy vs. 50% exercise, p <0.05. SF-36 (baseline/week 29): manual therapy (41.1± 18/51.4±22) vs. exercise (37.9±18/49.9±24), NS. Harris hip scores manual (54.0±15/70.2±20) vs. exercise (53.1±14/59.7± 18), p <0.05. Pain scores at rest, NS. Pain scores: walking favored manual therapy (p <0.05).	“The effect of the manual therapy program on hip function is superior to the exercise therapy program in patients with OA of the hip.”	Exercise program unstructured. Manual therapy group also included advice to exercise, potentially confounding results and impairing an ability to draw a firm conclusion.
Lim 2008 RCT	6.5	N = 107 with tibiofemoral joint OA (ACR)	More varus malalignment (>5° varus) separated from more neutral alignment, then both groups randomized to quadriceps strengthening program (5 quadriceps strengthening exercises, 5 days a week using ankle weights and black Thera-	Adjusted mean±SD change for quadriceps strength (N/kg) more malaligned/more neutrally aligned strength training group vs. control: 0.28±0.05/0.36± 0.05 vs. 0.04±0.06/0.01± 0.05, main effect of strengthening p <0.001, main effect of alignment p = 0.673; unadjusted: 0.29±0.05/0.36±0.05 vs. -0.01±0.05/0.05±0.05, main effect of	“[Q]uadriceps strengthening did not have any significant effect on knee adduction moment in participants with either more malaligned or more neutrally aligned knee OA. However, the benefits of quadriceps strengthening on pain were more evident in those with more neutral alignment.”	Some baseline differences. Trial assessed malalignment. Results suggest strengthening program more effective for neutrally aligned knees.

			Band) vs. control, 5 days a week for 12 weeks using ankle weights and a black Thera-Band at home and a total of 7 meetings with a physiotherapist; 13 weeks follow-up.	strengthening p <0.001, main effect of alignment p = 0.204. Adjusted WOMAC pain score mean±SD change: -6.3± 2.4/-4.5±2.5 vs. -11.7 ±2.3/1.0±2.4, main effect of strengthening p = 0.002, main effect of alignment p = 0.981; unadjusted: -4.6±2.5/-13.0±2.3 vs. -3.1±2.68/-0.7± 2.5, main effect of strengthening p = 0.007, main effect of alignment p = 0.231. Unadjusted WOMAC function score mean±SD: -2.1±2.1/-9.2± 2.1 vs. -2.0±2.1/-3.7±2.0, main effect of alignment p = 0.036, main effect of strengthening p = 0.179; adjusted: -3.7±2.1/-8.4± 2.0 vs. -3.3±2.1/-1.9±2.1, main effect of alignment p = 0.476, main effect of strengthening p = 0.086. Step test and stair climb test not statistically significant for main effect of alignment and strengthening.		
McCarthy 2004 RCT	6.0	N = 214 with knee OA (ACR) with osteophytes	Small 8 week class exercise program (progressive resistance training, accelerated walking, stretching, balance, 45 minute session, 2 times a week) plus HEP (2 strengthening, balance exercises, endurance exercise for fatigue) 2 times a week vs. home exercise program alone; 12 months follow-up.	ALF scores for class exercise were 14, 11, 15% greater at post-treatment, 6-month, and 12-month vs. HEP alone. VAS score reductions were 33, 21, and 25% greater in class than HEP.	“The supplementation of a home-based exercise programme with a class-based exercise programme led to superior improvement in walking pain and to a lesser extend in the locomotor function of the supplemented group. Importantly, the improvement was still evident 12 months following the cessation of the exercise classes.”	Progressive strengthening and walking exercises plus HEP superior to HEP and data suggest persistence of benefits to 1 year.

Jan 2009 RCT	6.0	N = 106 with bilateral knee OA (ACR), grade ≤3 KL, 6+ months duration	Weight-bearing exercises (WB, Resisted knee extension/leg press while seated, EN-Dynamic, 90°/2s) vs. non-weight bearing exercises (NWB, knee extension, EN-Dynamic, 90°/2s) vs. no exercise. Both groups 3 sessions a week, begun with stationary cycle 10min mild resistance, then 4 sets of 6 reps a session); 8 weeks follow-up.	WOMAC function (pre/ post): WB (22.6±10.1/ 12.3±9.8) vs. NWB (27.3±9.5/10.1±10.3) vs. no exercise (24.8±10.7/ 25.0±11.8). WOMAC walking times on 4 different terrains improved both intervention groups. Improvements in walking speed on figure 8 and spongy surface for WB vs. NWB and control. Peak torque values for knee extensors and flexors greater post intervention for WB and NWB at 3 velocities of muscle contraction. WB and NWB had greater increase in knee extensor and flexor torque vs. control.	"[E]ven simple knee flexion and extension exercises performed over 8 weeks significantly improve knee strength and functional capacity in participants with knee OA. There were no significant differences in functional improvements after WB exercise and NWB exercise. Based on the results of our study, we suggest that participants with mild and moderate knee OA perform either WB exercise or proprioceptive training in addition to NWB exercise to improve gait."	Probable imprecision as all data reported out as p <0.008. Data suggest comparable efficacy with a few data suggesting weight bearing may be superior.
Weng 2009 RCT	6.0	N = 123 with bilateral, moderate knee OA Altman Grade II	Isokinetic muscular strength exercise (Group 1) vs. bilateral knee static stretching therapy before isokinetic exercise (Group 2) vs. proprioceptive neuromuscular facilitation stretching therapy before isokinetic exercise (Group 3) vs. no treatment except 10-min warm-up cycling that was given to all groups; 1 year follow-up.	ROM mean±SD baseline/ after treatment/1 year follow-up for Group 2: 97±12/107±16/110±14 ; Group 3: 98±16/115±17/ 126±17. VAS mean±SD for Group 1: 4.7±1.6/ 3.6±0.7/3.6±1.6; Group 2: 4.7±1.2/3.1±0.8/ 2.9±1.4; Group 3: 4.9±1.4/2.7±1.9/2.0±1.4; Group 4 baseline/1 year follow-up: 4.5±1.5/ 5.0±1.4. Lesquesne's index mean±SD for Group 1: 7.3±2.5/5.6±0.9/6.3±1.7; Group 2: 7.1±1.5/5.0±1.0/4.0±1.3; Group 3: 7.2±1.5/4.2±0.5/2.9±1.7. Mean peak torque at knee flexion and extension during concentric and eccentric contractions at 60° and 180° statistically significant for all treatment groups within comparison and between-group comparison for all measures.	"[S]tretching therapy is recommended as an adjuvant treatment to isokinetic exercise for patients with knee OA. PNF stretching is more effective than static stretching exercise."	Data suggest group III superior (proprioceptive neuromuscular facilitation stretching and isokinetic exercises). Controls and isokinetic strengthening had poorer outcomes.

Deyle 2005 RCT	5.5	N = 134 with knee OA	Clinic treatment group (stretching, strengthening exercise, stationary bicycle, individualized manual therapy with passive stretching and mobilization) vs. home-based PT program (same exercises as clinic group); 52 weeks follow-up.	WOMAC (baseline/Week 4/Week 8): clinic (1038.2/503.5/513.4) vs. home (1035.8/766.2/730.2). Six-minute walk: clinic (431.0/473.1/483.6) vs. home (408.1/444.3/441.4).	"[A] home exercise program for patients with OA of the knee provides important benefit. Adding a small number of additional clinical visits for the applications of manual therapy and supervised exercise adds greater symptomatic relief."	Different contact time between groups may have biased. Multiple co-interventions present and not well controlled. Physical therapy was individualized, thus precluding assessment of specific exercises.
Jessep 2009 RCT	5.5	N = 64 over age 50 with mild, moderate, or severe non-specific knee pain lasting more than 6 months, diagnosed with knee OA	Outpatient physiotherapy vs. ESCAPE-knee pain for maximum of 10 sessions.	Exercise beliefs and self-efficacy score, mean (SD): outpatient physiotherapy 68.2 (60) post intervention, 66.2 (6.9) 12 month follow-up compared to ESCAPE-knee pain 71.5(8.4) and 70.8 (8.2), p = 0.035.	"The hypothesis that ESCAPE-knee pain would sustain greater benefits than outpatient physiotherapy was not supported as both interventions produced similar sustained improvements in physical function and other clinical outcomes. Lower intervention costs and reduced healthcare utilisation did support the hypothesis that ESCAPE-knee pain would be less costly and more cost-effective than outpatient physiotherapy."	High dropouts. Multiple co-interventions. Data suggest comparable results at 1 year.
Chaipinyo 2009 RCT	5.0	N = 48 with knee OA (1986 ACR), age 50+years	Balance training group (stepping forward and backward and sideways for each leg, bilateral mini squat pain free) vs. strength training group (isometric knee extension for each leg, isometric contractions holding for 5 seconds). Both groups 30 reps per leg a day, 5 days a week for 4 weeks; 4 weeks follow-up.	No significant difference between groups. With both groups considered together, statistically significant differences for all outcomes: mean (95% CI) KOOS (0 to 100) pain, other symptoms, function in daily living, function in sport/ recreation, knee-related quality of life: 9 (5-13), 9 (4-13), 9 (5-14), 11 (4-19), 13 (7-19).	"[B]alance training carried out in the home over four weeks was comparable to strength training in terms of pain, self-reported outcomes, extensor strength of the involved knee, and mobility. Thus, either program can be used as home-based exercise for patients with knee osteoarthritis where pain and activity limitations are problem."	Lower males in strength group (8% vs. 38%). Some outcome measures different at baseline (e.g., KOOS quality of life balance 64 vs. 39, only reported for completers). High dropouts in strength group. Data suggest comparable efficacy, although differences in baseline concerning for randomization failure or dropouts confounding results.

Huang 2003 RCT	5.0	N = 132 with Altman Grade II bilateral knee OA	Isokinetic muscle strengthening (60% average peak torque) vs. isotonic muscle-strengthening (5 reps concentric/ eccentric at maximum velocity lever arm could achieve) vs. isometric muscle strengthening (speed of passive forward or backwards motion at 30°/s) vs. control. Exercises 3 times a week for 8 weeks (24 sessions). All treated with 20 minutes of hot packs, passive ROM with electric stationary bike for 5 minutes. Isokinetic and isotonic given HEP after completing program; 1 year follow-up.	“Patients with OA in each treated group had significant improvement in pain reduction, disability reduction, and in walking speed after treatment and at follow-up when compared with their initial status. Isotonic exercise had the greatest effect on pain reduction after treatment, and fewer participants discontinued the treatment because of exercise knee pain. Isokinetic exercise caused the greatest increase of walking speed and decrease of disability after treatment and at follow-up. The greatest muscle-strength gain in 60 degrees/ second angular velocity peak torques was found in the isokinetic and isotonic exercise groups. A significant muscle-strength gain in 180 degrees/second angular velocity peak torques was found only in the isokinetic group after treatment.”	“Isotonic exercise is suggested for initial strengthening in patients with OA with exercise knee pain, and isokinetic exercise is suggested for improving joint stability or walking endurance at a later time.”	No baseline demographic data. Compliance measured to end of treatment not 1 year followup. Data suggest isotonic results better than isokinetic. Isometric appears least successful among exercise groups.
Mangione 1999 RCT	5.0	N = 39 with knee OA	High (70% heart rate max from graded exercise test) vs. low (40% HR max) intensity stationary cycling for 1 hour session, 3 times a week for 10 weeks.	Chair rise time (baseline/ post): HI 23.54±10.15/ 19.26±8.18 vs. LO 23.09 ±8.21/18.96±4.83 (NS). 6-minute walk test: HI 488.06±117.72/540.6 2±98.72 vs. LO 491.12± 103.74/526.94±113.7 4 (NS).	“Cycling may be considered as an alternative exercise modality for patients with knee OA. Low-intensity cycling was as effective as high-intensity cycling in improving function and gait, decreasing pain, and increasing aerobic capacity.”	Data suggest no meaningful differences between low vs. high bicycle exercise program.
Minor 1989 RCT	4.0	N = 120 with hip, knee, or tarsal OA or RA	Aerobic walking vs. aerobic pool vs. range of motion exercise classes, 1 hour sessions, 3 sessions a week for 12 weeks. Both aerobic	Aerobic capacity (baseline/12 weeks): walk (18.9±4.8/22.4±4.8 mL/kg/minutes) vs. pool (19.3±6.7/23.2±7.2) vs. ROM (17.4±5.9/17.3± 3.6)	“Our findings document the feasibility and efficacy of conditioning exercise for people who have rheumatoid arthritis or osteoarthritis.”	Data suggest efficacy of walking or pool exercise for arthrosis. Targeted 60-80% HR maximum in walking and pool groups. Improve greater OA vs.

			groups targeted 60-80% of HR maximum for 30 minutes.	(p = 0.009 comparing walk plus pool vs. ROM). AIMS pain scores (baseline/12 weeks): walk (5.1±1.9/ 3.9±1.9) vs. pool (5.0±1.6/4.4±1.7) vs. ROM (5.5±1.6/4.8±1.9) (p = 0.22). Active joints (n): aerobic OA - 2.0±5.2 vs. ROM (-1.8±5.9). Active RA joints aerobic (-6.8±11.8) vs. ROM (3.3±10.9).		RA for exercise endurance, but better for total active RA joints. Both appear to benefit. Suggests aerobic exercise reduces active RA joints.
McKnight 2010 RCT	4.0	N = 273 with knee OA (age 35-64) pain most days, KL Grade II, self-reported disability, BMI <37.5kg/m ² , <120 minutes a week walking, exercise, chores, no resistance training); duration <5 years	Two-phase strength training: 1st phase (9 months stretching, balance, ROM, flexibility, isotonic strengthening) 3 sessions a week, 1 hour each; 2nd phase (15 months self-directed long-term exercise habits) vs. 2-phase self-management intervention: 1st phase (9 months with 12 weekly 90-minute class sessions for coping and self-efficacy skills then weekly calls); Phase 2 (15 months bi-monthly calls vs. combined treatment of full, independent treatment protocols for both strength training and self-management programs; 2 year follow-up.	Linear mixed-effects models created to assess relationships between BMI, age, gender, and arthritis VAS and 7 outcomes (leg press, ROM, ERGOS, get up and go, stair climbing, pain, disability). Unstandardized parameters (standard errors) for BMI statistically significant for leg press, ROM, get up and go, stair climbing, disability (p <0.0001): 0.03 (0.01), -0.03 (0.005), -0.03 (0.005), -0.02 (0.005), 0.01 (0.004). Age statistically significant for leg press, ERGOS, get up and go (p <0.0001). Gender statistically significant for leg press, ROM, ERGOS, stair climbing, pain (p <0.0001). Arthritis VAS statistically significant all outcomes.	"Middle-aged, sedentary persons with mild early knee osteoarthritis benefited from strength training, self management, and the combination program. These results suggest that both strength training and self-management are suitable treatments for the early onset of knee osteoarthritis in middle-aged adults. Self-managements alone may offer the least burdensome treatment for early osteoarthritis."	Large sample size and longer term, 2-year trial. High dropouts (26.4%) and poor compliance (56-70%) may have resulted in no differences. Data suggest equal efficacy.
Topp 2002	4.0	See Exercise vs. non-Exercise Control for Osteoarthritis table above.				
Exercise vs. Other Treatments for Osteoarthritis						
Karatosun 2006 RCT No mention of	6.0	N = 105 with radiographic Kellgren Lawrence grade 3 OA; Mean Age	Intent to treat Group 1 (n = 52) received 3 injections of hyaluronic acid (G-F 20) vs. Group 2 (n = 53)	Treatment outcomes between groups 1 and 2 at weeks 1, 2, 3, and 6, in the pain during transfer activities was significantly significant in favor of group 2 (p	"As a result we conclude that hyaluronic acid of progressive knee exercise are effective in alleviating the	Comparison of HA to exercise for knee OA for functional improvement. At 6 months, there was no statistical

sponsorship or COI.		Group 1 = 57.8 ± 12.1 Group 2 = 55.3 ± 13.6	Physical exercise group included a series of progressive simple, range of motion and resistance exercise. Effectiveness Population Group 3 (n = 31) received 3 injections of hyaluronic acid (G-F 20) vs. Group 4 (n = 53) Physical exercise group Follow up at 1, 2, 3, 6 weeks and after 3, 6, 12, and 18 months.	= 0.042, 0.000, 0.010, 0.024, respectively). Group 1 vs Group 2 pain during activity at 6 weeks and 3 months (p = 0.039). Walking distance at 3 months (p = 0.001) Total HSS score at 3 months (p = 0.023); Group 2 significantly better at performing transfer activity and HSS score at 12 months (no p value). Group 3 total HSS scores significantly improved from baseline (57.0±12.9) to 18 months 76.7 ± 11.9, (p = 0.0002) All groups had significant improvement from baseline.	symptoms of osteoarthritis, postponing total knee replacement for 18 months, and increasing the satisfaction levels of the patients.”	difference between groups.
Kawasaki 2009 RCT No sponsorship or COI.	6.0	N = 102 females with primary OA with no other inflammatory diseases; mean age 70.4.	Group 1: Home Exercise completed isometric muscle exercises of bilateral lower limbs and range-of-motion exercises (ROM) (n = 52) vs. Group 2: Intra-articular injections of hyaluronate sodium in affected knee once a week for 5 weeks and once a month until 24 th week (n = 50). Regular check-up done every 4 weeks and comparison of both groups done at 24 weeks.	All patients who finished at least 12 weeks were included in an intent-to-treat analysis. VAS and JKOM scores were significantly significant in both groups at 24 weeks (p = 0.001, p = 0.000). In patients with early OA, the exercise group was significantly favored, (p = 0.019). Range of motion was not significantly different between groups.	“Taking into account the cost, convenience, and invasiveness to patients, exercise is thought to have some advantage over intraarticular injection of hyaluronate for the therapy of OA of the knee.”	Results for pain relief and functional improvement similar in both groups at 24 weeks.
Ravaud 2004	6.0	See Exercise vs. non-Exercise Control for Osteoarthritis table above.				
Huang 2005 RCT	6.0	N = 140 with Altman Grade II bilateral knee OA	Isokinetic muscular strengthening (stretching, strengthening, 3 times a week for 8 weeks, 60%	ROM (SD) increased in all treatment groups after treatment and in follow-up period (baseline/after treatment/at follow-up) for isokinetic	“An integrated therapy deals with the extra- and intraarticular progressive pathologic changes, and	No demographic data. Data suggest Group III (combined treatment) performed better

			mean peak torque vs. same plus periarticular US (individualized, 1MHz, 2.5W/cm ² , 25% duty cycle; 3 times a week for 8 weeks) vs. exercise plus ultrasound plus intraarticular hyaluronan (Hyalgan 20mg, mean MW 630,000 daltons, Q week for 5 weeks) vs. no treatment controls for bilateral moderate knee osteoarthritis; 1 year follow-up.	103±13/108±17/110±4, p <0.05 compared to control vs. with ultrasound 104±10/114±15/118±14, p <0.05 compared to control vs. with ultrasound and intraarticular hyaluronan 103±12/120±13/124±18 vs. control 101±13/98±10/98±17. Significant VAS score difference compared with control for isokinetic after treatment and at follow-up and for isokinetic exercise with ultrasound after treatment. Significant VAS difference for isokinetic after treatment and at follow-up and compared with control for isokinetic exercise with ultrasound after treatment, significant VAS difference between after treatment and at follow-up for isokinetic exercise with ultrasound, p <0.05. Significant VAS difference for isokinetic exercise with ultrasound and intra-articular hyaluronan for follow-up after treatment and at follow-up compared to other groups and control, p <0.05.	kinesiologic management of OA is suggested for the management of knee OA."	than other groups.
Cetin 2008 RCT	5.5	N = 100 females with knee OA (ACR)	Short wave diathermy (SWD, 27.12MHz, 15 minutes) plus hot packs (HP) plus isokinetic exercises (Group 1, n = 20) vs. TENS (20 minutes at 60-100Hz, PD 60ms) plus HP plus isokinetic exercises (Group 2, n = 20) vs. ultrasound (US, 1.5W/cm ² , 10 minute) plus HP plus isokinetic	Groups 1-4 showed greatest pain reduction vs. controls, p = 0.019. Walking time not significant between groups, p = 0.589. Lequesne index scores significant for Groups 1 and 2 vs. controls, p = 0.022 and 0.001 respectively. Groups 1-3 had higher PT values vs. controls at all angular velocities, p <0.05. Left knee torque values different.	"Using physical agents before isokinetic exercises in women with knee osteoarthritis leads to augmented exercise performance, reduced pain, and improved function. Hot pack with a transcutaneous electrical nerve stimulator or short-wave diathermy has the best outcome."	Modest sample sizes in each group. Treatment times differed between groups and data suggest better results with longer treatment times, thus potential study flaw. Most data suggest minimal differences between groups other than compared with controls.

			exercises (Group 3, n = 20) vs. HP plus isokinetic exercises (Group 4, n = 20) vs. isokinetic exercises (Group 5, control, n = 20) 3 times a week for 8 weeks.			
Doi 2008 RCT	4.5	N = 142 with knee OA (ARA), age ≥50	Exercise (knee extensions while seated, 2 sets of 20 reps BID) vs. NSAID (loxoprofen sodium 180mg TID, diclofenac sodium 75mg TID, zaltoprofen 240mg TID plus rebamipide 100mg, sodium azulenesulfonate 0.5g or teprenone 50mg). Permitted sticky plaster of flurbiprofen, indomethacin, ketoprofen and felbinac BID. Follow-up weekly or QO week; 12 weeks follow-up.	“The difference in improvement rate of each score between the two groups was not statistically significant, though the mean rank score measured with JKOM in the exercise was slightly better than that of the NSAIDs.”	“Home-based exercise using quadriceps strengthening improves knee osteoarthritis no less than NSAIDs.”	Labor intensive protocol with weekly or biweekly doctor appointments. Data may be uninterpretable due to co-interventions and confounding with uncontrolled use of topical NSAIDs in both groups.
Chamberlain 1982 RCT	4.0	N = 42 with knee OA	Three times a week for 4 weeks short-wave diathermy vs. exercise instruction for knee osteoarthritis.	Pain scores at 4 weeks: difference 1.68 between groups, p <0.05. Range of movement at 12 weeks: difference of 2.76 between groups, p<0.01. Pain score at 12 weeks: difference of 4.99, p <0.001.	“[A]ll except two patients completing the basic study showed improvement; that improvement occurred irrespective of whether treatment was given in hospital or at home; and that benefit could be retained by the simple expedient of continuing daily exercises.”	Data suggest comparable results at 1 month.
High vs. Low Exercise Levels for Osteoarthritis						
Mangione 1999	5.0	See Exercise vs. Other Exercise for Osteoarthritis table above.				
Exercise for Pre-Surgical Patients with Osteoarthritis						
Borjesson 1996 RCT	4.0	N = 68 unilateral Grade I-III medial knee OA with symptoms	Physiotherapy (bicycle ergometer, knee extension/flexion, standing on heel/toes,	Subjective patient improvement for 20/34 vs. 1/34 for treatment. No differences in pain during walking, passive range of	“Physiotherapy... made our patients feel better according to their own opinion, and the ability to	Data suggest this PT protocol largely ineffective for pre-surgical patients.

		lasting 3-10 years, wait-listed for TKA or osteotomy	hamstrings stretch, hip abduction, side-lying, hip extension, passive knee extension) 3 times a week vs. control for knee OA for 5 weeks; 3 months follow-up.	motion. Ability to descend steps improved for treatment group 13/34 vs. 4/34, p <0.05.	descend steps improved. However, our data do not support the continued use of this type of therapy in patients with osteoarthritis of the knee before surgery.”	
Educational Programs for Osteoarthritis						
Ettinger 1997 Rejeski 1997, 1998 Mangani 2006	8.0	See Exercise vs. Exercise Controls for Osteoarthritis table above.				
O’Reilly 1999 RCT	6.5	N = 191 with knee pain	General advice vs. graded exercise program (isometric quadriceps contractions, isotonic hamstring contractions, dynamic stepping exercise) for knee OA; 6 months follow-up.	WOMAC pain scores favored exercise, 22.5% for exercise vs. 6.2% for control, p <0.05. WOMAC physical function decreased by 17.4% vs. unchanged for control, p <0.05.	“A simple programme of home quadriceps exercises can significantly improve self reported knee pain and function.”	Data suggest exercise program effective. Better results in those with greater compliance as measured by VAS scores or quadriceps strength.
Dias 2003 RCT	5.5	N = 50 over 65 years old with knee OA referred for rehab	Exercise (walking 40 minutes, 3 times a week) plus exercise (stretching, concentric eccentric isotonic progressive resistance, closed kinetic chain weight bearing)] plus education (2 sessions a week, 12 total) vs. education controls for knee OA; 6 months follow-up.	Significant difference between 3 vs. 6 months comparison between subjects across Lesquesne index (p = 0.011), health assessment questionnaire (p = 0.036), SF-36 functional capacity (p = 0.040). Median scores for Lequesne index (control/exercise) at 3 months: 13/5.3, p = 0.001; 6 months: 13/4.3, p = 0.001. Median scores for Health Assessment Questionnaire (control/exercise) at 3 months: 1.1/0.4, p = 0.020; at 6 months 1.1/0.3, p = 0.006. Median score for SF-36 domains (control/exercise) for functional capacity at 3 months: 45/72.5, p = 0.011; 6 months: 40/77.5, p = 0.000.	“The exercise protocol and walking programme had a positive effect on the quality of life of elderly individuals with knee OA.”	Study protocol has heavy walking program component. Data suggest exercise of additive benefit to education program.

				Physical Role Limitations at 3 months: 25/100, p = 0.0004; 6 months: 75/92.5, p = 0.001. Bodily pain at 3 months: 64/100, p = 0.024; 6 months: 0/100, p = 0.002. General health at 3 months: 82/92, p = 0.027; 6 months: 51/100, p = 0.021. Vitality at 6 months: 87/93.5, p = 0.027.		
Ravaud 2009 RCT Cluster randomized doctors, analysis of patients' results	5.5	N = 198 rheumatologists providing care for patients age 45-75 with knee OA (ACR criteria)	Rheumatologists (n = 198) with 336 patients assigned to usual care vs. 3 goal oriented standardized consultation (education, advice for OA, treatment options, how to protect joints, need for physical activity (rapid walking or cycling per patient desire), and weight loss importance) with 3 visits over 30 days; 12 months follow-up.	Mean change±SD at 4 months for standardized consultation vs. unusual care for weight (kg): -1.11±2.49 vs. -0.37±2.39, p = 0.007. Physical exercise in leisure subscale of Baecke index (0-5): 0.20±0.65 vs. 0.04±0.78, p = 0.013. Pain (NS 0-10): -1.65±2.32 vs. -1.18±2.58, p = 0.041. Global assessment of disease status (NS 0-10): -1.66±2.26 vs. -0.90±2.48, p = 0.003. Number of patients (percentages) knowledge regarding obtaining information on need for regular exercise: 117 (92.9) vs. 95 (65.1), p <0.001. Obtaining information on need to lose weight: 116 (92.1) vs. 111 (76.0), p = 0.001. Obtained documents on knee osteoarthritis: 99 (78.6) vs. 40 (27.4), p <0.001. Obtained documents on exercise: 93 (73.8) vs. 13 (8.9), p <0.001. Obtained documents on weight loss: 80 (63.5) vs. 22 (15.1), p <0.001. Patient knowledge that exercise is always bad for knee OA statement is wrong: 89 (70.6) vs. 83/145 (57.2), p = 0.024.	“Our study shows that rheumatologists offering a programme of standardised consultations about non-drug treatment for osteoarthritis of the knee could be useful for patients with osteoarthritis of the knee. Such a programme led to weight loss, increased physical activity, and improved pain after four months and improved patients' physical activity, pain, and function at one year. This programme of standardised consultation should help rheumatologists to follow international guidelines for care of patients with osteoarthritis of the knee.”	Data suggest 3 appointments for goal-oriented education including education, treatment management, exercise and weight loss is effective over 4 months by many outcome measures, although overall impact modest. Higher dropouts at 12 months.
Murphy 2008	5.0	N = 44 hip or knee OA	Exercise (both groups with	WOMAC pain did not differ (5.1 vs. 5.2, p =	“Although participants were	Baseline walk favored Ex+Ed

RCT		(ACR) and difficulty with at least 1 of 4 ADLs	resistance training, ankle weights) plus activity strategy training vs. exercise plus health education (pain management, exercise importance, diet, medication options); eight 1.5 hour sessions, 2 times a week for 4 weeks and 2 follow-up sessions; 6 weeks follow-up.	0.47). 6-minute walk test (pre/post): Ex+Ed (332.8/346.6) vs. Ex+AST (279.9/301.0). Peak physical activity differed between groups with education (635.4±172) and activity strength training (739.3±271), p = 0.02.	involved in identical exercise programs, participants who received [activity strength training] tended to have larger increases in [physical activity] at posttest compared with participants who received health education.”	as had longer walk distance (333vs. 280m, p = 0.07). Nearly all data at 6 weeks although article mentions 6 months. Data suggest few differences between 2 interventions added to an exercise resistance program.
Halbert 2001 RCT	4.5	N = 69 hip or knee OA	Individualized physical activity advice (at 0, 3, 6 months; emphasis on aerobic 3 sessions a week for ≥20minutes) vs. nutritional pamphlet.	More intervention moved up category or 2 to intend to exercise (p = 0.013). Somewhat more exercise in intervention group. OA symptoms unchanged and not different between groups. Well-being did not change between groups.	“An offer of primary care-based physical activity advice, with an emphasis on the benefits for general health (rather than “treatment” for OA), will attract individuals with OA symptoms. Although the present study was unable to demonstrate intervention-control group differences for the majority of outcomes, intention to exercise did appear to be positively influenced.”	Differences in exercising between groups minimal, suggesting advice had minimal influence.
Diet and Exercise for Osteoarthritis						
Sevick 2009 RCT	7.0	N = 316 participants in ADAPT study	Healthy lifestyles control vs. diet vs. exercise vs. exercise and diet for older overweight and obese individuals with knee OA.	Most expensive interventions costs for exercise (\$2,307) and exercise and diet (\$4,998) compared to diet only (\$2,415) and control lifestyle (\$157). For reducing weight, diet intervention was most cost-effective approach.	“Although it was not consistently the most efficient use of resources, the Exercise and Diet intervention was usually the most cost-effective approach to improving clinically meaningful outcomes of self-reported physical function, pain, and stiffness.”	ADAPT trial report on cost effectiveness.
Sevick 2000 RCT	7.0	N = 439 participants ≥60 years old, radiographic evidence of knee OA, pain on most days	Health education control vs. aerobic exercise vs. resistance exercise for knee OA.	Total cost of education intervention \$343.98 per participant; aerobic intervention \$323.55 per participant, resistance training intervention \$325.20 per participant. “When	“[C]ompared with education control, resistance training for seniors with knee OA is more economically efficient than aerobic exercise in improving physical	ADAPT trial. Exercise plus diet most costly intervention.

		of month, and difficulties with at least one activity of daily living		comparing incremental cost per each unit of measure gained, resistance training is superior to aerobic exercise training on all outcome variables with the exception of frequency ambulatory pain, and transfer pain intensity.”	function, when self-reported disability and various measures of physical function are the outcome variables considered. However, the magnitude of differences in efficiency between the two approaches is small.”	
Messier 2004 RCT	7.0	N = 316 from ADAPT trial	Exercise vs. exercise plus dietary weight loss vs. diet-only vs. healthy lifestyle control for overweight and obese older adults with knee OA (see above).	WOMAC pain scores (baseline/6, 18 months): healthy lifestyle (7.25/6.19/6.02) vs. diet only (6.58/5.10/5.51) vs. exercise only (6.64/6.22/6.24) vs. diet plus exercise (7.27/5.47/5.07).	“The combination of modest weight loss plus moderate exercise provides better overall improvements in self-reported measures of function and pain and in performance measures of mobility in older overweight and obese adults with knee OA compared with either intervention alone.”	ADAPT trial. Data suggest efficacy of exercise plus weight loss by WOMAC, 6min walk, and stair climb.
Van Gool 2005 RCT	N/A	N = 316 participants from ADAPT RCT: BMI $\geq 28\text{kg/m}^2$, over age 60, sedentary lifestyle, and self-reported difficulties with activities of daily living, and radiographic evidence of tibiofemoral OA	Exercise vs. exercise plus dietary weight loss vs. diet-only vs. healthy lifestyle control for overweight and obese older adults with knee OA (see above).	Continuous exercise adherence during initial phase with changes in walking distance ($p = 0.002$), and disability score ($p = 0.001$) at 6 months. At 18 months, overall exercise adherence with changes in walking distance ($p < 0.001$) but not disability score ($p = 0.052$). Correlation between 6-month change in pain and exercise adherence months 1-6 ($r = -0.20$, $p < 0.05$), 6-month change in pain and 6 month change in walking distance ($r = -0.21$, $p < 0.05$), 6-month change in pain and 6 month change in disability score ($r = 0.64$, $p < 0.01$), 18-month change in pain and 18 month change in walking distance ($r = -0.27$, $p < 0.01$), 18-month change in pain and 18-month change	“[P]romoting exercise adherence appears to be clinically relevant when prescribing exercise regimens, which also focus on improvements in knee pain and BMI, to overweight older adults with knee OA.”	Largely post-hoc analyses of an ADAPT RCT reported elsewhere (Rejeski 2002, Messier 2004, Miller 2003). As post-hoc, rating for article is N/A. Data suggest better outcomes with higher adherence.

				in disability score (r = 0.68, p <0.01).		
Focht 2005 RCT	7.0	N = 316 over age 60 with BMI ≥28 kg/m ² , self reported knee pain, sedentary lifestyle, and difficulties with activities of daily living	Exercise alone vs. dietary weight loss alone vs. exercise in combination with dietary weight loss vs. healthy lifestyle control for knee OA; 18 month follow-up.	Statistical change in stair-climbing self efficacy for exercise and dietary weight loss intervention group vs. healthy lifestyle control group (p = 0.05). Statistical change in walking self-efficacy for exercise and diet weight loss and exercise alone groups vs. healthy lifestyle control (p = 0.0006). Exercise and diet weight loss group significant improvements in pain vs. healthy lifestyle control (p = 0.09,) as well as improvement in stair climb time (p = 0.0249). Significant improvements for walking distance for exercise and diet group (p <0.0001) and exercise alone (p <0.0001) vs. healthy lifestyle control.	"[C]ombined dietary weight loss and physical activity intervention had unique effects on changes in self efficacy for a weight-dependent stair-climb task as compared with exercise alone. Additionally, both baseline values and changes in self efficacy and pain were significant predictors of improvement in mobility disability above and beyond the effects of the interventions."	ADAPT trial. Data suggest diet plus exercise produced improvements in self efficacy for stair climbing.
Messier 2000 RCT	5.5	N = 24 community-dwelling obese older, ≥60 years, BMI ≥28, knee pain, x-rays with knee OA, and self-reported physical disability	Exercise alone (E; 2x10-minute walking sessions, 50-75% heart rate reserve; 20-30 minute strength training, knee flex/ext, toe raise military press, upright row, chest fly, pelvic tilt, weights plus ankle cuffs) for 1 hour, 3 times a week) vs. exercise plus dietary intervention (E&D; included weekly sessions with nutritionist with cognitive-behavior modification to change dietary habits, goal 15lb. weight loss) over 6 months; 6 months follow-up.	E&D group lost mean 18.8 lb (8.5 kg) at 6 months vs. 4.0 lb (1.8 kg) in E group (p = 0.01). At 6 months, E&D group had greater loading rate (p = 0.03) and maximum braking force (p = 0.01) during gait. Stair climb differed between groups favoring E&D (7.39 vs. 8.67s), p <0.02.	"Weight loss can be achieved and sustained over a 6-month period in a cohort of older obese persons with osteoarthritis of the knee through a dietary and exercise intervention. Both exercise and combined weight loss and exercise regimens lead to improvements in pain, disability, and performance. Moreover, the trends in the biomechanical data suggest that exercise combined with diet may have an additional benefit in improved gait compared with exercise alone. A larger study is indicated to determine if weight loss provides additional benefits to	Pilot study. Small sample size. Data suggest short to intermediate term weight loss success and improvements in some measures. IL-1 also reduced in 8 who had synovial fluid analyses.

					exercise alone in this patient population.”	
Jenkinson 2009 RCT	5.5	N = 389 with knee OA with BMI $\geq 28\text{kg/m}^2$ and age 45 or older	Diet (individualized to create 600kcal a day deficit, weight loss of 0.5-1.0kg a week) plus quadriceps strengthening exercises (flexibility, strengthening, resisted exercises, aerobics) vs. diet intervention alone vs. quadriceps strengthening exercises alone vs. advice leaflet only. Monthly home visits by dietician for diet/exercise interventions 1st 6 months. Exercise only or control groups visited Q4months for 24 months; 24 months follow-up.	Successful outcomes for reduced pain $\geq 30\%$ at 24 months: controls 30% vs. diet 35% vs. exercise only 47%, vs. diet plus exercise 43%. WOMAC pain scores at 24 months for controls 7.04 ± 4.21 vs. diet 6.96 ± 4.33 vs. exercise only 5.70 ± 3.96 vs. diet plus exercise 6.39 ± 4.15 . Reduced knee pain for exercise groups vs. non-exercise groups, $p = 0.022$. Net reduction in WOMAC mean change score for physical function for exercise groups (-3.64 ± 1.21 , $p = 0.003$) and stiffness for exercise groups (-0.35 ± 0.16 , $p = 0.030$).	“A home based, self managed programme of simple knee strengthening exercises over a two year period can significantly reduce knee pain and improve knee function in overweight and obese people with knee pain. A moderate sustained weight loss is achievable with dietary intervention and is associated with reduced depression but is without apparent influence on pain or function.”	Low compliance with exercise. High dropouts with exercise (25% and 32 % vs. 11% and 9%). Compliance may have resulted in lack of more positive results for exercise on pain and function. Data suggest better outcomes for groups that included exercise.
Barton 2009 RCT 2nd report of Jenkinson 2009	5.5	N = 389 as above	As above.	Advice leaflet cost £31. Dietary plus strengthening cost £10,469 per quality adjusted life year (QALY) and 23.1% chance of cost effectiveness at £20,000 QALY threshold.	“Dietary intervention plus strengthening exercises was estimated to be cost effective for individuals with knee pain, but with a large level of uncertainty.”	Results may have been impacted by compliance and dropout issues with exercises.
Brinkworth 2009 RCT	4.0	N = 60 sedentary overweight and obese subjects	Very low carbohydrate, high fat (LC) diet (35% protein, 61% fat, 4% carbs) vs. isocaloric conventional high carbohydrate (HC) diet (24% protein, 30% fat, 46% carbs) to assess aerobic exercise capacity, muscle strength, and metabolic adaptations to	Time to exhaustion during incremental treadmill exercise increased for both groups, $p < 0.001$. Increased relationship between increase in time to exhaustion and weight change, $r = -0.31$, $p = 0.02$. Significant diet effect on RER peak, $p = 0.005$.	“[T]he current data suggest that in untrained, overweight individuals, the consumption of an LC weight loss diet for 8 weeks, does not adversely affect physical function or exercise tolerance compared with an HC diet. This suggests that, at least over the short-term, an LC weight loss diet is unlikely to limit an individual's ability or	Many details sparse. Data suggest greater short term weight loss in very low carbohydrate/high fat diet vs. high carbohydrate/low fat diet.

			exercise; 8 weeks follow-up.		desire to participate in concomitant exercise which is unequivocally recognized as an important adjunct to diet for obesity treatment.”	
Exercise for Rheumatoid Arthritis						
Baillet 2009 RCT	7.0	N = 50 with RA, at inclusion all being treated with a DMARD	Dynamic exercise program (DEP) 5 hours a day for 4 weeks (n = 25) vs. conventional joint rehabilitation group (n = 25).	Mean±SD HAQ comparing DEP vs. control group at 1 month: 0.7±0.6 vs. 0.7±0.6; p = 0.04. At 6 months and 12 months no significant changes observed.	“DEP was effective on functional status assessed by HAQ, quality of life and aerobic fitness at 1 month.”	All on DMARDs. Some baseline differences. Data suggest short term efficacy but at 1 yr, most measured NS.
van den Ende 2000 RCT	6.5	N = 64 with active RA, ESR>28, able to walk 50 feet, admitted to hospital with loss of functional ability	Intensive exercise (conservative plus isometric and isokinetic knee flexor/extensor strength exercises, 3 series of 5 reps at 70% MVC; stationary bicycle 3 times a week for 15 minutes) vs. conservative exercise program for active RA. All treated with ROM and isometric exercises and supervised 4 times a week, group ROM session 1 time a week; 24 weeks follow-up.	No differences in swollen joints, VAS pain, and disease activity score. By Week 24, ESR favored intensive exercise group. Mean difference in VAS score between intense exercise (-0.4) and conservative exercise (-1.6) at 3 weeks statistically significant, p = 0.03.	“A short term intensive exercise programme in active RA is more effective in improving muscle strength than a conservative exercise programme and does not have deleterious effects on disease activity.”	High dropouts. Higher initial pain in exercise group. Data suggest exercise reduced medications and less disease activity with intensive program superior for RA.
Van den Berg 2006 RCT	6.5	N = 160 physically inactive patients with RA	Internet-based physical activity program with individual guidance, a bicycle ergometer, and group contacts (individualized training [IT] group; n = 82) vs. Internet-based program providing only general information on exercises and physical activity (general training group; n = 78).	Proportion of physically active at a moderate intensity level for 30 minutes in succession on at least 5 days a week: at 6 months: IT group 38% vs. GT group 22%; p = 0.041. At 9 months: 35% vs. 11%; p = 0.001).	“An Internet-based physical activity intervention with individually tailored supervision, exercise equipment, and group contacts is more effective with respect to the proportion of patients who report meeting physical activity recommendations than an Internet-based program without these additional elements in patients with RA. No differences were	No non-exercise group. Data suggest more activity in individualized group.

					found regarding the total amount of physical activity measured with an activity monitor.”	
de Jong 2003 RCT	6.5	N = 309 RA patients, ACR functional classes I-III, Stable DMARD regimen in past 3 months	RAPIT group participated in a supervised bi-weekly group exercise program (bicycle training (20 minutes, exercise circuit, sport or game), 1.25 hours each session vs. UC group treated by physical therapist only.	Functional ability by MACTAR questionnaire score after 12 months comparing UC vs. RAPIT: -0.9 ± 9.8 vs. 2.1 ± 11.2 ; $p = 0.034$. After 24 months: 0.7 ± 9.4 vs. 3.6 ± 9.8 ; $p = 0.017$.	“A long-term high-intensity exercise program is more effective than UC in improving functional ability of RA patients. Intensive exercise does not increase radiographic damage of the large joints, except possibly in patients with considerable baseline damage of the large joints.”	Large sample size. Low Compliance rates. Co-interventions of +/-PT and bisphosphonates . Data suggest exercise superior to usual care.
de Jong 2004 RCT	6.5	N = 309 RA patients, ACR functional classes I-III, Stable DMARD regimen in past 3 months	Second report of de Jong 2003 above.	Total hip BMD remained stable in RAPIT group (median change 0.0% [IQR - 2.0, 2.0]) and decreased in usual care group (median change 1.0% [IQR - 3.7, 0.5]) ($p < 0.01$). After 2 years, hip BMD decreased by median 1.1% (IQR -3.8, 1.3) and 1.9% (IQR -5.6, 0.2) in RAPIT and usual care group, respectively ($p = 0.06$).	“A long-term high-intensity weight-bearing exercise program for RA patients is effective in slowing down the loss of BMD at the hip. The exercise modalities associated with this effect are muscle strength and aerobic fitness.”	Co-interventions of +/-PT and bisphosphonates . Primary analyses data suggest no differences in bone mass loss. Post hoc data suggest faster bone loss in those exercising less.
Stenström 1994 RCT	6.0	N = 42 ARA class II, age <70	“Goal-setting” subgroup (individual goals for exercise set and exercise encouraged despite pain, $n = 22$) vs. “pain attention” subgroup (advice to decrease exercise load in case of pain given, $n = 20$).	Mean±SD walking pain outcomes at baseline/ 12 weeks for home exercise program: 25/ 13; $p \leq 0.001$. All functional tasks improved ($p \leq 0.001$); except for maximum walking speed.	“Home exercise influences self-efficacy for mood and fatigue, physical capacity, and pain. Additional cognitive treatment seems to positively influence the perception of pain.”	Data suggest goal setting superior to pain attention as assessed with functional measures.
Hall 1996 RCT	6.0	N = 139 with chronic RA	Hydrotherapy ($n = 35$) vs. seated immersion ($n = 35$) vs. land exercise ($n = 34$) vs. progressive relaxation ($n = 35$), 30-minute sessions twice a week for 4 weeks.	Reduction in evaluative/affective pain scores between pre- and post-test; $p = 0.005$.	“Although all patients experienced some benefit, hydrotherapy produced the greatest improvements. This study, therefore, provides some justification for the	Somewhat variable results between groups though progressive relaxation tended to underperform exercise groups (either land- or water-based).

					continued use of hydrotherapy.”	
Lyngberg 1994 RCT	6.0	N = 24 with RA treated with low dose steroids for 2 years	Progressive interval training – aerobic with ergometer – bicycling and strengthening exercises, stretching trained muscles twice a week, 45 minutes for 3 months vs. no program.	Tended towards lower tender joints with exercise. Changes in medication use NS. Borderline reduction in number of swollen joints (p = 0.06). ESR (baseline/post): training (33/22) vs. control (17/23) favored treatment p = 0.13.	“Individually adapted exercise programs can therefore be recommended for elderly rheumatoid arthritis patients on steroid treatment.”	Data suggest physical training in elderly, fragile patients does not increase RA disease activity measured by blinded assessor. ESR reduced with exercise vs. with controls.
Lyngberg 1988 Crossover Trial	6.0	N = 20 with moderately active RA	Training program of aerobic capacity training and dynamic strength exercises 45 minutes twice a week for 8 weeks vs. no program.	No significant change in ESR, C3. Number of swollen joints decreased after training (77 to 56, p <0.02). No comparable reduction in swollen joints during control period (42 to 49). Hemoglobin level increased approximately 8% (p <0.01) with training.	“RA-patients with some activity are trainable without aggravating the disease, even in the chronically swollen joints. The rheumatoid arthritis activity decreased with fewer swollen joints and higher hemoglobin level after training.”	Main outcomes of serological markers of inflammation negative. However, disease activity reduced with exercise as measured with blinded assessor.
Bilberg 2005 RCT	5.5	N = 46 with chronic RA	Treatment group (n = 20) exercised in temperate pool twice a week for 12 weeks vs. control group (n = 23) continued with their previous activities.	Post test mean±SD comparing training group vs. control group: Shoulder endurance right: 90.3±52.2 vs. 58.2±35.4; p <0.001. Left shoulder endurance: 80.5±54.6 vs. 59.8±32.4; p <0.001. No differences between groups found for primary outcome measures.	“Pool exercise therapy of moderate intensity significantly improved muscle endurance in the upper and lower extremities in patients with RA, while no impact on aerobic capacity was found. However, the study population was small and there is a need for further studies with larger populations.”	Modest sized groups. Many data trended in favor of exercise group suggesting underpowering.
Neuberger 2007 RCT	5.0	N = 220 adults with RA, ages 40-70	Class exercise (n = 102), home exercise using videotape (n = 103), and control group (n = 105) for 12 weeks.	Symptoms (latent variable for pain, fatigue, and depression) decreased at 12 weeks (p <0.04) for class exercise group compared with control group.	“This study supported the positive effects of exercise on walk time and grip strength, and demonstrated that fatigue and perceived benefits/barriers to exercise influenced exercise participation. Furthermore, overall symptoms of fatigue, pain, and depression were positively influenced in this selective	Large sample size. High dropouts. Patients not well described. Best results tended to occur in class exercise group.

					group of patients with RA ages 40-70 years.”	
Melikoglu 2006 RCT	5.0	N = 40 female RA patients	Dynamic (n = 20) exercises on a treadmill vs. ROM exercise groups (n = 20), active, low pace vs. control group with same dynamic exercise protocol.	Mean±SD VAS score in dynamic group: 7th day (4.42±1.42; p<0.001); 15th day (4.26±1.24; p = 0.001. IGF-1 on 7th day dynamic group: 460.42±225.25; p <0.01. 15th day (496.89± 252.61; p <0.001). ROM exercise group levels: 7th day (462.58±211.89; p <0.05. 15th day (440.47±222.73; p <0.05.	“IGF-1 can be increases by dynamic exercise treatment in patients with RA.”	Very short trial. IGF-1 differed at baseline (398 vs. 530). Variable results without clear pattern of responses.
Baslund 1993 RCT	4.5	N = 18 with RA	Progressive bicycle training (ergometric bicycle 4-5 times a week with 3 short exercise periods of 5 minutes to target HR) vs. controls for 8 weeks.	VO2max training (27.2±1.7/33.3±1.9) vs. controls (20.9 ±2.9/ 22.2±2.6) mL/kg/minute (p = 0.04). HR decreased, RPE reduced, work load increased in exercise group. No difference in leukocytes, lymphocytes, neutrophils, C-reactive protein or erythrocyte sedimentation rate. Concentrations of IL-1α, IL-1β, and IL-6 not changed in training group. NK cell activity and lymphocyte proliferative responses did not differ.	“8 wk of bicycle training does not influence the immune system of patients with rheumatoid arthritis.”	Small sample size. Baseline higher VO2max in training group (27.2 ±1.7 vs. 20.9±2.9 mL/kg/minute). No immunological effects found (were trial’s primary outcome measures). Training group’s VO2max improved despite use of short bursts of exercise. May be underpowered.
van den Ende 1996 RCT	4.5	N = 100 with RA	High intensity group exercises (12 exercises, 20 minute cycling to 70-85% HR Max, 1 hour sessions, 3 times a week), vs. low intensity group exercise program (ROM, isometric strengthening, 1 hour sessions, twice a week) vs. low intensity individual exercise program (same exercises, durations unclear) vs. home exercise program (ROM and isometric	Mean aerobic capacity (VO ₂ max) increases: high intensity (27.6 to 32.3) +4.7mL/kg/minute (17%) vs. low group +0.9 vs. low individual -1.2 vs. home +0.3 (p <0.001 for high intensity group). Joint mobility (EPM-ROM) improved from 10.9 to 9.2 (15.6%) in high intensity group (p <0.001) compared with other groups. Muscle strength in high intensity group superior to HEP (p = 0.02), but not to low intensity groups; HAQ and Dutch AIMS NS. Medications unchanged.	“Intensive dynamic training is more effective in increasing aerobic capacity, joint mobility, and muscle strength than ROM exercises and isometric training in rheumatoid arthritis patients with well controlled disease.”	High intensity group tended towards longer disease duration and more active disease at baseline, potentially biasing against that group. Unequal treatment contact times among groups. Pain and/or physical fitness impaired ability of some to complete ergometer test. Data suggest best improvements in aerobic capacity and joint mobility with high intensity exercises. Data suggest results

			exercises at least 2 times a week for 15 minutes); all 12 weeks.			did not persist to 24 weeks.
Daltroy 1995 RCT	4.5	N = 71 with RA or systemic lupus erythematosus	Twelve-week home cardio-pulmonary conditioning program with stationary bicycles provided. Prescription 60-80% HR max, 3 times a week for 30 minute sessions vs. controls to maintain current activity level for 12 weeks.	Measures favored exercise (mostly NS). ETT minutes at 12 weeks: exercise 9.6 vs. 9.2 minutes controls (p = 0.33). CES-D depression scores 11.3 vs. 15.0 (p = 0.07). POMS fatigue 7.6 vs. 10.3, p = 0.03. Exercise group averaged 2.7 sessions a week. Patients reporting greater physical activity had greater baseline exercise tolerance, p = 0.0003 and at 3 months, p = 0.002.	"[A]lthough safe, un-supervised home exercise programmes may benefit few patients."	Data suggest exercise program may be relatively unsuccessful, although fatigue measures positive. Mixed rheumatological disorders. RA controls exercised somewhat longer at baseline, providing some potential bias against exercise.
Hansen 1993 RCT	4.5	N = 75 with RA	Five groups: 1 non-exercise controls (E). All exercise groups self training with 15 minute overall training and 30 minute aerobic (swim, cycle, run, jog) 3 times a week, up to 90 minutes a day. (A) Self training only; (B) weekly PT (15 minute standard program, 15 minute biking, 15 minute relaxation; (C) weekly in-hospital training as per B; (D) Same as C except hot pool instead of bicycles. All for 2 years.	ESR (baseline/24 months): A (35/22) vs. B (28/19) vs. C (20/17) vs. D (22/16) vs. E (23/28). Numbers of swollen joints not different. Pain scores: A (1.6/1.4) vs. B (1.8/1.9) vs. C (1.9/2.1) vs. D (1.9/1.4) vs. E (1.9/1.9). Average aerobic fitness declined in all 5 groups. Attendance rate for training sessions >50% for groups B, C, and D. "There were no statistically significant effect of the training on any of the measured variables; 66% of all patients experienced a general improvement of disease activity or activity of daily living. [T]here were no statistically significant differences between the groups."	"[A]lthough most patients are in favour of training, the present study does not support that training lessons per se affect the disease activity or the progression of the disease."	Subgroups are small at 15 subjects each arm. No aggregate analyses reported although some groups may have been comparable. Only no-exercise controls had rise in ESR. Lack of increases in aerobic capacity suggest lack of compliance with HEP. Lack of data from end of training impair ability to conclude short to intermediate term efficacy (or lack) of program.
Smith 1998 RCT	4.5	N = 24 with RA	Aquaerobics 1 hour, 3 times a week vs. 8-10 ROM exercises, isometric strengthening (possibly home exercise program) 10 each, 2-3 times a day for 10 weeks.	Active joints (baseline/11 weeks): aquaerobics (8.3±6.0/7.5±6.1) vs. ROM (10.6±5.6/7.1±4.6). Both groups improved duration on treadmill. ROM group alone showed improvement in walking category and total HAQ.	"[P]articipation in either program may result in improved exercise tolerance without exacerbating joint activity."	Small sample size. Arthritis duration longer in controls. Possible randomization failure. Controls not well described, appears a home exercise program which would provide different treatment contact

						times between 2 groups biased in favor of aquaerobics. Active joints trended to ROM group by blinded assessor. Weaknesses impair ability to draw conclusion.
McMeeken 1999 RCT	4.5	N = 36 with non-acute RA	Exercise group (quadriceps and hamstring concentric exercises, 70% maximum speed) vs. controls; 6 weeks follow-up.	Peak speed (pre/post): exercise (132.0/154.0) vs. control (125.2/121.6), p = 0.005; timed up and go test: exercise (11.7/10.4) vs. control (12.6/12.2), p = 0.01.	“Specific knee muscle training can be administered safely in people with non-acute rheumatoid arthritis, and may produce functional benefits.”	Dropouts unclear as results appear to report completions. Suggests no aggravation of disease with strengthening exercises.
Ekdahl 1990 RCT	4.5	N = 67 with RA	Dynamic program, strengthening and aerobic capacity 12 visits (2 per week for 6 weeks) vs. dynamic program, ROM and strengthening exercises 4 visits (2 at 1 week, 1 at 3 weeks, 1 at 6 weeks) vs. static program 12 visits vs. 4 visits. HEP daily.	VO2Max (baseline-6 weeks difference/baseline-18 weeks): dynamic (5.6/2.6) vs. static (0.9/-0.1). VAS pain muscle tests (-0.5/0.0) vs. (-0.2/0.4). Walking 60m (-3.7/-1.9s) vs. -0.5/0.1). All changes for dynamic group on 25 subtests positive vs. 12 subtests negative among static group. During 18 weeks, significant difference on 17 of 25 subtests.	“[D]ynamic training gives a greater increase in physical capacity than does static training.”	No differences between 4 and 12 visits, so data collapsed. Data suggest dynamic exercise superior to static.
Eklom 1975 RCT	4.5	N = 34 with RA, hospitalized but “non-acute stage	“Ordinary physical rehabilitation program” QAM, 5 a day 1 week (control) vs. ordinary program plus training group (bicycle ergometer and quadriceps table strengthening) 20-40 minutes BID for 5 weeks.	850m walk test (baseline/post): training group (9.36/8.02, p <0.05) vs. control group (9.17/8.97). Stair test up: TG (6.92/5.25s) vs. control (5.53/4.54).	“[T]he intensive physical training program resulted in a considerable improvement in physical performance capacity, cardio-respiratory fitness and leg muscle strengths in the (training group), indicating that lack of physical activity could be a major reason for the low physical fitness in the RA patient.”	Practicality of a 6-week hospital stay limits the utility of the results. Group sizes unequal and possible 2:1 randomization process, but not described. Data suggest training program successful.
Harkcom 1985 RCT	4.0	N = 20 females with RA, functional Class II	Bicycle ergometer 3 times a week for 12 weeks, 3 different exercise time progressions.	Aerobic capacity Group A (lowest) vs. B vs. C (baseline/post): A (14.6± 4.9/21.5±6.5) vs. B (20.3± 15.8/22.9± 17.9) vs. C (21.9 ±9.0/	“Exercise duration up to 35 minutes of exercise 3 times/week is sufficient to improve aerobic capacity in rheumatoid arthritis	Pseudo-randomization (patient chose a time block to show up for assignment). Suggests

				29.1±17.4). Joint count: A (38.0±21.7/24.0 ± 10.9) vs. B (26.0± 15.1/ 10.3±7.0) vs. C (32.5± 19.4/23.0± 10.7).	patients with severe limitations.”	increased benefits with increased exercise time.
Komatireddy 1997 RCT	4.0	N = 49 age 35-76 (mean 60.5 years), with definite RA functional class II and III (mean disease duration of 10.5 years)	Exercise vs. control groups for a 12-week resistive muscle training program.	Improvement at 12 weeks in exercise group for self-reported joint count (p = 0.02), number of painful joints (p = 0.004), HAQ (p = 0.012), sit-to-stand time (p = 0.02), grip strength (p = 0.05) knee extension 60° (p = 0.03).	“Low load resistive muscle training increased functional capacity as reported by patients and is a clinically safe form of exercise in functional class II and III RA. Screening this population for dormant coronary artery disease is recommended.”	Many baseline differences with more joints affected in exercise group. Data suggest better function and fewer painful joints in exercise group.
Westby 2000 RCT	4.0	N = 53 females with RA, duration ≥1 year, taking low dose prednisone	No steroid therapy receiving steroid therapy and in American College of Rheumatology functional class I or II vs. 30 steroid treated patients with similar demographics vs. control. Subjects receiving low dose prednisone were randomized to: usual care (n = 16) vs. an aerobic, weight bearing exercise program (n = 14) 3 times a week for 12 months.	Mean±SD function fitness scores comparing control vs. exercise group at 1 year: 27.5±13.7 vs. 49.4±15.8; p = 0.001.	“Women with RA taking low dose steroid therapy can safely participate in a dynamic, weight bearing exercise program with positive effects on their physical function, activity and fitness levels, and BMD with no exacerbation of disease activity.”	Small numbers. Some baseline differences including joint count (30 vs. 17.5). High dropouts. Low compliance. Variable results with higher fitness scores with exercise.
Häkkinen 2001 RCT	4.0	N = 70 with RA	Strength training (50-70% repetition max) vs. ROM exercise 45 min sessions, 2/week for 24 months. Strength group encouraged to do recreational physical activity (walk, cycle, swim, ski) 2-3 times a week 30-45 minutes vs. ROM “free to continue their	ESRs (baseline/6 months/12 months/24 months): strengthening (24.4±17.8/9.7±9.5/9.5 ± 7.5/10.9±9.8) vs. controls (24.8±15.7/ 16.7±12.7/17.3±16.1/ 15.4±11.5). VAS: strengthening (41.7±19.5/20.0±16.4/ 21.1±20.6/13.7±16.2) vs. controls (41.3± 27.1/28.6 ±23.1/24.2± 22.7/24.9± 22.8) (p <0.05 Months 18-24). Compliance average 1.5 times a week first	“Regular dynamic strength training combined with endurance-type physical activities improves muscle strength and physical function, but not (bone mineral density), in patients with early RA, without detrimental effects on disease activity.”	Data suggest superiority of strength training likely combined with aerobic exercise to range of motion exercises. As aerobic activities handled differently in the two groups, impacts of either strengthening or aerobic exercise alone are unclear. Strength training reduced

			recreational physical activities” except strengthening.	12 months; 1.4 times a week Months 13-24 both groups. Muscle strength increased with strength training except trunk flexion. Joint damage not significant. Walking speed increased 16±17% in strength training vs. 9±12% in controls.		ESR and pain ratings more.
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AQUATIC THERAPY (HYDROTHERAPY)

Aquatic therapy involves the performance of aerobic and/or flexibility and/or strengthening exercises in a pool to minimize the effects of gravity, particularly where reduced weight-bearing status is believed to be desirable.(548, 605-607) However, as per the above review of exercise, there is quality evidence that weight-bearing exercise is beneficial for treatment of knee osteoarthritis.

Recommendation: Aquatic Therapy for Knee Osteoarthritis

A trial of aquatic therapy is recommended for patients with knee osteoarthritis who meet the referral criteria for supervised exercise therapy, have co-morbidities (e.g., extreme obesity, significant degenerative joint disease, etc.) that preclude effective participation in a weight-bearing physical activity, and are planned to transition either to a land-based program or a self-administered water-based program.

Frequency/Duration – Begin with 3 to 4 visits a week. Functional improvement should be documented within the first 2 weeks to justify additional visits. The program should include up to 4 weeks of aquatic therapy with progression towards a land-based, self-directed physical activity or self-directed aquatic therapy program by 6 weeks. For some patients with knee osteoarthritis, aquatic exercise may be the preferred method. In these cases, the program should become self managed. If any membership to a pool is covered, coverage should be continued if it can be documented that the patient is using the facility at least 3 times a week and following the prescribed exercise program.

Indications for Discontinuation – Non-tolerance, failure to progress, or reaching conclusion of program at 4 to 6 weeks.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

Aerobic exercise is beneficial for treatment of knee osteoarthritis compared to no program(605); however, evidence of superiority to land-based programs is lacking.(548, 606-608) Instead, the quality literature appears to document comparable efficacy between land and water-based exercise programs.(548, 606, 607) These water programs are performed in lukewarm rather than higher temperature settings to allow for aerobic exercise to be performed. Spa water has been found to be no different than tap water.(609) There may be a select minority of patients in whom it is thought to be advantageous to reduce the effects of gravity. As noted previously, other forms of exercise have been shown to be effective in the treatment of knee OA, but for a few select patients who are unable to tolerate those land-based therapies, aquatic therapy is moderate costly, not invasive, and has little potential for adverse effects.

Evidence for the Use of Aquatic Therapy for Knee Osteoarthritis

There is 1 high-(605) and 7 moderate-quality(548, 557, 606-610) RCTs incorporated into this analysis

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Hinman 2007 RCT	8.0	N = 71 with hip or knee OA	Aquatic PT (45-60 minute sessions, twice weekly) vs. no aquatic PT for 6 weeks.	WOMAC pain scores (baseline/6 weeks): aquatic (202±79/143±79) vs. controls (199±85/198±108), p <0.001. VAS pain with movement (p = 0.003), WOMAC stiffness (p = 0.007), WOMAC function all favored aquatic therapy.	"[A] 6-week program of aquatic physical therapy results in small improvements in pain, stiffness, hip strength, and quality of life in people with hip OA or knee OA compared with no intervention."	Data suggest aquatic therapy superior to no aquatic therapy program, although study design is biased towards intervention as controls had no intervention.
Silva 2008 RCT	7.0	N = 64 with knee OA	Subjects randomly assigned to 1 of 2 groups that performed exercises for 18 weeks: a water-based exercise group and a land-based exercise group.	Both groups homogenous all parameters at baseline. Reductions in pain and improvements in WOMAC and Lequesne index scores similar between groups. Pain before/after decreased significantly in both groups. Water-based exercise group experienced a significantly greater decrease in pain than land-based group at the week-18 follow-up.	"Both water-based and land-based exercises reduced knee pain and increased knee function in participants with OA of the knee."	Only 18 weeks follow-up. WOMAC, VAS and Lequesne all trended in favor of water-based.
Nguyen 1997 RCT	6.5	N = 180 with lumbar spine, knee and hip OA	Spa therapy vs. "usual therapy" for 3 weeks. Spa included "journey, rest, balneotherapy, spring water and medical attention."	NSAID tablets consumed over 24-week follow-up period: spa 144±192 vs. 216±240, p = 0.01. Graphic data suggest reduction in benefits over time. VAS pain scores (9 baseline/4 weeks/24 weeks): spa (50±20/-15±29/-9±28) vs. controls (47±22/1±22/ 3±24), p <0.0001.	"This study suggests that spa therapy of 3 weeks duration has a prolonged, beneficial, symptomatic effect in osteoarthritis."	Treatments likely heterogeneous with multiple co-interventions, precluding conclusions. No long-term follow-up beyond 6 months; results not significantly different by months 4-6 by tablet count.
Fioravanti 2009 RCT	6.5	N = 80 with primary knee OA (ACR), ages 54-81	Spa treatment (daily mud packs, bicarbonate-sulfate mineral bath water) vs. controls ("regular routine ambulatory care"; 9 months follow-up.	Lequesne (baseline/2 weeks/3, 6, 9 months): Spa (10.32/7.99/7.65/7.27/7.27) vs. controls (11.47/11.40/10.83/10.45/10.43). WOMAC total scores: spa (36.54/24.54/20.53/20.18/20.04) vs. controls (36.82/39.06/38.13/35.08/35.76).	"The results from our study confirm that the beneficial effects of spa therapy in patients with knee osteoarthritis lasts over time, with positive effects on the painful symptomatology and a significant improvement on functional capacities."	No sham treatment. Use of "more of the same" control group likely biases in favor of intervention.
Foley 2003 RCT	6.5	N = 105 with hip and/or knee OA	Water exercise (walking, strengthening) vs. gym (cycling, strengthening) vs. no-exercise. Exercise 3	WOMAC function (baseline/follow-up): hydro (34.0/33.0) vs. gym (28.0/27.0) vs. control (37.0/37.0). No differences in pain and most other measures. Walking speed and	"[B]oth the gym and hydrotherapy interventions produce positive functional outcomes for patients with OA."	Some baseline differences with less distance walked in hydrotherapy (257m) vs. gym (336m) vs. control (388m). WOMAC

			sessions a week for 6 weeks. Control group had nightly calls to record changes in condition, drug use, or injuries.	distance improved significantly from baseline in both exercise groups, $p < 0.001$. Increases in some strength measures in both exercise groups. Stated decline in WOMAC from baseline in hydrotherapy, but data do not support a change (both 10.0).		function also different. Graphic data support increases in distance walked and walking speed.
Yurtkuran 2006 RCT	5.5	N = 56 ages 40-65 with knee OA (ACR criteria) KL Grade s 2-3	Spa water (CaCO, Cl, Ca, Mg, NH, NO ₃ , NO ₄ , FR Orthophosphate, SO, Na, K, Mn, Free CO ₂ , Li, S ₂) 37°C vs. placebo (regular water) at 37°C. All 20 minutes a day, 5 days a week for 2 weeks. All bed rest for 3 hours after treatment. Both groups taught 10 minutes isometric contraction to quadriceps muscles exercises 20 times a day for 12 weeks; 12 weeks follow-up.	Between group differences present for 2 of 15 variables (Tenderness score $p = 0.002$ favoring tap water, and Nottingham Health Profile Pain Score ($p = 0.02$) favoring balneotherapy). Results showed improvement in Group 1 only for pVAS ($p = 0.015$) at 2nd week. 5.3+1.69 vs. placebo 6.11+1.59.	“The thermal treatment modalities were found to be effective in the management of the clinical symptoms and quality of life in KOA patients. However, pain and tenderness improved statistically better with balneotherapy.”	No control/sham group. Success of double blinding seems questionable. Treatments largely not performed in US, thus applicability minimal. Data suggest no differences between groups.
Sylvester 1990 RCT	4.5	N = 14 with hip OA	Hydrotherapy (2-1/2 hour sessions a week for 6 weeks) vs. diathermy and supervised exercises (same exercises as in pool).	VAS pain (median pre/post treatment): hydrotherapy 78/41 vs. 83/51. Oswestry questionnaires: hydrotherapy 49/27 vs. 67/58.	“Functional ability had improved in the group treated by hydrotherapy ($p < 0.05$, who also reported a higher score on the life satisfaction scale...It would be of interest to expand this study to include a greater number of subjects in order to attempt to validate the use of hydrotherapy in this patient population.”	Small sample size. Pilot study. Both groups improved markedly on VAS but hydrotherapy improved more.
Minor 1989 RCT	4.0	N = 120 with hip, knee or tarsal OA or RA	Aerobic walking vs. aerobic pool vs. ROM exercise classes, 1 hour sessions, 3 sessions a week for 12 weeks. Both	Aerobic capacity (baseline/12 weeks): walk (18.9±4.8/22.4±4.8mL/kg/ minute) vs. pool (19.3±6.7/ 23.2±7.2) vs. ROM (17.4± 5.9/17.3±3.6) ($p = 0.009$ comparing walk plus	“Our findings document the feasibility and efficacy of conditioning exercise for people who have rheumatoid arthritis or osteoarthritis.”	Data suggest efficacy of walking or pool exercise for arthrosis patients. Targeted 60-80% HR maximum in walking and pool groups. Improvements

			aerobic groups targeted 60-80% of HR Maximum for 30 minutes.	pool vs. ROM). AIMS pain scores (baseline/12 weeks): walk (5.1±1.9/3.9±1.9) vs. pool (5.0±1.6/4.4±1.7) vs. ROM (5.5±1.6/4.8±1.9) (p = 0.22). Active joints (n): aerobic OA - 2.0±5.2 vs. ROM (-1.8±5.9). Active RA joints aerobic (-6.8±11.8) vs. ROM (3.3±10.9).		greater in OA vs. RA for exercise endurance, but better for total active RA joints. Both appear to benefit. Suggests aerobic exercise reduces active RA joints.
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YOGA

Yoga has been used successfully for treatment of low back pain patients(611-613) (see Low Back Disorders guideline).

Recommendation: Yoga for Chronic Knee Pain

There is no recommendation for or against the use of yoga for treatment of chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are no quality studies of yoga for treatment of these patients. Yoga may be appropriate for highly motivated patients; however, compliance is an issue.

Follow-up Visits.

Patients with knee symptoms should have follow-up approximately every three to seven days, depending on severity of the condition, limitations, and workplace accommodation of limitations. Considerations for the initial follow-up visits include: response to treatment, further education, advice to avoid static positions, medication use, activity modification, and other concerns. The practitioner can answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery. If the patient has returned to work, these interactions may be done on site or by telephone to avoid interfering with modified- or full-work activities.

Medications

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AND ACETAMINOPHEN (Including Cytoprotection)

NSAIDs are widely used for treatment of osteoarthritis (OA) and have been considered efficacious. However, the duration of follow-up in most studies does not exceed 6 weeks.(614-616) Most quality studies have included both knee and hip OA patients; however, outcomes in these two patient populations are similar.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis, impairing inflammation. There are several classes of NSAIDs: 1) salicylates – aspirin, diflunisal, salicyl salicylate (salsalate); 2) arylalkanoic acids – diclofenac, etodolac, ketorolac, nabumetone, sulindac, tolmetin; 3) 2-arylpropionic acids – ibuprofen, fenoprofen, ketoprofen, naproxen; 4) n-arylanthranilic acids – mefenamic acid; 5) oxicams – piroxicam, meloxicam; 6) COX-2 inhibitors – celecoxib, rofecoxib, etoricoxib; and 7) sulphonanilides – nimesulide. Acetaminophen is considered an analgesic and not an anti-inflammatory agent. Acetaminophen blocks the activation of COX by another enzyme, peroxidase. Tissues with high levels of peroxidase (i.e., platelets and immune cells) are “resistant” to acetaminophen, but tissues with low levels of peroxidase (i.e., nerve and endothelial cells that participate in pain and fever) are “sensitive” to acetaminophen.(617) There have been recent suggestions that NSAIDs may reduce cartilage

synthesis.(618) However, there also are many articles documenting reductions in inflammatory mediators,(619-625) thus raising the possibility that NSAIDs delay cartilage destruction.

There are two isoenzymes of cyclooxygenase, COX-1 and Cox-2. NSAIDs are COX (non)selective to different degrees. COX-2 selective agents were designed to reduce inflammation without increasing risks for gastrointestinal (GI) bleeding. It appears that certain COX-2 selective agents may increase the risk of cardiovascular events (see Hip and Groin Disorders guideline for more information).

1. Recommendation: NSAIDs for Treatment of Acute, Subacute, Chronic, or Post-operative Knee Pain

NSAIDs are recommended for treatment of acute, subacute, chronic, or post-operative knee pain. There is no consistent quality evidence that one NSAID is superior to another, thus there is **No Recommendation, Insufficient Evidence (I)**, nor is there consistent quality evidence for superiority of one dosage form(626) or enteric-coated or sustained release preparations.(627-630) Due to their inhibitory effects on platelet function, non-selective COX inhibitors should be used with caution, or avoided altogether, in the post-operative period if patients are also receiving pharmacoprophylaxis (e.g., warfarin, low molecular weight heparins) to prevent venous thromboembolic disease. Concomitant use of non-selective COX inhibitors and anti-coagulation regimens may increase the risk of hemorrhage. There is also concern that COX inhibitors, particularly COX-2 inhibitors, may inhibit bone healing. Therefore, these agents should be used with caution, or avoided altogether, in the acute post-operative period in situations where bone healing is required, such as in fracture repair or in knee replacements where cementless components are utilized.

Acetaminophen (or the analog, paracetamol) may be a reasonable alternative for treatment of acute, subacute, chronic or post-operative knee pain,(631, 632) although quality evidence suggests that acetaminophen is less efficacious than NSAIDs.(633-639) At least two quality trials of acetaminophen compared to placebo have been negative, including one with a large sample size of 779 patients.(637, 640) Of note, a recent FDA advisory committee recommended reduction of the maximum dose of acetaminophen to 650mg, which is less than the 1gm dose used in most quality trials. Consequently, the degree of successful treatment of osteoarthritis with lower doses of acetaminophen is somewhat unclear. There is evidence that NSAIDs are as effective for pain relief as tramadol(641, 642) and dextropropoxyphene, although slightly less efficacious than codeine.(643, 644)

Indications – Acute, subacute, chronic, or post-operative knee pain. OTC agents may suffice and be tried first.

Frequency/Duration – Per manufacturer’s recommendations; essentially all NSAIDs have proven efficacious for this indication. As-needed use may be reasonable for many patients. However, nearly all trials used scheduled doses.(645) There is evidence that nocturnal dosing is superior if patient primarily has morning or nocturnal pain,(646) although this may only apply to agents with shorter half-lives, including indomethacin.(647)

Indications for Discontinuation – Resolution of knee pain, lack of efficacy, or development of adverse effects that necessitate discontinuation.

Strength of Evidence – **Strongly Recommended, Evidence (A)** – Chronic knee pain(231, 631, 637, 648-660)

Recommended, Evidence (C) – Acute flares(648, 661, 662)

Recommended, Insufficient Evidence (I) – Acute, subacute, post-operative knee pain(663)

2. *Recommendation: NSAIDs for Patients at Risk for GI Adverse Effects*

Concomitant prescriptions of cytoprotective medications are recommended for patients at substantially increased risk for gastrointestinal (GI) bleeding. There are four commonly used cytoprotective classes of drugs: misoprostol, sucralfate, histamine Type 2 receptor blockers (famotidine, ranitidine, cimetidine, etc.), and proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole). It is generally thought that there is no significant difference in efficacy between these classes for the prevention of GI bleeding.(664) However, evidence suggests that histamine-2 blockers are less effective for protection of the gastric mucosa and sucralfate is weaker than proton pump inhibitors. There also are combination products of NSAIDs/misoprostol that have documented reductions in the risk of endoscopic lesions.

Indications – Patients with high GI risk factor profiles who also have indications for NSAIDs, cytoprotective medications should be considered, particularly if longer term treatment is planned. At-risk patients include those with a history of prior GI bleeding, elderly patients, diabetics, and cigarette smokers. Providers are cautioned that H2 blockers might not protect from gastric ulcers.(665-667)

Frequency/Dose/Duration – Proton pump inhibitors, misoprostol, sucralfate, and H2 blockers recommended. Dose and frequency as recommended by manufacturer for duration of NSAID therapy or permanently for those with recurrent bleeds or other complications.

Indications for Discontinuation – Intolerance, development of adverse effects, or discontinuation of NSAID.

Strength of Evidence – **Strongly Recommended, Evidence (A)** – Proton pump inhibitors, misoprostol

Moderately Recommended, Evidence (B) – Sucralfate
Recommended, Evidence (C) – H2 blockers

3. *Recommendation: NSAIDs for Patients at Risk for Cardiovascular Adverse Effects*

Patients with known cardiovascular disease or multiple risk factors for cardiovascular disease should be counseled about the risks and benefits of NSAID therapy.(668)

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Acetaminophen or aspirin should be considered as the first-line therapy for these patients with cardiovascular disease risk factors.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

If needed, NSAIDs that are non-selective are preferred over COX-2 specific drugs. In patients receiving low-dose aspirin for primary or secondary cardiovascular disease prevention, NSAID should be taken at least 30 minutes after or 8 hours before the daily aspirin to minimize the potential for the NSAID to counteract the beneficial effects of aspirin.(669)

4. *Recommendation: Acetaminophen for Treatment of Acute, Subacute, Chronic or Post-operative Knee Pain*

Acetaminophen is recommended for treatment of acute, subacute, chronic or post-operative knee pain, particularly for those with contraindications for NSAIDs.

***Indications* – All patients with knee pain, including acute, subacute, chronic and post-operative.**

Dose/Frequency – Per manufacturer’s recommendations; may be utilized on an as needed basis. It has been suggested that 1gm doses are more effective than 650mg doses, particularly in post-operative patients.(670, 671) However, this dose is now above the maximum dose recommended by an FDA advisory committee of 650mg, as evidence of hepatic toxicity has been reported at 4gms per day, particularly among those consuming excessive alcohol. There is no quality evidence for superiority of 1gm dosing for treatment of osteoarthritis.

Discontinuation – Resolution of pain, adverse effects or intolerance.

Strength of Evidence – **Recommended, Evidence (C)**

Rationale for Recommendations

There is abundant quality evidence that NSAIDs improve pain and function among chronic knee pain patients, particularly those with osteoarthritis or rheumatoid arthritis. There are a few studies of NSAID use for osteoarthritis flares that consistently document benefits. There are no quality studies of NSAID use for acute, subacute or post-operative knee pain. However, by analogy to other MSDs including LBP (see Low Back Disorders guideline), successful treatment of knee pain with NSAIDs may be reasonably anticipated. Results are similar for non-selective or COX-2 (selective) NSAIDs, although the magnitude of benefit is generally not large for any given medication. There are many quality trials comparing various NSAIDs,(68, 631, 638, 639, 648, 654, 658, 659, 661, 672-722) and there is no consistent quality evidence suggesting superiority of one over another or of one class over another class. Most studies have not found cyclooxygenase-2 selective medications to be superior to other NSAIDs for pain control.(614, 615, 723) However, there is quality evidence that COX-2 selective NSAIDs reduce the risk of gastrointestinal adverse effects.(614, 615, 723) In terms of the timing of NSAID dosing, there is one quality study suggesting that evening dosing of indomethacin resulted in better pain control.(646) There is no similar result with the longer-acting agent celecoxib.(647) There is quality evidence that NSAIDs are less impairing than opioids, yet efficacy is comparable (see Chronic Pain and Low Back Disorders guidelines). For most patients, generic ibuprofen, naproxen or other older generation NSAIDs are generally recommended as first-line medications. Second-line medications should generally include other generic medications.

There are several quality studies of acetaminophen and a few of paracetamol, a close analog.(724) All trials that compared acetaminophen with NSAIDs found either that NSAID significantly reduced pain more than acetaminophen or that differences were not statistically significant but favored NSAIDs.(633, 634, 636-639, 724-726) There is superior symptom relief at 2 hours with ibuprofen compared to paracetamol. These findings are consistent with quality evidence for the treatment of low back pain (see Low Back Disorders guideline). Subanalyses have suggested that NSAIDs are particularly more efficacious for those with more severe osteoarthritis. However, evidence also indicates higher rates of gastrointestinal adverse effects among NSAID users and lower overall adverse effects profiles for acetaminophen.

A systematic review and meta-analysis of observational studies of NSAIDs found that the risk for serious cardiovascular events was elevated in combined analyses for some NSAIDs, but not for others.(727) Many of the studies supporting these estimates were based on large pharmaceutical databases that were adequately powered to detect effects, but had limited ability to control for potential confounding. There is one reported study of NSAIDs and myocardial infarctions that controlled for two major confounders – aspirin and body mass index.(728) Summary estimates from that study for non-selective NSAIDs suggested that they are protective against cardiovascular events. Study weaknesses included a 50% participation rate and reliance on recall. However, the American Heart Association has cautioned against the use of NSAIDs,

especially COX-2 inhibitors.(669) Thus, current evidence is unclear if there is increased risk, no risk, or reduced risk of cardiovascular events from the use of any NSAIDs other than rofecoxib, which appears to have a modestly elevated relative risk.(727) It is recommended that risks of NSAIDs be discussed with patients, particularly patients with cardiovascular risk factors.

Risks of gastrointestinal events should be assessed, including prior history of gastrointestinal bleeding and source, length of treatment, age, smoking, diabetes mellitus, and other medical factors. Treatment with either acetaminophen, NSAIDs plus misoprostol, proton pump inhibitors (see below) or a COX-2 selective agent should be considered in those at high risk for gastrointestinal complications.(231, 614, 615, 650, 683, 723, 729-733)

Gastrointestinal adverse events are generally considered the most significant of the risks of NSAIDs. A large volume of high and moderate quality evidence has consistently shown that proton pump inhibitors are effective for prevention and or treatment of gastric and duodenal ulcers and erosions.(734-748) Different proton pump inhibitors are probably equally effective. There is one quality head-to-head trial, and it found no difference in efficacy between pantoprazole and omeprazole.(735) Misoprostol has also been consistently shown to be effective compared with placebo.(749-759) Relatively fewer studies have shown sucralfate to be effective compared with placebo.(760) H2 blockers appear more effective for treatment of duodenal than gastric mucosa.(665-667) There are relatively few quality trials comparing efficacy of the different classes of agents. Pantoprazole but not lansoprazole has been reported to be modestly superior to misoprostol.(761, 762) No difference was found between famotidine and lansoprazole.(763) Misoprostol has been reported superior to placebo(764) and ranitidine,(765, 766) cimetidine(756) and sucralfate.(755, 767) In short, while the evidence is not definitive, available quality evidence suggests proton pump inhibitors and misoprostol appear superior to H-2 blockers and sucralfate. While COX-2 selective agents have generally been recommended as either third- or fourth-line medications for routine use in osteoarthritis patients, they are often preferred when there is a risk of gastrointestinal complications. For patients at high risk of gastrointestinal bleeding, there is evidence that a combination of proton pump inhibitor plus COX-2 selective agent is efficacious.(768) There is consistent quality evidence that NSAIDs prevent heterotopic bone formation in post-arthroplasty patients.(769-773) but there is no quality evidence that prophylactic treatment with NSAIDs results in improved functional outcomes.(769)

NSAIDs are not invasive, have low side effect profiles in a healthy working patient population, and are low cost when generic medications are used. The potential for NSAIDs to increase the risk of cardiovascular events needs to be carefully considered

Evidence for the Use of NSAIDs and Acetaminophen

There are 26 high and 114 moderate-quality RCTs and randomized crossover trials incorporated in this analysis. *Note: Trials are aggregated within these categories to provide some structure. However, while many of these could be listed in multiple categories, they are listed only once to conserve space.*

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
NSAIDs vs. Placebo						
Kruger 2007 RCT	9.5	N = 167 knee or hip OA	Oxaceprol 400mg TID vs. placebo for 3 weeks.	Pain following exercise (baseline/3 weeks): Oxaceprol 61.8±14.9/45.2±22.2 vs. placebo 63.0±13.9/58.5±21.6 (p = 0.002). Adverse effects in 50/77	“A statistically significant and clinically relevant efficacy of oxaceprol was shown. The good safety and tolerability of oxaceprol was confirmed.”	Forty-six (46) of 159 subjects excluded after randomization due to inclusion/exclusion or protocol violations, which were not included in

				(64.9%) oxaceprol vs. 65/76 (85.5%) placebo.		modified intent to treat.
Pope 2004 N of 1 trials	8.5	N = 51 hip, knee or hand OA	Multiple crossover trials of diclofenac 50mg plus misoprostol 200µg vs. placebo for 2 week durations for 6 months.	In one group, 11 patients preferred diclofenac, none preferred placebo, and 11 had no preference. NSAID appeared to be effective in 81% of patients.	"N of 1 trials were time-consuming in these patients and are more expensive, but with slightly better outcomes. In addition, NSAID seem to be effective in a majority of subjects with OA who have been uncertain of their benefit."	Subjects at enrollment "uncertain the nonsteroidal anti-inflammatory drugs were helpful." Results suggest NSAIDs are efficacious for majority who were uncertain if they were effective.
Berry 1992 RCT	5.5	N = 184 with hip or knee OA	Lornoxicam 6mg QD vs. 4mg BID vs. 6mg BID vs. placebo for 4 weeks.	Mean pain relief scores superior with lornoxicam 8mg daily (p <0.002) and lornoxicam 12mg daily (p <0.0001) vs. placebo. (Graphic data). Scores for lornoxicam 12mg daily greater than lornoxicam 6mg daily (p <0.02). No differences in adverse GI symptoms, but trended to higher adverse events at higher doses (placebo 9% vs. 7, 12, 17% lornoxicam doses).	"Lornoxicam at doses of 8 mg and 12 mg daily was significantly more effective than placebo in the relief of joint pain associated with osteoarthritis of the hip and knee."	High dropout rate and possibility of effects from co-interventions. Data suggest lornoxicam effective.
Caroit 1976 Crossover Trial	5.5	N = 9 with hip OA	Ketoprofen 50mg TID vs. placebo; 2 week treatment each treatment.	Aggregate data not presented on pain ratings, etc. In 8 patients, ketoprofen preferred; in 1 case no preference.	"Nine cases were sufficient to produce a significant statistical results in favour of ketoprofen."	Very small sample. Limited data presented. Overall preferences suggest ketoprofen superior to placebo.
Petrick 1983 2 RCTs	5.5	N = 180 with hip OA N = 237 with knee OA	Meclofenamate sodium 100mg TID vs. placebo for 4 weeks. Meclofenamate dose could be reduced.	Night pain (baseline/4 weeks): meclofenamate (1.24/-39%) vs. placebo (1.49/-25%), p <0.03. Similar results with pain on walking, starting motion, pain on passive motion (p <0.01). Meclofenamate sodium caused more GI symptoms.	"[T]he antirheumatic efficacy and favorable tolerance picture of meclofenamate sodium demonstrated that the drug is also clearly effective in the management of acute and chronic osteoarthritis of the hip and knee."	Blinding, randomization, unclear. Suggests meclofenamate superior to placebo.
Ogilvie-Harris 1985 RCT	5.0	N = 139 torn meniscus with arthroscopic meniscectomy between ages 16-65	Naproxen sodium 550mg twice a day for 6 weeks (n = 67) vs. placebo (n = 72) with follow-up at 7, 21, 42, and 84 days post-surgery; 3 month follow-up.	Pain at rest p-values favor active treatment (7 days/ 21 days /42 days/84 days): p = 0.0001/0.005/0.34/0.94. Pain with normal activities p-values between groups favor active treatment: p = 0.0001/0.0001/0.00003 /0.18. Pain with increased activities favored active treatment. Pain relative	"[P]rovided there are no contraindications, a prostaglandin inhibitor should be used after arthroscopic procedures."	Dropouts unclear as 139 were noted to have completed study. Some details sparse. Data suggest naproxen accelerated recovery, including earlier RTW (5d vs. 14d, p = 0.002).

				to activity favored active treatment. Consumption of analgesic pills favored active treatment. Return to work: 14 days placebo vs. 5 days to active, p = 0.0021. Return to sport: 56 days placebo vs. 22.5 days active p = 0.0001. Patients with side effects: 13 active vs. 3 placebo, p = 0.005 at Day 7.		
Gillgrass 1984 Crossover Trial	4.5	N = 18 with hip or knee OA	Nabumetone 1gm BID vs. placebo for 2 weeks each.	Reduced pain (p <0.02). Intermalleolar straddle, intercondylar distance, knee flexion and extension showed little variation. Clinical assessment of response with 11/17 better on nabumetone, 3 were same on both, and 3 were better on placebo (p = 0.037).	"A 2-week, double-blind controlled crossover study in patients with osteoarthritis has shown a statistically significant drug-related beneficial effect with respect to patient preference (P<0.001) and clinical response (P=0.037). Most clinical parameters assessed improved and no significant side-effects or drug-related adverse events were noted."	Small sample size, sparse study details. Few data.
Famaey 1976 Crossover Trial	4.0	N = 20 with hip OA	Ketoprofen 50mg TID vs. placebo for 2 weeks.	Three of 20 (15%) did not complete. Patients favored ketoprofen (p <0.05).	"[K]etoprofen was significantly better than placebo."	Small sample size. Lack of details and results. Study appears to be a crossover trial.
Acetaminophen or Paracetamol vs. Placebo						
Amadio 1983 Crossover Trial	7.0	N = 25 with knee OA	Acetaminophen 1gm QID vs. placebo for 6 weeks.	Pain at rest better on acetaminophen (32 vs. 2 on placebo vs. 10 no difference, p = 0.0001). Pain on motion better on acetaminophen (29 vs. 4, p = 0.011). Tenderness better on acetaminophen (p = 0.0022). Swelling and heat not different (p = 0.5). Time to walk 50 feet 17.6s; after placebo 17.4± 1.2 vs. after acetaminophen 14.9±0.8, p = 0.05.	"Acetaminophen in a dose of 4000 mg/day is an effective alternative to salicylates in the treatment of osteoarthritic pain of the knees, with few adverse effects."	Suggests efficacy of acetaminophen.
Miceli-Richard 2004 RCT	6.5	N = 779 with knee OA	Paracetamol 1gm QID vs. placebo for 6 weeks.	Changes in VAS scores at 1 week: paracetamol 16±21 vs. placebo 15±21, p = 0.40; 6 weeks: paracetamol 23±27 vs. 23±26, p = 0.66. WOMAC scores did not differ. Patient global assessments 1 week: paracetamol	"A statistically significant symptomatic effect of oral paracetamol 4 g/day over placebo was not found, suggesting that paracetamol use in symptomatic OA of	Large sample size. Suggests paracetamol is not clearly effective for knee OA.

				14±21 vs. 12± 22, p = 0.063; 6 weeks: 22±26 vs. 20±27, p = 0.23.	the knee should be further explored.”	
NSAIDs vs. Acetaminophen or Paracetamol						
Golden 2004 2 RCTs	8.5	N = 465 with knee OA	Naproxen sodium 220mg TID (BID if over 65 years) vs. acetaminophen 1gm QID vs. placebo QID.	Nearly all measures improved for naproxen (rest pain, pain on passive motion, pain on weight bearing, stiffness, day pain, night pain), but only day pain relief improved for acetaminophen compared with placebo. (Graphic data). Adverse effects in 17.4% of placebo vs. 20.9% acetaminophen vs. 24.2% naproxen.	“Nonprescription doses of naproxen sodium (440/660 mg) effectively relieve pain and other symptoms of osteoarthritis. Naproxen sodium is an alternative initial treatment of osteoarthritis and may be preferred to acetaminophen as first-line therapy in patients with moderate or severe pain.”	Two very short-term studies of 7 days each reported in pooled analyses. Submaximal naproxen dose vs. full acetaminophen dose. Acetaminophen appears inferior to naproxen, and not clearly superior to placebo.
Temple 2006 RCT	8.0	N = 581 with mild to moderate hip or knee OA	Acetaminophen 1g Q4-6 hours vs. naproxen 375mg BID for up to 12 months. Single dummy.	WOMAC scores at 6 months improved in both groups, not significantly different. Adverse effects in 38.3% acetaminophen vs. 43.4% naproxen (NS). More constipation with naproxen (9.9% vs. 3.1%, p <0.002) and more peripheral edema (3.9% vs. 1.0%, p <0.033).	“With physician supervision, acetaminophen was found to be generally well tolerated in these patients for the treatment of osteoarthritis pain of the hip or knee for periods up to 12 months.”	Few data on efficacy presented. Maximal dose acetaminophen vs. submaximal dose naproxen likely biases in favor of acetaminophen. No significant differences in primary outcomes. Both groups had high dropouts.
Pincus 2001 Randomized Crossover Trial	7.5	N = 227 with hip or knee OA	Diclofenac 150mg plus misoprostol 400µg vs 4000mg acetaminophen for 6 weeks.	WOMAC scores for most-involved joint (baseline/6 weeks): diclofenac plus misoprostol (42.5±2.1/30.3±2.0) vs. acetaminophen (37.4±2.5/35.3±1.9). Acetaminophen 1st, results (baseline/6 weeks): 44.8±2.1/38.2±1.7) vs. diclofenac+ misoprostol (40.5±2.6/27.6±2.1) (p <0.01). Multidimensional Health Assessment Questionnaire VAS and SF-36 favored diclofenac. Results comparing treatments by OA severity index [WOMAC total score estimate (p-values) for quartiles lowest to highest): 0.78 (0.86), -1.45 (0.70), -6.72 (0.63), -14.70 (p <0.001). Non-serious adverse GI events more common for diclofenac + misoprostol (p = 0.006).	“Patients with osteoarthritis of the hip or knee had significantly greater improvements in pain scores over 6 weeks with diclofenac + misoprostol than with acetaminophen, although patients with mild osteoarthritis had similar improvements with both drugs. Acetaminophen was associated with fewer adverse effects.”	No placebo arm. Data demonstrate diclofenac superior for pain relief and measures of function to acetaminophen, particularly for moderate to severe disease.

				Diclofenac + misoprostol reported "better" or "much better" by 57%.		
Boureau 2004 RCT	7.5	N = 222 with knee or hip OA	Ibuprofen 400mg TID vs. paracetamol 1,000mg TID for 14 days. Double dummy.	Pain intensity over hours or days reduced to greater extent with ibuprofen (p <0.05). Stiffness scores (baseline/final): ibuprofen 56.2±17.5/32.5±18.7 vs. paracetamol 56.2±17.5/43.7±20.0 (p = 0.002). Pain scores: ibuprofen 50.0±13.5/27.0±17.0 vs. 50.0±12.5/35.5±18.0 (p <0.001). Physical function scores: -19.8 vs. -12.8 (p = 0.002). Global efficacy higher for ibuprofen (67.5%) than paracetamol (37.8%), p = 0.001. Adverse effects did not differ (23.4% vs. 22.5%) (NS).	"[S]hows that a significant and a more marked reduction in pain was experienced by patients with OA of the hip or knee with ibuprofen 400 mg than with the paracetamol 1000mg."	Study used sub-maximal doses and demonstrated Ibuprofen 400 mg TID was more effective than paracetamol for OA of hip and knee at every time interval from hours to days 1 to 14.
Case 2003 RCT	6.5	N = 82 with medial knee OA	Diclofenac 75mg BID vs acetaminophen 1000mg QID vs. placebo for 12 weeks. Double dummy.	WOMAC pain scores (baseline/Week 2/Week 12): diclofenac (199.8±101.5/139.6±105.2/146.0±101.2) vs. acetaminophen (310.8±86.3/206.1±101.2/186.9±121.5) vs. placebo (198.6±110.9/197.1±118.8/183.4±122.9). Diclofenac significant (p <0.002), while acetaminophen p = 0.13 for Week 0-12 differences and other pain changes negative. Acetaminophen never superior to placebo.	"Diclofenac is effective in the symptomatic treatment of OA of the knee, but acetaminophen is not."	Moderate sample size, lack of study details somewhat weaken results. Placebo arm strengthens conclusions that acetaminophen may be weakly effective or ineffective.
Blandino 2001 Crossover Trial	4.5	N = 227 with hip or knee OA	Diclofenac plus misoprostol vs. acetaminophen.	WOMAC improved 12.2 points for diclofenac vs. 6.6 for acetaminophen. Second 6-week period improvement 12.9 vs. 2.1 points. MDHAQ scale improved more with diclofenac plus misoprostol 20.8 points vs. 13.1 acetaminophen period 1, and 24.6 points vs. 0.4 acetaminophen in period 2.	"The NSAID diclofenac was found to be more effective than acetaminophen in patients with moderate to severe arthritis."	Few study details. Results suggest diclofenac more effective than acetaminophen for pain and functional improvement.
NSAIDs vs. Opioids						

Beaulieu 2008 RCT	7.5	N = 129 with hip and/or knee OA	Tramadol CR 200mg vs. diclofenac SR 75mg. Doses titrated (up to 400mg a day vs. up to 150mg).	Significant improvement both groups for physical functioning: CR tramadol mean change of 257.0±354.4, p = 0.0005, SR diclofenac mean change 247.4±379.5, p = 0.0001, and stiffness: CR tramadol mean change of 34.3±61.4 p = 0.0005, SR diclofenac mean change 36.8±57.4, p = 0.0001. Adverse events or withdrawals related to study drug similar for both treatments (tramadol 16.1%/27.4% vs. diclofenac 15.2%/21.2%) (NS).	“CR tramadol, a once-daily formulation marketed as Zytram XL, is as effective as SR diclofenac in the treatment of pain due to knee or hip OA.”	Baseline comparability not presented. Study results suggest equal efficacy.
Pavelka 1998 Crossover Trial	7.0	N = 60 with hip or knee OA without clinical joint inflammation	Tramadol 50-100mg up to TID vs. diclofenac 25-50mg up to TID for 4 weeks. Doses titrated.	Mean tramadol dose 164.8 ±54.1mg, mean diclofenac dose 86.9±21.4mg; 3 in each group terminated (reasons not noted). Adverse events greater during tramadol treatment (20.0% vs. 3.3%, p = 0.0056). No patient preference (46.7% tramadol vs. 45.0% diclofenac, p = 0.85). Functionality scores improved in tramadol group: 39.6±16.0 to 32.0±17.4 vs. diclofenac 40.0±17.2 to 30.1±17.0; no significant difference between groups.	“OA patients’ response to analgesic treatment was highly individual and the response to one drug was not predictive of that to another drug. As functional scores improved (lower WOMAC scores) on analgesic vs. NSAID, pain rather than inflammation may be the most important aspect of treatment. A significant proportion of patients were not treated satisfactorily with diclofenac or tramadol alone.”	The results suggest and support other studies (Bradley 1991) that OA pain is not necessarily caused by inflammation, as both paracetamol and in this study tramadol had similar analgesic efficacy with improvement in functional scores to that of NSAIDs.
Parr 1989 RCT	6.5	N = 846 mostly hip or knee OA	Diclofenac sodium slow release 100mg QD vs. dextropropoxyphene 180mg plus paracetamol 1.95gm QD.	Dizziness, lightheadedness less common from diclofenac (14 vs. 30, p <0.05), as was CNS symptoms (48 vs. 93, p <0.01). Abdominal pain higher with diclofenac (40 vs. 18, p <0.01) and diarrhea (14 vs. 2, p <0.01). Overall GI effects not different (63 vs. 60). Pain ratings (change in VAS): diclofenac -27.0 vs. dextropropoxyphene plus paracetamol -22.7, p <0.05. Physical mobility scores: -10.8 vs. -7.4 (p <0.01). Interference of work less common with	“Pain as measured by a visual analogue scale (VAS) showed 8% greater pain reduction with DSR as compared with D&P (P<0.05). Physical mobility as measured by the (Nottingham Health Profile) improved by 13% more with DSR as compared with D&P (P<0.05).”	Study suggests greater efficacy of diclofenac vs. dextropropoxyphene plus acetaminophen. Benefits suggested for working populations from diclofenac including lower incidence of problems at work and lost work time.

				diclofenac (3 vs. 11, p <0.05), and lost work time (3 vs. 16, p <0.05).		
Quiding 1992 Crossover Trial	6.0	N = 26 with hip OA	Ibuprofen 200mg plus codeine 30mg vs. ibuprofen 200mg plus placebo. Used single and repeated dosings; 6 doses in 24-hour period each regimen.	Pain intensity ratings after 1st dose (baseline/1-8 hours later): IBU plus codeine (34/25) vs. IBU (37/27) vs. placebo (31/26). Pain intensity ratings after 6th dose: IBU plus codeine (11/10) vs. IBU (19/17) vs. placebo (33/29) (p <0.05 comparisons with placebo or ibuprofen).	"[A]nalgesic efficacy was better differentiated after repeated-doses than after single-dose administration...study design was able to differentiate between 200mg ibuprofen plus 30 mg codeine and 200 mg ibuprofen alone in a relatively small number of patients."	Study purpose is for analgesic effects prior to surgery. Very short-term treatment intervals of 3 days preclude assessments of long-term safety and efficacy.
Kjaersgaard-Andersen 1990 RCT	6.0	N = 158 with hip OA	Codeine plus paracetamol (60mg/1g TID) vs. paracetamol (1g TID).	First week, more use of rescue medication in paracetamol (21% vs. 5%). Difference disappeared 2nd week (20% vs. 21%). Significantly more adverse reactions with codeine (1st week: nausea 34 vs. 6; dizziness 26 vs. 1; somnolence 14 vs. 5; fatigue 10 vs. 1). Most codeine patients had an adverse reaction 1st week (86.7% vs. 37.8% placebo); 6 (13.9%) vs. 4 (6.7%) patients reported very good or excellent results.	"When evaluated after 7 days of treatment, the daily addition of codeine 180 mg to paracetamol 3 g significantly reduced the intensity of chronic pain due to osteoarthritis of the hip joint. However, several adverse drug reactions, mainly of the gastrointestinal tract, and the larger number of patients withdrawing from treatment means that the addition of such doses of codeine cannot be recommended for longer-term treatment of chronic pain in elderly patients."	Study prematurely terminated due to high rates of adverse reactions and dropouts. Overall drop-out rate was 51.8% vs. 23.0%.
NSAIDs vs. Other NSAIDs and/or Trials with Multiple Treatment Arms						
Zacher 2003 RCT	11.0	N = 516 with knee or hip OA	Etoricoxib 60mg QD vs. diclofenac 50mg TID for 6 weeks.	WOMAC pain subscale changes over 6 weeks: etoricoxib -31.3 (-33.6, -29.0) vs. diclofenac -30.9 (-33.2, -28.6) (NS). Other WOMAC scales NS. Percent patients good or excellent 65.6% vs. 66.5% (NS). Etoricoxib demonstrated greater benefit (good/excellent responses) first 4 hours after 1st dose (p = 0.007). GI adverse effects in E 12.9% vs. D 14.2%.	"Etoricoxib is clinically effective in the therapy of osteoarthritis providing an effect similar to the maximum dose of diclofenac."	Equivalency demonstrated with no significant difference in adverse effects.
Puopolo 2007 RCT	10.0	N = 548 with hip or knee OA	Etoricoxib 30mg QD vs. Ibuprofen 800mg TID vs. placebo for 12 weeks.	WOMAC pain scores (baseline/12 weeks): etoricoxib 66.46/-28.14 vs. ibuprofen 64.74/-24.10 vs. placebo 64.66/-16.47. Both active treatments	"Treatment with etoricoxib 30 mg q.d. for the treatment of OA is well tolerated and provides therapeutic effectiveness that is superior to placebo and	High dropout rate in this 2-week study for adverse effects. Results suggest comparable efficacy.

			Double dummy.	superior to placebo for multiple endpoints. Etoricoxib superior to ibuprofen at some time intervals after randomization. Post-hoc analysis for minimally clinically important improvement among 80.0% etoricoxib vs. 70.1% ibuprofen vs. 55.1% placebo.	comparable to ibuprofen 2400 mg (800 mg t.i.d)."	
Saag 2000 RCT (2 trials)	9.5	N = 736 with knee or hip OA	Two trials: 1) Rofecoxib 12.5 QD vs. 25mg QD vs. ibuprofen 800 TID vs. placebo for 6 weeks; 2) rofecoxib 12.5mg QD vs. 25mg QD vs. diclofenac 50mg TID for 1 year.	Study 1: rofecoxib superior to placebo (p <0.001) and comparable with ibuprofen for WOMAC pain, physical function, and stiffness subscales. Adverse effects placebo 5.8% vs. rofecoxib 12.5mg (5.5%), 25mg (6.6%), ibuprofen (4.1%). Discontinuation higher in placebo (27.5%, p <0.05). Rofecoxib 25mg produced marked improvement and comparable efficacy with diclofenac on WOMAC physical function, stiffness, pain subscales over 1-year treatment period. Rofecoxib 12.5mg was significantly different from diclofenac. Greater adverse effects diclofenac (17.8%) vs. rofecoxib (8.7%, 10.3%). Discontinuance rates not different.	"Rofecoxib is effective in treating OA with once-daily dosing for 6 weeks and 1 year. Rofecoxib was generally safe and well-tolerated in OA patients for 6 weeks and 1 year."	Rofecoxib comparable with ibuprofen 800mg. Diclofenac similar to rofecoxib at 1 year
Bellamy 1992 RCT	9.5	N = 85 with hip or knee OA	Flurbiprofen-SR 200mg vs. diclofenac sodium-SR 100mg QHS for 6 weeks.	Joint pain on active movement at final assessment: flurbiprofen SR -0.83 (SE 0.13) vs. diclofenac-SR -0.91 (SE 0.13), p = 0.64. Other outcomes (e.g., pain on passive motion, joint swelling) NS. More drug-related adverse reactions in diclofenac sodium-SR (n = 15) than flurbiprofen-SR (n = 9), NS.	"Flurbiprofen-SR 200 mg is similar in efficacy, tolerability and safety to Diclofenac Sodium-SR."	Dosages were low, considered to be frequent starting doses for general population. Data suggest comparable efficacy.
Hawel 2003 RCT	9.0	N = 148 with hip OA	Dexibuprofen 400mg BID vs. celecoxib 100mg BID for 15 days. Double dummy.	Improvements WOMAC OA indices: dexibuprofen -5.97±3.72 vs. celecoxib -5.82±2.84 (NS). Patient global judgment of efficacy (excellent/very good): dexibuprofen	"[D]exibuprofen has at least equal efficacy and a comparable safety/tolerability profile as celecoxib in adult patients suffering from osteoarthritis of the hip."	Data suggest equivalent efficacy.

				61.3% vs. celecoxib 50.0%. GI complaints: 8.1% vs. 9.5% (NS).		
Fleischmann 2008 RCT	9.0	N = 3,036 with hip, knee, or spine OA	Lumiracoxib 100mg QD vs. lumiracoxib 100mg BID vs. celecoxib 200mg QD. Double dummy.	Improvements in target joint pain did not differ (improvement in 50.6% vs. 52.3% vs. 53.6%). Global assessment of disease activity and physician assessments did not differ. Adverse events nearly identical (12.7% vs. 12.3% vs. 11.7%, NS). One-year retention rates not different (46.9% vs. 47.5% vs. 45.3%, NS).	“Long-term treatment with lumiracoxib 100 mg o.d., the recommended dose for OA, was as effective and well tolerated as celecoxib 200 mg o.d. in patients with OA.”	No significant differences in efficacy. Only 50% retention rate at 1-year for all treatment arms, with 70% of participants reporting adverse events.
Geba 2002 RCT	9.0	N = 382 with knee OA	Rofecoxib 12.5mg a day vs. rofecoxib 25mg a day vs. celecoxib 200mg a day vs. acetaminophen 1gm QID for 6 weeks.	Changes in night pain first 6 days: acetaminophen (-18.8) vs. celecoxib (-18.7) vs. rofecoxib 12.5mg (-22.0) vs. rofecoxib 25mg (-25.2), p <0.05 comparing rofecoxib 25mg to acetaminophen or celecoxib. Rest pain results: -12.5, -15.5, -18.6, -21.8. Walking pain after 6 weeks: -30.3, -36.2, -35.1, -42.0 (p <0.01 comparing rofecoxib 25mg to acetaminophen).	“Rofecoxib, 25 mg/d, provided efficacy advantages over acetaminophen, 4000 mg/d, celecoxib, 200 mg/d, and rofecoxib, 12.5 mg, for symptomatic knee OA.”	More discontinued acetaminophen than other treatments. Rofecoxib appeared superior to other treatment arms.
Day 2000 RCT	8.5	N = 809 with knee or hip OA	Rofecoxib 12.5mg QD vs. 25mg QD vs. ibuprofen 800mg TID for 6 weeks.	Rofecoxib 25mg superior to ibuprofen for 2 of 3 primary end points (graphic presentations, p <0.05). All active treatments superior to placebo (p <0.001). Significant discontinuation rate due to adverse effects from ibuprofen (p <0.05), but not rofecoxib.	“Rofecoxib was well tolerated and provided clinical efficacy comparable with a high dose of the NSAID ibuprofen.”	Data suggest superiority of rofecoxib vs. ibuprofen. Suggests rofecoxib better tolerated than ibuprofen.
Bellamy 1986, 1988 RCT	8.0	N = 57 with hip and/or knee OA	Isoxicam 200mg QD vs. piroxicam 20mg QD for 6 weeks.	Night pain (baseline/6 weeks): isoxicam (1.68± 0.72/0.63) vs. piroxicam (1.83±1.0/0.77). No differences in outcome measures between groups (p >0.05). Total adverse reactions: isoxicam 12/28 (42.9%) vs. piroxicam 24/29 (82.8%). Totals with	“[I]soxicam is an efficacious and well-tolerated once-daily NSAID for elderly patients with osteoarthritis.”	Comparable efficacy in elderly population, although trends favored isoxicam over piroxicam.

				severe adverse drug reaction higher in piroxicam (0 vs. 5, p = 0.03); 93% isoxicam vs. 69% piroxicam improved.		
Fioravanti 2002 RCT	8.0	N = 287 with moderate or severe hip and/or knee OA	Nimesulide-beta-cyclodextrin 400mg BID vs. naproxen 500mg BID for 2 weeks scheduled treatment and 5.5 months on-demand dosing.	VAS scores (baseline/2 weeks): NBC 67.9/39.7 vs. naproxen 66.9/39.8 (NS). Other outcomes (e.g., pain on movement, morning stiffness) not different between treatments; 37 discontinued nimesulide-beta-cyclodextrin vs. 38 naproxen; 19 nimesulide-beta-cyclodextrin group, 8 naproxen took other NSAIDs as additional treatment for OA.	"[N]imesulide-beta-cyclodextrin is comparable to naproxen in terms of therapeutic efficacy in the short-term treatment of OA. Medium-term treatment on demand was also similar with the 2 drugs."	Lack of compliance data, high dropout rate weaken conclusions. Data suggest comparable efficacy.
Le Loët 1997 RCT	8.0	N = 290 with knee or hip OA	Diclofenac SR 75mg BID vs. diclofenac 50mg TID for 7 days. Double dummy.	Mean spontaneous pain intensity decreased in both groups within 1st 36 hours and from Day 1 to 7 (p = 0.0001). 24.5% and 31.3% adverse effects (NS). Good compliance greater with diclofenac 75mg (81.6%) vs. 50mg (53.1%), (p <0.001).	"The results...show the equivalence of efficacy of diclofenac SR 75 mg one tablet 2x daily and diclofenac enteric coated 50 mg one tablet 3x daily given for 7 days for the symptomatic treatment of painful osteoarthritis."	Despite difference in "good compliance (>90%)," treatment groups had similar efficacy. Very short term trial of 7 days.
Bradley 1991 RCT	7.5	N = 184 with knee OA	Ibuprofen 600mg QID vs ibuprofen 300mg QID vs. acetaminophen 1gm QID for 4 weeks.	Walking pain score changes: acetaminophen (0.13) vs. ibuprofen 1200mg (0.31) vs. ibuprofen 2,400mg (0.45), p = 0.10. Rest pain scores: 0.06 vs. 0.33 vs. 0.40, p = 0.05.	"[S]ymptomatic treatment of osteoarthritis of the knee, the efficacy of acetaminophen was similar to that of ibuprofen, whether the latter was administered in an analgesic or an anti-inflammatory dose."	At baseline, trend toward more advanced disease in high-dose ibuprofen group. Walking pain score, rest pain both favored ibuprofen (some measures showed no difference).
Leung 2002 RCT	7.5	N = 501 with knee or hip OA	Etoricoxib 60mg QD vs. naproxen 500mg BID vs. placebo for 12 weeks. Double dummy.	WOMAC pain scale responses over 12 weeks: placebo -15.33 (95% CI -20.7, -9.96) vs. etoricoxib -25.76 (-28.58, -22.94) vs. naproxen -25.32 (-28.13, -22.50). Etoricoxib equivalent to naproxen, and both superior to placebo. Adverse effects higher for naproxen (n = 69, 31.2%) vs. etoricoxib (n = 57, 25.4%) vs. placebo (n = 14, 25.0%). More etoricoxib patients completed trial (91.1%)	"Etoricoxib showed rapid and durable treatment effects in patients with OA of the knee or hip."	No significant differences between naproxen and etoricoxib. Power may have been limited to detect adverse effect differences, but trends in favor of etoricoxib present.

				than naproxen (83.3%) and placebo (78.6%).		
Reginster 2007 RCT	7.5	N = 997 with hip or knee OA	Etoricoxib 60mg QD vs. naproxen 500mg BID vs. placebo, 12 weeks. Then placebo randomized to active treatment 40 weeks, 86-week follow-up.	Active treatments with comparable efficacy over 12-week trial; 52 week results for WOMAC pain scale: etoricoxib -31.03 vs. naproxen -30.60 (NS). Over 12 weeks, discontinuation due to adverse effects: placebo 17.0% vs. etoricoxib 21.5% vs. naproxen 29.2%.	“Both etoricoxib and naproxen demonstrated long-term clinical efficacy for the treatment of OA. Etoricoxib and naproxen were generally well tolerated.”	Low power to detect differences in adverse effects between active treatment groups. Both drugs had comparable efficacy over placebo. Data suggest higher adverse effects for naproxen.
Kidd 1996 RCT	7.5	N = 135 with hip or knee OA	Lornoxicam 4mg TID vs 8mg BID vs diclofenac 50mg TID for 12 weeks with 40 week continuation phase. Double dummy.	37% failed to complete RCT phase. 28/85 (32.9%) failed to complete continuation phase due to inefficacy. Functional indices of severity (baseline/difference): lornoxicam 4mg TID (11.1±4.4/-2.4±4.2) vs. lornoxicam 8mg BID (10.6±2.2/-1.7±5.9) vs. diclofenac (10.1±1.8/-2.7 ±2.2) (p = 0.013 comparing lornoxicam doses, p <0.01 comparing either lornoxicam doses with diclofenac. Other measures of disease activity, pain relief not different.	“[L]ornoxicam is an effective treatment for OA when administered in a 3 times daily (4 mg) or twice daily (8 mg) regimen. Furthermore, it has an efficacy and tolerability profile comparable to that of the well established drug diclofenac.”	No placebo control. High dropout rate in both phases of study. No clear superiority of any arm.
Lisse 2003 RCT	7.0	N = 5,557 with knee, hip hand or spine OA	Rofecoxib 25mg a day vs. Naproxen 500mg twice daily for 3 months. Double dummy.	Discontinuation due to adverse GI events lower in rofecoxib group (5.9% vs. 8.1%), RR = 0.74 (95% CI 0.60-0.92, p = 0.005). Similar findings in low-dose ASA takers. Less GI medications in rofecoxib group (9.1% vs. 11.2%, p = 0.014); 2 perforations, ulcers, or bleeding episodes rofecoxib vs. 9 naproxen (RR = 0.22, p = 0.038).	“[R]ofecoxib, 25 mg once daily, was as efficacious as naproxen, 500 mg twice daily, in controlling symptoms over a 3-month period and was associated with significantly better GI tolerability.”	Very large sample size. No placebo. Participants allowed to take H-2 blockers. Results suggest equivalent efficacy for pain, but higher adverse GI symptoms and bleeds for naproxen vs. rofecoxib.
Wegman 2003 N of 1 trials	7.0	N = 13 with hip or knee OA	Each patient received 5 treatment pairs with 2 weeks NSAID (ibuprofen 400mg TID, diclofenac 50mg BID, diclofenac 25mg TID, naproxen	Largely no difference in preference of either paracetamol or NSAIDs found.	“The results of n 1 trials varied across patients. n of 1 trials can be used to investigate which treatment is best for any specific person, thus avoiding unnecessary prolonged treatment with NSAIDs. However, practical reasons may cause patients to switch from	Small sample size. Many did not complete the trial (6/13). Submaximal NSAID doses preclude conclusions on relative merit of paracetamol vs. NSAID.

			375mg BID) and 2 weeks paracetamol 1gm TID.		NSAIDs to paracetamol or not.”	
Smugar 2006 2 RCTs	7.0	N = 2,603 with knee or hip OA	1) Rofecoxib 12.5mg vs. rofecoxib 25mg vs. celecoxib 200mg vs. placebo QD for 6 weeks; 2) same medications except no rofecoxib 12.5mg arm	Rofecoxib 25mg provided faster relief than celecoxib 200mg in both studies (Study 1 median 3 vs. 5 days, p = 0.004; Study 2 median 4 vs. 5 days, p <0.001). Study 1, pain at night not significantly different between active treatments. Study 2, rofecoxib 25mg significantly reduced pain at night over 6 weeks compared to celecoxib (p <0.05, graphic data). Higher dropouts in placebo vs. other treatment arms in both studies (approximately 62% vs. 82-88% completions).	“Rofecoxib 25 mg was significantly better than celecoxib 200 mg in relieving night pain at 6 weeks in one study; this was not confirmed in the accompanying study.”	Results between two studies conflict somewhat with no clear superiority of one NSAID over another for pain relief during 6 week trial, although rofecoxib 25mg provided faster pain relief in both studies and trends in night pain also favored rofecoxib over celecoxib.
Perpignano 1994 RCT	7.0	N = 120 with knee and/or hip OA	Etodolac SR 600mg QD vs. tenoxicam 20mg QD for 8 weeks. Double dummy.	Significant improvements from baseline in all efficacy assessments at Weeks 2, 4, last visit each group. No differences between groups. VAS scores (ITT): etodolac 69.2±11.8 vs. tenoxicam 72.0±13.0 (NS). No difference in erosive GI lesions after 8 weeks. Adverse reactions in 14/60 (23.3%) patients treated with tenoxicam vs. 5/60 (8.3%) etodolac (p <0.05).	“[E]todolac SR 600 mg once daily is as effective as tenoxicam 20 mg once daily in relieving symptoms of OA of the knee and of the hip. Both the overall and the G-I specific safety profiles were found to be more favorable in patients treated with etodolac SR.”	Randomization, allocation details missing. Although author reports safety .3 for total adverse events, the study data do not reflect all conclusions. Data suggest equal efficacy.
Pincus 2004 Randomized Crossover Trial	6.5	N = 1,080 with knee or hip OA	Placebo vs. acetaminophen 1000mg QID vs. celecoxib 200mg QAM. 6 weeks each. Double dummy. Patients received 2 of 3 treatments.	Percent improvement in WOMAC scores averaged over treatment: celecoxib 21.6% vs. acetaminophen 13.0% vs. placebo 7.9%. Similar VAS score results. Patient preference strongest for celecoxib, then acetaminophen, then placebo.	“[D]ata indicate a gradient of efficacy from celecoxib to acetaminophen to placebo”	Some variation in results in the two trial periods for acetaminophen vs. placebos. Patients generally reported preference for celecoxib over others.
Lussier 1980 Crossover Trial	6.5	N = 27 with knee or hip OA	Floctafenine 300mg QID vs. enteric-coated aspirin (ACSA) 625mg QID vs. placebo for 6 weeks.	Pain score: placebo 1.93 vs. floctafenine 1.80 vs. ASA 2.00 (NS). Walking times did not differ at 6 weeks. Patient assessment of efficacy: placebo 2.78, floctafenine 2.00 and	“[F]loctafenine was more effective than placebo; (2) floctafenine was found to be approximately equivalent or superior to ACSA; and (3) although the results	No washout periods before or during trial crossovers. Adjuvant (rescue medication) was the same as control arm

				ASA 2.33 (p = 0.05 comparing placebo vs. floctafenine).	showing a statistical decrease in (hemoglobin) with floctafenine are not clinically significant.”	(aspirin), weakening conclusions.
Mylykangas-Luosujärvi 2002 RCT	6.5	N = 944 with knee or hip OA	Rofecoxib 12.5 QD vs. naproxen 500mg BID for 6 weeks.	Treatment outcomes for efficacy did not differ. Fewer rofecoxib patients reported AEs considered to be drug-related than naproxen [19.5% vs. 31.3%; p <0.001]. More GI-related AEs among naproxen treated patients.	“[I]n two separate six-week OA treatment trials, the lowest indicated dose of rofecoxib (12.5 mg) demonstrated comparable onset of action and clinical efficacy to naproxen 1000mg with superior GI tolerability profile.”	More than 50% of both groups took escape medication. Results suggest comparable efficacy, but higher adverse effects for naproxen.
Hosie 1996 RCT	6.5	N = 336 with hip or knee OA	Meloxicam 7.5mg QD vs. diclofenac sodium SR 100mg QD for 6 months.	VAS pain ratings (baseline/last visit): meloxicam (65.9±16.9/-28.1±29.4) vs. diclofenac (67.2±14.2/-30.9±29.1), NS. Other measures of pain on movement, global efficacy stiffness and quality of life all were not different. Adverse events in 59.8% of meloxicam vs. 60.5% diclofenac.	“Meloxicam 7.5 mg once daily and diclofenac 100 mg slow release once daily showed comparable efficacy in the treatment of OA, although diclofenac was associated with somewhat higher incidence of severe adverse events, treatment withdrawals and laboratory test abnormalities.”	Allocation unclear with at least 1 baseline variable difference (duration of osteoarthritis, p <0.05) that may favor meloxicam.
Bellamy 1995 RCT	6.0	N = 382 with hip, knee, or shoulder OA	Nabumetone 1,000mg vs. diclofenac SR 200mg QPM for 3 months. Dose could be titrated once after 2 weeks of initial dose. Double dummy.	More on nabumetone titrated to higher dose (69% vs. 53%, p = 0.002). Physician assessments of disease activity: 63% improved on nabumetone vs. 70% diclofenac. Pain ratings reduced 40% by either treatment. Adverse effects in 43 diclofenac vs. 27 nabumetone (p <0.04).	“Nabumetone is efficacious and well tolerated in patients with OA of the hip, knee or shoulder. In this group of patients it is similar in efficacy and superior in tolerability to diclofenac SR.”	Variable doses used. High dropout rate (43%) at 6 months precludes conclusions.
Herrman 2000 RCT	6.0	N = 263 with knee and/or hip OA	Oxaceprol 400mg TID vs. Diclofenac 50mg TID for 21 days.	Mean total scores (baseline/Day 21): oxaceprol 14.0±3.5/11.5±3.8 vs. 14.0±4.1/11.2±3.9 (NS). Lequesne indices decreased, but not different between treatments (-2.5 points oxaceprol vs. -2.8 points diclofenac, NS); 47% treated with oxaceprol and 56% treated with diclofenac judging efficacy. Adverse effects for 18.9% oxaceprol vs. 25.2% diclofenac.	“The results of this phase IV study demonstrate that oxaceprol is as effective as diclofenac in the therapy of osteoarthritis of the knee and/or hip, but is significantly better tolerated.”	Blinding unclear. Patients allowed physical therapy. Was phase II trial. Data suggest equal efficacy for total scores, but with lower adverse effects.
Ginsberg 1984	6.0	N = 26 with	Oxaprozin 1,200mg QD vs. naproxen	Patient opinion of efficacy (baseline/8 weeks): oxaprozin	“1200 mg oxaprozin once daily is an effective and relatively	Small sample size and comparison is sub-maximal

RCT		knee or hip OA	250mg TID for 8 weeks. Double dummy.	(4.3/-1.9) vs. naproxen (4.4/-2.5). Observer opinion, pain intensity, activity impairments all improved, but favored naproxen, not statistically significant.	well-tolerated form of treatment in osteoarthritis and is at least comparable to 250mg naproxen 3-times daily..."	naproxen, limiting conclusions.
Schnitzer 2004 RCT	6.0	N = 583 with knee or hip OA	Lumiracoxib 50mg vs. 100mg vs. 200mg BID vs. 400mg QD vs. diclofenac 75mg BID vs. placebo for 4 weeks.	Patient assessments (baseline/4 weeks): lumiracoxib 50 BID (63.1±17.5/38.8±21.5) vs. L 100BID (62.0±18.5/ 37.8±22.2) vs. L200BID (64.0±17.3/ 37.5±24.0) vs. diclofenac (62.2±16.2/ 34.4±23.0) vs. placebo (62.5±18.1/50.0±23.0). Lumiracoxib, diclofenac superior to placebo.	"Throughout the study, all dosages of lumiracoxib were equally effective in lowering pain intensity, although at week 1 there was a modestly greater improvement in pain relief with the 400 mg once daily lumiracoxib dose when compared with the 50 and 100 mg twice daily doses."	Sparse details on randomization, allocation, and blinding. Efficacy comparable between lumiracoxib and diclofenac, however adverse effects higher with diclofenac.
Morgan 2001 RCT	6.0	N = 335 with moderate to severe knee or hip OA	Nabumetone 1,000-2,000mg QD vs. diclofenac 50mg BID-TID for 12 weeks. Doses titrated.	Patient global assessments not different (nabumetone 75% vs. diclofenac 79%). Pain score changes: nabumetone - 3.1±0.2 vs. diclofenac - 3.7±0.2. No difference Arthritis Impact Measurement Scales. More diclofenac patients on maximum dose (46% vs. 66%). Nabumetone more acetaminophen 2nd week (p <0.05). More diclofenac than nabumetone patients (p <0.05) had ALT level 2 times or more than upper limit of normal (6 or 161 [3.7%] vs. 0 of 155 [0%]).	"Nabumetone was as effective as diclofenac in the treatment of elderly patients with moderate-to-severe osteoarthritis. However, the gastrointestinal safety profile of nabumetone was superior to that of diclofenac with respect to elevation of liver enzymes."	Blinding, randomization, compliance and co-intervention details missing.
Cannon 2000 RCT	6.0	N = 784 with hip or knee OA	Rofecoxib 12.5 QD vs. 25mg QD vs. diclofenac 50mg TID for 1 year.	448/784 (57.1%) completed 1 year. No differences in discontinuation due to lack of efficacy or adverse effects. Mean response for primary end point of patient assessment of response to therapy similar among all treatment groups. Patient assessment comparing rofecoxib 25mg vs. diclofenac favored diclofenac (0.19, 95% CI 0.05-0.33). Rofecoxib 12.5mg also significant. Physician assessment of disease activity also	"In this 1-year study that included patients with cardiovascular risk factors (hypertension in 45%, angina in 3%, hypercholesterolemia in 16%, and diabetes in 7%), the incidence of thromboembolic cardiovascular events, such as myocardial infarction, stroke, transient ischemic attack, and peripheral arterial occlusions, was numerically lower in the rofecoxib groups (1.5%, 2.3%, and 3.4% in the 12.5 mg rofecoxib, 25-mg rofecoxib, and diclofenac groups). The	Lack of details for compliance, blinding co-interventions. High dropout rate 42% at one year may reduce differences. Most data suggest comparable efficacy, however some data suggest diclofenac superior.

				<p>favored diclofenac for both rofecoxib doses ($p < 0.05$). Only pain when walking WOMAC outcome did not demonstrate statistical superiority of diclofenac.</p>	<p>specific inhibition of COX-2 with rofecoxib at a dosage of 12.5 mg and 25 mg once daily provided comparable clinical efficacy to that of the knee and hip. Rofecoxib was generally well tolerated.”</p>	
Alho 1988 RCT	6.0	N = 252 with severe hip OA	Piroxicam 20mg QAM vs. naproxen 500mg QAM and 250mg. QPM. Trial length unclear (possibly 1 month), but observed for 5 months.	<p>Pain at rest at 4-5 weeks compared with baseline: piroxicam -1.5 ± 1.7 vs. naproxen -0.9 ± 0.6 ($p = 0.056$). Pain on movement/ impairment of daily activities improved, but not different between groups. Night pain piroxicam -2.0 ± 2.1 vs. naproxen -1.3 ± 2.1 ($p = 0.01$). Modified Harris hip score improved from baseline more for piroxicam than naproxen ($p < 0.01$). No differences between groups at later follow-up visits.</p>	<p>“[I]t is profitable to continue a previous NSAID medication or re-establish such therapy while the patient waits for a planned operation for OA. The NSAIDs seem to be effective even in advanced OA where the mechanical joint incongruity component may be dominating. However, only 7% of the patients wanted to postpone the planned operation after regular medication.”</p>	<p>Lack of study details-allocation, blinding. Data support equal efficacy, with a few data suggesting piroxicam superior to naproxen at 4 to 5 weeks.</p>
Baumgartner 1996 RCT	6.0	N = 61 with knee or hip OA	Two SR tablets of ibuprofen 1600mg vs, diclofenac 100mg SR QPM for 21 days.	<p>Investigator’s opinion of much improved patients at Day 21: ibuprofen 37% vs. diclofenac 10%, $p = 0.04$. Patient severity of day pain was ibuprofen 1.2 vs. diclofenac 1.8, $p = 0.006$. Night pain ($p = 0.048$), quality of sleep ($p = 0.03$), ability to carry out normal activities ($p = 0.01$) all favored ibuprofen. No difference in adverse event reporting rates.</p>	<p>“[S]ignificant differences in favour of once-daily-sr ibuprofen (1600 mg) were demonstrated in terms of efficacy, indicating a potential therapeutic advantage for this formulation. Ibuprofen was also better tolerated than diclofenac sodium (100 mg/daily), the latter being associated with gastrointestinal side effects in a significant proportion of patients. Sustained-release ibuprofen thus represents an important addition to the available therapeutic armamentarium of once-daily NSAID formulation.”</p>	<p>Lack of patient blinding. Data may suggest sustained relief ibuprofen superior to diclofenac, however the lack of blinding weakens conclusions although differences also included blinded investigator’s assessments of change.</p>
Shiple 1983 Crossover Trial	6.0	N = 36 with knee or hip OA	Rhus Tox vs. placebo vs. fenoprofen 600mg TID	<p>VAS scores (baseline/ placebo/Rhus/fenoprofen): $53.4 \pm 25.1 / 61.0 \pm 27.6 / 58.2 \pm 25.5 / 41.5 \pm 29.0$. Patients preferred fenoprofen. More adverse effects for fenoprofen.</p>	<p>“There was no significant difference between the effects of Rhus tox. and placebo. Fenoprofen produced highly significant pain relief compared with Rhus tox and placebo.”</p>	<p>Rhus tox, 6X is poison ivy extract and appears not efficacious. NSAID efficacious vs. placebo or Rhus.</p>
Brown 1986	6.0	N = 143 with hip	Flurbiprofen 50mg BID vs. sulindac	<p>At 6 weeks, (knee/hip) 70.2%/82.6% flurbiprofen vs.</p>	<p>“Despite its half-life of 5.5 hours, flurbiprofen twice daily is as</p>	<p>Comparable efficacy although flurbiprofen</p>

RCT		and/ or knee OA	150mg BID for 42 days.	76.7%/66.7% sulindac improved. Weight-bearing pain not different. Pain with active movement: 72.3%/91.3% flurbiprofen vs. 76.7%/56.5%. Flurbiprofen superior to sulindac for hip OA regarding pain with movement (p = 0.002).	effective as twice-daily sulindac, which has a much longer half -life of 7.8 hours, for patients with osteoarthritis.”	superior for hip pain with active movement.
Cardoe 1986 RCT	6.0	N = 230 with hip and/or knee OA	Isoxicam 200mg QD vs. Naproxen 500mg BID for 4 weeks. Double dummy.	No apparent differences in most treatment outcomes including pain ratings. Isoxicam superior for night pain at 4 weeks (52% better vs. 36%, p <0.05). Comparable adverse effect profile (details sparse).	“[I]soxicam produced comparable benefits to naproxen and for some parameters was superior.”	Study details are sparse. Second trial reported on rheumatoid arthritis (n = 249) with isoxicam more effective as rated by patients (p = 0.04).
Gordin 1984 Crossover Trial	6.0	N = 44 with hip or knee OA	Slow-release formulation of indomethacin (50mg) vs. diflunisal (250mg); 2 tablets daily for 6 weeks.	Both treatments reduced pain, 22 preferred slow-release indomethacin; 7 diflunisal; 13 no preference. Patient overall evaluation of efficacy was indomethacin slightly more effective than diflunisal (p <0.01). Total use of rescue analgesics: 540 tablets in indomethacin vs.711 with diflunisal.	“The indomethacin formulation alleviated pain slightly better than diflunisal in patients with arthrosis, and the patients preferred indomethacin to diflunisal in this respect. The tolerability of the drug was about the same.”	Suggests indomethacin slightly superior to diflunisal.
Bauer 1999 RCT	5.5	N = 150 with knee or hip OA	Oxaceprol 200mg TID vs. diclofenac 25mg TID for 20 days.	Pain at rest reduced: oxaceprol from 4.1 to 2.1 pts vs. diclofenac 4.3 to 2.5 pts (NS). Therapeutic equivalence also for changes in Lequesne index, weight-bearing pain, and pain-free walking time.	“[W]ith comparable therapeutic efficacy and a favorable spectrum of ADR, oxaceprol is a good alternative to standard NSAIDs, such as diclofenac, in the treatment of osteoarthritis.”	Although author reports better tolerance, no significant differences were reported. Treatments appear comparable.
Ginsberg 1982 Crossover Trial	5.5	N = 25 with hip or knee OA	Nabumetone 1gm QHS vs. naproxen 250mg BID for 7 days each.	Both treatments efficacious. Nabumetone better tolerated. Among nabumetone, 1st group, 7/13 considerably better vs. 10/13 naproxen. For naproxen 1st group, rates 5/12 vs. 5/12.	“Nabumetone (1g at night) appeared, thus, to be a good and very well tolerated anti-inflammatory drug in the treatment of osteoarthritis.”	Submaximal naproxen dose used. Small sample size, groups tended to select their last treatment as best (p = 0.02), possibly a recall bias.
Adelowo 1998 RCT	5.5	N = 48 with knee or hip OA	Tenoxicam 20mg QD vs. piroxicam 20mg QD vs. placebo for 6 weeks.	Slight superiority of tenoxicam vs. piroxicam for pain. No difference in GI adverse effects. Excellent or good tolerability tenoxicam 88.2% vs. 60.0%, p =	“Tenoxicam is an efficacious and well tolerated NSAID which proved useful among Nigerian osteoarthritis patients.”	Study in Nigeria. Generally comparable efficacy, although trends tenoxicam may be superior but underpowered

				0.06. All other measures of success/tolerability did not differ. Piroxicam and tenoxicam did not alter laboratory measures.		for those outcomes.
Kivitz 2001 RCT	5.5	N = 1,061 with hip OA	Celecoxib 100mg vs. 200mg vs. 400mg QD vs. naproxen 500mg BID vs. placebo for 12 weeks.	Patient global assessments 12 weeks: placebo (-0.5) vs. celecoxib 100mg (-0.9) vs. 200mg (-1.1) vs. 400mg (-0.9) vs. naproxen (-1.1) (naproxen superior to 100 and 400mg doses, p <0.05). All medications favored over placebo. Patients withdrew at significantly higher rate in celecoxib 100mg a day vs. 400mg a day (p = 0.04) or naproxen (p = 0.02).	“Celecoxib doses of 200 and 400 mg/day were similarly efficacious and comparable to naproxen. The overall incidence of adverse events in patients receiving celecoxib 100-400 mg/day or naproxen 1000mg/day was comparable, and similar to those receiving placebo.”	Dropout rate due to failure high in placebo and treatment groups (52% vs treatment [25-35%]). Total number of adverse events similar in all groups. Comparable efficacy shown for active treatments.
Telhag 1981 RCT	5.5	N = 70 with knee or hip OA	Tolmetin sodium 400mg BID vs. naproxen 250mg BID for 12 weeks.	Patient overall assessment to responses (very good or good): tolmetin (15/34 = 44.1%) vs. naproxen (18/35/51.4%), NS. No differences in physician assessment, pain on active motion, pain at rest, localized tenderness. For patients evaluated at 12 weeks who had “pain symptomatology” initially, more tolmetin had reductions in severity of pain at rest and pain on active motion (p <0.05).	“Tolmetin sodium given twice a day seems to be at least as effective as naproxen in relieving pain in osteoarthritis; tolerability for the two drugs was comparable.”	Submaximal naproxen dose used. Overall responses were comparable over 12 weeks.
Yocum 2000 RCT	5.5	N = 774 with hip or knee OA flare	Meloxicam 3.75 vs. 7.5 vs. 15mg a day vs. diclofenac 50mg BID vs. placebo for 12 weeks. Double dummy.	Discontinuation rates due to lack of efficacy at day 84 were 41% placebo vs. meloxicam 31/18/17% vs. diclofenac 12%. Rates of discontinuation Day 84 due to adverse events: 7/10/8/10/9%. Composite adverse events comparable among 3 meloxicam groups and higher than placebo group (66.0%). No differences GI adverse events between placebo and meloxicam groups. GI adverse events higher in diclofenac than placebo. Other adverse	“For both patient’s and investigator’s final global assessment of efficacy, the 15-mg/d dosages of meloxicam and diclofenac were statistically significantly superior to placebo for all comparisons.”	12 week trial with similar efficacy results for meloxicam 15mg/d vs. diclofenac 50mg BID. GI effects on diclofenac were higher for diarrhea and N/V, but overall pain improvement trended in favor of diclofenac.

				effects, e.g., headache, not different between any groups.		
Corts Giner 1991 RCT	5.0	N = 85 with knee or hip OA	Droxicam 20mg QHS vs. diclofenac 50mg TID for 6 weeks.	Weeks 1, 3, 6, 49 knee OA patients taking droxicam had improvements for severity of knee disease (p <0.0001), pain intensity (p <0.0001), duration of morning stiffness (p <0.0001), range of maximal forced flexion (p <0.0001), and extension (p <0.05). Diclofenac also had statistically significant results. More rescue paracetamol in diclofenac than droxicam at 3 (p = 0.0119) and 6 weeks (p = 0.0142). After 1, 3, 6 weeks, 31 with hip OA treated by droxicam or diclofenac improved for hip disease (p <0.01) and pain intensity (p <0.0001). No differences between treatments. Fewer GI symptoms in droxicam group at 6 weeks.	“Both oral droxicam and diclofenac are of benefit in reducing pain and improving joint motion and function in patients with osteoarthritis of the hip and knee.	Methodology details and some results sparse, especially for hip OA. Very high dropout (55.3%) precludes conclusions.
Bingham 2007 2 Identical RCTs	5.0	N = 1,207 (Study 1: N = 599; Study 2: N = 608) prior NSAID or acetaminophen users	Etoricoxib 30mg QD vs. celecoxib 200mg QD vs placebo for 12 weeks.	WOMAC pain scores (baseline/12 weeks): etoricoxib 67.4±16.2/39.6±22.9 vs. celecoxib 67.5±16.3/42.8±22.9 vs. placebo 66.6±16.2/54.2 ±24.6 (p >0.05 comparing active treatments; p <0.001 compared with placebo). Safety and tolerability of etoricoxib and celecoxib appeared similar.	“Etoricoxib 30mg qd was at least as effective as celecoxib 200mg qd and had similar safety in the treatment of knee and hip OA; both were superior to placebo.”	No significant differences in efficacy or side effects prolife of etoricoxib compared to celecoxib. 20% dropout at 12 weeks in both groups.
Kiff 1994 RCT	5.0	N = 1,023 with RA or OA	Diclofenac 50mg misoprostol 200µg vs. diclofenac 50mg vs. ibuprofen 600mg. All BID or TID at physician discretion for 4 months.	Total good/very good patient ratings: 51, 50, 45% (graphic interpretations). Physician ratings of good/very good: 51, 49, 46% (graphic interpretations). Adverse effects in 336 (66.3%), 159 (60.5%) and 152 (60.1%). Dyspepsia in 11.0%, 6.5%, 6.3% respectively.	“Arthrotec...was as effective as diclofenac sodium 50 mg alone and more effective than ibuprofen 600 mg for the treatment of arthritis.”	Some details sparse. High dropout rates. Submaximal ibuprofen dose and variable dosing frequency in all 3 arms precludes conclusion regarding more efficacious treatment.
Clarke 1975	5.0	N = 50 with knee	Naproxen 250mg BID vs	Night pain changes: naproxen -0.53±1.01 vs. indometacin -	“In almost all parameters there was significant improvement	No washout period prior to trial start. Comparable

Crossover Trial		and/or hip OA	indometacin [sic] 25mg QID for 4 weeks for each drug. Double dummy.	0.48±0.85 (NS). Other measures of rest pain, pain on moving after rest, prolonged standing, walking not different between treatments. Sub-analyses suggest knee pain more difficult to treat. Objective assessments of stair climbing and walking times improved for knee and hip patients on both treatments, but not different between treatments. Indometacin adverse effects 128 vs. naproxen 85, p <0.01.	from baseline on both drugs, the magnitude of improvement being statistically equivalent. Side-effects recorded during the naproxen treatment period were significantly fewer than during indometacin treatment.”	efficacy suggested. Quality evidence indomethacin has higher adverse effect profile.
Singer 2000 RCT	5.0	N = 178 with hip OA	Dexibuprofen (400mg TID) vs. dexibuprofen (200mg TID) vs. ibuprofen (800mg TID) for 15 days.	Improvements in WOMAC pain: ibuprofen 800mg (5.50±3.28) vs. dexibuprofen 400mg (6.30±3.95). Dexibuprofen 400mg failed to show superiority to racemic ibuprofen, but borderline (p = 0.055). Dexibuprofen 200mg less effective than dexibuprofen 400mg (p = 0.023). Patient global efficacy (excellent and very good): Dex 200mg 56.7% vs. Dex 400mg 47.1% vs. IBU 40.6%.	“The active enantiomer dexibuprofen (S (+)-ibuprofen) proved to be an effective non-steroidal anti-inflammatory drug with a significant dose-response relationship in patients with painful osteoarthritis of the hip. Compared with racemic ibuprofen half of the daily dose of dexibuprofen shows at least equivalent efficacy.”	Blinding, allocation, and compliance details are sparse. Suggests dexibuprofen at ½ dose is equivalent to racemic ibuprofen. However, there is no clear clinical advantage reported.
Meurice 1983 RCT	5.0	N = 60 with knee or hip OA	Tiaprofenic acid 200mg TID vs indomethacin 33.3mg TID for 3 months.	Data mostly for knee. Both treatments efficacious at reducing pain scores, pain with movement, overall severity ratings (p <0.05). Tiaprofenic acid scores for pain at rest lower at multiple time points (graphic data, p <0.05). Mean time to achieve initial benefit 18.9 days tiaprofenic acid vs. 26.4 days indomethacin (p <0.05). Time to achieve maximum benefit similar (61.3 days for tiaprofenic acid vs. indomethacin 63.0 days).	“[T]his study has shown that tiaprofenic acid was better tolerated and at least as effective as indomethacin in the treatment over a 3-month period of elderly patients with osteoarthritis of the hips and knees.”	Outcome differences favoring tiaprofenic acid over indomethacin of clinical uncertainty as no differences in overall severity and efficacy ratings.
Kriegel 2001 RCT	5.0	N = 370 with hip or knee OA	Nimesulide 100mg BID vs. naproxen 250mg QAM and 500mg QPM.	Equivalence for knee and/or hip OA (data not given). WOMAC pain scores (baseline/12 months): nimesulide (234.1±86.9/172.7±116	“This study demonstrates nimesulide to be as effective as naproxen in the long-term treatment	Study details lacking. Differences in GI side effects did not reach statistical significance.

				.0) vs. naproxen (240.4±94.4/177.7±125.3); 152 (83.1%) on nimesulide and 160 (85.6%) on naproxen reported adverse events. Gastrointestinal adverse events reported with nimesulide (n = 77, 47.5%) vs. naproxen (n = 6, 54.5%), NS.	of patients with OA of the knee and hip.”	Results suggest comparable efficacy.
Keet 1979 RCT	5.0	N = 35 with hip and/ or knee OA	Diflunisal 250mg BID vs. ibuprofen 400mg TID for 8 weeks. Double dummy.	No symptoms or improvement at Week 8 in 16/17 (94.1%) diflunisal vs. 14/17 (82.4%) ibuprofen. All improved from baseline (p <0.01) in multiple pain measures at Weeks 2, 4, and 8. Except for significant decrease (p <0.01) in hemoglobin in ibuprofen group, no lab abnormalities.	“No significant differences between diflunisal and ibuprofen in the treatment of osteoarthritis of the hip and/or knee.”	Allocation and baseline variables unclear. No differences in efficacy or safety profile. OTC ibuprofen dosage used.
Valtonen 1979 Crossover Trial	5.0	N = 53 with hip or knee OA	Fenbufen 200mg TID vs. aspirin 1.2g TID for 8 weeks.	Pain at rest difference from baseline at Week 4 fenbufen 0.46 vs. aspirin 0.48. Week 8, differences aspirin 0.50 vs. fenbufen 0.39. Fenbufen preferred; 42.5% vs. 57.5% aspirin. Improvement better for knee than hip OA. No statistically significant differences between drugs. Adverse effects: 57% vs. 40% (significance not reported).	“It seems evident that the efficacy of 600 mg Fenbufen daily in the relief of symptoms and improvement in treating of osteoarthritis of the knee or hip joints is equivalent to that of 3.6 g Aspirin daily. In addition to that Fenbufen was associated with fewer side effects during the trial period.”	Allocation unclear. Blinding unclear. No significant differences exist based on information provided.
Kogstad 1981 Crossover Trial	4.5	N = 164 with hip or knee OA	Piroxicam 20mg QAM vs. naproxen vs. placebo 250mg BID for 4 weeks each.	Pain on movement: placebo 4.9, piroxicam 3.3, placebo 4.4, naproxen 3.5. Night pain, ability to walk similar findings. Reverse sequence with comparable findings. No differences in adverse effects.	“[P]atients’ and investigators’ preference for any of the three treatments, based on efficacy and toleration, significantly favoured piroxicam.”	Sparse details. Washout at pre-study and crossover unclear. Overall assessment suggests comparable efficacy, although submaximal naproxen dose used.
Liyanage 1977-1978 Two Randomized Crossover Trials	4.5	N = 24 N = 40 with hip and knee OA	Tolmetin 400mg TID vs. 200mg TID for 2 weeks. Tolmetin 400mg TID vs. ketoprofen 50mg TID	Comparing doses of tolmetin, physician assessments: 13 better after 600mg vs. 12 better after 1,200mg. Other data comparable. Differences between active medication and placebo (1 week washout phase with a	“[N]o significant differences in any of the clinical parameters could be found between the 600 mg and 1200 mg tolmetin daily dose. This may have been due to the small numbers involved in this study. However, it was	Short trial periods, small sample size, sparse study details. Suggests no difference between 1200mg and 600mg a day tolmetin. Suggests tolmetin and

			daily for 2 weeks. Double dummy.	placebo) favored active treatment with either tolmetin or ketoprofen. Blood urea nitrogen levels increased on tolmetin and ketoprofen ($p < 0.05$).	also considered that the methods used for monitoring the efficacy of treatment of osteoarthritis were probably not sufficiently sensitive to validate subjective changes. The results of the comparative study revealed that both tolmetin and ketoprofen are effective analgesics.”	ketoprofen equally effective.
Lund 1987 RCT Same trial as Jensen 1986	4.5	N = 108 with hip or knee OA	Tenoxicam 20mg QD vs. piroxicam 20mg QD for up to 24 months in this report.	Pain scores did not differ (graphic data). Excellent and good ratings were tenoxicam 81% vs. piroxicam 75% (NS). No differences in adverse effects.	“Both tenoxicam and piroxicam are effective in long-term treatment of osteoarthritis. No statistically significant differences between the efficacy and the tolerance of the drugs were seen. The fact that practically no withdrawals due to side-effects were seen after 12 months shows that the drugs once tolerated remain so despite long-term treatment.”	Interim report (2 years) in an ongoing study. Suggests equivalent efficacy.
Chikanza 1994 Crossover Trial	4.5	N = 56 with knee and/or hip OA	Etodolac 300mg BID vs. naproxen 500mg BID for 4 weeks each.	Patients favored naproxen (n = 18) more often than etodolac (n = 7); most favored neither (n = 47) for pain intensity. No differences in preferences for night pain or overall. Morning stiffness borderline favored naproxen (25 vs. 23). More withdrawals for adverse events in etodolac (n = 7) vs. naproxen (n = 2).	“[N]aproxen and etodolac were equally effective in the management of pain and stiffness in osteoarthritis. However, a significantly higher proportion of patients preferred naproxen to etodolac for the relief of pain intensity. The incidence of adverse events caused by either drug was the same.”	Lack of study details and lack of control for co-treatments. Data suggest etodolac may be slightly inferior to naproxen.
Levenstein 1985 RCT	4.5	N = 309 mostly hip or knee OA	Isoxicam 200mg QD vs. indomethacin 25mg TID for 2 weeks. Double dummy.	Patient assessments (good/very good): isoxicam 113/155 (72.9%) vs. indomethacin 111/154 (72.1%). Patient tolerance (good/very good): isoxicam 134/155 (86.5%) vs. indomethacin 128/154 (83.1%) (NS). Significant improvements both groups after 7 days drug therapy.	“[I]ndomethacin treatment for up to 14 days reduced the pain and severity of the clinical symptoms of acute flare-up episodes of osteo-arthritis.”	Lack of allocation and baseline details. Short trial period. No statistical analysis presented for adverse effects. Suggests equal efficacy.
Mcllwain 1988 RCT	4.5	N = 38 athletes with acute MSDs	Piroxicam 40mg QD for 2 days then 20mg QD vs. naproxen	Measures of physical discomfort improved ($p < 0.001$) after 3 and 7 days both treatments. Mean reduction in	“Piroxicam and naproxen are effective and well-tolerated short-term treatments for acute	Heterogeneity in disorders treated (e.g., sprains of ankle, AC, hand IP, soft tissue

			500mg BID for 2 days then 375mg BID for 7 days.	spontaneous pain, swelling, tenderness statistically superior (p <0.05) in piroxicam. Overall patient impressions of efficacy (excellent): piroxicam 11/16 (68.8%) vs. naproxen 7/18 (38.9%). No difference between treatments for days lost due to injury. Piroxicam larger mean reductions from baseline for spontaneous pain (p = 0.047), swelling (p = 0.035), and tenderness (p = 0.017) at 1st return visit compared to naproxen.	musculoskeletal injuries in athletes."	injuries of shoulder, knee or hip). No placebo group. Data suggest piroxicam superior to naproxen.
The Manchester General Practitioner Group 1984 Crossover Trial	4.5	N = 226 with hip, knee, or spine OA	Naproxen 500mg BID vs. ibuprofen 400mg TID for 6 weeks total.	Both drugs reduced inactivity stiffness, pain, interference with daily activities, overall disease severity. At 3 weeks, naproxen superior to ibuprofen in relieving movement pain, night pain; 10 patients on naproxen, 5 on ibuprofen withdrew from trial because of side effects.	"Naproxen and ibuprofen were both effective treatments for this group of osteoarthritis seen in general practice. Naproxen was more effective than ibuprofen and was preferred by more patients, but was associated with a larger number of side-effects."	Use of submaximal dose ibuprofen compared with full dose naproxen precludes an ability to assess which is more efficacious.
Gordin 1985 Crossover Trial	4.0	N = 21 with hip or knee OA	Slow-release indomethacin (50mg) vs. naproxen (250mg), 2 tablets daily for 3 weeks	Most patients pain-free at end of both treatment periods, 2 almost no change; 9 preferred slow-release indomethacin tablets; 6 naproxen; 4 no preference (NS).	"Analysis of results from 19 patients showed that both drugs effectively alleviated pain, and there was no difference between indomethacin and naproxen in this respect."	Small sample size. Sparse data. Suggests comparable efficacy.
Björkenheim 1985 Crossover Trial	4.0	N = 75 with hip or knee OA	Naproxen 1000mg QD vs. Piroxicam 20mg QD for 4 weeks each.	Global assessment disease activities (asymptomatic plus mild): naproxen (51/ 66 = 77.3%) vs. piroxicam (63.6%), p = 0.04. Treatment differences favored naproxen (p <0.05) for weight-bearing pain, physician/patient global assessments of patient response to therapy. Both groups chose naproxen.	"[N]aproxen 100 mg once daily was more effective than piroxicam 20 mg once daily for the treatment of osteoarthritis."	Sparse study details. Data suggest naproxen superior to piroxicam.
Verbruggen 1982 Crossover Trial	4.0	N = 21 with hip, knee or spine OA	Nabumetone 1gm QHS vs. naproxen 250mg BID for 2 weeks each.	Patients improved both treatments. No patient preferences. Tolerance: 15 no preference, 6 preferred nabumetone, 0 preferred naproxen.	"Both drugs were considered to be equally effective and were both well tolerated... No evidence was found of changes in renal, hepatic or haematopoietic function with the two drugs tested."	Small sample size, scant statistical analysis provided.

Gastrointestinal Complications						
Agrawal 1999 RCT	9.5	N = 1,398 with hip or knee OA	Upper gastrointestin al (UGI) safety of Arthrotec 75 (diclofenac sodium 75mg misoprostol 200µg) BID vs. nabumetone 1500mg QD vs. placebo for 6 weeks.	Overall adverse events in 67% arthrotec vs. 61% nabumetone vs. 57% placebo. Final endoscopy showed lower combined incidence of gastric and duodenal ulcers Arthrotec 4% vs. nabumetone 11% (p <0.001). No significant differences in combined gastric and duodenal ulcers based on H pylori status among groups (p = 0.560).	“There appeared to be no consistent correlation between the presence or absence of H pylori infection and an increase or decrease in the overall incidence of ulcers associated with NSAID use.”	Naproxen arm discontinued due to high incidence of ulceration rate (37%). Data suggest diclofenac/misopro stol effective at reducing gastric ulcers compared with nabumetone and naproxen.
Bocanegra 1998 RCT	7.5	N = 572 with knee or hip OA	Diclofenac (D50/M200) 50mg plus misoprostol 200µg TID vs. diclofenac 75mg plus misoprostol 200µg BID (D75/M200) vs. diclofenac 75mg bid (D) vs. placebo for 6 weeks.	Patient global assessments Week 6: D (-1.46±1.21) vs. D50/M200 (-1.38± 1.03) vs. D75/M200 (-1.50 ± 1.12) vs. placebo (-0.85 ±1.27). Improvements on all active treatments (p <0.002); no differences among active treatments. Dyspepsia most common adverse event in all treatment groups. Endoscopic stomach and/or duodenal ulcers: diclofenac 17% vs. 8% D50/M200 vs. 7% D75/M200 vs. 4% placebo (p <0.04 between diclofenac and other active treatments). Overall withdrawals from adverse events not different.	“Diclofenac 50 mg/misoprostol 200 µg tid and diclofenac 75 mg misoprostol 200 µg bid are as efficacious as diclofenac 75 mg bid in the treatment of OA, but are associated with significantly lower incidence of gastric and/or duodenal ulcers.”	Lack of details on blinding, randomization. 6 week study with pre and post endoscopy demonstrated GI protective effect of misoprostol.
Lisse 2003 RCT	7.0	N = 5,557 with knee, hip, hand, or spine OA	Rofecoxib 25mg day vs. naproxen 500mg twice daily for 3 months. Double dummy.	Discontinuation due to adverse GI events lower in rofecoxib (5.9% vs. 8.1%), RR = 0.74 (95% CI 0.60-0.92, p = 0.005). Similar findings in low-dose ASA takers. Less GI medication use in rofecoxib group (9.1% vs. 11.2%, p = 0.014). Two perforations, ulcers, or bleeding episodes in rofecoxib vs. 9 naproxen (RR = 0.22, p = 0.038).	“[R]ofecoxib, 25 mg once daily, was as efficacious as naproxen, 500 mg twice daily, in controlling symptoms over a 3- month period and was associated with significantly better GI tolerability.”	Very large sample size. No placebo. Participants allowed H-2 blockers. Results suggest equivalent efficacy for pain, but higher adverse GI symptoms and bleeds for naproxen vs. rofecoxib.

Gomes 1993 RCT	6.5	N = 643 with hip and/or knee OA	Diclofenac sodium 50mg plus misoprostol 200µg BID vs. piroxicam 10mg BID vs. naproxen 375mg BID for 4 weeks.	Changes in OA severity indices: diclofenac/ misoprostol -4.27 vs. piroxicam -3.19 vs. naproxen -3.79, p = 0.015. Global assessment scores did not differ. On endoscopy, proportion with gastroduodenal ulcers: diclofenac/ misoprostol 3 (1.5%) vs. piroxicam 21 (10.3%) vs. naproxen 17 (8.6%) (p = 0.001).	“[T]he fixed combination of diclofenac and misoprostol is associated with fewer gastroduodenal ulcers than either piroxicam or naproxen.”	Regular adult dosages not used. Assessor blinding not clear. Endoscopic results suggest diclofenac/misoprostol reduces risk of adverse GI events compared with 2 other NSAIDs.
Lohmander 2005 RCT	6.5	N = 970 with hip or knee OA	AZD3582 750mg BID vs. naproxen 500mg BID vs. placebo for 6 weeks.	Endoscopic evidence of significant GI damage (Lanza scores 3 and 4): AZD3582 (32.2%) vs. naproxen (43.7%) vs. placebo (7.0%). WOMAC: AZD3582 (-15.9) vs. naproxen (-14.7) vs. placebo (-5.8). WOMAC scores tended to decrease more in knee than hip patients.	“AZD3582 had similar analgesic effects to naproxen...the 30% difference in the incidence of gastroduodenal ulcers after six weeks of treatment...was not (significant).”	Lacks methodology details. Study shows no advantage of AZD3582 after 6-week trial for endoscopic GI outcomes or pain outcomes. Trends in data suggest hip OA less treatable with either medication.
Hayllar 1996 Crossover Trial	5.0	N = 19 with hip or knee OA	Flosulide 20mg BID vs. naproxen 500mg BID each for 2 weeks.	Flosulide tolerated better than naproxen (90% vs. 47% good to excellent, p <0.005). Gastric Lanza damage scores (combined grades 2, 3, 4): flosulide (n = 5, 26%) vs. naproxen (12, 63%), p = 0.0006.	“The selective COX-2 inhibitor, flosulide, is significantly better tolerated and causes less gastric mucosal damage than naproxen when given for two weeks.”	Small sample size. Endoscopic study suggests fewer mucosal (gastric) erosions with flosulide after 2 week treatment period compared with naproxen.
Becvár 1999 RCT	5.0	N = 394 with hip or knee OA	Nabumetone 1500mg QHS vs. diclofenac retard 100mg QHS for 12 weeks.	Complete and moderate pain relief nabumetone 103/177 (58.2%) vs. diclofenac retard 74/156 (47.4%). Fewer mucosal changes in esophagus, stomach, but not duodenum among nabumetone vs. diclofenac. Data graphically interpreted, appear to be nabumetone 20% erosions at baseline, 16% after treatment, no ulcers vs. diclofenac 19% erosions at baseline, 17% at followup, 9% ulcers.	“[N]abumetone and diclofenac retard have similar efficacy in the treatment of OA, but nabumetone has significantly fewer GIT side effects.”	Diclofenac retard worse than nabumetone for mucosal erosions in the stomach and esophagus, but not in the duodenum. Drugs have comparable efficacy.
Høyeraal 1993 RCT	4.0	N = 208 with hip and knee OA	Tiaprofenic acid 300mg BID vs. naproxen 500mg QAM and 250mg QPM vs.	Twenty-eight drops, 17 discontinued for reasons related to treatment. Excellent or good responses: tiaprofenic acid 19/62 (30.6%) vs. naproxen	“[I]t appears that what characterizes a responder/nonresponder to one NSAID does not necessarily apply to another. These sets are related to dosage of the	Suggests treatments better guided by predictive variables. Better responders to naproxen young females with high

			placebo BID for 3 weeks. Double dummy.	23/58 (39.7%) vs. placebo 12/60 (20.0%). Percentages of responders in 3 patient groups were 52, 59, and 30 respectively.	drug, assessment by patient/physician and objective measurements.”	disease activity, low leisure physical activity, few affected joints. Responder to tiaprofenic acid tended to high disease activity, high leisure physical activity, high platelet count, little morning stiffness, few affected joints, gradual disease onset.
Education Regarding NSAIDs						
Edworthy 1999 RCT	7.0	N = 252 with hip or knee OA	Diclofenac with misoprostol treatment with in depth computer program about disease, treatment, patient involvement vs. medication with generic information about OA.	Significant effect of education on appropriate utilization (p = 0.029). Changes in medication knowledge (p = 0.02), self-efficacy (p = 0.005), ease of adherence (p = 0.002), realistic expectations (p = 0.01) greater intervention group. No difference between groups for illness intrusiveness, pain, disability; greater improvement in stiffness in experimental group.	“Patient education emphasizing the distinction between appropriate and inappropriate utilization of medication is a promising new adjunct to the management of OA. Patient involvement is essential in proper treatment of disease.”	Blinding methods are not clear. The study demonstrated positive benefits of educational material in improving compliance and setting realistic expectations.
Heterotopic Bone Prevention						
Fransen 2006 RCT	9.0	N = 902 with THA	Ibuprofen 400mg TID vs. placebo for 14 days after total hip arthroplasty	No differences in hip pain after 6 to 12 months (mean difference -0.1, p = 0.59) or physical function (-0.1, p = 0.48). Secondary outcomes (global assessments and physical activity) also negative. Risk of severe ectopic bone formation Booker Grade 3 or 4 with ibuprofen (0.69, 95% CI 0.57-0.83). Bleeding risk, ibuprofen RR = 2.09, p = 0.46.	“These data do not support the use of routine prophylaxis with NSAIDs in patients undergoing total hip replacement surgery.”	Author suggests guidelines should be based on clinically important outcomes and not on radiographic findings. Data show ibuprofen significantly reduces risks of ectopic bone formation, but with double risk of major bleeding.
Sell 2004 RCT	7.5	N = 245 with THA	Cholestyramin e-bound diclofenac 75mg QD vs. BID for 14 days post-op.	In diclofenac 150mg, 19% slight heterotopic ossification (Booker 1, none more severe) vs. 75mg which had 17% grade 1 and 4% grade 2 Booker. No clinical difference after 6 months.	“Although the two doses displayed similar efficacy the author recommends the lower dose because of the lower instance of adverse gastrointestinal event (23% vs. 38%, p=0.02).”	Co-administration of proton pump inhibitors likely resulted in lower side effect profile. No placebo control.

Kjaersgaard -Andersen 1989 RCT	5.0	N = 176 with lubinus THA	Indomethacin 25mg TID vs. placebo for 6 weeks post-op.	One year after THA, development of Grace II or III heterotopic bone formation differed: indomethacin 0/90 (0%) vs. placebo 44/86 (51.2%). Six weeks after arthroplasty, mean ESR: indomethacin 15mm an hour vs. placebo 21mm an hour.	“The present study has shown the development of severe ecotopic ossification after THA to result in a significant elevation in the six-weeks ESR. Moreover, at 12 weeks after arthroplasty, reasons other than deep infection may cause ESR to rise above 35 mm/hour.”	Data suggest indomethacin reduces heterotopic bone formation. Trend towards higher ESR in those forming heterotopic bone.
Persson 1998 RCT	4.5	N = 144 with Charnley THA	Ibuprofen 400mg TID for 3 weeks vs. ibuprofen for 1 week and placebo for 2 weeks vs. placebo for 3 weeks.	Both ibuprofen-treated groups showed less HO than placebo-treated group (p = 0.001 for 21 days of treatment, and p = 0.008 for 8 treatment days). After 12 months, 21-day treatment group had no patient with Grade III or IV HO vs. 2 Grade III in 8-day group vs. 5 Grade III and 2 Grade IV in placebo (p = 0.002), 21-day treatment group and p = 0.005 for 8-day group). No difference between 2 active treatments (p = 0.8).	“[P]ostoperative prophylaxis with NSAIDs is highly effective in preventing clinically relevant degrees of HO after THA. The treatment should start early postoperatively and continue for at least 8 days. It appears to be cost-effective and the treatment of choice in patients at risk for HO.”	Lack of study details. Data suggest at least one week of treatment after hip arthroplasty is effective to prevent heterotopic bone formation. Data suggest larger trial may indicate 3 weeks is superior for prevention of more advanced bone formation, however this study underpowered for that outcome.
Dorn 1998 RCT	5.0	N = 249 with cementless THA	Indomethacin 50mg TID for 4 days vs. 8 days.	At 1 year, Booker grades II, III and IV heterotopic bone: 4 days 13/104 (12.5%) vs. 8 days 3/105 (2.9%) (p <0.05).	“[T]he incidence of heterotopic bone formation after total hip arthroplasty was not statistically different after 4-day and 8-day treatment. The incidence of substantial heterotopic bone formation was statistically significantly less (p=0.03) after the 8-day treatment.”	No placebo group. Randomized by government ID number. Data suggest longer treatment superior.
Osteoarthrosis Measurement Tools						
Averbuch 2004 RCT	5.5	N = 206 with hip OA flare-up	Naproxen sodium 500mg BID vs. placebo for 12 weeks. Pain measured in visual analog vs. categorical scales.	Results taken at screening, baseline, 2, 6, and 12 weeks. Visual analog and categorical scales appear similarly effective in determining average osteoarthritis pain.	“Looking at the OA pain model as an exemplar for chronic pain generally, we found a good correspondence between unconstrained VAS and 5-point CAT scale pain measurements.” However, some variance likely “due to individual judgment differences as to how to relate to the VAS line.”	Study of subjective pain assessment tools (outcome measurement) as comparison was not the variable randomized.
Miscellaneous						

Wagentiz 2007 RCT	10.0	N = 210 with hip and/ or knee OA	Diclofenac 100mg in a SR-cap vs. SR-tab QAM for 14 days.	VAS pain scores (ITT) (baseline/Day 14): cap 64.8±11.2/21.2±19.7 vs. tab 63.8±11.0/27.7±23.0. Total adverse events higher tab group (39.0%) than cap group (30.8%).	“Diclofenac was found to be clinically non-inferior to the reference formulation for reducing pain in patients with painful OA of the knee and/or hip.”	Diclofenac in both formulations effective for pain relief, but SR-capsule had modestly lower reported adverse effects.
Timing of Medication						
Vinje 1993 Crossover Trial	7.0	N = 163 with hip or knee OA	Ketoprofen 200mg QAM vs. QPM for 4 weeks each.	Both schedules effective; most results NS between treatment. Mean unused ketoprofen tablets: 1.2am vs. 0.6pm dosings. Rescue use higher with evening dosing; 64 preferred morning dosing vs. 52 evening. Total frequency of GI symptoms not different.	“No significant differences were detected in degree of GI-symptoms between the two treatment periods.”	Although statistical significance needed for differences on VAS pain scale, patient preference was only 53% for morning dose over evening dose. Data suggest no meaningful differences.
Levi 1985 Crossover Trial	7.0	N = 66 with hip or knee OA	Indomethacin SR 75mg. Medication taken 8am vs. noon vs. 8pm vs. placebo for 1 week intervals.	Circadian pain rhythms confirmed 23/57 (40%) of subjects and suspected in 9 (15.8%). More adverse effects for morning dosing (p <0.001); 96% of 25 subjects with undesirable adverse effects found changed dosing time changed tolerance.	“Evening dosing was most effective in subjects with predominantly nocturnal or morning pain; conversely, morning or noon dosing was most effective in subjects with greater afternoon or evening pain.”	Study suggests relationship of optimal dosing to circadian pain rhythms, suggesting optimal dosing of SR indomethacin should be individualized (taken anticipating when maximal pain occurs).
Stengaard-Pedersen 2004 RCT	5.5	N = 697 with knee or hip OA	Celecoxib 200mg QAM vs. celecoxib 200mg QPM vs. celecoxib 100mg BID for 12 weeks.	WOMAC composite scores were -11.19 vs. -12.23 and -11.69 for each group (NS). No differences in patient satisfaction with pain relief, ability to walk or bend, and willingness to continue medication.	“[R]egardless of the time of day at which celecoxib 200 mg q.d. is administered, patients are equally satisfied with the pain relief, ability to walk and bend, and willingness to continue medication.”	Sparse methodology details. Data suggest timing of NSAID is not important.
Enteric-coating						
Bakshi 1993 RCT	7.0	N = 129 with knee and/or hip OA	Diclofenac dispersible vs. enteric-coated 50mg TID for 12 weeks.	No differences in treatment efficacy (graphic data, approximately 60% reductions in VAS joint pain with activity). No differences in adverse events (40.3% vs. 37.3%, p <0.73). Total GI adverse events (++ and +++): dispersible 21/62 (33.9%) vs. EC 16/67 (23.9%).	“Overall assessments of efficacy by the patients and the investigator indicated a positive response rate for both diclofenac formulations ranging between 71% and 82%. The proportion of patients reporting adverse effects, predominantly gastrointestinal, was slightly higher in the dispersible group, 40.3%, compared to 37.3% with enteric-coated diclofenac sodium.”	Data suggest comparability with no benefits of enteric coating of diclofenac.
Bakshi 1996	5.5	N = 216	Diclofenac resinate	VAS rest pain (baseline/ 12 weeks):	“[T]he results of this trial confirm the well-	No placebo comparisons. No

RCT		with hip or knee OA	capsules 75mg BID vs. enteric-coated diclofenac sodium tablets 50mg TID. Double dummy.	diclofenac resinate (55.6/22.5) vs. diclofenac sodium (56.9/25.4). Similar results for activity pain and stiffness. Patients much better/better: diclofenac resinate (75/85 = 88.2%) vs. diclofenac sodium (72/94 = 76.6%). Functional limitation improvements compared with baseline in 59% diclofenac resinate vs. 37% diclofenac sodium.	established favourable tolerability profile of diclofenac sodium and also show that this NSAID administered once or twice daily at 75 mg as a resinate formulation is effective for controlling the symptoms of osteoarthritis."	baseline provided on comparability. Generally comparable medication preparations, however trends in favor of diclofenac resinate.
Sustained Release vs. Immediate Release						
Toft 1985 Crossover Trial	5.0	N = 84 with hip and/or knee OA	Ketoprofen sustained-release formulation 200mg QD vs. normal formulation 100mg BID 3 weeks each.	Both treatments effective. No differences in preferences between preparations (SR preferred by 23 vs. 19, NS).	"No significant differences between the treatments were found."	No mention of compliance. Sparse data presented. Data suggest comparable efficacy.
Bacon 1990 Randomized Crossover Trial	4.5	N = 77 with hip and/or knee OA	Indomethacin controlled-release tablet 75mg QD vs indomethacin immediate release capsule 25mg TID for 4 weeks.	No difference in rescue paracetamol use between treatments. Pain on passive movement after treatments combining mild and none: controlled-release 43/66 (65.2%) vs. immediate-release indomethacin 37/66 (56.1%), both improved compared with baseline. Patient assessment of global efficacy showed no statistically significant treatment differences; light-headedness significantly greater with immediate-release than controlled-release.	"Both immediate-release and controlled-release indomethacin significantly reduced pain on passive movement of the worst affected joint compared to baseline. No treatment differences were found, however, for this or any of the other efficacy measures."	Lack of details. No baseline data of population although was a cross-over study, yet had significant dropouts. No clear differences or advantages of either treatment.
GI Issues: Proton Pump Inhibitors						
Chan 2002 RCT	9.5	N = 210 with RA, OA, and other forms of arthritis with ulcer bleeding	Omeprazole 20mg plus amoxicillin 1g plus clarithromycin 500mg vs. omeprazole 20mg and placebo antibiotics each BID for 1 week	H pylori eradicated in 90% vs. 6% controls. 6-month probability of ulcers 12.1% (95% CI 3.1-21.1) in eradication group vs. 34.4% (21.1-47.7) in controls (p = 0.0085); 6-month probabilities of complicated ulcers 4.2% (1.3-9.7) vs. 27.1% (14.7-39.5), p = 0.0026.	"Screening and treatment for H pylori infection significantly reduces the risk of ulcers for patients starting long-term NSAID treatment."	One week treatment 6 months diclofenac SR. Data suggests antibiotics plus omeprazole effective.
Labenz 2002	9.0	N = 832 H	Omeprazole 20mg BID vs.	Relative risk reduction (%) (95% CI) and	"In H pylori infected patients, all three active	All diclofenac 50mg twice a day

RCT		pylori positive	amoxicillin 1g BID vs. clarithromycin 500mg BID for 1 week (OAC), plus 4 weeks of placebo QD (OAC-P); OAC for 1 week plus 4 weeks omeprazole 20mg QD (OAC-O); omeprazole 20mg QD for 1 plus 4 weeks (O-O); or placebo for 5 weeks (P-P).	absolute risk reduction (%) (95% CI) for the treatment groups was as follows: OAC-P: 79 (4.5-95), 4.6 (0.7-8.5); OAC-O: 80 (11.1-96), 4.7 (0.8-8.6); O-O: 100, 5.8 (2.1-9.5).	therapies reduced the occurrence of NSAID associated peptic ulcer and dyspeptic symptoms requiring therapy.”	for 5 weeks. Other arms treatment for 1 week. Three treatment arms all reduced risk comparably. Results may not be generalized beyond H pylori infected patients.
Scheiman 2006 RCT	9.0	N = 844 (VENUS study); N = 585 (PLUTO study); at-risk patients (≥60 years and/or ulcer history)	Esomeprazole 20mg vs. esomeprazole 40mg vs. placebo QD for 6 months.	16.5% (95% CI: 9.7–23.4) on COX-2s or placebo developed ulcers over 6 months vs. 0.9% (95% CI: 0–2.6) esomeprazole 20mg and 4.1% (95% CI: 0.6–7.6) esomeprazole 40mg (p < 0.001, p = 0.002) vs. placebo, respectively.	“For at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors.”	Two RCTs with large sample size. Study suggests efficacy.
Regula 2006 RCT	9.0	N = 595 rheumatic patients on continual NSAIDs with at least 1 more recognized risk factor that contributes to GI injury	Pantoprazole 20mg vs. pantoprazole 40mg vs. omeprazole 20mg QD for 6 months.	At 6 months, probability of therapeutic remission 90% pantoprazole 20mg QD, 93% pantoprazole 40 mg QD, and 89% omeprazole 20mg QD. Probabilities of endoscopic failure 9% vs. 5% vs. 7% respectively (NS).	“For patients taking NSAIDs continually, pantoprazole 20 mg o.d., pantoprazole 40 mg o.d., or omeprazole 20 mg o.d. provide equivalent, effective, and well-tolerated prophylaxis against GI lesions, including peptic ulcers.”	Large population of rheumatoid arthritis, osteoarthritis, multiple conditions and spine for 6 months of treatment. Suggests equal efficacy.
Yeomans 2008 RCT	9.0	N = 991 ≥60 years without baseline	Esomeprazole 20mg QD vs. placebo for 26 weeks.	Twenty-seven (5.4%) in placebo group with gastric or duodenal ulcer during 26-week treatment vs. 8 (1.6%) in esomeprazole group (life-table estimates:	“Esomeprazole 20 mg once daily reduces the risk of developing gastric and/or duodenal ulcers and symptoms associated with the continuous use of low-	Large population. Suggests efficacy.

		gastro- duoden al ulcer receivin g aspirin 75- 325mg daily		6.2%vs 1.8%; p = 0.0007). At 26 weeks, cumulative proportion with erosive esophagitis lower for esomeprazole vs. placebo (4.4% vs. 18.3%, respectively; p <0.0001).	dose aspirin in patients aged > or =60 yr without preexisting gastroduodenal ulcers.”	
Dorta 2000 RCT	8.5	N = 12 healthy volunte ers	2-week course of omeprazole (40mg) plus “separate 2- week course of an identical looking placebo.” Water-soluble diclofenac (50mg) taken 2nd week.	No differences in healing scores after administration of placebo/diclofenac (median = 6; range 0-6) and omeprazole/ diclofenac (median = 9; range 0-6; p = 0.17) were found.	“In healthy subjects, omeprazole does not accelerate the healing of pre-existing mucosal lesions or prevent the development of small diclofenac-induced mucosal lesions.”	Crossover study with small sample size. Short-term treatments of unclear clinical significance.
Bianchi Porro 2000 RCT	8.5	N = 104 with RA or OA	40mg pantoprazole vs. placebo QD for 12 weeks.	Difference in probability of remaining free of peptic ulcer 5% (95% CL-13%, = 23%) at 4 weeks and 13% (-9%, = 33%) at 12 weeks.	“Pantoprazole 40mg once daily was well tolerated and is more effective than placebo in the prevention of peptic ulcers in patients with rheumatic diseases who require continuous, long-term, treatment with NSAIDs.”	RA or OA 12 week treatment. Suggests efficacy.
Hawkey 2005 2 RCT	7.5	N = 608 and N = 556 (NASA1 , SPACE 1); continuo us NSAID users free of gastro- duoden al ulcers, erosive esopha g-itis, and H pylori	Esomeprazole 20mg, vs. esomeprazole 40mg vs. placebo QD for 4 weeks.	Time to relief superior with active treatments with esomeprazole 20mg and 40mg vs. placebo (NASA1: p = 0.0137, p = 0.0053; SPACE1: p < 0.0001, p = 0.0002). Symptom relief shorter for esomeprazole 20mg and 40mg vs. placebo in each study (11 and 10 days vs. 17 days NASA1 and 10 and 11 days vs. 21 days in SPACE1). Symptom- free days over 4 weeks higher for esomeprazole in both studies (31% esomeprazole 20mg, 29% esomeprazole 40mg vs. 21% on placebo in NASA1, p = 0.0025 and p = 0.0103, respectively, 29%, 27% and 14% respectively, in SPACE1, p <0.0001 vs. placebo both esomeprazole doses).	“Esomeprazole 20 mg and 40 mg improve upper GI symptoms associated with continuous, daily NSAID therapy, including selective COX-2 inhibitors.”	2 large studies. NASA I-E40 group had higher percentage >75 years old.
Cullen 1998 RCT	6.5	N = 169 taking NSAID	Omeprazole 20mg vs. placebo,	Fourteen (14) patients treated with placebo (16.5%) developed 15 ulcers compared to 3	“Omeprazole is an effective agent for gastroduodenal prophylaxis in patients	Up to 6 months of treatment.

		s regularly, chronic-ally, and above defined minimum doses	given for up to 6 months.	patients (3.6%) on omeprazole (p <0.01).	taking NSAIDs. Its main effect is to reduce the rate of development of gastric and duodenal ulcers.”	
Stupnicki 2003 RCT	6.5	N = 515 rheumatic patients likely to take NSAIDs continuously for at least 6 months	Pantoprazole 20mg plus placebo vs. misoprostol 200µg.	Pantoprazole superior to misoprostol (p = 0.005) for endoscopic failure. Estimated remission rates 3 and 6 months, 98 and 95% (pantoprazole); 95 and 86% (misoprostol). Discontinuations for likely/definitely drug-related adverse effects: 13/257 (5%) pantoprazole vs. 33/258 (13%) misoprostol.	“Pantoprazole 20 mg o.d. is superior to misoprostol 200 microg b.i.d. in the prevention of NSAID-induced gastrointestinal lesions and symptoms in patients on continuous long-term treatment with NSAIDs due to rheumatic diseases and at risk to develop such lesions or symptoms.”	Six-month treatment. Study suggests pantoprazole superior to misoprostol.
Desai 2008 RCT	6.5	N = 70 healthy adults aged 50-75 not taking chronic NSAIDs	Naproxen 500mg BID plus omeprazole 20mg QD vs. naproxen 500mg BID plus placebo for a 6.5-day treatment.	Less gastroduodenal ulcers in naproxen plus omeprazole vs. naproxen plus placebo [11.8% (4 ulcers/34 subjects) vs. 46.9% (15/32), RR = 0.25, p = 0.002]. NPX plus OMP associated with decreased risk of ulceration and erosion [5 erosions [38.2% (13/34) vs. 81.3% (26/32), RR = 0.47, P B 0.001].	“[O]MP at the U.S. OTC dosage of 20 mg daily begun on Day 1 of NSAID treatment reduces both GDUs and dyspepsia with OMP. Therefore, in view of the relatively low cost, availability, and good safety profile of OTC OMP, co-prescription of a PPI in relatively healthy older patients requiring short-term non-specific NSAID therapy may be reasonable.”	“Pilot Study”; unclear whether endoscopy data translate to clinical outcomes to support conclusion.
Bianchi Porro 1998 RCT	6.0	N = 114 arthritic disorders requiring indomethacin, ketoprofen, diclofenac, or ketoprofen	Omeprazole 20mg QD vs. placebo for 3 weeks. All patients given indomethacin 100mg, ketoprofen 150mg, and diclofenac 150mg.	26/57 (46%) of omeprazole vs. 20/57 (35%) of placebo group with normal gastroduodenal mucosa (score = 0). Clinically significant gastric lesions (score 3-4) in 6/57 (11%) omeprazole vs. 11/57 (19%) on placebo.	“Omeprazole 20mg once daily is significantly more effective than placebo in the prevention of gastric and duodenal ulcers due to chronic NSAIDs treatment and may provide clinical advantages, in terms of tolerability, over currently available prophylactic therapies.”	Three weeks of treatment added to NSAID. Data support treatment.
Bergmann 1992 RCT	6.0	N = 12 healthy volunteers	Lansoprazole 30mg QD vs. placebo plus aspirin for 1 week.	Mean Lanza scores 0.67±0.98 with lansoprazole vs. 2.25±1.1 with placebo (p <0.005).	“[I]t is possible to distinguish the functional and morphologic effects of a gastrototoxic drug such as aspirin during experimental studies in humans. Lansoprazole prevents hemorrhagic lesions without	Crossover study with small sample size (n = 12). Short experimental design of 1 week.

					reinforcing the mucosal barrier.”	
Niwa 2008 RCT	5.5	N = 10 healthy subjects	Rebamipide 300mg plus diclofenac 75mg plus omeprazole 20mg vs. placebo plus diclofenac 75mg plus omeprazole 20mg QD for 1 week.	Number of subjects with small intestinal mucosal injuries significantly higher in placebo group (8/10) than rebamipide group (2/10) (p = 0.023).	“Rebamipide had significantly higher efficacy than placebo in preventing NSAID-induced small-intestinal mucosal injury.”	Crossover trial with small sample size (n = 10). Evaluation of small intestine. 7 day treatment. Data suggests efficacy for small intestine.
Miyake 2005 RCT	5.0	N = 194 with RA, treated over long-term with NSAIDs	Famotidine 20mg BID vs. lansoprazole 15mg QD for 24 weeks.	8% (1/13) peptic ulcer onset rate infamotidine vs. 2/13 (15%) lansoprazole (NS).	“In Japan, normal-dose H2RA is expected to be a new PU preventive treatment strategy in patients requiring long-term NSAID therapy.”	RA patients on NSAIDs with peptic ulcers scars 24-week treatment; small sample (n = 26). Under-reported study.
Scheiman 1994 RCT	4.5	N = 20 healthy volunteers	Omeprazole 40mg QD vs. placebo plus aspirin 650mg QID for 2 weeks.	Omeprazole reduced PUD 55% vs. 10% (p <0.01). Endoscopic evidence of intraluminal bleeding or ulceration in 70% of placebo vs. 15% of omeprazole (p <0.001).	“Omeprazole 40mg/day significantly prevented both gastric and duodenal injury due to 2600mg aspirin/day over the two-week period of our study... Omeprazole 40mg/day prevented 95% of subjects from developing ulceration, 85% from having >15 erosions (all ≤3mm in size), and 55% from having >5 erosions. In the subjects given placebo, 25% developed gastric ulcers, 70% had grade 3 injury or worse, and all 95% had at least grade 2 injury.”	Crossover, short 2 week study.
Pilotto 2000 RCT	4.0	N = 127 H pylori positive patients with no severe gastroduodenal lesions	Pantoprazole 40mg QD plus amoxicillin 1g BID and clarithromycin 250mg BID for 1 week vs. pantoprazole 40mg QD for 1 month.	Higher incidence of severe gastroduodenal damage in Group PAC vs. Group P (29% vs. 9%, p <0.05). Percent of patients worsened, unchanged, improved after 1 month Group PAC: 46%, 46%, and 9% vs. Group P: 7%, 65%, 29% (p <0.0008).	“One month of pantoprazole was more effective than a proton pump inhibitor-based triple therapy in the prevention of gastroduodenal damage in elderly H. pylori-positive NSAID users.”	Triple therapy for 1 week pantoprazole for 1 month reduces strength of conclusion regarding what is efficacious vs. efficacy of 1 month when 1 arm still actively treated.
GI Issues: Misoprostol						
Raskin 1995 RCT	9.0	N = 1,623 with upper GI	Placebo QID vs. misoprostol 200µg BID and placebo	Gastric ulcers in 51/325 (15.7%) on placebo vs. 29/358 (8.1%) on misoprostol BID vs. 13/336 (3.9%) on	“In patients receiving long-term NSAID therapy who are being considered for misoprostol therapy,	Twelve week trial. Data support BID or TID dosing as well as QID.

		symptoms during NSAID therapy and no endoscopic evidence of gastric or duodenal ulcers	BID vs. misoprostol 200µg TID and placebo QD vs. misoprostol 200µg QID.	misoprostol TID vs. 6/152 (4.0%) on QID. The incidence of gastric ulcers lower compared with placebo with misoprostol BID (difference, 7.6% [95% CI, 2.7% to 12.5%]; p = 0.002), TID (difference, 11.8% [CI, 7.4% to 16.3%]; p < 0.001), and QID (difference, 11.7% [CI, 6.7% to 16.8%]; p < 0.001).	dosages of 200 µg twice or three times daily are effective and better tolerated alternatives to the 200 µg four times daily regimen. Protection against NSAID-induced gastric ulcers increases with the dose of misoprostol, but maximum protection appears to be achieved with doses of 400 to 600 µg daily. Maximum protection against NSAID-induced duodenal ulcers can be achieved with doses as low as 400 µg daily. Physicians prescribing misoprostol should choose a dosage that best balances the drug's mucosal protective effects with its side effects."	
Bianchi Porro 1997 RCT	7.5	N = 70 with RA or OA with endoscopically normal mucosa	Misoprostol TID: misoprostol 200µg and ranitidine placebo after every meal 3 times daily vs. misoprostol BID: misoprostol 200µg after breakfast and dinner, misoprostol placebo after lunch; ranitidine placebo after every meal vs. ranitidine 150mg after breakfast and dinner, ranitidine placebo after lunch, and misoprostol placebo after each meal for 14 days.	70% of MISO TID group vs. 48% in MISO BID group vs. 21% in RAN group with normal gastroduodenal mucosa (score = 0) (p<0.01 between MISO TID and RAN). Incidence of gastrointestinal symptoms did not differ between 3 treatment groups. 56% with gastroduodenal ulcer had no gastrointestinal symptoms.	The study confirms that "[M]isoprostol is as effective as ranitidine in the short-term prevention naproxen-induced duodenal lesions, but significantly better as far as the gastric mucosa is concerned. Because the dosages used in this specific study proved to be effective and well tolerated, misoprostol b.i.d. might, in our opinion, be proposed as an alternative in patients who need prophylaxis against NSAID damage."	RA or OA. Data suggest misoprostol is superior to ranitidine.
Raskin 1996 RCT	7.0	N = 538 chronic NSAID therapy with NSAID-related	Misoprostol 200µg QID vs. ranitidine 150mg BID for 8 weeks.	More gastric ulcers (p = 0.009) in ranitidine group (11 ulcers with a rate of 5.64%) vs. misoprostol (1 ulcer with a rate of 0.55%). Total gastrointestinal AEs more (p <0.05)	"[M]isoprostol and ranitidine are equally effective for the prevention of duodenal ulcers. NSAID-induced ulcers can occur in either the stomach or duodenum. Since only	Eight week trial. Data suggest misoprostol is superior to ranitidine for prevention of GU.

		upper GI pain without gastric or duodenal ulcers		more often in misoprostol group.	misoprostol has been shown effective in the prevention of both NSAID-induced gastric and duodenal ulcers, misoprostol should be the therapy of choice for the prevention of such ulcers in patients at risk.”	
Graham 1993 RCT	7.0	N = 638 with chronic inflammatory or non-inflammatory arthritis taking an NSAID but no gastric or duodenal ulcer	Misoprostol 200µg vs. placebo for 12 weeks.	At 12 weeks, duodenal ulcer in 2/320 (0.6%; 95% CI, 0.2% to 3.9%) misoprostol, vs. 15/323 (4.6%; CI, 2.8% to 8%) placebo (p = 0.002).	“Misoprostol significantly lowers the frequency of both duodenal and gastric ulcer development in patients who require long-term therapy with NSAIDs.”	Twelve week trial. Data support misoprostol efficacious.
Bardhan 1993 RCT	7.0	N = 358 requiring chronic NSAID therapy (Group 1 = normal; Group 2 = non-ulcer lesions)	Misoprostol 400-800µg daily vs. placebo tablets for 2 weeks.	Incidence of severe mucosal damage reduced by misoprostol (odds ratio; 95% CI). Group I: 4.52; 1.94, 10.51 (p = 0.018); Group II: 10.93; 1.09, 109.60 (p = 0.014); Groups I and II combined: 5.95; 3.23, 10.94 (p = 0.0003). Misoprostol protected from progression of minor to severe damage in Group II (p <0.001).	“Significant GD damage occurs early in the course of NSAID treatment and misoprostol significantly reduces the incidence of such damage.”	Variable dose NSAID and variable misoprostol. Supports misoprostol and reduces early NSAID damage.
Lanza 1988 RCT	6.5	N = 90 normal volunteers	Misoprostol 200µg QID vs. cimetidine 300mg QID vs. placebo for 7 days.	Overall success rates 8/30 (26.7%) for placebo, 19/30 (63.3%) cimetidine, 27/29 (93.1%) misoprostol (p <0.001). Pairwise comparisons: misoprostol vs. placebo (p <0.001), misoprostol vs. cimetidine (p = 0.006), cimetidine vs. placebo (p = 0.004).	“[M]isoprostol is highly effective and significantly better than cimetidine in protecting the gastric mucosa from tolmetin-induced injury; however, both agents were highly protective in the duodenum.”	Short-term study. Suggest cimetidine inferior for gastric mucosa but not duodenal.
Agrawal 1991 RCT	6.5	N = 253 with OA receiving ibuprofen, piroxicam	Misoprostol 200µg vs. sucralfate 1g QID a day for 12 weeks.	Gastric ulcer developed in 2/122 (1.6%, 95% CI, 0.3% to 6.4%) on misoprostol vs. 21/131 on sucralfate (16%, CI, 10.4% to 23.7%). Difference in ulcer rates: 14.4% (CI, 10.4% to 19.5%).	“In patients receiving chronic NSAID therapy for osteoarthritis, treatment with misoprostol for 3 months was associated with a significantly lower frequency of gastric ulcer formation, compared with	OA patients. Study suggests misoprostol is effective compared with sucralfate.

		naproxen with abdominal pain			treatment with sucralfate (P less than 0.001)."	
Graham 2002 RCT	6.0	N = 537 without H pylori and long-term users of NSAIDs with history of gastric ulcer	Placebo plus Misoprostol 200µg QID vs. 15 or 30mg of lansoprazole QD for 12 weeks.	Patients on NSAIDs. Either dose lansoprazole remained free from gastric ulcer longer than placebo (p <0.001). Misoprostol group remained free of gastric ulcers longer than placebo (p <0.001), 15mg lansoprazole (p = 0.01), or 30mg lansoprazole (p = 0.04).	"Proton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-induced gastric ulcers but not superior to misoprostol, 800 microg/d. When the poor compliance and potential adverse effects associated with misoprostol are considered, proton pump inhibitors and full-dose misoprostol are clinically equivalent."	Not blinded to misoprostol. H pylori negative.
Elliot 1994 RCT	6.0	N = 83 arthritic patients on chronic NSAID therapy	Misoprostol 200µg vs. placebo tablets for 12 months.	4/32 (12.5%) on misoprostol developed gastric ulcer vs. 11/38 (28.9%) on placebo (p <0.05); 6/11 with initial gastric ulcer developed further gastric ulcer vs. 9/58 without an initial ulcer (p <0.05).	"[M]isoprostol decreases the cumulative development of NSAID-induced gastric ulcers. Patients with a previous NSAID-ulcer have a higher risk of further ulceration."	Study suggests that misoprostol is effective.
Chandrasekaran 1991 RCT	5.5	N = 90 arthritic patients	Diclofenac sodium 150mg a day OA subjects vs. indomethacin 75mg a day for seronegative spondarthropathy subjects vs. ibuprofen 1.2g a day and aspirin 2.7g a day for rheumatoid arthritis subjects for 4 weeks.	Patients on placebo with more post-therapy abnormal endoscopy findings. 24.4% of misoprostol group vs. 28.8% in placebo group had UGI symptoms during the trial (NS).	"Arthritic patients requiring long term NSAID therapy appear to benefit from misoprostol because of its cytoprotective effect on the gastrointestinal mucosa."	4 weeks RA, OA, and seronegative spondarthropathy. NSAIDs differed by diagnosis but results in aggregate.
Lanza 1988 RCT	5.5	N = 30 healthy volunteers	Misoprostol 200µg vs. sucralfate 1g vs. placebo, co-administered with 650mg of aspirin 4 times a day 7 days.	Misoprostol superior to sucralfate (p = 0.0001) and placebo (p = 0.00001). Differences in success rates between misoprostol and sucralfate and misoprostol and placebo (44%; 100%) and (61%; 100%), respectively.	"[M]isoprostol at a dose of 200µg, 4 times a day, when dosed concurrently with aspirin, was highly effective in protecting the gastroduodenal mucosae from aspirin-induced injury."	Suggests misoprostol is superior to placebo and sucralfate. Sucralfate not blinded.
Jiranek 1989 RCT	5.5	N = 130 healthy subjects	Misoprostol 50µg vs. 100µg vs. 200µg vs. placebo plus	Fewer endoscopic gastric ulcers in misoprostol vs. placebo (1% vs. 43%). No DU on 100 or 200µg	"[M]isoprostol can protect the normal gastroduodenum from acute ulceration and reduce the chance of	

			aspirin 975mg (given as three 325mg tablets) for 7 days.	misoprostol vs. 13% placebo (p <0.05). Fewer gastric and duodenal erosions in 3 misoprostol groups vs. placebo (p <0.01). Fewer gastric erosion (p <0.05) and duodenal erosion (p <0.05) in misoprostol 200µg vs. 50µg doses.	erosion after 1 week of aspirin ingestion.”	
Donnelly 2000 RCT	5.0	N = 32 healthy volunteers	Misoprostol 100µg plus aspirin 300mg vs. placebo plus aspirin 300mg once daily for 28 days.	Gastric erosion in 52% on aspirin plus placebo vs. 17% on aspirin plus misoprostol (OR = 0.18, CI: 0.07-0.48), averaged over Days 5, 14, and 28. Percent gastric petechiae: 42% and 23% (OR = 0.42, CI: 0.17-0.97).	“Misoprostol 100 µg daily can prevent low-dose aspirin induced gastric mucosal injury without causing identifiable adverse effects.”	Misoprostol 100QD vs. placebo plus ASA 300QD for 28 days. Data suggest misoprostol protects from gastric injury associated with ASA.
Silverstein 1986 RCT	5.0	N = 60 healthy male volunteers	Misoprostol 200µg vs. placebo for 24 hours.	Mucosal protection in 20/30 on misoprostol (67%) vs. 1/30 on placebo (3%) (p <0.001).	“[F]ive 200-micrograms doses of misoprostol given over 24 hr protects the gastric mucosa from the injurious effect of a single dose of aspirin.”	Short-term experimental study. Suggests misoprostol reduces risk.
Medina Santillan 1999 RCT	4.5	N = 38 healthy volunteers	Sodium diclofenac 75mg plus misoprostol 50µg vs. diclofenac for 14 days.	Misoprostol showed scores of 0-1 in 89% of cases versus 63% in diclofenac sodium/placebo group (p <0.05).	The “[C]ombination of diclofenac and low-dose of misoprostol (50µg; bid) is associated with mucosal protection against NSAID-induced gastroduodenal damage.”	Sparse data support misoprostol efficacy.
Koch 2000 RCT	4.0	N = 8,843 with RA	Misoprostol plus NSAID vs. NSAID plus placebo.	Relative risk reduction of gastrointestinal complications 40% with misoprostol. Number needed to treat to prevent 1 event 250 in 6 months or 125 when normalized at 1-year treatment.	“[M]isoprostol prevention of severe complications is effective.”	Large study. All RA over a 6-month trial. Endoscope based on symptoms and signs. Study helpful for developing clinical risk estimates.
GI Issues: Sucralfate						
Miglioli 1996 RCT	5.0	N = 107 with arthritis	Diclofenac 200mg a day vs. naproxen 1g a day plus sucralfate gel 1gm BID or placebo for 14 days.	More GU/DU ulcers in placebo group (p <0.05). More on placebo had heartburn and epigastric pain at final evaluation (51 vs. 30% and 49 vs. 28%; p <0.05).	“Sucralfate gel reduces both the incidence of acute gastroduodenal mucosal lesions and symptoms in patients with arthritis receiving short-term nonsteroidal anti-inflammatory drugs.”	Data support efficacy in prevention.
GI Issues: H-2 Blockers						
Ehsanullah 1988 RCT	6.0	N = 297 with RA or OA without lesions in the stomach and	Ranitidine 150mg twice daily vs. placebo twice daily. NSAID drug treatment included:	Cumulative incidence of peptic ulceration at 8 weeks 10.3% (27/263); 2/135 (1.5%) developed duodenal ulceration in the ranitidine group vs. 10/126 (8%) taking	“Ranitidine 150 mg twice daily significantly reduced the incidence of duodenal ulceration but not gastric ulceration when prescribed concomitantly with one	RA or OA. Also treatments with naproxen, diclofenac, indomethacin or piroxicam. Suggests

		duo- denum	naproxen 750mg a day; piroxicam 20mg a day; diclofenac 100mg a day; indomethacin 100mg a day.	placebo. Frequency of gastric ulceration same (6%) for the 2 groups at 8 weeks. Fewer gastric lesions in ranitidine group.	of four commonly used non-steroidal anti- inflammatory drugs.”	ranitidine prevents DU, not GU.
Robinson 1989 RCT	5.5	N = 144 with normal endosco- pic findings requirin- g NSAIDs	Ranitidine 150mg twice daily vs. placebo plus ibuprofen, indomethacin , naproxen, sulindac, or piroxicam for 8 weeks.	47/57 (82%) of ranitidine had no mucosal damage in the duodenum by study end vs. 32/49 (65%) on placebo.	“[R]anitidine therapy (150mg bid) was effective in preventing duodenal, but not gastric injury resulting from eight weeks of NSAID treatment.”	8 weeks treatment also included with NSAID (ibuprofen, naproxen, sulindac, indomethacin, piroxicam).
Robinson 1991 RCT	4.5	N = 673 receivin- g NSAIDs for arthritic or MSD conditio- ns	Ranitidine 150mg twice daily vs. placebo for 4 weeks or 8 weeks.	Protective effect against duodenal mucosal lesions including duodenal ulcers (3 studies) and gastric mucosal lesions including gastric ulcers (1 study) observed vs. placebo.	“[R]anitidine is effective in preventing NSAID- associated duodenal ulcers and may be appropriate prophylaxis for certain high-risk patients.”	4 RCTs for 4 weeks or 8 weeks treatment. Data suggests protective for DU not GU.

OPIOIDS – Oral, Transdermal, and Parenteral (Includes Tramadol)

Opioids are addressed in a separate guideline. The treatment recommendations are summarized below. (See Opioids guideline for all supporting evidence.)

Acute Pain (Up to 4 Weeks)

1. *Recommendation: Routine Use of Opioids for Treatment of Non-Severe Acute Pain*

Routine opioid use is strongly not recommended for treatment of non-severe acute pain (e.g., low back pain [LBP], sprains, or minor injury without signs of tissue damage).

Harms – May inadequately treat acute, severe pain.

Benefits – Faster recovery, less debility, reduced accidents risks, risks of dependency or addiction.

Strength of Evidence – **Strongly Not Recommended, Evidence (A)**

Level of Confidence – High

2. *Recommendation: Opioids for Treatment of Acute, Severe Pain*

Opioids are recommended for treatment of acute, severe pain (e.g., crush injuries, large burns, severe fractures, injury with significant tissue damage) uncontrolled by other agents and/or with functional deficits caused by pain. A brief course of opioids may also be indicated at the initial visit for anticipated pain accompanying severe injuries (i.e., failure of other treatment is not mandatory). A Schedule IV^{iv} opioid may be indicated if

^{iv}USA classifies controlled substances that includes a classification system, ranging from Class 1 to Class V corresponding to lower risks of abuse and dependence. Class I includes substances with a high potential for abuse and without a recognized medical use (e.g., heroin, marijuana, LSD). Class II includes most opiates, amphetamines and cocaine. Class III includes buprenorphine, dihydrocodeine, hydrocodone/codeine when compounded with an NSAID, Marinol. Class IV includes tramadol (in some states), carisoprodol, benzodiazepines, and long-acting barbiturates. Class V includes small amounts of codeine (e.g., 30mg, 60mg).

there is a true allergy to NSAIDs and acetaminophen, other contraindication to an alternative medication, or insufficient pain relief with an alternative. Recommend to taper off opioid use in 1 to 2 weeks.

Indications – Patients should meet all of the following:

- 1) Severe injury with a clear rationale for use (objective functional limitations due to pain resulting from the medical problem, e.g., extensive trauma such as forearm crush injury, large burns, severe radiculopathy).^v
- 2) Other more efficacious treatments should have been instituted,^{vi} and either:
 - 2a) failed and/or
 - 2b) have reasonable expectations of the immediate need for an opioid to obtain sleep the evening after the injury.
- 3) Where available, prescription databases (usually referred to as a Prescription Drug Monitoring Program [PDMP]) should be checked and not show evidence for conflicting opioid prescriptions from other providers or evidence of misreporting.^{vii}
- 4) Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) absent contraindication(s) should nearly always be the primary treatment and accompany an opioid prescription.
- 5) Low-dose opioids may be needed in the elderly who have greater susceptibility to the adverse risks of opioids. Those of lower body weight may also require lower opioid doses.
- 6) Dispensing quantities should be only what is needed to treat the pain. Short-acting opioids are recommended for treatment of acute pain. Long-acting opioids are not recommended.
- 7) Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances including: i) benzodiazepines; ii) anti-histamines (H₁-blockers); and/or iii) illicit substances.(774-777) Patients should not receive opioids if they use illicit substances unless there is objective evidence of significant trauma or moderate to severe injuries. Considerable caution is also warranted among those who are unemployed as the reported risks of death are also greater than 10-fold.(774, 775) Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: depression, anxiety, personality disorder, untreated sleep disorders, substance abuse history, current alcohol use or current tobacco use, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), suicidal risk, impulse control problems, thought disorders, psychotropic medication use, chronic obstructive pulmonary disease (COPD), asthma, or recurrent pneumonia.(774, 778-798) Considerable caution is also warranted among those with other comorbidities such as chronic hepatitis and/or cirrhosis,(799) as well as coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, recurrent pneumonia, thermoregulatory problems, advanced age (especially with mentation issues, fall risk, debility), osteopenia, osteoporosis, water retention, renal failure, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, pregnancy, human immunodeficiency virus (HIV), ineffective birth control, herpes, allodynia, dementia,

^vOther indications beyond the scope of this guideline include acute myocardial infarction or agitation interfering with acute trauma management.

^{vi}Treatments to have tried generally include NSAIDs and acetaminophen. For LBP patients, additional considerations include muscle relaxants, progressive aerobic exercise, and directional exercise.

^{vii}Exceptions such as acute, severe trauma should be documented.

cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3 of Opioids guideline).

Frequency/Duration – Generally, opioids should be prescribed at night or while not working.(800) Lowest effective, short-acting opioid doses are preferable as they tend to have the better safety profiles, less risk of escalation,(801) less risk of lost time from work,(802) and faster return to work.(803) Short-acting opioids are recommended for treatment of acute pain and long-acting opioids are not recommended. Recommend opioid use as required by pain, rather than in regularly scheduled dosing.

If parenteral administration is required, ketorolac has demonstrated superior efficacy compared with opioids for acute severe pain,(804, 805) although ketorolac’s risk profile may limit use for some patients. Parenteral opioid administration outside of obvious acute trauma or surgical emergency conditions is almost never required, and requests for such treatment are clinically viewed as red flags for potential substance abuse.

Indications for Discontinuation – Resolution of pain, sufficient improvement in pain, intolerance or adverse effects, non-compliance, surreptitious medication use, consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines), or use beyond 2 weeks.

Harms – Adverse effects are many (see section below on “Opioids Benefits and Harms”).

Benefits – Improved short-term pain control.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – High

3. Recommendation: Screening Patients Prior to Initiation of Opioids

Initial screening of patients is recommended with more detailed screening for: i) requiring continuation of opioids beyond 2 weeks for those with an acute severe injury; and ii) at consideration of initiation for severe pain but no objective evidence. Screening should include history(ies) of depression, anxiety, personality disorder, other psychiatric disorder, substance abuse, sedating medication use (e.g., anti-histamine/anti-H₁ blocker(774)), benzodiazepine use, opioid dependence, alcohol abuse, current tobacco use, other substance use history, COPD, PTSD, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1 of Opioids guideline). Those who screen positive, especially to multiple criteria, are recommended to: i) undergo greater scrutiny for appropriateness of opioids (may include psychological evaluation); ii) consideration of consultation and examination(s) for complicating conditions and/or appropriateness of opioids, and iii) if opioids are prescribed, more frequent assessments for compliance, achievement of functional gains,(775, 806, 807) adverse effects, and symptoms and signs of aberrancy.

Harms – Negligible. If a consultation is needed, there are additional costs that are incurred.

Benefits – Improved identification of more appropriate candidates for opioids. Identification of patients at increased risk of adverse effects. In cases where someone has elevated, but potentially acceptable risk, may alert the provider to improve surveillance for complications and aberrant behaviors.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

4. Recommendation: Opioid Dose Limits in Acute Pain

Dispense only that which is required. The maximum daily oral dose recommended for opioid-naïve, acute pain patients based on risk of overdose/death is 50mg morphine equivalent dose (MED)^{viii}(808) (see Figure 1). In rare cases with documented functional improvement (see Appendix 1 of Opioids guideline), higher doses may be considered, however, risks are substantially higher and greater monitoring is also recommended (see Subacute/Chronic Opioid recommendations below). Lower doses should be used for patients at higher risk of dependency, addiction and other adverse effects. Monitoring is also recommended and consultation may be considered for those patients on higher doses.

Harms – Theoretical potential to undertreat pain in some patients with increased pain sensitivity.

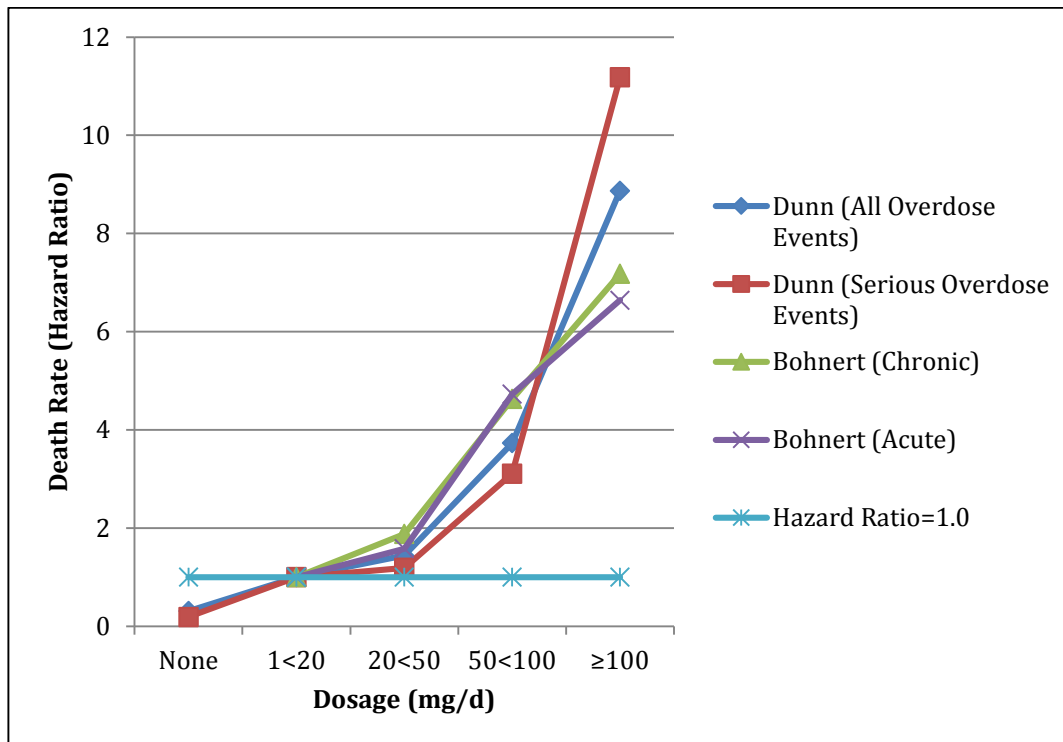
Benefits – Reduced risk for adverse physical and cognitive effects, dependency, addiction and opioid-related overdoses and deaths.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – Moderate

^{viii}Statistical significance present for acute and chronic pain at and above 50 mg per day of oral morphine equivalent dose.

Figure 1. Death Rate (Hazard Ratio) vs. Morphine Equivalent Dosage (mg/d)*



Adapted from Dunn 2010 and Bohnert 2011.

*Statistical significance present for acute and chronic pain at and above 50 mg per day of oral morphine equivalent dose.

Post-Operative Pain Up to 4 Weeks (After 4 weeks, see Subacute Pain)

Oral opioids are commonly prescribed after sinus surgery,(809) major noncardiac surgical procedures,(810) mastectomy and immediate breast reconstruction (IBR),(811, 812) coronary artery bypass graft surgery,(813) major abdominal surgery (abdominal laparoscopic, abdominal hysterectomy, bowel resection or radical hysterectomy),(814-817) orthopedic surgery,(818) and molar extraction.(819)

1. Recommendation: Limited Use of Opioids for Post-operative Pain

Limited use of opioids is recommended for post-operative pain management as an adjunctive therapy to more effective treatments.

Indications – For post-operative pain management, a brief prescription of short-acting opioids as an adjunct to more efficacious treatments (especially Cox-2 NSAIDs such as celecoxib, non-selective NSAIDs after risk of bleeding is no longer a concern).^{ix} A brief course of opioids is often needed for minor surgical procedures. However, minor wound laceration repairs often require no opioids. Evidence suggests perioperative pregabalin for 14 days and/or continuous femoral nerve catheter analgesia instead of solely using oral opioids results in superior knee arthroplasty functional outcomes with less venous thromboses.(820) Additional considerations include:

^{ix}More efficacious treatments also include therapeutic exercises, e.g., progressive ambulation especially for moderate to extensive procedures (e.g., arthroplasty, fusion).

- 1) Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) should nearly always be the primary treatment and accompany an opioid prescription. Computerized programs may also assist in optimal management.(821)
- 2) The lowest effective dose of a short-acting opioid should be used,(801) as well as weaker opioids if possible.(802, 803)
- 3) Short-acting opioids are recommended for treatment of acute pain.
- 4) Dispensing should be only what is needed to treat the pain.^x
- 5) Long-acting opioids are not recommended.
- 6) Low-dose opioids may be needed in the elderly who have greater susceptibility to the adverse risks of opioids. Those of lower body weight may also require lower opioid doses.
- 7) Where available, prescription databases (usually referred to as Prescription Drug Monitoring Program (PDMP)) should be checked for other opioid prescriptions. Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances including: i) benzodiazepines; ii) anti-histamines (H₁-blockers); and/or iii) illicit substances.(774-777) Patients should not receive opioids if they use illicit substances unless there is objective evidence of significant trauma or moderate to severe injuries. Considerable caution is also warranted among those who are unemployed as the reported risks of death are also greater than 10-fold.(774, 775)

Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: depression, anxiety, personality disorder, ADHD, PTSD, suicidal risk, impulse control problems, thought disorders, psychotropic medication use, substance abuse history, current alcohol use or current tobacco use, untreated sleep disorders, COPD, asthma, or recurrent pneumonia.(774, 778-798, 822) Considerable caution is also warranted among those with other comorbidities such as chronic hepatitis and/or cirrhosis,(799) as well as coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, thermoregulatory problems, advanced age (especially with mentation issues, fall risk, debility), osteopenia, osteoporosis, water retention, renal failure, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, pregnancy, HIV, ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3 of Opioids guideline). Inpatient management may moderate these recommendations provided there is careful monitoring, although these same management issues then apply post-discharge.

- 8) For patients taking opioids chronically prior to surgery, consultations with anesthesiology and/or pain management are generally needed as post-operative dosing may be very high and management is often challenging.
- 9) Ongoing prescriptions of opioids after the immediate post-operative period should generally be for patients who have undergone a major surgery or have other condition(s) necessitating opioids. Most patients should be making progress towards functional restoration, pain reduction and weaning off the opioids. Patients who have not

^xGenerally, this should be sufficient to cover two weeks of treatment. Prescriptions of 90-day supplies in the post-operative setting are not recommended.

progressed should be carefully evaluated for physical complications or psychiatric comorbidity, adherence to active treatments, and pending development of addiction or dependency.

Frequency/Duration – For moderate and major surgeries, opioids are generally needed on a scheduled basis in the immediate post-operative period. Other post-operative situations may be sufficiently managed with an as needed opioid prescription schedule. Provision of opioids sufficient to participate in therapeutic exercise (e.g., progressive ambulation) and allow sleep may be needed. However, high dose use at night is not recommended due to respiratory depression and disruption of sleep architecture. Weaning should begin as soon as function is recovering and pain is subsiding. Subsequent weaning to as needed opioid use is recommended.

Indications for Discontinuation – The physician should discontinue the use of opioids based on sufficient recovery, expected resolution of pain, lack of efficacy, intolerance or adverse effects, non-compliance, surreptitious medication use, self-escalation of dose, or use beyond 3-5 days for minor procedures, and 2-3 weeks for moderate/less extensive procedures. Use for up to 3 months may occasionally be necessary during recovery from more extensive surgical procedures (e.g., spine fusion surgery). However, with rare exceptions, only nocturnal use is recommended in months 2-3 plus institution of management as discussed in the subacute/chronic guidelines below. For those requiring opioid use beyond 1 month, subacute/chronic opioid use recommendations below apply.

Harms – Adverse effects are many (see section on “Opioids Benefits and Harms”).

Benefits – Improved short-term, post-operative pain control. Some studies suggest this may modestly improve functional outcomes in the post-operative population.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – High

2. Recommendation: Screening Patients Prior to Continuation of Opioids

Screening of patients is recommended for those requiring continuation of opioids beyond the second post-operative week. Screening should include history(ies) of:

depression, anxiety, personality disorder, pain disorder, other psychiatric disorder, substance abuse history, sedating medication use (e.g., anti-histamine/anti-H₁ blocker), benzodiazepine use, opioid dependence, alcohol abuse, current tobacco use, and other substance use history, COPD, PTSD, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1 of Opioids guideline). Those who screen positive, especially to multiple criteria, are recommended to: i) undergo greater scrutiny for appropriateness of opioids (e.g., may include psychological and/or pain evaluation); ii) compliance with active therapies (e.g., ambulation and other exercise after arthroplasty); iii) consider consultation examination(s) for complicating conditions and/or appropriateness of opioids; and iv) if ongoing opioids are prescribed, ensure more frequent assessments for treatment compliance, achievement of functional gains, (775, 806, 807) and symptoms and signs of aberrancy.

Harms – Negligible. If a consultation is needed, there are additional costs that are incurred.

Benefits – Identification of patients at increased risk of adverse effects. Improved identification of more appropriate and safe candidates for opioids compared with attempting post-operative pain control with non-opioids. This should reduce adverse effects. In cases where someone has elevated, but potentially acceptable risk, this may alert the provider to improve surveillance for complications and aberrant behaviors.

Strength of Evidence – Recommended, Insufficient Evidence (I)
Level of Confidence – High

3. Recommendation: Opioid Dose Limits in Post-operative Pain

The maximum daily oral dose recommended for opioid-naïve, acute pain patients based on risk of overdose/death is 50mg morphine equivalent dose (MED)^{xi}(808) (see Figure 1). Post-operative patients particularly require individualization due to factors such as the severity of the operative procedure, response to treatment(s) and variability in response. Higher doses beyond 50mg MED may be particularly needed for major surgeries in the first 2 post-operative weeks to achieve sufficient pain relief; however, greater caution and monitoring are warranted and reductions below 50mg MED at the earliest opportunity should be sought. Lower doses should be used for patients at higher risk of dependency, addiction and other adverse effects. In rare cases with documented functional improvement, ongoing use of higher doses may be considered, however, risks are substantially higher and greater monitoring is also recommended (see Subacute/Chronic Opioid recommendations below).

Harms – Theoretical potential to undertreat pain, which could modestly delay functional recovery.

Benefits – Reduced risk for adverse effects, dependency, addiction and opioid-related deaths.

Strength of Evidence – Recommended, Insufficient Evidence (I)
Level of Confidence – Low

Subacute (1-3 Months) and Chronic Pain (>3 Months)

- 1. Recommendation: Routine Use of Opioids for Subacute and Chronic Non-malignant Pain*
Opioid use is moderately not recommended for treatment of subacute and chronic non-malignant pain. Opioid prescription should be patient specific and limited to cases in which other treatments are insufficient and criteria for opioid use are met (see below).

Harms – May inadequately treat severe subacute or chronic pain.

Benefits – Less debility, fewer adverse effects, reduced accident risks, lower risks of dependency, addiction, overdoses, and deaths.

Strength of Evidence – Moderately Not Recommended, Evidence (B)
Level of Confidence – High

- 2. Recommendation: Opioids for Treatment of Subacute or Chronic Severe Pain*

The use of an opioid trial is recommended if other evidence-based approaches for functional restorative pain therapy have been used with inadequate improvement in function.(823, 824) Opioids are then recommended for treatment of function impaired by subacute or chronic severe pain (e.g., inability to work due to any of the following: chronic severe radiculopathy, chronic severe peripheral neuropathies, complex regional pain syndrome (CRPS), and severe arthroses)(806) (see Appendix 1 of Opioids guideline).

Indications – Patients should meet all of the following:

- 1) Reduced function is attributable to the pain. Pain or pain scales alone are insufficient

^{xi}Statistical significance present for acute and chronic pain at and above 50 mg per day of morphine equivalent dose.

reasons.(775, 806, 825-836)

- 2) A severe disorder warranting potential opioid treatment is present [e.g., CRPS, severe radiculopathy, advanced degenerative joint disease (DJD)].(827)
- 3) Other more efficacious treatments have been documented to have failed.(827) Other approaches that should have been first utilized include physical restorative approaches, behavioral interventions, self-applied modalities, non-opioid medications (including NSAIDs, acetaminophen, topical agents, norepinephrine adrenergic reuptake blocking antidepressants or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain) and functional restoration. For LBP patients, this also includes^{xii} fear avoidant belief training and ongoing progressive aerobic exercise, and strengthening exercises. For CRPS patients, this includes progressive strengthening exercise. For DJD, this includes NSAIDs, weight loss, aerobic and strengthening exercises.
- 4) An ongoing active exercise program is prescribed and complied with.
- 5) Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) absent a contraindication should nearly always be the primary pain medication and accompany an opioid prescription. Other medications to consider include topical agents, norepinephrine adrenergic reuptake blocking antidepressants or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain).
- 6) The lowest effective dose should be used.(801) Weaker opioids should be used whenever possible.(802, 803) Meperidine is not recommended for chronic pain due to bioaccumulation and adverse effects.
- 7) Low-dose opioids may be needed in the elderly who have greater susceptibility to the adverse risks of opioids. Those of lower body weight may also require lower opioid doses.
- 8) Dispensing should be only what is needed to treat the pain.^{xiii}
- 9) Extended-release/long-acting opioids are recommended to be used on a scheduled basis, rather than as needed.(827) As needed opioids should generally be avoided for treatment of chronic pain, although limited use for an acute painful event (e.g., fracture, sprain) is reasonable. Sublingual fentanyl is not recommended for treatment of subacute or chronic pain. Caution is warranted with fentanyl patches due to unpredictable absorption.
- 10) Where available, prescription databases (usually referred to as a Prescription Drug Monitoring Program [PDMP]) should be checked for conflicting opioid prescriptions from other providers or evidence of misreporting.
- 11) Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances including: i) benzodiazepines; ii) anti-histamines (H₁-blockers); and/or iii) illicit substances.(774-777) Patients should not receive opioids if they use illicit substances unless there is objective evidence of significant trauma or moderate to severe injuries. Considerable caution is also warranted among those who are unemployed as the reported risks of death are also greater than 10-fold.(774, 775)

Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics:

^{xii}A previous trial of a muscle relaxant is generally recommended. However, if an opioid trial is contemplated, cessation of all depressant medications including muscle relaxants is advisable.

^{xiii}Generally, this should be sufficient to cover one week of treatment at a time during the trial phase. If a trial is successful at improving function, prescriptions for up to 90-day supplies are recommended.

depression, anxiety, personality disorder, untreated sleep disorders, substance abuse history, current alcohol use or current tobacco use, ADHD, PTSD, suicidal risk, impulse control problems, thought disorders, psychotropic medication use, COPD, asthma, recurrent pneumonia.(774, 778-798, 822) Considerable caution is also warranted among those with other comorbidities such as chronic hepatitis and/or cirrhosis,(799) as well as coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, recurrent pneumonia, thermoregulatory problems, advanced age (especially with mentation issues, fall risk, debility), osteopenia, osteoporosis, water retention, renal failure, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, pregnancy, HIV, ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3 of Opioids guideline).

Frequency/Duration – Opioids use is generally initiated as a “trial” to ascertain whether the selected opioid produces functional improvement (see Appendix 1 of Opioids guideline). Opioid use is generally prescribed on a regular basis,(837) at night or when not at work.(800) Only one opioid is recommended to be prescribed in a trial. More than one opioid should rarely be used. Lower opioid doses are preferable as they tend to have the better safety profiles, less risk of dose escalation,(801) less work loss,(802) and faster return to work.(803) Patients should have ongoing visits to monitor efficacy, adverse effects, compliance and surreptitious medication use. Opioid prescriptions should be shorter rather than longer duration.(838)

Indications for Discontinuation – Opioids should be discontinued based on lack of functional benefit(824) (see Appendix 1), resolution of pain, improvement to the point of not requiring opioids, intolerance or adverse effects, non-compliance, surreptitious medication use, medication misuse (including self-escalation and sharing medication), aberrant drug screening results, diversion, consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines).

Harms – Adverse effects are many (see section on “Opioids Benefits and Harms”). May initiate path to opioid dependency.

Benefits – Improved short-term pain ratings. Theoretical potential to improve short-term function impaired by a painful condition.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

3. Recommendation: Screening Patients Prior to Initiation of Opioids

Screening of patients is recommended prior to consideration of initiating a trial of opioids for treatment of subacute or chronic pain. Screening should include history(ies) of depression, anxiety, personality disorder and personality profile,(803, 839, 840) other psychiatric disorder, substance abuse history, sedating medication use (e.g., anti-histamine/anti-H₁ blocker),(781) benzodiazepine use, opioid dependence, alcohol abuse, current tobacco use, and other substance use history, COPD, PTSD, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1 of Opioids guideline). Those who screen positive, especially to multiple criteria, are recommended to: i) undergo greater scrutiny for appropriateness of opioids (may include psychological and/or psychiatric evaluation(s) to help assure opioids are not being used instead of appropriate mental health care); ii)

consideration of consultation and examination(s) for complicating conditions and/or appropriateness of opioids; and iii) if opioids are prescribed, more frequent assessments for compliance, achievement of functional gains and symptoms and signs of aberrant use.

Harms – Negligible. If a consultation is needed, there are additional costs that are incurred.

Benefits – Identification of patients at increased risk of adverse effects. Improved identification of more appropriate and safe candidates for treatment with opioids. This should reduce adverse effects. In cases where someone has elevated, but potentially acceptable risk, this may alert the provider to improve surveillance for complications and aberrant behaviors.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

4. Recommendation: Opioid Dose Limits in Subacute and Chronic Pain

The maximum daily oral dose recommended for subacute or chronic pain patients based on risk of overdose/death is 50mg Morphine Equivalent Dose (MED).(782, 808) In rare cases with documented functional improvements occurring with use above 50mg MED, subsequent doses up to 100mg may be considered, however, risks of death are much greater and more intensive monitoring is then also recommended. Lower doses should be considered in high risk patients. Caution appears warranted in all patients as there is evidence the risk of dose escalation is present even among patients enrolled in a “hold the line (stable dose) prescribing strategy” treatment arm.(841)

For those whose daily consumption is more than 50mg MED, greater monitoring is recommended to include: i) at least monthly to not more than quarterly appointments with greater frequencies during trial, dose adjustments and with greater co-morbid risk factors and conditions; ii) at least semiannual attempts to wean below 50mg MED if not off the opioid; iii) at least semiannual documentation of persistence of functional benefit; iv) at least quarterly urine drug screening (see drug screening section); and v) at least semiannual review of medications, particularly to assure no sedating medication use (e.g., benzodiazepine, sedating anti-histamines).

Harms – None in a short-term trial. For chronic pain patients, theoretical potential to undertreat pain and thus impair function. However, there is no quality literature currently available to support that position.

Benefits – Reduced risk for adverse effects, dependency, addiction, and opioid-related deaths.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – High

5. Recommendation: Use of an Opioid Treatment Agreement (Opioid Contract, Doctor/Patient Agreement, Informed Consent)

The use of an opioid treatment agreement (opioid contract, doctor/patient agreement, or informed consent) is recommended to document patient understanding, acknowledgement of potential adverse effects, and agreement with the expectations of opioid use (see Appendix 1 of Opioids guideline). (823, 842-853) If consent is obtained, it is recommended that appropriate family members be involved in this agreement.

Harms – Negligible.

Benefits – Educates the patient and significant others that these medications are high risk, with numerous adverse effects. It allows for a more informed choice. It provides a framework for initiation of a trial, monitoring, treatment goals, compliance requirement, treatment expectations,

and conditions for opioid cessation. It should reduce risk of adverse events and opioid-related deaths, although that remains unproven to date.

Strength of Evidence – Recommended, Insufficient Evidence (I)
Level of Confidence – Moderate

6. Recommendation: Urine Drug Screening

Baseline and random urine drug screening, qualitative and quantitative, is recommended for patients prescribed opioids for the treatment of subacute or chronic pain to evaluate presence or absence of the drug, its metabolites, and other substance(s) use. In certain situations, other screenings (e.g., hair particularly for information regarding remote use(854-859) or blood (for acute toxicity) may be appropriate.

Indications – All patients on opioids for subacute or chronic pain.

Frequency – Screening is recommended at baseline, randomly at least twice and up to 4 times a year and at termination. More intensive screening is recommended for those consuming more than 50mg MED (see above). Federal guidelines recommend at least 8 tests a year among those utilizing opioid treatment programs.(860) Screening should also be performed “for cause” (e.g., provider suspicion of substance misuse including over-sedating, drug intoxication, motor vehicle crash, other accidents and injuries, driving while intoxicated, premature prescription renewals, self-directed dose changes, lost or stolen prescriptions, using more than one provider for prescriptions, non-pain use of medication, using alcohol for pain treatment or excessive alcohol use, missed appointments, hoarding of medications, and selling medications). Standard urine drug/toxicology screening processes should be followed (consult a qualified medical review officer).(861-863) If there is an aberrant drug screen result (either positive for unexpected drugs or unexpected metabolites or unexpectedly negative results), there should be a careful evaluation of whether there is a plausible explanation (e.g., drug not tested, drug metabolite not tested, laboratory cutpoint and dosing interval would not capture the drug/metabolite, laboratory error). In the absence of a plausible explanation, those patients with aberrant test results should have the opioid discontinued or weaned.(824)

Harms – No adverse clinical effects if properly interpreted.

Benefits – Identifies aberrant medication(s) and substance(s) use. Such uses are high-risk for opioid events including fatalities (see tables below). It provides objective evidence to cease an opioid trial or ongoing treatment. Identifies patients who may be diverting medication (those screening negative for prescribed medication).

Strength of Evidence – Recommended, Evidence (C)
Level of Confidence – High

Evidence for Use of Opioids

There are 2 high-(864, 865) and 21 moderate-quality(642, 866-885) RCTs incorporated in this analysis (see Opioids guidelines for additional evidence).

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Silverfield 2002 RCT	8.5	N = 308 with hip or knee OA	Tramadol/acetaminophen (37.5/325mg) vs. placebo 1-2 QID for 10 days	Discontinuation from adverse effects was tramadol/acetaminophen 12.7% vs. 5.4% placebo. Pain intensity scores (baseline/final):	“[A]ddition of tramadol/acetaminophen to NSAID or COX-2-selective inhibitor therapy was well	Short-term trial of 10 days of addition of tramadol for OA flare in addition to NSAID suggests modest efficacy.

				Tramadol/ acetaminophen (2.4/1.3) vs. placebo (2.4/1.6), p <0.001. Patients' overall assessments (very good and good): Tramadol (80.0%) vs. placebo (56.4%), p <0.001.	tolerated and effective in the treatment of OA flare pain."	
Caldwell 1999 RCT	8.0	N = 107 with spine or knee OA	Oxycodone controlled release 10mg q 12 hours vs. oxycodone plus acetaminophe n 5/325mg TID vs. placebo. All on NSAID. Open label titration run-in for 30 days then 30 day RCT. Double dummy.	Mean global pain intensity scores increased from open label to DB-RCT [mean (SE)]: placebo +1.0 (0.13) vs. controlled release oxycodone 0.44 (0.13) vs. oxycodone- ASAP 0.49 (0.11), p <0.004 comparing active treatments vs. placebo, NS between active treatments. Overall adverse reactions included 50% somnolence rates in oxycodone group during titration.	"[C]ontrolled release oxycodone q12h and immediate release oxycodone-APAP qid, added to NSAID, were superior to placebo for reducing OA pain and improving quality of sleep. The active treatments provided comparable pain control and sleep quality. Controlled release oxycodone was associated with a lower incidence of some side effects."	Most (60%) taking opioids previously. Dropout rates very high with 35.9% lost during initial open label titration phase; additional 33.6% lost during trial (total 57.5% dropouts). Suggests equivalency of 2 opioids. Modest efficacy vs. placebo, results also only directly applicable to patients previously treated with opioids.
Malonne 2004 RCT	7.5	N = 230 with hip or knee OA rated ≥35mm on 100-mm Huskisson VAS. Symptoms ≥6 months, requiring regular analgesics or NSAIDs for ≥1 month.	Tramadol LP 200mg QD vs. placebo for 14 days.	Mean pain decrease 2.43 vs. 1.55 cm, p <0.01. Improvement before Day 7 comparing tramadol vs. placebo: 88.2% vs. 65.2%; p = 0.021. Mean time to report improvement: 3 vs. 6 days; p <0.001. Reports of adverse events: 45% vs. 19.3%; p <0.001.	"[T]ramadol LP 200 mg was significantly more effective than placebo in alleviating pain in patients with osteoarthritis of the hip or knee. It appeared to be relatively well tolerated for an opioid compound."	Short-term study. Modest improvement over placebo. Approximately 2.5- fold adverse effects; 21.6% dropouts in tramadol.
Fleischman 2001 RCT	7.5	N = 129 with knee OA	Titrated doses of tramadol 1-2 50mg tablets QID vs. placebo for 91 days; 10-day washout period.	Final pain intensity scores: tramadol 2.10±1.06 vs. 2.48±1.13 placebo, p = 0.082. Patient overall assessment tramadol 0.10±1.41 vs. placebo - 0.44±1.3, p = 0.038. Dropout rates were high (41.3% tramadol vs. 65.2% placebo).	"Tramadol may be useful as monotherapy in the treatment of joint pain associated with OA."	High dropout rate (41.3% tramadol vs. 65.2% placebo), limits strength of conclusions; may limit generalizability. Data statistically negative for main outcome, but positive for others suggesting modest efficacy.
Langford 2006 RCT	7.5	N = 399, ≥40 years old with hip or knee OA requiring	Tramadol fentanyl (TDF, 25µg per hour, titrated up to 100µg per	Mean±SEM VAS score change from baseline to last visit comparing placebo vs. fentanyl:	"TDF can reduce pain and improve function in patients with knee or hip OA."	Results generalizability limited to pre- arthroplasty patients. High dropouts

		arthroplasty ; mean daily VAS score ≥ 50 at start and end of 7-day pre-treatment and inadequate control on "weak" opioids	hour with 4 patches) n = 202 vs. placebo n = 197; 6 weeks treatment; allowed metoclopramide.	-17.9 \pm 1.9 vs. -23.6 \pm 1.8; p = 0.0025.		(52.5%) despite requirement for opioids treatment for study eligibility. High adverse effects in TDF group. Pain change from baseline benefits shown at Weeks 1-4, but differences with placebo disappeared at Weeks 5 and 6 per graph, though other data suggest modest efficacy.
Pavelka 1998 Crossover Trial	7.0	N = 60 with hip or knee OA	Tramadol 50-100mg up to TID vs. diclofenac 25-50mg up to TID for 4 weeks. Doses titrated.	Mean tramadol dose 164.8 \pm 54.1mg; mean diclofenac dose 86.9 \pm 21.4mg; 3 in each group terminated. Adverse events greater during tramadol treatment (20.0% vs. 3.3%, p = 0.0056). No patient treatment preference (46.7% tramadol vs. 45.0% diclofenac, p = 0.85). Functionality scores (WOMAC) improved in tramadol group 39.6 \pm 16.0 to 32.0 \pm 17.4 vs. diclofenac 40.0 \pm 17.2 to 30.1 \pm 17.0 with no significant difference between groups.	"OA patients' response to analgesic treatment was highly individual and the response to one drug was not predictive of that to another drug. As functional scores improved (lower WOMAC scores) on analgesic vs. NSAID, pain rather than inflammation may be the most important aspect of treatment. A significant proportion of patients were not treated satisfactorily with diclofenac or tramadol alone."	Data suggest tramadol equivalent to diclofenac on average. Study suggests some preferred different medications and results not predictable.
Burch 2007 RCT	7.0	N = 1,028 age 40-80 years with knee OA and taking NSAIDs, COX-2 inhibitors, or tramadol regularly past 30 days	Tramadol contramid OAD increased gradually by 100mg to 200-300mg vs. placebo for 12 weeks. Titration followed by 7-day taper.	Mean \pm SD absolute improvement comparing placebo vs. tramadol: 2.29 \pm 1.97 vs. 3.03 \pm 2.12. Difference in absolute improvement between tramadol and placebo; p <0.0001.	"Tramadol Contramid OAD given once daily is an efficacious and safe treatment for pain due to OA."	Open label (66% with adverse effect) followed by DB RCT. High placebo dropouts. Data suggest modest pain reduction and high adverse effects despite open label phase.
Gana 2006 RCT	7.0	N = 1020 with ACR functional Class I-III knee or hip OA who took acetaminophen, NSAID, COX-2, or opioid for at least 75 of	Tramadol ER 100, 200, 300, or 400mg QD vs. placebo. Titration over up to 15 days for 400mg dose; 12 weeks follow-up.	Mean \pm SE WOMAC Index for physical function (0-1700) comparing placebo vs. tramadol 100 vs. 200 vs. 300 vs. 400mg.	"Tramadol ER 100-300 mg once daily was associated with significant improvement in pain intensity and physical function, and was well tolerated, despite the use of a fixed-dose study design not reflective of usual clinical	High dropouts (44.8%). Overall global assessment trended in favor of treatment (p = 0.079). Data suggest modest efficacy, particularly 100mg vs. placebo with minimal incremental gain with higher doses, but more

		prior 90 days			practice. Tramadol ER is a useful treatment option for patients with osteoarthritis pain.”	adverse effects. No long-term follow-up.
Florete 2008 2 RCTs, 2nd report combined analyses	7.0	N = 1,608 at least 18 years with x-ray confirmed ACR functional Class I or II knee or hip OA	Study A: Tramadol ER 100 vs. 200 vs. 300 vs. 400mg vs. placebo. Study B: Tramadol ER 100 vs. 200 vs. 300 mg vs. placebo; 12 weeks follow-up.	All tramadol ER groups improved in sleep quality vs. placebo at Week 1; $p \leq 0.022$ in final visit for all tramadol ER groups ($p \leq 0.022$) (mostly graphic data). For morning awakening due to pain, improvement started at Week 1 thru to final visit for tramadol ER 200 and 300mg dosage (all $p \leq 0.017$); Week 3 and continuing to final visit for tramadol ER 100mg dosage (all $p \leq 0.046$). Awakening at night, falling asleep also improved.	“In this post hoc analysis, a reduction in pain was associated with a significant reduction in (pain-related sleep disturbances) due to OA.”	Two trials combined in 1 report with only post-hoc analyses. Main outcome was sleep disturbance; however, study is short- to intermediate-term. Data suggest modest improvement in short term. High dropouts.
Matsumoto 2005 RCT	7.0	N = 489 with hip or knee OA, >40 years old, at least Grade 2 Kellgren-Lawrence scale, prior treatment with acetaminophen, NSAID, COX-2, or opioid analgesic for at least 75 of 90 prior days	Oxymorphone ER 20mg (n = 121) vs. oxymorphone ER 40mg (n = 121) vs. oxycodone controlled release 20mg (n = 125) vs. placebo (n = 124); Q12 hours for 4 weeks.	Arthritis pain intensity Week 3 oxymorphone ER least squares mean difference (LSMD) from placebo -9.0 (95% CI -16.2 to -1.8; $p = 0.015$). Secondary efficacy analysis with improvements at Week 4 (LSMD from placebo, -10.3 [95% CI: -17.7 to -2.8]; $p = 0.007$) and with oxymorphone ER 20mg at Week 3 (LSMD from placebo, -7.7 [95% CI: -15.0 to -0.4]; $p = 0.039$) and Week 4 (LSMD from placebo, -7.5 [95% CI: -15.0 to 0.0]; $p = 0.050$). WOMAC scores favored active treatment. Patient’s global assessments at Week 4: placebo, -19.5 vs. oxycodone CR 20mg -25.4 vs. oxymorphone ER 20mg -23.2 vs. oxymorphone ER 40mg -28.6.	“In this short-term study, oxymorphone ER was superior to placebo for relieving pain and improving function in patients with moderate to severe chronic OA pain, and is an alternative to other sustained-release opioids.”	Short-term study only. Modestly lower pain and improved function with active treatment, but high dropouts (45.2%), mostly adverse effects in medicated groups.
Markenson 2005 RCT	7.0	N = 107 with moderate to severe OA (ACR; hip 18%, knee 30.8%, spine 45%), taking scheduled	CR oxycodone 10mg vs. placebo. Q12 hours for 90 days. Dose titrated. Follow ups on days 15, 30, 45, 60 and 90.	Least square means \pm SE for observed average pain intensity at Day 90: 6.0 \pm 0.4 (placebo) vs. 4.9 \pm 0.3 (O=oxycodone); $p = 0.024$. Stiffness and difficulty in physical function and in composite score observed in CR	“Treatment with controlled-release oxycodone of patients with osteoarthritis with persistent moderate to severe pain uncontrolled by standard therapy resulted in significant pain	Mixed OA joints. May have enrolled if under opioid treatment, thus data may not be applicable to population not under treatment. Allowed adjusted doses. Large dropout rate (66%), mostly

		NSAID or APAP at least 2 prior weeks or oral opioid therapy ≤60mg oxycodone a day		oxycodone group (48.7±6 3.2, 45.4±6 2.6, and 46.6±6 2.7, respectively, vs. 68.9±3.5, 58.6±2.9, and 62.2±3.0, respectively, for placebo; p <0.001).	control and improvements in physical functioning.”	ineffective in placebo and adverse effects in active treatment. 41% of active treatment finished trial.
Lloyd 1992 RCT	6.5	N = 86 with severe hip OA	Controlled-release dihydrocodeine 60mg to 120mg BID vs. dextropropoxyphene/paracetamol 32.5 to 325mg 2 tablets TID-QID for 2 weeks.	Average daily pain scores Week 2: dihydrocodeine 39.2±5.3 vs. dextropropoxyphene 39.8±4.6 (NS). Pain on hip ROM better in hydrocodeine group. Adverse effects worse with dihydrocodeine and more dropouts (total dropout rate 33.7%) Overall adverse effects: dihydrocodeine 102AEs/ 43 patients (2.4/patient) vs. dextropropoxyphene (84/43) (2.0/patient).	“[A]fter 2-weeks’ treatment CR dihydrocodeine provided superior analgesia to dextropropoxyphene/ paracetamol with no difference in side-effects.”	Short-term study. Described as double blind, but different dosing regimens raise questions about blinding success. Data suggest short-term equivalency by most measures, but higher dropouts for dihydrocodeine (43% vs. 21%) and more adverse effects (39.5% vs. 9.3% of dropouts).
Parr 1989 RCT	6.5	N = 846 mostly hip or knee OA	Diclofenac sodium slow release 100mg QD vs. dextropropoxyphene 180mg plus paracetamol 1.95gm QD for 4 weeks.	Pain ratings (change in VAS): diclofenac -27.0 vs. dextropropoxyphene plus paracetamol -22.7, p <0.05 (8% greater reduction with diclofenac). Physical mobility scores: -10.8 vs. -7.4 (p <0.01) (13% better with diclofenac). Work interference less common with diclofenac (3 vs. 11, p <0.05), and time lost (3 vs. 16, p <0.05). Dizziness, lightheadedness less common for diclofenac (14 vs. 30, p <0.05), as was CNS symptoms (48 vs. 93, p <0.01). Abdominal pain higher with diclofenac (40 vs. 18, p <0.01) and diarrhea (14 vs. 2, p <0.01). Overall GI effects not different (63 vs. 60); comparable dropouts.	“Pain as measured by a visual analogue scale (VAS) showed 8% greater pain reduction with DSR as compared with D&P (P<0.05). Physical mobility as measured by the (Nottingham Health Profile) improved by 13% more with DSR as compared with D&P (P<0.05).”	No regular NSAID use prior 6 months. Dropouts 15.3% diclofenac vs. 17.0%. Suggests greater efficacy of diclofenac vs. dextropropoxyphene plus acetaminophen. Benefits suggested for working populations from diclofenac including lower incidence of problems at work and lost worktime.
Emkey 2004 RCT	6.5	N = 307 with moderate or severe knee or hip OA	Tramadol/acetaminophen vs. placebo up to 4 tablets a day 10 days, then up to 8 tablets a day for duration as added therapy to celecoxib or	Mean VAS scores were (baseline/final) tramadol 69.0±12.5/41.5±26.0 vs. placebo 69.5±13.2/48.3± 26.6. Discontinuations due to lack of efficacy higher in the placebo group (17% vs. 8.5%).	“Tramadol 37.5mg/APAP 325 mg combination tablets were effective and safe as add-on therapy with COX-2 NSAID for treatment of OA pain.”	Data suggest modest efficacy of tramadol/acetaminophen vs. placebo. Overall dropouts 26.1% equal in both groups, but more insufficient pain relief in placebo

			rofecoxib for 91 days.			(66.7% dropouts) and adverse events in active treatment (48.8% dropouts).
Kean 2009 2 RCTs in 1 report	6.5	N = 685 females with moderate-to-severe OA pain	100mg Tramadol Contramid® OAD vs. 200mg Tramadol Contramid® OAD vs. 300 mg Tramadol Contramid® OAD vs. placebo. Titrated dose in run-in. Treatment for 12 weeks.	87.7% tramadol vs. 75.7% placebo found overall pain relief effective or very effective. WOMAC pain scores from Week 0 to 12 improvement for 100mg vs. 200mg vs. 300mg vs. placebo: 58.8% vs. 53.0% vs. 58.9% vs. 45.2% (p = 0.018, p = 0.175, p = 0.023 vs. placebo). Mean WOMAC physical function improvement score for 100mg vs. 200mg vs. 300mg vs. placebo: 56.9% vs. 54.0% vs. 53.4% vs. 41.9% (p = 0.009, p = 0.034, p = 0.043 vs. placebo).	“The efficacy and safety of Tramadol Contramid® OAD in women with pain due to OA of the knee were demonstrated in this analysis that further supports its recommended use as an alternate treatment to NSAIDs and strong opioids.”	Short- to intermediate-term study. Data suggest modest efficacy for pain vs. placebo. High dropouts (54.9%), mostly adverse effects except placebo. Data suggest minimal efficacy and modest differences between doses.
Roth 2000 RCT	6.0	N = 133 with moderate to severe spine, knee or other OA	Oxycodone controlled release 10mg Q12 hour vs. 20mg Q 12 hr. vs. placebo for 14 days; 6 month open label extension and optional 12 month extension.	Mean pain intensities (baseline/14 days, interpretation of graphic data): oxycodone 10mg (2.5/1.9) vs. oxycodone 20mg (2.5/1.6) vs. placebo (2.4/2.2), p <0.05 compared with placebo.	“Around-the-clock controlled-release oxycodone therapy seemed to be effective and safe for patients with chronic, moderate to severe, osteoarthritis-related pain.”	Short-term trial. Overall dropouts 47.4% (81.5% of placebo dropouts ineffective, 60.5% oxycodone dropouts with adverse events). Somnolence in 25-27%, dizziness in 20-30%, nausea in 27-41% of active treatment groups. Data suggest modest efficacy. In long-term open-label extension, 10-21% required dose titration at each visit. Dose appeared to trend upwards modestly over 72 weeks.
Schnitzer 1999 RCT	6.0	N = 236 with knee OA	Tramadol 200mg a day vs. placebo over 8 weeks with 5 weeks open label run-in. All treated with naproxen 500mg BID and those with marked relief excluded.	In open-label, tramadol reduced VAS pain scores by 19mm in naproxen non-responders vs. 5mm in responders, p <0.05. Maximum effective naproxen dose for naproxen responders, 221 for tramadol vs. 407 placebo, p = 0.021. For naproxen non-responders, mean effective doses: 419 vs. 396mg, p = 0.71.	“In patients with painful OA of the knee responding to naproxen 1,000mg a day, the additional of tramadol 200mg/day allows a significant reduction in the dosage of naproxen without comprising pain relief.”	Overall dropouts in active treatment 19.3%. Main utility of data may be in treatment of patients not responsive to naproxen.

Roth 1998 RCT	6.0	N = 63 with OA breakthrough pain	Tramadol 50mg 1-2 Q 4-6 hour PRN vs. placebo. Open label run-in for 1 day, then 13 day RCT.	Patient assessments (excellent/very good): tramadol (11/20 = 55%) vs. placebo (5/20 = 25%). Mean resting pain scores at end: tramadol 0.85±0.32 vs. placebo 1.32±0.33, p = 0.46. Cumulative continuation rates 13 days: tramadol 84% vs. 53% (graphic data). Adverse effects in somnolence in tramadol 25% vs. 14%, nausea 35% vs. 14%, vertigo 20% vs. 5%.	"Tramadol may have a role as adjunctive treatment for breakthrough pain in patients receiving NSAID therapy for musculoskeletal pain attributed to OA."	20.6% discontinued open-label from adverse effects. Only 36.5% (23/63) of original study population completed RCT. Data suggest limited efficacy for breakthrough pain reduction in OA flares, but dropouts very high.
Peloso 2000 RCT	6.0	N = 66 with hip and/ or knee OA	Control-released codeine vs. placebo. Dose titrated from 100mg/day up to 400mg/day for 4 weeks.	WOMAC pain scale 44.8% improved (263.5/145.4) in codeine vs. 12.3% (252.4/221.3) controls (p = 0.0004). Rescue medication with acetaminophen averaged 4.2 codeine vs. 9.2 controls. Patient clinical effectiveness CR codeine 2.1±0.9 vs. 0.9±1.0, p = 0.0001.	"Single entity controlled release codeine is an effective treatment for pain due to OA of the hip or knee."	Total 39.2% codeine withdrew vs. 32.7%; 75% codeine withdrawals due to adverse effects; 16.2% of placebo withdrawals due to inadequate pain control.
Fishman 2007 RCT	6.0	N = 552 age 40-75 years with knee OA and required WOMAC OA index pain subscale score of >150mm	Four groups: Tramadol Contramid OAD 100 mg QD (n = 103) vs. 200mg (n = 107) vs. 300 mg (n = 105) vs. placebo (n = 224). During 6 day run-in, dose titrated by 100 mg increments every 2-3 days until randomized dose reached. Treated with randomized dose for 12 weeks.	WOMAC pain score % improved from baseline: 100mg (41.6±50.2, [31.5;51.6] CI), 200mg (42.8±46.4, [33.9;51.6] CI), 300mg (46.0±39.9, [38.2;53.7] CI), and placebo (32.3±48.2, [25.9;38.6] CI). For difference in improvement between active and placebo estimate (mean), 95% CI, and p-value were Tramadol Contramid groups 100mg (9.50, [-1.60;20.60] CI, p = 0.0933), 200mg (10.81, [-0.02;21.64] CI, p = 0.0504) and 300mg (13.41, [2.49;24.33] CI, p = 0.0162). Responder analysis-WOMAC pain score (30% improvement from baseline): Tramadol Contramid OAD 100 mg (58%, p = 0.2236), 200mg (65%; p = 0.0095) and 300mg (65 %; p = 0.0104) vs. placebo (50%).	"This study shows the efficacy and safety of Tramadol Contramid OAD 200 mg and 300 mg in patients with moderate or severe pain of the knee due to OA."	High dropouts (55.3%). Data suggest slight benefits for pain with only 300mg statistically significant.
Babul 2004	5.5	N = 246 with functional	Tramadol ER initiated at 100mg QD and	WOMAC pain subscale, LS mean change greater for tramadol ER	"Treatment with tramadol ER results in statistically	Two to 7 day washout before RCT; 49.6%

RCT		Class I-III primary OA meeting ACR diagnostic criteria; age >50 years, morning stiffness <30 minutes in duration, and/ or crepitus, warranted acetaminophen, COX-2, NSAIDs, tramadol, or opioids at least 75 of 90 days prior to study, baseline VAS ≥ 40 mm	increased to 200mg QD by end of 1 week with further increases to 300-400mg QD vs. placebo; 12 week follow-up.	vs. placebo (change from baseline over 12 weeks: 120.1 vs. 69.0 mm, LS mean difference 51.1mm; $p < 0.001$). WOMAC physical function scale: 407.0 vs. 208.5; $p < 0.001$.	significant and clinically important and sustained improvements in pain, stiffness, physical function, global status, and sleep in patients with chronic pain. A once-a-day formulation of tramadol has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep and improved compliance.”	dropouts. Data suggest modest benefit and high adverse effects.
Zautra 2005 RCT	5.5	N = 107 with OA as defined by ACR guidelines, moderate to severe pain	CR oxycodone 10mg vs. placebo Q 12 hours, 90 days treatment and follow-up on Days 15, 30, 45, 60, and 90.	Discontinued from study: 38/51 (75%) placebo vs. 33/56 (59%) CR oxycodone. Discontinuation due to reported lack of efficacy: 34/51 (67%) placebo, 9/56 (16%) CR oxycodone ($p < 0.001$). Ratings of acceptability of pain medication higher for CR oxycodone vs. placebo (3.4 vs. 2.2; $p < 0.001$). Coping outcomes efficacy favored oxycodone 0.46, SE0.17, $p < 0.007$.	“[C]ontrolled-release oxycodone treatment accounted for improvements in coping with pain beyond that of placebo controls. This medication may be most beneficial to osteoarthritis patients when incorporated as part of a multidisciplinary approach to pain management.”	Many details sparse. Arthritis joint(s) not defined. Allowed up to 60mg/day prior oxycodone in study. High dropouts in oxycodone group (41%) mostly adverse effects. Data suggest modest benefit on efficacy beliefs and coping but with high adverse effects.
Caldwell 2002 RCT	5.0	N = 295 with moderate to severe hip and/or knee OA	Extended release morphine 30mg QAM vs. ER morphine 30mg QPM vs. morphine controlled release (MS Contin) 15mg BID vs. placebo for 4 weeks. Double dummy.	Reductions in WOMAC OA index pain by 17% with morphine ER QAM dose vs. 20% QPM vs. 18% MS-controlled release vs. 4% placebo (not different between 3 active treatments). ER morphine had better quality of sleep. Dropouts high at 40% of active treatments, with similar dropout rates across groups, except placebo with more due to lack of efficacy and fewer from adverse effects. Somnolence in 12-16%,	“Controlled release oxycodone q12h and immediate release oxycodone-APAP qid, added to NSAID, were superior to placebo for reducing OA pain and improving quality of sleep. The active treatments provided comparable pain control and sleep quality. Controlled release oxycodone was associated with a lower	Data suggest modest efficacy. 39.6% (88/222) of active treatment patients dropped out, with 60.2% (53/88) of those due to adverse effects. A subsequent randomized open label trial of 181 of patients who completed compared QAM and QPM regimens and 52.5% of those patients withdrew with 33.1%

			dizziness in 10-12% of active treatment patients.	incidence of some side effects.”	experiencing adverse effects.
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SKELETAL MUSCLE RELAXANTS

Skeletal muscle relaxants comprise a diverse set of pharmaceuticals designed to produce muscle relaxation through different mechanisms of action, including central nervous system (CNS) mechanisms.(886, 887) These medications are widely used in primary care to treat painful conditions, including LBP,(888-894) muscle spasms,(895) and myalgias. They are generally not used for treatment of knee disorders.

Recommendation: Muscle Relaxants for Acute and Subacute Knee Pain with Significant Muscle Spasm

There is no recommendation for or against the use of muscle relaxants for treatment of acute or subacute, moderate to severe knee pain from muscle spasm that is unrelieved by NSAIDs, avoidance of exacerbating exposures, or other conservative measures (generally not indicated for chronic knee pain).

Indications – Moderate to severe chronic pain syndromes and radicular pain syndromes thought to be musculoskeletal in nature.

Frequency/Dose – Initial dose in evening (not during workdays or if patient operates a motor vehicle, though daytime use is acceptable if CNS-sedating effects are minimal). Duration for exacerbations of chronic pain is limited to a couple weeks. Longer term treatment is generally not indicated.

Indications for Discontinuation – Resolution of pain, non-tolerance, significant sedating effects that carry over into the daytime, other adverse effects.

***Strength of Evidence* – No Recommendation, Insufficient Evidence (I)**

Rationale for Recommendation

There are no quality studies of these agents for treatment of patients with knee pain. Skeletal muscle relaxants have been evaluated in quality studies evaluating acute LBP and also chronic back and neck pain(896-899) (see Chronic Pain and Low Back Disorders guidelines). The quality of the studies comparing these agents to placebo is limited due to probable unblinding from adverse effects. The adverse effect profile is concerning,(900) with CNS sedation rates ranging from approximately 25 to 50% and a low but definite risk of abuse.(901, 902) Thus, prescriptions for skeletal muscle relaxants for daytime use should be carefully weighed against the need to drive vehicles, operate machinery, or otherwise engage in occupations where mistakes in judgment may have serious consequences (e.g., crane operators, air traffic controllers, operators of motorized vehicles, construction workers, etc.). Skeletal muscle relaxants have beneficial uses, particularly for nocturnal administration to normalize sleep patterns disrupted by skeletal muscle pain, as well as for daytime use among the few patients who do not suffer from the CNS depressant effects. They are low cost if generic medications are prescribed. Skeletal muscle relaxants are not recommended for continuous management of subacute or chronic knee pain, although they may be reasonable options for selected patients with acute pain exacerbations or for a limited trial as a third- or fourth-line agent in more severely affected patients in whom NSAIDs and exercise have failed to control symptoms.

Evidence for the Use of Skeletal Muscle Relaxants

There are no quality studies evaluating the use of skeletal muscle relaxants for treatment of patients with knee pain.

ANTI-DEPRESSANTS

Antidepressants have been used for treatment of chronic pain disorders.

1. *Recommendation: Norepinephrine Reuptake Inhibiting Anti-depressants for Knee Osteoarthritis or Subacute or Chronic Knee Pain*

There is no recommendation for or against the use of norepinephrine reuptake inhibiting anti-depressants for treatment of knee osteoarthritis, subacute or chronic knee pain (see Chronic Pain guideline).

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

2. *Recommendation: Norepinephrine Reuptake Inhibiting Anti-depressants for Acute Knee Pain*
Norepinephrine reuptake inhibiting anti-depressants are not recommended for treatment of acute knee pain.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

3. *Recommendation: Selective Serotonin Reuptake Inhibitors for Acute, Subacute, or Chronic Knee Pain*

Selective serotonin reuptake inhibitors (SSRIs) are not recommended for treatment of acute, subacute, or chronic knee pain as there is strong evidence of their lack of efficacy in treating chronic low back pain, thus they appear unlikely to be successful in treating acute, subacute, or chronic knee pain.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

4. *Recommendation: Selective Serotonin Reuptake Inhibitors, SSRIs, or Tricyclic Anti-depressants for Chronic Knee Pain in Patients with Co-morbid Depression*

Selective serotonin reuptake inhibitors (SSNRIs), SSRI, and/or tricyclic anti-depressants are recommended for patients with chronic knee pain and co-morbid depression.

Indications – Patients with diagnosed depression of at least moderate severity and with chronic pain, in conjunction with a behavioral program focusing on function with chronic pain.(903)

Duration – Therapy for up to 12 months.(903)

Indications for Discontinuation – No response to medication after 3 months; adverse effects or unwillingness or incapable of participating in behavioral therapy program.

Strength of Evidence – Recommended, Evidence (C)

Rationale for Recommendations

Norepinephrine reuptake inhibiting anti-depressants (e.g., amitriptyline, doxepin, imipramine, desipramine, nortriptyline, protriptyline, maprotiline, and clomipramine) and mixed norepinephrine and serotonin inhibitors (SNRIs) have evidence of efficacy for treatment of chronic low back pain and some other chronic pain conditions (see Low Back Disorders guideline). However, there is no quality, placebo-controlled evidence evaluating these medications for treatment of knee osteoarthritis or other knee pain. There also are no clear analogous disorders for which evidence-based guidance may be reliably derived. There is one moderate-quality study evaluating SNRI, SSRI and tricyclic antidepressants in patients with chronic low back, hip and knee pain. This study reported a significant improvement in depression severity and pain in patients taking antidepressant medications in conjunction with education focused on how to function with chronic pain compared to usual care controls.(903) A moderate-quality study evaluated amitriptyline 50mg a day for 3 days post-operatively and

reported no benefits for pain control.(904) Thus, there is not enough quality evidence of efficacy to warrant a recommendation.

Evidence for the Use of Anti-depressants for Knee Pain and Osteoarthritis

There is 1 high-quality RCT (with two reports) and 1 moderate-quality RCT incorporated into this analysis.

Author/Title Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Kroenke 2009a, b RCT	8.0	N = 250 with low back, hip, or knee pain for 3 months or longer and at least moderate depression severity	Anti-depressant medications, pain self management program, continuous therapy vs. continued care.	At 12 months, intervention greater reduction in depression severity. Pain reduction more likely in intervention group, including global improvement in pain (p <0.05).	“Optimized antidepressant therapy followed by a pain self-management program resulted in substantial improvement in depression as well as moderate reductions in pain severity and disability.”	Low back pain, hip and knee pain all included in analysis without individual results based on pain location. SNRI, SRI, tricyclic medications all used by patients. No placebo control. Anti-depressant therapy in patients with depression and chronic pain improves depression and improves pain in patients with low back, hip and knee pain.
Kerrick 1993 RCT	5.0	N = 28 undergoing total hip or knee arthroplasty	Amitriptyline 50mg vs. placebo both in conjunction with supplemental PCA (opioid) therapy for 3 days post-op after total knee or hip arthroplasty.	No significant pain relief or improvement in mood reported.	“The data from this pilot study failed to show that amitriptyline had an opioid sparing or potentiating effect, or any appreciable salutary effect on pain or symptoms control, during the acute postoperative period.”	Both knee and hip patients included. Small numbers. Data suggest lack of efficacy, but potentially underpowered.

ANTI-CONVULSANT AGENTS (including Gabapentin and Pregabalin)

Anti-convulsant agents have been utilized off-label for some chronic pain syndromes since the 1960s.(905) They have been particularly used for treating neuropathic pain.(906) Anti-convulsants are thought to have analgesic properties. Several have been used to manage chronic pain conditions include carbamazepine, valproic acid, gabapentin, phenytoin, clonazepam, lamotrigine, tiagabine, pregabalin, topiramate, levetiracetam, oxcarbazepine, and zonisamide.

- 1. Recommendation: Topiramate for Knee Osteoarthritis or Subacute or Chronic Knee Pain*
There is no recommendation for or against the use of topiramate for treatment of knee osteoarthritis or other subacute or chronic knee pain (see Chronic Pain guideline).
Strength of Evidence – No Recommendation, Insufficient Evidence (I)
- 2. Recommendation: Topiramate for Acute Knee Pain*
Topiramate is not recommended for treatment of acute knee pain.
Strength of Evidence – Not Recommended, Insufficient Evidence (I)
- 3. Recommendation: Gabapentin for Knee Osteoarthritis or Subacute or Chronic Knee Pain*
There is no recommendation for or against the use of gabapentin for treatment of knee osteoarthritis or subacute or chronic knee pain (see Chronic Pain guideline).
Strength of Evidence – No Recommendation, Insufficient Evidence (I)

4. *Recommendation: Gabapentin for Acute Knee Pain*

Gabapentin is not recommended for the treatment of acute knee pain.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

5. *Recommendation: Gabapentin for Peri-Operative Pain*

Gabapentin is recommended for the peri-operative management of pain to reduce the need for opioids, particularly in those with adverse effects from opioids.

Indications – Peri-operative pain management.

Frequency/Dose – Limit to immediate peri-operative period, usually a few days.

Indications for Discontinuation – Resolution, intolerance.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendations

There are no quality studies involving knee pain patients, and quality evidence suggests that topiramate is weakly effective for treatment of low back pain patients and gabapentin is not helpful. However, there is quality evidence that gabapentin reduces the need for opioids when administered as part of perioperative pain management for other patients, thus by inference, gabapentin is recommended for knee surgery patients.(907-910)

Evidence for the Use of Anti-convulsant Agents

There are no quality studies evaluating the use of topiramate or gabapentin for knee osteoarthritis or other knee pain. There are 4 high-quality RCTs incorporated in this analysis for peri-operative pain that are described in the Chronic Pain guideline. (907-910)

TUMOR NECROSIS FACTOR-ALPHA BLOCKERS

A variety of tumor necrosis factor (TNF) alpha blockers, including infliximab (a chimeric monoclonal antibody directed against TNF-alpha), etanercept (a recombinant molecule comprising part of the TNF receptor plus the constant region of human immunoglobulin G1 that binds to TNF-alpha) and adalimumab (an IgG1 monoclonal antibody that binds to TNF-alpha) are in widespread use for rheumatologic and other inflammatory disorders. There may be indications for treatment of some patients with these agents in the setting of inflammatory rheumatologic disorders. However, this is beyond the scope of this guideline.

1. *Recommendation: Tumor Necrosis Factor-alpha Blockers for Osteoarthritis or Acute, Subacute, or Chronic Knee Pain or Other Non-inflammatory Knee Disorders*

Tumor necrosis factor-alpha blockers are not recommended for the treatment of osteoarthritis or acute, subacute, or chronic knee pain, including other non-inflammatory knee disorders.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

2. *Recommendation: Tumor Necrosis Factor-alpha Blockers for Arthroplasty Patients with Osteolysis*

Tumor necrosis factor-alpha blockers are not recommended for the treatment of arthroplasty patients with osteolysis.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Rationale for Recommendations

One quality study has reported evaluating etanercept for attempted treatment of periacetabular osteolysis in arthroplasty patients, but found a lack of efficacy.(911)

Evidence for the Use of Tumor Necrosis Factor-alpha Blockers for Knee Pain

There is 1 moderate-quality RCT incorporated in this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Schwarz 2003 RCT	6.0	N = 20 arthroplasty patients with periacetabular osteolysis	Etanercept (25mg SQ, twice a week) vs. placebo for 12 months.	Mean change in periacetabular osteolysis: etanercept 3.40± 3.61cm ³ vs. placebo 3.00±3.90cm ³ . Some reduction attributed to cup migration. Study not powered to detect clinical significance of treatment.	“Volumetric CT was able to measure progression of osteolysis over the course of a year. Varying results were found.”	Small sample size. Low power. No difference demonstrated from treatment. Study proposes volumetric CT for assessment.

GLUCOSAMINE, CHONDROITIN AND METHYLSULFONYLMETHANE (MSM)

Glucosamine, chondroitin, and methylsulfonylmethane (MSM) are over-the-counter nutraceuticals(912) advocated as safe and effective treatment alternatives to NSAIDs for the management of osteoarthritis. These supplements have also gained additional interest as agents that may potentially modify or slow the progression of osteoarthritis.

Glucosamine is an amino acid monosaccharide that occurs naturally in the human body, and is one of the principle substrates in the biosynthesis of cartilaginous glycosaminoglycans, proteoglycans, and hyaluronic acid.(913) Although the specific cause of osteoarthritis is unknown, turnover of the cartilage matrix is mediated by a multitude of complex autocrine and paracrine anabolic and catabolic factors, leading to loss of articular cartilage, subchondral bone remodeling, and low-level inflammation of the synovial membrane.(914) Glucosamine supplementation is hypothesized to beneficially affect the imbalance between rates of synthesis and degradation of cartilage proteoglycans.(913, 915) Glucosamine reportedly has anti-inflammatory properties.(916, 917) Glucosamine preparations come in two forms, glucosamine sulfate (pill and crystalline powder) or glucosamine hydrochloride,(918, 919) and are often combined with chondroitin sulfate and sometimes combined with methylsulfonylmethane. Most studies have utilized glucosamine sulfate rather than glucosamine hydrochloride, although there are no quality comparative head-to-head trials. Glucosamine sulfate is also available in suspension for intramuscular and intra-articular injection.(920-922)

Glucosamine generally has few adverse effects with safety profiles comparable to placebo in the reviewed trials. However, there are two hypothetical risks that may suggest select patient groups to avoid these supplements. First, there is debate as to whether or not glucosamine, which is an aminoglycan, promotes insulin resistance.(923-925) However, no adverse effects have been found in patients who have well-controlled diabetes mellitus or even in persons with glucose intolerance.(926, 927) Second, glucosamine preparations are commonly produced from the shells of shrimp and crabs (chitin) – seaweed and shark cartilage has also been used,(928, 929) leading to concerns for potential allergic responses in persons with shellfish allergies. In a trial sponsored by the U.S. National Institutes of Health (NIH) of 15 patients with known systemic allergies to shrimp, administration of glucosamine sulfate was not found to result in any immediate hypersensitivity reactions.(930) Glucosamine products in the U.S. are now also commonly synthesized from grains, providing an alternate source for persons concerned with shellfish allergies. Therefore, these hypothetical risks appear to be low. The most common glucosamine dose is 1500mg per day in single or divided doses.

Chondroitin, a sulfated glycosaminoglycan matrix, provides structural elasticity. Chondroitin is thought to work via anti-inflammatory activity, stimulation of proteoglycans and hyaluronic acid synthesis, and decrease chondrocytic catabolic activity, although the exact mechanisms are

unclear.(931) As with glucosamine, there are few reported adverse effects from chondroitin sulfate though some patients have GI tract effects.(932) This supplement is produced from animal cartilage such as bovine trachea, porcine and sharks. The most common dose is 1,200mg per day in single or divided dosages. Chondroitin is most commonly combined with glucosamine in commercial preparations, sometimes additionally including MSM.

1. *Recommendation: Glucosamine Sulfate, Chondroitin Sulfate, or Methylsulfonylmethane for Knee Osteoarthritis*

There is no recommendation for or against the use of glucosamine sulfate 1,500mg daily (single or divided dose), chondroitin sulfate, or methylsulfonylmethane for the treatment of knee osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

2. *Recommendation: Glucosamine Sulfate Intra-Muscular Injections for Knee Osteoarthritis*
There is no recommendation for or against the use of glucosamine sulfate intra-muscular injections for the treatment of knee osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

3. *Recommendation: Glucosamine Sulfate Intraarticular Injections for Knee Osteoarthritis*
There is no recommendation for or against the use of glucosamine sulfate intraarticular injections for the treatment of knee osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

4. *Recommendation: Glucosamine Sulfate, Chondroitin Sulfate, or Methylsulfonylmethane for Osteoarthritis Prevention*

There is no recommendation for or against the use of glucosamine sulfate, chondroitin sulfate, or methylsulfonylmethane for prevention of osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

There has been some debate over the efficacy of these preparations in reducing pain, improving function, and slowing the progression of the joint space narrowing in osteoarthritis. Six quality studies have followed knee joint spaces using x-rays(933-938) and one has objectively followed the hip joint.(939) Four utilized glucosamine sulfate(936-939) while three utilized chondroitin sulfate.(933-935) Four studies demonstrated preservation of joint spaces compared with placebo, including some suggestion that there was no joint space narrowing in the active treatment group over 2 years.(933, 934, 936, 937) Two studies were negative (one was the study of the hip joint(939) and the other the knee(938)), but both studies suggested a trend towards efficacy in both symptoms and x-ray findings. Two studies found some beneficial x-ray findings, but the change in joint space was not statistically significant.(935, 938) Thus, the studies that utilized x-rays generally suggested benefits from the treatment of knee osteoarthritis with either glucosamine sulfate or chondroitin sulfate; however, quality evidence of objective benefit utilizing x-rays of glucosamine or chondroitin for the treatment of hip OA is not clearly present.

There are 14 quality studies that included a comparison of glucosamine sulfate with placebo. Of the 6 highest quality studies,(506, 940-944) one was negative, although it trended towards benefits.(944) There are 10 quality studies that included a comparison of chondroitin sulfate with placebo.(933-935, 944-950) Most of the studies on chondroitin are heavily weighted toward benefit over placebo; however, symptoms were not improved in 2 studies.(934, 944) Two quality studies that assessed MSM found it to be beneficial .(951, 952)

Studies compared these treatments with traditional NSAIDs(938, 945, 953-957) or acetaminophen.(958, 959) Glucosamine hydrochloride, chondroitin sulfate and the combination were not superior to celecoxib 200mg per day or diclofenac 50mg TID(938, 945, 954); however, the combination was successful for treatment of moderate to severe osteoarthritis compared with placebo(945) and chondroitin sulfate had longer lasting pain relief compared to diclofenac.(954) Three studies found glucosamine sulfate comparable to ibuprofen 1200mg per day.(953, 955, 956) Acetaminophen was found to be inferior to glucosamine sulfate.(958)

Glucosamine and chondroitin, alone or in combination, are not invasive, appear relatively safe, do not result in gastrointestinal erosions or the other common side effects of NSAIDs, are relatively inexpensive, and may provide some modest relief of knee osteoarthritis pain, particularly in patients with more advanced pain. These medications may modify or slow the progression of knee OA as measured by slowing of cartilage destruction and joint narrowing, although the clinical significance of this effect is not entirely clear.(938)

One major limitation of these studies is that different glucosamine formulations (hydrochloride versus sulfate), different frequencies and dosage strengths, and different durations and severities of disease of the study populations are present in different studies.(960) Dose has not been standardized and reportedly ranges widely in available preparations. There is evidence that the sulfate salt rather than the hydrochloride formulation of glucosamine may be more effective. There is also some evidence that a single daily dose of chondroitin sulfate may be as or more effective than divided doses.(949)

Evidence for the Use of Glucosamine, Chondroitin, and Methylsulfonylmethane for Knee Pain
There are 19 high and 19 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT in Appendix 1.(961)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Glucosamine or Chondroitin vs. Placebo						
Uebelhart 2004 RCT	10.0	N = 110 with knee OA	Chondroitin sulfate 800mg QD vs. placebo for two 3-month periods during 1 year.	Chondroitin group improved vs. placebo at Months 9 and 12 (p <0.05; p <0.01). Pain intensity decreased 42% Month 9 and 12 in CS group vs. 25% in placebo (p <0.05). Differences in VAS scores and physician and patient efficacy assessments favored CS at 6, 9, and 12 months (p <0.01). CS treatment had significant role on variation of joint space surface area and mean joint space width (p = 0.03) but not on minimum joint space width vs. placebo.	“This study supports the evidence that oral CS of bovine origin and high pharmaceutical quality is a well-tolerated drug, which is effective in reducing pain and improving function in patients suffering from symptomatic knee osteoarthritis.”	Dropout rate was 26% with no difference between groups.
Clegg 2006 RCT	9.5	N = 1,583 with knee OA	Oral glucosamine hydrochloride (500mg TID) vs. chondroitin sulfate (400mg TID) vs. both glucosamine and chondroitin sulfate vs.	Combined glucosamine and chondroitin sulfate was borderline vs. placebo in reducing WOMAC pain score 20% (p = 0.09). As compared with rate of response to placebo (60.1%), rate of response to combined treatment was 6.5% points higher (p = 0.09) and celecoxib response rate was 10.0%	“Celecoxib was demonstrated to reduce pain effectively in the overall group of patients with osteoarthritis of the knee. The combination of glucosamine and chondroitin sulfate	Results showed combination glucosamine-chondroitin to have significantly better outcomes in subgroup of moderate-to-severe group (WOMAC pain score 301-400) in

			celecoxib 200mg QD vs. placebo in treatment of knee OA in 6 month trial.	points higher (p = 0.008). For patients with moderate-to-severe pain at baseline, response rate significantly higher with combined therapy vs. placebo (79.2% vs. 54.3%, p = 0.002). OMERACT-OARSI response rates showed a similar result.	may be effective in the subgroup of patients with moderate-to-severe knee pain.”	WOMAC pain reduction of 50% or more, WOMAC pain score change from baseline and WOMAC function score. Results with Celecoxib not significant in these categories. Study used non-conventional glucosamine preparation.
Pavelká 2002 RCT	9.5	N = 202 with knee OA	Oral glucosamine sulfate (1,500mg once daily) vs. placebo for knee osteoarthritis in 3-year trial of disease progression.	After 3 years, average change in progressive joint space narrowing with placebo use - 0.19mm (95% CI, -0.29 to -0.09mm) while no narrowing change with glucosamine sulfate use (0.04mm; 95% CI, -0.06 to 0.14mm), with a significant difference between groups (p = 0.001). Glucosamine sulfate significantly higher improvement in 20% on Lequesne index and 15% on WOMAC index joint stiffness (p <0.001 and p = 0.002, respectively) compared with placebo.	“Glucosamine sulfate is the first pharmacologic intervention that slowed the progression of knee osteoarthritis during the long-term treatment.”	High dropout rate (81/202 = 41% dropout) over the 3 year study, although results reported by intent-to-treat.
Herrero-Beaumont 2007 RCT	9.0	N = 318 with OA	Oral glucosamine sulfate (1,500mg once daily) vs. acetaminophen (1,000mg TID) vs. placebo using double dummy technique in treatment of knee OA for 6 months.	Glucosamine sulfate more effective than placebo in improving Lequesne score with decrease of 3.1 points, vs. 1.9 for placebo (mean difference = -1.2 [95% CI, -2.3 to -0.8]; p = 0.032); 2.7-point decrease with acetaminophen not significant vs. placebo (mean difference = -0.8 [95% CI, -1.9 to 0.3]; p = 0.18). Similar results observed for WOMAC. More responders to glucosamine sulfate (39.6%) and acetaminophen (33.3%) than placebo (21.2%) (p = 0.004 and p = 0.047 vs. placebo).	“The glucosamine sulfate at the once-daily dosage is an effective medication for knee osteoarthritis symptoms, compared with placebo. Although acetaminophen also had a higher responder rate compared with placebo, it failed to show significant effects on the algofunctional indexes.”	Glucosamine appeared superior to acetaminophen as well as placebo.
Usha 2004 RCT	9.0	N = 118 with OA	Oral glucosamine (Glu) 500mg TID vs. methylsulfonylmethane (MSM) 500mg TID vs. both Glu and MSM vs. placebo in osteoarthritis of knee for 12 weeks.	Placebo showed insignificant change in mean pain index (mean difference = 1.57 [SD, ± 0.5]) to (mean difference = 1.16 [SD, ± 0.76]). Glu showed significant decrease in mean pain index (mean difference = 1.74 [SD, ± 0.47]) to (mean difference = 0.65 [SD, ± 0.71]; p <0.001). MSM significantly decreased mean pain index from (mean difference = 1.53 [SD, ± 0.51]) to (mean difference = 0.74 [SD, ± 0.65]) and combination treatment highly significant decrease in	“The therapy with Glu, MSM and their combination produced an analgesic, anti-inflammatory effect in patients with osteoarthritis. Combination therapy showed better efficacy in reducing pain, swelling and improving the functional ability of joints over	Unclear whether study medication was Glu sulfate or Glu hydrochloride. Combination of Glucosamine and MSM appears superior.

				mean pain index (mean difference = 1.7 [SD, ± 0.47]) to (mean difference = 0.36 [SD, ± 0.33]; p <0.001). After 12 weeks, mean swelling index significantly decreased with Glu and MSM, while decrease in swelling index with combination therapy greater (mean difference = 1.43 [SD, ± 0.63]) to (mean difference = 0.14 [SD, ± 0.35]; p <0.05).	individual therapy. All the treatments were well tolerated.”	
Mazières 2007 RCT	9.0	N = 307 with knee OA	Chondroitin sulfate 500mg BID vs. placebo for 24 weeks for knee OA.	Decrease in pain was -26.2 (24.9) and -19.9 (23.5) mm and improved function - 2.4(3.4) (-25%) and -1.7 (3.3) (-17%) in chondroitin sulfate and placebo groups, respectively (0.029 and 0.109). OMERACT-OARSI responder rate was 68% in chondroitin sulfate and 56% in placebo group (p = 0.03). No significant difference observed for changes in biomarkers of inflammation.	“This study failed to show an efficacy of chondroitin sulfate on the two primary criteria considered together, although chondroitin sulfate was slightly more effective than placebo on pain, OMERACT-OARSI response rate, investigator’s assessment and quality of life.”	Baseline differences between groups on variable of stage of disease appear to be present 69% vs. 59% of chondroitin group rated as intermediate OA disease. No information on other percentage of groups.
Hughes 2002 RCT	8.5	N = 80 with knee OA	Oral glucosamine sulfate (500mg TID) vs. placebo with knee OA for 6 months.	Area under curve (AUC) analysis revealed no significant difference between placebo [mean = 1065.45, SD=398.07] and glucosamine [mean = 1081.28, SD = 577.69]; p = 0.89 in primary outcomes measures. No differences between placebo and glucosamine for treatment response (x ² statistic 0.006, p = 0.94). No significant difference in use of rescue analgesia between glucosamine (mean paracetamol tablets taken 43, S.D. 63.92, range 0-252) and placebo (mean paracetamol taken 45, S.D. 75.64, range 0-264).	“As a symptom modifier in OA patients with a wide range of severities, glucosamine sulfate was no more effective than placebo.”	Permitted co-treatment with NSAIDs may have confounded results. Relatively small sample size.
McAlindon 2004 RCT	8.5	N = 205 with knee OA	Oral glucosamine (1,500mg once daily) and placebo in 12-week trial for knee OA.	At Week 12 followed-up from baseline; no difference between glucosamine and placebo groups in terms of change in pain score (2.0±3.4 vs. 2.5±3.8, p = 0.41), and analgesic use (133±553 vs. -88±755, p = 0.12), after adjusting covariates.	“Although glucosamine appears to be safe, it is no more effective than placebo in treating the symptoms of knee osteoarthritis.”	Baseline differences of comparison groups. Medication supplier changed during trial, resulting in initial use of glucosamine sulfate capsules replaced by glucosamine hydrochloride powder. Study completed through Internet.

Mehta 2007 RCT	8.5	N = 95 with OA	Oral glucosamine sulfate (750mg BID) vs. Reparagen (900mg BID) in mild to moderate knee OA for 8 weeks.	Glucosamine sulfate and reparagen showed significant benefits in WOMAC and VAS outcomes (20% improvement from baseline) within 1 week of treatment ($p < 0.05$) and over 8 weeks of treatment ($p < 0.001$). Overall WOMAC score benefit was 60% reduction for glucosamine vs. 62% reparagen. Response rate of 50% reduction in WOMAC scores significantly greater for reparagen (58.3%) than glucosamine (38.2%) at Week 4 ($p = 0.05$). Rescue medication (paracetamol) significantly lower in reparagen group ($p < 0.01$).	“Glucosamine sulfate and reparagen provided effective relief of mild to moderate osteoarthritis of the knee in this population, with continued improvements upon sustained treatment.”	No placebo group. Data suggest reparagen may be superior to glucosamine
Messier 2007 RCT	8.5	N = 89 with knee OA	Glucosamine hydrochloride 1,500mg chondroitin sulfate/1,200mg QD vs. placebo for 6 months for knee OA. Both groups received exercise training and instruction.	Mean function did not vary significantly between groups at 6-month ($p = 0.52$) or 12-months ($p = 0.50$). Mean WOMAC function combining both groups improved significantly over time ($p = 0.005$). No difference in pain measures, 6-minute walk distance, or knee strength at 6 or 12 months between groups.	“Glucosamine hydrochloride/chondroitin sulfate group was not superior to the placebo group in function, pain, or mobility after both phases of the intervention (pill only and pill plus exercise).”	Allocation unclear with baseline differences in function present.
Noack 1994 RCT	8.5	N = 252 with knee OA	Oral glucosamine sulfate (500mg TID) vs. placebo for knee OA over 4 weeks.	Lequesne index decreased to 7.45 ± 0.5 points in glucosamine group (average 3.2) and 8.4 ± 0.4 points in placebo group (average 2.2) ($p < 0.05$). Proportion of responder patients: 52% with glucosamine, 37% placebo in an intention-to-treat analysis ($p = 0.016$).	“The treatment with glucosamine sulfate resulted in a significantly higher improvement knee osteoarthritis in relation to placebo.”	Blinding of assessor not clear. Results of per-protocol analysis similar to intent-to treat.
Haupt 1999 RCT	8.0	N = 118 with knee OA	Oral glucosamine hydrochloride (500mg TID) vs. placebo for knee OA for 8 weeks.	Glucosamine reduced WOMAC pain scores over 8 weeks (mean difference = 46.36 [SD, 13.1]) to (mean difference = 36.57 [SD, 19.5]) vs. placebo reduced WOMAC pain scores (mean difference = 42.42 [SD, 14.9]) to (mean difference = 38.57 [SD, 19.3]). Glucosamine hydrochloride more than 2 times improvement compared to placebo (21 vs. 9.1%). Between Week 5 and 8, knees of patients taking glucosamine appeared to show improvement vs. placebo ($p = 0.026$).	“There was no significant difference in pain reduction between the glucosamine hydrochloride and placebo group as measured by WOMAC. Secondary endpoints of cumulative pain reduction as measured by daily diary and knee examination were favorable, suggesting that glucosamine hydrochloride benefits some patients with knee OA.”	The methods state pharmacists were blinded to treatment allocation, however, that seems impossible. Outcomes measures trend towards positive results.

Reginster 2001 RCT	8.0	N = 212 with knee OA	Oral glucosamine sulfate (1,500mg QD) vs. placebo for knee OA in 3 year trial of disease progression.	No average loss of joint-space width in patients receiving glucosamine sulfate (0.07mm, 95% CI, -0.17 to 0.32); placebo had significant mean and minimum joint-space narrowing (-0.31mm, 95% CI, -0.57 to -0.04). As assessed by WOMAC scores, symptoms worsened slightly in placebo vs. glucosamine sulfate (p = 0.016).	“The long-term effect of glucosamine sulfate was proved to benefit for both combined joint structure-modifying and symptom-modifying. No alteration in glycemic homeostasis was found.”	High dropout rate (73/212 = 34%), although demographic data suggest a lack of bias. NSAIDs allowed during study.
Michel 2005 RCT	8.0	N = 300 with knee OA	Oral chondroitin sulfate 800mg QD vs. placebo for 2 years for knee OA.	Difference in joint space loss between 2 groups was significant for mean joint space width (0.14 ±0.57 mm, p = 0.04) and for minimum joint space width (0.12 ± 0.52 mm, p = 0.05) favoring chondroitin sulfate group (no loss in chondroitin group). No difference in WOMAC pain or function scores.	“Chondroitin sulfate halted structural changes in osteoarthritis of the knee as assessed by radiographic follow-up over 2 years. There were no significant symptomatic effects in this study. The clinical relevance of the observed structural results has to be further evaluated.”	Dropout was 26% at 2-years. Study population had relatively low pain severity scores to begin with, which may have contributed to lack of improvement of pain and function scores.
Rozendal 2008 RCT	7.5	N = 222 with hip OA	Oral glucosamine sulfate (750mg BID vs. placebo for hip osteoarthritis over 2 years.	Change from baseline, WOMAC pain score for glucosamine sulfate (mean difference = -1.90 [SD±1.6]) compared to placebo (mean difference = -0.30 [SD±1.6]). Joint space narrowing for glucosamine sulfate group (mean difference = -0.094 [SD ± 0.32]) compared to placebo (mean difference = -0.057 [SD±0.32]). Over 2 years daily therapy after adjusting for covariates, glucosamine sulfate no better than placebo in reducing WOMAC pain scores (mean difference = -1.54 [95% CI, -5.43 to 2.36]), or reducing WOMAC function scores (mean difference = -2.01 [95% CI, -5.38 to 1.36]). Joint space narrowing not significantly different between glucosamine sulfate and placebo.	“Glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip osteoarthritis.”	Data suggest non-statistically significant trends in symptoms and joint space narrowing in favor of glucosamine. Baseline disease was mild based on radiographic grading overall.
Müller-Fassbender 1994 RCT	6.5	N = 199 with knee OA	Oral glucosamine sulfate 500mg. TID vs. ibuprofen 400mg TID for 4 weeks treatment of knee osteoarthritis.	Lesquesne’s index value progressively decreased in both groups, although no statistical significance between groups. Ibuprofen treated patients experienced more prompt relief, mainly evident during first 2 weeks. GS exerted its main clinical effect from 3rd week onward. GS group had significantly fewer adverse effects (p <0.001).	“This 200 patient comparative 4-week study demonstrated that oral glucosamine sulfate was as effective as ibuprofen (1200 mg/day) in controlling symptoms in patients with active OA of the knee. Conversely,	Blinding and allocation unclear. No placebo control. No statistical difference in efficacy between OTC ibuprofen and GS in 4 week trial.

					glucosamine was better tolerated than ibuprofen.”	
Scroggie 2003 RCT	6.0	N = 38 with Type 2 diabetes mellitus	Glucosamine sulfate 1,500mg/chondroitin sulfate 1200mg vs. placebo for 90 days in patients with type 2 diabetes mellitus.	HbA1c mean values changed very little in both treatment groups during study. No significant differences between baseline measures or between groups. No changes in medical therapy in either group during the study period.	“This study demonstrated that oral glucosamine supplementation does not adversely affect glycemic control when administered to patients with type 2 diabetes mellitus at doses recommended by the manufacturer.”	Study goal to assess glycemic control among diabetics prescribed GS/CS. Patients in placebo group had milder condition of diabetes. Allocation unclear.
Villacis 2006 Crossover Trial	5.5	N = 15 with shrimp allergy and an ImmunoCAP class level of 2 or greater	Glucosamine hydrochloride 1500mg chondroitin/1200mg using shell-fish derived vs. synthetic manufactured glucosamine in patients with confirmed shrimp/shell fish allergies.	Fifteen (15) subjects in crossover trial of 1 dose oral challenge with 24-hour follow-up. All subjects tolerated shell-derived glucosamine without incident or an immediate hypersensitivity response.	“Glucosamine supplements from specific manufacturers do not contain clinically relevant levels of shrimp allergen and therefore appear to pose no threat to shrimp-allergic individuals.”	Small sample size. Randomization and allocation unclear. Results cannot be inferred to all manufacturers of shrimp/shell fish derived glucosamine.
Lopes Vaz 1982 RCT	5.0	N = 40 with unilateral knee OA	Glucosamine sulfate (1.5g) vs. ibuprofen (1.2g) daily over 8 weeks.	Pain scores showed a significant decrease during both treatments. No significant differences were detected in the general symptoms which appeared during treatment. No significant variations were recorded in the hematological tests.	“The authors suggest that the best therapeutic results in osteoarthritis could possibly be obtained by giving glucosamine sulfate along with an anti-inflammatory agent during an initial period of about 2 weeks to ensure prompt reduction of pain and then to continue treatment for a further 6 to 10 weeks or longer with oral glucosamine sulfate.”	Comparison is made with OTC strength ibuprofen. Allocation, baseline characteristics and blinding are unclear. There was no control for co-interventions.
Invasive Preparations						
Reichelt 1994 RCT	8.5	N = 155 with knee OA	Intramuscular injection glucosamine sulfate (400mg twice per week) vs. placebo for knee osteoarthritis over 6 weeks.	Intramuscular glucosamine sulfate vs. placebo showed improvement in symptoms of knee OA (pain and movement limitation) over 6-week therapeutic course (p <0.05). Response rate 55% glucosamine (n = 73) vs. 33% placebo (n = 69) (p = 0.012). Local and systemic tolerability of intramuscular glucosamine sulfate were good and without	“Intramuscular glucosamine sulfate reduced pain and improved functional in knee osteoarthritis patients.”	Some details missing of randomization, allocation, and blinding.

				significant difference compared to placebo.		
Gramajo 1989 RCT	7.0	N = 62 with hip or knee OA	Glycosaminoglycan-peptide complex (GPC) ("Rumalon") injections vs. placebo injections. 3 injections a week for 8 week course, 3 courses per year.	Night pain (before/after treatment): GPC 2.4±2.9/0.4±0.69 vs. placebo 2.1±1.58/1.9±0.83, p <0.001. Results comparable for day pain (p <0.01) and joint mobility (p <0.005). Time to walk 10 meters: GPC 21.8±6.88/18.0±4.86 vs. 24.1±7.31/23.9±3.3 seconds, p <0.001. No adverse effects reported.	"[G]lycosaminoglycan-peptide complex ('Rumalon') offers not only an effective but also a well-tolerated form of treatment which can be used to replace or supplement non-steroidal anti-inflammatory drugs, particularly in long-term therapy."	Co-interventions uncontrolled. Therapy required 72 injections per year.
Vajaradul 1981 RCT	5.0	N = 54 with gonarthrosis	Intra-articular injection of glucosamine sulfate (dose not reported) vs. saline placebo in affected knee.	After 5 consecutive weeks of treatments, both treatments significantly improved pain scores, although pain reduction with glucosamine was greater (mean difference = 0.18, ±0.03; p <0.01) vs. placebo (mean difference = 0.69, ±0.18; p = 0.01).	"Glucosamine treatment provided a greater freedom from pain than that given by the mere injection of placebo into the joint. Moreover, glucosamine showed no resulting side effects."	Glucosamine group somewhat older. Details sparse, especially blinding.
Glucosamine vs. Placebo Discontinuation Trial						
Cibere 2004 RCT	8.5	N = 137 with knee OA	Oral glucosamine sulfate (up to 1,500mg a day) vs. placebo for knee OA in 6 month trial. Randomized discontinuation trial (control was discontinuation of treatment) in patient group already using glucosamine sulfate with reported efficacy; primary outcomes measures disease flare-up and flare severity.	After 6 months, disease flares in intention-to-treat analysis were seen in 21 (45%) of 71 patients in glucosamine group and 28 (42%) of 66 patients in placebo group. Between-group difference not statistically significant (95% CI, -19 to 14; p = 0.76). After adjustments, no difference in risk of flare (Hazard ratio 0.8, (95% CI 0.5 to 1.4, p = 0.45) or use of acetaminophen and NSAIDs, mean changes in WOMAC pain scores on walking, pain, stiffness, or function scales, or adverse effects between glucosamine and placebo groups (p >0.05).	"This study provided no evidence of symptomatic benefit from continued use of glucosamine sulfate over and above found with placebo."	Glucosamine group had more severe knee OA based on radiography at baseline providing an uncontrolled potential confounder. Cannot rule out possibility of long-term benefit in placebo (discontinuation group) from earlier use of glucosamine.
Glucosamine						

Das 2000 RCT	8.5	N = 93 with Grade 2 or more knee OA, age 45-75, arthritic symptoms >6 months duration	Glucosamine hydrochloride 500mg plus chondroitin 400mg plus manganese 76mg vs. placebo for 6 months.	Month 4: Lequesne index of severity better in glucosamine/chondroitin group (p = 0.003). Month 6: mild/moderate group better in glucosamine/chondroitin group (p = 0.04). No significant difference in severe arthritis group.	"The studied combination of glucosamine hydrochloride, sodium chondroitin sulfate and manganese ascorbate is effective in the management of osteoarthritis of the knee."	Response to medications considered at 25% improvement. Glucosamine can decrease pain as measured by Lequesne index in patients with mild or moderate knee OA, but not in severe knee OA patients.
Braham 2003 RCT	7.0	N = 46 volunteers aged 20-70 with regular knee pain	Glucosamine hydrochloride 2,000mg vs. placebo for 12 weeks.	No significant difference in joint line palpation tenderness. Knee pain scores were better in glucosamine group at 8 weeks p = 0.004, but not at week 12; 88% of glucosamine group reported improvement in pain after treatment; 17% of placebo group reported improvement in pain after treatment.	"...this study supports the findings of the majority of similar studies conducted into glucosamine supplementation, showing that it can provide some pain relief and self reported improvements in functional ability in subjects who suffer from regular knee pain..."	Small numbers. Improvements seen in subjective areas of pain relief only. No significant objective findings reported. Different types of knee pain not analyzed separately.
Frestedt 2008 RCT	7.0	N = 50 ambulatory patients aged 25-75 with normal digestion and absorption, moderate to severe knee OA	Glucosamine sulfate 1,500mg vs. Aquamin 2,400mg vs. Glucosamine plus+ Aquamin vs. placebo for 12 weeks	WOMAC pain score glucosamine vs. placebo (p = 0.003), Aquamin vs. placebo (p = 0.003) WOMAC activity score glucosamine vs. placebo (p = 0.008), Aquamin vs. placebo (p = 0.010) WOMAC total score, glucosamine vs. placebo (p = 0.007), Aquamin vs. placebo (p = 0.006) WOMAC stiffness score Aquamin vs. placebo (p = 0.002). All measured after 12 weeks of therapy	"These pilot trial results suggest a potential treatment effects for Aquamin among subjects with moderate to severe OA and this preliminary finding warrants further study."	WOMAC pain scores were different at baseline. Small numbers in each intervention group. Glucosamine plus Aquamin group showed no improvement over placebo.
Cohen 2003 RCT	6.5	N = 59 with knee OA	Topical glucosamine plus chondroitin plus shark cartilage plus peppermint oil vs. placebo plus peppermint oil 6 weeks.	VAS at 4 weeks between groups when compared to baseline was greater in intervention group by 1.2 (0.1-2.4) (p = 0.03) VAS at 8 weeks between groups when compared to baseline was greater in intervention group by 1.8 (0.6-2.8) (p = 0.002)	"Topical application of glucosamine and chondroitin sulfate is effective in relieving the pain from OA of the knee and improvement is evident within 4 weeks."	Small numbers. Patients able to continue current treatments. No mention of compliance.
Sawitzke 2008 RCT	6.0	N = 357 aged 40 and older with knee pain for at least 6 months and Kellgren/Lawrenc	Glucosamine sulfate 1,500mg vs. chondroitin sulfate 1,200mg vs. glucosamine plus chondroitin sulfate vs.	No significant differences in joint space width after 24 months of therapy. Glucosamine had the least amount of joint space width loss.	"At 2 years no treatment achieved a predefined threshold of clinically important difference in joint space width as compared to placebo. However, knees with	Trend reported for glucosamine and decreased joint space width loss. Glucosamine plus chondroitin group had more Grade 3 than Grade 2 knees, which may explain decreased

		e Grade 2 or 3 knee OA	celecoxib 200mg vs. placebo for 24 months.		Kellegran/Lawrence grade 2 appeared to have the greatest potential for modification by these treatments.”	effect when compared to glucosamine and or chondroitin alone.
Qiu 1998 RCT	4.5	N = 178 with knee OA	Glucosamine sulfate 1,500mg vs. ibuprofen 1,200mg a day for a total of 4 weeks.	After 4 weeks of therapy, both groups improved in pain and swelling. No significant difference between groups seen. Less patients complained of adverse events in glucosamine group	“Glucosamine appears therefore particularly useful in the long-term therapeutic courses needed in chronic knee pain.”	Lack of details lowered score. Both groups reported as having significant improvement over baseline pain and swelling, but glucosamine had fewer adverse effects reported.
Marti-Bonmati 2009 RCT	4.5	N = 16 non-advanced degenerative patellar conditions where surgery not indicated	Glucosamine sulfate 1,500mg vs. acetaminophen 650mg for 6 months.	Glucosamine significantly increased vascular permeability at 6 months (p <0.001) it decreased pain (p <0.001) and increased function (p <0.01).	“Glucosamine sulfate decreases pain while improving functional outcomes in patients with cartilage degeneration.”	Small numbers. Lack of study details lowered scores. No baseline data on BMI or duration of symptoms given. MRIs were done at baseline and at 6 months to evaluate vascular permeability.
Chondroitin						
Kahan 2009 RCT	8.5	N = 622 with knee OA	Chondroitin sulfate 800mg vs. placebo for 2 years	Percent patients with >/+0.25mm loss in joint space width decreased in chondroitin group when compared to control (p <0.0005) NNT 8, relative risk reduction 33%. Pain improved faster in CS group (p <0.01). BMI significantly interacted with treatment, CS helped patients with higher BMI more.	“The long-term combined structure-modifying and symptom-modifying effects of chondroitin sulfate suggest that it could be a disease-modifying agent in patients with knee OA”	Large numbers of participants. Chondroitin sulfate decreased joint space width loss in patients over 2 years of therapy vs. placebo. Also reported to help with pain control.
Mazieres 2001 RCT	8.0	N = 131 with knee OA (ACR, x-ray confirmed) >50 years old	Chondroitin sulfate 500mg vs placebo BID for 3 months; 6 months total follow-up.	CS group showed improved Algofunctional index vs. placebo (ITT -1.6±3.1 vs. -2.4±3.1, p = 0.12 vs. p = 0.02 in completers). Pain at rest improved vs. placebo (ITT analysis with -8.0±21.2 vs. -14.9±21.8, p = 0.08 vs. p = 0.03 in completers).	“[A] daily dose of 1 g may be sufficient to relieve symptoms.”	ITT population trended towards efficacy in multiple measures while completers were significant. Data suggest modest efficacy compared with placebo.
Bucsi 1998 RCT	6.5	N = 80 with knee OA	Chondroitin sulfate 800mg a day vs. placebo for 6 months.	Pain decreased in more in CS vs. placebo and was significant starting at 3 months (p <0.01). Walking time for 20 meters significantly decreased in CS group at 6 months.	“Chondroitin sulfate given orally for 6 months at 800mg/day is a safe symptomatic slow-acting drug in patients suffering from knee OA.”	Decrease in pain became significant in CS vs. PBO group at 3 months and remained at 6-month follow-up.
Kerzberg 1987 RCT	6.0	N = 17 with knee OA	Chondroitin 150 UB IM vs. placebo.	No difference in about of aspirin used. N radiological changes noted over the 6 weeks of therapy. Pain control with articular movement were better controlled in chondroitin group compared to placebo	“In the present study, GAG, chondroitin sulfate, combined with aspirin use affords significantly better results vis-à-vis the	Small numbers; 11/17 were women. Cross-over study design with 4-week washout period. No changes seen

					administration of aspirin plus placebo, in the same patients.”	in x-rays, but patients did have decreased pain. Medications given IM.
Bourgeois 1998 RCT	5.5	N = 127 with mono or bilateral knee OA	Chondroitin sulfate gel 1200mg vs. chondroitin sulfate 400mg capsule TID vs. placebo for 3 months.	Lequesne’s index reduction significantly greater in 2 CS groups compared to PBO (p <0.0001). Reduction significant at Day 14 for 1,200mg gel, Day 42 for CS capsule. No differences noted between 2 different CS groups. Pain significantly decreased at Day 91 in both CS groups vs. placebo (p <0.0005).	“The results confirm the progressive efficacy of CS on the subjective painful symptomatology and on the articular mobility in patients suffering from knee OA.”	Lack of details lowered score. Chondroitin sulfate vs. placebo decreases pain and increase function in knee OA. No difference between 1,200mg single dose vs. 400mg TID; 1,200mg dose was oral gel, 400mg dose TID was a capsule.
Morreale 1996 RCT	5.5	N = 146 with knee OA	Chondroitin sulfate 1200mg a day for 3 months vs. diclofenac sodium 150mg a day for 1 month.	After 1st month of therapy, pain decreased in both groups, but faster and greater degree in diclofenac group (p <0.01). Lequesne’s index scores at 6 months changed by 64.4% in CS, 29.7% in DS. Pain at end of study decreased 82% in CS, 36% in DS.	“CS seems to have slow but gradually increasing clinical activity in OA; these benefits last for a long period of time after the end of treatment.”	Complicated study design, both groups ended up taking placebo last 3 months. CS group took active medication first 3 months, DS for only 1 month.
Uebelhart 1998 RCT	5.0	N = 42 with knee OA	Chondroitin 800mg a day vs. placebo for 1 year.	At 12 months, pain decreased by 63% in CS vs. 25% in placebo (p <0.01). Mobility increased by 69% in CS vs. 19% in placebo (p <0.01). Joint space width: decreased in placebo (p <0.05).	“Oral chondroitin sulfate is an effective and safe slow-acting drug for the treatment of knee OA. In addition, CS might be able to stabilize the joint space width and to modulate bone and joint metabolism.”	Small numbers, only 26/46 had x-rays done at 12-month follow up. Pain significantly decreased in CS vs. placebo at 3-month follow up assessment.
MSM						
Kim 2006 RCT	5.5	N = 50 with at least 3 months knee OA, VAS pain >40mm	MSM 3g BID vs. placebo for 12 weeks.	WOMAC pain-decreased in MSM group (p = 0.04), WOMAC physical function-improved in MSM group (p = 0.045).	“MSM 3g BID improved symptoms of pain and physical function during the short intervention without major adverse events.”	Pilot study, small numbers. Higher dropouts in placebo due to lack of efficacy. MSM appeared to trend toward improvement.

COMPLEMENTARY, ALTERNATIVE TREATMENTS OR DIETARY SUPPLEMENTS, ETC.

Many treatments have been attempted to treat chronic pain conditions, including knee pain. Some of these interventions might be classified as dietary supplements or as complementary or alternative treatments.(962-965) These include homeopathic treatments, naturopathic treatments, vitamins, herbal remedies (certain exceptions discussed below), spiritual healing, touch for healing, craniosacral therapy, aromatherapy, energy healing, and neural therapy. Most of these do not have any quality evidence of efficacy. Some controversy surrounds the issue of the value of placebo effects in healing.(966) There are many interventions shown to be efficacious for the treatment of acute, subacute, and/or chronic pain and it is strongly

recommended that patients be treated with therapies proven to be efficacious, whether the intervention is considered complementary.

Recommendation: Complementary or Alternative Treatments, Dietary Supplements, Etc., for Acute, Subacute, or Chronic Knee Pain

Complementary and alternative treatments and dietary supplements, etc., are not recommended for treatment of acute, subacute, or chronic knee pain, as they have not been shown to produce meaningful benefits or improvements in functional outcomes.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Rationale for Recommendation

As there is no evidence of their efficacy, complementary and alternative treatments including dietary supplements, etc., are not recommended.

Evidence for the Use of Complementary or Alternative Treatments Dietary Supplements, Etc. There is 1 high-(967) and 4 moderate-quality(968-971) RCTs incorporated into this analysis. There are 2 low-quality RCTs in Appendix 1.(972, 973)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Jacquet 2009 RCT	9.0	N = 81 aged 40-80 with chronic OA of knee or hip who use NSAIDs regularly	Phytalgic supplement (fish-oil, vitamin E, Urtica dioica) vs. placebo for 3 months.	WOMAC scores improved in pain, stiffness, function in Phytalgic group vs. placebo (p = <0.001). Active arm after 1, 2, 3 months mean use of concomitant slow acting treatment for OA (p = 0.51, 0.001, 0.001 respectively compared to pre-treatment. Placebo arm: pre-treatment 0.93±0.44, and 0.81±0.51, 0.70±0.45 and 0.73±0.52 after 1, 2, and 3 months; NS from pre-treatment values, p = 0.020 between groups.	“[T]hree capsules a day over three months of this nutraceutical compound might decrease disease scores in patients with osteoarthritis of the knee and/or hip, and reduce their use of analgesics and NSAIDs.”	Study funded by Laboratoires Phythea. Higher dropouts in placebo due to lack of efficacy. Data suggest efficacy. 3 months follow-up.
Wluka 2002 RCT	7.5	N = 136 with OA (ACR), age >40, pain on more than half days of previous month and at least one pain dimension of the WOMAC pain score above 20%, pain had to be frequent but tolerable and worsened by unusual activity	Group 1 (natural vitamin E 500 IU daily, n = 67) vs. Group 2 (placebo: containing soybean, identical in appearance to the vitamin E, n = 69). A validated food frequency questionnaire completed by subjects at baseline, 12 months, and 24 months was used to estimate dietary antioxidant intake.	Effect of vitamin E on volume of cartilage lost reported as mean±SD. Medial tibial cartilage µm baseline cartilage volume vitamin E vs. placebo: 1692 ±405 vs. 1785±532. Follow-up cartilage volume: 1534±405 vs. 1597±441. Lateral tibial cartilage µm: baseline cartilage volume: 1836±537 vs. 2010±603. Follow-up cartilage volume: 1650±473 vs. 1759±548. WOMAC: reported as mean ±SD, vitamin E vs. placebo, pain score: -2.1±47.7 vs. -12.9±49.4, p = 0.22. Stiffness: -4.7±22.1 vs. -8.8±20.9, p = 0.29. Function: -17.3±155.5 vs. -58.7±170.4, p = 0.16. Total	“Vitamin E does not appear to have a beneficial effect in the management of knee OA: it does not affect cartilage volume loss or symptoms.”	Data suggest vitamin E ineffective for cartilage loss.

				score: 24.1±209.1 vs. -80.5±226.9, p = 0.16		
Frestedt 2009 RCT	7.0	N = 14 with moderate to severe knee OA currently taking NSAIDs	Aquamin (167mg maltodextrin, 88.1mg calcium) vs. placebo (434mg maltodextrin) capsules 3 times daily for 12 weeks.	No statistically significant difference between groups in WOMAC pain (p = 0.63), stiffness (p = 0.83), activity (p = 0.43), and ROM passive flexion (p = 0.54) and active flexion (p = 0.23). Aquamin significantly superior compared to placebo in ROM passive extension (p = 0.028) and active extension (p = 0.028).	“[P]ositive results did not continue once NSAID use was abolished completely...Aquamin cannot entirely replace NSAIDs as a treatment for OA...Aquamin may allow for a reduced need for NSAIDs which may have substantial health benefits.”	Pilot study. High dropouts with tiny number remaining in active group. Very high dropouts and small sample size negate other good design features; 14 weeks follow-up.
Ruff 2009 RCT	6.5	N = 67 with persistent OA knee pain of at least 30mm on VAS scale	Natural eggshell membrane (NEM) vs. placebo 500 mg capsule for 8 weeks.	At 60 days post treatment NEM group improved in pain (p = 0.038) and stiffness (p = 0.005) compared to placebo; 1/3 of all patients had a minimum of 40% reduction in pain at 60 day followup.	“The inclusion of a comparative treatment agent may have provided additional information, but would have required a significantly larger study population.”	High dropout rate of 43% from enrollment. Small study population. High dropouts, worse in placebo. Groups not well described. Data suggest efficacy; 2 months follow-up.
Tao 2009 RCT	4.0	N = 90 confirmed knee OA	Gubitong Recipe (GBT) 200mL 2 times daily (n = 45) vs. glucosamine sulfate 500mg 3 times daily (n = 45) for 8 weeks.	WOMAC index scores improved significantly in both groups from pre to post treatment 54.31±12.86 to 23.46±10.68 for GBT and 53.69±15.12 to 30.34±11.37 for glucosamine (p <0.05). Integral VAS scores improved in both groups 66.06±18.77 to 29.81±18.74 for GBT and 64.79±17.08 to 31.56±18.64 for glucosamine (p <0.05).	“Results showed that both GBT and glucosamine sulfate could alleviate pain and stiffness, and improve the function of joint, showing statistical meaning as compared with those before treatment.”	Trial compared with glucosamine. No placebo group. Data suggest comparability.

HERBAL AND OTHER PREPARATIONS

Many complementary and alternative treatments, including herbal treatments, have been used to treat chronic knee pain, especially pain due to osteoarthritis.(974) Most of these treatments do not have any quality evidence of efficacy.(975) However, there are some remedies which may be efficacious in the management of acute LBP and osteoarthritis. White willow bark (Salix) extract has been studied in LBP. A principal ingredient is salicin, with salicylic acid as the principal metabolite. Daily doses of 240mg salicin, approximately equivalent to 50mg of acetylsalicylate (which was sufficiently low as to suggest that this may not be the sole reason for its analgesic effect), have been shown to be more effective than placebo in alleviating pain and improving physical impairment scores in patients with acute LBP, with gastrointestinal complaints occurring no more frequently than with placebo. Topical copper salicylates have also been used for treatment of arthrosis.(976, 977) Extract of *Harpagophytum procumbens* (devil's

claw root) has been used in Europe to treat musculoskeletal symptoms, and there is some evidence that it may relieve acute LBP, acute episodes of chronic LBP, and osteoarthritis more effectively than placebo in doses that have consisted of the equivalent of 50 to 100mg of harpagoside daily. Mild gastrointestinal upset has been reported at higher doses. Other treatments include ginger extract(978-986) , rose hips,(987-996) s-adenosylmethionine,(997-1007) Camphora molmol, Maleluca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe peperita, Arnica Montana,(1008) Curcuma longa, Tancaetum parthenium, avocado soybean unsaponifiables,(912, 1009-1019) oral enzymes,(1020-1025) and others.(1026-1029)

Recommendation: Willow Bark (Salix), Ginger Extract, Rose Hips, Camphora Molmol, Maleluca Alternifolia, Angelica Sinensis, Aloe Vera, Thymus Officinalis, Menthe Peperita, Arnica Montana, Curcuma Longa, Tancaetum Parthenium, and Zingiber Officinicalis, Avocado Soybean Unsaponifiables, Oral Enzymes, Topical Copper Salicylate, S-Adenosylmethionine, and Diacerein Harpagoside for Acute, Subacute, or Chronic Knee Pain

There is no recommendation for or against use of willow bark (Salix), ginger extract, rose hips, camphora molmol, maleluca alternifolia, angelica sinensis, aloe vera, thymus officinalis, menthe peperita, arnica montana, curcuma longa, tancaetum parthenium, and zingiber officinicalis, avocado soybean unsaponifiables, oral enzymes, topical copper salicylate, S-Adenosylmethionine, or diacerein harpagoside for treatment of acute, subacute, or chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

Most of these agents have no quality evidence available (e.g., Camphora molmol, Maleluca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe peperita, Arnica Montana, Curcuma longa, Tancaetum parthenium, Harpagoside) for acute, subacute, or chronic knee pain. Some have conflicting results, e.g., willow bark (Salix),(1030, 1031) rose hips, avocado soybean unsaponifiables, and ginger extract. Still others have no quality studies comparing the active ingredient with placebo (e.g., S-Adenosylmethionine, harpagoside, oral enzymes), and one agent appears ineffective (copper salicylate).

None of these agents has had a standardized dose, resulting in a lack of clarity of patient dosing. All of the studies comparing the agent to a standard NSAID dose found the NSAID superior. Only those studies with lower doses of NSAIDs found evidence suggesting equivalency (see herbal and other preparations evidence table). These agents are not invasive, have unclear adverse effect profiles, and over time are moderate to highly costly. There is no recommendation for or against use of these agents.

Evidence for the Use of Herbal and Other Preparations

There are 12 high- and 14 moderate-quality RCTs or crossover trials incorporated into this analysis. There are 4 low-quality RCTs in Appendix 1.(986, 993, 1025, 1032)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
S-Adenosylmethionine						
Najm 2004 Crossover Trial	9.0	N = 61 with knee OA	SAMe 600mg BID vs. celecoxib 100mg BID for 8 weeks each. Double dummy.	Celecoxib superior for pain relief in 1st month (p = 0.024). During 2nd month, no differences in pain. Total COOP score: baseline 48.7±8.7 vs. SAMe 39.9±9.3 vs.	“SAMe has a slower onset of action but is as effective as celecoxib in the management of symptoms of knee osteoarthritis.	No placebo comparison. Data suggest SAMe is equally effective, although celecoxib 100mg BID has faster

				celecoxib 39.8±11.3. SF-36 scores did not differ.	Longer studies are needed to evaluate the long-term effectiveness of SAmE and the optimal dose to be used."	onset of pain relief.
MacCagno 1987 RCT	8.0	N = 45 unilateral OA for at least 1 year	S-adenosylmethionine 400mg TID vs piroxicam 20mg QD; 140 days follow-up.	During active treatment, piroxicam superior in pain score, morning stiffness, and distance walked. No differences between groups in pain scores Day 112 or 140. Morning stiffness improved in both groups; no difference between. No difference between groups in active or passive knee motility.	"[S]AmE at a daily dosage of 1,200 mg is as effective as 20 mg daily piroxicam in improving clinical symptoms of knee osteoarthritis. Both drugs were well tolerated."	Double dummy. Data suggest piroxicam superior.
Glorioso 1985 RCT	7.5	N = 150 with hip or knee OA	SAmE 400mg vs. ibuprofen 400mg TID for 30 days.	"Pain pool" average symptoms: SAmE (10.32±2.8) vs. ibuprofen (10.29 ± 2.9), NS. Rigidity in minutes: SAmE (19.45±14.8 vs. ibuprofen 17.85±15.20, NS). Patient and physician assessments not different between groups. Patient judgment (much better and better combined): SAmE (44/58.7%) vs. ibuprofen (40/75 = 53.3%), NS.	"The reported data confirmed that SAmE is effective in the treatment of symptoms of degenerative joint decreases; moreover SAmE exhibited a slightly more marked activity than the reference drug in particular."	No placebo control. Comparison to OTC dosage of ibuprofen with similar efficacy.
Vetter 1987 RCT	4.5	N = 36 with OA knee, hip, or spine	S-Adenosylmethionine 400mg TID vs. indomethacin 50mg TID for 4 weeks.	Global clinical scores (baseline/post-treatment): SAmE (12.6/8.2) vs. indomethacin (11.1/5.9). Scores mostly improved for each diagnostic group: knee (p <0.02), hip (SAmE p = 0.043 vs. indomethacin p = 0.11) and spine (SAmE p = 0.11 vs. indomethacin p = 0.043).	"SAmE in the treatment of osteoarthritis does not seem to differ from that of indomethacin, but its tolerability appears to be better compared with that of indomethacin."	No placebo group. Small sample size and likely underpowered. Suggests SAmE may be effective in reducing symptoms.
Müller-Fassbender 1987 RCT	4.0	N = 36 with OA of hip, knee or spine	S-Adenosylmethionine 400mg TID vs. ibuprofen 400mg TID for 4 weeks.	Global clinical scores (baseline/post treatment): SAmE (31.7/17.6) vs. ibuprofen (35.6/16.6). Scores also improved for knee, hip and spine with both treatments (p <0.01). Reductions in scores trended towards favoring ibuprofen.	"Both treatments were well tolerated and no patient from either group withdrew from the study."	Submaximal ibuprofen dose bias favors SAmE; no placebo. Small sample with study likely underpowered for detecting differences. Suggests SAmE equivalent to low dose ibuprofen.
Willow Bark (Salix)						
Biegert 2004 2 RCTs	9.0	N = 127 with hip or knee OA plus	Willow bark extract (240mg salicin a day) vs. diclofenac 100mg a day vs. placebo	WOMAC pain scores: diclofenac -23±20 vs. willow bark -8±21 vs. placebo -5±23. (NS between willow bark and	"[N]o evidence of relevant analgesic or antiinflammatory efficacy in willow bark extract for	Two RCTs both suggest diclofenac superior to willow bark

		RA (n = 26)	for 6 weeks; 2 RCTs, 1 for OA and 1 for RA.	placebo but p = 0.003 between diclofenac and placebo). Other WOMAC subscores and total scores had similar results. Most improvement was achieved after 2 weeks of treatment.	patients with OA and RA.”	extract or placebo for OA or RA. Some baseline differences; 12 % of willow bark group, 40 % diclofenac group and 27% in placebo group received physical therapy, p = 0.01).
Schmid 2001 RCT	8.0	N = 86 with hip or knee OA	Willow bark extract (240mg salicin a day) vs. placebo for 2 weeks.	WOMAC pain indices (baseline/Day 14): willow bark 34.1±19.3/29.3) vs. placebo (44.1±26.5/45.1), p = 0.047. Patient assessments differed between the 2 groups (p = 0.0002) as did physicians (p = 0.0073).	“[W]illow bark extract showed a moderate analgesic effect in osteoarthritis and appeared to be well tolerated.”	Pain scores somewhat worse in placebo at baseline suggesting trial favored active treatment. Data suggest willow bark superior to placebo.
Ginger Extract						
Bliddal 2000 Randomized Crossover Trial	7.5	N = 75 with hip or knee OA	Ginger extract 170mg EV.ext-33 TID vs. ibuprofen 400mg TID vs. placebo TID. Double dummy.	Ranking of efficacy of 3 treatments: ibuprofen, ginger extract, placebo found for VAS (Friedman test: 24.65, p <0.00001) and Lequesne-index (p <0.00005). In crossover study, no difference between placebo and ginger extract. Explorative tests of differences for 1st treatment period showed better effect of ibuprofen and ginger extract than placebo (p < 0.05).	“[A] statistically significant effect of ginger extract could only be demonstrated by explorative statistical methods in the first period of treatment before cross-over, while a significant difference was not observed in the study as a whole.”	Ginger in studied dosage not shown to provide relief. Comparative arm is OTC ibuprofen dose. OTC ibuprofen dose superior to other 2 arms.
Wigler 2003 Crossover Trial	7.0	N = 29 with knee OA	Zintona EC vs. placebo QID for 3 months each treatment.	Mean VAS on movement scores (baseline/post): ginger (76.1/41.0) vs. placebo (76.9/50.0), NS. Handicap scores also reduced both groups, but NS between groups. Reduction in knee circumference favored ginger (p = 0.15).	“Zintona EC was as effective as placebo during the first 3 months of the study, but at the end of 6 months, 3 months after crossover, the ginger extract group showed a significant superiority over the placebo group.”	Data mostly negative for efficacy of ginger compared with placebo. Some data suggest some efficacy.
Altman 2001 RCT	6.5	N = 247 with knee OA	Ginger extract (255mg EV.EXT 77 extracted from 2.5-4.0gm dried ginger rhizomes plus 0.5-1.5gm dried galanga rhizomes) vs. placebo for 6 weeks.	Pain after walking 50 feet (baseline/post): ginger (49.9 ±24.3/34.6±29.5) vs. placebo (53.1±25.1/44.2 ±28.3), p = 0.016. WOMAC pain favored treatment (p = 0.11) as did function (p = 0.13), while stiffness statistically positive (p = 0.018). More reductions in knee pain on standing with ginger (63%)	“A highly purified and standardized ginger extract had a statistically significant effect on reducing symptoms of OA of the knee. This effect was moderate”	Somewhat greater advanced disease in ginger group at baseline (7.3% vs. 4.1% Stage 4) favors placebo. Adequacy of blinding unclear as placebo had coconut oil. Data

				vs. placebo 50%, p = 0.048.		suggest modest reduction in symptoms.
Haghighi 2005 RCT	4.0	N = 120 with hip or knee OA	Ginger extract 30mg BID vs. ibuprofen 400mg TID vs. placebo for 1 month.	VAS pain (baseline/1 month): ginger (71.7±3.5/30±3.7) vs. ibuprofen (71.2±2.4/28±3.4) vs. placebo (64.2±2.8/56.5±3.6) (p <0.0001 but NS comparing ginger vs. OTC ibuprofen).	“Ginger extract and ibuprofen were significantly more effective than the placebo in the symptomatic treatment of OA, while there was no significant difference between the ginger extract and ibuprofen groups in a test for multiple comparison.”	Methodological issues including blinding not well described. Baseline data demonstrate statistically significant differences in disease severity measures yet appear to represent these as “P>0.05.” If methodological issues overcome, data suggest comparable efficacy between ginger and OTC ibuprofen and superiority to placebo.
Rose Hips						
Winther 2005 Crossover Trial	9.0	N = 94 with knee or hip OA	Rose-hip powder 5g a day vs. placebo for 3 weeks.	WOMAC pain scores (baseline/3 weeks/3 months): rose hips (33.7±19.4/29.4±18.3/32.8±20.6) vs. placebo (33.7±19.4/35.3±21.5/35.6±20.4), p = 0.014 at 3 weeks and p = 0.125 at 3 months. Stiffness, ALD, PGAD all statistically negative at 3 weeks.	“[T]he present herbal remedy can alleviate symptoms of osteoarthritis and reduce the consumption of ‘rescue medication.’”	Data are mixed with some outcomes positive and some not different.
Rein 2004 Crossover Trial	8.5	N = 112 with OA in hip, knee, hand, shoulder, neck	Rose-hip powder 5g a day vs. placebo for 3 months each treatment arm	Pain reduction in placebo first group: 1.02±1.45 vs. 1.91±1.43, p = 0.008. Among those given rose hip first, pain reduction 1.45±1.28 vs. 1.72±1.37, p = 0.61. Consumption of rescue medication showed similar effects.	“Hyben Vital reduces the symptoms osteoarthritis. We interpret the marked differences in the response of the two groups as indicating a strong “carryover” effect of Hyben Vital.”	Dropout rate high. Assumes lack of pain rebound in group given active medication first is due to carry forward effect of prior active treatment. No data to show wearing off over time.
Copper Salicylate						
Shackel 1997 RCT	9.5	N = 116 hip and/or knee OA	Topical copper-salicylate gel vs. placebo gel 1.5g to the forearm BID for 4 weeks	Pain scores: (baseline/Week 4): CS 34.8±29.3/28.4±25.4 vs. placebo 30.5±29.7/24.9±25.8, p = 0.94. Other outcomes NS. Number requiring paracetamol for adjunctive analgesia: 77% copper-salicylate, 71% for placebo. More skin rashes	“Copper-salicylate gel applied to the forearm was no better than placebo gel as pain relief for patients with osteoarthritis of the hip or knee, but produced	Data suggest lack of efficacy of copper-salicylate gel applied on the forearm for hip/knee OA.

				observed in C-S group (83%) vs. placebo (52%) (p = 0.002).	significantly more skin rashes.”	
Oral Enzymes						
Akhtar 2004 RCT	7.5	N = 103 with knee OA	Enteric-coated Phlogenzym® (bromelain 90mg, trypsin 48mg and rutosid 100mg) TID vs. diclofenac 50mg BID. Double dummy.	Lequesne’s Algorfunctional Index improved in 6 weeks among ERC 13.0 to 9.4 (26.3%) vs. DC from 12.5 to 9.4 (23.6%) (non-inferiority demonstrated). Index of severity/complaint indices did not differ, improved for each arm compared with baseline. Adverse events did not differ (27.5% v. 23.1%).	“ERC can be considered as an effective and safe alternative to NSAIDs such as diclofenac in the treatment of painful episodes of OA of the knee. Placebo-controlled studies are now needed to confirm these results.”	Results suggest Phlogenzym equivalent to diclofenac.
Klein 2006 RCT	6.5	N = 90 with hip OA	Enteric-coated Phlogenzym® 2 TID vs. EC diclofenac 50mg BID. Double dummy.	Phlogenzym not inferior using multiple measures including pain, joint stiffness, physical function, and Lequesne’s index.	“This study showed significant non-inferiority from 6 weeks treatment with PE in patients with OA...there was no real difference between PE and DC 100mg per day, implying an equal benefit-risk relation.”	Study suggests comparable efficacy between phlogenzym and diclofenac.
Singer 2001 RCT	6.0	N = 63 with knee OA	Enteric-coated Phlogenzym® 6 per day vs. Diclofenac 50mg TID for 1 week then BID for 3-week treatment. Double dummy.	Lequesne indices improved in 93.6% of enzyme group vs. 87.5% diclofenac. Sum of Lequesne indices over 14 days: enzyme 12.27 vs. diclofenac 10.79 (NS). At Day 49, enzymes 9.81 vs. 12.77 (p = 0.0165). Pain on movement scores did not differ over active treatment, but favored enzyme group at Day 49, 28 days after 3-week treatment stopped.	“[S]hort-term evaluation indicates that Phlogenzym® as an oral enzyme formulation can be considered as an effective and safe alternative to non-steroidal anti-inflammatory drugs such as diclofenac in the treatment of active osteoarthritis of the knee.”	Some details sparse. Data suggest comparable efficacy between Phlogenzym and diclofenac.
Avocado Soybean Unsaponifiable						
Maheu 1998 RCT	9.5	N = 164 with knee or hip OA	Avocado/Soybean Unsaponifiables (ASU) 300mg daily for 6 months vs. placebo for symptomatic efficacy	Significantly greater improvement in all outcome measures (Lequesne’s Functional Index p <0.01, Pain on VAS p = 0.02, Functional disability p <0.001) in ASU group compared with placebo at 6 months.	“ASU treatment showed significant symptomatic efficacy over placebo in the treatment of OA, acting from month 2 and showing a persistent effect after the end of treatment.”	The study does not have demonstrated changes in outcomes measures such as RTW.
Lequesne 2002 RCT	9.0	N = 163 with hip OA	Avocado/Soybean Unsaponifiables (ASU) 300mg daily for 2 years vs. placebo for joint space narrowing.	At 2-year follow-up, mean joint space width in ASU and placebo groups was 1.87±1.0mm and 1.90±1.33 (p = 0.90). However, in a subgroup of patients with initially more severe narrowing, joint space loss between initial	“The clinical results concerning symptoms in this study were surprising. No difference on clinical parameters was observed between ASU and placebo	High withdrawal rate over 2-year period (41%), although ITT and per-protocol analyses were similar.

				and final radiograph in ASU group was half that in placebo group (-0.43±0.51mm vs. -0.86±0.62mm, p <0.01). No differences in regard to symptomatic effects in each of subpopulations, and NSAID use similar in both groups.	groups, which contrasts with previous results significantly favoring ASU over placebo. ASU seemed to statistically significantly reduce progression of the narrowing of the joint space in a post-hoc analysis in the subpopulation of more severely affected patients, compared with those receiving placebo.”	
Blotman 1997 RCT	9.0	N = 164 with primary femoro-tibial or hip OA	Avocado/soybean unsaponifiables (ASU) 300mg daily for 3 months vs. placebo for symptomatic efficacy.	Mean cumulative dose of NSAID used between Day 45 and 90 significantly lower in ASU group reflecting smaller proportion of patients in group who resumed NSAID use. For patients with hip osteoarthritis who went back on NSAID, cumulative dose, time spent back on drug significantly lower in ASU. No difference in knee OA. Algofunctional index score fell in both groups, but significantly larger in ASU group vs. placebo, p <0.01. No difference in VAS scores.	“Over 6 weeks, ASU reduced the need for NSAID in patients with lower limb OA. Further studies are needed to evaluate the duration of the persistence of this effect and its impact on patient care and on treatment costs.”	Phase III trial. Unclear if this is preliminary report of same study (Maheu).
Appelboom 2001 RCT	6.5	N = 260 with femoro-tibial knee OA (ACR), ages 45-80 years, VAS ≥30mm, taking NSAIDs at least 3 months	ASU 300mg vs ASU 600mg vs placebo for 3 months.	VAS pain scores improved in both ASU groups. More NSAID use reduction in ASU groups (26% placebo vs. 49% vs. 51%, p <0.01). Decrease in pain scores of 30mm statistically significant when comparing placebo to ASU 600mg (p = 0.004). Decrease in VAS of 60mm statistically significant when comparing placebo to both ASU groups (p<0.01) and 90mm (p<0.01).	“[R]esults obtained here confirm the efficacy of ASU as a symptomatic drug in osteoarthritis...one single tablet of 300mg daily appears sufficient to obtain maximal therapeutic effect.”	Randomization and blinding not well described. Data suggest modest efficacy.
Arnica						
Brinkhaus 2006 3 RCTs	8.0	N = 343 with knee surgery (arthroscopy, arthroplasty, ACL)	Arnica montana 30x vs placebo for post-op swelling for 3 different groups: Arthroscopy (ART), artificial knee implantation	Change in swelling significant different in CLR group comparing placebo and arnica (p = 0.019). ART and AKJ studies showed no significant difference (p = 0.204 and p = 0.184).	“[H]omeopathic arnica was more effective in reducing postoperative swelling than placebo in CLR, whereas there was no significant difference between	Combined report of 3 trials. Data suggest some efficacy for ACL surgery but not others, for unclear reasons.

			joint (AKJ) and cruciate ligament reconstruction (CLR). Variable follow-ups of 2, 8, and 11 days.		either intervention in ART and AKJ.”	
Other Herbal Treatments, Combinations						
Jung 2004 RCT	9.0	N = 249 with knee OA (ACR), ages 35 to 75 years, VAS >35mm.	SKI306X (herbal extract mixture of Clematis radix, Trichosanthes root and Prunella spike) 200mg TID vs diclofenac sustained release 100mg QD for 4 weeks.	No difference (p = 0.50) between groups in VAS scores (pain relief). Global satisfaction assessment by patients (p = 0.26) and investigators (p = 0.93) was not different between groups (completely effective per 7.6% of each patient group; 35.6% vs. 35.0% per investigators).	“[I]mprovement of primary efficacy variable, VAS, was not significantly different between the two groups...This short treatment is not sufficient to fully reveal the beneficial and adverse effects of SKI306X.”	No placebo control. Short-term trial. Double dummy. Data suggest herbal treatment not superior to diclofenac.
Paris 2008 RCT	7.5	N = 158 undergoing knee ligament reconstruction, ages 18 to 60	Standardized pain management after surgery plus either 5 granules of homeopathic complex (Arnica montana, Bryonia alba, Hypericum perforatum, and Ruta graveolens) vs placebo vs no intervention.	No difference between groups in morphine consumption 24 hours after surgery and 24-72 hours after. No difference in quality of life assessment between groups.	“The homeopathic treatment tested in this study was no better than placebo for postoperative pain management after knee ligament construction.”	Data suggest lack of efficacy.
Teekachuhatean 2004 RCT	7.0	N = 200 with unilateral and bilateral knee OA (ACR), over 40 years of age, >3 months	Duhuo Jisheng Wan (DJW) Chinese herbal medicine 3gm TID vs diclofenac 25mg TID for 4 weeks.	Percent improvement in walking pain (72.0% vs. 77.9%), NS. Patient’s overall assessment favored diclofenac at Week 1 (32.58 vs. 37.48). By Week 4 both groups have statistically significant improvement in all VAS categories including walking and standing pain, night, and resting pain, morning stiffness, stiffness after rest, and time for climbing steps.	“[T]his study demonstrated that approximately 30% of study subjects experienced adverse events...the toxicity profiles of DJW are similar to diclofenac...cautious use of DJW should be considered in the same manner as using diclofenac including other NSAIDs.”	Double dummy. Data suggest comparable efficacy, although diclofenac associated with earlier onset of efficacy.
Calcitonin						
Manicourt 2006 RCT	5.0	N = 41 OA of medial tibiofemoral compartment (KL III), ages 55-80 with morning	Oral salmon calcitonin (sCT) 0.5mg vs sCT 1mg vs placebo QD for 84 days.	Pain index scores decreased in placebo (p <0.01), 0.5mg sCT (p <0.05), and 1mg sCT (p <0.001) from day 0 to day 84. Functional index scores were lower with 0.5mg sCT (p <0.01) and	“[O]ral sCT at a daily dose of 1mg might be a potential pharmacologic treatment in patients with knee OA in an active state of bone and cartilage remodeling, as	Dropout rates unclear as number enrolled not specified. Many details sparse. Unclear if treatment

	joint stiffness <30 minutes, pain on weight-bearing and motion		1mg sCT (p <0.001) from day 0 to day 84.	assessed by bone scintigraphy and biomarkers of joint metabolism.”	superior to placebo.
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DIACEREIN (Diacerhein)

Diacerein is an alternative pharmaceutical therapy developed for the treatment of osteoarthritis and purported to have inhibitory action on interleukin-1, metalloproteases and other inflammatory mediators involved in cartilage destruction in in vivo and animal models, including of inflammatory arthropathies.(1033-1041) It also stimulates prostaglandin E₂ synthesis without affecting phospholipase A₂, cyclooxygenase (COX), or lipoxygenase, and thus does not affect the gastric mucosa.(1042) Diacerein has been used as a disease modifying agent in patients with moderately progressive joint narrowing.(1043-1046) It is available by prescription in only a few countries in Asia and Europe, and it is not currently available in the U.S. The adverse effect profile is generally significantly higher than placebo, mostly due to higher incidence of diarrhea(1034, 1047) and darkening of the urine, and the magnitude of its effects on pain are small.(1035) Diacerein is not widely available and may not be a treatment option for most patients. Optimal dose has been suggested to be 50mg twice daily.(1034) It may be an alternative to NSAIDs as a second- or third-line treatment, particularly for patients with a history of upper gastrointestinal bleeding, as it appears to be potentially associated with lower rates of gastric lesions.(1042) However, one quality study suggests NSAIDs are superior to diacerein for relief of pain.(1047) There are a few quality studies of diacerein in knee or combinations of hip and knee osteoarthritis patients in this analysis.(1034, 1048-1057)

Recommendation: Diacerein for Treatment of Osteoarthritis

There is no recommendation for or against the use of diacerein for the treatment of knee osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

Of the eight high- or moderate-quality studies evaluating diacerein, all five that compared it against placebo demonstrated modest pain relief from diacerein.(1034, 1043, 1048) A study to establish dose-response showed statistically significant improvement of symptoms with 50, 100, and 150mg daily dose, but with fewest side effects and best efficacy with the 100mg per day group.(1034) There is evidence suggesting that the effects of diacerein last weeks to months after cessation of therapy,(1047, 1048) which is not the case for NSAIDs.(1047) In addition to the symptomatic relief reported, there is one high-quality study of the hip that demonstrated a significant difference in joint space narrowing versus placebo.(1043) A 2x2 factorial study of the hip comparing diacerein, tenoxicam, diacerein with tenoxicam and placebo demonstrated early efficacy of tenoxicam. However, after 4 weeks, the diacerein plus placebo group also reached statistically significantly better symptomatic relief than placebo alone.(1047) There was no added synergistic effect; diacerein plus tenoxicam was no better or worse than each alone.

Examination of diacerein efficacy in two studies that used diacerein as one of the control arms rather than the main active research arm were not as conclusively in favor of diacerein. A comparison of diacerein to hyaluronic acid intra-articular injections over 1 year did not demonstrate diacerein to be more effective than an oral placebo, but the study had significant

methodological weaknesses including a possible placebo effect of intra-articular injection masking the effect of oral diacerein treatment.(1058) Two studies comparing diacerein to Harpagophytum procumbens (Devil's Claw Root) demonstrated both to be effective in improving pain and functional scores over baseline, but there was no placebo group for comparison.(1059, 1060)

Evidence for the Use of Diacerein

There are 6 high- and 4 moderate-quality RCTs or randomized crossover trials incorporated in this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Diacerein vs. Placebo						
Dougados 2001 RCT	9.0	N = 507 with hip OA	Diacerein 50mg twice daily vs. placebo for 3- years.	Radiographic progression of at least 0.5mm during study lower and occurred later in diacerein group vs. placebo. Cumulative radiographic progression rates of 0.5mm: 29.2% diacerein vs. 35.7% placebo at end of 1st year, and 42.5% diacerein vs. 50.2% with placebo at end of 2nd year. No difference observed in use of analgesics and NSAIDs.	"This study confirms previous clinical findings indicating that the demonstration of a structure-modifying effect in hip OA is feasible, and shows, for the first time, that treatment with diacerein for 3 years has a significant structure- modifying effect as compared with placebo, coupled with a good safety profile."	Large sample size. Study suggests small benefit in delayed radiographic progression.
Pavelka 2007 RCT	9.0	N = 168 with knee OA	50mg diacerein BID vs. placebo for 3 months, followed by 3 month off- treatment period.	WOMAC A scores (baseline/ Month 5): diacerein (261±87.3/ 144±105.7) vs. placebo (239±80.2/191±108.3), p <0.0001. Total WOMAC scores p <0.0001. Acetaminophen consumption favored diacerein (1.0±1.11 vs. 1.5±1.34), p = 0.0018.	"[T]he findings of this study indicate that diacerein is an effective treatment for symptomatic knee OA. In addition, it has long carryover effect and an acceptable safety profile."	Allocation method unclear. Results suggest mild benefit of diacerein.
Lingetti 1982 Randomiz ed Crossover Trial	8.5	N = 20 with hip or knee OA	Placebo x 2 weeks, diacerein 25mg BID x 4 weeks x 50mg BID for 8 weeks	Total score (includes pain) baseline 9.25±1.17, 9.15±1.69 after placebo, 5.50±2.42, diacerein 50mg a day, and 1.90±1.77. Diacerein 100mg a day (p <0.001 for diacerein vs. placebo). Walking speed significantly decreased on diacerein.	"The results obtained confirm the therapeutic value of diacetylrhein in the treatment of osteoarthritis of the hip and knee."	Crossover trial with small sample size. Unclear if treatment sequence completely randomized and blinded. Comparisons with no/low dose intervals.
Pelletier 2000 RCT	6.0	N = 484 with knee OA	Placebo BID vs. diacerein 25mg BID vs. diacerein 50mg BID vs. diacerein 75mg BID for 4 months.	VAS pain rating differences to Week 24: placebo -10.9±19.3 vs. 50mg a day -15.6±21.0 vs. 100mg a day -18.3±19.3 vs. 150mg a day - 14.3±23.7 (p <0.05 100mg a day vs. placebo). WOMAC pain, stiffness scores significant for 100mg a day dose (p <0.05). Patient global efficacy assessments:	"The results of this dose- finding study confirm previous study findings that diacerein is an effective treatment for the signs and symptoms of knee OA, and that based on the results from ITT analysis, the optimal daily dosage is 100mg/day (50mg twice daily)."	High drop-out rate (28%-39%) in all groups. Compliance rate uncertain. Suggests mild benefit of diacerein.

				<p>placebo 52.9±30.9 vs. 50mg a day 62.7±28.1 vs. 100mg a day 61.1 ±24.6 vs. 150mg a day 61.0±29.3 (p <0.05 50mg a day vs. placebo). Significantly higher frequency of AEs observed for 150mg a day diacerein (18.9%) vs. other groups (11.2% placebo, 12.7% 50mg a day, 9.9% 100mg a day).</p>		
Kay 1980 Crossover Trial	5.0	N = 12 with hip or knee OA	Diacerein 50mg a day for 4 weeks preceded and followed by 4 weeks of placebo	Data not in aggregate. Overall improvements on Diacerein marked in 3/12 (25%) and slightly improved in 3/12 (25%). Remainder 4/12 (33.3%) unchanged; 2/12 worse.	“Improvement was not apparent for several weeks after starting active treatment and remission lasted for 2 weeks to 3 or more months after the drug was withdrawn.”	Sparse details and limited analyses. Appears a crossover trial, but randomization and blinding unclear.
Diacerein vs. NSAID						
Nguyen 1994 RCT	7.5	N = 280 with hip OA	2x2 factorial design: diacerein placebo plus tenoxicam placebo vs. tenoxicam 20mg and diacerein placebo vs. diacerein 50mg BID and tenoxicam placebo vs. diacerein 50mg BID and tenoxicam 20mg for 8 weeks.	<p>Patient overall assessments rated good or very good: placebo (41%) vs. tenoxicam (61%) vs. diacerein (49%) vs. combination (66%). Functional Lequesne impairment index ratings (8.4±4.1 vs. 6.9±4.6 vs. 7.7±4.6 vs. 6.3±3.8). Number needing analgesic rescue lower in tenoxicam than diacerein group. Tenoxicam began to differ from control after 2 weeks with persistent beneficial effects through trial. Diacerein differed from controls after 6 weeks for pain and functional impairment.</p>	“Both tenoxicam and diacerein appear to be superior to placebo, and neither agent appears to significantly enhance or detract from the efficacy of the other when they are administered concomitantly. The onset of action of diacerein appears to be delayed (> or = 4 weeks).”	Allocation method unclear. Results suggest tenoxicam modestly superior to diacerein for both speed of onset and magnitude of response. Diacerein has higher adverse effect of diarrhea (37% v. 4%).
Diacerein vs. Other Interventions						
Pham 2004 RCT	8.5	N = 301 with medial knee OA	Three courses of 3 intra-articular (IA) injections of 2.5mL hyaluronic acid (HA) +oral placebo vs. IA injections of saline solution + diacerein 50mg BID vs. IA injections of saline solution + oral placebo, 1 year.	<p>VAS pain ratings: injections -33.5±28.5 vs. diacerein -33.9±25.7 vs. placebo -34.5±27.4, p = 0.96. Patient’s global assessments: -29.7±26.9 vs. -32.8±24.0 vs. -31.1±42.7, p = 0.82. Percentage patients’ very good or good responses: 72% v. 65% v. 76%. No differences in adverse effects (p = 0.76)</p>	“A weak but statistically significant structural deterioration occurred over 1 year, together with clinically relevant symptomatic improvement in patients receiving oral drug and iterative IA injections. Symptomatic and/or structural effects for both this new HA compound and diacerein were not demonstrated.”	Study suggests no clear benefit of any treatment arm.
Diacerein vs. Harpagophytum						
Leblan 2000	8.5	N = 122 with hip and	Diacerein 50mg BID vs. harpagophytu	Mean pain score reductions on Day 20: harpagophytum – 30.6±3.3	“Harpagophytum was at least as effective as a reference drug	Data suggest harpagophytum at least as

RCT		knee OA	m (2,610mg a day) for 4 months. Double dummy.	vs. diacerein -25.5±3.6. Cumulative doses of NSAID used at Day 20: harpagophytum 20.9 vs. diacerein 55.15, p <0.05.	(diacerhein) in the treatment of knee or hip osteoarthritis and reduced the need for analgesic and nonsteroidal anti-inflammatory therapy.”	effective as diacerein and more effective by some measures. Adverse effects of diacerein appear greater.
Chantre 2000 RCT	8.0	N = 122 with hip and knee OA	Diacerein 50mg BID vs. Harpadol (6 capsules/day, each containing 435mg of powder Harpagophytum procumbens) for 4 months. Double dummy.	VAS pain scores (baseline/16 weeks): harpagophytum (63.6±13.2/31.3±22.9) vs. diacerein (61.6±11.1/35.8±22.8), p = 0.34. Lequesne functional indices were not different (p = 0.71). Diclofenac rescue tablets consumed at week 12 favored harpagophytum (20.9 vs. 55.51), p = 0.01.	“The results confirm that the two drugs are equally effective in the treatment of osteoarthritis of the knee or the hip. Improvements in all efficacy parameters were observed within each treatment group but there was no significant difference in the therapeutic response between the 2 groups for any efficacy parameters.”	No placebo comparison group. Suggests harpagophytum at least comparable to diacerein, if not superior based on NSAIDs consumed.
Gastric Erosions						
Petrillo 1991 2 RCTs in 1 report	4.5	Study 1: N = 23 with normal or minor endoscopic findings. Study 2: N = 30 with Grade 2 or 3 gastric lesions	Study 1: diacetylrhein 50mg BID vs. naproxen 250mg TID for 4 weeks. Study 2: diacetylrhein 50mg BID vs. placebo for 4 weeks.	Study 1: 1/10 (10%) developed gastric lesions on endoscopy vs. 5/10 (50%), p >0.05. Study 2: 11/13 (85%) of diacerein group improved at 4 weeks vs. 9/15 (60%), p >0.05.	“[D]iacetylrhein possesses a good degree of gastric tolerability and may be used in antirheumatic maintenance treatment even when gastric lesions are present.”	Some details sparse. Underpowered. Suggests higher gastric erosions in naproxen than diacerein.

Devices

Some patients with knee pain might benefit from limited use of devices, particularly as an assistive aid while improved or full function is sought. These aids include crutches, walkers, canes, motorized scooters, heel wedges and insoles, and functional braces.(1061-1075) However, aids might also be detrimental, as they may discourage therapeutic physical activity. In general, a device is **Recommended, Insufficient Evidence (I)** when it is either part of a plan to regain better or normal function or it is essential to achieve the maximum function possible within the limits of fixed defects (see diagnostic sections for devices used for specific disorders).

BRACING/SLEEVES/LATERAL WEDGES

Knee bracing has been used for some cases of knee osteoarthritis.(1076, 1077) Braces include unloader or off-loader braces designed to reduce force on one tibiofemoral compartment.(1078-1085) Most commonly, an “off-loader” brace has been utilized to attempt to reduce force on the medial compartment in cases of medial or largely medial joint OA. They also have been utilized to prevent sports injuries, especially in football athletes,(1086-1091) although there are concerns that the use of a brace leads to reduced performance.(1090) Knee sleeves and other appliances have also been utilized. Foot orthotics, most commonly lateral wedges, have been used to attempt to redirect force from the medial compartment to the lateral compartment in patients with primarily medial compartment disease.(1092-1094)

1. *Recommendation: Off-loader Braces for Knee Osteoarthritis*

Off-loader braces are recommended for treatment of select patients with medial joint osteoarthritis.

Indications – Patients should generally have attempted other non-operative treatments, including NSAIDs, analgesics, weight loss, exercise and glucocorticosteroid injections. Additionally, patients must be highly motivated to be compliant with the device.

Strength of Evidence – **Recommended, Evidence (C)**

2. *Recommendation: Knee Braces for Moderate to Severe Chronic Knee Osteoarthritis*

Knee braces (e.g., unloader braces) are recommended for treatment of moderate to severe chronic knee pain due to osteoarthritis (medial or lateral joint OA) that is largely or totally unicompartmental.

Indications – Moderate to severe chronic unicompartmental (e.g., medial) knee osteoarthritis, particularly if other treatments have failed and device is used in an attempt to delay surgical treatment.(1062, 1095, 1096) Patient must be motivated to comply with brace use.

Strength of Evidence – **Recommended, Evidence (C)**

3. *Recommendation: Knee Braces for All Other Osteoarthritis*

There is no recommendation for or against the use of knee braces (e.g., unloader braces) for treatment of all other osteoarthritis including symmetrical OA.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

4. *Recommendation: Sleeves for Knee Osteoarthritis*

Sleeves are moderately not recommended for the treatment of knee osteoarthritis.

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**

5. *Recommendation: Neoprene Knee Sleeves for Moderate to Severe Chronic Knee Osteoarthritis*

There is no recommendation for or against use of neoprene knee sleeves for treatment of knee osteoarthritis.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

6. *Recommendation: Lateral Wedges for Medial Compartment for Knee Osteoarthritis*

Lateral wedges are moderately not recommended for treatment of medial compartment knee osteoarthritis.

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**

7. *Recommendation: Post-operative Braces for Knee Arthroplasty Patients*

Post-operative knee braces are moderately not recommended for knee arthroplasty patients.

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**

Rationale for Recommendations

There are a few moderate-quality trials that have addressed bracing for unicompartmental osteoarthritis. Two trials comparing bracing with no bracing or usual care found bracing to be superior,(1095, 1096) while another trial comparing bracing with usual care and usual-care-only found bracing beneficial.(1062) One trial suggested bracing to be superior to neoprene sleeves.(1095) Another crossover trial suggested a valgus brace was superior to a simple

hinged brace.(1097) Thus, there is moderate-quality evidence that unloader bracing is helpful in the short- to intermediate-term. There is no recommendation for or against the use of neoprene sleeves as there is moderate-quality evidence braces are superior(1095) and the evidence for neoprene sleeves compared to no treatment or another treatment is sparse. Thus, the evidence from moderate quality trials suggests these devices have modest benefits. They are not invasive and have low adverse effects, although compliance and ability to tolerate them are problematic. Thus, they are recommended for recommended for select patients with moderate to severe osteoarthritis that is either largely in the medial or lateral compartments. Patients must be willing to comply with treatment.

Knee sleeves have been evaluated in moderate quality trials and have not been found to produce clinically meaningful benefits.(1095, 1098, 1099) Thus, knee sleeves are not recommended. One trial attempted blinding of shoes with wedges and suggested no differences with lateral wedging.(1092) One trial compared lateral wedges to knee braces and found comparable results,(1094) while another trial was negative.(1093) Thus, the quality trials suggest a lack of efficacy.

Two moderate-quality trials both suggested a lack of benefit from post-arthroplasty bracing.(1100, 1101) Thus, post-operative bracing is not recommended.

Evidence for the Use of Knee Braces, Sleeves and Lateral Wedges for Knee Osteoarthritis

There are 12 moderate-quality RCTs or crossover trials incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Braces or Sleeves						
Pajareya 2003 RCT	7.5	N = 119 with unilateral or bilateral OA of knee included in study if met current American College of Rheumatology criteria for knee OA, were between age 40 and 85, had mild to moderate knee pain for at least 1 month and no drugs for arthritis over last week	Control group (acetaminophen, non-steroidal anti-inflammatory drugs and education, n = 60) vs. study group (same treatment but combined with daytime elastic knee sleeve, n = 59). Treatment for 8 weeks; assessed on 1st day and during 8th week. Primary outcome is long-term effect on functional performance measured by difference between 1st record of follow-up aggregated functional performance time (AFPT) and 1st record of baseline AFPT.	Immediate effects; mean and SD of AFPT change of second test from first test control vs. study group: 0.97±3.61 vs. 2.60±3.81, p = 0.025. Late effect of AFPT change from baseline: 5.08±12.27 vs. 6.91±9.81, p = 0.315. Global rating of improvement, complete recovery: 0±0 vs. 2±3.4. No change: 14 ±23.3 vs. 14±23.7, p = 23.7. Median and interquartile range of Lequesne index: 3.0(5.0) vs. 4.0(3.2), p = 0.124.	“This study shows small short-term beneficial effects of an elastic sleeve in patients with knee OA in cases with acute exacerbation.”	Study assessed knee sleeve with vs. without numerous other co-interventions. Data suggest no significant enduring effects.

van Raaij 2010 RCT	6.0	N = 91 symptomatic medial compartmental knee OA with KL Grade I+ located over medial tibiofemoral compartment of knee	10 mm laterally wedged insole (n = 45) vs. valgus knee brace (n = 46) for 6 months.	Pain severity: insole group -0.9 ± 2.4 vs. brace group -1.0 ± 2.2 , $p = 0.03$. Function (WOMAC): insole 4.2 ± 16.9 vs. brace 4.0 ± 18.9 .	"[A] laterally wedged insole may be an alternative to valgus bracing for noninvasively treating symptoms of medial knee OA."	Data suggest comparability over 6 months.
Kirkley 1999 RCT	5.5	N = 110 with varus gonarthrosis excluded if BMI of more than 35 kilograms	Medical treatment only (education pamphlet, acetaminophen, home flexibility exercises, n = 33) vs. medical treatment plus neoprene sleeve (n = 36) vs. medical treatment plus unloader brace (Generation II valgus-producing brace, n = 41) for 6 months.	WOMAC total score at 6 months 229.1mm unloader v. 97.6 sleeve vs. -27.9 controls ($p = 0.001$). Pain scores at 6 months changed 43.2mm unloader vs. 13.1mm sleeve vs. -13.1mm controls ($p = 0.001$). WOMAC stiffness, physical function, MACTAR scores also favored unloader brace.	"The results indicate that patients who have varus gonarthrosis may benefit significantly from use of a knee brace in addition to standard medical treatment. The unloader brace was, on the average, more effective than the neoprene sleeve."	Somewhat more ACL tears in unloader group. Compliance unclear. Data suggest unloader brace superior to neoprene sleeve and controls.
Brouwer 2006 RCT	5.5	N = 118 age 18 and older with uni-compartmental knee OA and malalignment	Brace (Oasys brace) plus conservative treatment (education, weight loss, PT, analgesics, brace group, n = 60) vs. conservative treatment alone (control, n = 57) with 12 months follow up.	VAS scores trended lower with brace than controls ($p < 0.1$). Knee function (HSS) better with brace vs. controls at 3 months, 6 months, and overall, $p < 0.1$. Walking distance longer in brace group at 3 months (mean difference 1.2km, $p = 0.03$), 12 months (mean difference 1.25km, $p = 0.04$), overall ($p = 0.02$).	"The results indicate that a brace intended to reduce load shows small effects in patients with unicompartmental OA. However, many patients do not adhere in the long run to this kind of conservative treatment."	Some baseline differences of uncertain significance. Low compliance. Only differences were in walking distance which tended to differ at baseline (2.6 v. 4.0km) raising concerns of spurious results. Study compared additive effect of brace plus usual care vs. usual care. Higher dropouts in controls (31.0% vs. 18.3%, 72% were knee surgeries). Data suggest brace superior.

Draganich 2006 Crossover Trial	4.5	N = 10 patients age 43-59 with varus gonarthrosis of knee	Pre-fabricated patient adjustable brace (OADjuster) vs. custom patient adjustable brace (adjustable OA Defiance) for 4-5 weeks.	Pain reduction 71mm custom vs. 120mm pre-fab (off shelf). Stiffness reduced 91 to 36 with custom to 63 with off shelf. Greater reduction in stiffness with custom (p = 0.030. Function improved with custom brace (p = 0.010) but not with off-shelf brace.	"We investigated only the short-term effects of custom and off-the-shelf patient-adjustable valgus producing knee 'unloader' braces and found that patients with varus gonarthrosis of the knee may benefit significantly with respect to pain relief and reduced stiffness from use of either brace."	Timing of follow-ups unclear. No placebo group. Small sample size. Data suggest comparable outcomes.
Chuang 2007 RCT/Cross-over trial	4.0	N = 50 with knee pain and diagnosed with knee OA	No sleeve (Group A, n = 25) vs. neoprene sleeves (Group B, CB0601, n = 25).	For static balance, scores lower in group A (p <0.05) than those with no sleeves. For dynamic balance group, group A had lower scores vs. no sleeves, p <0.05. Also seen in group B, p <0.05.	"[K]nee OA patients wearing knee sleeves showed a better balance control in static and dynamic conditions than those without neoprene sleeves."	No short-term follow-up or longer as biomechanical, experimental study; unable to use for guidance. Sparse methods and results. Data do not show meaningful outcome differences.
Richards 2005 Crossover Trial	4.0	N = 12 physically active patients aged 50-75 with unilateral OA of medial compartment	Off-the-shelf hinged brace vs. Generation II ADJ. Unloader for 6 months	Significant difference between hinged brace and unloader brace for knee flexion during swing phase in favor of unloader brace, p = 0.048. Mean group reaction forces improved in unloader brace compared to no brace for peak vertical loading force (p = 0.042), peak vertical propulsive force (p = 0.020), and posterior loading force (p = 0.048).	"Our study supports the use of valgus knee braces as an alternative treatment option for carefully selected patients with OA of the medial compartment."	Small sample size, but crossover. Compliance unclear. Data suggest valgus brace superior to simple hinged brace.
Braces: Prevention						
Sitler 1990 RCT	4.0	N = 1,396 males from U.S. Military Academy playing football	Prophylactic knee braces (n = 691) vs. no brace (n = 705) for 2 years (total 21,570 person-games, all on grass, all converse LE shoes, all DonJoy double-hinged braces).	Injury rates over 2 years: brace 1.33/1000 person-games vs. 3.19, p <0.005. More total knee injuries in controls (29 vs. 12). MCL injuries particularly reduced with braces (12 vs.	"[A] unilateral0biaxial prophylactic knee brace significantly reduced the frequency of knee injuries, both in the total number of	Data suggest knee brace protective for knee injuries among defensive football players, but not offensive.

				25, p <0.05); ACL were 4 vs. 12. Defense had reduced risks (5 vs. 25) while offense did not (11 vs. 9 injuries).	subjects injured and in the total number of MCL knee injuries incurred.”	Primary benefit was MCL.
Post-Operative Bracing						
Horton 2002 RCT	7.0	N = 55 with OA or rheumatoid arthritis undergoing primary total knee replacement	No splints (n = 28) vs. splint for 48 hours post surgery (n = 27); 2 weeks follow-up.	No significant differences between groups.	“[R]outine use of a semi-rigid splint following primary total knee replacement has no advantage over simple wound dressing.”	Short trial of 2 weeks. Data suggest splinting unhelpful.
Zenios 2002 RCT	6.0	N = 81 undergoing total knee replacement with patellar resurfacing	Splint (knee in extension, n = 42) until patient could do a straight leg raise vs. no splint (wool and crepe bandage applied around their knee, n = 39) for 48 hours.	Without a splint achieved greater flexion vs. splint at 5 days (73.8 vs. 63.2) and 6 weeks (96.3 vs. 86.7). Without a splint group lost significantly more blood from wound vs. splint group. Drainage post-op: splint 874.4±383.8 vs. no splint 1374.2±624.0. PCA, amount used post-op: splint 81.6±81.5 vs. no splint 58.6±50.7. Flexion 5 days post-op: splint 63.2±17.6 vs. no splint 73.8±10.7. Flexion 6 weeks post-op: splint 86.7±15.0 vs. no splint 96.3±12.2.	“In conclusion we found no evidence to advocate the use of knee splints following total knee arthroplasty.”	Data suggest splinting not helpful.
Insoles or Wedges						
van Raaij 2010	6.0	See Braces or Sleeves above.				
Maillefert 2001 RCT	5.0	N = 156 with medial compartment femorotibial knee OA	Laterally elevated wedged insole (n = 82) vs. neutrally wedged insole (control, n = 74) for 6 months	Reduction in NSAIDs use and analgesia intake in laterally wedged insole group but these parameters remained unchanged in control group.	“The study failed to demonstrate a relevant short-term symptomatic effect of laterally-wedged insoles in medial femoro-tibial OA.”	Data do not suggest meaningful differences.
Barrios 2009 RCT	4.0	N = 66 with medial tibiofemoral OA with K-L grade of II-IV	Fitted with a pair of walking shoes and a non-custom pair of neutral foot orthoses with no wedging (neutral, n = 31) vs. fitted with a pair of walking shoes and a non-custom pair of neutral foot orthoses with wedging individually	NS between groups for WOMAC scores. 6 minute walk test: significant improvement in lateral wedge group at 1 month (p <0.001) and 1 year (p <0.001) compared to control group; NS between groups for stair negotiation.	“[B]oth neutral and laterally wedged orthoses may be beneficial in the management of medial knee osteoarthritis when used with walking shoes. However, the addition of lateral wedging was associated with	One-year follow-up. Attempted patient blinding. High dropouts, especially for lateral wedge. Data suggest no significant differences.

			prescribed (lateral wedge, n = 35) for 1 month to 1 year.		early improvements in 6-minute walk test pain change not seen in the control group.”	
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ORTHOSES (including wedged insoles)

Orthoses have been used for treatment of knee osteoarthritis.(1063, 1067, 1070, 1092, 1102-1115)

Recommendation: Orthoses for Moderate to Severe Chronic Knee Osteoarthritis

Orthoses (lateral wedges for medial joint disease) are moderately not recommended for treatment of moderate to severe chronic knee pain due to osteoarthritis.

Strength of Evidence – Moderately Not Recommended, Evidence (B)

Rationale for Recommendation

There are eight moderate-quality trials of orthoses in osteoarthritis.(1092, 1093, 1114, 1116-1120) The highest quality trial was a randomized crossover trial that reported a lack of benefit from lateral wedging.(1116) The next highest quality studies included two reports and a 2-year follow-up report that found no meaningful benefit of orthoses.(1093, 1117) There are no trials comparing braces and orthoses. Lateral edge insoles and similar devices are not invasive, have few adverse effects, are low cost, but are not effective and thus are not recommended.

Evidence for the Use of Orthoses for Osteoarthritis

There are 8 moderate-quality RCTs or randomized crossover trials incorporated into this analysis. There are 6 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Orthotics, Shoe insoles, Shoe Lifts, Braces						
Baker 2007 Randomized Crossover Trial	7.5	N = 90 aged 50 and older with medial tibiofemoral narrowing	Five degree lateral-wedge insole (n = 46) vs. neutral insole 0° (n = 44) for 6 weeks.	Improvement with wedged sole 21 vs. 19 with neutral, p = 0.75. No significant differences between groups including WOMAC.	“The effect of treatment with a lateral-wedge insole for knee OA was neither statistically significant nor clinically important.”	Data suggest lack of efficacy. Sample size modest and no long term follow-up.
Barrios 2009 RCT	6.0	N = 66 radiographically diagnosed medial knee OA	Lateral-wedge between 5-15° vs. neutral insole (n = 31) for 1 year.	Both groups had similar improvements, except treatment group had significant improvement in pain during test (p = 0.039).	“With respect to the WOMAC scores, our results suggest that subjects with MOA responded favorably to both wedged and neutral orthoses when used in conjunction with walking shoes.”	High dropouts (31.8%). Success of patient blinding unclear. Compliance unclear. Results suggest no differences.
Maillefert 2001 RCT	5.5	N = 156 medial compartment femorotibial knee OA	Laterally elevated wedged insole (n = 82) vs. neutrally wedged insole (control, n = 74) for 6 months.	No differences in overall patient assessments at 1 (22% lateral vs. 25.7%), 3 (24.4 vs. 24.3%), and 6 months (24.4 vs. 23%), although all improved vs. baseline. WOMAC pain, joint stiffness, physical function	“The study failed to demonstrate a relevant short-term symptomatic effect of laterally-wedged insoles in medial femoro-tibial OA.”	Some baseline differences. Unclear how assessor blinded. Data suggest no meaningful improvements.

				subscales results similar to above. Less NSAID use in lateral wedge group (baseline: lateral vs. neutral use of NSAIDs prior 3 months): lateral (14.1±28 vs. 15.5±24). At 6 months: (9.9±27 vs. 15±28).		
Pham 2004 RCT	4.5	N = 156 outpatients with knee OA (follow-up study of Meillefert 2001)	Bilateral laterally elevated wedged insoles (valgus, n = 82) vs. bilateral neutrally wedged insoles (control, n = 74); 2 year follow-up.	No significant differences between groups. Compliance modestly better with lateral wedge.	"This study failed to demonstrate a relevant symptomatic and/or structural effect of laterally-wedged insoles in medial femoro-tibial OA."	Two-year follow-up study. Data suggest no meaningful differences.
Hinman 2009 Randomized Crossover Trial	4.5	N = 20 ≥50 years of age with medial compartment knee OA	Patients' own shoes with no insoles vs. insoles wedged laterally 5° for 1 month.	No differences between groups, including walking speed (p = 0.94). Modest changes in adduction moment with wedged insoles, 4.2-5.1%.	"Effects of laterally wedged insoles on the adduction moment do not appear to decline after one month of continuous use, suggesting that significant wedge degradation does not occur over the short-term."	Data suggest no significant effects. Primary focused on knee adduction moment changes.
Berry 1992 RCT	4.0	N = 170 >18 years old with symptomatic knee OA	Genutrain knee support vs. control for 6 weeks. All received analgesics and/or anti-inflammatories, physiotherapy including heat.	Greater improvements in Genutrain group vs. controls; p <0.05 for daytime rest; p <0.0001 for pain during activity; p = 0.060 for night pain.	"Genutrain is very acceptable to patients with osteoarthritis of the knee and its use increases the alleviation of symptoms. Its use should therefore be considered in patients being managed conservatively for osteoarthritis of the knee."	Many details sparse. Data suggest support helpful.
Horlick 1993 Randomized Double Crossover Trial	4.0	N = 39 medial compartment gonarthrosis (history of medial joint line pain; findings of medial joint line tenderness plus x-ray of medial joint compartment narrowing	Brace in neutral, brace in valgus, no brace vs. brace in neutral, no brace, brace in valgus vs. brace in valgus, no brace, brace in neutral vs. brace in valgus, brace in neutral, no brace.	Mean±SD pain levels lateral vs. medial: pre-brace: 3.53±1.92 vs. 4.14±1.73; valgus: 2.30±2.04 vs. 2.55±1.26; neutral: 2.82±2.07 vs. 2.98±1.08; no brace: 2.98±2.11 vs. 3.81±2.08; p = 0.005 decrease from baseline to valgus using lateral hinge; p = 0.0017 from baseline to valgus using medial hinge.	"Valgus bracing using a GII brace, especially with a medial hinge, can be a useful treatment modality for reducing pain in the patient with medial gonarthrosis to replace or delay surgery."	Data suggest valgus bracing superior.
Trotter 2008	4.0	N = 40 lower extremity MSD pain (plantar fasciitis,	Custom-made orthoses vs. prefabricated	Path length scores favored custom orthoses (p <0.001). Significant	"[I]mmediate improvements in economy of gait can be expected with both	Mixed disorders. Not a study of OA. Utility of results

Randomized Crossover Trial		metatarsalgia, tibialis anterior/posterior tendinitis, etc.)	inserts for 4 weeks each.	improvements in path length ratio if prefab first, then custom; but not reverse order.	interventions....however, that only the custom-made orthoses maintain economy of gait for 4 weeks.”	with diverse MSDs unclear.
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CANES AND CRUTCHES

Recommendation: Canes and Crutches for Moderate to Severe Acute, Subacute, or Chronic Knee Pain

Canes and crutches are recommended for treatment of moderate to severe acute knee pain or subacute and chronic knee pain when the device is used to advance the activity level.

Indications – Moderate to severe acute knee pain or subacute or chronic knee pain, particularly when the device is utilized to increase activity level.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

Crutches and canes may be helpful for treating acute injuries during the recovery phase. They also may be helpful during the rehabilitative phase to increase functional status (e.g., from wheelchair to walker to cane). However, for chronic knee pain, crutches may paradoxically increase disability through debility. In those circumstances, institution or maintenance of advice for crutch or cane use should be carefully considered against potential risks.

Evidence for the Use of Canes and Crutches

There are no quality studies evaluating the use of canes and crutches for knee pain.

MOTORIZED SCOOTERS

Motorized scooters have been used for treatment of severe knee arthrosis.(1121)

Recommendation: Motorized Scooters for Severe Chronic Knee Osteoarthritis

Motorized scooters are recommended for highly select patients who have severe chronic knee pain due to osteoarthritis.

Indications – Severe chronic knee osteoarthritis accompanied by major impairment in mobility that has either not responded well to arthroplasty and/or other significant impairments are present that necessitate use of a motorized scooter. Patients should also have had inadequate response to multiple other treatments including at least 2 different NSAIDs, aerobic exercise, strengthening exercise, weight loss, and aquatic therapy program.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

There is one moderate-quality trial of intermittent motorized scooter use in knee osteoarthritis patients.(1121) The trial reported no meaningful increases in manual activity and long-term effects, including deconditioning, are unclear. Scooters are costly, thus, they are recommended for highly select use.

Evidence for the Use of Motorized Scooters for Knee Osteoarthritis

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Power Mobility Devices						

Hoening 2007 RCT	5.5	N = 43 adults, able to walk independently for at least 15 months who met ARA criteria for knee OA or RA	Motorized scooter (n = 22) vs. usual care (n = 21) for 3 months.	6-minute walk distances (baseline to 3 months): scooter 16.9±73.0 vs. 17.2±69.6), p = 0.55. 41% reported daily scooter use.	“Motorized scooters provided to ambulatory persons with arthritis were used intermittently. The greatest short-term risk from scooter usage appeared to be minor collisions.”	Study population moderately affected. Baseline differences with scooter group older (67 vs. 58 years, and more difficulty climbing stairs (91 vs. 81%).
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MAGNETS AND MAGNETIC STIMULATION

High intensity magnetic stimulation purportedly causes depolarization of nerves and has been found to result in an antinociceptive effect in rats.(1122) Electromagnetic fields have also been reported to increase osteoblastic activity.(1123) Therefore, proponents of magnet therapy believe that magnetic fields have value in the treatment of musculoskeletal disorders. Many studies of magnet therapy have been negative, although several studies have reported benefits.(1124, 1125) Magnets have been studied in rheumatoid arthritis,(1126) which is beyond the scope of this guideline.

Recommendation: Magnets and Magnetic Stimulation for Osteoarthritis, Acute, Subacute and Chronic Knee Pain

There is no recommendation for or against the use of magnets and magnetic stimulation for treatment of osteoarthritis or acute, subacute and chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are quality sham-controlled trials that evaluate the use magnets for treatment of knee osteoarthritis. However, it cannot be assumed that subjects in these trials were successfully blinded.(1127-1131) One trial reported that most of the subjects accidentally or purposefully were unblinded to the intervention,(1127) and other trials did not report on the success of blinding. Therefore, the evidence base is limited. One trial that included a sham control (active magnets that were shielded from the skin) did not find meaningful outcomes at follow-up.(1127) While magnets are not invasive, have no adverse effects, and are relatively inexpensive, there is no quality evidence of their intermediate- or long-term efficacy and other treatments have proven efficacy; thus, there is no recommendation for or against their use.

Evidence for the Use of Magnets and Magnetic Stimulation

There is 1 high- and 4 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Magnets vs. Placebo						
Harlow 2004 RCT	8.0	N = 194 aged 45-80 with hip or knee osteoarthritis	Standard strength static bipolar magnetic bracelet (Group A, n = 65, 170-220m Tesla) vs. weak magnetic bracelet (Group B, n = 64, 21-30m Tesla) vs. non-magnetic bracelet (Group C, n = 64); 12 weeks follow-up.	WOMAC A (baseline/4 weeks/12 weeks): standard (10.7±2.1/8.9±3.8/7.8±3.9) vs. weak (11.0±2.0/9.1±2.8/8.8±3.2) vs. dummy magnets (10.9±2.1/9.5±3.1/9.3±3.2), p = 0.03 standard vs. dummy. Difference in WOMAC C scores standard vs. dummy magnets, p = 0.01. VAS scores significant standard vs. dummy,	“Pain from osteoarthritis of the hip and knee decreases when wearing magnetic bracelets. It is uncertain whether this response was due to specific or non-specific (placebo) effects.”	Study of bracelets. Some baseline differences with trend toward worse baseline severity in control groups (median painkiller use in prior week of 5.5 vs. 6.5 vs. 7.0 days). Dropouts said to be low. Mechanism of action unclear, as field of magnet strength approx. 2cm. No long-term follow-up.

				11.4 95% CI of 3.0-19.8.		
Wolsko 2004 RCT	7.0	N = 29 with idiopathic or post-traumatic knee osteoarthritis	High strength magnetic knee sleeve (n = 13, 40-850G) vs. placebo magnetic knee sleeve (n = 13) for 6 weeks.	At 4 hours, change in pain favored magnet (-79±18 vs. -10±21, p = 0.03). Primary and secondary outcomes of WOMAC Osteoarthritis Index not different between groups at 1 and 6 weeks.	"[M]agnets showed significant efficacy compared to placebo after 4 hours under rigorously controlled conditions."	Pilot study, no long-term follow-up. Some baseline differences (more continuous pain in active magnet group). Magnet trended toward more use in active group (10.5 vs. 7.6 hours a day, p <0.10). Data suggest lack of efficacy.
Chen 2008 RCT	6.0	N = 50 mild to moderate knee OA (Ahlbäck I)	Active magnetic knee wrap (n = 24, 35mT) vs. sham magnetic knee wrap (n = 26) for 12 weeks. Lower extremity exercise prohibited.	Isokinetic quadriceps strength in magnet group increased at both angular velocities, p = 0.007, p = 0.022. Changes in quadriceps strength scores in magnet group superior to control group at 12 weeks, p = 0.031.	"Magnetic knee wrap may significantly facilitate isokinetic quadriceps strength in patients with mild to moderate knee OA."	Baseline comparability unclear. No long-term follow-up. Co-interventions uncontrolled. High dropouts.
Jacobson 2001 RCT	6.0	N = 176 osteoarthritic knees	Active magnet treatment (low-amplitude extremely low frequency) vs. placebo; 6-minute sessions (8 over 2 weeks).	Active group perceived mean 46% pain reduction vs. 8% for placebo, p <0.001. At 2 weeks follow-up, mean pain reductions of 49% vs. 9%.	"Low-amplitude, extremely low frequency magnetic fields are safe and effective for treating patients with chronic knee pain due to osteoarthritis."	Magnetic therapy not self-treated. Requires considerable equipment, patient time. Dropouts unclear as analyzed completers. No baseline data. Limited outcomes data. Robustness of conclusions unclear.
Hinman 2002 RCT	4.0	N = 43 chronic pain in 1 or both knee joints	Pads 7.6x7.6cm with magnets (n = 18, 1.08T) vs. placebo pads (n = 25) for 2 weeks. Pads worn when pain felt, removed when relieved.	Sum of VAS pain ratings (pre/post): magnets (19.4/7.4) vs. placebo (19.6/16.1). WOMAC physical function also favored active magnets.	"The application of static magnets over painful knee joints appears to reduce pain and enhance functional movement."	Differences in magnet use between 2 groups, potentially based on PRN usage (5.87 vs. 2.90 hours used). Results in difficulty interpreting outcomes.

PULSED ELECTROMAGNETIC FIELDS

High-intensity magnetic stimulation purportedly causes depolarization of nerves and has been found to result in an antinociceptive effect in rats.(1122, 1132) Electromagnetic fields have been known to increase osteoblastic activity. Therefore, proponents believe that magnetic fields have therapeutic value in the treatment of musculoskeletal disorders.

Recommendation: Pulsed Electromagnetic Fields for Osteoarthrosis, Acute, Subacute, or Chronic Knee Pain

Pulsed electromagnetic fields are not recommended for the treatment of osteoarthrosis or acute, subacute, or chronic knee pain.

Strength of Evidence- Not Recommended, Insufficient Evidence (I)

Rationale for Recommendation

There are multiple trials of magnetic fields.(1133-1139) Most trials are negative, although there are a few that suggest modest benefit. A moderate-quality study using PEMF after ACL reconstruction found significant recovery compared to placebo.(1140) A moderate-quality study evaluated PEMF after arthroscopic surgery and reported improved recovery at 3 years and decreased NSAID use 45 days post-operatively.(1141) These results require replication. Magnetic field treatments are not invasive and have no adverse effects, but as they are moderately costly and most studies suggest no benefit, these treatments are not recommended.

Evidence for the Use of Pulsed Electromagnetic Fields

There are 9 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Trock 1994 RCT	7.0	N = 86 with knee OA	Pulsed electromagnetic field therapy (treated group, n = 42) vs. placebo (n = 44) for 18 treatments.	Pain scores not significant between groups at 1 month follow-up, p = 0.08. ADL difficulty also not different between groups. Pain on passive motion did not differ at 1 month follow up, p = 0.07, but tenderness significant between groups, p = 0.03 in favor of treated group.	"PEMF has therapeutic benefit in painful OA of the knee or cervical spine."	PEMF compared to NG treatment can improve tenderness in knee OA patients at one month. No functional analysis. Need longer term follow-up and cost benefit analysis.
Trock 1993 RCT	7.0	N = 27 with OA	PEMF therapy (active group, n = 15) vs placebo (n = 12) for 18 treatments	The observers assessment of improvement significant, p = 0.0134 after 1 month in favor of active group.	"The decreased pain and improved functional performance of treated patients suggests that is configuration of PEMF has potential as an effective method of improving symptoms in patients with OA."	Small numbers of knee patients. Pilot study reported improvement in OA, did not delineate which joint if any had different outcomes.
Thamsborg 2005 RCT	6.5	N = 83 older than 45 years with painful knee OA of femorotibial compartment	Pulsed electromagnetic field (PEMF) therapy (n = 42) vs. placebo (n = 41) 6 weeks.	No significant difference between groups for WOMAC scores.	"Applying between group analysis we were unable to demonstrate a beneficial symptomatic effect of PEMF in the treatment of knee OA in all patients. However, in patients <65 years of age there is significant and beneficial effect of treatment related to stiffness."	No significant differences found. Lack of details of score. PEMF did not have significant effect on outcomes except for stiffness in <65 years of age.
Zorzi 2007 RCT	6.5	N = 31 age 18-70 with painful symptoms at knee	I-ONE magnetic field stimulator with peak intensity of 1.5 mT at 75 Hz frequency (active group, n = 19) vs. control (n =	KOOS scores higher in active group compared to control, p <0.05. 75% of control patients used NSAIDs compared to 26% in active group, p = 0.015.	"[P]atients' acceptance of I-ONE PEMF treatment is high and it can be applied immediately after arthroscopic surgery, without side effects, to improve functional recovery."	Small numbers. Co-interventions not mentioned. Patients had painful knee syndrome after chondroabrasion.

			12) for 90 days.			
Gremion 2009 RCT	5.5	N = 89 with knee OA at stage II-III	Pulsed signal therapy (PST, n = 48) vs. conventional physiotherapy (n = 41) for 4 weeks.	No differences between the groups for passive and active mobility, Lequesne score, and VAS scores by end of study.	"Like physiotherapy, pulsed signal therapy has improved the clinical state of treated patients but with no significant statistical difference. Pulsed signal therapy is, however, more expensive."	Lack of details. Both groups improved but physical therapy improved more with 1/2 the cost.
Benazzo 2008 RCT	5.5	N = 60 undergoing ACL reconstruction	I-ONE magnetic field stimulator with peak intensity of 1.5 mT at 75 Hz frequency (active group, n = 31) vs. placebo (n = 29) for 60 days	Less patients in active group used NSAIDs at 30 days vs. placebo, p <0.05. Mean changes in SF 36 scores at 6 months higher in active group vs. placebo, p <0.05. Passive ROM of knee more limited in placebo than active group, p <0.05.	"I-ONE should always be considered after ACL reconstruction, particularly in professional athletes, to shorten the recovery time, to limit joint inflammatory reaction and ultimately for joint preservation."	No mention of co-interventions and lack of baseline characteristics creates same questions as to which patients may benefit.
Ay 2009 RCT	5.0	N = 55 with knee OA	Hot-pack plus TENS over knees for 20 minutes both groups vs. with vs. sham pulsed electro-magnetic field (PEMF) therapy for 30 minutes (n = 30 vs. n = 25) for 3 weeks.	No significant difference between two groups for VAS (p = 0.343) and Likert (p = 0.400) scores at end of therapy.	"[T]here is no standard treatment procedure for certain musculoskeletal diseases. The beneficial effect of PEMF on pain relief makes it a potential alternative treatment modality for OA."	All patients were not allowed to take analgesic medication and had physical therapy for 15 sessions over 3 weeks. They reported no difference from PEMF therapy.
Zizic 1995 RCT	4.0	N = 78 with knee OA	Bionicare pulsed electrical stimulation (n = 41) vs. placebo (n = 37) for 4 weeks.	Percent change between groups from baseline to end of study significant favoring active group (p <0.05) for physician global evaluation, patient evaluation of pain, and patient evaluation of function of treated knee. Morning stiffness decreased by 20 minutes in active group and 2 minutes in placebo, p <0.05. Knee flexion improved by 5° or more in 45% of active group and 18% of placebo, p <0.05.	"The improvements in clinical measures for pain and function found in this study suggest that pulsed electrical stimulation is effective for treating OA of the knee."	Lack of study details, no baseline characteristics comparisons given. Cost-benefit analysis is recommended. PES appears to be an option for knee OA pain control and treatment.

Pipitone 2001 RCT	4.0	N = 69 with symptoms of OA	Pulsed electromagnetic field (PEMF) therapy (active group, n = 34) vs. placebo (n = 35) for 6 weeks.	No differences between groups at the end of study except for a difference in EuroQol perception of health status score, which was significantly better for active group, p = 0.01.	"[T]his study has demonstrated a statistically significant benefit in terms of reduction of pain and disability in patients with knee OA resistant to conventional treatment in the absence of significant side-effects."	Disease duration was 48 months in active and 96 months in control. Baseline quality of life significantly different and that difference remained at end of study. Conclusion of improvement in EuroQol results suspect because of baseline difference.
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Physical Methods

HOT AND COLD THERAPIES

It has been proposed that cold and heat have actual therapeutic benefits to modify the disease processes (e.g., cold to allegedly reduce acute inflammation and swelling and heat to speed healing through increased blood supply).(1142, 1143) However, it has been proposed that these various modalities are distractants that apparently do not materially alter the clinical course.(1144) Still, it is postulated that the distractants allow increased activity levels.(1145) Many patients with chronic pain report a temporary soothing effect from the application of heat or the use of ice packs in the home setting. Cryotherapies have also been utilized in peri- and post-operative patients to speed healing and attempt to reduce opioids requirements.(1146-1155)

Cryotherapies

Cold or cryotherapies involve application of cold or cooling devices to the skin. They have been used for treatment of non-operative pain and post-operative pain.(1156)

1. *Recommendation: Home Use of Cryotherapies for Osteoarthritis or Acute, Subacute, or Chronic Knee Pain*

Cryotherapies are recommended for home use if efficacious for the temporary relief of osteoarthritis or acute, subacute, or chronic knee pain.

Frequency/Duration – Education regarding home cryotherapy application may be part of the treatment if cold is effective in reducing pain.

Indications for Discontinuation – Non-tolerance, including exacerbation of knee pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. *Recommendation: Cryotherapy for Treatment of Knee Arthroplasty and Arthroscopy and Other Surgery Patients*

Cryotherapy is recommended for select treatment of knee arthroplasty and surgery patients.

Frequency/Duration – Pain relief with cold therapy for the first several post-operative days with duration commensurate with extent of surgery. Some devices may be helpful for select patients, particularly if they are unable or unwilling to tolerate other measures to manage pain.

Indications for Discontinuation – Non-tolerance, adverse effects.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

There is one trial in non-operative patients, but it is difficult to develop evidence-based guidance as that trial is likely biased in favor of cryotherapy.(1157) While cryotherapy is generally not helpful in patients with osteoarthritis, a small minority may find benefit. Thus, cryotherapy is recommended as a potential distractant or counter-irritant and is recommended for self-application.

There are many post-operative studies, although few are moderate in quality with significant methodological limitations. The available studies confirm that there is no effect of cryotherapy on swelling. Nearly all studies also show that cryotherapy has no significant impact on blood loss. The available quality trials conflict with two suggesting no benefit (one compared cold therapy with lukewarm water(1146)) and one suggesting benefits, including opioid sparing (compared cold therapy with traditional post-operative regimens not including epidural anesthesia(1152)).

Self applications of cryotherapies using ice bags, towels or reusable devices are non-invasive, minimally costly, and without complications. Other forms of cryotherapy are moderately costly and may be reasonable for selected patients who are unwilling to undergo epidural anesthesia or have other indications for these devices.(1152)

Evidence for the Use of Cryotherapies

There are 5 moderate-quality RCTs incorporated into this analysis. There are 7 low-quality RCTs in Appendix 1. requirements.(596, 1147-1149, 1151, 1154, 1158)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Cryotherapy during Rehabilitation						
Ivey 1994 RCT	5.0	N = 90 with primary TKA	Thermal pad circulating temperatures at 50° vs. 60° vs. 70°F for 72 hours post-op.	No differences in morphine consumption post- op.	“There was no correlation between thermal-pad temperature or any other parameter and the amount of morphine injected after surgery.”	Data suggest lack of efficacy of cryotherapy.
Lin 2003 RCT	4.5	N = 71 with limited post- operative ROM due to traumatic fractures, knee flexion <110°.	All treated 20 minutes with heat then static stretching for 10 minutes, then, superficial cold (5°C) vs. heat (75°C).	Knee ROM (pre- treatment/post heat/post randomization): heat (75.97±24.81/82.70 ±25.91/81.86±25.62) vs. cold (84.24±11.78/90.29 ±13.03/92.53±12.90) , p <0.05.	“Cold pack application had a limited but significant effect during mechanical stretching for restricted knee motion.”	Many details sparse. Ultra-short term trial. All treated with heat, then cold or heat, thus not a clear head-to-head trial design. As reapplication of more heat would be more of same, trial may be biased in favor of cold.
Perioperative Cryotherapy						
Konrath 1996 RCT	6.0	N = 103 having arthroscopic ACL reconstructio n	Group 1 (Polar Care device with ice water, 40-50°F) vs. Group 2 (Polar Care device with lukewarm water, 70-80°F) vs. Group 3 (bag of crushed ice) vs. Group 4 (no cold therapy controls).	Lengths of stay did not differ (1.1-1.2 days, p = 0.62). Drain outputs (p = 0.38) and range of motion also did not differ (p = 0.84). Equianalgesic doses of pain medication per kg did not differ (0.521- 0.598/kg, p = 0.71).	“[B]oth ice packs and cooling pads significantly decreased knee temperature, but we found no objective benefits in the early postoperative course due to this decrease in temperature.”	Data suggest no meaningful differences.

Holmström 2005 RCT	4.5	N = 60 with 61 knees with OA undergoing unicondylar knee arthroplasty	Cryo (48 hours continuously, 10-15°C) vs. epidural anesthesia (2.5-5.0mg/mL bupivacaine; continuous pump administration for 48 hours) vs. control (traditional analgesics or paracetamol 500mg, dextropropoxyfene 50-100mg, MS oral 5mg or IV 5mg/mL). All treated with rehabilitation program; 6 weeks follow-up.	In first POD, higher MS consumption in traditional group, then cryo then epidural (21 vs. 13 vs. 7.5mg, interpretations of graphic data). Over first 3 days, consumption averaged 28.4 vs. 18.7 vs. 14.2mg, p = 0.005. No differences in blood loss or swelling. No differences in ROM.	“Cryo-Cuff seems to be a rational, effective, risk-free, and well-tolerated alternative to (epidural anesthesia) to reduce pain and morphine after unicondylar knee arthroplasty.”	Data suggest comparable efficacy for all 3 treatment arms.
Smith 2002 RCT	4.0	N = 84 undergoing total knee arthroplasty	Compression bandaging for 24 hours then ice bags TID for 24-48 hours vs. 6 hours then cryo pad machine (2-5°C) for 24 hours then ice bags TID for 24-48 hours.	No differences in length of stay (8.0 vs. 7.8 days, p = 0.91), drainage (p = 0.267), transfusion requirements (p = 0.99), swelling, pain or opiate consumption.	“Unlike other studies, the results of these data showed no significant differences between groups on the measured outcomes.”	Durations of treatment not standardized. Data suggest lack of efficacy.

Heat Therapies

Many forms of heat therapy have been used to treat musculoskeletal pain including hot packs, moist hot packs, sauna, warm baths, infrared, diathermy, and ultrasound. The depth of penetration of some heating agents is minimal since transmission is via conduction or convection, but other modalities have deeper penetration.(1159) A particular methodological problem with most studies of heat therapy is that, despite occasional attempts at, and claims of, successful blinding, it is impossible to blind the patient to these interventions, as they produce noticeable, perceptible tissue warming. Not surprisingly, some of these heat-related modalities have been shown to reduce pain ratings more than placebo for patients with low back pain. It is less clear whether there are meaningful, long-term benefits. Heat therapies are passive treatments. In chronic pain settings, use of heat should be minimized to self-treatments of flare-ups with primary emphasis on functional restoration elements (e.g., exercises).

Recommendation: Self-application of Heat Therapy for Osteoarthritis or Acute, Subacute, or Chronic Knee Pain

Self-application of low-tech heat therapy is recommended for treatment of osteoarthritis or acute, subacute, or chronic knee pain.

Indications – Applications may be periodic or continuous and should be home-based, as there is no evidence for efficacy of provider-based heat treatments. Primary emphasis should generally be on functional restoration program elements, rather than on passive treatments in patients with chronic pain.

Frequency/Duration – Self-applications may be periodic. Education regarding home heat application should be part of the treatment plan if heat has been effective for reducing pain.

Indications for Discontinuation – Intolerance, increased pain, development of a burn, other adverse event.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendation

Self-application of heat using towels or reusable devices is non-invasive, minimally costly, and without complications. There is one trial with heat administered by a sleeve that failed to find evidence of efficacy.(1160) Another trial evaluated heat and cold as an adjunctive treatment for stretching along with a prior treatment with heat and found cold to be superior.(1157) A third trial compared ice water to lukewarm water to crushed ice, but found no benefit in the early post-operative stage due to decreased knee temperature.(1146) While they are generally not helpful in patients with osteoarthritis, heat therapy may be helpful in a small minority, and thus is recommended as self-treatment as potential distractant or counter-irritant. It may also be helpful for purposes of stretching when there is a limited range of motion. Some forms of heat can be considerably more expensive, including chemicals, and are not recommended.

Evidence for the Use of Heat Therapy

There are 3 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Heat Therapy						
Mazzuca 2004 RCT	5.0	N = 52 with knee OA, moderate or greater pain, Grade 2 or higher Kellgren, Lawrence severity	Verum sleeve (heat retaining) vs. placebo sleeve (standard cotton/elastane sleeve). Subjects wore sleeve over more painful knee at least 12 hours a day for 4 weeks.	Mean±SD for WOMAC pain score (baseline-follow-up) comparing verum sleeve group vs. placebo group: Verum: -3.8±2.3 vs. - 1.0±0.8; p0.003. Placebo: -2.6± 3.5 vs. -1.4±1.8; p = 0.37. Uncertain: 0.3±0.3 vs. -1.2±2.4; p = 0.37.	“This pilot study was insufficiently powered to be a definitive trial of the heat-retaining sleeve. Given the magnitude of changes in knee pain in the active treatment group, heat retention merits further scientific investigation as a treatment modality for patients with knee OA.”	Heat combined with sleeve. No placebo group for sleeve. Some details sparse. Data suggest no significant differences between groups.
Lin 2003 RCT	4.5	N = 71 with limited post-op ROM due to traumatic fractures, knee flexion <110°	All treated 20 minutes with heat, then static stretching for 10 minutes, then superficial cold (5°C) vs. heat (75°C). One treatment follow-up.	Knee ROM (pre- treatment/post heat/post randomization): heat group (75.97±24.81/82.70± 25.91/81.86±25.62) vs. cold group (84.24±11.78/90.29± 13.03/92.53±12.90), p <0.05.	“Cold pack application had a limited but significant effect during mechanical stretching for restricted knee motion.”	Many details sparse. Ultra short-term trial. All treated with heat, then cold or heat, thus not a clear head-to- head trial design. As re-application of more heat would be more of same, trial may be biased in favor of cold.
Post-operative Heat Therapy						
Konrath 1996 RCT	6.0	N = 103 having arthroscop ic ACL reconstructi on	Group 1 (Polar Care device with ice water, 40-50°F) vs. Group 2 (Polar Care device with lukewarm water, 70-80°F)	Lengths of stay did not differ (1.1-1.2 days, p = 0.62). Drain outputs (p = 0.38) and ROM did not differ (p = 0.84). Equianalgesic doses of pain medication	“[B]oth ice packs and cooling pads significantly decreased knee temperature, but we found no objective benefits in the early postoperative course	Data suggest no meaningful differences.

			vs. Group 3 (bag of crushed ice) vs. Group 4 (no cold therapy controls).	per kg did not differ (0.521-0.598/kg, p = 0.71).	due to this decrease in temperature.”	
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ULTRASOUND

There are many commercial modalities that deliver heat; these generally differ on how deeply the heat is felt. None of these modalities have demonstrated major efficacy for any disorder, however there have been limited uses for treatment of specific disorders with a specific intervention (see Hand, Wrist, and Forearm Disorders, Elbow Disorders, Low Back Disorders, and Chronic Pain guidelines). There are more trials that include ultrasound to treat the knee than the hip.(1161)

Recommendation: Ultrasound for Treatment of Knee Osteoarthritis

There is no recommendation for or against the use of ultrasound therapy for knee osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

The highest quality trial comparing ultrasound with sham treatment found a lack of benefit.(1162) The moderate quality trials conflict – some suggest benefits,(577, 1163, 1164) while others suggest a lack of benefit.(575, 1165) Given that results conflict, there is no recommendation for or against ultrasound for treatment of knee OA.

Evidence for the Use of Ultrasound for Knee Osteoarthritis

There is 1 high- and 5 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT in Appendix 1.(1166)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Ultrasound						
Reed 2000 RCT	8.0	N = 21 non-impaired adult females aged 18-53	Valgus stretch and simultaneous continuous wattage ultrasound (CWUS) vs. sham CWUS for 28 days at a time.	Greatest increase in mean valgus displacement was from 0 to 40 minutes of observation for stretch and CWUS group, p <0.05.	“Brief static stretching increased valgus displacement of the knee for up to 30 minutes in a sample of nonimpaired women, but simultaneous heating with CWUS at a commonly-used clinical intensity did not augment the effects of stretching.”	Only females. Crossover study after 28 days. Ultrasound heated to attempt disguise sham ultrasound. No significant difference over stretching alone.
Huang 2005 RCT	6.0	N = 120 with bilateral moderate knee OA	Isokinetic muscular strengthening exercises (Group 1, n = 30) vs. isokinetic exercise and continuous ultrasound (US) (Group 2, n = 30) vs. isokinetic exercise and pulsed ultrasound (Group 3, n = 30) vs. neither strengthening exercise nor ultrasound treatments (controls,	Average knee ROM significantly improved in Groups 2 and 3 vs. controls after and at follow-up. Average VAS scores significantly improved in Groups 1-3 vs. controls after and during follow-up. Average Lequesne scores better in Groups 1-3 vs. control (Group 4), p <0.05. Average ambulation speed more improved	“US treatment, especially pulsed US, can enhance the therapeutic effects of isokinetic strengthening exercise for treating periarticular soft tissue pain in patients with knee OA.”	Unsure if sham ultrasound used in Groups I and IV. Group IV had significant improvement.

			Group 4, n = 30) 3 times a week for 8 weeks.	in Groups 1-3 vs. Group 4, p <0.05.		
Özgonene I 2009 RCT	5.5	N = 67 with knee OA	Therapeutic ultrasound (n = 34) vs. sham ultrasound (n = 33) for 2 weeks.	WOMAC total score significant in favor of treatment group compared to control group, p = 0.006.	"[T]herapeutic US is a safe and effective treatment modality in pain relief and improvement of function in patients with knee OA."	Majority females. Placebo group showed improvement in pain and WOMAC.
Falconer 1992 RCT	5.0	N = 74 with knee OA	Ultrasound (n = 37) vs. placebo (n = 37) for 12 treatments.	No differences between groups for active ROM and pain at post-treatment or follow-up evaluations.	"Patients with connective tissue knee contracture possess good potential for nonsurgical improvements in joint function. Although ultrasound may not contribute to the management of patients with chronic knee stiffness or osteoarthritis, exercise or structured activity programs may be beneficial."	No difference attributed to ultrasound noted.
Huang 2005 RCT	5.0	N = 140 with bilateral moderate knee OA	Isokinetic muscular strengthening exercises (Group 1, n = 35) vs. isokinetic exercise and pulsed ultrasound (Group 2, n = 35) vs. isokinetic exercise, pulsed US and intraarticular hyaluronan therapy (Group 3, n = 35) vs. no treatment except warmup exercises (Group 4, n = 35).	Knee ROM significantly better for Group 1 vs. Group 4, p <0.05. Average VAS scores significantly improved for Groups 1 and 2 vs. Group 4, p <0.05. Average Lequesne's Index significantly better in Groups 1 and 2 vs. Group 4, p <0.05. Average Ambulation speed significantly improved in Group 1 vs. Group 4, p <0.05.	"[A]n integrated therapy including US, isokinetic strengthening exercise, and intraarticular hyaluronan therapy that deals with the intraarticular and extraarticular progressive pathologic changes of knee OA is suggested for the management of knee OA."	Patients had either unilateral or bilateral knee osteoarthritis. All interventions had an impact compared to control of only warm up exercises. Ultrasound did not increase outcomes compared to exercise only.
Cetin 2008 RCT	4.0	N = 100 females with knee OA	Short-wave diathermy (SWD) plus hot packs (HP) plus isokinetic exercises (Group 1, n = 20) vs. TENS plus HP plus isokinetic exercises (Group 2, n = 20) vs. ultrasound (US) plus HP plus isokinetic exercises Group 3, n = 20) vs. HP plus isokinetic exercises (Group 4, n = 20) vs. isokinetic exercises (Group 5, control group, n = 20) 3 times a week for 8 weeks.	Groups 1-4 showed greatest degree of pain reduction compared to control group, p = 0.019. Walking time not significant between groups, p = 0.589. Lequesne index scores significant for Groups 1 and 2 vs. control, p = 0.022 and 0.001 respectively. Groups 1-3 had significantly higher PT values compared to control group at all angular velocities, p <0.05.	"Using physical agents before isokinetic exercises in women with knee osteoarthritis leads to augmented exercise performance, reduced pain, and improved function. Hot pack with a transcutaneous electrical nerve stimulator or short-wave diathermy has the best outcome."	Placebo effect not well accounted for, no sham in control. All benefited from exercises. TENS and shortwave diathermy, seem more likely to be effective than US. Sham-controlled trials of TENS or short-term diathermy recommended.

PHONOPHORESIS

Recommendation: Phonophoresis for Knee Osteoarthritis

Phonophoresis is not recommended for knee osteoarthritis.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

There is one moderate-quality study evaluating phonophoresis with ibuprofen compared to ultrasound and found no difference between the two therapies. The authors reported that both groups were improved over the 2 weeks of therapy.(1167) Thus, as there is not evidence of efficacy, phonophoresis is not recommended.

Evidence for the Use of Phonophoresis for Knee Osteoarthritis

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Kozanoglu 2003 RCT	5.0	N = 60 with knee OA (duration ≥ 6 months); Kellgren-Lawrence scale II-IV; minimum WOMAC score of 25	Ibuprofen phonophoresis (PH) using a 5cm long strip of cream containing 5% ibuprofen vs. conventional ultrasound waves of 1 MHz frequency and 1 watt/cm ² power for 5 minutes to target knee joint for a total treatment period of 10 sessions.	No significant difference in 30% improvement rate was detected between 2 groups; p >0.05).	“Both therapeutic modalities were found to be effective and generally well tolerated after 10 therapy sessions. Ibuprofen PH was not superior to conventional ultrasound in patients with knee osteoarthritis.”	Lack of study details. No sham arm to control for placebo effect. No adverse events. PH vs. ibuprofen did not increase benefit in study.

MASSAGE

Massage is a commonly used treatment for chronic muscular pain and usually administered by multiple health care providers as well as family or friends. It is most typically used for treatment of spine and torso pain (see Chronic Pain and Low Back Disorders guidelines), although it has been used for the treatment of knee pain.(1168, 1169)

Recommendation: Massage for Knee Osteoarthritis or Acute, Subacute, or Chronic Knee Pain
There is no recommendation for or against the use of massage for knee osteoarthritis or acute, subacute, or chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

Massage is a commonly used treatment for musculoskeletal pain, but few studies evaluated disorders other than LBP.(1170-1172) There is one moderate-quality trial for treatment of knee OA. However, significant limitations of the study include randomization failure and use of wait-listed controls, thus biasing the study in favor of massage. While massage is not invasive and has few adverse effects, it is moderately to highly costly (when professionally administered), depending on the number of treatments. Also, other treatments with documented efficacy are available.

Evidence for the Use of Massage

There are 2 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Yip 2008 RCT	5.5	N = 59 with moderate to severe	Six massage sessions with ginger and orange oil vs. massage with olive oil vs.	WOMAC pain (baseline/1 week/4 weeks): massage plus ginger (5.74±2.40/4.26±2.26/3.91±1.93) vs.	“The aroma-massage therapy seems to have potential as an alternative	Most results suggest no differences, though may have

		knee pain, $\geq 4/10$ pain	no massage. Massages over 2-3 weeks; 4 weeks follow-up.	massage oil (4.53 \pm 2.21/3.94 \pm 2.11/2.88 \pm 1.50) vs. control (6.35 \pm 2.37/5.24 \pm 2.33/5.64 \pm 2.55).	method for short-term knee pain relief.”	been underpowered.
Perlman 2006 RCT	4.0	N = 68 with knee OA (ACR), ≥ 35 years old, WOMA C 40-90/100	Swedish massage twice a week for Weeks 1-4 then weekly for Weeks 5-8 vs. non-interventional control; 16 weeks follow-up.	WOMAC pain scores at 8 weeks: massage - 23.19 \pm 24.30 vs. controls - 3.08 \pm 17.58; p <0.001 pooled analyses at 16 weeks. Significant changes in other WOMAC indices, VAS pain, ROM.	“Massage therapy seems to be efficacious in the treatment of OA of the knee. Further study of cost effectiveness and duration of treatment effect is clearly warranted.”	Baseline difference in WOMAC pain (40.6 vs. 52.1 in controls) suggests randomization failure. High overall dropouts (51.5%). Wait-listed controls likely biases in favor of intervention.

REFLEXOLOGY

Reflexology is a complementary or alternative treatment. It entails the physical act of applying pressure to the feet and hands with specific thumb, finger, and hand techniques without the use of oil or lotion. Reflexology is based on a system of zones and reflex areas that reflect an image of the body on the feet and hands. Work on the feet and hands are thought to effect physical changes to the body.

Recommendation: Reflexology for Knee Osteoarthritis or Acute, Subacute, or Chronic Knee Pain

Reflexology is not recommended for the treatment of knee osteoarthritis or acute, subacute, or chronic knee pain.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Rationale for Recommendation

There are no quality studies of reflexology for knee pain. It also has not been shown to be efficacious for the treatment of chronic LBP in a moderate-quality study.(1173) Other treatments have been shown to be efficacious.

Evidence for the Use of Reflexology

There are no quality studies evaluating the use of reflexology for knee osteoarthritis or acute, subacute, or chronic knee pain.

ACUPUNCTURE

Acupuncture has been used to treat many musculoskeletal conditions including hip(1174) and spine pain and osteoarthritis, particularly of the knee,(486, 1175) and there is some evidence that patients seek this treatment if they have more severe pain.(1176) Multiple techniques have been used, including manual needle stimulation, electrical needle stimulation(1177-1179) (electroacupuncture), superficial dry needling, and deep dry needling.(1180, 1181) Acupuncture administration may involve moxibustion and cupping.(1182) Moxibustion is a traditional Chinese therapy involving burning of an herb (mugwort) to stimulate blood flow and balance “Qi.” Cupping is another ancient Chinese practice involving placement of a cup on the skin with negative pressure induced either through heat or suction with tension placed on the underlying tissue. Besides traditional acupuncture, there are many other types of acupuncture that have arisen, including accessing non-traditional acupuncture points.(1183) Quality evidence has documented that use of traditional acupuncture locations is not necessary to derive equivalent

benefits from treatment of low back pain (see Chronic Pain and Low Back Disorders guidelines).(1184-1186)

1. *Recommendation: Acupuncture for Chronic Osteoarthritis of the Knee*

Acupuncture is moderately recommended for select use for treatment of chronic osteoarthritis of the knee as an adjunct to more efficacious treatments.

Indications – Moderate to severe chronic osteoarthritis of the knee. Prior treatments should include NSAIDs, weight loss, and exercise, including a graded walking program and strengthening exercises. Should be considered as an adjunct to a conditioning program that has resulted in insufficient clinical response.

Frequency/Duration – A limited course of 6 appointments(1187) with clear objective and functional goals to be achieved. Additional appointments would require documented functional benefits, lack of plateau in measures and probability of obtaining further benefits. There is quality evidence suggesting traditional acupuncture needle placement may be unnecessary(1188) and that superficial needling is as successful as deep needling.(1189, 1190) There is evidence suggesting it is not necessary to perform bilateral needling,(1191) although that result has not been replicated.

Indications for Discontinuation – Resolution, intolerance, and non-compliance, including non-compliance with aerobic and strengthening exercises.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

2. *Recommendation: Acupuncture for Acute or Subacute Knee Pain*

There is no recommendation for or against the use of acupuncture for the treatment of acute or subacute knee pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Rationale for Recommendations

There are several high- and moderate-quality studies that evaluated acupuncture for the treatment of knee osteoarthritis.(1190, 1192-1204) Trials of auricular acupuncture suggests efficacy in reducing analgesia requirements peri-operative,(1205) intra-operative,(1206) and post-operative.(1174) Some have concluded that the evidence suggests that there is no effect of acupuncture on pain.(1012) Some trials have combined acupuncture with electrical currents, others have applied electrical currents to acupuncture sites,(1201, 1207, 1208) and one involved periosteal stimulation.(1209) There are no quality studies to show clear benefit of electroacupuncture over needling. There continue to be some questions about efficacy of acupuncture,(1210, 1211) with concerns about biases, e.g., attention and expectation bias in these study designs as well as the adequacy of placebo acupuncture treatments.(1212, 1213) One trial demonstrated acupuncturist behaviors to set positive expectations had a significant impact on outcomes from acupuncture.(1214)

Studies reporting results after the cessation of acupuncture have nearly all found lasting benefits,(1187, 1192, 1215) although there are no long-term follow-up reports. Although not all studies have been positive,(1216) acupuncture has been found to be superior to no acupuncture ,(1192, 1217) superior to more of the same medication,(1202) superior to usual care,(1218-1221) and also an additive benefit to an NSAID.(1198) Results of three trials involving shams have indicated the sham was approximately equivalent to acupuncture,(1189, 1190, 1222) but acupuncture(1196) and electroacupuncture(1207) were superior to sham in two other trials. High-quality studies with sizable populations and long follow-up periods are needed for all of these potential indications. Acupuncture when performed by experienced professionals is

minimally invasive, has minimal adverse effects, and is moderately costly. Despite significant reservations regarding its true mechanism of action, a limited course of acupuncture may be recommended for treatment of knee osteoarthritis as an adjunct to a conditioning and weight loss program. Acupuncture is recommended to assist in increasing functional activity levels more rapidly. Primary attention should remain on the conditioning program. Acupuncture is not recommended for those not involved in a conditioning program or who are non-compliant with graded increases in activity levels.

Evidence for the Use of Acupuncture

There are 8 high- and 16 moderate-quality RCTs incorporated into this analysis. There are 4 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Osteoarthritis						
Witt 2005 RCT	8.5	N = 300 with knee OA (ACR, KL Grade ≥ 2), average pain intensity $\geq 40/100$ mm VAS.	Acupuncture at 6 points (n = 150) vs. minimal acupuncture treatment (n = 76) with superficial insertion of fine needles at non-acupuncture points vs. wait-list (WL) control (n = 74). Assessments baseline, Week 8, 26 and 52.	WOMAC index scores (SE): acupuncture, 26.9 (1.4) vs. minimal acupuncture, 35.8(1.9) vs. WL controls, 49.6(2.0).	"[P]ain and joint function are improved more with acupuncture than with minimal acupuncture or no acupuncture in patients with osteoarthritis of the knee. However, this benefit decreases with time."	Attempted blind with minimal acupuncture group. Data not provided but qualitatively reported effective blinding. Trial uses wait-listed controls which biases in favor of other arms. Data suggest acupuncture effective, but no long-term efficacy clearly demonstrated.
Witt 2006 RCT	6.0	N = 712 with hip or knee OA	Acupuncture (up to 15 sessions) vs. no acupuncture (delayed treatment for 3 months). Acupuncture individualized.	WOMAC scores improved with acupuncture (17.6, SE 1.0; WOMAC 30.5 ± 1.0) vs. controls (0.9, SE 1.0; WOMAC 47.3 ± 1.0), $p < 0.001$. All other WOMAC indices significantly improved ($p < 0.001$). Quality of life scores also improved, $p < 0.001$. Treatment success also occurred in those with delayed treatment.	"[A]cupuncture plus routine care is associated with marked clinical improvement in patients with chronic OA-associated pain of the knee or hip."	Large sample size; additional 2,921 received acupuncture, but not randomized. Individualized acupuncture treatments modestly weaken conclusion. Treatment made no difference. Non-randomized had almost identical results to those randomized to immediate acupuncture. Data support efficacy of acupuncture for intermediate-term symptom relief, but non-interventional control biases in favor of intervention.
NSAID plus Acupuncture vs. Placebo Acupuncture						
Vas 2004 RCT	7.0	N = 97 age 45 years and older with pain in one or both knees for	Acupuncture and diclofenac 50mg taken every 8 hours (n = 48) vs. placebo acupuncture plus diclofenac 50mg taken every 8	Final pain VAS: intervention (10.6 ± 10.8) vs. control (37.2 ± 26.3), $p < 0.001$. WOMAC total: intervention (9.5 ± 13.7) vs. control (33.4 ± 28.0), $p < 0.001$.	"Acupuncture plus diclofenac is more effective than placebo acupuncture plus diclofenac for the symptomatic treatment of	Trial described as single blinded assessor but had a sham so appears to be double blinded. High dropouts in control (8/49 vs. 1/48) due mostly to

		3 or more months with radiological evidence of knee OA	hours (n = 49) for 12 weeks; 13 weeks follow-up.	WOMAC pain: intervention (1.7±2.6) vs. control (6.4±5.8), p <0.001. WOMAC stiffness: intervention (0.4±1.3) vs. control (2.1±2.6), p <0.001. WOMAC function: intervention (7.4±10.3) vs. control (24.9±20.4), p <0.001. PLQC physical capability: intervention (2.8±0.7) vs. control (2.5±0.8), p = 0.021. PLQC psychological functioning: intervention (2.7±0.4) vs. control (2.5±0.6), p = 0.046.	osteoarthritis of the knee.”	lack of efficacy. Data suggest acupuncture is of additive benefit to diclofenac.
Acupuncture with vs. without Medication						
Tukmachi 2004 RCT	6.0	N = 30 older than 18 years suffering from knee OA Grade I-III for 6 months or longer	Acupuncture alone, no NSAID and analgesic drugs (Group A, n = 9) vs. acupuncture, existing NSAID, analgesic medication (Group B, n = 10) vs. taking current medication 1st 5 weeks then 5 weeks acupuncture and current medication (Group C, control, n = 10) acupuncture twice a week from baseline to 5 weeks.		“[M]annual and electroacupuncture causes a significant improvement in the symptoms of osteoarthritis of the knee, either on its own or as an adjunct therapy, with no loss of benefit after one month.”	Small groups. Data suggest acupuncture superior to continuing medications (i.e. 'more of the same') for which there is a probable bias.
Different Types of Acupuncture						
Usichenko 2007 RCT	9.0	N = 120 between ages 18-70 undergoing arthroscopic ambulatory knee surgery under general anesthesia	Auricular acupuncture at 3 acupuncture points (n = 61) vs. invasive needle control at 3 non-acupuncture points (n = 59) before surgery and stayed in situ until following morning.	Ibuprofen requirement, mg: control (600) vs. acupuncture (200), p = 0.012. NS between groups for tramadol use, piritramide dose, discharge time, follow up time, night sleep after surgery, number of night arousals after surgery, and adverse effects. Require no post-op analgesia with ibuprofen for acupuncture vs. control group: 20/52 (38%) vs. 10/52 (19%), p = 0.025.	“[A]uricular acupuncture applied to specific acupuncture points reduced the requirement for ibuprofen relative to invasive needle control after ambulatory arthroscopic knee surgery.”	Attempted sham. Follow-up time frame somewhat unclear. Data suggest efficacy.

Suarez-Almazor 2010 RCT	7.5	N = 560 with radiological diagnosis of OA, pain in knee preceding 2 weeks \geq 3/10; outcome assessment at 4 weeks, 6 weeks, and 3 months	Acupuncturists randomized to high expectation style vs. neutral expectation style. Patients within each acupuncturist group randomized to receive traditional Chinese acupuncture (TCA) vs. sham acupuncture vs. wait listed. Study duration 6 weeks; 3 month follow-up.	Outcome measures between TCA and sham not significant; both styles of acupuncture significantly different than wait-listed group. Outcome measures for communication style for joint-specific multidimensional assessment of pain between high vs. neutral styles baseline/4 weeks/6 weeks/3 months: 4.3 (1.3)/3.2 (1.2)/3.0 (1.3)/3.2 (1.4) vs. 4.5 (1.2)/3.5 (1.4)/3.4 (1.4)/3.6 (1.5), $p = 0.006$; Satisfaction with knee procedure: n/a /4.22 (0.65)/4.13 (0.78)/4.06 (0.78) vs. n/a /4.01 (0.69)/4.01 (0.79)/3.88 (0.82), $p = 0.004$.	"In summary, TCA was not superior to sham acupuncture, and needling of meridian points was not more effective than use of sham points. Continuous electrical stimulus or increased needle penetration in the TCA group did not improve response. Acupuncturists' communication style had a small but statistically significant effect in pain reduction and satisfaction suggesting that the perceived benefits of acupuncture may be partially mediated through placebo effects related to the acupuncturists' behavior."	Three month follow up. Data suggest acupuncturist behavior may modulate pain.
Tillu 2001 RCT	5.0	N = 60 waiting for total knee replacement with no acupuncture treatment in last year, no intra-articular injections within last 3 months.	Unilateral acupuncture (Group A, n = 22) vs. bilateral acupuncture (Group B, n = 22) 6 acupuncture treatments at weekly intervals; 6 mo follow-up.	No significant between group differences.	"[U]nilateral acupuncture is as effective a bilateral acupuncture in increasing function and reducing pain associated with OA of the knee."	Patients not well described. Data suggest no need to treat both knees, instead just most symptomatic. Six month follow up.
Electroacupuncture						
Sangdee 2002 RCT	6.5	N = 200 with unilateral or bilateral knee OA	Placebo tablet plus placebo EA (placebo group, n = 47) vs. diclofenac tablet plus placebo EA (diclofenac group, n = 49) vs. placebo tablet plus EA (EA group, n = 48) vs. diclofenac tablet plus EA (combined group, n = 49); 4 weeks follow-up.	Placebo (n = 45) vs. diclofenac (n = 49) vs. EA (n = 46) vs. combined (n = 46) change in outcome parameters after 4 weeks of treatment mean \pm SEM for number of paracetamol taken (tablets per week), 50 feet walk time (sec), VAS, WOMAC pain index, WOMAC stiffness index, WOMAC disability index, WOMAC total score, and Lequesne's functional	"[E]A was significantly more effective than placebo regarding reductions in 100 mm VAS and Lequesne's functional index, but was significantly more effective than diclofenac in only the reduction of 100 mm VAS."	Placebo controlled (diclofenac) and attempted acupuncture sham. Sham with patches instead of needles. Data suggest electroacupuncture superior to other arms and combination not superior.

				score index: overall opinions of change and number of responders evaluated for Week 4 for orthopedists overall opinion (p = 0.01); much better, better, same, worse: 6/18/21/16, 22/21/20/23, 16/10/5/7, 1/0/0/0. Patient's overall opinion (p = 0.09): 19/25/31/22, 16/17/11/23, 9/7/4/1, 1/0/0/0. No. of responders (p = 0.02): 13/18/27/24.		
Acupuncture vs. Standard Care						
Foster 2007 RCT	8.0	N = 352 from physiotherapy centers; outcome measures assessed at 2, 6 weeks, 6 and 12 months.	Advice with exercise (n = 116) of six 30 minute sessions over 6 weeks vs. advice, exercise and true acupuncture (n = 117) 6 treatments over 3 weeks vs. advice, exercise, and non-penetrating acupuncture (n = 119) same treatment time period as other groups; 1 year follow-up.	Mean±SD crude change pain score at 6 weeks for advice and exercise vs. advice, exercise, and true acupuncture: 2.10±3.5 vs. 2.38, p = 0.1; vs. advice, exercise, non-penetrating acupuncture: vs. 3.02±3.6, p = 0.05; adjusted change score not significant. Crude change function score at 6 week exercise vs. true acupuncture: 6.21±11.4 vs. 8.18±11.5, p = 0.2; vs. non-penetrating exercise: 9.32±11.4, p = 0.05. Mean±SD change in knee pain intensity for exercise vs. true acupuncture at 2 weeks: 0.27±2.2 vs. 1.31 ±2.2, p <0.0001; vs. non-penetrating acupuncture: vs. 1.51±2.1, p <0.0001. At 6 weeks: 0.90±2.5 vs. 1.81±2.4, p = 0.004; vs. 2.18±2.5, p <0.001; at 6 months exercise vs. non-penetrating: 0.95±2.6 vs. 1.95±2.6, p = 0.006.	"The addition of acupuncture to a course of advice and exercise for osteoarthritis of the knee delivered by physiotherapists provided no additional improvement in pain scores."	Study protocol published as Hay 2004. Data suggest acupuncture not of additive benefits to exercise.
Williamson 2007 RCT	7.0	N = 181 subjects waiting for knee replacement surgery	Acupuncture once a week for 6 weeks (n = 60) vs. physiotherapy for 6 weeks (n = 60) vs. standardized advice (n = 61).	No baseline difference between groups. At 7 weeks, 10% reduction in OKS in acupuncture group was a significant difference between acupuncture and control group: Mean	"We have demonstrated that patients with severe knee OA can achieve a short-term reduction in OKS when treated with	High dropouts. Data suggest slight difference between groups.

				(s.d.) acupuncture 36.8 (7.20); physiotherapy 39.2 (8.22); control 40.3 (8.48) (p = 0.0497). Effects no longer present at 12 weeks. Trend (p = 0.0984) towards a shorter in-patient stay of 1 day for physiotherapy group [mean 6.50 days (s.d. 2.0)] compared with acupuncture group [mean 7.77 days (s.d. 3.96)].	acupuncture, in an NHS out-patient group setting. However, we failed to demonstrate any other clinically or statistically significant effects between the groups. Both interventions can be delivered effectively in an out-patient group setting at a district general hospital.”	
Lansdown 2009 RCT	6.5	N = 30 from a GP with clinical symptoms of OA but no x-ray confirmed diagnosis	Acupuncture up to 10 treatments vs. usual care including appointments, medication and interventions sought by participants from any health practitioner; 1 year follow-up.	WOMAC pain decreased significantly in acupuncture group compared to usual care at 3 months by -2.62 points (95% CI: -0.77 to -4.47) but no longer significant at 12 months. Usual care dropout rates was 6.7% (n = 1) at 3 months compared to 46.7% (n = 7) at 12 months.	“This study has been shown that it is feasible to recruit patients to a primary care trial to receive acupuncture for osteoarthritis of the knee, and that the tentative findings support conducting a full-scale trial. The pilot data have led to an estimate of the sample required for a full scale trial as well as the expected recruitment rates.”	Very high dropouts in usual care at 12 months (47%). Pilot study. Comparison group in usual care, thus 'more of the same' and probable bias in favor of the intervention. Data suggest short but not long term efficacy of acupuncture added to usual care.
Berman 1999 RCT	5.5	N = 73 with symptomatic knee OA for at least 6 months, moderate pain for most days in last month, and Kellgren-Lawrence Grade 2 or more radiographic changes of OA; outcome measures assessed at 9, 4, 8, and 12 weeks	Acupuncture (n = 37) vs. standard conventional care of oral therapy (n = 36); 12 weeks follow-up.	“Patients randomized to acupuncture improved on both WOMAC and Lequesne indices compared to those who received standard treatment alone. Significant differences on total WOMAC Scale were seen at 4 and 8 weeks. There appears to be a slight decline in effect at 4 weeks after cessation of treatment (12 weeks after first treatment). No adverse effects of acupuncture were reported.”	“The results of this study indicate that a group of elderly patients with moderate/severe OA of the knee showed significant improvement at the 4, 8, and 12 week measurement points over their baseline pain and function scores. As OA is the most prevalent form of arthritis and a leading cause of disability in the elderly, the identification of adjunctive acupuncture therapy as one which demonstrates effectiveness in decreasing pain and improving function is a	12 week follow up. Data suggest acupuncture superior to usual care.

					potentially useful clinical finding. This improvement was produced by an 8 week course of acupuncture delivered biweekly along with the current conventional therapy regime.”	
Reinhold 2008 RCT	5.0	N = 489 with hip or knee OA	Acupuncture plus routine care (10-15 appointments) vs. routine care for 3 months.	Costs higher for acupuncture over 3 months [mean cost-difference: 469.50 euros (95%CI 135.80-803.19). Overall ICER 17,845 euros per QALY gained. Cost effectiveness better for females.	“Acupuncture was a cost effective treatment strategy in patients with chronic osteoarthritis pain.”	Acupuncture administered by multiple providers and relatively unstructured. Unclear if economic data from Germany applies to U.S.
Acupuncture vs. Sham						
Scharf 2006 RCT	8.5	N = 1,039 with chronic knee joint pain lasting 6 months as defined by American College of Rheumatology criteria, radiologic confirmation by Kellgren-Lawrence score 2 or 3, and WOMAC score of at least 3 points, and chronic pain score of at least 1	Conservative therapy (n = 342) consisting of 10 visits to practitioner, diclofenac up to 150mg/d or rofecoxib 25mg/d as needed up to 23 weeks vs. traditional chinese acupuncture (TCA, n = 330) 10 sessions over a 6-week period vs. sham acupuncture (n = 367) with standardized minimal-depth needling without stimulation at 10 points. Outcome measures assessed at Weeks 13 and 26.		“Compared with physiotherapy and as-needed antiinflammatory drugs, addition of either TCA or sham acupuncture led to greater improvement in WOMAC score at 26 weeks. No statistically significant difference was observed between TCA and sham acupuncture, suggesting that the observed differences could be due to placebo effects, differences in intensity of provider contact, or a physiologic effect of needling regardless of whether it is done according to TCA principles.”	Large sample size. Data suggest acupuncture or sham superior and results lasted 6 months. Six month follow up.
Tsang 2007 RCT	8.0	N = 36 aged 60 and older diagnosed with bilateral primary knee osteoarthritis having undergone bilateral total knee	Acupuncture and physiotherapy (n = 18) vs. sham acupuncture and physiotherapy (n = 18) for 10 sessions. Acupuncture sites were ST32, ST33, GB31, GB35, GB34, ST36. Needles left for 20 minutes and	No significant between group differences.	“There is no difference between the acute effects of acupuncture and sham acupuncture in addition to standard postoperative physiotherapy programme in patients with knee osteoarthritis undergoing bilateral	Baseline up and go test differed between groups. Data suggest equivalency between acupuncture and sham when added to physiotherapy for postoperative TKA care.

		arthroplasty	manipulation of needles used every 5 minutes to achieve deQi; 15 day follow-up.		total knee arthroplasty."	
Berman 2004 RCT	7.0	N = 570 subjects diagnosed with OA of the knee	Twenty-three acupuncture sessions over 26 weeks (n = 190) vs. 6 2-hour education-attention control sessions over 12 weeks (n = 189) vs. 23 sham acupuncture sessions over 26 weeks (n = 191).	Acupuncture vs. sham vs. control mean change from baseline at week 4 for WOMAC pain score, p value, WOMAC function score, p value, patient global assessment score, and p value.	"Acupuncture seems to provide improvement in function and pain relief as an adjunctive therapy for osteoarthritis of the knee when compared with credible sham acupuncture and education control groups."	Data suggest sham only partially successful. High dropouts. Data suggest true acupuncture superior to sham superior to educational control. Benefits lasted up to 26 weeks.
Jubb 2008 RCT	6.5	N = 68 who had symptomatic and radiologic OA for longer than 6 months and who had previously failed more conventional treatments; outcome assessments conducted at 5 and 9 weeks	Acupuncture (n = 34) vs. sham acupuncture (n = 34) twice weekly for five weeks; 9 week follow-up.	Mean change (SD, 95% CI) in WOMAC pain between baseline and 5 weeks for acupuncture vs. sham 60 (110, 5-116), p = 0.035; at 9 weeks differences no longer significant. Mean change (SD, 95% CI) in WOMAC pain between baseline and 5 weeks for acupuncture 95 (96, 60-130); at 9 weeks, difference still significant, p = 0.009. Mean change in VAS pain scores between baseline and 5 for acupuncture vs. sham for weight bearing pain in study knee: 20 (7-33), p = 0.003; overall pain in study knee: 21 (8-34), p = 0.001. For acupuncture weight bearing pain in study knee: 32 (23-41), p = 0.001; overall pain in study knee: 29 (21-38), p = 0.001; night pain in study knee: 22 (12-32), p = 0.001. For sham weight bearing pain in study knee: 11 (1-21), p = 0.025. Mean change (95% CI) in VAS pain scores between baseline and 9 weeks for acupuncture weight bearing pain in study knee: 19 (9-30), p = 0.001; overall pain in study knee: 14 (5-24), p = 0.005. For acupuncture vs. sham	"The present study confirms the beneficial effect of acupuncture for treating the symptoms of osteoarthritis of the knee and suggests that skin penetration of the needle is required... Acupuncture gives symptomatic improvement for patients with osteoarthritis of the knee, and is significantly superior to non-penetrating sham acupuncture."	High dropouts in acupuncture group. Data suggest electroacupuncture superior to sham.

				general body pain: 13 (0-27), p = 0.048.		
Takeda 1994 RCT	5.0	N = 40 volunteers Grade I-IV knee OA with pain in one or both knees, radiologic al evidence of OA, and no previous experienc e with acupunctu re of knee	Acupuncture treatment (n = 20) where needles left in subject for 30 minutes and each rotated back and forth for 5 minutes vs. sham acupuncture (n = 20) inserted superficially 3 times a week for 3 weeks with assessments before treatment, after 3 weeks of treatment, and 4 weeks later; 7 weeks follow-up.	No significant between group differences.	"[B]oth the real and placebo acupuncture decreased pain, stiffness, and physical difficulty in persons with OA of the knee. There was a tendency for the true acupuncture group to show a greater response, but the difference was not significant. It is possible that both groups had a placebo response or that both groups responded in some physiological manner to their respective treatments."	Follow up times not clear. Data suggest acupuncture and sham equivalent.
Periosteal Stimulation Therapy						
Weiner 2007 RCT	6.0	N = 88 with knee pain of moderate intensity or greater most or all days for ≥3 months, Kellgren-Lawrence Grade 2, 3, or 4 radiograph ic knee OA; outcome assessed at 6 weeks and 3 months.	Periosteal stimulation therapy (PST, n = 44) vs. control PST (n = 44) once a week for 30 minutes for 6 weeks; 3 month follow-up.	No significant difference between groups.	"This initial controlled clinical trial indicates that PST is safe and effective in providing modest, short-term pain reduction for older adults with chronic knee pain associated with advanced OA."	Data suggest short-term pain reduction, but no intermediate or long-term benefits.
Undefined Subtopic						

Kim 2010 RCT	9.5	N = 60 who met American College of Rheumatology classification criteria, knee pain on VAS scale >4cm on a 10 cm VAS scale; outcome measures assessed at 3, 6, and 16 weeks	UDP pharmacopuncture vs. normal saline for 6 weeks; 4 months follow-up.	Mean 100 mm VAS decreased in both groups, after 7th treatment, UDP pharmacopuncture treatment group significantly lower than control group, p = 0.04. WOMAC pain score, total WOMAC score and KHAQ score of UDP group not significantly different between groups during study duration.	"In summary, UDP pharmacopuncture, compared with normal saline injection, caused pain improvement after the seventh treatment session, but over-all, differences were generally insignificant. This may be due to the inappropriateness of the control intervention. For accurate reassessment of pharmacopuncture, an inert control intervention such as dry needling or a waiting list control should be used in future studies."	Borderline high dropouts in control group. Data suggest comparable results.
Nejrup 2008 RCT	8.5	N = 102 clinically diagnosed with OA of the knee, and had pain/stiffness from knee OA ≥1 year	Gold implantation (n = 21) vs. sham (n = 19); 1 year follow up.		"This 1-year double-blind, randomised controlled trial of extraarticular gold bead implantation shows no statistically significant effect for primary outcomes. The subgroup of patients who were responsive to the initial conventional acupuncture, however, had a greater self-assessed benefit of gold implantation. The treatment was well tolerated."	Pilot study. Article score reflects successful blinding although that is unclear and may be overstated.
Gluteal Muscle Trigger Points						
Huguenin 2005 RCT	7.5	N = 60 male soccer runners	Dry needling of gluteal trigger points (most upper outer buttocks, 3-5 points each, 0.3mm diameter, 25mm long acupuncture needles) vs. placebo needling (blunted needle to 1 minute).	VAS pain did not differ between groups (graphic data). No significant changes in ROM in either group. ROM with straight leg raise did not differ between groups.	"Neither dry needling nor placebo needling of the gluteal muscles resulted in any change in straight leg raise or hip internal rotation. Both interventions resulted in subjective improvement in activity related muscle pain and tightness."	Short-term trial of 3 days. No long-term outcomes data. Attempted blinding failed (p <0.001 between groups). Study also involves athletes from soccer clubs, thus applications to other populations unclear.
Acupuncture for Arthroplasty Patients						
Usichenko 2005 RCT	8.0	N = 61 with hip arthroplasty	Auricular acupuncture (hip joint, shenmen, lung, thalamus) vs. sham	Auricular acupuncture received 32% less piritramide vs. control in 1st 36 post-op hours (37 vs. 54mg, p	"(Auricular acupuncture) could be used to reduce postoperative	No differences in rates of belief of receipt of real acupuncture.

			acupuncture (4 helix points) for up to 3 post-op days	= 0.004). Total dose 36% lower (0.54 vs. 0.84mg/ kg, p = 0.002). Time to 1st request lower (40 vs. 25 minutes, p = 0.04).	analgesic requirement.”	
Usichenko 2006 RCT	7.5	N = 64 with THA	Auricular acupuncture (lung, shenmen, forehead, hip) vs. sham (4 helix points).	21% less fentanyl (3.9±1.4 vs. 4.9±1.2, p = 0.005) in acupuncture group vs. sham. 6 in acupuncture group required intraoperative atropine vs. 3 (NS).	“Auricular acupuncture reduced fentanyl requirement compared to sham procedure during hip arthroplasty.”	Data suggest mild reduction in fentanyl. No other differences. Considering quality evidence, traditional acupuncture not superior to sham for LBP, arthrosis. Study requires replication.

MANIPULATION AND MOBILIZATION

Manipulation and mobilization are two types of manual therapy. Manipulation has been used to treat knee disorders.(571, 1223-1243) It has been particularly utilized for post-operative patients with inadequate range of motion that affects function that is sometimes termed arthrofibrosis.(1223, 1229, 1232, 1244, 1245) There is quality evidence of efficacy of manipulation particularly for treatment of acute low back pain and neck pain (see Low Back Disorders, and Cervical and Thoracic Spine Disorders guidelines).

1. *Recommendation: Manipulation or Mobilization for Acute Knee Pain, Knee Osteoarthritis, or Surgical or Knee Fracture Patients*

There is no recommendation for or against the use of manipulation or mobilization for treatment of acute knee pain, knee osteoarthritis, or for surgical or knee fracture patients.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

2. *Recommendation: Manipulation or Mobilization for Subacute or Chronic Knee Pain*

Manipulation or mobilization is recommended for patients with subacute or chronic knee pain.

Strength of Evidence – Recommended, Evidence (C)

3. *Recommendation: Manipulation or Mobilization for Post-operative Patients with Significantly Reduced Range of Motion*

Manipulation or mobilization is recommended for select post-operative patients with significantly reduced range of motion.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendations

There are no quality trials of manipulation or mobilization compared with sham or incorporating a clinical prediction rule that demonstrate efficacy. There is quality evidence of efficacy for manipulation or mobilization in treating knee osteoarthritis,(571, 1226, 1246) but further quality studies are needed, as it is difficult to separate out the effect of other interventions included such as exercise. There is one high-quality study of manipulation in hospitalized knee and hip patients that found a lack of efficacy.(1247) However, this study did not include treatment to the hip or knee. Despite these study weaknesses, the orthopaedic manual physical therapy

(OMPT)^{xiv} approach(571, 1226) is believed to provide clinically important benefit for patients with knee OA. This treatment approach has been suggested to reduce the need for medication and total knee replacement. However, from the design of these pragmatic trials it cannot be determined what aspect of the OMPT approach is most responsible for the improvement. Manipulation is not invasive, has low adverse effects, but is moderately costly depending on the number of treatments. There is no recommendation for or against use in these patients, with the exception of patients with subacute or chronic knee pain or select post-operative patients.

Evidence for the Use of Manipulation or Mobilization

There is 1 high- and 8 moderate-quality RCTs incorporated in this analysis. There are 2 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Licciardone 2004 RCT	8.5	N = 60 patients undergoing hospitalized knee or hip OA surgery or hip fracture	Osteopathic manipulative treatment protocol (OMT) vs. sham treatment protocol. Manipulation was individualized (myofascial release, strain/counterstrain, muscle energy, soft tissue, high-velocity low amplitude mobilization, craniosacral). All received standard care.	Functional Independence Measure total scores improved: OMT 26.5 points vs. sham 26.2 points, $p = 0.86$. Lengths of stay were OMT 15.4 days vs. sham 12.3 days ($p = 0.09$). All measures were not different except rehabilitation efficiency, which favored the sham group over OMT (2.0 vs. 2.6 for sham, $p = 0.01$).	“The (osteopathic manipulative treatment) protocol used does not appear to be efficacious in this hospital rehabilitation population.”	Heterogeneous mixture of patients, diagnoses and individualization of treatments preclude robust conclusions about efficacy for any single diagnosis. Inpatient rehab population may also limit generalizability. Data suggest OMT not effective.
Bennell 2005 RCT	7.0	N = 124 with knee OA (x-ray confirmed) age ≥ 50 with knee pain most days of past month	Standardised physiotherapy vs. sham ultrasound for 12 weeks with 12 week follow-up.	At 24 weeks, 77% of physiotherapy participants vs. 49 % reported global improvement from baseline ($p = 0.005$); 66% vs. 48% reported a clinically relevant reduction in pain on VAS ($p = 0.027$). Mean difference (95% CI) for AQoL between groups at 24 weeks was 0.5 (0.01 to 0.10), physiotherapy 0.07 (0.03 to 0.10) vs. placebo 0.01 (-0.01 to 0.04).	“[Study] showed significantly improved pain and function with both physiotherapy and placebo interventions. Pain reduction was similar in both groups, and of a clinically relevant magnitude in around half the participants. This suggests that the physiotherapy package investigated in this trial offered no greater benefits than regular contact with a therapist.”	Higher dropouts with physiotherapy. Study claims double blinding, but appears incapable between groups for patients. Low compliance with HEP and taping. Treatment arm has numerous co-interventions that reduces utility of results. Despite somewhat biased in favor of active treatment, no efficacy of combined treatment shown.

^{xiv}OMPT is a formalized type of physical therapy based on skills developed with entry level professional programs through advanced fellowship training. OMPT generally includes: 1) a manual examination to identify impairments to movement, strength, coordination, and balance, and to identify symptom producing structures; 2) manual interventions to determine techniques and movements to reduce symptoms and improve function; 3) exercise prescription that reinforces movement from manual treatment and provides the appropriate dose of strengthening and/or balance exercises.

Deyle 2000 RCT	7.0	N = 83 with knee OA	Manual therapy to knee, spine, hip, ankle plus knee exercise program in clinic and home vs. sub-therapeutic ultrasound (0.1W/cm ² at 10% pulsed mode) twice a week for 4 weeks, 4 weeks, 8 weeks, 1 year follow- up.	Mean WOMAC scores at baseline/Week 8 for treatment group: 1046.7/ 462.4. Placebo group: 1093.5/ 934.3. By 8 weeks, WOMAC scores improved by 55.8% in treatment group; p <0.05.	“A combination of manual physical therapy and supervised exercise yields functional benefits for patients with osteoarthritis of the knee and may delay or prevent the need for surgical intervention.”	Study of combination of manual therapy and exercise program precludes assessment of efficacy of individual treatment. Symptoms duration trended to differ at baseline (81 vs. 57). Vigorous activity differed at baseline. High dropouts in treatment group. WOMAC and 6- minute distance superior in treatment group.
Deyle 2005 RCT	5.5	N = 134 with knee OA (Altman) required eligibility for military health care and no untreated knee physical impairment; excluded cortisone injection in prior 30 days or lower extremity surgical procedures in past 6 months	Clinic treatment (n = 66, received standardized knee exercise program at each session. A PT or PT technician supervised exercises including active ROM, muscle strengthening, muscle stretching, and stationary bicycle) vs. home exercise group (n = 68, received detailed instructions for home- based program of same exercises as clinical treatment group.) 4 weeks duration, 8 sessions for clinic treatment group)and subjects in both groups continued daily HEP, 1 year follow-up.	Group Comparisons: Means and 95% CI for the WOMAC at 0, 4, and 8 weeks. WOMAC Clinical vs. Home. Baseline: 1, 038.2 (921.6-1,154.8) vs. 1035.8 (908.3- 1,163.2). Week 4: 503.5 (399.6- 607.4) vs. 766.2 (632.7- 899.7). Week 8: 513.4 (392.7-634.2) vs. 730.2 (584.7-875.8)	“(H)ome exercise programs for patients with OA of the knee provides important benefits. Adding a small number of additional clinical visits for the application of manual therapy and supervised exercise adds greater symptomatic relief.”	More contact time in treatment group. Individualized treatment, including treatments beyond knee. Data suggest both groups improved. Differences at 8 weeks favored clinic treatment group over HEP especially for WOMAC. At 1 year, improvements in both groups, but not different.
Tucker 2003 RCT	5.5	N = 60 with OA on x- rays; age18-85	Manipulation (low- amplitude, high- velocity thrust to restore movement in direction of restrictions, n = 30) vs. Meloxicam (7.5mg QD after main meal, n = 30). Patients taking NSAIDs before entering study had to undergo 2-week washout period; 8 treatment/consultati ons over 3-week period.		“The results of the present study indicate that both manipulation and Meloxicam are equally effective in the short-term treatment of OA of the knee. At the 95% level of confidence, neither group showed any advantage over the other in treatment efficacy. The intra- group comparison indicated that	Contact lies in favor of manipulation as would prior experience with NSAIDs (more of the same).

			Consultations QOD, unless became asymptomatic.		manipulation was more effective in the mean objective measurements; however, this was not conclusive in inter-group analysis using the statistical parameters employed in this study."	
Pollard 2008 RCT	5.5	N = 43 with knee OA on x-ray, mild to moderate pain for 1+ years, self reported knee crepitus, self reported restricted ROM and/or knee joint deformity; no arthroplasty, recent history of meniscal or other knee surgery (less than 6 months)	Group 1 (n = 26, MIMG chiropractic knee protocol. It consists of non-invasive myofascial mobilization procedure and an impulse thrust procedure performed on symptomatic knee of participants) vs. Group 2 (n = 17, control: palmar contact to the knee without the application of force followed by interferential set at zero). Treatment consisted of 3 treatments per week for 2 consecutive weeks with a follow-up assessment after final treatment.	Changes in group pain scores between the control and treatment groups. Pre-test mean vs. post-test mean and confidence intervals (CI): Control group: 3.5(2.2, 4.7) vs. 3.1 (2.1, 4.1), p = 0.602. Treatment group: 3.3 (2.6, 4.0) vs. 1.9 (1.3, 2.6), p = 0.0004. Changes between control group and treatment group in pain scores: pre-test: 0.2 (-1.1, 1.5), p = 0.771. Post-test: 1.1 (0.1, 2.2), p = 0.042.	"A short-term manual therapy knee protocol significantly reduced pain suffered by participants with osteoarthritis knee pain and resulted in improvements in self-reported knee function immediately after the end of the 2 week treatment period."	Multiple interventions used. Adequacy of control group questionable and appears incapable of blinding.
Taylor 2003 RCT	4.5	N = 15 with patellafemoral pain syndrome over 1 months duration	Patella mobilization/manipulation 2 times a week for 4 weeks vs. mobilization/manipulation plus exercise twice a week for 4 weeks. Approximately 5 weeks of follow-up.	Graphic data presented. Some results favored combination group (e.g., SMPQ p = 0.009 post-treatment; NPRS-101 p = 0.037 at 2nd treatment).	"[T]he design and results of the present study cautiously suggest that there is a possibility that combined mobilization/manipulation and exercise may produce a marginally better outcome than patella mobilization/manipulation alone in the short-term treatment of PFPS."	Follow-up of Rowlands' pilot study (however that study design was different). Under-enrollment of 12 instead of 30. Population not described. Many details sparse. Study would address additive value of exercise if powered. Tiny groups too small for evidence-based guidance.
Brantingham 2009 RCT	4.5	N = 31 with patellafemoral pain syndrome of >3months duration	Chiropractic manipulative therapy (CMT) to the knee joints only, exercise, and Graston Technique or Graston Instrument-assisted Soft Tissue Mobilization (GISTM) (Group A, n = 25) vs. CMT to	NS between groups at baseline, after 6th treatment and 2 month follow-up for VAS (usual or worst), AKPS, or PSS. AKPS at 2 month follow-up change from baseline to follow-up: Group A increased 13.23 points, Group B by	"A feasibility study investigating the ability to conduct a (RCT) of a manipulative therapy protocol of PFPS using available chiropractic college infrastructure was accomplished."	Feasibility study to plan for fully powered RCT. As study compares 2 chiropractic protocols, it cannot in isolation address utility of either treatment

			the full kinetic chain (FKC) including manipulative therapy to the lumbosacral, sacroiliac, and all lower extremity joints including knee, exercise, and soft tissue (GISTM) treatment (Group B, n = 22) 1-3 times per week for 2-6 weeks for a total of 6 treatments. All treated with exercise; 2 months followup.	13.05 points, p = 0.003 for both. VAS usual decrease from baseline to 2 month follow-up: Group A: 1.48 (p = 0.021), Group B: 0.76cm (p = 0.230). VAS worst decrease from baseline to 2 month follow-up: Group A: 2.04 (p = 0.013), Group B: 2.73cm (p = 0.002). AKPS (baseline/change after 6th treatment): Local 71.85±9.75/9.46 vs. extended 75.83±9.02/6.05.		compared with no treatment or other treatment.
Hoskins 2010 RCT	4.0	N = 59 Australian football players participated in study unless had fractures, infections, inflammatory diseases, tumors, and/or causes of destructive lesions of spine	Group 1 (n = 29) received chiropractic intervention. Treatment for intervention group individually determined, could involve manipulation/mobilization and or soft tissue therapies to spine and extremity) vs. Group 2 (n = 30, control received current best practice medical and sports science management). Treatment scheduled 1 per week for 6 weeks, 1 treatment per fortnight for 3 months, 1 treatment per month for remainder of season (3 months).	Difference between the intervention and control group for injury incidence at the completion of season (24 matches, 30 weeks of intervention) Intervention incidence vs. control: 1 vs. 7, p = 0.051 Odds Ratio (OR): 0.116 CI: 0.013-.019. 1° Lower limb muscle strain: 1 vs. 8, p = 0.025. OR: 0.097 CI: 0.011-0.839. 1° Non-contact knee: 1 vs. 7, p = 0.051. OR: 0.116 CI: 0.013-1.019.	“This study demonstrated a trend toward lower limb injury prevention with a significant reduction in primary lower limb muscle strains and weeks missed due to non-contact knee injuries through the addition of a sports chiropractic intervention to the current best practice management.”	Study used multiple co-interventions that were individualized, limiting utility for evidence-based guidance.

MANIPULATION UNDER ANESTHESIA (MUA)

Recommendation: Manipulation under Anesthesia for Post-operative Patients with Significantly Reduced Range of Motion

Manipulation under anesthesia is recommended for select post-operative patients with significantly reduced range of motion. This may be performed selectively under general or regional anesthesia typically by the operating orthopedist.(1245)

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendation

There is no quality evidence of efficacy of manipulation of the knee, typically performed under anesthesia but also commonly performed by physical therapists, for post-arthroplasty patients with insufficient range of motion.(1225, 1228, 1230, 1248, 1249) One low-quality trial suggested significantly improved range of motion immediately after MUA in the manipulated group compared with the group that declined manipulation with differences persisting for 2

years.(1228) For patients with insufficient range of motion, manipulation under anesthesia is modestly invasive, has adverse effects, and is moderately costly, but it appears helpful for some patients to improve range of motion. Thus, it is a viable option for selected use.

LOW-LEVEL LASER THERAPY

Low-level laser treatment (LLLT) usually involves laser energy that does not induce significant heating. Low-level laser exposures are theorized to induce photoactivation of the oxidative chain.(1250-1252) LLLT is low risk and without significant reported side effects.(1253)

Recommendation: Low-level Laser Therapy for Knee Osteoarthritis or Acute, Subacute, or Chronic Knee Pain

The use of low-level laser therapy is not recommended for treatment of osteoarthritis and acute, subacute, or chronic knee pain.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

There are several moderate-quality trials that evaluated use of low level laser therapy for treatment of knee pain and osteoarthritis,(1252, 1254-1258) and while they conflict on efficacy to some extent,(1259) most trials with sham are negative.(1260, 1261) LLLT is not invasive, has low adverse effects, is moderately to highly costly based on the number of treatments required, has mostly negative results in quality trials for the treatment of the knee, and other effective treatment options exist. Thus, LLLT is not recommended for treatment of knee pain or osteoarthritis.

Evidence for the Use of Low-Level Laser Therapy for Knee Pain or Osteoarthritis

There is 1 high- and 7 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Bülow 1994 RCT	6.5	N = 29 with knee OA from exercise induced pain for at least 6 months	LLLT of 15 minutes at 1.5-4.5 J (n = 14) vs. placebo (n = 15) for 9 treatments over 3 weeks.	No significant differences between groups for pain, medicine, palpation tenderness, or muscle strength at any point during study.	"[L]ow level lasers should not be used in routine treatment nor approved by the health authorities before more solid scientific evidence documenting any beneficial effects is available."	Low numbers. Data suggest lack of efficacy.
Hegedüs 2009 RCT	6.0	N = 27 with mild to moderate knee OA	LLLT 48 J (n = 18) vs. placebo (n = 9) 2 times a week for 4 weeks.	Joint flexion, pressure sensitivity, and pain in treated joint better at follow-up periods for active group but not placebo group, p <0.05.	"[L]ow-level laser represents an effective treatment for short-term improvement in patients suffering from painful KOA."	Small number of participants. No reported significant difference between groups.

Gur 2003 RCT	5.0	N = 90 with knee OA	Actual laser therapy of 5 minutes with 3 J total dose plus exercise (Group 1, n = 30) vs. actually laser therapy of 3 minutes with 2 J total dose plus exercise (Group 2, n = 30) vs. placebo laser plus exercise (Group 3, n = 30) for 2 weeks for laser therapy and 14 weeks for exercise.	Improvements of pain measures in both groups with laser therapy significant compared to placebo group, p <0.05. Improvement in knee flexion significant for Group 1 compared to placebo, p <0.05. Improvements in WOMAC scores significantly better for both laser groups compared to placebo, p <0.05. Improvements in morning stiffness significantly better for Group 1 vs. placebo group, p <0.05. Group 2 had more improvement of pain during flexion at 6 weeks compared to Group 1, p <0.05.	"[S]hort-period application of LPLT plus exercise is more effective in pain relief and in the improvement of functional ability and QoL than that of placebo laser plus exercise in patients with knee OA. In addition, our study demonstrated that application of LPLT in different doses and durations did not significantly influence the findings and both therapy regimes were safe and effective methods in the treatment of knee OA. Thus, LPLT can be an important adjunct with exercise in the treatment of knee OA, especially in patients with adverse side effects to drug treatment."	Data suggest laser plus exercise and exercise alone improve outcomes.
Tascioglu 2004 RCT	5.0	N = 60 with knee OA	LLLT for 10 minutes at 15 J (Group 1, n = 20) vs. LLLT for 5 minutes at 7.5 J (Group 2, n = 20) vs. placebo (n = 20) for 10 days.	No differences among groups for WOMAC scores or VAS scores during treatment and during follow up.	"[L]ow power laser, given at two different dosages, does not play a significant role in reducing pain in the treatment of knee OA."	Lack of study details, no differences seen.
Rogvi-Hansen 1991 RCT	5.0	N = 36 with chondromalacia of patella	LLLT (n = 19) vs. sham therapy (n = 17) 8 times in a 5-week period.	Rate of improvement not significant between groups.	"Although this study has not established a significant benefit from low level laser treatment compared to sham laser treatment of chondromalacia of the patella, further investigation on its use is warranted."	Small numbers, lack of details, short-term follow-up. Lasers did not have an effect.
Montes-Molina 2009 RCT	4.0	N = 152 ambulatory patients with knee pain	Interferential laser treatment plus exercise (Group 1, n = 76) vs. conventional laser treatment plus exercise (Group 2, n = 76).	No differences between groups for VAS scores, p >0.05.	"[I]nterferential laser therapy applied transcutaneously, combined with quadriceps exercise, is a safe and effective method for reducing knee pain, but it did not show better results than those seen with conventional therapy with a single laser probe."	No placebo or control group. Improvement could be from exercise alone.
Laser Acupuncture vs. Placebo						
Yurtkuran 2007 RCT	8.0	N = 55 with OA of knee	904-nm LLLT (n = 28) on medial side of knee to acupuncture	LLLT vs. placebo PVAS mean±SD for before therapy-after	"[L]aser acupuncture of 0.48 J per session on the Sp9 point was effective only in	Data mostly suggest weak efficacy when

			point Sp9 vs. placebo (n = 25).	therapy, and before therapy-12th week.	reducing the periarticular swelling evaluated by the measurement of the KC when compared with placebo. This result may be explained by the resolution of inflammation due to reduction in prostaglandin synthesis or the improvement of local circulation. However, there is still insufficient evidence to have firm conclusion regarding the use of laser acupuncture for treatment of OA.”	added to a HEP.
Shen 2009 RCT	5.0	N = 40 OA diagnosed, radiographic evidence of at least 1 osteophyte at tibiofemoral joint, Kellgren-Lawrence Grade 2 or more and moderate or greater, clinically significant knee pain most days previous month	Active laser activated for 20 minutes vs. placebo laser 3 times per week for 4 weeks for a total of 12 treatments or every other day for a total of 12 treatments. Acupuncture site used was ST 35. Outcome measures assessed at baseline, Week 2, and Week 4.	Mean±SD of WOMAC index score difference in pain (percentage) for active laser vs. placebo at week 2: -49 ± 34 (7.79 ± 3.42) vs. -13 ± 62 (6.20 ± 3.68), p = 0.047; no significant difference in stiffness, function or global evaluation between groups at Week 2.	“[D]ue to the small sample size and high dropout rate of the control group, we cannot conclude whether the results were due to the therapeutic effect of this combined laser treatment or to a placebo effect.”	Pilot study. High dropouts in placebo group make results difficult to interpret.

ELECTRICAL THERAPIES

There are multiple forms of electrical therapies used to treat musculoskeletal pain. These include electrical stimulation therapies, iontophoresis, interferential therapy (IFT or IT), microcurrent therapy, percutaneous electrical nerve stimulation (PENS), and transcutaneous electrical stimulation (TENS).(1138, 1262-1268) The mechanism(s) of action, if any, are unclear.

ELECTRICAL STIMULATION THERAPIES

Neuromuscular electrical stimulation has been used particularly to strengthen the quadriceps femoris.(1269-1272) Many studies using electrical stimulation have been reported both for treating patients with osteoarthritis,(1273) patellofemoral pain,(1274) post-surgical knee patients,(1275-1279), as well as in healthy athletes to attempt to improve performance.(1280-1289)

Recommendation: Electrical Stimulation Therapies for Treatment of Knee Osteoarthritis or Acute, Subacute, or Chronic Knee Pain

There is no recommendation for or against the use of electrical stimulation therapies outside of research settings for the treatment of knee osteoarthritis or acute, subacute, or chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are is one moderate-quality trial of electrical stimulation in in knee osteoarthritis patients; however, the results are inconsistent.(1273) There are numerous low-quality trials attempting to address utility of electrical stimulation either alone or as an adjunct to exercise (see Appendix 1). The overall findings in those studies are exercise outperforms electrical stimulation. There are some suggestions electrical stimulation may have modest efficacy in comparison with control. Electrical stimulation is non-invasive, has low adverse effects, but is moderate to high cost with prolonged treatment. Other treatments shown to be effective are available. There is no recommendation for or against the use of these therapies.

Evidence for the Use of Electrical Stimulation Therapies

There is 1 moderate-quality studies evaluating the use of electrical stimulation for knee osteoarthritis and none for acute, subacute, or chronic knee pain. There are 16 low-quality trials in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Electrical Stimulation for Osteoarthritis						
Oldham 1995 RCT	5.0	N = 30 elderly subjects with knee OA	Contraction via either PNMS vs. uniform frequency vs. random pattern vs. sham stimulation.	Uniform frequency showed improved MVIT over PNMS groups (p <0.05) and sham (p <0.02). For sustained contraction PNMS and sham out-performed uniform frequency (p <0.02 and p <0.05 respectively).	“Following stimulation, some descriptive improvements in outcome measures were observed in favour of PNMS, particularly in functional tests such as walking speed and sit to stand time. No stimulation pattern emerged as being significantly better than another.”	Small groups and subjects not well described though all elderly with OA. Data suggest inconsistent results.

IONTOPHORESIS

Recommendation: Iontophoresis for Knee Osteoarthritis

There is no recommendation for or against the use of iontophoresis for the treatment of knee osteoarthritis or acute, subacute or chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

There are no quality studies for any of these therapies in occupational populations with knee osteoarthritis. There is one quality study suggesting efficacy of iontophoresis with morphine for post-operative knee and hip patients(1265); however, applicability to outpatient knee osteoarthritis populations and others is unclear. Some of these types of electrical therapies are thought to be of greater benefit for certain types of disorders such as iontophoresis with glucocorticosteroid for rheumatoid arthritis knee patients.(1268) These therapies are mostly non-invasive with low adverse effects but are moderately to highly costly when examined in aggregate. Other treatments shown to be effective are available. There is no recommendation for or against the use of these therapies for knee osteoarthritis.

Evidence for the Use of Iontophoresis

There are 2 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Li 1995 RCT	6.5	N = 10 with a diagnosis of RA with at	Experimental group receiving iontophoresis on days 1, 3, and 5 plus	Mean pain on movement in experimental group on Days 1, 5, 20:	“The results suggest that DEX iontophoresis is more effective than	Low numbers, 20 days follow-up. RA patients.

		least 1 painful knee	a mixture of 1ml of DEX (4mg/ml) and 1ml of injectable sterile water vs. iontophoresis Days 1, 3, and 5 plus 2ml of saline solution for 20 days.	3.00, 1.40, 1.60; p = -0.0224. Between group difference for pain at rest different; p = 0.0317.	placebo in relieving pain at rest and on movement in the RA knee. Based on the study data, a total of 40 subjects will be required for an RCT of a similar nature.”	Unable to draw much conclusion after ...how to design further studies.
Ashburn 1992 RCT	5.0	N = 38 scheduled for elective total knee or hip replacement, ASA classification I-III	Iontophoresis devices plus morphine for 6 hour vs. iontophoresis devices plus lactated ringers solution. During this period and for 12 hours following completion of iontophoresis, PCA analgesia remained available to patients.	Less PCA requests for periods during iontophoresis, for 1st and 2nd 6 hour postiontophoresis for morphine group compared to control group; p = 0.0071.	“Iontophoresis can deliver morphine systemically in sufficient quantities to provide early postoperative pain relief in patients undergoing total knee replacements or total hip arthroplasties.”	Post-op patients. Minimal baseline characteristics given. Morphine levels detected in blood, no IV morphine for comparison.

INTERFERENTIAL THERAPY

Recommendation: Interferential Therapy for Post-Operative Knee Patients

Interferential therapy for post-operative ACL reconstruction, meniscectomy, and knee chondroplasty is recommended immediately post-operatively in an elderly population. Patients should be engaged in an appropriate post-operative rehabilitation program in combination with interferential therapy.

Indications – Elderly patients, post-operative from ACL reconstruction, meniscectomy, or knee chondroplasty.(1267)

Duration – At home, 3 times a day for up to 9 weeks.(1267)

Indications for Discontinuation – Unable to participate in active rehabilitation program; no response after 1 to 3 treatments.

Strength of Evidence – **Recommended, Evidence (C)**

Rationale for Recommendation

There is one moderate-quality placebo-controlled trial among elderly residence home patients reporting improved pain, range of motion, and post-operative edema up to 9 weeks compared to placebo therapy.(1267) (Interferential therapy is not invasive, has few adverse effects, and is moderately costly. As there is evidence of efficacy, it is recommended.

Evidence for the Use of Interferential Therapy

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Jarit 2003 RCT	5.5	N = 87 undergoing ACL reconstruction, meniscectomy, or knee chondroplasty with no previous history of back injuries causing referred pain or impairment of extremities	Home interferential therapy 3 times per day for 28 minutes for 7-9 weeks vs. placebo.	All IFC patients experienced significantly less pain than placebo at all time points.	“These findings indicate that home IFC may help reduce pain, pain medication taken, and swelling while increasing range of motion in patients undergoing knee surgery. This could result in quicker return to activities of daily living and athletic activities.”	Patients selected from an elderly residence home, 23/24 women, mean age 85. No blinding, no inter-group comparisons. Need study with placebo treatment and younger age groups.

MICROCURRENT THERAPY

Recommendation: Microcurrent Therapy for Post-Operative Total Knee Arthroplasty Patients

There is no recommendation for or against the use of microcurrent therapy for total knee arthroplasty post-operative pain control.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There is one moderate-quality pilot study reporting improvement in post-operative pain and pain medication use and wound healing and decreased wound drain volumes.(1266) However, that trial was not sham controlled and therefore likely biased in favor of treatment. A single pilot study with these flaws is unable to be used for development of evidence-based guidance. Therefore, there is no recommendation.

Evidence for the Use of Microcurrent Therapy

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Microcurrent Skin Patches						
El-Husseini 2007 RCT	4.5	N = 24 undergoing TKA	Microcurrent therapy (MCT) with tramadol maximum 400mg a day (MCT group, n = 12) vs. tramadol only (control group, n = 12) for 10 post-op days.	Lower VAS scores were observed in MCT group. MCT used less tramadol than controls to control pain, p <0.001. MCT had higher frequency of Grade 1 wounds, controls higher frequency of Grade 2 and 3 wounds, p <0.001. Lower drain volume for MCT group, p <0.05.	"[M]CT led to better pain control, with a markedly lower requirement for tramadol as compared to the control group. This improved pain control was accompanied by a better healing of the wound and a lower drain volume. There were neither adverse effects nor a need to discontinue MCT therapy."	Small numbers. MCT appears to decrease post-op pain. Need further investigation, need to have a look at functional outcome and cost-benefit.

PERCUTANEOUS ELECTRIC THERAPY

Recommendation: Percutaneous Electric Therapy for Knee Osteoarthritis or Other Knee Pain

Percutaneous electric therapy is recommended for assistance with pain control for knee osteoarthritis or other knee pain.

Indications – As part of an active rehabilitation and exercise program.(1138, 1263, 1264)

Duration – Up to 3 times a week as part of a rehabilitation program.(575, 1290, 1291)

Indications for Discontinuation – Patient unable to participate in active rehabilitation program. No response after first treatment.(1263)

Strength of Evidence – Recommended, Evidence (C) (Knee OA)

Recommended, Insufficient Evidence (I) (Other knee pain)

Rationale for Recommendation

Two moderate quality sham-controlled trials evaluated patients with knee osteoarthritis reporting greater pain control compared to placebo.(1263, 1264) (A low-quality study evaluated PENS in post-operative patients and reported less muscle atrophy in the PENS group.(1292)) A moderate-quality study reported improved patient and physician rated outcomes in the active treatment group after 4 weeks of daily treatment.(1138) Percutaneous Electric Therapy is not

invasive, has few adverse effects, is moderately to highly costly, depending on duration of use, and has evidence of efficacy. Thus, it is recommended.

Evidence for the Use of Percutaneous Electric Therapy

There are 2 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Garland 2007 RCT	7.0	N = 58 moderate to severe knee OA	Pulsed electrical stimulation (n = 39) vs. placebo (n = 19) for 12 weeks.	Percent change between groups for baseline to 12 weeks for total WOMAC significant in favor of active group, p = 0.014.	“A highly optimized, capacitively coupled, pulsed electrical stimulation device significantly improved symptoms and function in knee OA without causing any serious side effects.”	Large dropout rate; lost an entire site, lack of baseline characteristics; good follow-up and documentation of compliance. Need a cost-benefit ratio and a comparison to other treatment modalities (i.e., exercise).
Kang 2007 RCT	5.0	N = 63 with knee pain secondary to OA	Biowave deep tissue neuromodulation pain therapy device (n = 35) vs. sham (n = 28).	Treated group had greater efficacy for pain intensity difference vs. sham right after treatment. VAS scores significantly reduced in treated group than sham right after treatment, p = 0.0494; 48 hours after treatment, pain control better for treated group than sham, p = 0.039. At 1 week follow-up, treated group used less medication than sham, p <0.0001. WOMAC scores better for treated group for pain (p = 0.1483), stiffness (p = 0.0296), function (p = 0.0539).	“The Deepwave percutaneous neuromodulation pain therapy device has significant promise as an effective component of the nonoperative treatment algorithm for symptomatic osteoarthritis of the knee. The results of this pilot study have determined the safety and efficacy of a single dose treatment of the Deepwave percutaneous neuromodulation pain therapy device.”	Difficult to blind because of sensation, no functional outcome measured. Need further study in larger groups because of functional outcomes in order to make treatment recommendation.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

TENS is a modality to control pain through electrical stimulation delivered by pads placed on the surface of the skin. TENS is used for the treatment of many painful conditions, including both non-inflammatory and inflammatory disorders; although it has more typically been used for spine disorders(1293-1299) (see Chronic Pain and Low Back Disorders guidelines).

Recommendation: TENS for Knee Osteoarthritis or Acute, Subacute, or Chronic Knee Pain
There is no recommendation for or against the use of TENS for knee osteoarthritis or acute, subacute or chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are many moderate-quality trials, and one of high-quality(1300) that evaluated TENS for knee pain. Some low-quality trials have suggested modest benefits from TENS,(1301-1304)

while others have suggested no benefits.(1305-1308) Seven of the moderate-quality studies did not find any significant improvement with the use of TENS,(575, 1290, 1291, 1309-1312) while nine reported some benefit compared to control.(1177, 1178, 1313-1319) TENS is not invasive, has few adverse effects, and is moderately costly. However, as there are many conflicts in the literature, there is no recommendation for or against its use to treat knee OA or pain.

Evidence for the Use of TENS for Knee Osteoarthritis and Knee Pain

There is 1 high- and 16 moderate-quality RCTs incorporated into this analysis. There are 8 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Burch 2008 RCT	8.0	N = 116 with knee OA	Fifteen minutes of interferential therapy and 20 minutes of patterned muscle stimulation vs. TENS for 35 minutes at 0.2 Hz.	IF vs. TENS had lower pain (p = 0.002) physical function (p = 0.003) and stiffness (p = 0.000).	“IF plus patterned muscle stimulation was more efficient than low-current TENS in relieving pain, increasing function and decreasing stiffness.”	TENS setting was low. No blinding of patients. IF and muscle stimulation appeared to decrease pain and increase function in patients with knee OA. IF and muscle stimulation not compared to exercise.
Lewis 1994 RCT	7.5	N = 28 with knee OA pain for at least 6 months	Active drug (naproxen) and placebo TENS (AD) vs. active TENS and placebo drug (AT) vs. placebo TENS and placebo drug (PP) 3 successive treatment phases, each of 3 weeks.	No significant differences between AT and PP groups for any measure. Small advantage of AD over AT on every measure.	“[N]o difference in efficacy between TENS and naproxen was established, but also that naproxen (and TENS) could not be reliably distinguished from placebo.”	Cross-over study design that could not find significant improvements of TENS and Naproxen over placebo.
Law 2004 RCT	7.5	N = 39 with knee OA	TENS (n = 22) vs. placebo TENS (n = 17) 5 days a week for 2 weeks.	Pain limited knee ROM not significant between groups at follow-up, p = 0.060. Maximum knee ROM between groups significant at follow-up in favor of TENS group, p = 0.025. No significant difference between groups for Timed-Up-and-Go Test, p = 0.246.	“[2] weeks of repeated applications of TENS significantly increased the maximum passive knee range of motion. However, it did not significantly increase pain-limited knee range or improve the performance of Timed-Up-and-Go Test. There was only a weak-to-moderate correlation between the VAS pain scores and various physical outcome measures.”	Blinding questionable. TENS may increase passive range of motion but no report of functional improvement.

Law 2004a RCT	7.0	N = 36 with knee OA	TENS at 2 Hz vs. TENS at 100 Hz vs. TENS 2/100 Hz vs. placebo TENS.	Between-group differences for VAS scores by follow-up session significant in favor of all treated groups, $p = 0.002$. Maximum passive knee motion significant at follow-up in favor of 3 treated groups, $p = 0.032$. No significant difference among groups for pain limited knee ROM during any treatment session.	“[2] weeks of repeated applications of TENS at 2 Hz, 100 Hz, or 2/100 Hz significantly reduced OA knee pain, whereas the placebo group experienced no such reduction. Pain reduction occurred in a cumulative manner from day 1 to day 10. The analgesic effects produced by the 10-day repeated applications of TENS were able to carry out at least up to the 2-week follow-up. However, no significant between-group differences were noted among the 3 active TENS groups (TENS ₂ , TENS ₁₀₀ , TENS _{2/100}) in all treatment sessions.”	Small sample sizes at 8 patients per group. Analgesic effect started at day one. Use of alternating stimulation frequency did not demonstrate any greater analgesic effects than fixed stimulation frequency.
Breit 2004 RCT	6.0	N = 69 undergoing primary TKA	Patient controlled analgesia (PCA) (Group 1, $n = 22$) vs. TENS plus PCA (Group 2, $n = 25$) vs. TENS sham plus PCA (Group 3, $n = 22$).	No significant differences between groups.	“[T]here was no benefit from the use of TENS as a modality for postoperative pain relief after TKA.”	TENS did not affect need for medication 24 hours post-op.
Lewis 1984 RCT	6.0	N = 30 with knee OA and chronic knee pain for at least 12 months	TENS 3 times a day for 30-60 minutes vs. placebo TENS for 3 weeks.	Active and placebo TENS provided more relief than paracetamol alone, $p < 0.005$. Pain relief following each treatment 151 minutes for active and 110 minutes for placebo, $p < 0.01$.	“Effective pain relief for OA of the knee was achieved during this trial, but the analgesic efficacy of TENS in the long term, and the significance and duration of its placebo effect, require further evaluation before the value of TENS as a therapeutic alternative in OA can be established.”	Lack of details makes interpretation difficult. No significant difference between active and placebo except a duration of relief of 40 minutes.
Lone 2003 RCT	6.0	N = 35 with knee OA for more than 6 months	Phase 1 (placebo drug and placebo TENS) vs. Phase 2 (diclofenac sodium 50 mg orally 3 times a day and placebo TENS) vs. Phase 3 (placebo drug and active TENS) for 2 weeks in each phase.	Significant pre-treatment to post-treatment pain relief after all phases; 2 weeks after Phase 3, mean pain intensity significant lower compared to Phases 1 and 2.	“There are indications that TENS is superior to diclofenac sodium as a primary therapy used in isolation, not only in reducing pain but also in improving walking.”	Small numbers due to large drop-out rate 42%. Cross-over study design. Suggestive that TENS is more effective than diclofenac in pain relief over short term.

Grimmer 1992 RCT	6.0	N = 60 with chronic knee OA	High-rate TENS (n = 20) vs. strong Burst Mode TENS (n = 20) vs. placebo (n = 20) for a 1-time application.	Burst mode TENS vs. placebo had significant length of pain relief, p = 0.014. High rate TENS compared to placebo had a significant amount of immediate stiffness relief, p = 0.03. Differences in length of stiffness relief for burst mode TENS and placebo, p = 0.005, and between high rate TENS and placebo, p = 0.004.	“[S]trong Burst Mode TENS does not produce universally greater changes in pain, stiffness and range of movement, than those produced by High Rate TENS, when both are applied at a strong, tolerable intensity for 30 minutes to the same acupuncture points on painful osteoarthritic knees. The results from both active TENS applications are similar, and, despite the size of the placebo response, must be considered to be superior to the placebo.”	One treatment session. Patients in placebo had no sensations vs. the active.
Ng 2003 RCT	5.5	N = 24 knee OA	Electroacupuncture (EA, n = 8) vs. TENS (n = 8) vs. controls (n = 8) for 8 sessions.	Changes in mean NRS of knee pain for EA group after 8 sessions (p <0.01), and for TENS group (p <0.01), but no changes for control group.	“[B]oth EA and TENS treatments demonstrated a significant pain reduction effect on patients with OA-induced knee pain. Therefore, both treatments are recommended for treating OA knee pain.”	Patients selected from an elderly residence home, 23/24 women, mean age 85. No blinding, no inter-group comparisons.
Taylor 1981 RCT	5.0	N = 12 with knee OA	Active TENS for 30 minutes at a time vs. placebo TENS for 30 minutes at a time for 2 weeks initial trial.	Significant differences between groups seen with pain evaluate subjective (p = 0.03) and medication (p = 0.06) criteria.	“[T]ENS may be an alternative method of short-term pain relief in patients with knee arthritis who for some reason are not thought suitable for total knee replacement surgery.”	Tiny numbers. Patients needed arthroplasty but were not surgical candidates. Subjective pain and medication use less than placebo groups.
Yurtkuran 1999 RCT	4.5	N = 100 with knee OA	TENS for 20 minute session, electro-acupuncture, Ice message, vs. placebo TENS.	No significant difference between 3 treatment groups. All 3 treatments more effective than placebo.	“Electro-acupuncture may be an important modality in relieving pain and related symptoms such as stiffness, long walking time, quadriceps weakness in knee OA patients.”	Lack of details lowered score. No comparison to exercises done. It appears that any treatment is better than placebo TENS.
Cheing 2004 RCT	4.5	N = 66 with knee OA	TENS at 80Hz for 60 minutes 5 days a week for 4 weeks; placebo TENS, exercise, TENS plus exercise.	No significant difference found between treatment groups. Intra-group comparison best in group with TENS and exercise in isometric peak torque (p = 0.000)	“No significant difference was found among the four treatment protocols, but the addition of TENS to exercise training tended to produce the best overall improvement in physical weakness.”	Lack of details lowered score. Exercise and TENS had the most within-group improvements. However, TENS vs. placebo vs. exercise had no significant differences.

Itoh 2008 RCT	4.5	N = 32 age 60 or older with knee OA	Control vs. acupuncture for 15 minutes vs. TENS for 15 minutes at 122 Hz vs. acupuncture and TENS (15 minutes of each once a week for 5 weeks.	WOMAC scores not significantly different between treatment groups.	“Combined acupuncture and TENS treatment was effective in pain relief and knee function improvement for the sampled patients suffering from knee OA.”	Small numbers. No blinding different exposure to clinical care between groups. Need a larger blinded trial to make firm conclusion.
Cetin 2008 RCT	4.0	N = 100 females with knee OA	Diathermy, hot packs, isokinetic exercises vs. TENS, hot packs, isokinetic exercises vs. Ultrasound, hot packs, isokinetic exercises vs. hot packs, isokinetic exercises vs. isokinetic exercises.	All groups had a decrease in VAS. Groups 1-4 vs. 5 ($p = 0.019$), Walking time significantly decreased in all groups. Lequesne score groups 1-2 vs. control ($p = 0.022$) and in group 3-4 vs. control ($p = 0.102$).	“Exercise and physical agents can reduce pain and improve function and health status in patients with knee OA.”	Women only. Small differences with short-wave diathermy and TENS may be related to non-blinding. Exercise appears key therapy with other modalities able to help augment pain relief. No evidence ultrasound or hot packs have significant influence.
Parker 2006 RCT	4.0	N = 60 with knee OA, aged 40-80	Intra-articular hylan G-F 20, 3 injections (n = 25) vs. TENS 20 minutes 5 times a week for 3 weeks (n = 27).	WOMAC physical function scores and WOMAC stiffness scores significantly improved in injection group compared to TENS at 6 months, $p < 0.05$.	“[B]oth TENS and viscosupplementation with hylan G-F 20 were effective in providing pain relief and restoring physical function to patients with knee OA during the first month of treatment and during the 6-month follow-up period.”	Both treatments had improvement. No reporting on adverse reactions. Best to do placebo controlled arm and cost-benefit analysis to help make a decision.
Adedoyin 2005 RCT	4.0	N = 51 with knee OA	Interferential current (IC) and exercise (n = 16) vs. TENS at 80 Hz and exercise (n = 15) vs. exercise only (n = 15) for 4 weeks.	No significant differences between groups for VAS or WOMAC scores.	“All treatment protocols led to significant improvements in pain and function over time. Neither IFC nor TENS displayed significant additional effects over exercise alone.”	Small numbers. Lack of details lowered score. IFC and TENS at 80Hz did not change outcomes when compared with exercise.
Paternostro-Sluga 1999 RCT	4.0	N = 24 after ACL repair and 25 after ACL reconstruction	Neuromuscular electrical stimulation and exercise therapy (Group 1, n = 16) vs. TENS and exercise therapy (Group 2, n = 14) vs. exercise only (Group 3, control group, n = 17) for 6 weeks.	No significant differences between groups.	“Patients in this study did not benefit significantly in terms of muscle strength from neuromuscular electrical stimulation treatment, although descriptive evaluation showed a tendency in favor of the neuromuscular electrical stimulation group at 6 weeks after surgery.”	Baseline all actively involved in sports. No difference found. Exercise beneficial after ACL repair.

Injections

There are several types of injections that have been used for patients with knee pain using different approaches. These include intra-articular glucocorticosteroid injections,(1320-1326)

viscosupplementation,(922) arthroscopic and non-arthroscopic joint lavage, and prolotherapy injections.(1320) Percutaneous needle tenotomy has been attempted for chronic tendinoses.(1327-1330) Tidal volume irrigation of the knee has been utilized for treatment of both inflammatory arthritides as well as osteoarthroses.(1331-1335) Additionally, radiation synovectomy has been utilized for treatment of patients with undifferentiated arthritis and rheumatoid arthritis.(1336, 1337)

Glucocorticosteroid injections, which have been used for the treatment of rheumatoid arthritis and juvenile idiopathic arthritits, are beyond the scope of this guideline.(1338) Intra-articular methotrexate and orogtein, which have been used for treatment of rheumatoid arthritis, psoriatic arthritis, and other arthritides(1339-1342) and oral methotrexate and leflunomide, which have been used for treatment of rheumatoid arthritis, are also beyond the scope of this guideline.(1343)

Transcranial magnetic stimulation has been used to attempt to make rehabilitation more effective. One small crossover trial with 1 hour follow-up suggested it may make rehabilitation more effective.(1344)

PLATELET RICH PLASMA, PLASMA RICH IN GROWTH FACTOR AND AUTOLOGOUS BLOOD INJECTIONS

Autologous blood injections have been used to treat osteoarthritis.(1345-1350) Autologous growth factors can be injected with autologous whole blood or platelet-rich plasma (PRP).(1351) These injections have been evaluated in studies of plantar foot pain, lateral epicondylalgia, and several other disorders.(1351, 1352)

1. Recommendation: Intraarticular Platelet Rich Plasma and Plasma Rich in Growth Factor, and Injections for Moderate to Severe Knee Osteoarthritis

Intraarticular platelet rich plasma and plasma rich in growth factor are not recommended for treatment of moderate to severe knee osteoarthritis.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – Low

2. Recommendation: Autologous Blood Injections for Moderate to Severe Knee Osteoarthritis

There is no recommendation for or against the use of autologous blood injections for moderate to severe knee osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale for Recommendations

Although there are 4 moderate- to high-quality trials,(1346-1348, 1353) they are comparative trials against viscosupplementation rather than placebo-controlled. This body of evidence suggests PRP injections tend to be superior to viscosupplementation injections, which appear superior to glucocorticosteroids (see below). There is one placebo-controlled trial that also suggests efficacy.(1349) With limited placebo-controlled trials, the evidence was considered too limited by the panel for evidence-based recommendations.

PRP injections appear superior to placebo over 6 months,(1349) superior to viscosupplementation over 6 months,(1346-1348) and up to 1 year of follow-up.(1347) Yet, there is some evidence suggestive that the injections may be better when the disease is less severe,(1347) raising concerns about its overall efficacy. PRP injections are invasive and have a

low risk of adverse effects but are high cost. The Evidence-based Practice Knee Panel downgraded the evidence from “C” to “I” and a majority concluded (60% agrees, 20% disagrees, and 20% neutral) that platelet rich plasma injections should not be recommended for moderate to severe knee osteoarthritis based on the lack of quality placebo-controlled trials. In addition, the Evidence-base Practice Knee Panel concluded there is insufficient evidence to conclude either for or against a recommendation (40% agree, 40% disagree, and 20% neutral) for autologous blood injections for moderate to severe knee osteoarthritis based on the lack of quality trials regarding the overall efficacy of these injections.

Evidence for the Use of Autologous Blood Injections and PRP Injections

There are 4 high-(1346, 1347, 1353, 1354) and 2 moderate-quality(1348, 1349) RCTs incorporated into this analysis.

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Knee Pain, patellar, tendonitis OR tendinitis, tendinopathy, Knee Arthritis, Knee Osteoarthritis, knee degenerative joint disease, Meniscal tear, Meniscal tears, Meniscus Tears, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed, we found and reviewed 21 articles, and considered 5 for inclusion. In Scopus, we found and reviewed 198 articles, and considered 2 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 3 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 11 articles considered for inclusion, 7 randomized trials and 3 systematic studies met the inclusion criteria.*

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Autologous Blood Injections vs. Placebo						
Baltzer 2009 RCT No mention of sponsorship. No COI except Krauspe received consultant fees from Orthogen in the initiating period prior to start of the study.	8.5	N= 376 osteoarthritis patients with age range of 30 years and older	Autologous conditioned serum (ACS) (n = 134) vs. Hyaluronan (HA) (n = 135) vs. saline (placebo) (n = 107). All groups had 50mL of whole blood. All received intra-articular injection of assigned treatment for 32 weeks, and followed for 2 years after last trial injection.	ACS group scored better than controls on all WOMAC subscale after injections (p <0.001) vs. comparison group. No difference between HA and NS in WOMAC scores (p >0.05). VAS ratings at week 7, 13, and 26 lowest in ACS group (p <0.001 each group). GPA score at all follow-up visits higher in ACS vs. HA or saline (p <0.001 each).	“[T]he data show that ACS (Orthokine) represents an effective and well-tolerated alternative to currently predominant treatments of OA.”	Eight subjects from ACS, 15 from HA, and 8 from NS group dropped out after randomization. Three arms to study. ACS better than HA and placebo group with only slight improvement between HA and placebo (NS) group.
PRP Injections vs. Placebo						
Patel 2013 RCT Sponsored by Prof D.S. Grewal Memorial	7.5	N = 78 with bilateral early osteoarthritis with grade 1 or 2 knees without deformity	Group A: single PRP (8mL per knee, mean platelet count 310.14 x 10 ³ µL) injection (n = 27) vs. Group B: 2 PRP (8mL per knee, mean platelet	Both group A and B improved in VAS pain scores at 1.5 month and 3 months vs. placebo. C: VAS- Group A and B, p = 0.001. Group C, p = 0.598. (No difference	“A single dose of WBC-filtered PRP in concentrations of 10 times the normal amount is as effective as 2 injections to	Data suggest PRP superior to placebo and benefits last > 6 months.

Orthopaedics Society and the Indian Arthroplasty Association. COI, one or more authors has declared COI.			count 310.14 x 10 ³ µL) injections (n = 25) vs. Group C: NS injection (n = 26). Follow ups at 1.5, 3 and 6 months.	between groups A and B, p = 0.410). Both groups A and B improved in physical function and stiffness levels vs. group C (p <0.001).	alleviate symptoms in early knee OA. The results, however, deteriorate after 6 months. Both groups treated with PRP had better results than did the group injected with saline only.”	
PRP vs. Hyaluronic Acid						
Filardo 2012 RCT Sponsored by RICERA FINALIZZATA , Health Department. COI, Filardo is affiliated with Nano-Biotechnology Laboratory, Italy. All authors mention no COI.	8.0	N = 109 with DJD defined as chronic knee pain or swelling lasting >4 months, monolateral lesions, verified DJD changes via x-ray or MRI, mean age 55 for PRP vs. 58 for HA groups	3 intra-articular platelet rich plasma injections (n = 54) vs. 3 hyaluronic acid injections (>1500 KDa; Hyalubrix) (n = 55). Follow ups at 2, 6 and 12 months.	PRP group improved vs. HA group for subjective IKDC results, approaching significance at 6 months (p = 0.08) and 12 months (p = 0.07).	“Results suggest that PRP injections offer a significant clinical improvement up to one year of follow-up. However...for middle-aged patients with moderate signs of OA, PRP results were not better than those obtained with HA injections...More promising results are shown for its use in low grade degeneration, but they still have to be confirmed.”	No placebo. Data suggest trend towards modest efficacy which is small.
Sanchez 2012 RCT No mention of sponsorship. No COI.	9.5	N = 176 with symptomatic tibiofemoral knee OA, diagnosed by x-ray, joint paint >35mm, BMI between 20 and 32, Ahlback grade <4, ages 40-72 years (mean 59.8)	Plasma Rich in Growth Factor (PRGF)-Endoret (8mL total per visit) group (n = 89) vs. Hyaluronic Acid (Euflexxa) group (n = 87). Both groups received 3x weekly treatments. Follow-up at 1, 2, and 6 months.	PRGF-Endoret group had significant decrease in WOMAC pain scores (50% decrease) vs. Hyaluronic Acid. Proportion mean Difference (95% CI)- 14.1 (0.5-27.6), p= 0.044.	“Plasma rich in growth factors showed superior short-term results when compared with HA in a randomized controlled trial, with a comparable safety profile, in alleviating symptoms of mild to moderate osteoarthritis of the knee.”	PRGF vs HA showed similar result except PRGF had minimal efficacy vs HA at 24 week period (WOMAC decreased by 14%).
Vaquerizo 2013 Sponsored by the Biomedical Research Foundation of Principe de Asturias University Hospital and Ministry of	8.5	N = 96 with symptomatic knee OA (mean age 63.6 years)	PRGF Endoret or 3 injections on a weekly basis (n = 48) vs. One infiltration with Durolane HA injection (n = 42). Follow-up at 24 and 48 weeks.	Patients having a 30% decrease, rate of response to PRGF-Endoret was 66% points (95% confidence interval [CI], 48±84; p <0.001), 43% points (95% CI, 23±64; p <0.001), and 23% points (95% CI, 2±47; p = 0.02) higher than rate of response	“Our findings show that PRGF-Endoret is safe and significantly superior to Durolane HA in primary and secondary efficacy analysis both at 24 and 48 weeks, and it provides a significant clinical	Comparison of PGRF-Endoret to Durolane HA showed a 50% reduction in knee OA pain, stiffness and function favoring PGRF-Endoret on most measures at 24 and 48

Health, Social Policy and Equality of Spain. COI, all but one author (Padilla) receive support from BTI Biotechnology Institute.				to HA for WOMAC pain. A 50% decrease, rate of response to PRGF-Endoret was 43 % points (95% CI, 25±62; p <0.001), 29% points (95% CI, 11±48; p = 0.001), and 19% points (95% CI, 0±37; p = 0.035) higher than rate of response to HA for WOMAC pain, physical function, and stiffness subscales, respectively.	improvement, reducing patients' pain and improving joint stiffness and physical function, with respect to basal levels in patients with knee OA.”	weeks (p = 0.001).
Cerza 2012 RCT No mention of sponsorship. No COI.	4.5	N = 120 with x-ray diagnosed Grades I, II or III knee OA. All had prior physical or pharmacological therapy without success, mean age 66.5 years (SD 11.3) for group ACP and 66.2 years (SD 10.6) for group HA	ACP group (4 intra-articular injections; mean 5.5mL ACP per injection) (n = 60) vs. Hyaluronic Acid group (4 intra-articular injections; 20mg/2mL) (n = 60). Follow up assessments at 4, 12 and 24 weeks after injection.	At weeks 4, 12 and 24, ACP showed improvement vs. HA. Week 4: ACP with mean (range; ±SD) score of 49.6 (5-80; ±17.8) vs HA with 55.2 (25-78; ±12.3), p <0.001. Week 12: ACP with mean (range; ±SD) score of 39.1 (5-76; ±17.8) vs. HA with increasing 57.0 (32-78; ±11.7), p <0.001. Week 24: ACP with mean (range; ±SD) score of 36.5 (5-76; ±17.9) versus HA with increasing 65.1 (41-82; ±10.6), p <0.001.	“Treatment with ACP showed a significantly better clinical outcome than did treatment with HA, with sustained lower WOMAC scores. Treatment with HA did not seem to be effective in the patients with grade III gonarthrosis”	PRP superior to HA through 24 weeks.

VISCOSUPPLEMENTATION INJECTIONS

Viscosupplementation has been used for knee osteoarthritis (15, 1350, 1355-1372) and to treat pain after arthroscopy and meniscectomy.(1373, 1374)

Recommendation: Intraarticular Knee Viscosupplementation Injections for Moderate to Severe Knee Osteoarthritis

Intraarticular knee viscosupplementation injections are not recommended for treatment of moderate to severe knee osteoarthritis.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)
Level of Confidence – Low

Rationale for Recommendation

There are 11 high and 7 moderate-quality trials comparing injections with viscosupplementation with placebo (see evidence table).(1058, 1375-1383) Fourteen of the 18 trials show pain reductions from 2-weeks to 6 months and most trials suggesting superiority at approximately 3 months after injection.

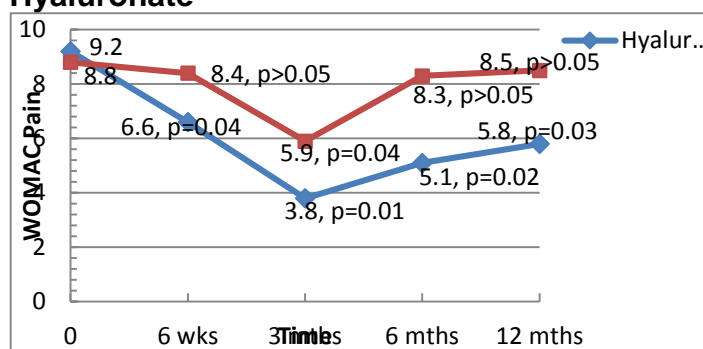
There are 1-high and 9-moderate trials comparing injections with viscosupplementation with glucocorticosteroid. Most of these trials comparing viscosupplementation with glucocorticoid injection suggested glucocorticosteroid injections are inferior for the knee;(1384-1390) however, for the hip the reverse may be true.(1383) None of the knee trials reported superior results with

glucocorticosteroid. One high-quality trial suggested comparable results until 26 weeks at which point the glucocorticoid appeared to be losing benefit while the benefits of the viscosupplementation had greater persistence.(1389) The next highest quality trial suggested comparable efficacy over 3 months.(1383, 1389)

A moderate-quality, blinded trial reported that viscosupplementation improved articular cartilage appearance significantly compared with glucocorticosteroids,(1386) but those results have not been replicated. One quality trial also documented these injections provide additive benefit over appropriate care(1391) and usual NSAID therapy.(1392)

No quality treatment trials with follow-up beyond 1 year have been published. There is one moderate-quality trial reporting a lack of synergism with combined glucocorticoid injection.(1393) There is no clear preponderance of evidence that high or low molecular weight preparations are superior, although one trial suggested hyaluronan tended to be superior(1394) (see Figure 2). Both resulted in approximately 40% reductions in pain ratings with benefits lasting 6 months. Various combinations of injections have not shown one regimen to be clearly superior.(1395) These injections are invasive and have a low risk of adverse effects but are relatively costly. The Evidence-based Practice Knee Panel has downgraded the evidence from “C” to “I” and came to a limited conclusion (50% agrees, 16.7% disagrees, and 33.3% is neutral) that these injections should not be recommended for moderate to severe knee osteoarthritis based on their understanding of the current peer-reviewed literature, the adverse effects, and the overall efficacy of viscosupplementation injections.

Figure 2. WOMAC Scores Comparing Viscosupplementation with Hyaluronan vs. Sodium Hyaluronate



Adapted from Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee -- a prospective randomized clinical trial. *Knee*. 2008;15(4):318-24.

Evidence for the Use of Intraarticular Knee Viscosupplementation Injections

There are 28 high-(1346, 1347, 1353, 1376, 1378-1380, 1382, 1389, 1396-1413) and 59 moderate-quality RCTs(576, 579, 922, 1058, 1348, 1371, 1375, 1377, 1381, 1383, 1384, 1386-1388, 1390-1395, 1414-1452) incorporated into this analysis. There are 25 low-quality RCTs in Appendix 1.(1347, 1358, 1453-1475)

Author/Title Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Viscosupplementation Injections vs. Placebo						
Lundsgaard 2008 RCT	10.0 8.0 (for distension)	N=251 age>59 years, with knee OA, Kellgren/Lawrence Grade	Intra-articular aspiration then sodium hyaluronate 2mL (20.6mg) vs. isotonic saline 20mL vs. isotonic saline	Primary outcome of VAS pain with movement was hyaluronate 5.46 (-0.08 to 11.) vs. 20mL 3.87 (-1.69 to 9.44) vs. 0 (NS).	“Intra-articular hyaluronate or distention with physiological saline did not significantly	Data suggest no meaningful differences, though weak trends favoring hyaluronate.

Sponsored by Glostrup Hospital, The Danish Society of Rheumatism, and the Copenhagen Trial Unit, Center for Clinical Intervention Research. No mention of COI.		I-II, VAS pain >20/100mm.	2mL 4 weekly injections; 26 weeks follow-up.	Only differed between 20mL and 2mL saline (p = 0.033). Investigators' global assessment favored hyaluronate, then 20mL.	reduce pain compared with physiological saline placebo in patients with osteoarthritis of the knee."	
Day 2004 RCT Sponsored by the Seikagaku Corporation . No mention of COI.	9.5	N=223 mild to moderate, idiopathic, painful femorotibial knee OA	Hyaluronan 25mg in 2.5mL in phosphate buffered solution intraarticular injection (n=108) vs. 2.5 ml placebo injections (n=115). Five weekly injections; 18weeks total follow-up.	HA vs. placebo WOMAC pain scores for primary efficacy analysis using ANCOVA model for baseline mean (SD), scores during treatment mean (SD), mean difference, p value: 7.96 (3.10)/8.68 (3.72), 3.84 (3.27)/4.61 (3.14), 0.77, (1.53, 0.02), 0.045. WOMAC scale for disability: 28.07 (11.81)/31.25 (13.68), 15.37 (11.41)/17.81 (10.53), 2.44, (5.11, 0.22), 0.064. WOMAC scale for stiffness: 3.70 (1.54)/3.79 (1.95), 2.11 (1.42)/2.46 (1.44), 0.36, (0.68, 0.03), 0.024. WOMAC pain vs. WOMAC disability vs. WOMAC stiffness vs. Lequesne index mean (95%CI) differences Week 6, 10, 14, 18: 0.56 (1.40,-0.28)/2.32 (5.07,-0.42)/ 0.25 (0.58,-0.08)/ 0.53 (1.37,-0.32), 0.59 (1.40,-0.22)/1.88 (4.74,-0.97)/ 0.44 (0.83,0.04)/ 0.79 (1.74,-0.17), 1.02 (1.85,0.19)/2.44(5.29,-0.41)/0.42 (0.79,0.05)/ 1.23 (2.19,0.28), 0.93 (1.80,0.06)/3.13 (6.09,0.16)/0.32 (0.71,-0.08)/1.10 (2.10,0.10).	"Intraarticular HA treatment was significantly more effective than saline vehicle in mild to moderate OA of the knee for the 13 week postinjection period of the study."	Data suggest efficacy and benefits persisting to end of observation at 18 weeks.

<p>Puhl 1993</p> <p>RCT</p> <p>Sponsored by Luitpold Pharma München. No mention of COI.</p>	<p>9.0</p>	<p>N=209 with idiopathic knee OA</p>	<p>Sodium hyaluronate (6.0-12.0x10⁵ Da) 25mg/2.5 ml (n=102, verum) vs. sodium hyaluronate 0.25mg/2.5 ml (n=107, control). Both injections administered weekly for 5 weeks.</p>	<p>Verum (n=95) vs. control (n=100) clinical examination findings for pain at rest (severe to moderate) at baseline, week 6, 10, and 14: 41.1%/35.0%, 14.7%/23.0%, 13.7%/24.9%, 13.7%/26.0%. Pain when starting to walk (severe to moderate): 73.3%/63.0%, 24.2%/34.0%, 27.4%/36.0%, 25.2%/36.0%. Pain under load (severe to moderate): 90.5%/87.0%, 34.8%/37.0%, 37.9%/39.0%, 35.8%/38.0%. Crepitation (severe to moderate): 58.9%/59.0%, 23.2%/21.0%, 25.3%/19.0%, 24.2%/19.0%. Joint effusion: 17.9%/13.0%, 10.5%/11.0%, 11.6%/10.0%, 7.4%/5.0%. Neutral-0 (improvement to baseline in degrees) at week 6, 10, and 14: 5.6/4.9, 5.5/4.8, 6.3/5.3. Reduction of the Lequesne index of severity p values for week 6, 10, 14, and 4-14: p=0.043, p=0.0088, p=0.0053, p<0.025. Pain reduction on VAS p values at week 10 and 14: p=0.037, p=0.023.</p>	<p>"Most of the individual secondary endpoints demonstrated a much better response to the active treatment without reaching the significance level in the intergroup comparisons for the single time-points. Side-effects were confined to local reactions of minor severity and short duration in four patients (six events) of the verum group and in five patients of the control group. Clinical chemistry and hematology remained essentially unchanged."</p>	<p>Some baseline differences of uncertain significance. Data suggest efficacy and differences that persisted throughout the 14weeks of observation.</p>
<p>Wobig 1998</p> <p>RCT</p> <p>Sponsored by Biomatrix, Inc. No mention of COI.</p>	<p>9.0</p>	<p>N=117 patients with knee OA, Larsen radiographic grade I-III, ESR <40mm/hr, RF titer <1:160.</p>	<p>Hylan G-F 20 2mL vs. saline 2mL series of 3 weekly injections. 26 wks follow-up.</p>	<p>Percentage symptom-free for weight bearing pain by evaluator assessments at weeks 12/26: Hylan GF20 (47/39%) vs. saline (8/13%). Mean score for improvement in hylan G-F 20 group increased steadily from 38 at week 1 to 745 at Week 12. Saline group, scores ranged from 29 at Week 1 to 37 last visit; p <0.003 between group difference from Week 2; p<0.0001 between group difference from Week 12.</p>	<p>"These data indicate that hylan G-F 20 is effective in relieving pain and increasing mobility in patients with chronic idiopathic OA of the knee."</p>	<p>Some baseline differences in gender and duration of unclear significance. Data suggest efficacy.</p>

<p>Neustadt 2005</p> <p>RCT</p> <p>Sponsored by Anika Therapeutics, Inc. No mention of COI.</p>	<p>9.0</p>	<p>N = 372 with osteoarthritis of the knee, grade 2 or 3 osteoarthritis on the Kellgren and Lawrence scale rated via radiograph; Mean (SD) age 58.4 (8.9) for O4 group, 58.9 (8.9) for O3A1 group, and 59.1 (8.3) for A4 group</p>	<p>O4 Group receiving 4 HMW hyaluronan injections (n = 128) vs. O3A1 Group receiving 3 HMW hyaluronan injections and one control arthrocentesis procedure (n = 119) vs. A4 Group receiving 4 control arthrocentesis procedures (n = 123).</p> <p>Assessments at baseline, 1 week, 2, 3, 8, 12, 16, 22 and 28 weeks after injections.</p>	<p>There was no significant difference between groups for WOMAC pain scores, Investigator Global Score, Pain on standing scores and Patient Global score during assessments.</p>	<p>"[O]ur data demonstrate that high molecularweight hyaluronan (Orthovisc®) is a safe product for treatment of knee osteoarthritis. These data indicate that Orthovisc® seems to be effective in reducing the pain and symptoms associated with OA of the knee using a series of 3 or 4 injections. The potential benefit for clinically significant pain reduction using Orthovisc® outweighs the potential risk of a low rate of minor adverse effects."</p>	<p>High molecular weight HA in higher frequency per weekly injections did not significantly improve WOMAC pain scores when compared to less frequent injections of the same HA preparation or compared to placebo. This study showed a strong placebo response.</p>
<p>Chevalier 2010</p> <p>RCT</p> <p>Sponsored by Genzyme Biosurgery. COI, XC, JJ, and PG have been reimbursed by Genzyme Biosurgery for attending symposia and have also received speaker fee; JJ received research funds from Genzyme Biosurgery; FB is employee of Genzyme Biosurgery; NvD, FPL, DLS, and</p>	<p>8.5</p>	<p>N=253 patients with knee OA (ACR) with score of 2 or 3 on first WOMAC A question and mean 1.5-3.5.</p>	<p>One 6 ml hylan G-F 20 vs. placebo injection after arthrocentesis. 26 wks follow-up.</p>	<p>WOMAC A scores (baseline/week 26): Hylan G-F 20 (2.30 (SE 0.038)/1.43 (0.060) vs. placebo (2.25 (0.036)/1.59(0.058); change -0.84 (0.06) vs. -0.69(0.058), p = 0.047. No statistically significant differences in WOMAC C.</p>	<p>"[I]n patients with knee osteoarthritis, a single 6 ml intra-articular injection of hylan G-F 20 is safe and effective in providing statistically significant, clinically relevant pain relief over 26 weeks, with a modest difference versus placebo."</p>	<p>Data suggest modest efficacy, with benefits lasting 26 wks.</p>

KP have no COI						
Altman 2009 RCT Sponsored by Ferring Pharmaceuticals Inc. COI, Korner is affiliated with Ferring Pharmaceuticals.	8.5	N = 588 with knee osteoarthritis, a VAS pain rating of 41 mm to 90 mm after walking 50 feet, grade 2 or 3 osteoarthritis on the Kellgren and Lawrence scale rated via bilateral standing anterior-posterior radiograph; Mean (SD) age 60.8 (10.0) for IA-SA group and 62.5 (11.0) for IA-BioHA group	Treatment group receiving bioengineered 1% intra-articular sodium hyaluronate (IA-BioHA) (n = 293) vs. Placebo group receiving intra-articular saline (IA-SA) (n = 295). Both groups agreed to only taking acetaminophen for pain relief. Assessments at baseline, 1 week, 2, 3, 6, 12, 18 and 26 weeks.	The IA-BioHA group exhibited significantly more ≥ 20 mm improvements in VAS pain than the IA-SA group; OR 1.7, 95% CI- 1.2-2.4, ($p = 0.006$). The IA-BioHA group compared to the IA-SA group presented least-squares means of -6.6 mm; -36.4mm vs. -29.7mm, 95% CI- -10.8 to -2.5mm, ($p = 0.002$).	“Results of the FLEXX trial demonstrate significant OA knee pain relief with IA-BioHA therapy, which is sustained for 6 months. The utility of IA-BioHA therapy for knee OA is further supported by significant improvements in subject function, subject satisfaction with treatment, and HRQoL. The results of this study also support the favorable safety profile of IA-BioHA.”	IA-BioHA was statistically significant in decreasing OA knee pain ($p = 0.002$) when compared with IA-SA.
DeCaria 2012 RCT Sponsored, in part, by grants from the Physicians' Services Incorporated Foundation (PSI), and by the Canadian Institutes of Health Research (CIHR). Dr. Montero Odasso is the first recipient of the Schulich Clinician-Scientist Award and recipient of the CIHR New Investigator Award (2011–	8.5	N = 33 knee OA patients (Kellgren Lawrence II–III), mean \pm SD age 72.44 \pm 6.11 years	3 weekly injections of hyaluronic acid (HA 2ml of 20mg/ml HA) (n = 15) vs. placebo (P) (1.2ml of 0.001mg/ml HA) (n = 15). Assessments at baseline, 4 weeks, 3 and 6 months.	Overall improvement in pain greater in HA group when compared to P group ($p = 0.04$). WOMAC pain mean \pm SD change (HA-P) was -2.47 \pm 6.39.	“The preliminary results of improved fast gait velocity following HA treatment should be investigated further, along with the incidence of falls, in a larger sample of older knee OA patients.”	Small sample size. Both HA and placebo groups demonstrated improvement in gait velocity (HA better than placebo) but WOMAC pain scores improved with HA.

2016). No COI.						
Huang 2011 RCT Sponsored by Fidia Farmaceutici SpA and Med Pharma Co., Ltd. No COI.	8.0	N = 200 with knee osteoarthritis meeting ACR criteria for diagnosis for 5 years prior to entering study, grade 2 or 3 osteoarthritis primarily in tibio-femoral compartment on Kellgren and Lawrence scale rated via x-ray, VAS pain scores ≥ 40 mm during 50 foot walking exam; Mean (SD) age 65.9 (8.1) for Hyalgan group and 64.2 (8.4) for placebo group	Sodium Hyaluronate (Hyalgan, 20mg/2mL) group receiving 5 injections for a week (n = 100) vs. placebo group receiving similar controlled treatment (n = 100). Assessments at baseline, 1 week, 2, 3, 4, 5, 13 and 25 weeks.	At 25 weeks assessment, Hyalgan group decreased VAS scores significantly vs. placebo group compared to baseline values: 30.85 \pm 14.1 vs. 23.63 \pm 16.38, (p = 0.002). At 25 weeks assessment, Hyalgan group also decreased WOMAC Pain and Function scores significantly vs. placebo group compared to baseline values: WOMAC Pain mean (SD)- 29.28 (1.92) vs. 21.52 (1.94), (p = 0.005); WOMAC Function mean (SD)- 25.16 (1.67) vs. 18.2 (1.69), (p = 0.0038).	"[O]ur results showed that a 5-injection course of this sodium hyaluronate was effective, in terms of a significantly greater improvement from baseline to Week 25 in VAS score, WOMAC pain and function score than the placebo group. The whole course was safe and well tolerated both in sodium hyaluronate treatment group and the placebo."	HA showed significant improvement from baseline to week 25 in VAS pain on a 50 foot walking test as compared to placebo (p =0.0020).
Jorgensen 2010 RCT Sponsored by Nycomed Denmark A/S. No COI.	8.0	N = 337 with knee osteoarthritis meeting the ACR criteria for diagnosis, a LFI score >10 ; Mean (\pm SD) age 62.6 (\pm 11.4) for Hyaluronan ITT group and 61.4 (\pm 11.1) for placebo ITT group	Hyaluron ITT group receiving 2mL of Hyalgan (10mg/mL) weekly for 5 weeks (n = 165) vs. Placebo ITT group (n = 170). Assessments at baseline, 3, 6, 9, and 12 months.	No significant differences in time to recurrence, VAS, and LFI reported between the Hyaluron group and placebo group.	"[R]esults showed that in patients fulfilling the ACR criteria for knee osteoarthritis and having moderate to severe disease activity with a LFI score of 10 or more, five intra-articular injections of hyaluronan did not improve pain, function or other efficacy parameters 3, 6, 9 and 12 months after treatment."	High noncompliance rate. Survival study at 1 year showed no significant differences between groups.
Petrella 2006 RCT Sponsored by a grant from Bioniche Life Sciences. COI,	8.0	N = 106 patients with knee OA	20mg/ml, 2.0mL hyaluronic acid (HA) sodium salt vs. 2.0ml NS injected once weekly for 3 weeks.	At week 3 both groups showed improvement vs. baseline (p <0.05). Improvements in WOMAC pain, stiffness, physical function, and QOL scores were better with HA vs. placebo (p <0.05). By week 6 and 12, no further differences.	"[P]atients who received HA had greater improvement in knee pain and function than placebo patients."	Double blinding questionable due to viscosity. Data suggest efficacy compared with placebo but no benefit of 6 injections

Petrella is supported by a Canadian Institutes of Health Research Investigator Award in Healthy Aging.						compared to 3 injections.
Karlsson 2002 RCT Sponsored by grants from Astra Läkemedel. No mention of COI.	7.5	N=210 with knee OA, ≥60 years old, Ahlbäck grade I-II, ≥40/100mm weight bearing VAS pain.	Artzal hyaluronan 1% 2.5 ml (n=92) vs. Synvisc 0.8% 2.0 ml hyaluronan injection (n=88) vs. placebo (n=66). All injections weekly for 3 weeks; 1 year follow-up.	Artzal vs. Synvisc vs. placebo change [100-mm VAS scale, mean(SD)] weight-bearing pain from baseline at week 1, 2, 3, 12, 20, and 26: -5(16)/-7(17)/-7(22), -12(21)/-16(21)/-11(25), -20(23)/-18(24)/-21(28), -22(26)/-22(29)/-19(32), -21(26)/-27(29)/-19(29), -16(31)/-20(31)/-21(31). Lequesne index change from baseline at week 20, and 26: -4.2(3.7)/-4.9(3.6)/-5.1(4.4), -3.9(4.6)/-4.4(4.1)/-4.7(4.4). Mean change from baseline at WOMAC score 12 weeks, WOMAC score 26 weeks, pain 12 weeks, pain 26 weeks, physical function 12 weeks, physical function 26 weeks, stiffness 12 weeks, and stiffness 26 weeks: -14.0/-17.0/-18.2, -11.3/-16.8/-16.8, -3.5/-4.0/-3.9, -3.1/-3.6/-3.8, -9.3/-11.4/-12.6, -7.3/-11.7/-11.1, -1.2/-1.6/-1.4, -0.9/-1.4/-1.6.	"[T]hree intra-articular injections at intervals of 1 week produced a pronounced reduction in weight-bearing pain, resting pain, maximum pain, Lequesne index and WOMAC score during a period of 26 weeks of the study. Furthermore, no difference in pain relief was demonstrated between the two hyaluronan preparations studied here. However, in the study period between 27 and 52 weeks, significantly more patients in the placebo group than in the hyaluronan groups dropped out (requiring further treatment) because of knee pain."	Most patients (60%) did not complete 1 year follow-up. Data do not suggest efficacy compared with placebo
Lohmander 1996 RCT Sponsored by the Medical Faculty of Lund University, the Swedish Medical Research Council. KaroBio	7.5	N=240 (106 men, 134 women) with symptomatic, radiological knee OA.	Five weekly intraarticular injections of 25 mg of high molecular weight hyaluronan (n=120) vs. placebo (n=120); 20 weeks follow-up.	P values for change from baseline VAS for pain in unstratified groups: Week 1 = 0.260, 2 = 0.941, 3 = 0.923, 4 = 0.840, 5 = 0.376, 13 = 0.608, 20 = 0.538. Change in VAS pain for stratified subgroups: Week 1 = 0.008, 2 = 0.387, 3 = 0.181, 4 = 0.09, 5 = 0.07, 13 = 0.014, 20 = 0.004. VAS for activity in stratified groups: Week 1 = 0.117, 2 = 0.047, 3 = 0.232, 4 =	"Patients older than 60 years with knee osteoarthritis and with significant symptoms corresponding to an index of severity of knee disease of 10 or more, comprise the group most likely to benefit from treatment with intra-articular hyaluronan injections."	Large sample size. Data suggest efficacy with differences persisting to 20 weeks (last observation) in the 60-75 year old subgroup, but not younger patients.

AM, and Astra Läkemedel AB. No mention of COI.				0.001, 5 = 0.037, 13 = 0.03, 20 = 0.028. Lequesne index of severity of knee disease for stratified subgroups: Week 1 = 0.765, 2 = 0.317, 3 = 0.104, 4 = 0.043, 5 = 0.165, 13 = 0.032, 20 = 0.056.		
Diracoglu, 2009 RCT No mention of sponsorship or COI.	7.5	N=60 with knee OA (ACR), Kellgren/Lawrence grade II-III, pain during motion \geq 50/100mm VAS.	Hylan G-F 20 (n=42) vs. placebo (n=21) 3 weekly injections. 1 week follow-up.	Mean \pm SD VAS activity pain before/ after injection comparing treatment vs. placebo group: 6.47 \pm 1.56/ 4.0 \pm 1.47 vs. 6.45 \pm 1.53/ 5.55 \pm 1.47; p=0.001.	"[I]ntraarticular injection of hyaluronan in patients with knee OA led to a short-term increase in proprioception and isokinetic muscle force, and also significant improvements in the functional conditions of patients. Long-term studies are needed."	Only short term follow-up. Data suggest injection superior to placebo.
Qvistgaard 2006 RCT Sponsored by the Oak Foundation and the Erna Hamilton Foundation . Hyaluronic acid donated by Fida Inc. No mention of COI.	7.5	N = 104 patients with hip osteoarthritis defined by the ACR criteria, >18 years of age, and stable medication for at least 3 weeks. Mean age 66 \pm 12 years.	Single injection 1mL (40mg Depo-medrol [®]) methylprednisolone followed by 2 sham injections (n = 34) vs. 3 injections of 2mL hyaluronic acid, HA, Hyalgan [®] (n = 34) vs. 3 intra-articular injection of 2mL saline water (n = 36). All injections included 1mL of 1% lidocaine. Injections given at 14 day intervals. Follow-up at 3 months.	There was no significant difference between groups for the primary outcome, pain on walking at 3 months (p=0.14).	"[T]his controlled study could not demonstrate a 3-month effect on hip OA using HA."	A 3-armed parallel group design comparing HA to corticosteroid and placebo (NS) for pain on walking at 2 weeks better with steroids (p = 0.04) but at 3 months no significant differences between treatment groups.
Altman 2004 RCT Sponsored by Q-Med AB. No mention of COI.	7.5	N = 347 with OA of the knee, mean age for NASHA and Saline; 62.9 and 63.3.	NASHA a single 3ml injection (n = 173) vs. saline or placebo administered intra-articularly into the study knee, placebo contained identical buffered sodium chloride (n = 174). Follow-up at 2, 6, 13, and 26 weeks.	There was no significant difference between the number of responders between placebo and NASHA groups at 26 weeks, (p statistic not reported). A greater response to NASHA than placebo observed at week 6 (p = 0.025).	"In conclusion, although NASHA failed to demonstrate statistical benefit over placebo, NASHA was found to be superior to placebo in the subset of patients with OA isolated to the signal knee; this superiority was present at 6 weeks, consistent with the half-life of the agent."	NASHA decreased pain at 2 weeks persisted for 26 weeks (p = 0.02).
Brandt 2001	7.0	N = 226 with knee osteoarthritis	3 weekly injections of 30mg Sodium hyaluronate Na-Ha	WOMAC stiffness and function scores used as well as Time to Walk 50	"The results indicate that sodium	Large sample size. HA showed some

RCT Supported by a grant from Anika Therapeutics, Inc, Woburn, MA. No mention of COI.		(mean age 66 years)	group (n = 114) vs. saline injection control group (n = 112). Follow-up conducted every 3 weeks for 30 weeks.	feet (seconds). No significant differences between groups for weeks 1-10. At week 11, Na-Ha group showed significant mean change vs. control for WOMAC stiffness; -1.9 vs. -1.2 (p <0.05), WOMAC function; -15.0 vs. -10.5 (p <0.05) and Time to Walk; -2.1 vs. -1.0. Time to walk was also significant at week 21; -2.2 vs. -0.7 (p < 0.05).	hyaluronate treatment is well tolerated and produces statistically and clinically significant improvement of symptoms in patients with mild to moderate knee osteoarthritis in whom pain in the contralateral knee is relatively modest.”	improvement at 11 weeks but not beyond.
Pham 2004 RCT No mention of sponsorship or COI.	7.0	N = 301 with symptomatic primary painful medial femorotibial knee OA defined by daily pain visual analogue scale (VAS) score .30 mm in previous month. Mean±SD age 64.9±8.4 years (hyaluronic acid (NRD101)), 64.5±7.8 years (Diacerein), 64.9±7.7 years (Placebo).	Diacerein 50mg twice daily as well as 3 courses every 3 months of 3 weekly of IA injections (n = 85) vs. placebo 50mg twice daily as well as 3 courses, every 3 months, of 3 weekly IA injections (n = 85) vs. HA (NRD101) 50mg twice daily as well as 3 courses, every 3 months, of 3 weekly IA injections (n = 131). Follow-up not specified.	No significant changes in VAS score observed in either group. More knee pain observed in NRD101 (n = 24) group during or after IA injections compared to diacerein (n = 9) and placebo (n = 19) (p = 0.0088). Diacerein group had more diarrhea (n = 41) (p <0.0001) and urine coloration (n = 7) (p = 0.0009) than patients of the other two groups.	“A weak but statistically significant structural deterioration occurred over 1 year, together with clinically relevant symptomatic improvement in patients receiving oral drug and iterative IA injections. Symptomatic and/or structural effects for both this new HA compound and diacerein were not demonstrated.”	Three arms to study, 2 treatment groups and placebo showing no difference between groups.
Kul-Panza 2010 RCT No mention of sponsorship or COI.	7.0	N = 48 with diagnosed knee osteoarthritis , the mean (±SD) age 59.5 (±8.8) for Hyaluronic acid group and 62.8 (±7.8) for placebo control group.	2mL of 1.5% Hyaluronic acid (MW 1,500,000 Da) injection group receiving 3 injections in one week (n = 25) vs. placebo group (n = 23). Evaluations at baseline, 1 week, 3, 5, and 14 weeks.	At 14 weeks, hyaluronic acid group showed significantly higher participant improvement percentages in WOMAC pain on walking scores vs. placebo group; 35.2±24.4% vs. 9.1±5.7%, (p = 0.01). No other significant differences between groups for primary outcome measures of other WOMAC sub scores and VAS pain scores.	“[O]utcome on pain and functional parameters after intra-articular HA treatment for knee OA was similar to that achieved with placebo.”	HA compared with placebo at 1, 3, 4, 5 and 14 months showed similar results but at week 14 the HA group showed better WOMAC pain scores on walking (p = 0.01).

Gramajo 1989 RCT No mention of sponsorship or COI.	7.0	N = 62 Hip or knee OA	Glycosaminoglycan-peptide complex (GPC) ("Rumalon") injections vs. placebo injections. 3 injections a week for 8 week course, 3 courses per year.	Night pain (before/after treatment): GPC 2.4±2.9/0.4± 0.69 vs. placebo 2.1±1.58/1.9 ±0.83, p <0.001. Results comparable for day pain (p <0.01) and joint mobility (p <0.005). Time to walk 10 meters: GPC 21.8±6.88/ 18.0±4.86 vs. 24.1±7.31/ 23.9±3.3 seconds, p <0.001. No adverse effects reported.	"[G]lycosaminoglycan-peptide complex ('Rumalon') offers not only an effective but also a well-tolerated form of treatment which can be used to replace or supplement non-steroidal anti-inflammatory drugs, particularly in long-term therapy."	Co-interventions uncontrolled. Therapy requires 72 injections per year, although data suggest efficacy.
Altman 1998 RCT Sponsored by Fidia Pharmaceutical Corporation. COI, authors acknowledged the following people who are affiliated with Fidia Pharmaceutical Corporation: Fiorentini for guidance, Dorsey and Patarnello for statistical support, and Westcott for secretarial assistance.	6.5	N = 495 with knee OA (ACR). Knee pain for ≥ 1 year, pain severity ≥ 20 mm on ≥1 WOMAC pain scale items.	Hyalgan 20mg (n=105) plus oral placebo vs. placebo lidocaine injection but no joint penetration plus oral placebo (n=115) vs. sham injection as above plus naproxen 500mg BID (n=113). Injections weekly for 5 weeks. 26 weeks follow-up.	HA vs. placebo vs. placebo-HA difference 50 foot walk test mean VAS for pain Week 3, 4, 5, 9, 12, 16, 21, 26: 27.2/32.4/5.2/p = 0.057, 21.5/28.6/7.1/p = 0.011, 19.3/25.7/6.4/p = 0.015, 20.0/24.3/4.3/p = 0.114, 20.3/26.7/6.4/p = 0.027, 20.8/25.4/4.6/p = 0.111, 18.4/24.8/6.4/p = 0.022, 17.9/26.7/8.8/p = 0.004. Percentage and number with ≥20mm improvement in VAS for 50 foot walk test Week 5, 9, 12, 16, 21, 26, 5-26: 65 (68)/57 (66)/8/p = 0.268, 67 (70)/56 (64)/11/p = 0.165, 64 (67)/50 (58)/14/p = 0.040, 63 (66)/54 (62)/10/p = 0.170, 68 (71)/52 (60)/15/p = 0.027, 68(71)/51 (59)/17/p = 0.013, 56 (59)/41 (47)/15/p = 0.030. All randomized patients success/failure analysis: 36(59)/28(47)/8/p=0.127. HA vs. placebo vs. naproxen 50 foot walk test VAS for pain at baseline, week 1, 2, 3, 4, 5, 9, 12, 16, 21, 26, and last observation.	"[I]A HA (Hyalgan) was an effective and safe therapy for patients with OA of the knee, in that it was more efficacious than placebo and as effective as oral naproxen with fewer adverse reactions."	High dropouts. Data suggest efficacy. Improvements persisted through end of 26 weeks observation.
Vangsness 2014 RCT No mention of sponsorship. COI, one or more of	6.5	N = 60 who were a candidate for a partial medial meniscectomy based on MRI; mean age was 46 years.	Group A: 50 million human mesenchymal stem cells (n = 20) vs. Group B: 150 million human mesenchymal stem cells (n = 20) vs. Control Group Vehicle Control (n = 20).	Meniscal volume was the primary outcome of the study. At 6 months, Group A and B each had one patient with >15% volume increase (p = 0.535). At 12 months, Group A showed a significant increase compared to control with 4 patients	"The results of this study suggest that mesenchymal stem cells have the potential to improve the overall condition of the knee joint... The data do not suggest that there was increased	Suggests mesenchymal cells may improve knee joint via tissue regeneration via MRI at 12 months (p=0.02).

the authors received payments or services, either directly or indirectly (i.e., via his or her institution) , from a third party in support of an aspect of this work.			Follow-up assessments were made at 6 weeks, 6 months, 1 year, and 2 years post operation.	above the 15% volume increase (p=0.04). At year 2, Group B and control had 0 patients with >15% meniscal volume increase and Group A had 3 patients with >15% volume increase (p = 0.029).	benefit from the higher dose.”	
Chareanch olvanich 2014 RCT Sponsored by TRB Chimerical. No COI.	6.5	N = 40 suffering medial compartment knee osteoarthritis with VAS >40mm, knee ROM >90° with less than 10° extension deficit, coronal knee deformity < 15° from normal alignment, grade 2 or 3 osteoarthritis on Kellgren and Lawrence scale rated via radiograph, failure of conservative treatment for >6 months, ages 35-65 years; mean (± SD) age 57.7 (± 5.3) for IA-HA group and 58.8 (± 4.0) for control group	Intra-articular Hyaluronic Acid (IA HA), or ‘Hyalgan’, injection group receiving a first wave of 5 injections at 2, 3, 4, 5, and 6 weeks followed by a second wave of 5 injections at 24, 25, 26, 27 and 28 weeks (n = 20) vs. Control group with no intra-articular injections (n = 20). Assessments at baseline, 6, 12, 24 and 48 weeks.	No significant differences reported between groups for WOMAC pain score, stiffness score, and physical function difficulty score and overall mean WOMAC. The IA-HA group showed significantly increased total cartilage volume, (p = 0.033), lateral femoral cartilage volume, (p = 0.044) and lateral tibial cartilage volume, (p = 0.027) over the control group.	“High tibial osteotomy is a surgical procedure that results in significant pain relief and functional improvement by WOMAC score assessment in patients with OA of the knee joint.”	Sample size is small but at one year follow-up MRI evidence of significant increase in cartilage volume (p = 0.03) in patients receiving HA after a high tibial osteotomy.
Dahlberg 1994 RCT Sponsored by KaroBio,	6.0	N = 52 with diagnosed cartilage abnormalities of knee, mean (±SD) age 46 (±8) for	Treatment group receiving 2.5mL hyaluronan (sodium hyaluronate; MW 600-1200 kd) injections along with knee aspirations of synovial fluid (n =	No statistically significant differences between the hyaluronan injection and placebo groups for total knee function, ROM, pain in the knee and knee activity level.	“[T]his study has shown a significant effect of intraarticular injections in the knee in patients with knee pain and arthroscopic	No significant differences between HA and placebo.

the Medical Faculty of Lund University, and the Swedish Medical Research Council. No mention of COI.		Hyaluronan group and 44 (± 9) for placebo control group	28) vs. placebo control group (n = 24). Assessments at baseline, 2, 4, 13, 26 and 52 weeks.		cartilage degeneration, without any severe side effects."	
Huskiison 1999 RCT No mention of sponsorship or COI.	6.0	N = 100 with knee OA (ARA), KL grade II to III and moderate to severe pain for 3+ months prior to enrollment	Five weekly intraarticular injections of HA (20 mg/2 ml, Hyalgan, Fidia, Abano Terme, Italy) vs. placebo; 6 months follow-up.	HA (n = 39) vs. placebo (n = 41) mean \pm SD pain on walking by VAS at week 0, 5, month 2, 4, and 6: 65.8 \pm 18.0/61.9 \pm 22.9, 27.5 \pm 22.7/40.6 \pm 29.4, 32.3 \pm 26.6/42.1 \pm 29.3, 33.0 \pm 29.2/48.3 \pm 31.6, 39.4 \pm 27.8/53.7 \pm 29.9. HA (n = 40) vs. placebo (n = 41) Lequesne functional index: 13.4 \pm 3.4/14.0 \pm 2.7, 10.0 \pm 4.6/12.1 \pm 3.8, 9.9 \pm 4.8/12.0 \pm 4.0, 10.2 \pm 4.8/12.4 \pm 4.2, 11.2 \pm 4.4/12.6 \pm 4.8.	"This study demonstrates that a course of five weekly injections of HA (Hyalgan) is effective, superior to placebo, and acceptable to patients with OA of the knee."	Randomization and blinding not well described. Data suggest efficacy.
Payne 2000 RCT Sponsored in part by Bioniche, Inc. No COI.	5.5	N = 46 patients with unilateral knee OA, grade I-III.	Hyaluronan 2% (730kD hyalgen) vs. saline, 3 weekly 2mL injections. All treated with stretching, flexibility and acetaminophen. 3 months follow-up.	No differences found for proprioception measurements between groups at any time. No AAE differences found between groups.	"Other studies have found that proprioception may be impaired in osteoarthritic knees and that viscosupplementation therapy with hyaluronan may decrease pain and increase function in these knee joints. The results of the present study suggest that this therapy does not adversely affect proprioception and that a longer, longitudinal study is required to determine if viscosupplementation treatments could attenuate proprioceptive decline."	Study to address effects on proprioception. Blinding not well described. Data suggest no effects on proprioception.

<p>Kotevoglou 2006</p> <p>RCT</p> <p>No mention of sponsorship or COI.</p>	<p>5.5</p>	<p>N = 78 with knee OA (ACR), Kellgren/Lawrence grade ≥ 2.</p>	<p>Group 1: Hyaluronan (Orthovisc) vs. Group 2: Synvisc (higher molecular weight) vs. Group 3: 2 mL of NS. 6 months follow-up.</p>	<p>Mostly graphic data. Total pain score better at 6 months than baseline for both HA groups ($p < 0.05$).</p>	<p>"All patients either injected with HA or placebo showed clinical improvement during the first 26 weeks of treatment, but neither of the hyaluronan preparations was more effective than the other."</p>	<p>Many details sparse. Only results from completers presented. Data suggest active treatments effective vs. placebo. Most data without differences between active groups, but physician's global assessment favored high molecular weight.</p>
<p>Navarro-Sarabia 2011</p> <p>RCT</p> <p>Sponsored by Tedec Meiji Farma SA. COI, PG and MG work at Tedec Meiji Farma SA, other authors received research funds from Tedec Meiji Farma SA as study investigators.</p>	<p>5.5</p>	<p>N = 306 with osteoarthritis of knee; mean age for HA / and placebo groups: 63 and 63.9.</p>	<p>Hyaluronic acid (HA) 2.5ml 1% (n = 153) vs. placebo or saline solution 2.5 ml (n = 153).</p> <p>Follow-up for 40 months.</p>	<p>77.85% of HA patients and 82.24% in the placebo group had bilateral osteoarthritis ($p = 0.341$), 55.17% of HA patients and 56.02% of placebo group ($p = 0.7992$) were also treated in the contralateral knee.</p> <p>Significantly more patients receiving HA responded to treatment vs. placebo according to OARSI 2004 criteria ($p = 0.004$), number of responders being 22% higher in HA group after the four treatment cycles (RR 1.22, 95% CI 1.07-1.41).</p>	<p>"The results of AMELIA offer pioneer evidence that repeated cycles of intra-articular injections of HA not only improve knee osteoarthritis symptoms during the in-between cycle period but also exert a marked carry-over effect for at least 1 year after the last cycle."</p>	<p>High dropout rate. HA at 40 months significantly better than placebo ($p = 0.004$) in improving knee OA symptoms and effects increased throughout study.</p>
<p>Bunyaratavej 2001</p> <p>RCT</p> <p>No mention of sponsorship or COI.</p>	<p>5.5</p>	<p>N = 49 patients with mono or bilateral congenital or locally acquired painful osteoarthritis clinically ascertained in past 6 months. Age range: 50-75 years.</p>	<p>Hyalgan® 20mg/2ml (n = 24) vs. placebo 2ml saline (n = 25). Intra-articular injection once per week for 4 injections. Two week washout period for those on NSAIDs. Patients allowed max dose of six 500mg tablets of paracetamol daily. Assessments at each injection (days 0, 7, 14, and 21) and days 35, 49, 82, 115, 148, and 180.</p>	<p>Pain on movement from baseline: significant in favor of treatment on days 148 ($p = 0.05$) and 180 ($p = 0.05$). Morning stiffness: improved in favor of treatment on days 49 ($p = 0.01$), 82 ($p = 0.008$), 115 ($p = 0.007$), 148 ($p = 0.03$), and 180 ($p = 0.03$).</p>	<p>"Our study has preliminary confirmed the beneficial effects of treatment with Hyalgan® in clinical aspects of Asian populations suffering from osteoarthritis of the knee."</p>	<p>Unknown compliance and dropout rates. Study suggests that HA decreased pain, and increased mobility when compared to placebo at a statistically significant value ($p < 0.01$).</p>

<p>Carrabba 1995</p> <p>RCT</p> <p>No mention of sponsorship or COI.</p>	<p>5.0</p>	<p>N = 100 (37 males, 63 females) with clinical history of painful knee osteoarthritis for >6 months, knee effusions (>3ml), pain on movement >40mm evaluated on 100mm visual analogue scale.</p> <p>Mean±SD age placebo group (60.0±7.0 years), Arthrocentesis group (56.8±7.5 years).</p>	<p>Placebo group 2ml Hyalgan® (n = 20) vs. Arthrocentesis group (n = 20) vs. 20mg/2ml Hyalgan® 1 injection (n = 20) vs. 20mg/2ml Hyalgan® 3 injections (n = 20) vs. 20mg/2ml Hyalgan® 5 injections (n = 20).</p> <p>Follow up in weekly intervals for first 5 weeks and on day 60.</p>	<p>Mean±SD pain at rest VAS score at baseline vs. Day 60: HA-1: 40.5±11.7 vs. 34.1±15.2. HA-3: 44.7±13.5 vs. 33.0±15.8. HA-3 and HA-5 had greater improvements from Day 28 onwards compared to HA-1; (p < 0.0051) at Day 60.</p>	<p>“[A] dose regimen of 3-5 intra-articular injections of Hyalgan® at a rate of 1 injection per week is effective and well tolerated in the treatment of osteoarthritis of the knee.”</p>	<p>Baseline comparability is uncertain as Tables 5 and 7 do not match. Study suggestive of more frequent HA injections leading to better clinical outcomes.</p>
<p>Dougados 1993</p> <p>RCT</p> <p>No mention of sponsorship or COI.</p>	<p>5.0</p>	<p>N = 110 with an ACR knee osteoarthritis diagnosis located in the femoro-tibial area, knee effusions, knee pain ≥40mm VAS; Mean (±SD) age 67.0 (±9.7) for Hyalectin group and 69.0 (±10.6) for placebo group</p>	<p>Hyalectin (20mg) group (n = 55) vs. saline placebo group (n = 55). Both groups received one injection weekly for 4 weeks.</p> <p>Assessments at baseline, 7 weeks and 52 weeks.</p>	<p>At 7 weeks evaluation, Hyalectin group exhibited significant changes from baseline compared to placebo group: VAS pain after exercise- -35.5±26.4 vs. -25.8±21.4, (p = 0.026); Lequesne’s index score- -3.8±4.3 vs. -2.3±3.3, (p = 0.027). During 52 weeks assessment, Hyalectin group had significant changes from baseline in Lequesne’s index vs. placebo group: -4.4±5.1 vs. -2.7±4.1, (p = 0.046).</p>	<p>“This study suggest that intra-articular injections of hyalectin may (1) improve clinical condition and (2) have a long-term beneficial effect in patients with osteoarthritis of the knee...However, no definite conclusion can be drawn up from this study because of its design, the control differed from active drug in its viscosity so the administrating physician (also the assessor) may not have remained blind, this might affect some outcome measures such as the requirement for further intervention and overall physician assessment.”</p>	<p>HA vs. placebo was better both short term and up to 12 month for knee OA symptoms.</p>

<p>Henderson 1994</p> <p>RCT</p> <p>No mention of sponsorship or COI.</p>	<p>5.0</p>	<p>N = 91 (28 men, 63 women) with history of knee OA. Patients stratified into 2 groups by severity of x-rays: Grade I or II assigned to severity group I, and grade III or IV assigned to severity group II.</p>	<p>Hyalgan 750kD 20mg injection (Group I n=10, group II n=25) in 2 ml of NS vs. placebo (Group I n=20, group II n=26) with 4 weekly injections. 5 months follow-up.</p>	<p>Hyalgan group I vs. hyalgan group II vs. placebo group I vs. placebo group II VAS pain scores at Week 0 for pain in morning, evening, climbing stairs, rising from a chair, and nominated activity at Week 0 (mean±SD): 62.2±6.3/58.5±6.4/63.6±5.5/65.7±5.2, 69.6±4.5/68.3±4.7/68.0±4.7/73.3±3.9, 67.8±6.7/72.4±4.3/71.7±4.4/80±3.2, 71.2±5.8/66±4.4/65.9±5.0/72.7±3.7, 71±5.4/71.6±4.5/67.2±4.4/74.3±3.6. Week 5: 44.5±7.3/49.4±7.5/51.3±6.7/58.8±6.3, 45.4±6.7/60.2±6.4/54.2±6.2/60.8±5.1, 56.9±7.9/63.9±5.8/55±5.9/73.1±4.4, 48.5±7.2/62.8±5.7/54.7±6.3/65.2±4.9, 48.6±6.6/60.9±6.5/53.9±5.6/63±5.1. Pain at rest, active movement, passive movement, horizontal pressure, and vertical pressure at week 0: 20.8±5.5/25.2±5.8/30.3±6.9/38.9±6.3, 43.7±7.8/48.5±5.5/53.0±7.2/49.3±6.2, 44.8±8.0/41.1±5.3/42.2±6.6/44.8±6.3, 51.5±8.0/43.7±6.1/38.4±6.4/44.3±6.6, 42.4±8.0/44.8±6.6/46.2±8.0/47.2±5.9. Week 5: 17.7±5.6/25.3±6.5/31.3±7.2/24±6.0, 28.1±7.6/39.8±7.3/38.8±6.5/31.3±6.1, 27.3±7.5/37.7±7.5/33.8±6.4/34.9±5.8, 25.8±6.5/34.5±7.2/34.7±7.0/29.3±6.5, 22.6±6.1/32.9±6.9/39.2±7.1/28.7±6.1.</p>	<p>"[I]ntraarticular administration of the preparation of 750 hyaluronan offers no significant benefit over placebo during a five week treatment period, but incurs a significantly higher morbidity, and therefore has no place in the routine treatment in osteoarthritis."</p>	<p>Under-enrolled final target of 100. Some baseline differences. High dropout rate. Some data trend towards efficacy. Weaknesses suggest underpowered.</p>
<p>Scale 1994</p> <p>2 RCTs</p> <p>Sponsored by Biomatrix, Inc. No</p>	<p>4.0</p>	<p>N = 80 with knee OA, Larsen Grade II-IV. Subjects were randomized to either study 1 or 2.</p>	<p>Study 1: Two weekly 2.0 ml (16mg) hylan G-F 20 injections (n=25, 2-INJ) vs. placebo (n=25). Study 2: Three weekly 2.0 ml hylan G-F 20 injections (n=15, 3-INJ) vs. placebo (n=15); 6</p>	<p>P value between groups for duration of disease, p=0.03. Subjects with grade IV roentgenograms, p=0.01. 3-INJ vs. 2-INJ percent of subjects who fulfilled successful treatment criterion for pain under weight-</p>	<p>"The results suggest that hylan is an extremely effective and safe viscosupplementat ion therapy for the management of degenerative osteoarthritis of the knee.</p>	<p>Two RCTs in 1 report and combined controls into 1 control group. Baseline differences present and controls had more severe</p>

mention of COI.			months follow-up both studies.	bearing movement: 80% to 90%/30% to 50%, p<0.05. 3-INJ vs. 2-INJ vs. control subjects who fulfilled successful treatment criterion for improvement in most painful knee movement at 8 and 12 weeks: $\geq 70\%/\leq 40\%/\leq 10\%$, p <0.05. Successful treatment criterion for global evaluation of improvement due to treatment at week 2, 3, 4, 8, and 12: $\leq 5\%/\leq 5\%/\leq 5\%$, $\leq 30\%/0\%/\leq 5\%$, $0\%/\leq 10\%/\leq 7\%$, $\leq 60\%/\leq 20\%/\leq 15\%$, $\leq 70\%/\leq 35\%/\leq 10\%$, p<0.05.	Beneficial results can be maximized using a treatment schedule of three hylan injections administered at 1-week intervals."	disease significantly raising potential of randomization failure. Many details sparse. Did not directly compare 2 vs 3 injection regimens in 1 trial (and those 2 groups differed), thus limiting strength of conclusion regarding which regimen is more efficacious. Both trials suggest efficacy.
Dixon 1988 RCT Sponsored by Fidia SpA. COI, Massarotti, Massari, and Cornelli of Fidia SpA, Italy supported the study and supplied clinical trial material.	4.0	N = 63 with osteoarthritis of knee; mean age 68.5 years (range 43 to 85).	2ml of intra-articular injections of 20mg sodium hyaluronate (n = 30) vs. 2ml injections of placebo 0.2mg sodium hyaluronate (n = 33). Up to 11 injections over a 23-week period. Follow-up during treatment and week 23 weeks after first injection.	Greatest pain on movement score reduction at 9 weeks: Mean reductions of 21.9 in active group vs. 7.7 in placebo group; p <0.05).	"There were small improvements with both treatments, significant at some assessments and somewhat greater with sodium hyaluronate than placebo, but there were no statistically significant differences between the groups."	Pragmatic RCT. Methods sparse. Study includes a range (1-11) injections. Both placebo and HA groups showed decreasing pain at 11 weeks. No statistically significant differences beyond 23 weeks.
Dose-Ranging and High vs. Low Dose Studies of Viscosupplementation						
Conrozier 2009 RCT Sponsored by Genzyme Europe b.v. No mention of COI.	5.0	N = 100 with knee tibiofemoral OA (ACR), Kellgren-Lawrence grade II-III, VAS 50-80/100mm	Intra-articular hylan G-F 20 (1 x 6mL vs. 1 x 4mL vs. 2 x 4mL 2 wks apart vs. 3x4mL 1 wk apart vs. 3 x 2mL 1 wk apart). 24 wks follow-up.	3x4mL group had highest adverse events (30%). 3x2mL had greatest improvement in knee OA pain. Greatest improvements in Patients and Physicians' Global Assessments both favored 1x6mL. Mean VAS improvements were respectively -34.9 vs. -24.3 vs. -24.0 vs. -32.6 vs. -36.7.	"This study suggests that a single 6 mL injection of hylan G-F 20 may be as efficacious, and as well tolerated, as 3 x 2 mL one week apart. A double-blind, controlled trial is needed to confirm these data."	Open label. Largest improvements in single 6mL injection, or 3x4mL or 3x2mL groups. Fewest retreatments in 1x6mL group (n=3 vs. 4-7), NS. Patient and Physicians' Global Assessments ranked 1x6mL best of groups. Data suggest single 6mL

injection may be sufficient.

High vs. Low Viscosity Viscosupplementation

<p>Kirchner 2006</p> <p>RCT</p> <p>Sponsored by Ferring Pharmaceuticals, Inc., Suffern, New York. COI, Kirchner is affiliated with NOVA-CLINIC/Germany. Marshall is affiliated with Ferring Pharmaceuticals/NY.</p>	<p>9.5</p>	<p>N = 321 patients with osteoarthritis of the knee; mean±SD age was 63.2±7.4 years.</p>	<p>High molecular weight hyaluronan (Bio-HA) (n = 160) vs. avian-derived hyaluronan (CL-HA) (n = 161).</p> <p>Both products administered as three 2 ml injections weekly.</p> <p>Follow-up evaluations at weeks 3, 6 and 12.</p>	<p>Mean±SD improvement from baseline of 5 WOMAC index pain scores (p <0.0001): Bio-HA group 29.9±1.7; CL-HA group 28.4±1.7.</p>	<p>“The effectiveness of Bio-HA was not inferior to that of CL-HA. The significantly higher incidence of post-injection effusion in the CL-HA group provides a safety advantage for Bio-HA. These data suggest that Bio-HA has an improved benefit-risk profile compared with CL-HA.”</p>	<p>Baseline data in Synvisc group trended towards worse severity of disease at start of study and data trended towards worse results with Synvisc.</p>
<p>Berenbaum 2012</p> <p>RCT</p> <p>Sponsored by Rottapharm and Madaus. COI, Sara Cazzaniga, Massimo D’Amato, Giampaolo Giacobelli and Lucio Rovati are scientists from the Department of Clinical Pharmacology of Rottapharm.</p>	<p>8.5</p>	<p>N = 426 with knee osteoarthritis > 6months who did not benefit from analgesics, NSAIDs or weak opioids, VAS global knee pain ≥40mm, grade 2 or 3 osteoarthritis on Kellgren and Lawrence scale rated via x-rays in past 12 months, WOMAC score ≥25 or Lequesne index of ≥4, ages 50-80 years; mean (± SD) age 67.2 (± 7.8) for GO-ON group and 66.1 (± 8.1) for Hyalgan group.</p>	<p>Intermediate molecular weight hyaluronic acid, “GO-ON” treatment group (MW 800-1500 kD, 25mg/2.5mL) (n = 217) vs. low molecular weight hyaluronic acid, “Hyalgan” treatment group (MW 500-730 kD, 20mg/2mL) (n = 209).</p> <p>Both groups received 3 injections weekly.</p> <p>Assessments at baseline, 6, 14, 20, and 26 weeks.</p>	<p>In a comparison of baseline and week 26 results, mean difference (95% CI) between GO-ON group and Hyalgan varied significantly in GO-ON’s favor for WOMAC pain, WOMAC function, WOMAC stiffness, WOMAC total, VAS pain, and Lequesne index: WOMAC Pain difference- -4.5 (-8.5 to -0.5), (p = 0.021), WOMAC Function difference- -6.8 (-10.7 to -2.8), (p=0.0004), WOMAC Stiffness difference; -5.3 (-10.0 to -0.6), (p = 0.027), WOMAC Total difference- -6.2 (-11.1 to -1.8), (p = 0.001), VAS pain difference- -6.4 (-11.1 to -1.8), (p=0.004), and Lequesne index difference- -1.2 (-2.0 to -0.6), (p = 0.0002).</p>	<p>“[T]his trial shows that the intermediate MW HA preparation GO-ON is effective on knee osteoarthritis symptoms over 6 months after a 3-weekly injection course, and may be more effective than the reference low MW formulation.”</p>	<p>Intermediate weight HA was significantly better than low molecular weight HA in treating knee OA symptoms at 6 months (p=0.021).</p>

<p>Wobig 1999</p> <p>RCT</p> <p>Sponsored by Biomatrix, Inc. COI, Balazs is inventor of both NIF-NaH and hylan G-F 20.</p>	<p>8.5</p>	<p>N = 70 with knee OA (Larsen x-rays grades I-III, ESR <40mm/hr, RF titer <1:160.</p>	<p>Hylan G-F 20 vs. Lower-Molecular Weight Hyaluronan 2mL each injection at Weeks 0, 1 2. 12 wks follow-up.</p>	<p>Overall patient pain assessments VAS Hylan 67 vs. LMW HA 51 (p <0.05). Weight bearing pain (patient or evaluator), overall condition, most painful knee movement all favored hylan (p <0.05). No differences in adverse events between groups (1.8 vs. 0.9%, NS).</p>	<p>"The higher-molecular-weight, more elastoviscous hylan G-F 20 had significantly greater pain-relieving effects than did the lower-molecular-weight, less elastoviscous hylauronan."</p>	<p>Data suggest higher viscosity is superior.</p>
<p>Jüni 2007</p> <p>RCT</p> <p>Sponsored by the Swiss Federal Office of Social Insurance, the Swiss Federal Office of Public Health, and the Swiss Association of Health Insurers (santésuisse). COI, Schwarz provided expert testimony for insurance companies located in Zurich and Winterthur; Theiler received consulting fees, speaking fees, and/or honoraria (>\$10,000 each) from Pfizer, Novartis, Roche, Amgen, and</p>	<p>8.0</p>	<p>N = 660 with knee OA, Kellgren/Lawrence grade ≥2 (duration ≥6 months).</p>	<p>1 cycle of 3 intraarticular injections (2mL each) of: 1) a high molecular weight cross-linked hylan derived from rooster combs vs. a non-cross-linked medium molecular weight HA derived from rooster combs (avian HA) vs. a non-cross-linked low molecular weight HA obtained through bacterial fermentation (bacterial HA); 12 month follow-up.</p>	<p>Difference between hylan and HAs was 0.1 at 3 and 6 months (95% CI). Hylan group costs \$1,459, \$1,238 for avian HA group and \$1,017 for bacterial HA group (p<0.001).</p>	<p>"We found no evidence for a difference in efficacy between hylan and HAs. In view of its higher costs and potential for more local adverse events, we see no rationale for the continued use of hylan in patients with knee OA."</p>	<p>Large sample size. Co-interventions appear not well controlled. Data suggest lack of differences between groups.</p>

Merck, Sharp, and Dohme.						
Raman 2008 RCT No sponsorship. No mention of COI.	5.5	N = 392 with knee OA.	Hyaluronan (Hylan G-F 20), 3 weekly injections vs. Sodium Hyaluronate (Hyalgan) weekly injections. 12 months follow-up.	WOMAC pain scale scores (baseline/6 weeks/3/6/12 months): hyaluronan (9.2/6.6/3.8/5.1/5.8) vs. sodium hyaluronate (8.8/8.4/5.9/8.3/8.5), favoring hyaluronan at 3/6/12 months with (p=0.02/p=0.01/p=0.007). WOMAC physical activity and Oxford knee scores also favored hyaluronan at 6 and 12 months (all p<0.02).	"Viscosupplementation is a valuable tool in the armamentarium of orthopaedic surgeons and rheumatologists who provide secondary care for patients with symptomatic OA. Although both treatments offered significant pain reduction, it was earlier and sustained for a longer period in patients with Hylan G-F 20 as seen in other studies."	Large sample size and one year follow-up. Some details sparse. Dropout rate unclear. Data suggest both effective, but hyaluronan more effective.
Kotevoglou 2006 RCT No mention of sponsorship or COI.	5.5	N = 78 with knee OA (ACR), Kellgren/Lawrence grade ≥2.	Group 1: Hyaluronan (Orthovisc) vs. Group 2: Synvisc (higher molecular weight) vs. Group 3: 2 mL of NS. 6 months follow-up.	Mostly graphic data. Total pain score better at 6 months than baseline for both HA groups (p<0.05).	"All patients either injected with HA or placebo showed clinical improvement during the first 26 weeks of treatment, but neither of the hyaluronan preparations was more effective than the other."	Many details sparse. Only results from completers presented. Data suggest active treatments effective vs. placebo. Most data without differences between active groups, however physician's global assessment favored high molecular weight.
Lee 2006 RCT Sponsored by LG Life Sciences. No COI.	5.5	N = 157 with diagnosed osteoarthritis of knee(s), >40 years old, inadequate response to conservative treatment of NSAIDs and analgesics, >30mm VAS pain score while bearing weight, grade 1 to 3 osteoarthritis	Hyruan Plus (MW 3000 kD) injection group receiving 3 weeks of treatment (n = 75) vs. Hyal (MW 750 kD) active control group receiving 5 weeks of treatment (n = 71). Assessments at baseline, 1, 6, and 12 weeks after final treatment.	No significant differences reported between groups for VAS pain during weight-bearing, mean pain reduction and WOMAC-Likert scores (function, stiffness and pain).	"[T]he efficacy and safety of HMW HA administered once a week for 3 weeks is comparable to that of LMW HA administered once a week for 5 weeks and that, by reducing injection frequency, patient discomfort will probably be reduced."	High and low molecular weight HA showed similar efficacy.

		on Kellgren and Lawrence scale rated via radiograph; mean (\pm SD) age 59.6 (\pm 8.8) for Hyruan Plus group and 61.1 (\pm 7.4) for Hyal group.				
Viscosupplementation Injections: Comparison of Injection Approaches						
Wind 2004 RCT No sponsorship or COI.	4.0	N = 131 with knee OA	Injections of 4mL saline plus methylene blue: superomedial vs. superolateral vs. lateral joint areas. Evaluations by arthroscopy.	Percentages graded as good methylene blue staining were: superolateral 89% vs. superomedial 93% vs. lateral 43%. Percentages poor were 0% vs. 2% vs. 39%.	"[A] lateral joint line injection site may not be reliable for routine injections of low volumes into knees, because it results in good intra-articular delivery less than half of the time, with a high incidence of soft-tissue infiltration."	Number of physician(s) unclear. Data suggest lateral approach inferior to either superomedial/lateral approaches.
Viscosupplementation Injections: Assessment of Additive Treatment						
De Campos 2013 RCT Sponsored by the Sao Paulo Research Foundation . No mention of COI.	7.0	N = 104 with knee osteoarthritis who had no previous intra-articular knee injections or typical osteoarthritis care in the past 6 months, no past knee surgeries, fractures or rheumatoid arthritis; mean (SD) age 61 (12) for VS group and 65 (9) for VS+T group	Viscosupplementation (VS) Group receiving one 6mL intra-articular injection of Hylan GF-20 (n=52) vs. Viscosupplementation plus triamcinolone (VS+T) Group receiving one 6 mL intra-articular injection of Hylan GF-20 and 1 mL (20mg) triamcinolone hexacetonide (n=52). Assessments at baseline, 1 week, 4, 12, and 24 weeks.	During 1 week assessment, VS+T group demonstrated significantly lower WOMAC and VAS levels over the VS group: WOMAC mean (SD)- 46 (19) vs. 34 (20), (p=0.038); VAS mean (SD)- 55 (27) vs. 39 (25), (p=0.014). No other significant differences reported groups at other follow up assessments.	"The addition of 1 mL of triamcinolone hexacetonide improved the first-week symptom and functional scores of viscosupplementation, and it did not alter its adverse effects or the 6-month symptom and functional improvement."	At weeks 4, 12 and 24, both groups showed some differences but at 6 months, both groups showed similar WOMAC scores suggesting that adding triamcinolone to HA improves symptoms and functional scores very short term.
Palmieri 2013 RCT No mention of sponsorship. No COI.	6.5	N = 62 with bilateral medial tibiofemoral knee osteoarthritis ; mean age 50.9 years for both groups.	Group 1: Hyaluronic Acid (66mg) - 1 time injection (n = 20) vs. Group 2: Hyaluronic acid (49.5mg) plus diclofenac sodium (5mg) (n = 21) - 1 time injection vs. Group 3: Hyaluronic acid (49.5mg) plus	At 3 months, Group 1 showed a decrease in mean VAS pain score from 67.5 to 46.8, Group 2; 71.9 to 48.86, Group 3; 76.9 to 47.5. At 6 months, Group 1 showed a decrease from 46.8 to 31.1, Group 2; 48.86 to 32.1,	"According to these results, highly cross-linked hyaluronic acid is suitable for use in combination with other drugs, namely NSAIDs or bisphosphonates	All groups showed similar results.

			sodium clodronate (5mg) - 1 time injection (n = 21). Follow up assessments made at 3 and 6 months after treatment.	Group 3; 47.5 to 26.8. Results at 3 months and 6 months significant within groups compared to baseline, however, results were not significant compared to other groups (p <0.05).	without complications."	
Adams 1995 RCT Sponsored by Biomatrix, Inc. No mention of COI.	6.5	N = 102 patients with knee OA, KL Grade I-III, ESR<30mm/hr, RF titer <1:160.	NSAID continuation plus 3 weekly arthrocenteses vs. NSAID discontinuation plus 3 weekly intra-articular injections of hylan G-F 20 (2.0ml) vs. NSAID continuation plus 3 weekly hylan G-F 20 injections. 26 weeks follow-up.	Mean±SE VAS score comparing NSAID vs. Hylan G-F 20 vs. Hylan G-F 20+NSAID: Pain with motion: 52±4* vs. 40±5 vs. 37±4*. Pain at rest: 22±3* vs., 25±3† vs. 11±3*†; p* <0.05 group 3 superior to group 1; p† <0.05 group 3 superior to group 2.	"Hylan G-F 20 is a safe and effective treatment for OA of the knee and can be used either as a replacement for or an adjunct to NSAID therapy."	Data suggest injections provide additive benefit.
Raynauld 2002 RCT Sponsored by Biomatrix, Inc and Rhone-Poulenc Rorer Canada Inc. COI, Band affiliated with Biomatrix Inc; authors thanked several individuals involved in study from Biomatrix Inc and Innovus Research Inc.	6.5	N = 255 with knee OA, knee most symptomatic or most predominant musculoskeletal problem, KL < Grade IV, >175/500 mm WOMAC scale.	Appropriate care (NSAIDs, steroid injections, education, weight loss, joint rest, heat, ice, devices, PT, arthroscopy, arthroplasty) with vs. without Hylan G-F 20. 1 yr follow-up.	Mean+SD change from baseline to termination in WOMAC pain score comparing AC+H vs. AC: -4.4+3.9 vs. -1.8+3.8; p<0.0001. Patients global assessment at month 12 over the past 4 weeks: OA in study knee: 76% vs. 43%, p<0.0001.	"The data presented here indicate that the provision to patients with knee OA of viscosupplementation with hylan G-F 20 within an appropriate care treatment regimen provides benefits in the knee, overall health and health related quality of life at reduced levels of co-therapy and systemic adverse reactions."	Open label, pragmatic. Data suggest viscosupplementation provides additive benefit.
Torrance 2002 RCT 2 nd report (Raynauld 02) Sponsored by Biomatrix, Inc and Rhone-	6.5	N=255 as above.	Appropriate care with Hylan vs. appropriate care without Hylan for 12 weeks.	AC+H group had higher costs (\$2125-\$1415=\$710, p< 0.05), more patients improved (69%-40%=29%, p=0.0001), greater increases in HUI3 (0.13-0.03=0.10, p< 0.0001) and increased quality-adjusted life years (QALYs) (0.071, p< 0.05).	"The cost-utility ratio is below the suggested Canadian adoption threshold. The results provide strong evidence for adoption of treatment with hylan G-F 20 in the patients and settings studied in the trial."	Economic study. Higher costs in viscosupplement group by approximately 50%. Increased quality adjusted life years of 0.071 and incremental cost-effectiveness

Poulenc Rorer Canada Inc. COI, Band affiliated with Biomatrix Inc; authors thanked several individuals involved in study from Biomatrix Inc and Innovus Research Inc.						ratio \$2505/patient.
Ozturk 2006 RCT No mention of sponsorship or COI.	4.0	N = 47 with knee joint osteoarthritis lasting >6 months meeting grade 2 or 3 osteoarthritis on Kellgren and Lawrence scale rated via radiograph; mean (\pm SD) age 58.0 (\pm 7.7) for Group A and 58.06 (\pm 10.3) for Group B	Group A receiving 2mL intra-articular sodium hyaluronate injections weekly for 3 weeks followed by weekly injections for 3 weeks after 6 months (n = 24) vs. Group B receiving same treatment as Group A, along with aspirations of knee effusions prior to 1st and 4th injections (n = 16). Assessments at baseline, 1 month, 2, 3, 6, 7, 9 and 12 months.	At 6 months follow-up, Group B exhibited significantly less WOMAC pain subscale scores than Group A (p <0.05). During 7 months assessment, Group B demonstrated significantly lower VAS difference scores vs. Group A (p <0.05).	“[T]his study demonstrates that HA together with corticosteroid provides rapid pain relief, has beneficial effects during 1 year after treatment, is well tolerated, and has no deleterious effects on joint structure in the management of knee OA. For the choice of IA treatment in patients with knee OA, our findings support that HA combined with corticosteroid should be preferred instead of HA alone.”	Actual p-values and analyzed variable values not reported.
Viscosupplementation vs. Platelet Rich Plasma Injections						
Sánchez 2012 RCT No mention of Sponsorship. No COI.	9.5	N = 176 with symptoms of tibiofemoral OA, x-ray diagnosed, joint pain >35mm, BMI 20-32kg/m ² , Ahlback grade <4, ages 40-72 years (mean 59.8).	Plasma Rich in Growth Factor (PRGF)-Endoret (8mL total per visit) group (n = 89) vs. Hyaluronic Acid (Euflexxa) group (n = 87). Both groups received 3x weekly treatments, follow-up at 1, 2, and 6 months.	PRGF-Endoret group had significant decrease in WOMAC pain scores (50% decrease) vs. Hyaluronic Acid. Proportion mean Difference (95% CI) - 14.1 (0.5-27.6), p= 0.044.	“Plasma rich in growth factors showed superior short-term results when compared with HA in a randomized controlled trial, with a comparable safety profile, in alleviating symptoms of mild to moderate osteoarthritis of the knee.”	PRGF vs HA showed similar result except PRGF had minimal efficacy vs. HA at 24 week period (WOMAC decreased by 14%).
Vaquerizo 2013 RCT	8.5	N = 96 with symptomatic knee OA;	PRGF Endoret or 3 injections on a weekly basis (n = 48) vs. one	Patients having a 30% decrease, the rate of response to PRGF-Endoret was 66%	“Our findings show that PRGF-Endoret is safe and significantly	Comparison of PRGF-Endoret to Durolane HA showed a

<p>Sponsored by the Biomedical Research Foundation of Príncipe de Asturias University Hospital and Ministry of Health, Social Policy and Equality of Spain. The authors report the following source of funding: V.V., M.Á.P., I.A., R.S., G.O., and E.A. receive support from BTI.</p>		<p>mean age 63.6 years.</p>	<p>infiltration with Durolane HA injection (n = 42). Follow-up at 24 and 48 weeks.</p>	<p>points (95% confidence interval [CI], 48 ± 84; p < 0.001), 43% points (95% CI, 23 ± 64; p < 0.001), and 23% points (95% CI, 2 ± 47; p = 0.02) higher than rate of response to HA for the WOMAC pain. A 50% decrease, rate of response to PRGF-Endoret was 43 % points (95% CI, 25 ± 62; p < 0.001), 29% points (95% CI, 11 ± 48; p = 0.001), and 19% points (95% CI, 0 ± 37; p = 0.035) higher than the rate of response to HA for WOMAC pain, physical function, and stiffness subscales, respectively.</p>	<p>superior to Durolane HA in primary and secondary efficacy analysis both at 24 and 48 weeks, and it provides a significant clinical improvement, reducing patients' pain and improving joint stiffness and physical function, with respect to basal levels in patients with knee OA."</p>	<p>50% reduction in knee OA pain, stiffness and function favoring PGRF-Endoret on most measures at 24 and 48 weeks (p=0.001).</p>
<p>Filardo 2012 RCT Sponsored by RICERA FINALIZZATA, Health Department. COI, Filardo is affiliated with Nano-Biotechnology Laboratory, Italy. However, all authors mention no COI.</p>	<p>8.0</p>	<p>N = 109 with DJD defined as chronic knee pain or swelling lasting >4 months, monolateral lesions, verified DJD changes via x-ray or MRI; mean age 55 for PRP vs. 58 for HA groups.</p>	<p>3 intra-articular platelet rich plasma injections (n = 54) vs. 3 hyaluronic acid injections (>1500 KDa; Hyalubrix) (n = 55). Follow-up at 2, 6 and 12 months.</p>	<p>PRP group improved vs. HA group for subjective IKDC results, approaching significance at 6 months (p = 0.08) and 12 months (p = 0.07).</p>	<p>"Results suggest that PRP injections offer a significant clinical improvement up to one year of follow-up. However...for middle-aged patients with moderate signs of OA, PRP results were not better than those obtained with HA injections...More promising results are shown for its use in low grade degeneration, but they still have to be confirmed."</p>	<p>No placebo. Data suggest trend towards modestly better efficacy of PRP vs. HA.</p>
<p>Cerza 2012 RCT</p>	<p>4.5</p>	<p>N = 120 with x-ray diagnosed Grades I, II or III knee OA. All had</p>	<p>ACP group (4 intra-articular injections; mean 5.5mL ACP per injection) (n = 60) vs. Hyaluronic Acid group (4 intra-</p>	<p>At weeks 4, 12, and 24, ACP showed improvement vs. HA. Week 4: ACP with mean (range; ±SD) score of 49.6 (5-80;</p>	<p>"Treatment with ACP showed a significantly better clinical outcome than did treatment with HA, with</p>	<p>PRP superior to HA through 24 weeks.</p>

No mention of sponsorship. No COI.		prior physical or pharmaceutical therapy without success; mean age 66.5 years (SD 11.3) for ACP group and 66.2 years (SD 10.6) for HA group.	articular injections; 20mg/2mL) (n = 60). Follow-up assessments at 4, 12 and 24 weeks after injection.	±17.8) vs. HA with 55.2 (25-78; ±12.3), p < .001. Week 12: ACP with mean (range; ±SD) score of 39.1 (5-76; ±17.8) vs. HA with increasing 57.0 (32-78; ±11.7), p < .001. Week 24: ACP with mean (range; ±SD) score of 36.5 (5-76; ±17.9) vs. HA with increasing 65.1 (41-82; ±10.6), p < .001.	sustained lower WOMAC scores. Treatment with HA did not seem to be effective in the patients with grade III gonarthrosis”	
Viscosupplementation Injections vs. Glucocorticosteroid						
Leighton 2014 RCT Sponsored by Q-Med, AB and Smith & Nephew, UK Ltd. COI, Dr. Ross Leighton is a paid consultant for Etex Corporation, Mats Andersson was at time of study, a full time employee of Q-Med, AB, Martin Todman was at time of study a full time employee of Smith & Nephew, UK Ltd., and Prof Nigel Arden is a paid consultant for Q-Med, AB and Smith & Nephew, Inc.	8.0	N = 442 with unilateral knee osteoarthritis meeting the ACR criteria for diagnosis who can walk 50 meters without assistance, ages 35-80, BMI ≤ 40kg/m ² , WOMAC pain score of 7-17, grade 2 or 3 osteoarthritis on the Kellgren and Lawrence scale rated via radiograph; mean (SD) age 61.9 (9.6) for NASHA group and 61.5 (9.9) for MPA group.	Intra-articular NASHA hyaluronic acid (3mL containing 60mg DUROLANE) gel injection group (n = 221) vs. Methylprednisolone acetate (MPA; 50mg in 1mL) injection group (n = 221). Evaluations at baseline, 6, 12, 18, 26 and 52 weeks.	At 6 week follow-up, OMERACT-OARSI rates significantly higher in MPA group over NASHA group, (p = 0.0138). During 26 week assessment, NASHA group improved WOMAC pain scores significantly over MPA group, (p = 0.034). OMERACT-OARSI responder rates significantly higher at this assessment for NASHA group over MPA group, (p = 0.0237).	“In conclusion, this study showed that NASHA is a valuable treatment for knee OA, providing effectiveness that was non-inferior to MPA. It also indicated that the effect of NASHA is longer lasting, with significantly improved pain response at 26 weeks compared to MPA. NASHA is well tolerated in relation to both primary and secondary injections, with most AEs being anticipated and non-allergenic in nature.”	WOMAC pain scores remained stable in NASHA group but worsened with time in the MPA group at 18-26 weeks. Patients receiving NASHA at 26 weeks after first being in MPA group reported improvement. MPA response was best at 6 weeks and declined thereafter.
Qvistgaard 2006	7.5	N = 104 patients with	Single injection of 1mL (40mg Depo-	No significant difference between	“[T]his controlled study could not	A 3-armed parallel group

RCT Sponsored by the Oak Foundation and the Erna Hamilton Foundation . Hyaluronic acid donated by Fida Inc. No mention of COI.		hip osteoarthritis defined by the ACR criteria, >18 years of age, and stable medication for at least 3 weeks; mean age 66±12 years.	medrol®) methylprednisolone followed by 2 sham injections (n = 34) vs. 3 injections of 2mL hyaluronic acid, HA, Hyalgan® (n = 34) vs. 3 intra-articular injection of 2mL saline water (n = 36). All injections included 1mL of 1% lidocaine. Injections given at 14 day intervals. Follow-up at 3 months.	groups for primary outcome, pain on walking at 3 months (p = 0.14).	demonstrate a 3-month effect on hip OA using HA.”	design comparing HA to corticosteroid and placebo (NS) for pain on walking at 2 weeks better with steroids (p = 0.04) but at 3 months no significant differences between treatment groups.
Caborn 2004 RCT Sponsored by Wyeth Pharmaceuticals. Hylan G-F 20 provided by Genzyme Biosurgery . COI, Parenti is Assistant Vice President of Musculoskeletal Products; Murray is Director of Musculoskeletal Products, Global Medical Affairs, Wyeth Pharmaceuticals.	6.5	N = 215 knee OA (ACR), Kellgren/Lawrence grade ≥2, (duration ≥3 months), VAS pain 50-90/100mm	Hylan G-F 20, 3x2mL weekly injections (n=113) vs. Triamcinolone Hexacetonide 40mg (n=102). 26 wks follow-up.	14% of steroid group quit because of unsatisfactory efficacy vs. 0%. Week 12 hylan patients had greater improvement than steroid group WOMAC: 0.9±0.1 vs. 0.5±0.1, p=0.0071. Week 12 VAS score: 31.3±2.3 vs. 17.4±2.41, p<0.0001.	“Viscosupplementation with HG-F 20 resulted in a longer duration of effect than TH with a comparable tolerability profile. These data support the preferential use of HG-F 20 over TH for treatment of chronic OA knee pain.”	High dropouts, especially for steroid. Data suggest viscosupplementation superior.
Leopold 2003 RCT Sponsored by William Beaumont Army Medical	6.5	N=100 with knee OA and insufficient results from variable treatment including NSAIDs, braces, PT. Excluded	Hylan GF20 16mg three weekly injections vs. betamethasone sodium phosphate 2mL (dose not specified) plus 4mL bupivacaine plus 4mL lidocaine (doses not	WOMAC median scores (baseline/3/6mo): steroid (55/42/40) vs. Hylan GF20 (54/41/44). Knee Society Rating System: steroid (58/72/70) vs. Hylan (58/69/68). VAS mm:	“No differences were detected between patients treated with intra-articular injections of Hylan G-F 20 and those treated with the corticosteroid with respect to pain relief or function at	High dropout rate in viscosupplementation group. Steroid dose not specified. Co-interventions not well described. Data suggest

Center, Department of Clinical Investigation. No COI.		'bone on bone'	specified). 6 months follow-up.	steroid (64/52/52) vs. Hylan (70/45/52).	six months of follow-up."	no meaningful differences. Posthoc results suggest lower response rates in females.
Frizziero 2002 RCT No mention of sponsorship or COI.	5.0	N=99 with knee OA (ACR, KL grades I-III) either primary or secondary to trauma.	Intraarticular hyaluronic acid 20mg weekly for 5 weeks or methylprednisolone acetate weekly for 3 weeks. 180 days follow-up.	Arthroscopic improvements found in femoral condyles grades of 43% HA vs. 16% steroid. Medial tibial plateaus for 27% vs. 12%. Patella also favored HA (57% vs. 20%). VAS data suggest more rapid onset of pain relief with steroid, though non-significant higher pain rating in steroid Day 180.	"This study supports previous data on a potential structure-modifying activity of HA in OA of the knee."	Data suggest viscosupplementation superior to steroid.
Shimizu 2010 RCT No sponsorship or COI.	4.5	N=61 with knee OA, age ≥60, tibiofemoral and/or patellofemoral joint pain, hydroarthrosis, KL grade 2 or 3	Sodium hyaluronate 25mg, 5 weekly injections vs. decadron 4mg injection; 6 months follow-up.	Pain scores (baseline/5 weeks/6 month): HA (6.3±1.0/3.7±1.4/1.9±1.7) vs. CS (6.4±1.0/3.4±1.4/2.0±1.9). VAS scores: HA (69.0/37.4/21.5) vs. CS (68.0/35.2/22.6).	"Both Na-HA and CS intra-articular injection therapies...exerted favorable clinical effects. Considering the results of the measurements of biomarkers, compared with CS injection therapy Na-HA injection therapy may exert protective effects on the articular cartilage by increasing the HA concentration in synovial fluid as well as inhibitory effects on the catabolism of articular cartilage by reducing the MMP-9 concentration."	Randomization not well specified. No blinding. Cointerventions not controlled. Data suggest comparable efficacy and no meaningful differences including in joint biomarkers, though may be underpowered for biomarkers.
Leardini 1991 RCT No mention of sponsorship or COI.	4.5	N=40 knee OA	Three weekly injections of sodium hyaluronate 20mg vs. 6-methylprednisolone acetate 40mg intraarticular. 60 days follow-up.	Night pain no symptoms at day 21 in 11/19 HA vs. 3/16 MP, p<0.05 and at day 60 in 12/20 vs. 4/16, p<0.05. Rest pain, pain under load and touch pain all favored HA at day 60, p<0.01.	"[O]n a short-term basis, both HA and 6-MPA are efficacious in controlling the symptoms related to osteoarthritis disorders. In the long term assessment, some difference emerged between the two treatments, particularly on the 35 th and 60 th days	Data suggest viscosupplementation longer term superior to glucocorticosteroid.

					when, in the HA-treated group, the results obtained at the end of treatment still persisted and in some cases had even improved.”	
Guidolin 2001 RCT Sponsored by a grant from FIDIA SpA. COI, Guidolin is affiliated with FIDIA Research Laboratory, Italy.	4.5	N=24 biopsy samples from 50 patients with primary osteoarthritis (OA) of knee following criteria of American College of Rheumatology; patients aged between 38-73 years.	Hyaluronan (Hyalgan®, 20mg/2ml once a week for 5 weeks) (n = 11) vs. methylprednisolone (Depo-Medrol®, 40mg/1ml once a week for 3 weeks) (n = 13). Follow-up at days 7, 14, 21, 28, 35, 60, 120, and 180.	Superficial amorphous layer compactness score: HA treatment changes from baseline to final 0.70 ± 0.22 ($p = 0.005$). MP score changes 0.25 ± 0.33 , $p = 0.7580$. Thickness (μm) of the layer: HA group 0.28 ± 0.06 , $p = 0.0020$. MP group 0.02 ± 0.08 , $p = 0.7340$.	“These results cannot be explained simply by temporary restoration of the synovial fluid viscoelasticity, and provide further evidence that the specific fraction of hyaluronan used in this study is a useful tool in OA treatment, with a potential structure-modifying activity.”	Suggestive of a possible structural modification at 6 months when comparing HA to methylprednisolone. Sample size is small to generalize results ($n = 24$).
Jones 1995 RCT Sponsored by Fidia S.p.A (manufacturer of Hyalgan). No mention of COI.	4.0	N = 63 (24 male, 39 female) with bilateral knee osteoarthritis with bilateral effusion; mean age 70.5 years.	Worst knee: Weekly injection of 5 doses of 20mg HA (Hyalgan) vs. 20mg TH (Triamcinolone) followed by 4 placebo doses. Contralateral knee: 5 placebo injections (1ml of 0.9% saline).	No differences in VAS scores found between knees. Active knee pain during activity: HA baseline: 77.2 ± 3.3 vs. HA week 29: 44.3 ± 7.2 .	“In patients remaining in the study, significantly less pain was experienced by the HA group during the 6 month follow-up period. Other parameters showed a similar trend in favor of HA. We could not, however, demonstrate significant differences between the placebo and active treatments.”	High dropout rate with no significant difference between groups. In 6 month follow-up, there was less pain in HA group.
Pietrogran de 1991 RCT No mention of sponsorship or COI. Drugs were supplied by Fidia S.p.A.	4.0	N=90 with knee OA	HA 20mg five weekly injections vs. 6-methylprednisolone acetate 40mg three weekly injections; 2 months follow-up.	VAS pain levels decreased over the trial and favored HA at 60 days (graphic data, $p=0.003$). At end of trial, no/slight pain in 22.7%/47.7% HA vs. 13.3%/35.5% MP ($p = 0.052$).	“[B]oth treatments were efficacious... The steroid had a more rapid action, which did not, however, last as long as that of HA.”	Many details sparse including randomization and co-interventions. Good compliance and dropout rates. Data suggest HA resulted in longer benefits than steroid.
Viscosupplementation Injections: Additive treatment with Glucocorticosteroids						
Housman 2014 RCT Sponsored by Genzyme	8.5	N = 391 with knee osteoarthritis (OA); age group range for 2x4mL/1x4mL/and steroid	2x4mL hylastan received IA hylastan SGL-80 on Day 0 and same treatment at Week 2 ($n = 129$) vs. 1x4mL hylastan received single IA injection of hylastan	From baseline over 26 weeks similar in all three groups: 2 9 4mL hylastan -0.9 (95 % CI -1.0, -0.7); 1 9 4mL hylastan -0.8 (-0.9, -0.7); and steroid -0.9 (-1.0, -0.8), with no	“Hylastan had an acceptable tolerability profile; there were no safety concerns in the initial or the repeat 26-week treatment phases,	Study showed a significant reduction in pain in all 3 groups. HA may be more effective at weeks 5-13.

<p>Corporation. COI, Helen Varley provided medical writing assistance and her company is supported by Genzyme Corp; B.B.'s institution is receiving funding from Genzyme Corp; B.J.S. is paid employee of Genzyme Corp; C.E. and F.B. were paid employees of Genzyme Corp at time of study and manuscript writing; other authors declare no COI.</p>		<p>group: 39-82/43-85/42-85.</p>	<p>SGL-80 on Day 0 and arthrocentesis only at Week 2 (n = 130) vs. Steroid received a single 1mL IA injection of MPA (40mg/mL) at Day 0 and arthrocentesis only at Week 2 (n = 132).</p> <p>Follow-up for 4, 8, 12, 16, 20, and 26 weeks.</p>	<p>significant difference between hylastan and steroid. A significantly higher mean daily dose of rescue medication was taken in 2 x 4mL hylastan group vs steroid group.</p>	<p>and target knee AEs were similar to those reported in the steroid group.”</p>	
<p>Oztruk 2006 RCT No mention of sponsorship or COI.</p>	<p>6.5</p>	<p>N=47 with knee OA (ACR), KL grades II-III. All but one females.</p>	<p>All received weekly sodium hyaluronate 15mg injections for 3 weeks and repeated series at 6 months with vs. without triamcinolone acetate 1mL (dose not specified) with injections #1 and 4 of the HA series. 1 year follow-up.</p>	<p>VAS scores decreased both groups, then gradually rose (graphic data) over the year. Slight difference between the groups at 1 month.</p>	<p>“Although all patients had improvement for both pain and function, HA together with corticosteroid was superior to HA alone for early pain relief. The MRI findings showed that neither treatment showed a progression on the damage of the cartilage.”</p>	<p>Group sizes different (24 vs. 16) and not clearly explained although possibly related to inclusion of ineligible subjects all in one group. Data suggest glucocorticosteroid of minimal additive benefit in addition to viscosupplementation at 1st month follow-up only.</p>

Viscosupplementation Injections: Polynucleotide Gel Injection vs. Hyaluronan						
Vanelli 2010 RCT Sponsored by Mastelli s.r.l. No mention of COI.	6.5	N=60 patients with persistent pain (at least 2 months in duration) and affected by knee osteoarthritis	Intra-articular polynucleotide (PN) gel injections (n=30) vs. hyaluronan (HA) (n=30) five times weekly. 4 mo follow-up.	Both groups improved significantly in VAS pain scores. VAS scores for PN group decreased from 5.7± 1.9cm (T0) to 1.9±1.5cm (T16) and HA group 4.9 ± 2.0cm (T0) to 2.1 ±1.4cm (T16). Statistical analysis not performed due to high variability of groups.	"[P]olynucleotides can be considered as an alternative to hyaluronic acid for the treatment of symptomatic osteoarthritis; we reckon that this product may prove useful to extend the range of treatments available in this therapeutic field."	Data suggest equivalency.
Synovial Fluid Substitute (Viscoseal)						
Mathies 2006 RCT No mention of sponsorship or COI.	6.5	N = 40 patients aged 18-60 with meniscal pathology requiring arthroscopic intervention	Standard therapy (control group, n = 20) vs. 10 ml Viscoseal into joint (n = 20)	Viscoseal group superior to standard therapy group for pain at rest 1st day after surgery, p = 0.0525. Joint swelling improved in favor of viscoseal group Day 12 (p = 0.0150, Day 28 (p = 0.0072). Diclofenac consumption lower in viscoseal group Day 3 (p = 0.0093), Day 4 (p = 0.0075), Day 7 (p = 0.0195).	"These findings indicate that Viscoseal may be useful as a synovial fluid substitute after arthroscopy."	One month follow-up pilot study. Data suggest minimal benefit of a few days to a couple weeks by a couple parameters that were gone at 1 month.
Intramuscular Injections						
Chevallard 1993 RCT No mention of sponsorship or COI.	7.0	N = 40 patients suffering from mono or bilateral osteoarthritis of the knee.	Galactosaminoglycuronoglycan-sulfate GGGs (Matrix) vs. saline placebo intramuscular injections for 2 series of 25 injections.	GGGS had significant improvement in pain on passive movement, loading, and pressure vs. placebo after therapy (p <0.01). Spontaneous pain during trial: 90 days (Group A 3.5±0.8, p <0.01 vs. baseline), 180 days (Group A 3.6±0.9, p <0.01 vs. baseline and Group B 6.3±1.0, p <0.05 vs. baseline), 240 days (Group A 3.3±1.1, p <0.01 vs. baseline and Group B 6.0±1.1, p <0.05); 330 days (Group A 4.1±1.0, p <0.01 vs. baseline), 360 days (Group A, 4.4±0.8, p <0.01 vs. baseline).	"[T]he favourable clinical results observed associated with an excellent tolerability make GGGs a safe and effective chondroprotective drug that can be recommended for the basic treatment of OA."	Some details sparse. Regimen requires 50 IM injections. Data suggest superiority to placebo.
Katona 1987 RCT No mention of sponsorship or COI.	5.0	N = 50 patients with clinically and radiologically diagnosed knee arthrosis.	2 ml intramuscular injections of Glycosaminoglycan-peptide complex vs. placebo for 8 weeks at time (n=25 for both groups).	The week 48 the group treated with active treatment saw improvements in night pain, pain in standing, pain climbing stairs, and pain walking (p<0.01, p<0.01, p<0.005, p<0.05). By week 96 both groups improved significantly in morning stiffness (p<0.05).	"During the first year of the trial (double-blind phase) there were only small non-significant differences in favour of the glycosaminoglycan-peptide complex as	Blinding not well described. High dropouts. Treatment cumulatively requires 48-72 IM injections. Data suggest at least some efficacy although some dropouts

					compared with placebo."	presumably in those lacking efficacy thus potentially magnifying results.
Viscosupplementation Injections vs. Other Treatments						
Baker 2012 RCT No mention of sponsorship. No COI.	9.0	N = 98 patients undergoing arthroscopic knee surgery for the removal of loose bodies, cartilage debridement or meniscectomy; mean age 45.3 years for both groups.	10mL of 0.5% bupivacaine injections Control Group (n = 49) vs. 3 mL of Hyaluronic Acid into knee joint HA Group (n = 49). Follow-up at 2 hours, 1 day and 1, 2, and 6 weeks following injection.	WOMAC and VAS pain scores used to assess effect of injections. No significant differences between groups at any time point. Mean WOMAC score at 6 weeks, Control vs. HA group 89.09 vs. 90.58 (p = 0.498), VAS rest score 1.27 vs. 1.14 (p = 0.145), VAS movement 1.37 vs. 1.25 (p = 0.392) and VAS weight bearing 1.86 vs. 1.65 (p = 0.342). Results improved more for HA group compared to control. However, scores not significant compared to control.	"Our study has shown that infiltration of either bupivacaine or an HA injection (Durolane) at the completion of knee arthroscopy confers equivalent analgesic and functional benefit in the short term."	Study did not demonstrate differences between functional outcomes between HA and bupivacaine injections at 6 weeks post-surgery.
Nahler 1998 RCT No mention of sponsorship or COI.	8.0	N = 121 patients with primary osteoarthritis of the knee; Mean±SD age in Zeel® group 67±10, in Hyalart® group 66±10 years.	10 injections of Zeel® compositum (two 2ml intra-articular injections per week) vs. 5 injections of Hyalart® (one 2ml intra-articular injection per week). Follow up for 5 weeks.	Arthritic symptoms decreased 36mm for Zeel® compositum (from 67mm to 31mm) and 37mm for Hyalart® (from 63 to 26mm). No p-values given. Both treatments reported to be equally effective.	"Zeel® compositum and Hyalart® proved to be equally efficacious in treating patients with either mild or more severe pain."	Comparing Zeel (a homeopathic preparation) to Hyalart showed similar outcomes in patients with knee OA.
Strand 2012 RCT Sponsored by Seikagaku Corporation who also conducted study. COI, Strand has served as consultant to Seikagaku Corporation as well as Cypress, Logical Therapeutics, Nicox and Pfizer;	8.0	N = 379 with symptomatic OA; 40-80 years of age.	Gel-200 30mg cross-linked HA in 3.0mL at week 0 (n = 247) vs. PBS 3.0mL at week 0 (n = 128). Follow-up at weeks 1, 3, 6, 9, and 13 after injection.	Treatment differences at weeks 3 and 6 exceeded 8mm (p = 0.001 and 0.003, respectively), and overall difference over weeks 3 through 13 was 7.10mm (p = 0.005). No statistically significant differences in SF-36 between weeks 0 and 13.	"This trial demonstrated that a single injection of Gel-200 was well tolerated and relieved pain associated with symptomatic OA of the knee over 13 weeks."	HA Gel 200 vs placebo for knee pain was significant for pain reduction at weeks 3-13 (p=0.037).

Baraf was an investigator in this study and served as consultant to Seikagaku Corporation after study completion ; Lavin was statistical consultant to Seikagaku Corporation; Hosokawa and Lim are employees of Seikagaku Corporation.						
Giarratana 2014 RCT No mention of industry sponsorship. No COI.	8.0	N = 72 with knee osteoarthritis ; mean age 64 years for both groups.	Intra-articular polynucleotides (Condrotide) C group - 3 injections of Condrotide in a period of 1 week (n = 36) vs. Hyaluronic Acid Group (HA) -- 3 injections of HA in a period of 1 week (n = 36). Assessments were made at 1, 2, 6, 10, 18, and 26 weeks.	Compared to baseline, KOOS score became significant at 2 weeks in the C group, (p = 0.003) and became significant in the HA group at 18 weeks, (p = 0.01). There was a significant difference found between groups in favor of Group C for KOOS-pain, function in daily living and function in sports and recreation at week 10, (p <0.05).	“This study confirms that Condrotide is as effective as Hyalubrix in reducing knee OA symptoms, but it shows an earlier response on pain reduction, determining a faster improvement of the activities of daily living and, therefore, of a patient's quality of life.”	Short follow-up time. Condrotide decreased pain symptoms associated with knee OA earlier than HA. At 2 weeks, Condrotide significant at p = 0.003 and HA significant at 18 weeks, p = 0.01.
Lee 2011 RCT No mention of sponsorship or COI.	6.5	N = 43 with knee osteoarthritis ; mean age 68 years for both groups	Ketorolac Group - 3 weekly intra-articular injections of HA with ketorolac and 2 weekly injections of HA only (n = 21) vs. Hyaluronic Acid HA Group -- given 5 weekly intra-articular injections of HA (n = 22). Follow-up at 1, 3, 5, and 16 weeks.	Rubin scale was used for assessment. Ketorolac group showed a significant improvement in mean score compared to HA group at week 1; 2.4 vs. 1.5 (p = 0.001) and week 3; 2.7 vs. 1.6 (p < 0.001) but it was not significant at week 5; 3.2 vs. 2.8 (p = 0.116) or week 16; 3.1 vs. 2.9 (p = 0.530).	“Intraarticular HA with ketorolac showed more rapid analgesic onset than intraarticular HA alone and did not induce any serious complications.”	Small sample size and short follow-up time. But, initial results showed addition of ketorolac to intrarticular HA improved pain (p <0.05); 25% of those receiving ketorolac reported focal post injection knee pain at 8 hours after injection.

<p>Karatosun 2006</p> <p>RCT</p> <p>No mention of sponsorship or COI.</p>	<p>6.0</p>	<p>N= 105 with radiographic Kellgren Lawrence grade 3 OA; mean age Group 1 = 57.8 ± 12.1, Group 2 = 55.3 ± 13.6</p>	<p>Intent to treat Group 1 (n = 52) received 3 injections of hyaluronic acid (G-F 20) vs. Group 2 (n = 53) received physical exercise including a series of progressive simple, range of motion and resistance exercise vs. Effectiveness Population Group 3 (n = 31) received 3 injections of hyaluronic acid (G-F 20) vs. Group 4 (n = 53) received physical exercise.</p> <p>Follow up at 1, 2, 3, and 6 weeks and after 3, 6, 12, and 18 months.</p>	<p>Treatment outcomes between groups 1 and 2 at weeks 1, 2, 3, and 6, in pain during transfer activities significant in favor of group 2 (p = 0.042, 0.000, 0.010, 0.024, respectively).</p> <p>Group 1 vs Group 2 pain during activity at 6 weeks and 3 months (p = 0.039). Walking distance at 3 months (p = 0.001), Total HSS score at 3 months (p = 0.023). Group 2 significantly better at performing transfer activity and HSS score at 12 months (no p value). Group 3 total HSS scores significantly improved from baseline (57.0±12.9) to 18 months 76.7 ± 11.9, (p = 0.0002). All groups had significant improvement from baseline.</p>	<p>“As a result we conclude that hyaluronic acid of progressive knee exercise are effective in alleviating the symptoms of osteoarthritis, postponing total knee replacement for 18 months, and increasing the satisfaction levels of the patients.”</p>	<p>Comparison of HA to exercise for knee OA for functional improvement. At 6 months, there was no statistical difference between groups.</p>
<p>Kawasaki 2009</p> <p>RCT</p> <p>No sponsorship or COI.</p>	<p>6.0</p>	<p>N = 102 females with primary OA with no other inflammatory diseases; mean age 70.4.</p>	<p>Group 1: Home Exercise completed isometric muscle exercises of bilateral lower limbs and Range-of-motion exercises (ROM) (n = 52) vs. Group 2: Intra-articular injections of hyaluronate sodium in affected knee once a week for 5 weeks and once a month until the 24th week (n = 50).</p> <p>A regular check-up done every 4 weeks and comparison of both groups done at 24 weeks.</p>	<p>All patients who finished at least 12 weeks included in an intent to treat analysis. VAS and JKOM scores significantly significant in both groups at 24 weeks (p = 0.001, p = 0.000). In patients with early OA, the exercise group was significantly favored, (p = 0.019). Range of motion not significantly different between groups.</p>	<p>“Taking into account the cost, convenience, and invasiveness to patients, exercise is thought to have some advantage over intraarticular injection of hyaluronate for the therapy of OA of the knee.”</p>	<p>Results for pain relief and functional improvement similar in both groups at 24 weeks.</p>
<p>Kahan 2003</p> <p>RCT</p> <p>No mention of sponsorship or COI.</p>	<p>5.5</p>	<p>N = 506 with knee OA, VAS pain with walking ≥40/100mm.</p>	<p>Synvisc (G-F 20) 3 weekly injections vs. “conventional therapy” (not controlled, not described) Evaluation visits at 1, 3, 6, and 9 months.</p>	<p>Mean±SD Lequesne index change at study completion comparing control vs. Synvisc: 9.7±4.5 vs. 7.5±4.4; p = 0.0001. WOMAC scale at study completion: 39.7±22.1 vs. 26.5±20.0; p=0.0001. Mean medical plus sick leave costs over 9mo: €829.10 Synvisc vs. €829.40 conventional.</p>	<p>“Synvisc viscosupplementation is more effective than conventional treatment, at no additional cost. It takes a step toward answering the request of international experts for medicoeconomic</p>	<p>Primarily economic study. Data suggest viscosupplementation superior to conventional therapy and more economical. Conventional treatment not controlled and</p>

					data on viscosupplementation for osteoarthritis."	not well described.
Paker 2006 RCT No mention of sponsorship or COI.	5.5	N = 52 with knee OA (ACR, K-L grade II or III) aged 40-80.	Intra-articular hylan G-F 20, 3 injections (n=25) vs. TENS 20 minutes 5 times a week for 3 weeks (n=27); 6 month follow-up.	WOMAC physical function scores and WOMAC stiffness scores improved in injection group vs. TENS at 6 months, p <0.05.	"[B]oth TENS and viscosupplementation with hylan G-F 20 were effective in providing pain relief and restoring physical function to patients with knee OA during the first month of treatment and during the 6-month follow-up period."	Baseline differences with older age, (p<0.0001), higher WOMAC pain, function, Lequesne total/function scores at baseline suggesting randomization failure. Conclusion that both may be used in conjunction unable to be supported by study design.
Petrella 2002 RCT Sponsored by an unrestricted educational grant from Bioniche Life Sciences, INC. Dr. Petrella is a Canadian Institutes of Health Research investigator.	5.0	N = 120 with Stage 1 to 3 medial compartment knee osteoarthritis; mean age 67 years for all groups.	Group 1: 2mL of Hyaluronate Sodium (Na-Ha) at 10mg/mL and placebo (100mg lactose (n = 25) vs. Group 2: NSAIDS (75 mg of diclofenac and 200 micrograms of misoprostol and Na-Ha (n = 29) vs. Group 3: NSAIDS and Placebo (n = 26) vs. Group 4: Placebo (saline and lactate) (n = 28). Follow-up assessments took place 4 and 12 weeks after baseline.	At week 4, all groups significantly improved from baseline for WOMAC Disability and Stiffness. Groups 1-3 significantly improved in WOMAC pain score from baseline (p<0.05). At week 12, only group 2 showed a significant difference from baseline (p <0.05). There were no between group statistics reported.	"In summary, intra-articular hyaluronate sodium therapy was similar to NSAID therapy in improving pain at rest, while the introduction of a simple exercise program improved functional performance in all 4 groups compared with baseline measures."	Four arms of study showing similar results for HA and NSAIDs in treatment of resting OA knee pain.

Chen 2013 RCT Sponsored by the Taiwan National Science Council and Nihon Medix Co, Ltd. No mention of COI.	5.0	N = 54 with ACR clinical criteria fulfilling knee osteoarthritis, a VAS pain ≥ 4 , grade 2 to 4 changes on the Kellgren and Lawrence scale rated via radiograph, ages 50-80 years; mean (\pm SD) age 67.96 (\pm 9.94) for HA group and 66.52 (\pm 7.20) for TENS group.	Hyaluronic Acid (2.5mL of 1% sodium hyaluronate solution) injections weekly for 5 weeks (n = 27) vs. TENS (mixed frequency mode of 3Hz and 20Hz with a width of 200 μ s) group receiving three 20 minute sessions a week for 4 weeks (n = 27). Assessments at baseline, 2 weeks, 2 months and 3 months.	At 2 weeks, TENS group exhibited significantly lower change in VAS and Lequesne index from baseline vs. HA group: VAS- 6.11 \pm 1.37 to 4.17 \pm 1.98 vs. 6.46 \pm 1.82 to 5.31 \pm 1.78, (p = 0.03), Lequesne-10.20 \pm 2.25 to 7.78 \pm 2.08 vs. 12.35 \pm 3.00 to 9.85 \pm 3.54, (p = 0.01). At 3 months, TENS group exhibited a significantly lower Lequesne index score versus the HA group: 7.07 \pm 2.85 vs. 9.24 \pm 4.04, (p = 0.03). No significant differences reported between groups for ROM.	"This study demonstrated that TENS with SSP electrodes was more effective than intra-articular HA injection for patients with knee OA in improving the VAS for pain at 2 weeks' follow-up as well as the Lequesne index at 2 weeks' and 3 months' follow-up."	TENS vs. HA showed significance at 2 months (p=0.03) and was more efficacious than HA.
Listrat 1997 RCT Sponsored by a grant from Fidia SpA Italy and in part by a grant from the Société Française de Rhumatologie. No mention of COI.	5.0	N = 39 patients with painful knee osteoarthritis (ACR criteria); mean \pm SD age - Hyalgan group 60 \pm 7 years, control group 64 \pm 8 years.	Conventional therapy (n = 19) vs. three cycles (every 3 months) of three intra-articular injections of Hyalgan (once a week during 2 weeks) (n = 20).	Quality of life index - AIMS2: -0.4 \pm 0.7 vs. 0.2 \pm 0.9 in the Hyalgan and control groups respectively, p <0.05. Overall assessment (VAS) of chondropathy: 5.1 \pm 12.7 vs. 16.7 \pm 18.3 9 in Hyalgan and control groups respectively, p = 0.016.	"This study supports existing data concerning the favorable symptomatic effect of intra-articular injections of Hyalgan in osteoarthritis of the knee and suggests that repeated intra-articular injections of Hyalgan might delay the structural progression of the disease. Other studies are required to confirm these results and to determine the long-term monitoring of osteoarthritic patients using such local therapy."	No significant differences between groups in terms of pain but Hyalgan "may" delay disease progression in knee OA.
Rossini 2009 RCT Sponsored by Abiogen S.p.A. COI, G.B.	4.5	N = 145 with knee osteoarthritis (KOA), aged 50–75.	Clodronate 0.5mg one IA injection/week for 4 weeks (n = 28) vs. Clodronate 1mg one IA injection/week for 4 weeks (n = 30) vs. Clodronate 2mg one IA injection/week for 4 weeks (n = 30) vs.	No significant difference in any of the VAS scores was detected among the five treatment groups at any time point. A significant (p = 0.03) linear trend for a dose–response (0.5–2 mg clodronate) relationship was found	"This study indicates that IA clodronate provides symptomatic and functional improvements at least as good as those obtained with HA."	Comparability of baseline pain is different between groups. Best dose HA still unclear although 21% receiving highest

received honoraria and/or consulting fees from Abbot, Amgen, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Schering-Plough, Servier and Wyeth. All other authors declare no COI.			Clodronate 1mg two IA injections/week for 2 weeks clodronate 1p1mg (n = 29) vs. HA 20mg one IA injection/week for 4 weeks (n = 28). Follow-up for up to 4 weeks.	for active movement VAS pain.		clodronate dose (2mg), experienced burning at injection site. Active movement pain improved in 0.5-2mg clodronate group showing a dose response linear trend relationship (p=0.03).
Forster 2003 RCT No mention of sponsorship or COI.	4.5	N=38 patients on the waiting list for an arthroscopic washout for knee osteoarthritis ; mean age of Hyalgan group was 60 years; Arthroscopy group 63 years.	Five intraarticular injections of 20mg Hyalgan in affected knee at 1-week intervals (n = 19) vs. arthroscopic washout with either general or spinal anaesthesia (n = 19). Follow-up at pre-intervention, 6 weeks, 3 months, 6 months, and 1 year.	VAS score pre-trial to 1 year follow-up: Hyalgan: 7.6 to 5.7. Arthroscopy: 7.5 to 5.7. Only 1/5 Hyalgan patients had improved 1 year post-operatively. No p-values given. No significant difference in VAS, FS or LI between 2 groups at 6 weeks, 3 months, 6 months, or 1 year.	"[T]he use of intra-articular Hyalgan injections in patients with knee osteoarthritis without mechanical symptoms gave results comparable with arthroscopic washout. Hyalgan should be considered as an alternative to arthroscopy in this patient group."	Patients could not be blinded in this study (surgical procedure vs injection) and results for both were similar.
Graf 1993 RCT No mention of sponsorship or COI.	4.0	N = 60 patients with osteoarthritis of knee at least age 18 and no corticosteroid injections in past 3 months or NSAIDs in past 14 days; mean age: HA group 50.9±13.9 years, MPA group 59.2±14.7 years.	Hyaluronic acid, HA, molecular weight of 500-730 kDa at a dose of 20mg/2 ml once a week, 7 injections total (n = 33) vs. mucopolysaccharide polysulfuric acid ester, MPA, at dose of 50mg/ml twice a week, 13 injections total (n = 27) for 6 weeks. Assessments weekly during study period and 7 weeks, 3 months, and 6 months after baseline.	Larson subtotal for pain (mean±SD) – baseline/treatment end: HA 14.1±5.8/5.5±6.2 vs. MPA 16.2±5.5/1.5±5.6 (p = 0.01). Total Larson rating score (mean±SD) – baseline/treatment end: HA 45.7±11.6/8.4±1.03 vs. MPA 46.6±11.3/2.5±7.7 (p = 0.02).	"We found that both HA and MPA demonstrated efficacy, but hyaluronic acid was superior in the parameters investigated."	Single blind study comparing HA to mucopolysaccharide polysulfuric acid ester (MPA). HA group had more pain relief post injection and at 6 months (p = 0.02).

Stitik 2007 Quasi-randomized trial Sponsored by grant from Sanofi-Aventis Inc. No COI.	4.0	N = 60 with moderate to severe pain from knee OA	Five weekly hyaluronate injections vs. 3 weekly hyaluronate injections vs. 3 weekly injections plus HEP (quadriceps exercises and wall slides). 1 year follow-up.	WOMAC (1/3/6/9 months/1 year): 3 injections (11.58/20.53/19.90/12.16/12.32) vs. 3 injections plus HEP (20.31/19.81/23.76/21.61/26.11) vs. 5 injections (22.38/20.73/19.28/19.08/21.18).	“The combined use of hyaluronate injections with HEP should be considered for management of moderate-to-severe pain in patients with knee OA.”	Quasi-randomized with sequential allocation. Study claims injectors blinded, but this does not seem possible. Dropouts at 1 year of 53.3%. Data suggest 3 injections inferior to other 2 arms.
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Different forms of Viscosupplementation: Viscosupplementation Injection vs. Viscosupplementation Injection

Pavelka 2011 RCT Sponsored by IBSA. COI, the authors received a grant for this clinical study from IBSA.	10.0	N = 381 with knee osteoarthritis in index knee for >3 months verified by radiograph and ACR clinical standards, grade 2 or 3 osteoarthritis on Kellgren and Lawrence scale, mean WOMAC pain subscore ≥ 40 mm and < 80mm on VAS, ages 40-81 years; Mean (\pm SD) age 65.1 (± 9.1) for Sinovial group and 64.9 (± 8.7) for Synvisc group.	0.8% Biofermentative originating Hyaluronic Acid (16mg/2mL), “Sinovial” Group (n = 192) vs. 0.8% Hylan G-F20 (16mg/2mL), “Synvisc” Group (n = 189). Both groups received 3 injections at weekly intervals. Assessments at baseline, 1 month, 2, 3, 4, 5 and 6 months.	No significant differences reported between groups during the 6 months assessment for WOMAC Index pain scores, WOMAC Function, and WOMAC Stiffness.	“While the use of intra-articular hyaluronan in knee osteoarthritis is a well-established treatment, the generalizability of the findings in this study may be applied to those patients who fail to respond to non-pharmacologic therapy and simple analgesics, or in whom non-selective NSAIDs and cyclooxygenase-2 specific inhibitors are contraindicated or have been associated with lack of efficacy or adverse events. In conclusion, Sinovial and Synvisc treatments were found to be equivalent both in terms of efficacy and safety.”	Study well controlled for co-interventions. Synvisc compared to Synovial showed no significant differences at 26 weeks but Synovial patients had some better outcomes for select variables at earlier times.
Neustadt 2005 RCT Sponsored by Anika Therapeutics, Inc. No mention of COI.	9.0	N = 372 with osteoarthritis of the knee, Grade 2 or 3 osteoarthritis on Kellgren and Lawrence scale rated via radiograph; mean (SD) age 58.4 (8.9) for O4 group, 58.9 (8.9) for O3A1 group,	O4 Group receiving 4 HMW hyaluronan injections (n = 128) vs. O3A1 Group receiving 3 HMW hyaluronan injections and one control arthrocentesis procedure (n = 119) vs. A4 Group receiving 4 control arthrocentesis procedures (n = 123). Assessments at baseline, 1 week, 2, 3, 8, 12, 16, 22, and 28 weeks after injections.	There was no significant difference between groups for WOMAC pain scores, Investigator Global Score, Pain on standing scores, and Patient Global score during assessments.	“[O]ur data demonstrate that high molecular weight hyaluronan (Orthovisc®) is a safe product for treatment of knee osteoarthritis. These data indicate that Orthovisc® seems to be effective in reducing the pain and symptoms associated with OA of the knee using a series of 3 or 4 injections. The potential benefit for	High molecular weight HA in higher frequency per weekly injections did not significantly improve WOMAC pain scores when compared to less frequent injections of same HA

		and 59.1 (8.3) for A4 group.			clinically significant pain reduction using Orthovisc® outweighs the potential risk of a low rate of minor adverse effects.”	preparation or compared to placebo. Study showed strong placebo response.
Khanasuk 2012 RCT No sponsorship or COI.	8.5	N = 32 with primary OA having a Grade 2 on Kellgren-Lawrence criterias. No intra-articular injections within 1 year; mean age: Group 1: 65.1 ± 9.6, Group 2: 67 ± 9.5.	Group 1 received intra-articular injections of Hylan G-F 20 (n = 16) vs. Group 2 received intra-articular injections of Hyaluronic acid (n = 16). Follow up at baseline, 1, 4, 8, 12, and 26 weeks after injection	Based on VAS, WOMAC, and SF-36 scores, no significant difference in results between both groups. However, in both groups there was significant improvement between baseline and week 26 in WOMAC scores (p < 0.01) and VAS (p < 0.01). SF-36 scores did not deviate significantly from baseline at week 26 follow up.	“At the follow-up of 26 weeks, the intraarticular injection of a single 6-ml Hylan G-F 20 and a single 6-ml of HA in patients with primary osteoarthritis of the knee resulted in similar improved clinical outcomes, in terms of significant pain reduction of VAS during walking and WOMAC scores without adverse event.”	Both HA products showed similar results although Hylan G-F 20 is about double the cost of the other HA products. Relatively small sample size.
Maheu 2011 RCT No mention of sponsorship. COI, E. Maheu received honoraria for designing and conducting this trial as co-investigator, M. Zaim is an employee of Institut de Recherche Pierre Fabre, and F. Berenbaum serves as a consultant to and receives research support	8.0	N = 279 with knee osteoarthritis in the medial lateral femorotibial area for >6 months, VAS pain score >40mm, Lequesne index score >7, Grade 2 or 3 osteoarthritis on Kellgren and Lawrence scale rated via radiograph at least 12 months prior, ages 50-75; mean (SD) age 64.54 (7.13) for F60027 group and 63.00 (6.63) for Hylan G-F20 group.	Hylan G-F 20 “Synvisc” group receiving 3 2mL injections containing 16mg (n = 140) vs. F60027 “Structovial” group receiving 3 2mL injections containing 20mg of sodium hyaluronate (n = 139). Assessments at baseline, 6, 12, 18, and 24 weeks.	No statistically significant differences reported between two groups during assessments for mean Lequesne total index, VAS global pain, SF12 physical and SF12 mental scores.	“[I]n this trial there was no clinical difference with respect to efficacy on knee OA symptoms between a “medium” MW HA, F60027 and a “high” MW HA, Hylan G-F20. It can be concluded that both HA are clinically effective in reducing symptoms, and safe in the treatment of knee OA, and that higher MW HA preparations are probably not superior to lower MW compounds.”	Comparing F60027 vs G-F20 did not demonstrate one HA preparation was better than the other implying that high molecular weight HA is no better or worse than medium weight HA in knee OA patients.

from Pierre Fabre Laboratories						
McDonald 2000 RCT No mention of sponsorship or COI.	4.0	N = 270 with osteoarthritis (OA) of the knee. Age not reported.	Study device - Intra-articular Sodium Hyaluronate (HA) viscosupplement called Fermathron (n = 127) vs. Comparator device - Previously marketed source of HA obtained from rooster combs (n = 129). Follow-up at 1, 2, and 3 months or at visits 7 to 9.	Both groups showed significant reduction in Lequesne Index score in visits 2-9 compared to baseline (p <0.0001). There was no significant difference between groups at final visit (study vs. comparator) 6.91 vs. 6.36 (p >0.05) for LI score. Likewise, VAS pain score showed no significant difference between groups at any follow up point throughout study, and at final follow-up; 25.4 vs. 24.6 (p >0.05).	“The current study indicates a similar safety profile for the two products with both of them being well tolerated.”	Sparse baseline data. Fermathron compared to traditional HA showed no significant differences in efficacy or safety between products for knee OA.

INTRAARTICULAR GLUCOCORTICOSTEROID INJECTIONS

Intraarticular glucocorticosteroid injections are frequently performed to attempt to deliver anti-inflammatory medication to the joint with minimal systemic effects.(1336, 1337, 1383, 1390, 1436, 1476-1484) Their usual purpose is to gain sufficient relief to either resume conservative medical management or to delay operative intervention. These injections are generally performed without fluoroscopic or ultrasound guidance. Intraarticular injections have also been utilized intraoperatively at the close of procedures, including meniscectomy and(1485) arthroscopy.(1486, 1487) Periarticular injections have been used in arthroplasty patients(1488) in an attempt to facilitate recovery.

1. **Recommendation: Intraarticular Glucocorticosteroid Injections for Knee Osteoarthritis**
Intraarticular glucocorticosteroid injections are recommended for the treatment of knee osteoarthritis especially for short-term control of symptoms.

Indications – Pain from osteoarthritis sufficient that control with NSAID(s), acetaminophen, weight loss or exercise is unsatisfactory.(1320, 1321, 1332, 1333)

Frequency/Dose/Duration – Only 1 injection should be scheduled to start, rather than a series of three. Medications used in RCTs were triamcinolone acetonide 40mg, triamcinolone hexacetonide 20mg, betamethasone 6mg, hydrocortisone 25mg, and methylprednisolone 80mg and 120mg).(1320, 1321, 1333) One trial used cortivazol 3.75mg.(1332) Anesthetics have most often been bupivacaine or lidocaine. Whether aspiration should be performed for effusions in osteoarthritis patients is unknown; however, there is quality evidence that aspiration of effusions prior to injection results in greater effectiveness for rheumatoid arthritis patients.(1489) Many trials included aspiration prior to injection. There is moderate evidence that a superomedial or superolateral approach is

superior to a lateral approach.(1434) Bed rest has been used after treatment in rheumatoid arthritis patients to theoretically reduce speed of systemic absorption; however, a moderate-quality trial demonstrated no difference and there is no reason to believe the results would be different in osteoarthritis patients.(1323, 1324) Thus, post-injection bed rest is not recommended. There is no evidence to suggest limiting the number of injections, and a high-quality trial found both evidence of efficacy of glucocorticoid injections compared to placebo and no evidence of accelerated osteoarthritis when injected 4 times a year for 2 years.(1320) Multiple doses have been utilized in trials with no head-to-head comparisons of dosing regimens. Comparative trials have suggested methylprednisolone acetate 40mg is superior to triamcinolone hexacetonide 20mg, which is superior to betamethasone 6mg.(1490, 1491) However, those results have not been replicated. Another comparative clinical trial found greater efficacy for methylprednisolone 80mg over 40mg for the hip joint.(1482)

Indications for Discontinuation – A 2nd glucocorticosteroid injection is not recommended if the 1st has resulted in significant reduction or resolution of symptoms. If there has been no response to a 1st injection, there is less indication for a second. If it is believed that the medication was not well placed and/or if the underlying condition is so severe that 1 steroid bolus could not be expected to adequately treat the condition, a 2nd injection may be indicated. In patients who demonstrates a pharmacologically appropriate response consisting of several weeks of temporary, partial relief of pain, but who then have worsening pain and function and who are not (yet) interested in surgical intervention, a repeat steroid injection is an option. Benefits beyond approximately 4 injections per year are not thought to exist.(1320) Patients requesting more injections should have reassessment of conservative management measures and be evaluated for irrigation/lavage and surgical intervention.

Strength of Evidence – **Recommended, Evidence (C)**

2. *Recommendation: Intramuscular Glucocorticosteroid Injections for Knee Osteoarthritis*
There is no recommendation for or against the use of intramuscular glucocorticosteroid injections for the treatment of knee osteoarthritis.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

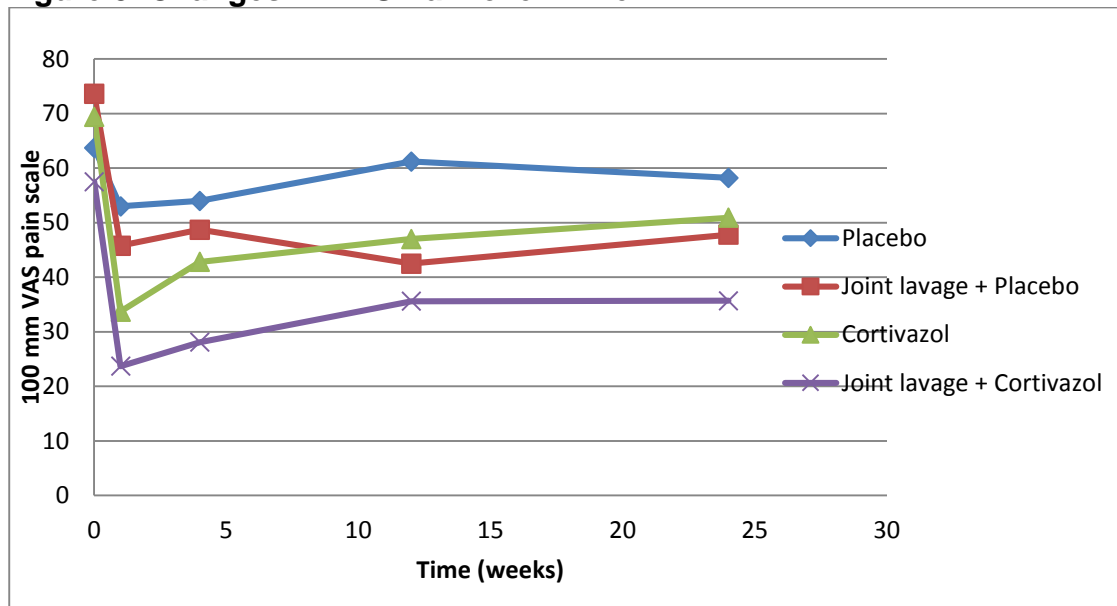
Rationale for Recommendations

There are high- and moderate-quality RCTs evaluating efficacy of glucocorticosteroid injections compared to placebo for treatment of knee OA(1341, 1492-1496) (see also Figure 3). These have uniformly found efficacy (however, the magnitude and duration of benefits is modest thus the reduction in the evidence based rating to “C”).(1320, 1321, 1325, 1332) There is moderate-quality evidence that tidal irrigation appears more effective for treatment of osteoarthritis in every trial that has compared these procedures(1331-1333) and there is evidence a that combination of tidal irrigation plus glucocorticosteroid injection is superior to either alone.(1332, 1333) Moderate-quality evidence suggests intraarticular injection is more effective for treatment of rheumatoid arthritis than intramuscular injection,(1322) although there is not quality evidence for osteoarthritis patients. Thus, there is no recommendation for intramuscular injections for osteoarthritis patients. Three moderate-quality trials have suggested viscosupplementation is superior to glucocorticoid injection,(1384, 1386, 1388) although the degree of benefits do not appear large.

Intraarticular glucocorticosteroid injections are invasive, have a low risk of adverse effects, are moderately costly, have evidence of short- to intermediate-term efficacy, and are recommended

for treatment of osteoarthritis patients, particularly after inadequate results from NSAIDs, acetaminophen, exercise, or other non-invasive interventions.

Figure 3. Changes in VAS Pain over Time



Adapted from Ravaut P, Moulinier L, Giraudeau B, et al. Effects of joint lavage and steroid injection in patients with osteoarthritis of the knee: results of a multicenter, randomized, controlled trial. *Arthritis Rheum.* 1999;42(3):475-82.

Evidence for the Use of Intraarticular Glucocorticosteroid Injections

There are 5 high- and 26 moderate-quality RCTs or crossover trials incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Corticosteroid Injection vs. Placebo						
Raynauld 2003 RCT	9.0	N = 68 age 40-80 with knee OA (ACR criteria), at least Grade 2 or 3 on KL scale, had symptomatic knee OA requiring treatment, and not responded adequately to treatment with acetaminophen or a traditional NSAID	IA steroid group (n = 34) who received IA injections of triamcinolone acetonide 40mg (1 cc) in affected knee every 3 months. IA saline group (n = 34) who received an injection of saline (1 cc) in affected knee every 3 months. Additional injections not allowed. Trial period 2 years.	Patients assessment of change in VAS pain at night after one year: steroid - 10.7±18.3 vs. 2.6±21.2, p = 0.08. Changes in knee pain at night, area under curve analysis, p = 0.0047 favoring steroid. AUC analysis borderline for knee stiffness (p = 0.051). Range of motion also favored steroid at 1 year (4.40±3.6 vs. 2.70±3.3), p = 0.05. AUC analysis favored steroids for night pain and stiffness. No differences in joint space measurements.	"[N]o significant deleterious effects of the steroids on the anatomical joint structure were seen in this study. This finding suggests that repetitive IA steroid injections appear to be safe. Moreover, the long-term use of IA injections of triamcinolone acetonide afforded relief of some of the symptoms of knee OA, including pain and stiffness."	Longer term study of glucocorticoids. Suggests no long term adverse effects of glucocorticoids including joint space narrowing. Data suggest steroid injection superior to saline and effective Q3 months over 2 years.

Hasso 2004 RCT	9.0	N = 38 with recurrent or persistent knee inflammation in the absence of generalized peripheral joint inflammation	Group 1 (n = 20) received 20mg IA MTX (methotrexate) plus 20mg TH (triamcinolone hexacetonide). Group 2 (n = 18) 20mg of TH. Both injections diluted with 2mL of 2% lidocaine. Assessments at baseline, Weeks 1, 6, 12, and 24 after injection.	No statistically significant difference between two groups at any time periods.	"We conclude from these results that, in the context of this study design, the addition of 20 mg MTX to TH did not enhance or prolong the effect of corticosteroid."	Exclude non-occupational patients. Mostly RA. Data suggest methotrexate of no additive benefit.
Ravaud 1999 RCT	8.5/7.5	N = 98 meeting ACR criteria for knee OA at least KL Grade II	Four groups: Group 1 (aspiration and intraarticular joint injection, n = 25, cortivazol 3.75 mg in 1.5 mL vs. Group 2 (aspiration plus placebo intraarticular injection 1.5mL NS, n = 28) vs. Group 3 (Joint Lavage 1L NS and IA placebo after aspiration, n = 21) vs. Group 4 (Joint lavage and IA corticosteroid as in group 1 after aspiration, n = 24); 24 weeks follow-up.	Baseline VAS score lower in joint lavage plus IA corticosteroid group (57±18) than other groups (IA placebo: 64±21, IA corticosteroid: 69±16, joint lavage plus placebo: 74±22), p = 0.04. No interaction between steroid injection and joint lavage. Statistically significant effect of lavage at 24 weeks (p = 0.02), whereas effect of steroid not significant. A 2-way ANOVA showed corticosteroid injection associated with decrease in pain at Week 1 (p = 0.003) and Week 4 (p = 0.020) in contrast, lavage showed a significant decrease in pain at Week 4 (p = 0.024), 12 (p = 0.011), and 24 (p = 0.020).	"[W]e found that IA injection of cortivazol and joint lavage, both alone and in combination, afforded improvement in pain but not in functional impairment in knee osteoarthritis. The effects of these 2 treatments over time differed, with a longer effect of joint lavage compared with IA corticosteroid injection."	Scores are 8.5 for corticosteroid injection and 7.5 for lavage which is not blinded. Data suggest intraarticular steroid injection more effective than placebo. Data also suggest lavage effective. Both result in superior results to either alone.
Wang 1998 RCT	7.0	N = 60 with ASA physical status I - III, aged 35-65 yr, with osteoarthritis (chronic degenerative arthritis) of knee, and scheduled for elective	Group 1 (n = 30) triamcinolone acetone 10mg in isotonic saline 20mL. Group 2 (n = 30) received 20mL of isotonic saline. At end of arthroscopic surgery but before arthroscope as removed, test solution administered. Post-	From 6 to 24 hours, Group 1 had lower pain scores than Group 2. Survival curve different from Group 2 (p < 0.01). In Group 1 and 2, 21% and 61% respectively, required rescue analgesia 0-24 hours post-op (6 of 29, 17 of 28, p < 0.01, Chi-Squared	"[I]ntraarticular triamcinolone acetone provides a valuable local therapy for acute joint pain after arthroscopic knee surgery. Patients who received triamcinolone acetone reported less pain and requested less rescue analgesia."	Blinding not well described. Short study (24 hours). Unclear procedure.

		arthroscopic knee surgery	op pain assessed by visual scale for 2 hour intervals for 24 hours after surgery except when sleeping.	Test). From 6 to 24 hours, none in Group 1, compared with 53% (15 of 28) in Group 2 requested rescue analgesia.		
Koyonos 2009 RCT	6.5	N = 58 (59 knees) who were between 18 and 65 years old, had to have an arthroscopic meniscectomy with confirmed chondral changes	Group 1 (n = 30 knees) received injection of 1mL 0.9% normal saline plus 9mL 1% lidocaine. Group 2 received injection of 1mL (40mg) DepoMedrol plus 9mL 1% lidocaine. Evaluations at pre-op, 6 weeks, 6 months, 9 months, and 12 months.	Group 1 scores higher at 6 weeks in KOOS Sport (Group 1: 29±24, Group 2: 50±26, p = 0.005), KOOS QOL (Group 1: 41±19, Group 2: 55±24, p = 0.035), and IKDC (Group 1: 49±16, Group 2: 59±20, p = 0.01). At later time points, no differences in 2 groups.	"In patients with OA of the knee, who are inherently at greater risk for poorer outcomes following meniscectomy, adding an intra-articular corticosteroid injection to postoperative care is safe and effective at decreasing pain and improving function for the first 6 weeks after surgery."	Data suggest short term benefit of adding glucocorticoid injection after meniscectomy if knee OA.
Dieppe 1980 2 RCTs	6.0	N = 48 joints with knee OA	Study 1: triamcinolone hexacetonide 20mg in 1 knee vs. saline in other knee; 6 weeks follow-up. Study 2: 1 or both knees with effusions of 16 (24 knees) treated. Crossover trial of saline vs. steroid (not specified, but possibly THA 20mg).	Study 1: Pain VAS pre 8.2±1.9 then placebo 7.0±3.0 vs. steroid 3.8±2.9, p<0.05. Study 2: VAS pain for placebo first, VAS pain before 8.2±1.9, then placebo 7.0±3.0 vs. steroid 3.8±2.9.	"[P]atients with OA of the knee and effusions respond transiently to intra-articular steroid therapy."	Data suggest efficacy.
Jones 1996 Crossover Trial	5.5	N = 59 with knee OA (ACR)	Methylprednisolone acetate 40mg vs. saline. Crossover to other arm at 8 weeks. Aspirated before injection. 8 weeks follow-up each arm.	Thirty patients favored steroid vs. 14 placebo (p <0.001).	"Intra-articular corticosteroids are effective for short term relief of pain in osteoarthritis but predicting responder is not possible."	Data suggest steroid effective.
Young 2001 RCT	5.0	N = 40 with 41 knees with symptomatic knee OA clinically assessed at time of initial arthroscopy and 2nd arthroscopy	Methylprednisolone acetate 120mg intraarticularly (n = 20) vs. NS placebo (n = 20). Assessments arthroscopically at initial and 1 month; 1 month follow-up.	Pre-treatment: no difference between methylprednisolone acetate and placebo. Posttreatment: Small reduction in CD68+ in methylprednisolone acetate (30%) vs. placebo group (p = 0.048). Data also support efficacy of injection by WOMAC scores.	"[T]he administration of intraarticular glucocorticoids was associated with a small reduction in CD68+ macrophage infiltration in the synovial lining but not the synovial sublining layers in human OA synovial membranes. There was no effect on the expression of	Experimental study regarding biomarkers. Data suggest glucocorticoid injections largely do not affect inflammatory mediators studied.

					MCP-1, MIP-1 α , MMP-1, MMP-3, TIMP-1, or TIMP-2. The observations from this study suggest that intraarticular glucocorticoids do not influence the expression of some of the important mediators of cartilage destruction in OA.”	
Miller 1958 RCT	5.0	N = 202 with knee OA	10mL injections every other week for 5 injections with 1) Lactic acid solution N/3 0.2mg, novocaine HCl 2.0gm NS 55mL distilled to 100mL vs. 2) Novocaine HCl 2.0gm, NS 55mL, distilled to 100mL vs. 3) NS vs. 4) hydrocortisone 25mg, 10ml, vs. 5) mock injection. 6 months follow-up.	At 6 weeks, percentages of patients felt improvement were (numbers 1-5): 88.2% vs. 91.9% vs. 77.8% vs. 83.8% vs. 81.1%. Objective assessments for men were: 91.7% vs. 91.0% vs. 72.7% vs. 81.8% vs. 85.7%. Objective assessments for women were 63.6% vs. 76.9% vs. 72.0% vs. 69.2% vs. 56.5%:	“The results of this inquiry show that the behavior of a joint may be influenced by intra-articular injections....there is no significant difference in the effects of the three therapeutic agents investigated.”	Score reflects blinded aspects of the study, rather than mock injection. Study score may underestimate quality. Suspected to be RCT, though randomization not clear; still had double blinding. Data suggest saline inferior for men. Low dose steroid used may have impacted results.
Friedman 1980 RCT	5.0	N = 34 with knee OA	Triamcinolone hexacetonide 20mg vs. vehicle without steroid.	Decreased pain in 88% steroid vs. 71% placebo. Only difference at Week 1, p <0.005, after which non-significant differences.	“Because the additional pain relief afforded by the steroid was temporary and the possible deleterious effects of intraarticular steroids are still debated, their judicious use of OA is advised.”	Small sample size. Many details sparse. Data suggest minimal benefit of steroid lasting one week.
Gaffney 1995 RCT	4.0	N = 84 with clinical and radiographic evidence of knee OA	Group 1 (THA, n = 42) with intra-articular triamcinolone hexacetonide 20mg vs. Group 2 (Placebo, 1mL NS, n = 42). VAS scale, walking distance (WD), and health assessment questionnaire (HAQ) recorded at baseline, weeks 1 and 6.	Group 1 and 2 with improvement in VAS at week 1 (Group 1: 21.7 \pm 20.7, p < 0.001, Group 2: 43.1 \pm 28.7, p < 0.05) and Week 6 (Group 1: 35.8 \pm 26.8, p < 0.01, Group 2: 42.9 \pm 26.0, p < 0.01). Only Group 1 demonstrated an improvement in WD at Week 1 (Group 1: 50.7 \pm 15.4, p <	“We suggest that a trial of intra-articular THA therapy should be considered in knee OA, and may be a useful adjunct to other therapies. This is particularly true of the elderly population, in whom knee OA is a source of considerable pain and disability and therapeutic options	Sparse details. Short term trial without intermediate or longer results. Data suggest early efficacy.

				0.001) and both groups improved at Week 6 (Group 1: 50.8±15.4, p < 0.001, Group 2: 51.6±14.5, p < 0.01). Only Group 1 demonstrated an improvement in HAQ at Week 1 and 6.	are often extremely limited.”	
Cederlof 1966 RCT	4.0	N = 44 with 44 knees and 51 injections for knee OA, x-ray c/w OA but not severe, over 40 years old, pain at least 2 months. ESR<16mm/hour	Prednisolone acetate 25mg vs. saline after aspiration; 8 weeks follow-up.	Sparse data. At 3 weeks after injection, 19/26 in prednisolone vs. 20/25 in placebo were improved. At 8 weeks, 17/26 vs. 19/25.	“The study afforded no support for the view that intraarticular injection of prednisolone acetate has more effect on the osteoarthritis knee than injection of physiologic saline solution.”	Many details sparse. Randomization not described. Unclear how additional injections incorporated or analyzed. Data suggest lack of efficacy, but low dose steroid used.
Comparison of Glucocorticosteroids						
Pyne 2004 RCT	6.5	N = 57 with knee OA (ACR)	Triamcinolone hexacetonide 20mg vs. methylprednisolone acetate 40mg after aspiration; 8 weeks follow-up.	VAS (0/weeks3/8): THA (66.0/33.1/58.4mm) vs. MPA (66.4/52.7/48.1mm). Lequesne index: THA (14.7/11.6/13.7) vs. MPA (15.0/12.7/12.5).	“(Triamcinolone hexacetonide) is more effective than (methylprednisolone acetate) at week 3, but its effect is lost by week 8. MPA still has an effect at week 8.”	Randomization not well described and cointerventions not controlled. Data suggest comparable efficacy, however also suggest duration of benefit may be modestly longer for methylprednisolone acetate at these doses. Only 8 weeks follow-up duration somewhat inhibits drawing conclusions.
Valtonen 1981 RCT	4.5	N = 42 with knee OA.	Triamcinolone hexacetonide 20mg vs. betamethasone 6mg.	Sparse data provided. Effect of triamcinolone superior at Week 1 (p <0.005). Patients without need for reinfection or other therapy favored triamcinolone over 6 months.	“The results confirm that intra-articular treatment of osteoarthrosis with TH is a highly effective treatment and provides a significantly prolonged duration of effect compared to BM. Therefore, TH is the preferred alternative in the treatment of many patients suffering from osteoarthrosis.”	Some details sparse. As article from 1981, score likely understates quality of trial. Data suggest triamcinolone hexacetonide has faster onset.
IA Corticosteroids vs. Other Treatments						

Caborn 2004 RCT	6.5	N = 215 with knee OA (ACR), Kellgren/Lawrence grade ≥ 2 , (duration ≥ 3 months), VAS pain 50-90/100mm	Hylan G-F 20, 3x2mL weekly injections (n = 113) vs. Triamcinolone Hexacetonide 40mg (n = 102); 26 weeks follow-up.	14% of steroid group quit because of unsatisfactory efficacy vs. 0%. Week 12 hylan patients had greater improvement than steroid group WOMAC: 0.9 ± 0.1 vs. 0.5 ± 0.1 , $p = 0.0071$. Week 12 VAS score: 31.3 ± 2.3 vs. 17.4 ± 2.41 , $p < 0.0001$.	"Viscosupplementation with HG-F 20 resulted in a longer duration of effect than TH with a comparable tolerability profile. These data support the preferential use of HG-F 20 over TH for treatment of chronic OA knee pain."	High dropouts, especially for steroid. Data suggest viscosupplementation superior.
Leopold 2003 RCT	6.5	N = 100 with knee OA and insufficient results from variable treatment including NSAIDs, braces, PT, excluded bone on bone	Hylan GF20 16mg 3 weekly injections vs. betamethasone sodium phosphate 2mL (dose not specified) plus 4mL bupivacaine plus 4mL lidocaine (doses not specified); 6 month follow-up.	WOMAC median scores (baseline/3/6 months): steroid (55/42/40) vs. Hylan GF20 (54/41/44). Knee Society Rating System: steroid (58/72/70) vs. Hylan (58/69/68). VAS mm: steroid (64/52/52) vs. Hylan (70/45/52).	"No differences were detected between patients treated with intra-articular injections of Hylan G-F 20 and those treated with the corticosteroid with respect to pain relief or function at six months of follow-up."	High dropouts in viscosupplementation group. Steroid dose not specified. Co-interventions not well described. Data suggest no meaningful differences. Post-hoc results suggest lower response rates in females.
Frizziero 2002 RCT	5.0	N = 99 with knee OA (ACR, KL grades I-III) either primary or secondary to trauma	Intra-articular hyaluronic acid 20mg weekly for 5 weeks or methylprednisolone acetate weekly for 3 weeks; 180 days follow-up.	Arthroscopic improvements found in femoral condyles grades of 43% HA vs. 16% steroid. Medial tibial plateaus for 27% vs. 12%. Patella also favored HA (57% vs. 20%). VAS data suggest more rapid onset of pain relief with steroid, though non-significant higher pain rating in steroid Day 180.	"This study supports previous data on a potential structure-modifying activity of HA in OA of the knee."	Data suggest viscosupplementation superior to steroid.
Shimizu 2010 RCT	4.5	N = 61 with knee OA, age ≥ 60 , tibiofemoral and/or patellofemoral joint pain, hydroarthrosis, KL Grade 2 or 3	Sodium hyaluronate 25mg 5 weekly injections vs. decadron 4mg injection; 6 month follow-up.	Pain scores (baseline/5 weeks/6 months): HA ($6.3 \pm 1.0/3.7 \pm 1.4/1.9 \pm 1.7$) vs. CS ($6.4 \pm 1.0/3.4 \pm 1.4/2.0 \pm 1.9$). VAS scores: HA (69.0/37.4/21.5) vs. CS (68.0/35.2/22.6).	"Both Na-HA and CS intra-articular injection therapies...exerted favorable clinical effects. Considering the results of the measurements of biomarkers, compared with CS injection therapy Na-HA injection therapy may exert protective effects on the articular cartilage by increasing the HA concentration in synovial fluid as well as inhibitory effects on the	Randomization not well specified. No blinding. Co-interventions not controlled. Data suggest comparable efficacy and no meaningful differences including in joint biomarkers, though may be underpowered for biomarkers.

					catabolism of articular cartilage by reducing the MMP-9 concentration.”	
Leardini 1991 RCT	4.5	N = 40 with knee OA	Three weekly injections of sodium hyaluronate 20mg vs. 6-methylprednisolone acetate 40mg intraarticular; 60 days follow-up.	Night pain no symptoms at day 21 in 11/19 HA vs. 3/16 MP, p<0.05 and at day 60 in 12/20 vs. 4/16, p<0.05. Rest pain, pain under load and touch pain all favored HA at day 60, p<0.01.	“[O]n a short-term basis, both HA and 6-MPA are efficacious in controlling the symptoms related to osteoarthritis disorders. In the long term assessment, some difference emerged between the two treatments, particularly on the 35th and 60th days when, in the HA-treated group, the results obtained at the end of treatment still persisted and in some cases had even improved.”	Data suggest viscosupplementation longer term superior to glucocorticosteroid.
Pietrogrande 1991 RCT	4.0	N = 90 with knee OA	HA 20mg 5 weekly injections vs. 6-methylprednisolone acetate 40mg, 3 weekly injections; 2 months follow-up.	VAS pain levels decreased over the trial and favored HA at 60 days (graphic data, p = 0.003). At end of trial, no/slight pain in 22.7%/47.7% HA vs. 13.3%/35.5% MP (p = 0.052).	“[B]oth treatments were efficacious...The steroid had a more rapid action, which did not, however, last as long as that of HA.”	Many details sparse including randomization and co-interventions. Data suggest HA resulted in longer benefits than steroid.
Lavage and Tidal Irrigation vs. IA Corticosteroid						
Ravaud 1999	See Corticosteroid Injection vs. Placebo above.					
Arden 2008 RCT	6.0	N = 150 age 40-90 years old with knee OA	Arthroscopic tidal irrigation (n = 71) with 10mL lignocaine 1% then up to 1L NS irrigation vs. glucocorticoid injection (n = 79) with triamcinolone acetate 40mg plus 2mL lignocaine 1%. Both groups then advised 48 hours bed rest; 26 weeks follow-up.	At baseline, Group 1 WOMAC total pain score 254±88 vs. Group 2, 247±97. No differences at Weeks 0, 2, and 4. At Week 12, Group 1 reported total pain of 79±106 vs. Group 2, 44±96. (p <0.05) At week 26, Group 1s WOMAC total pain score 75±114 vs. Group 2, 19±99 (p <0.01). Table and graphic data do not match. Both groups showed marked improvements in 50m walk, stair climbing, analgesics consumed with no	“CSI and TI both lead to substantial short-term pain relief in patients with knee OA and are well tolerated with few side effects. The benefits of CSI are most sustained in patients with milder radiographic OA and those with a clinically detectable effusion. The benefits of TI are more sustained than CSI, with the greatest additional benefit over and above CSI, seen in patients without a	Some baseline differences with higher rates of prior steroid injections in the steroid injection group (45.6% vs. 32.4%). Trend towards more severe disease in steroid group (K&L stages 3 and 4 20.3% vs. 11.3%). Data suggest tidal irrigation resulted in longer duration benefits.

				differences between groups at any point.	detectable knee effusion wand with more severe radiographic change. The benefits of TI need to be balanced against the increased time and resources required for this procedure.”	
van Oosterhout 2006 RCT	5.5/6.5	N = 75 who were a minimum of 18 years old with knee arthritis not due to gout, OA, or infection	Arthroscopic lavage with corticosteroid (ALC, n = 26) of methylprednisol one (80mg in 6mL) plus bupivacaine (30 mg in 6 mL) through inferior trocar vs. arthroscopic lavage plus placebo of bupivacaine (ALP, n = 23) vs. joint aspiration with administration of corticosteroid (JAC, n = 26) of methylprednisol one (80mg in 2 mL) plus bupivacaine (30 mg in 6 mL); 9 months follow-up.	Primary outcome measure event-free survival (time after treatment until local re-treatment, e.g., joint aspiration or injection, arthroscopy, or [radio]synovectomy due to recurrence or persistence of arthritis of knee). Median event-free survival time: 9.6 months after ALC; 3.0 months after JAC; 1.0 month after ALP. Relative risk of event during 9 months was 2.2 for JAC and 4.7 (95% for ALP compared with ALC. RR was 2.0 between ALP and JAC. Knee score (range 0-7) encompasses knee tenderness (0-3), knee swelling (0-3), patient VAS/100 (0-1). ALC had significant decrease after 1 month than ALP after 1 month (1.93 vs. 0.08; p <0.01) and 3 months (1.63 vs. 0.86, p <0.04) in knee score.	“ALC offers superior therapeutic benefit in patients with arthritis of the knee in comparison with arthroscopic lavage alone or JAC...ALC is well tolerated, safe, and effective and can be considered a valuable alternative for the local treatment of patients with arthritis of the knee.”	Scores are 6.5 for lavage with/out steroid and 5.5 for joint aspiration as latter not blinded. Mostly RA patients. Data suggest arthroscopic lavage plus steroid injection superior to lavage plus placebo injection or joint injection alone.
Glucocorticosteroid: Lavage and Corticosteroid Injection vs. Corticosteroid Injection vs. Placebo						
Ravaud 1999	See Corticosteroid Injection vs. Placebo above.					
Kirkley 2008 RCT	8.5	N = 188 age 18 or older with idiopathic or secondary knee OA	Surgical lavage with optimized physical and medical therapy vs. arthroscopic debridement with optimized physical and medical therapy vs. treatment with physical and medical therapy alone.	Mean±SD WOMAC score after 2 years for surgery group was 874±624 vs. 897±583 for control group (absolute difference [surgery-group score minus control-group score], -23±605; p = 0.22. SF-36 Physical Component Summary scores 37.0±11.4 and 37.2±10.6, respectively; p = 0.93.	“Arthroscopic surgery for osteoarthritis of the knee provides no additional benefit to optimized physical and medical therapy.”	Data suggest arthroscopic surgery not successful for treatment of OA.
van Oosterhout 2006	See Lavage and Tidal Irrigation v. IA Corticosteroid above.					

Intraarticular vs. Intramuscular Corticosteroid Injection						
Konai 2009 RCT	8.0	N = 60 RA ≥6 months, ACR functional class II or class III, VAS knee pain >5, stable doses of oral corticosteroid for prior 30 days and stable doses of DMARDs for 3 months, and active synovitis in 1+knee for >30 days	Intra-articular injection (IAI) (n = 30) with triamcinolone hexacetonide 60mg plus xylocaine chloride 2% (1ml) and 1 intramuscular injection of 1ml xylocaine chloride 2% vs. intramuscular (IM) group (n = 30) with xylocaine intra-articular injection plus IM steroid injection; 12 weeks follow-up.	IAI better outcomes by many measures including: VAS for knee pain at 4 weeks (IAI: 2.6±2.3, IM: 4.1±2.9, p = 0.07), 8 weeks (IAI: 2.1±2.3, IM: 4.3±2.8, p = 0.036), and 12 weeks (IAI: 2.6±2.6, IM: 4.5±2.7, p = 0.002); and knee morning stiffness (at 1 week (IAI: 6.4±15.3, IM: 26.7±54.0, p = 0.037). IAI better response to VAS for knee edema than IM (p < 0.01) and also in parameter of improvement percentage (p <0.0001).	"Our results demonstrate that intraarticular injection with glucocorticoids is superior to its systemic use for the management of monoarticular synovitis in rheumatoid patients."	Study of rheumatoid arthritis patients. Study included due to potential interest in the comparison of administrative routes, although whether applicable to OA could not be assessed based on this study. Data suggest intraarticular injection superior to systemic administration.
Injection vs. Injection and Corticosteroid						
Christensen 2009 RCT	6.5	N = 76 males and non-pregnant females scheduled to undergo unilateral primary knee arthroplasty in age group 18-95 years old	One group (n = 39) injection of 80mg bupivacaine hydrochloride, 4mg morphine, 300µg epinephrine, 100µg clonidine, 750mg cefuroxime and NS without corticosteroid; 2nd group (n = 37) same combination plus 40mg methylprednisolone acetate. Assessed pre-op, 1st post-op day, day of discharge, and at 6 and 12 weeks.	All scores in both groups improved significantly after following total knee arthroplasty and continued to improve during early post-op, but no statistical difference in 2groups. Mean ± SD Knee Society function score (points) pre-op/6 weeks/12 weeks for no steroid vs. steroid: 29.6±15.9/38.3±23.1/48.2±28.2 vs. 34.7±20.4/42.0±27.1/56.5±27.	"[T]he results of this study suggest that the addition of a corticosteroid to intraoperative periarticular injections does not provide benefit when compared with injections that do not contain a corticosteroid."	Data suggest intraoperative steroid injection unhelpful for TKA.
Injection vs. Corticosteroid Injection						
Konai 2009	See Intra-articular vs. Intramuscular Corticosteroid Injection above.					
Intraarticular vs. Peripatellar Corticosteroid Injection						
Sambrook 1989 RCT	4.5	N = 38 with knee OA, mixture of medial compartment (16), patellofemoral (7), and both (12)	Peripatellar (4 injections around patellar margin, methylprednisolone acetate 80mg plus xylocaine 1%) vs. intraarticular injections (same dose plus	Pain on movement reduced with both (graphic data), however, better improvement at visit #4 in the peripatellar group.	"Peripatellar injection is an alternative method of local administration of corticosteroid which is highly effective in a proportion of patients."	Study states double blinding but techniques not same and many details sparse. Included mixture of patients who had or did not have patellofemoral disease. Yet, did

			xylocaine injection to midpoint of lateral patellar border); 3 months follow-up.			not randomize on that criterion and did not report stratified outcome results, thus study appears without use for evidence-based guidance.
Bed Rest vs. Normal Activity after Injection						
Weitoft 2005 RCT	4.0	N = 20 who met 1987 ACR criteria for RA and with signs and symptoms of knee synovitis requiring treatment with intra-articular glucocorticoids	Group 1 (rest group, n = 10) 24-hour bed rest post injection; Group 2 (mobile group, n = 10) 24-hour normal activity post injection. Injections 20mg triamcinolone hexacetonide (Ledespan®). Non-fasting serum samples collected immediately before injection, after 24 hours, 48 hours, 1 week, and 2 weeks.	No statistical differences between groups.	"[O]ur results suggest that intra-articular glucocorticoid treatment of knee synovitis may reduce cartilage breakdown. Furthermore, if immobilisation of the patient for a period of 24 hours is included in the injection protocol, the reduction in cartilage breakdown may be even more pronounced. Bone formation is temporarily inhibited by the glucocorticoid injection, and bone resorption is unaffected, independent of the immobilisation procedure."	Data suggest no differences, thus suggesting bed rest is unhelpful after injection.
Weitoft 2006 RCT	4.0	N = 20 with RA and clinical signs of knee synovitis	Patients randomly allocated to 24 hour post injection of intra-articular glucocorticoid to bed rest supervised in hospital (Group 1, n = 10) or normal activity without restrictions (Group 2, n = 10).	Nothing statistically significant to report	"[T]he interaction between the anti-inflammatory effects of IA glucocorticoids and the beneficial effects of short term joint rest need to be studied further."	Second report of Weitoft 2005
Synovial Fluid Aspiration and IA Corticosteroid Injection vs. IA Corticosteroid Injection						
Weitoft 2000 RCT	5.5	N = 147 (191 knees) meeting 1987 ACR criteria RA and with signs and symptoms of knee joint arthritis	Knees randomized by patient date of birth to arthrocentesis (n = 95) no arthrocentesis (n = 96) before 20mg triamcinolone	At the end of the study, 23% of the arthrocentesis group relapsed in comparison to the no arthrocentesis which had 47% of the group relapse (p = 0.001).	"The result of our prospective randomized study comparing a complete synovial fluid aspiration and intra-articular corticosteroid injection with injection alone	Excluded, as all RA.

		(heat, tenderness, swelling and effusion) were asked to participate	hexacetonide injected into inflamed knee joint. Knees in arthrocentesis group aspirated of as much synovial fluid as possible. In no arthrocentesis group, aspirated to confirm existence of effusion, but fluid not removed.		indicates, that the arthrocentesis reduces the risk for arthritis relapse in RA patients. We conclude that synovial fluid aspiration, though time consuming, should be included in the intra-articular corticosteroid injection procedure.”	
Radiation Synovectomy vs. Intra-articular Glucocorticoids						
Jahangier 2005 RCT	7.5	N = 97 with arthritis in knee despite at least 2 IA injections of GCs and persists at least 4 weeks after last injection; clinical evaluations performed at study entry, hospital discharge, Week 6, and 3, 6, 12, and 18 months.	Group 1 (n = 57 knees) received IA treatment with 185 MBq (5 m Ci) of 90Y citrate and 20mg of triamcinolone hexacetonide. Group 2 (n = 56 knees) received a placebo of yttrium and 20 mg of triamcinolone hexacetonide.	No statistically significant data when groups were compared to each other. Only when all knees treated were considered together, and not if analyzed separately for each treatment group, was the clinical effect at 6 months predicted by Steinbrocker functional status (r = -2.0, p = 0.01) and by the radiologic status (logistic regression analysis, r = -0.7, p = 0.04) at study entry.	“RSO of the knees using 90Y plus GCs is not superior to treatment with IA GCs alone, since both therapies, which were followed by 3 days of bed rest and splinting in the hospital, resulted in a response rate of ~50%.”	Blinding not well defined. Included some who apparently had already had had the procedure.
Jahangier 2006 RCT	6.0	N = 68 who volunteered to have a synovial biopsy, arthritis persistent despite at least 2 IA GC injections, and ongoing for 4 weeks since last GC injection; clinical assessment done after 6 months	Group 1 (n = 37 knees) received IA treatment with 185 MBq (5m Ci) of 90Y citrate and 20 mg of triamcinolone hexacetonide. Group 2 (n = 29 knees) received a placebo of yttrium and 20mg of triamcinolone hexacetonide.	Overall, only number of CD68+ macrophages in synovial sub-lining higher in responders (411±208) than non-responders (272±148). Responders had more plasma cells. Clinical effect correlated with total number of macrophages (r = 0.28, p = 0.03), number of macrophages in synovial sub-lining (r = 0.34, p = 0.005) and VCAM1 expression (r = 0.25, p = 0.04). Group 1, clinical effect showed correlation with number of synovial sub-lining macrophages (r = 0.34, p = 0.04) as well as number of plasma cells (r = 0.39, p = 0.02). Group 2, CCI correlated with total	“The clinical effect of intra-articular treatment either with 90Y and glucocorticoids or with glucocorticoids alone is related to macrophage infiltration of the synovium, regardless of the diagnosis. The underlying rheumatic disease did not affect the clinical effect, probably because patients had a comparable degree of synovial inflammation. This observation supports the view that both therapeutic regimens are especially successful in patients with	Data may only be generalized from patients with significant, marked synovial inflammation.

				number of macrophages (r = 0.43, p = 0.02) and number of synovial sub-lining macrophages (r = 0.41, p = 0.03).	marked synovial inflammation.”	
Methotrexate plus Glucocorticosteroid vs. Glucocorticosteroid						
Hasso 2004	See Corticosteroid Injection vs. Placebo above.					

TIDAL KNEE JOINT IRRIGATION

Large-volume irrigation of the knee joint has been used for treatment of knee osteoarthritis.(1331-1333) Intraarticular glucocorticosteroid injections are frequently given simultaneously. This procedure may be performed in conjunction with arthroscopy, although it has also been performed without arthroscopy.

Recommendation: Tidal Knee Joint Irrigation for Knee Osteoarthritis

There is no recommendation for or against the use of tidal knee joint irrigation for the treatment of knee osteoarthritis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are three moderate-quality RCTs comparing the efficacy of tidal irrigation to glucocorticosteroid injection for treatment of knee OA, with all 3 trials finding evidence of superiority of irrigation to injection.(1331-1333) However, there are no sham controlled trials. Two of the trials comparing the two procedures found superiority for patients undergoing irrigation followed by glucocorticoid injection(1332, 1333). These procedures are invasive, have adverse effects, are moderate to high cost, but sham-controlled trials are lacking, and therefore, there is no recommendation for or against tidal irrigation.

Adjunctive treatment with glucocorticosteroids after lavage has been assessed in many studies with mixed results. Both the highest quality study(1334) and the largest trial(1335) were largely negative. However, other trials suggest modest benefit. Thus, adjunctive treatment may be reasonable as the joint is already accessed, however considerable benefits should not be expected.

Evidence for the Use of Tidal Knee Joint Irrigation

There are 2 high- and 3 moderate-quality RCTs incorporated into this analysis.

Author/Title Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Lavage and Tidal Irrigation vs. IA Corticosteroid						

Ravaud 1999 RCT	8.5/7.5	N = 98 meeting ACR criteria for knee OA at least KL Grade II	Four groups. Group 1 (aspiration and intraarticular joint injection, n = 25, cortivazol 3.75 mg in 1.5 mL vs. Group 2 (aspiration plus placebo intraarticular injection 1.5mL NS, n = 28) vs. Group 3 (Joint Lavage 1L NS and IA placebo after aspiration, n = 21) vs. Group 4 (Joint lavage and IA corticosteroid as in group 1 after aspiration, n = 24). 24 weeks follow-up.	Baseline VAS score lower in joint lavage plus IA corticosteroid group (57±18) than other groups (IA Placebo: 64±21, IA Corticosteroid: 69±16, Joint Lavage plus placebo: 74±22), p = 0.04. No interaction between steroid injection and joint lavage. Statistically significant effect of lavage at 24 weeks (p = 0.02), whereas effect of steroid not significant. A 2-way ANOVA showed corticosteroid injection associated with decrease in pain at Week 1 (p = 0.003) and Week 4 (p = 0.020). In contrast, lavage had significant decrease in pain at Week 4 (p = 0.024), Week 12 (p = 0.011), and Week 24 (p = 0.020).	“[W]e found that IA injection of cortivazol and joint lavage, both alone and in combination, afforded improvement in pain but not in functional impairment in knee osteoarthritis. The effects of these 2 treatments over time differed, with a longer effect of joint lavage compared with IA corticosteroid injection.”	Scores are 8.5 for corticosteroid injection and 7.5 for lavage which is not blinded. Data suggest intraarticular steroid injection more effective than placebo. Data also suggest lavage effective. Both result in superior results to either alone.
Arden 2008 RCT	6.0	N = 150 age 40-90 with knee OA	Arthroscopic tidal irrigation (n = 71) with 10mL lignocaine 1% then up to 1L NS irrigation vs. glucocorticoid injection (n = 79) with triamcinolone acetonide 40mg plus 2mL lignocaine 1%. Both groups then advised 48 hours bed rest; 26 weeks follow-up.	At baseline, Group 1 WOMAC total pain score 254±88 vs. Group 2, 247±97. No differences Weeks 0, 2, 4. At Week 12, Group 1 reported total pain of 79±106 vs. Group 2 44±96. (p < 0.05) At week 26, Group 1's WOMAC total pain score was 75±114 vs. Group 2 19±99. (p < 0.01). Table and graphic data do not match. Both groups showed marked improvements in 50m walk, stair climbing, analgesics consumed with no differences between the groups at any point.	“CSI and TI both lead to substantial short-term pain relief in patients with knee OA and are well tolerated with few side effects. The benefits of CSI are most sustained in patients with milder radiographic OA and those with a clinically detectable effusion. The benefits of TI are more sustained than CSI, with the greatest additional benefit over and above CSI, seen in patients without a detectable knee effusion wand with more severe radiographic change. The benefits of TI need to be balanced against the increased time and resources required for this procedure.”	Some baseline differences with higher rates of prior steroid injections in the steroid injection group (45.6% vs. 32.4%). Trend towards more severe disease in steroid group (K&L stages 3 and 4 20.3% vs. 11.3%). Data suggest tidal irrigation more effective than glucocorticoid injection.
van Oosterhout 2006 RCT	5.5/6.5	N = 75 minimum 18 years old, with knee arthritis	Arthroscopic lavage with corticosteroid (ALC, n = 26) of methylprednisolone (80mg in 6mL) plus bupivacaine (30mg	Primary outcome measure event-free survival (time after treatment until local re-treatment. Median event-free survival	“ALC offers superior therapeutic benefit in patients with arthritis of the knee in comparison with arthroscopic lavage	Scores are 6.5 for lavage with/out steroid and 5.5 for joint aspiration as latter not

		not due to gout, OA, or infection	in 6mL) through inferior trocar vs. arthroscopic lavage plus placebo of bupivacaine (ALP, n = 23) vs. joint aspiration with administration of corticosteroid (JAC, n = 26) of methylprednisolone (80mg in 2mL) plus bupivacaine (30mg in 6mL); 9 months follow-up.	time 9.6 months after ALC, 3 months after JAC, 1 month after ALP. Relative risk of an event during 9 months was 2.2 (95% CI: 1.2-4.2, p=0.02) for JAC and 4.7 for ALP compared with ALC. RR 2.0 (95% CI: 1.1-3.8, p = 0.01) between ALP and JAC. Knee score (range 0-7) encompasses knee tenderness (0-3), knee swelling (0-3), patient VAS/100 (0-1). ALC had significant decrease after 1 month than ALP after 1 month (1.93 vs. 0.08) and 3 months (1.63 vs. 0.86) in knee score.	alone or JAC...ALC is well tolerated, safe, and effective and can be considered a valuable alternative for the local treatment of patients with arthritis of the knee.”	blinded. Mostly RA patients. Data suggest arthroscopic lavage plus steroid injection superior to lavage plus placebo injection or joint injection alone.
Lavage and/or Tidal Irrigation with vs. without Corticosteroid						
Smith 2003 RCT	9.0	N = 77 with knee OA (ACR) that required NSAIDs or analgesics	Arthroscopic lavage with vs. without methylprednisolone acetate 120mg. Arthroscopy included grading cartilage, synovial biopsy and rule out mechanical cause of symptoms (excluded 7 with meniscal tears); 24 weeks follow-up.	Percent achieving at least 30% pain reduction (2/4/ 8/12/24 weeks): steroid (68/66/61/47/39) vs. placebo (55/58/55/55/42%). VAS pain at rest: steroid (4.44/2.08/2.16/ 2.51/2.57/2.55) vs. placebo (3.80/2.47/2.44/ 2.87/2.52/2.59). WOMAC pain: steroid (10.34/6.25/6.22/6.81/ 7.25/8.17) vs. placebo (9.18/7.13/7.55/7.84/ 7.23/7.26).	“The response to intra-articular corticosteroids following joint lavage is short-lived (2-4 weeks), achievement of an OARSI response criterion being the only difference between the two groups.”	All patients had lavage. Data suggest minimal improvements in steroid over placebo with most results negative.
Frias 2004 RCT	5.5	N = 205 with 299 knees with OA (ACR, KL Grades II-III)	Joint lavage (3L NS, performed without arthroscopy) vs. lavage plus triamcinolone acetate 40mg; 3 months follow-up.	No differences between groups in effusion, crepitation, restricted motion, spontaneous pain, pain on pressure, pain on passive motion, pain on active motion at 1 or 3 months.	“[B]oth joint lavage alone and with infiltration with corticoids can be concluded as similarly effective for the symptomatic management of osteoarthritis of the knee.”	Patient blinding claimed but unclear as no placebo arm.

RADIATION SYNOVECTOMY

Radiation synovectomy has been used for treatment of patients with knee arthritis, although mostly among those thought to have an inflammatory component or undifferentiated arthritis.(1336, 1337)

Recommendation: Radiation Synovectomy for Knee Osteoarthritis

Radiation synovectomy is not recommended for the treatment of knee osteoarthritis.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

There is one moderate quality trial comparing radiation synovectomy with glucocorticoid injection with a radiation sham plus glucocorticoid that suggested radiation synovectomy was ineffective for treatment of undifferentiated arthritis and rheumatoid arthritis.(1336, 1337) Radiation synovectomy is invasive, has adverse effects, is moderately costly, appears ineffective, and is not recommended.

Evidence for the Use of Radiation Synovectomy

There are 2 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Radiation Synovectomy vs. Intra-articular Glucocorticoids						
Jahangier 2005 RCT	7.5	N = 97 with arthritis in knee despite at least 2 intraarticular injections of glucocorticoids , persisting at least 4 weeks after last injection	Group 1 (n = 57 knees) with 185 MBq (5 m Ci) of 90Y citrate plus 20 mg of triamcinolone hexacetonide vs. Group 2 (n = 56 knees) with placebo of yttrium and triamcinolone hexacetonide 20mg. Clinical evaluations at baseline, hospital discharge, Week 6, Months 3, 6, 12, 18.	No differences between groups at follow-ups. Percentage of knees successful (0, 6 weeks; 3, 6, 12, 18 months): Radiation plus steroid (58/65/64/48/49/44) vs. placebo radiation plus steroid (48/48/47/48/48/41), NS.	“RSO of the knees using 90Y plus GCs is not superior to treatment with IA GCs alone, since both therapies, which were followed by 3 days of bed rest and splinting in the hospital, resulted in a response rate of ~50%. ...Over the short term, both treatments appeared to be safe, with only minor adverse effects, although a possible direct, negative effect of 90Y on cartilage and bone cannot be ruled out... it seems that for persistent arthritis of the knee, RSO with 90Y is no longer the treatment of first choice.”	Blinding not well described. Included some who had already had the procedure. Data suggest radiation synovectomy ineffective for undifferentiated arthritis and RA.
Jahangier 2006 RCT 2nd report of study	6.0	N = 68 of above who agreed to synovial biopsy	Group 1 (n = 37 knees) vs. Group 2 (n = 29 knees) with details as above; 6 months follow-up.	Only CD68+ macrophages in synovial sub-lining higher in responders (411±208) than non-responders (272±148) (p = 0.002). Responders had more plasma cells than non-responders (p = 0.03). Clinical effect correlated with total number of macrophages (r = 0.28, p = 0.03), number of macrophages in synovial sublining (r = 0.34, p = 0.005) and VCAM1 expression (r = 0.25, p = 0.04). In	“The clinical effect of intra-articular treatment either with 90Y and glucocorticoids or with glucocorticoids alone is related to macrophage infiltration or the synovium, regardless of the diagnosis. The underlying rheumatic disease did not affect the clinical effect, probably because patients had a comparable degree of synovial inflammation. This observation supports the view that both therapeutic regimens	Second report of same study.

				Group 1, clinical effect showed a correlation with numbers of synovial sublining macrophages (r = 0.34, p = 0.04) and numbers of plasma cells (r = 0.39, p = 0.02). In Group 2, CCI was correlated with total number of macrophages (r = 0.43, p = 0.02) and number of synovial sub-lining macrophages (r = 0.41, p = 0.03).	are especially successful in patients with marked synovial inflammation.”	
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PROLOTHERAPY INJECTIONS

Prolotherapy injections attempt to address a theoretical cause or mechanism for chronic pain. This therapy involves repeated injections of irritating, osmotic, and chemotactic agents (e.g., dextrose, glucose, glycerin, zinc sulphate, phenol, guaiacol, tannic acid, pumice flour, sodium morrhuate) combined with an injectable anesthetic agent to reduce pain, into knee structures, especially knee and other ligaments, with the theoretical construct that it will strengthen these tissues.

Recommendation: Prolotherapy Injections for Acute, Subacute, or Chronic Knee Pain

Prolotherapy injections are not recommended for treatment of acute, subacute, or chronic knee pain.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

There is one moderate quality studies of prolotherapy injections compared to placebo for treatment of patients with knee OA.(1497) The data from that trial are largely negative. Prolotherapy injections are invasive, have adverse effects, moderately to highly costly, depending on numbers of injections, thus they are not recommended.

Evidence for the Use of Prolotherapy Injections

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Title Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Reeves 2000 RCT	6.5	N = 68 (111 knees) with 6 plus months pain and Grade 2 joint narrowing or Grade 2 osteophytes in any knee compartment; included ACL laxity, but not randomized on that factor	Three bimonthly injections of 9mL of 10% dextrose plus 0.075% lidocaine plus bacteriostatic water vs. injection with same solution without dextrose.	Pain at rest (baseline/6 months): prolotherapy (2.15/1.61) vs. control (2.73/1.69). Pain with walking: prolotherapy (3.94/2.56) vs. control (3.83/2.85).	“Prolotherapy injection with 10% dextrose resulted in clinically and statistically significant improvements in knee osteoarthritis.”	Control is hypotonic saline. How bilateral knees treated not discussed. ACL issue is potential confounder and not included in randomization. Data between groups not tested, but data as given mostly negative statistically.

BOTULINUM INJECTIONS

Botulinum injections have antinociceptive properties and have been used to produce muscle paresis.(1498-1501) These injections have primarily been used for non-occupational conditions such as cervical dystonia,(1502) strabismus, blepharospasm,(1503) and severe primary axillary hyperhidrosis.(1503, 1504) In the lower extremities, there are treatments that have been used mainly for children with spasticity due to cerebral palsy.(1505-1507) These injections are thought to directly treat a taut muscle band and to have analgesic properties.(1499-1501)

Recommendation: Botulinum Injections for Knee Osteoarthritis or Other Knee Disorders
There is no recommendation for or against the use of botulinum injections for knee osteoarthritis or other knee disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

These costly injections have resulted in deaths.(1508) There are other treatment strategies with documented efficacy.

Evidence for the Use of Botulinum Injections

There are no quality studies evaluating the use of Botulinum toxin A for treating knee osteoarthritis or other knee disorders.

AUTOLOGOUS BLOOD DONATION AND BLOOD TRANSFUSION

Autologous blood donation has been used to attempt to reduce risks of bloodborne pathogen transmission in the event a blood transfusion is required.(1509-1519)

1. *Recommendation: Pre-operative Autologous Blood Donation*

Selective use of pre-operative autologous blood donation is recommended.

Indications – Particularly consider in those older and in more fragile health for whom the threshold for transfusion (tolerable hemoglobin loss) is lower. Also to be considered among those with procedures anticipated to be more difficult and/or resulting in greater blood loss (e.g., revisions), and difficult to transfuse patients (e.g., many prior transfusions resulting in many antibodies).

Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – Low

2. *Recommendation: Intra-operative Autologous Blood Transfusion*

Selective use of intraoperative autologous blood transfusion is recommended.

Indications – Particularly to be considered in those older and in more fragile health for whom the threshold for transfusion (tolerable hemoglobin loss) is lower. Also to be considered among those with procedures anticipated to be more difficult and/or resulting in greater blood loss (e.g., revisions), and difficult to transfuse patients (e.g., many prior transfusions resulting in many antibodies).

Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – Low

Rationale for Recommendations

There are two moderate-quality trials that provide different approaches to the need for post-operative transfusions. One suggests pre-operative autologous blood donation is ineffective for hip arthroplasty.(1511) The other suggests intraoperative blood salvage is effective to reduce transfusion needs for knee arthroplasty.(1520) More transfusions are required for those who have donated blood pre-operatively and the costs are higher without measurable benefits. However,

there are certain clinical scenarios in which pre-operative autologous blood donation may be beneficial, and the patient's age and health status needs to be considered. Therefore, pre-operative autologous blood donation is recommended for selective use.

There is one moderate-quality trial indicating that intra-operative autologous blood transfusion is associated with less need for blood transfusion,(1520) and thus is recommended.

Evidence for Autologous Blood Donation and Blood Transfusion

There are 2 moderate-quality RCTs incorporated in this analysis. There is 1 low-quality RCT in Appendix 1.(1521)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Autologous Blood Donation Before Hip Arthroplasty						
Billote 2002	7.0	N = 96 patients scheduled for primary THR	Autologous blood donation (2 units, last donation at least 2 weeks before surgery) vs. no donation pre-arthroplasty. All treated with FeSO4 325mg BID.	Hemoglobin levels lower on admission (129±13g/ L vs. 138±12g/L, p <0.05) as well as different in recovery room; 54/54 (100%) non-donors no transfusions vs. 13/42 (31.0%) donors.	"Preoperative autologous donation provided no benefit for nonanemic patients undergoing primary total hip replacement surgery."	Results suggest autologous blood donation ineffective as conducted in this trial and costs were \$758 higher per patient for this population.
Thomas 2001 RCT	4.5	N = 231 total knee replacement (TKR) patients	Post-op wound drainage. Transfused if hemoglobin fell below present trigger after auto transfusion (Autologous/Cell salvage, n = 115) vs. Transfused if hemoglobin fell below pre-set trigger of 9g dl ⁻¹ (Allogeneic (homologous), n = 116). In both groups, hemoglobin measured on Days 1, 2, 3, 4, and 7.	No difference in length of stay and post-op mean hemoglobin between groups. Difference in incidences of allogeneic blood transfusion in cell salvage group (7%) vs. allogeneic group (28%) (p <0.001).	"[T]his type of surgery post-operative cell salvage is a safe and effective method for reducing allogeneic blood use."	Autologous transfusion of wound drainage decreased need for blood transfusions.

INTERLEUKIN-1 RECEPTOR ANTAGONISTS

Interleukin-1 receptor antagonists have been used to treat rheumatoid arthritis. They have been investigated for treatment of osteoarthritis.(1522, 1523)

Recommendation: Interleukin-1 Receptor Antagonists

Interleukin-1 receptor antagonists are not recommended for treatment of osteoarthritis.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – Low

Rationale for Recommendation

There are two high-quality RCTs that somewhat conflict. One suggests slight benefits in some secondary outcome measures(1522) while the other suggests no benefits.(1523) Taken together, these results suggest additional studies are warranted. Meanwhile, the treatment is associated with significant adverse effects and there are other treatments with documented efficacy, thus

interleukin-1 receptor antagonists are not recommended without consistent evidence of efficacy and clear indications.

Evidence for the Use of Interleukin-1 Receptor Antagonists

There are 2 high-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Interleukin-1 Receptor Antagonist						
Auw Yang 2008 RCT	8.5	N = 182 patients with symptomatic knee OA	Interleukin-1 receptor antagonist, Orthokin (n = 94) vs. Placebo (n = 88). In both groups, procedures were similar and injections given on Days 0, 3, 7, 10, 14, and 21. Followed up to 12 months and allowed to use only acetaminophen.	Orthokin and placebo groups showed small improvement on WOMAC (28% vs. 23% at 3 months, 15% vs. 18% at 6 months, 14% vs. 17% at 9 months, and 19% vs. 13% after 12 months. Orthokin improved for KOOS symptoms (p = 0.002) and KOOS spot (p = 0.042) vs. placebo. Orthokin-improved vs. placebo-for all other outcomes but not significant.	“[O]rthokin appears to have a beneficial biological effect on patient documented symptoms arising from knee OA.”	Primary outcome indicator (WOMAC) negative between groups. Some secondary outcomes mildly positive. Secondary analyses also suggest possible differences dependent on whether patient on NSAID.
Chevalier 2009 RCT	8.0	N = 170 with symptomatic knee OA, >3/10 VAS pain, ages 18+ years	Anakinra 50mg vs. 150mg vs. NS as intraarticular injections. Assessments at 0, 4 days, 4, 8, 12 weeks.	Subjective assessment of pain (day 4/weeks 4/8/12): Placebo (-15.4±29.4/- 21.7±26.2/- 20.7±28.5/- 23.6±26.9) vs. Anakinra 50mg (- 18.5±28.7/- 24.1±26.0/- 27.3±29.9/- 18.9±31.1) vs. Anakinra 150mg (- 25.6±24.4/- 26.2±27.5/- 24.5±29.1/- 27.8±27.7).	“Anakinra was well tolerated as a single 50-mg or 150-mg intraarticular injection in patients with OA of the knee. However, Anakinra was not associated with improvements in OA symptoms compared with placebo.”	Data suggest lack of efficacy.

**SURGICAL CONSIDERATIONS FOR KNEE OSTEOARTHROSIS
CHONDROPLASTY AND DEBRIDEMENT**

Chondroplasty and debridement have been used to treat knee osteoarthritis.(1441, 1524, 1525)

Recommendation: Chondroplasty and Debridement for Knee Osteoarthritis

Chondroplasty and debridement are moderately not recommended for treatment of knee osteoarthritis.

Strength of Evidence – Moderately Not Recommended, Evidence (B)

Rationale for Recommendation

A high-quality, sham-controlled trial suggested there is no benefit of chondroplasty and debridement for treatment of knee osteoarthritis.(375) A second trial suggested debridement

was not helpful in comparison with joint lavage.(1526) One substantially lower quality trial provided conflicting evidence regarding how debridement compared with lavage.(1527) Other trials evaluating electrocautery and radiofrequency treatments suggest no benefits.(1528, 1529) Thus, the higher quality trials and balance of evidence indicate that chondroplasty and debridement are ineffective and are not recommended for treatment of knee osteoarthritis. However, there are lesions that are thought to be mechanical in nature and require debridement, typically in the context of arthroscopic evaluation of meniscal tears with mechanical symptoms.

Evidence for the Use of Chondroplasty and Debridement for Knee Osteoarthritis

There is 1 high- and 7 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Debridement and/or Chondroplasty						
Moseley 2002 RCT	8.5	N = 180 age 75 or younger with knee OA (ACR) and moderate pain despite maximal medical treatment for at least 6 months	Arthroscopic debridement (10+L NS lavage, rough articular cartilage shaved, chondroplasty, loose debris removed, all torn or degenerated meniscal fragments trimmed, remaining meniscus smoothed to firm, stable rim, n = 59) vs. arthroscopic lavage alone (10+L NS; would remove mechanically important unstable tear and smooth), n = 61) vs. placebo procedure: arthroscopic debridement simulated (n = 60). Follow-up over 24 months.	No significant differences between groups except objectively measured walking and stair climbing worse in debridement group vs. placebo at 2 weeks (PFS score 56.0±21.8 vs. 48.3±13.4 p = 0.02) and 1 year (PFS score 52.5±20.3 vs. 45.6±10.2 p = 0.04).	“[T]he outcomes after arthroscopic lavage or arthroscopic débridement were no better than those after a placebo procedure.”	Sham controlled. Data suggest debridement and lavage ineffective.
Chang 1993 RCT	7.0	N = 34, >20 years old, with knee OA, Kellgren and Lawrence grade 1-3, persistent pain >3 months (despite conservative medical and rehabilitation management which restricted work, athletic, or	Arthroscopic surgery (debride torn menisci, remove meniscal, cruciate fragments, remove proliferative synovium, excise loose articular cartilage fragments; no osteochondral drilling) and physical therapy (strengthening and flexibility exercises and gait training) (n = 18) vs. closed-needle joint lavage (control group; non-narcotic analgesia and physical therapy, 1L NS injected into and	NS between groups at 3 months (active ROM, tenderness, swelling, AIMS pain scale, functional status AIMS scores, 50ft walk time and Global Assessments). NS between groups at 12 months except knee tenderness scores in favor of arthroscopy group, p <0.05.	“The search for and removal of soft tissue abnormalities via arthroscopic surgery does not appear justified for all patients with non-end-stage OA of the knee who fail to respond to conservative therapy, but it may be beneficial for certain subgroups.”	Data suggest mostly no differences, although trend in favor of joint lavage with 44% vs. 58% improved at 1 year.

		self-care activities)	aspirated from knee in aliquots of 40-120mL (n = 14) with assessments at 3 and 12 months.			
Kang 2008 RCT	6.5	N = 29 failing 6 months of conservative treatments including activity modification, anti-inflammatory medications, and PT	Mechanical debridement with and without monopolar radiofrequency energy (mRFE) in treating chondral defects.	International Knee Documentation Committee (IKDS) scores: control vs. mFRE: Pre-op 36±2.8 vs. 30±3.5 (p >0.05), post-op 59±3.7 vs. 49±4.2 (p = 0.44). Both groups improved.	“The addition of radiofrequency energy to mechanical debridement led to a trend in increased stiffness of the lesion and yielded intermediate-term clinical outcomes that were equivalent to mechanical debridement alone.”	Small sample size. Co-interventions not described. Data suggest RF of no additive benefit.
Gibson 1992 RCT	5.5	N = 20 with moderate unilateral knee OA	Arthroscopic lavage under general anesthesia vs. debridement with removal of all osteophytes.	Only significant scores for mean weight of debris removed by irrigation: 2.4 g±1.9 after debridement vs. 0.9g±0.8 after lavage (p <0.05) and an increase in quadriceps isometric torque registered at 30° of knee flexion after debridement, at 6 weeks 36 Nm±19; 12 weeks, 48 Nm ±25; p <0.05.	“Our study suggests that in moderate osteoarthritis of the knee, joint lavage alone may have some short-term beneficial effect but there is no benefit from joint debridement. Future studies ought to include objective measurements of functional improvement and not depend on subjective assessment of symptomatic relief (Burks 1990).”	Small numbers. Osteophyte size was greater in the debridement group. Used other leg as control but no mention of OA in the control knees. No mention of co-interventions. No sham control for comparison.
Stein 2002 RCT	5.0	N = 146	Mechanical chondroplasty vs. electrocautery with mechanical chondroplasty.	No difference in those with Grade 2 chondromalacia in control or cautery groups. Groups with Grade 3 chondromalacia showed difference favoring control group. Difference found in comparing 2-compartment chondromalacia between 2 treatment cohorts, again, favoring control group.	“Electrocautery with chondroplasty does not produce a significant benefit compared with chondroplasty alone in the treatment of chondromalacic lesions of the knee. It appears to have a worsening effect on chondromalacic lesions of grade III and higher.”	Every-other allocation; 1-year follow-up suggesting no benefits of electrocautery.
Forster 2003 RCT No mention of sponsorship or COI.	4.5	N = 38 patients on the waiting list for an arthroscopic washout for knee osteoarthritis.	Five intraarticular injections of 20mg Hyalgan in to the affected knee at 1-week intervals (n = 19) vs. arthroscopic washout with either general or spinal anaesthesia (n = 19).	VAS score pre-trial to 1 year follow-up: Hyalgan: 7.6 to 5.7. Arthroscopy: 7.5 to 5.7. Only 1/5 Hyalgan patients had improved 1 year postoperatively. No p-values given. No	“[T]he use of intra-articular Hyalgan injections in patients with knee osteoarthritis without mechanical symptoms gave results comparable with arthroscopic washout. Hyalgan should be considered as an	Patients could not be blinded in this study (surgical procedure vs injection) and results for both were similar.

		Mean age of Hyalgan group was 60 years; Arthroscopy group 63 years.	Follow-up at pre-intervention, 6 weeks, 3 months, 6 months, and 1 year.	significant difference in VAS, FS or LI between the two groups at 6 weeks, 3 months, 6 months, or 1 year.	alternative to arthroscopy in this patient group.”	
Visually-guided Arthroscopic Irrigation						
Kalunian 2000 RCT	5.5	N = 90 with knee OA (ACR), >40 years of age, knee pain for ≤10 years,, KL Grade 0-2, unsatisfactory pain relief after at least 6 weeks of PT and 2 or more NSAIDs given for 3 or more weeks	Large volume irrigation (3L NS, n = 41) vs. Minimal volume irrigation (250ml NS, n = 49) all with minimal arthroscopy. Follow-ups at 1, 3, and 12 months.	Aggregate WOMAC from baseline to 12 months (mean/95% CI): Minimal (8.9/4.9, 13.0) vs. full (15.5/7.7, 23.4), p = 0.10. WOMAC pain: (2.3/-0.1, 4.7) vs. (4.2/-0.9, 9.4), p = 0.04. WOMAC stiffness: (0.7/-0.5, 1.9) vs. (1.2/-1.6, 4.0), p = 0.22. WOMAC function: (6.1/2.8, 9.4) vs. (9.9/4.9, 13.0), p = 0.15). Patient pain (VAS): (0.12/0, 0.3) vs. (1.47/-1.2, 4.1), p = 0.02.	“Visually-guided arthroscopic irrigation may be a useful therapeutic option for relief of pain in a subset of patients with knee OA, particularly in those who have occult intraarticular crystals.”	Both active treatment groups with no true sham. No differences at 4 months, but large volume irrigation superior to minimal for WOMAC pain at 2 months and most measures favored irrigation at 1 year. Post-hoc analyses support more efficacy if crystals found.
Arthroscopic Debridement						
Hubbard 1996 RCT	4.0	N = 76 knees undergoing arthroscopic surgery for degeneration of articular cartilage of knee; required to have Outerbridge Grade 3 or 4 at arthroscopy	Arthroscopic debridement (no chondroplasty, 3L NS irrigated, n = 40) vs. large volume irrigation with 3L NS (n = 36) with follow-ups for 5 years (means 4.3, 4.5 years).	At 1 year: 32 successes in debridement group vs. 5 in washout group; pain relief 80% in debridement group vs. 20% in washout group, p = 0.05.	“For knees with lesions of the medial femoral condyle of grades 3 or 4, arthroscopic debridement appears to be the treatment of choice with over half the patients free from pain after 5 years.”	Patients not described and many details sparse. Long-term study. By pain-free criteria, debridement superior at 1 year. However, at 1 and 5 years, Lysholm scores did not differ, producing conflicting results.

CARTILAGE GRAFTS, OSTEOCHONDRAL AUTOGRAFTS, AND/OR TRANSPLANTATION

Cartilage grafts and/or transplantations for osteochondral defects are used for treatment of articular cartilaginous defects.(349, 581, 1530-1564) These procedures are technically difficult and require specific physician expertise. They are thought to be effective in select patients generally less than 40 years old with active lifestyles having a traumatically induced, modest sized cartilage defect. These procedures are believed to delay or possibly prevent the development of osteoarthritis. However, a Cochrane review concluded there was insufficient evidence, opining that long-term studies are needed.(1530, 1565)

Recommendation: Cartilage Grafts, Osteochondral Autografts, and/or Transplantation
Cartilage grafting, osteochondral autografts, and/or transplantation is moderately recommended for select patients.

Indications – Select patients less than 40 years old with active lifestyles with a single, traumatically caused Grade III or IV femoral condyle deficit. Deficit diameter recommended not to exceed 20mm for osteochondral autograft transplants, although criteria up to 4cm² has been used. Grafts and transplants not recommended for those with obesity, inflammatory conditions or osteoarthritis, other chondral defects, associated ligamentous or meniscus pathology, or who are older than 55 years of age.

Strength of Evidence – Moderately Recommended, Evidence (B)

Rationale for Recommendation

There are no sham-controlled trials. However, there are quality trials that have compared different management approaches for these cartilaginous defects.(1566-1570) One trial with multiple reports suggests that at up to 10 years, autologous osteochondral transplantation is superior to microfracture in competitive athletes(349, 1540, 1571) and another trial by the same author also found superiority when performed in conjunction with ACL reconstruction.(1572)

Trials have included rigorous enrollment criteria that have on at least one occasion only included conditioned athletes.(349) As most trials have excluded obesity, it appears likely that at least 50% of the potential population would be excluded solely by that criterion. Thus, it is unclear how few patients would actually be eligible for these procedures. There are increasing numbers of longer term studies that have followed treated patients from 3-10 years(349, 1531, 1540, 1546, 1571, 1572) that have reported persistent benefits.Although, further studies with long follow-ups and larger sample sizes are needed. Cartilage grafts and/or transplants are invasive, have potential for adverse effects, and are high cost. These procedures have evidence of efficacy and are recommended for select patients.

Evidence for the Use of Cartilage Grafts and/or Transplantation

There is 1 high-(1571) and 4 moderate-quality(349, 1540, 1572, 1573) RCTs incorporated into this analysis.

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: autografts, osteochondral autograft transplant system, OATS, mosaicplasty, knee pain , patellar tendonitis, patellar tendinitis, patellar tendinopathy, knee arthritis, knee osteoarthritis, degenerative joint disease, meniscal tears, meniscus tear controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 12 articles, and considered 2 for inclusion. In Scopus, we found and reviewed 155 articles, and considered zero for inclusion. In CINAHL, we found and reviewed 13 articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 4 articles, and considered zero for inclusion. We also considered for inclusion one article from other sources. Of the 6 articles considered for inclusion, 2 randomized trials and 4 systematic studies met the inclusion criteria.*

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
OATS Mosaicplasty vs. Microfracture						
Gudas 2012 RCT 10 year follow-up	8.0	N= 57 with a single symptomatic osteochondral defect (OCD) or	Autologous osteochondral transplantation, OAT (n = 28) vs. Microfracture, MF (n = 29). Follow ups: 6, 12, 24	ICRS score was better in OAT vs. MF: OAT-OCD vs. MF-OCD: 87.5% vs. 74%, p <0.001; OAT-ACD vs. MF-ACD: 93% vs. 78%,	“Statistically significantly better results were detected in the OAT group compared with the	Data suggest OAT therapy provided better clinical results at 10 years follow-up (14% vs. 38% failures).

from Gudas 2005		full-thickness articular cartilage defect (ACD); mean age 24.3±6.80 years	months post-surgery.	p <0.001. Mean ± SD ICRS scores for MF-OCD: 73.9±1.5, MF-ACD: 78.2±1.4, OAT-OCD: 87.5±1.3, OAT-ACD: 92.9±1.4, p <0.001 in favor of OAT group. Mean ± SD for Tegner score: 3 years vs. 10 years: OAT-ACD: 7.5±0.5 vs. 7.0±0.4, p = 0.006; OAT-OCD: 7.2±0.4 vs. 6.7±0.4 p = 0.003; MF-ACD: 7.0±0.4 vs. 6.2±0.4, p < 0.001; MF-OCD: 6.8±0.7 vs. 6.1±0.7, p < 0.03. More athletes from OAT group returned to sports activity than MF group, p <0.001.	MF group at 10 years.”	
Gudas 2013 RCT	5.0	N = 102 with an ACL rupture and articular cartilage damage in the medial femoral condyle of knee; mean age of 34.1 years (range 22 to 45 years).	ACL reconstruction with simultaneously performed OAT procedure (OAT-ACL group) (n = 34) vs. ACL reconstruction with simultaneously performed microfracture procedure (MF-ACL group) (n = 34) vs. ACL reconstruction with simultaneously performed debridement procedure (D-ACL group) (n = 34) vs. Control group: ACL reconstruction with intact articular cartilage (IAC-ACL group) (n = 34). Mean follow-up 36.1 months (range, 34 to 37 months).	At 3 years, IKDC pivot-shift test normal or nearly normal for 29/33 (88%) in OAT-ACL vs. 28/32 (88%) in MF-ACL group, 27/32 (84%) in D-ACL group, and 31/34 (91%) in IAC-ACL group. At 3 years, mean Tegner activity scores in OAT-ACL, MF-ACL, D-ACL, and IAC-ACL groups were 7.1, 6.9, 6.2, and 7.5. At 11.1 months (range, 9-14 months) patients returned to previous level of activity, 30/34 (88%) in OAT-ACL, 28/34 (82%) in MF-ACL group, 27/34 (79%) in D-ACL group, and 32/34 (94%) in ACACL group.	“[I]ntact articular cartilage during ACL reconstruction yields more favorable IKDC subjective scores compared with any other articular cartilage surgery type. However, if an articular defect is present, the subjective IKDC scores are significantly better for OAT versus microfracture or debridement after a mean period of 3 years. Anterior knee stability results were not significantly affected by the different articular cartilage treatment methods.”	Included 3 randomized groups and one non-randomized control group. Data suggest higher function with OAT than MF or debridement at 3 years.
Gudas 2006 RCT	7.0	N = 57 with single symptomatic osteochondral defect (OCD) or full-	Autologous osteochondral transplantation, OAT (n = 28) vs. Microfracture, MF (n = 29).	OAT group had significantly better results in the Modified HSS evaluation at 12, 24, and 36 months (p<0.05, p<0.01, and p<0.01). The	“At an average of 37.1 months follow-up, our prospective, randomized, clinical study in athletes has shown significant superiority of the	Comparable to Gudas 2005.

		thickness articular cartilage defect (ACD); mean age 24.3 years (range, 15 to 40 years).	Follow ups at 6, 12, 24 and 36 months post-surgery.	average preoperative HSS score was 77.22±8.12 in the MF group and 77.88±6.23 in the OAT group. At 37.1 months (range from 36 to 38 months), average post-op HSS score increased to 80.60±4.55 in MF group and to 91.08±4.15 in OAT group (p <0.05 and p <0.0001). After operations, ICRS score increased to 75.59±4.64 in MF group and 85.88±4.69 in OAT group (p <0.05 and p <0.001). Twenty-four (86%) in OAT group had an excellent or good result vs. 22 (76%) in MF group at 12 months (p <0.05). Twenty-seven (96%) in OAT group had an excellent or good results vs. 15 (52%) in MF group at 24 and 36 months (p <0.0001).	OAT over MF for the repair of articular cartilage defects in the knee.”	
Gudas 2005 RCT	7.0	N = 57 with single symptomatic osteochondral defect (OCD) or full-thickness articular cartilage defect (ACD); mean age of 24.3 years.	Autologous osteochondral transplantation, OAT (n = 28) vs. Microfracture, MF (n = 29). Follow ups at 6, 12, 24, and 36 months post-surgery.	At 37 months, 27 (96%) in OAT group had excellent or good results vs. 15 (52%) in MF (p <0.0001). No difference in preoperative HSS score between groups; 37.1 months later (range, 36 to 38 months), average postoperative HSS score increased to 80.60 ± 4.55 in MF vs. 91.08 ± 4.15 in OAT group (p <0.05 and p <0.0001). OAT group had better results in modified HSS evaluation at 12, 24, and 36 months (p <0.05, p	“At an average of 37.1 months (range, 36 to 38 months) follow-up, our prospective, randomized, clinical study in young active athletes under the age of 40 has shown significant superiority of OAT over MF for the repair of articular cartilage defects in the knee.”	First report of this RCT that subsequently enrolled more subjects. Conditioned athletes. Data suggest OAT superior to MF (96% vs. 52% excellent or good results).

				<0.01, and p <0.01. At 37.1 months (range, 36 to 38 months) showed deterioration in MF group (p <0.05). OAT group had significantly better results in ICRS evaluation at 12, 24, and 36 months (p <0.03, p <0.001, and p <0.001).		
Ulstein 2014 RCT	4.0	N = 25 with a full-thickness chondral lesion of the articulating surface of the femur; mean age 32.3±7.7 years.	Microfracture (MF), arthroscopic awl, multiple holes, 3-4mm apart (n = 11) vs. OAT mosaicplasty, 3.5, 4.5, or 6.6mm in diameter (n = 14). Post-op care; passive motion 3-4 hours 2 times/day for 4 days; cold therapy and compression. Rehabilitation: exercises to restore full range of motion, dynamic strength exercises (6 weeks postoperatively). Follow-up: baseline, 6 weeks, 6, and 12 months.	No significant results to report between the groups in any of the outcomes measured. "The increase in Lysholm score from baseline to follow up was significant for both groups," however, no p-value was reported.	"At long-term follow-up, there were no significant differences between patients treated with MF and patients treated with OAT mosaicplasty in patient-reported outcomes, muscle strength or radiological outcome. Both MF-treated as well as OAT mosaicplasty-treated patients reported improved knee function compared to the preoperative level."	Suggests comparable results but small sample size substantially limits conclusion.

KNEE ARTHROPLASTY

Knee arthroplasty has been long used for treatment of end-stage knee degenerative joint disease. Outcomes have generally been excellent with 5 to 10 year survival rates of 95 to 99%.(1574-1585) A modestly worse prognosis including higher infection rates has been reported in rheumatoid arthritis patients.(1585, 1586) Unicompartmental arthroplasty has been used for medial joint arthrosis. However, patellar resurfacing is controversial.(1587)

Pain and functional loss have been shown to be predictors of arthroplasties(1588, 1589) (p <0.0001), as have visual analog scale ratings. Primary reasons for surgical failure are loosening, as well as infected, prostheses. Other predictors of suboptimal results include presence of effusion,(1590) older age(1591) more pre-operative debility,(1591, 1592) longer duration of disease,(1590) depressive symptoms,(1593) helplessness(1594) and catastrophizing.(1593, 1595, 1596) Similar to all arthroplasties, the literature has advanced more slowly than the technology resulting in challenges in analyzing the literature for purposes of evidence-based guidance.

1. Recommendation: Knee Arthroplasty for Moderate to Severe Arthritides **Knee arthroplasty is strongly recommended for severe arthritides.**

Indications – All of the following present: 1) severe knee degenerative joint disease that is unresponsive to non-operative treatment (rare cases may include osteonecrosis of the distal femur or tibial plateau with collapse or lack of response to non-operative treatment); 2)

sufficient symptoms and functional limitations, such as impairments of activities of daily living or occupational tasks, and 3) failure to successfully manage symptoms after a prolonged period of a conservative management plan that included NSAIDs, exercise, physical or occupational therapy, and where appropriate, weight reduction, intraarticular viscosupplementation, and corticosteroids. Carefully selected patients may be candidates for bilateral arthroplastic procedures. However, particular attention should be paid to pre-operative medical fitness and psychological fortitude.

Strength of Evidence – Strongly Recommended, Evidence (A)

2. *Recommendation: Unicompartmental Knee Arthroplasty for Largely Unicompartmental Disease*

Unicompartmental arthroplasty is recommended for largely unicompartmental disease.(1597, 1598)

Strength of Evidence – Recommended, Evidence (C)

3. *Recommendation: Knee Arthroplasty for Bilateral Disease*

For bilateral disease, carefully selected patients may safely undergo simultaneous bilateral knee replacement.

Strength of Evidence – Recommended, Evidence (C)

4. *Recommendation: Autologous Blood Re-infusion Systems*

Autologous blood re-infusion systems are moderately recommended for arthroplasty patients.

Strength of Evidence – Moderately Recommended, Evidence (B)

Rationale for Recommendations

There are numerous trials that have been performed of arthroplasty.(1599-1682) There are no trials that have compared arthroplasty or other surgical procedures with non-operative management. However, all quality trials have reported marked improvements in all surgical arms of the trials, thus arthroplasty is strongly recommended for select patients who fail non-operative management.

For largely unicompartmental disease, one moderate-quality trial has reported 5 and 15 year follow-ups and found better range of motion and “excellent” results with unicompartmental arthroplasty compared with total joint arthroplasty.(1597, 1598) Thus, unicompartmental arthroplasty is recommended for that select group of patients. One trial has compared high tibial osteotomy with unicompartmental arthroplasty and found that arthroplasty resulted in a longer time to failure, as defined as total joint arthroplasty, but most results were reasonably comparable.(1683)

There are several trials of surgical approaches, but data somewhat conflict. A quadriceps sparing or subvastus approach has been found to result in superior short-term results or trends towards superiority in most(1684-1687) but not all trials.(1688) Two older trials were negative.(1689, 1690) A mini-incision medial parapatellar approach has also been found to be associated with a shorter hospital stay in one trial,(1691) but was not found to be superior to a quadriceps sparing approach in another trial.(1692) As there are minimal differences in outcomes, there is no recommendation, although the subvastus approach has some evidence of very short-term superiority.

Computer navigation systems have been reported in many studies and quality trials.(1672, 1693-1705) Short-term results include better function,(1699) worse function,(1706) and no

differences in fat emboli.(1705) All trials that have reported on alignment found superior anatomic alignment with those systems. Superior alignment is presumed to result in superior outcomes long-term; however, to date only one trial has reported some results suggesting better outcomes at 1 year.(1693) While the reduction in malposition is hopeful, the increased cost and the lack of data to support a change in failure rate result in no formal recommendation for or against those systems.

Different prosthetic designs have been reported in quality trials.(1707-1715) (1716) Components have also been coated, uncoated, cemented and uncemented.(1717-1737) Quality trials demonstrating clear superiority of one design over another are not reported. Cemented prostheses tend to migrate less in the short term, but over the intermediate term, cemented prostheses migrate equivalent amounts, and longer term results are unclear comparing the two options.

Patellar resurfacing has been used in conjunction with arthroplasty. There are numerous trials that have been performed with durations of follow-up exceeding 10 years in two studies. A high-quality study found comparable results regardless of whether the patella was resurfaced or not.(1738) Moderate-quality trials also found no differences in outcomes for patellar resurfacing compared with patellar retention/non-resurfacing.(1739-1751) Four of the trials suggested modestly better results with patellar resurfacing that included less anterior knee pain and less need for reoperation.(1752-1755) Available studies have also suggested appearance of the patella does not predict need for resurfacing. Thus, there is no recommendation for or against patellar resurfacing; however, some caution appears warranted in the surgical performance of patellar resurfacing, particularly as complications that are difficult to treat may occur though infrequently.

Autologous blood reinfusion systems have been shown to reduce transfusion needs of patients in all studies.(1756-1762) Two low-quality trials also suggest efficacy,(1763, 1764) and thus autologous blood re-infusion systems are moderately recommended.

Drains have been used indwelling, as well as intraarticular.(1765-1772) One moderate-quality trial of hip and knee arthroplasty patients reported not using drains and found no advantage to drains.(1766) Comparative data suggest no differences in outcomes. Drains that have used higher suction pressures have resulted in greater fluid removal,(1767) but no documented improvements in outcomes. Thus, there is no recommendation for or against drains. There is evidence that drains become colonized within 48 hours and thus provide a theoretical conduit for infection, and prompt removal is generally indicated.

Tourniquets have been used to keep the operative field free of blood, but concerns about failure to identify bleeders after tourniquet release and subsequent impairments of lower extremity function have been addressed in research studies.(1773-1781) Two trials have compared tourniquet use with no tourniquet use.(1776, 1782) One high-quality trial suggested comparable results although there was earlier straight-leg raising capacity in the non-tourniquet group.(1782) The second study reported moderate to heavy bleeding issues in 15% without use of a tourniquet, but otherwise good outcomes.(1776) Other trials evaluated early tourniquet release vs. late release and have variously reported early release resulted in superior function,(1773) trends towards more complications in the late release group,(1773, 1775) and modestly higher blood loss with early release.(1777) Another trial found no differences between tourniquet at 350mm Hg vs. systolic blood pressure plus 100mm Hg,(1781) suggesting lower pressures may be preferable.

Infected prostheses are catastrophic events and infectious disease precautions including at least some barrier methods (e.g., surgical 'moon suits,' surgical masks, ventilation) combined with antibiotics are universally utilized. Antibiotic impregnated cement combined with intravenous antibiotics is used. There is increasing use of air flow controls(1783) and supplied air in operating suites to attempt to reduce these infections.

Evidence for the Use of Knee Arthroplasty

There are 10 high- and 144 moderate-quality RCTs or crossover trials incorporated into this analysis. There are 30 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Regional Block Anesthesia and Analgesia for Hip/Knee Arthroplasty						
Gao 1995 RCT	8.5	N = 30	Bupivacaine vs. bupivacaine with buprenorphine in caudal block for post-op pain relief in hip and knee arthroplasty.	Duration of analgesia much longer (mean 606 minutes vs. 126 minutes p <0.001) in those receiving added buprenorphine; mean morphine consumption in first 24 hours halved (14mg vs. 28mg) and patient satisfaction greatly increased.	"There were no significant differences in the incidence of complications although the group which had added buprenorphine had a lower incidence of vomiting."	Relatively low cost to add buprenorphine to caudal block increasing analgesic time on average 8 hours.
Wallace 2012 RCT	4.5	N = 46 total knee replacement (TKR) patients	Peri-articular injections (n = 23) vs. Femoral nerve blocks (n = 23). In both groups, an auto-transfusion drain (Belovac ABT retransfusion system) was inserted and then tourniquet was released.	Anesthetic detected in drain from local anesthetic vs. femoral nerve block (p <0.001).	"[I]t is safe to use peri-articular injection in combination with auto-transfusion of fluid from peri-articular drains used during TKR.	Few baseline characteristics and sample size too small to draw significant conclusions regarding safety.
Parenteral/Oral Anesthesia for Hip/Knee Arthroplasty						
Reiter 2003 RCT	8.5	N = 98	Pre-op oral administration of placebo vs. morphine sulfate (20mg) in hip or knee replacement surgery.	Group receiving morphine had significantly less cumulative piritramide (analgesic) consumption during 24 hours post-op than placebo (37.5 +/- 12.5mg vs. 46.8 +/- 22.1, t-test, p <0.05), although similar pain scores recorded (Group 1: 4.8 +/- 1.8 and 3.6 +/- 1.7, Group 2: 4.8 +/- 1.6 and 3.4 +/- 2.0, at 1 and 24 hours, respectively). No significant differences in side effects between groups.	"These data show that the preoperative oral administration of morphine sulfate, regardless of its short half-life, can reduce postoperative consumption of opioids at similar pain levels."	Pre-op oral morphine in patients undergoing hip or knee replacement may have a positive effect on pain relief. Piritramide, is a schedule I synthetic opioid narcotic in U.S.
Tarradell 1996 RCT	6.5	N = 48	Single doses of 100mg meperidine vs. 100mg tramadol	Thirty minutes after treatment, patients who requested additional analgesia rescued with	"In the present study, meperidine and tramadol produced	Both treatments at given dosage provided only partial analgesia.

			vs. saline after general anesthesia for hip/knee arthroplasty.	75mg diclofenac and morphine as required. Meperidine produced a significant depression of ventilation revealed by increase in PaCO ₂ and decrease in tidal volume, respiratory rate and %O ₂ saturation lasting approximately 1 hour. Onset for meperidine analgesia 10 minutes; >30 minutes for tramadol. Both opioids produced similar degree of analgesia in patients not rescued.	comparable analgesia, with a different time course profile, but meperidine induced sedation and respiratory depression while tramadol did not."	
Treatment of Adverse Anesthesia Effects						
Grattidge 1998 RCT	8.5	N = 82	Propofol infusion (10mg/ml at 3ml/hour) vs. inert lipid emulsion infusion in patients undergoing hip or knee arthroplasty using spinal anesthesia and IT morphine.	"Postoperative nausea and vomiting in the intervention group was 40% vs. 59% in the controls (P=0.1, not significant). Pruritus occurred in 34%, with a similar rate in both groups."	"These results suggest that routine use of postoperative, sub hypnotic propofol infusion as postoperative nausea and vomiting prophylaxis is not justified in this patient population."	Study focus not pain but side effects of anesthesia, particularly morphine. Propofol infusion not effective in controlling post-op nausea and vomiting.
Surgical Approach						
Lin 2009 RCT	7.5	N = 60 with primary OA of knee	Minimal-incision medial parapatellar approach MP (n = 30) vs. quadriceps sparing approach QS (n = 30); 2 months follow-up.	MP vs. QS mean±SD (range) VAS pain scores at pre-op, post-op Day 1, 3, and 2 months: 5.5±2.0 (2-9)/5.3±2.1 (2-10), 6.2±1.9 (2-10)/6.1±1.6 (2-10), 4.5±1.7 (2-8)/4.2±1.6 (2-8), 3.0±1.9 (0-8)/3.4±1.7 (0-8). Post-op/pre-operation (%) isokinetic peak muscle torques for 60°/s-quadriceps, 60°/s-hamstrings, 120°/s-quadriceps, 120°/s-hamstrings: 96±36/91±52, 99±39/95±41, 111±51/109±58, 103±50/105±43. Functional outcome knee score pre-op, 2 month post-op, patient satisfaction at excellent, good, fair, and poor: 64.8±12.1 (39-85)/64.3±12 (40-89), 78.5±6.7 (62-95)/76.8±6.8 (62-88), 20 (50%)/17 (43%), 16 (40%)/21 (53%), 4	"The overall postoperative hip-knee ankle axis was more varus, and surgical time was longer with QS TKA. Short term isokinetic peak muscle torque, postoperative pain, and functional outcomes did not differ between the approaches."	Data suggest comparable outcomes.

				(10%)/2 (5%), 0 (0%)/0 (0%).		
Roysam 2001 RCT	7.5	N = 89 knees undergoing primary TKA	Standard medial parapatellar approach (n = 43) vs. subvastus approach (n = 46). 3 months follow-up.	Medial vs. subvastus mean for unassisted straight leg, total blood loss, consumption of opiates in 1st week of surgery, knee flexion at 1 week, hospital stay, difference of knee flexion at 4 weeks, and 3 months: 5.8 days/3.2 days/p = <0.001, 748ml/527ml/p <0.0001, 102mg/78mg/p <0.001, 55°/78°/p <0.001, 20.7 days/17.3 days/p <0.068, p <0.052, p <0.07.	“The subvastus approach offers early advantages over the standard parapatellar arthrotomy. It preserves the integrity of the vastus medialis and peripatellar plexus of vessels.”	Data suggest subvastus approach results in very short term benefits, including lower blood loss, earlier SLR and ROM and lower opiate use but not intermediate or longer term benefits.
Aglietti 2006 RCT	7.5	N = 30 undergoing TKA with OA; all unilateral TKA performed by 1 surgeon	Minimally invasive techniques with either mini-subvastus vs. a modified “quadriceps-sparing” approach.	Mean±SD comparing mini-subvastus group vs. quadriceps-sparing group: Degrees flexion at 30 days: 115±4.4 vs. 112±5.2; p = 0.06. Degrees of flexion at 90 days: 118±7 vs. 115±6.6; p = 0.08. Active SLKR at 1.9 days vs. 1.4 days.	“We believe there was no difference between the mini-subvastus and “quadriceps-sparing” approach in relation to short term recovery or early results.”	Details of blinding unclear. Data suggest no significant differences in approaches.
Bäthi 2005 RCT	6.0	N = 50 undergoing TKA; nearly all OA	Standard medial parapatellar approach (n = 25) vs. midvastus approach (n = 25). All PCL preserving cemented prostheses (PFC-Sigma). No patellar buttons; 6 weeks follow-up.	Parapatellar vs. midvastus pre-op mean±SD knee society score, and ROM (°): 61.5±19.6/60.8±15/p = 0.88, 105.6±16/104.6±16.8/p = 0.83. 6 week post-op ROM (°): 95.8±9.2/ 97.1±12.1/p = 0.63. Isometric quadriceps strength (Nm) in leg extension at Week 3 exam, and 6 weeks post-op: 27.6±13.6/41.4±19/p = 0.005, 35.5±14.4/47.6±21.2/p = 0.02. Reproducing a given joint angles (°): 7.6±5.7/6±5.5/p = 0.064, 7.1±5.7/5.1±5.3/p = 0.029.	“The midvastus approach offers advantages over the standard parapatellar arthrotomy in the early rehabilitation period. No adverse effects associated with this approach were observed in this study. The midvastus approach should be considered as a valuable alternative to the medial parapatellar approach in TKA.”	Claims double blind but unclear how that was done. Did not give preoperative measures of some key outcome variables. Data suggest no long-term impacts; however, modestly lower pain immediately post-op in midvastus group.
Karachalios 2008 RCT	6.0	N = 106 with knee OA requiring TKR; criteria <15° varus/	Mini-midvastus approach (n = 50) vs. standard approach (n = 50).	Mini-midvastus vs. standard pre-op mean(range) for objective knee scores, objective function score, objective total score, and subjective Oxford knee score:	“Based on these results, the authors currently use minimally-invasive techniques in total knee replacement in selected cases only.”	Mean 23 month follow-up. Trends in favor of mini midvastus for outcomes, but more short-term pain.

		valgus deformity, fixed-flexion of <20°, flexion 90°, and BMI <35kg/m ²		35.7 (14-65)/31.6 (12-70), 46.4 (10-60)/46.5(20-50), 82.1 (35-115)/78.9 (57-110), 44.3 (38-50)/43.8 (39-51). Final follow-up: 97 (92-100)/93.8 (65-100), 97 (90-100)/84 (71-100)/p = 0.01, 192 (180-200)/184 (115-200), 20 (14-28)/23.3 (20-32). Difference (t test) p = 0.01 for objective knee score, objective function score, objective total score, and subjective Oxford knee score.		
Faure 1993 RCT	6.0	N = 20 with symmetric arthritis undergoing 1-stage bilateral knee arthroplasty	Standard median parapatellar arthroscopy vs. subvastus approach.	Subvastus vs. parapatellar ROM(°) flexion for all at preop, 1 week postop, 1 month, and 3 months: 112/111, 87/87, 97/97, 107/107. Flexion for TKA: 108/105, 85/85, 94/95, 103/105. Flexion for unilateral knee arthroplasty: 125/129, 94/92, 103/102, 118/115. Extension for all: -7/-5, -10/-11, -8/-6, -4/-4. Extension for TKA: -7/-6, -10/-11, -7/-6, -4/-4. Extension for unilateral knee arthroplasty: -6/-2, -10/-12, -9/-6, -2/-5. Differences between groups for quadriceps strength measured with LIDO showed increase of strength in subvastus approach, p<0.05.	"The subvastus approach offers a reasonable alternative to the paramedian arthroscopy and preserves greater quadriceps strength in the early postoperative period."	Data suggest comparable outcomes
Engh 1997 RCT	4.5	N = 106 who underwent primary TKA	Medial parapatellar MPP approach (n = 57) vs. midvastus muscle-splitting approach (n = 61).		"[T]he midvastus muscle-splitting approach is an efficacious alternative to the medial parapatellar approach for primary total knee arthroplasties."	Quasi-randomized on MRN. 6 weeks follow-up. Data suggest comparable results.
Carlsson 2006 RCT	4.5	N = 41 undergoing MGU knee arthroplasty with medial noninflammatory arthritis Grade I-III	Miller-Galante unicompartmental TKA with minimally invasive surgery vs. a standard exposure; 2 year follow-up.	No difference between groups for clinical or radiographic data. Hospital stay with miniarthrotomy vs. conventional: 3 vs. 6 days, p = 0.03.	"In conclusion, arthroplasty of the medial compartment for arthrosis grade 1 to 3, with the MGU knee prosthesis, through a minimally invasive approach, according to Ahlbäck, is a safe procedure	Randomization details sparse. Data suggest shorter hospital stay with miniarthrotomy approach.

					beneficial for both patients and society.”	
Juosponis 2009 RCT	4.5	N = 70 with OA admitted for primary TKR	Medial parapatellar MPP approach (n = 35) vs. mini-midvastus MMV approach (n = 35).		“[M]MV technique is associated with better early functional results after TKR. The MMV approach according our data can reproduce results similar to MMP in respect to component position. A precise operation technique and adequate visualisation of anatomical landmarks during implantation are the key points of success in MMV TKR.”	Twelve weeks follow-up. Data suggest comparable results by 12 weeks, but better results for mini-midvastus up to 6 weeks.
Capsular Repair						
Masri 1996 RCT	4.5	N = 64 (75 knees) for primary TKA	Capsular repair with the knee in extension (n = 31, 37 knees) vs. capsular closure with the knee in flexion (n = 34, 38 knees); 2-3 months follow-up.		“[T]he degree of knee flexion at the time of capsular closure in total knee replacement has no effect on early rehabilitation after total knee replacement.”	Quasi-randomized on MRN. Data suggest knee position for capsular closure does not impact outcomes.
Posterior Stabilized and Cruciate Retention						
Kim 2009 RCT	8.0	N = 256 who underwent bilateral TKA at 1 institution	NexGen CR-Flex vs. NexGen LPS-Flex TKA. All patellae resurfaced and all components cemented. At least 2 years follow-up.		“After a minimum duration of follow-up of two years, there was no difference in range of motion or clinical and radiographic results between knees that had received a high-flexion posterior cruciate-retaining total knee prosthesis and those that had received a high-flexion posterior cruciate-substituting total knee prosthesis.”	Large sample size. Randomized crossover and at least 2 years follow-up. Data suggest comparable results.
Kim 2009 RCT	8.0	N = 59 (118 knees) subjects who underwent bilateral TKA	NexGen CR-Flex vs. NexGen LPS-Flex TKA. All patellae resurfaced and all components cemented. At least 3 years follow-up.		“After a minimum duration of follow-up of three years, we found no significant differences between the two groups with regard to the range of knee motion or the clinical or radiographic parameters.”	Crossover design and at least 3 years follow-up. Data suggest comparable results.

Nutton 2008 RCT	7.5	N = 56 with OA who underwent TKR	NexGen-LPS design with standard flexion (n = 28) vs. high flexion (n = 28). Outcome measurements conducted at post-op and 1 year.		“Our results indicate that in patients with a mean pre-operative range of movement of < 120° and with the operative techniques used by the surgeons in this study, the high flexion design of the NexGen LPS will not improve the range of knee movement.”	Data suggest comparable results at 1 year.
Harato 2008 RCT	6.5	N = 222 knees with PCL macroscopically intact	Posterior cruciate-retaining CR (n = 99) vs. posterior cruciate- substituting PS (n = 93). Both treatments done using Genesis II TKA system; ≥5 years follow-up.		“The results of this investigation would suggest that, while comparable in regards to supporting good clinical outcomes, the PS Genesis II design does appear to support significantly improved postoperative range of motion when compared with the CR design.”	Five plus years of follow-up. Data suggest comparable outcomes, though improved post-op ROM with posterior stabilization.
Chaudhary 2008 RCT	6.5	N = 100 with difference >5° in knee flexion or knee extension scheduled for primary TKA for treatment of non- inflammatory OA; intact PCL at time of surgery	Posterior cruciate- substituting PCS (Scorpio, n = 49) vs. posterior cruciate-retaining PCR (n = 51); 2 years follow-up.		“Overall, the two treatment groups had a similar range of motion of the knee over the initial two- year postoperative time period. A satisfactory range of motion was achieved by three months postoperatively and was maintained at the final assessment.”	High dropouts. Data suggest comparable results.
Tanzer 2002 RCT	6.5	N = 37 (40 knees) subjects scheduled for bilateral TKA	NexGen CR TKA vs. Legacy PS TKA; 2 years follow-up.		“The evidence provided in this prospective, randomized, double- blind trial suggests that with careful attention to surgical technique and balancing the knee, orthopedic surgeons should expect similar results whether they use a CR or PS TKA. When the flexion- extension gaps were balanced accurately, we could find no difference in the clinical, functional, or radiographic outcome	Small sample sizes; 3 bilateral cases treated with different prosthesis in each knee. Attempted patient blinding. Data suggest comparable results.

					of CR or PS TKAs at 2 years postoperatively.”	
McCalden 2009 RCT	6.0	N = 100 with knee DJD with Charnley A or B classification between 50-85, knee flex $\geq 90^\circ$ and BMI <35, randomized into Genesis II Posterior Stabilized insert (n = 50) and Genesis II High Flexion insert (n = 50); 2 deaths during follow-up, with 98 points followed for mean of 2.7 years	Cemented posterior stabilized vs. cemented high flexion insert. Both groups had "identical" intraoperative and postoperative management, including routine in-hospital physiotherapy and outpatient therapy.	Both groups had significant improvement from pre-op scores to both 1 and 2 year time points for knee flexion, WOMAC, Knee Society clinical rating scores (KSCRS), and SF-12 physical (p <0.001 for all). No statistically significant differences between standard posterior stabilized inserts and high flexion inserts when assessing knee flexion (p = 0.811), WOMAC, KSCRS, SF-12 mental, and SF-12 physical.	“[T]here was no difference with respect to the clinical outcome scores between the 2 groups of patients." There was "No clear benefit to a high flexion polyethylene design vs a conventional PS polyethylene in this total knee arthroplasty design.”	Data suggest comparable outcomes.
Uvehammer 2001 RCT	6.0	N = 43 with non-inflammatory arthrosis, varus/valgus deformity $>5^\circ$ or extension defect of 10°	Concave components vs. posterior stabilized components. All surgeries done using same procedures and anterior cruciate ligament sacrificed in all TKAs; 2 years follow-up.	No statistically significant differences between 2 groups at 3, 12, or 24 month time points. Appears may be some divergence in maximum subsidence between 2 groups, but differences not statistically significant.	“Our hypothesis that the concave design would have less migration could not be verified.” The authors also state that “[v]ariations of the configuration of the polyethylene insert did not alter the outcome in the short term.”	Data suggest comparable outcomes.
Weeden 2007 RCT	6.0	N = 50 (25 each group) failed conservative measures, pre-op ROM of $10-115^\circ$, varus knee deformity not	Standard PS implant vs. implant designed for improved flexion. Unilateral operation only; 1 year follow-ups.	Average ROM at both timepoints (6 and 12 months) better with high flexion vs. standard implant (p <0.05). More patients who had flexion $>135^\circ$ or returned to pre-op ROM at 1 year in high flexion vs. standard group (p <0.05 for both). No significant radiographic	“Although long term follow-up is desirable, these early results support the use of ps implants designed for increased flexion.”	Short-term follow-up for TKA of 12 months. Modest sample size. Data suggest modestly better ROM in high flexion group of uncertain clinical significance.

		exceeding 10°, valgus knee deformity of ≤15°		differences between 2 groups.		
Matsumoto 2009 RCT	5.0	N = 40 consecutive females with OA	Cruciate-retaining TKR (mean age 73.7 years, range 63 to 86) vs. posterior stabilised TKR (mean age 73.8 years, range 55 to 86).	With posterior stabilised TKR, were increases in joint gap during first 45° of flexion with patella both everted (0° to 10°, p = 0.0002; 10° to 45°, p = 0.0151) and reduced (0° to 10°, p = 0.0004; 10° to 45°, p = 0.0152).	“We believe that by maintaining a reduced patella for each intra-operative measurement, the surgeon will be able to adjust the soft-tissue balance more accurately and thereby achieve a better outcome.”	No follow-up; an inter-operative trial.
Matsuda 2005 RCT	5.0	N = 80 (40 each group) mobile-bearing total knee arthroplasties	PCL-retaining prosthesis vs. PCL-sacrificing prosthesis in mobile-bearing TKAs.	Mean±SD range of movement 1 year after TKA pre-op vs. post-op: PCLR: 109.1±18.0 vs. 117.6±14.4; p = 0.0087. PCLS: 109.9±18.8 vs. 116.3±14.0; p = 0.0123.	“We conclude that both coronal laxity and varus-valgus balance affect the ROM after TKA. An adequate degree of laxity and balance should contribute positively to the outcome of TKA.”	One year follow-up. Some details sparse. Data suggest comparable outcomes for 2 prostheses.
Saari 2006 RCT	4.5	N = 83 with non-inflammatory OA of knee, and underwent AMK TKR	Flat vs. concave tibial insert with PCL retained. Concave vs. posterior stabilized PS tibial insert with the PCL resected; 5 years follow-up.		“[B]MD was decreased in the distal femur, even 5 years after TKA, and the most pronounced relative reduction was seen posterior to the anterior flange. There were no significant differences in relative change in BMD between flat and concave insert in the group with less preoperative deformation. Knees with PS insert had more reduction posterior to the flange than knees with concave insert in the subgroup with more advanced preoperative deformity, which may imply that use of a PS insert increases the risk for supracondylar fracture compared to concave insert.”	High dropout rate. Study may be a follow-up of other trial. Data suggest no significant differences.
Shoji 1994 Randomized	4.5	N = 28 undergoing bilateral total knee	Posterior cruciate ligament retention vs. posterior cruciate	No significant between group differences.	“Patients who ascended and descended stairs with one leg at a time tended to prefer the	Mean 3.2 years follow-up. Data report no differences except those

Crossover Trial		replacement	ligament excision.		posterior cruciate ligament retention side. Those who could use each leg in sequence to go up and down stairs, however, did not show preferential dependence on either knee.”	going up/down stairs 1 at a time preferred PCL retention.
Snider 2009 RCT	4.5	N = 200 scheduled for primary TKA	Genesis II CR vs. Genesis II PS vs. AMK CR vs. AMK PS. 50 subjects in each prosthesis group; 2 year follow-up.		“There were no statistically significant differences in the joint line elevation between posterior-stabilized and posterior cruciate-retaining designs within the same implant system as measured on lateral radiographs. There were no differences in clinical functional outcomes in patients with variable joint line elevation.”	Patients not well described. Data suggest comparable results with different implants and with posterior stabilization vs. PCL retention.
Lee 2005 RCT	4.0	N = 20 bilateral knee OA, bilateral TKAs ≤2 years prior, and correction with retention of PCL	Posterior cruciate-retaining PCR vs. posterior-stabilized protheses PS.	Most results do not compared 2 groups. Amount of condylar lift-off (mm) averaged (PCL retaining vs. posterior stabilizing): 0° flexion 11%/33%; 30° flexion 0%/22%; 60° flexion 0%/28%; 90° flexion 17%/39%.	“[A] significant difference in the incidence of condylar lift-off was seen, although the amount of lift-off was not different between the groups.”	Small groups. Wide-ranging follow-ups. Many details sparse. Unclear if randomized crossover knees.
Swanik 2004 RCT	4.0	N = 20 undergoing TKA	Cruciate retaining CR prosthesis (n = 10) vs. posterior stabilized PS prosthesis (n = 10). NexGen total knee prostheses used in both groups.		“Total knee arthroplasty results in mild improvements in proprioception, kinesthesia, and balance. These changes may result from the retensioned capsuloligamentous structures and reduced pain and inflammation. Retention of the posterior cruciate ligament does not appear to significantly improve proprioception and balance compared with those functions in patients with a posterior stabilized total knee design.”	Small sample sizes. Many details sparse. Data suggest comparable results.

Ishii 2008 RCT	4.0	N = 90 (100 knees) with OA who underwent TKA with LCS total knee systems	Meniscal bearing type prostheses PCLR (n = 50 knees) vs. rotating platform type prostheses PCLS (n = 50 knees).	PCLR vs. PCLS ROM for pre-op, intra-op, at discharge: 122.5 (103.8 -130.0)/115.0 (100.0 -125.0)/p = 0.114, 120.0 (120.0-125)/120.0 (110.0-125.0)/p = 0.293, 100.0 (90.0-110.0)/95.0 (90.0-106.3)/p = 0.503. In all knees, femoral components fixed without cement and tibial components fixed with cement. Patella not resurfaced.	"The PCLS design has the advantage in terms of rehabilitation planning because of the more predictable changes in ROM during the perioperative period, although the average acquired ROM at discharge in both designs did not differ statistically after aggressive rehabilitation with physical therapy."	Quasirandomized on MRN. Short term follow up to discharge. Data suggest comparable outcomes. Mean discharge at Day 41 suggest results may not apply to US.
Mobile vs. Fixed						
Aigner 2004 RCT	9.5	N = 50; AP glide, n = 23; rotating, n = 27	AP Glide bearing vs. deep-dish rotating platform bearing in the same tibial component in a unilateral total knee replacement.	Mean active non-weight-bearing ROM at 1 year was 113° (95% confidence interval, 108° to 118°) in 26 knees that received a rotating platform and 111° (95% confidence interval, 115° to 125°) in 22 knees that received an anterior-posterior gliding bearing (p = 0.57).	"The use of a mobile bearing that allowed free anterior-posterior translation did not regularly restore femoral rollback and did not improve range of motion after total knee arthroplasty compared with the findings seen in association with the use of a rotating platform."	Comparable results at 1 year.
Beard 2007 Follow-up and Cohort RCT	7.5	N = 40 (TMK vs. AGC follow-up study); N = 172 (unilateral TMK cohort study)	TMK mobile bearing prosthesis vs. AGC fixed bearing prosthesis in same patient in follow-up; unilateral TMK mobile bearing prosthesis in cohort study.	No statistically significant differences between groups or in outcomes in either study.	"The step-wise method, using an RCT to compare functional outcome against a standard implant, followed by a cohort study to estimate complication rate, is recommended as a useful strategy for the introduction of new implants into surgical practice."	Data suggest more asymptomatic clicking with TMK.
Price 2003 RCT	7.5	N = 40 (16 males, 24 females; mean age 73.1, range 54.8 to 86.4)	Fixed-bearing device (AGC) vs. mobile-bearing device (TMK), 1 each in each patient undergoing bilateral TKA.	Mean scores at 1 year follow-up for mobile-bearing device (TMK) better than AGC, using AKSS (p = 0.015), the OKS (p = 0.013) and both measurements of pain (AKSS, p = 0.015; OKS, p = 0.009).	"Our study has shown that a bilateral randomised, clinical trial can reveal significant differences while putting at risk many fewer subjects than in a unilateral randomised clinical trial. We believe that this is the first controlled, single-blind trial to have shown a small, but significant early clinical advantage for a mobile-bearing over a fixed-bearing TKA."	Data suggest lower pain scores with TMK.

Hasegawa 2009 RCT	7.0	N = 25 undergoing staged bilateral TKA with mobile-bearing TKA on 1 side and fixed-bearing TKA on other (average interval 8.7 months; range 2-28 months)	Staged bilateral TKA with mobile-bearing TKA on 1 side vs. fixed-bearing TKA on the other.	Both knee scores and function scores significantly improved post-op in mobile-bearing and fixed-bearing TKAs ($p < 0.01$).	“Although it is difficult to draw valid conclusions from our small and long-term results from our patients are required to provide useful information, early results indicate no significant differences in the clinical and radiographic findings between mobile-bearing and fixed-bearing posterior-stabilized TKAs using the same design of femoral component in the same patients. Satisfactory early results can be achieved in both prostheses. We could not demonstrate an early advantage for a mobile-bearing knee and our hypothesis was verified.	Average 40 month follow-up. Data suggest comparability.
Munro 2010 RCT	6.5	N = 46 (54 knees) with degenerative knee disease undergoing TKA; follow-up included 41 patients, 48 knees (25 rotating platform, 23 fixed platform knees)	PFC Sigma fixed-platform (fixed-bearing) vs. PFC Sigma rotating-platform (mobile-bearing) total knee system.	No major complications, no revisions, and no loose implants according to criteria of Knee Society score [3] in either group.	“Our qCT data concur with the current literature in showing substantial tibial BMD loss after TKA. Furthermore, we found tibial cancellous BMD loss is more pronounced than cortical BMD loss, a phenomenon that may not be apparent on conventional radiographic imaging. We were unable to detect a difference in tibial BMD change between rotating and fixed TKA platforms.”	Data suggest no differences in bone density loss at 2 years.
Kim 2007 RCT	6.5	N = 194 with 10 patients lost to follow up; 174 patients (348 knees)	Press-fit condylar Sigma mobile-bearing (rotating platform) vs. press-fit condylar Sigma fixed-bearing in primary bilateral simultaneous TKRs.	No differences found between groups regarding total knee score, pain score, functional score, and range of movement ($p > 0.05$).	“After a mean follow-up of 5.6 years, excellent clinical and radiological results can be achieved with both PFC Sigma mobile- and fixed-bearing cruciate-retaining total knee designs. However, there was no significant clinical advantage for a mobile-bearing over a fixed-bearing TKR.”	Data suggest comparable results.

Breugem 2008 RCT	6.5	N = 103 unilateral OA of knee	Posterior-stabilized fixed-bearing (PS) vs. posterior-stabilized mobile-bearing (PSM) prosthesis.	American Knee Society score comparing anterior knee pain vs. no anterior knee pain: 65.3 vs. 85.6; p <0.001. Knee pain walking up and down stairs (mild/severe pain): 75% vs. 12.5%; p <0.001.	“Our data support the notion that the PSM prosthesis reduces the short-term incidence of anterior knee pain relative to the PS prosthesis. Longer followup will determine whether this difference will persist or decrease.”	Blinding not well described. Data suggest less anterior knee pain in posterior stabilized weight-bearing group.
Wylde 2008 RCT	6.5	N = 242 (250 knees) 132 females, 110 males, mean age 68 (range 40 to 80); 12 lost to follow-up	Fixed-bearing vs. mobile-bearing.	No significant differences found for any of outcomes listed for either group.	“In conclusion, no statistically significant differences were found in patient-reported outcomes between the Kinemax Plus fixed- and mobile-bearing implants up to two years post-operatively.”	Two-year follow-up. Data suggest comparable outcomes.
Kim 2004 RCT	6.5	N = 190 (11 males, 179 females, mean age 64); 6 of initial 196 lost to follow-up and not included in study	Anterior-posterior glide Low Contact Stress mobile-bearing prosthesis vs. rotating-platform Low Contact Stress mobile-bearing prosthesis in consecutive primary bilateral total knee arthroplasties.	Post-op pain scores according to both knee-scoring systems not significantly different between groups, with numbers available (p = 0.4652).	“After a minimum duration of follow-up of five years, the results associated with the anterior-posterior-glide and rotating-platform Low Contact Stress mobile-bearing total knee replacements were favorable and comparable.”	Data suggest comparable outcomes.
Gleeson 2004 RCT	6.5	N = 91 (104 knees) with different arthroplasties implanted in each knee	St. Georg Sled fixed-bearing implant vs. Oxford meniscal-bearing (mobile-bearing) unicompartmental replacement.	Mean 2-year post-op Bristol knee score comparing St. Georg Sled vs. Oxford: 89 vs. 84.1; p = 0.013. Mean total pain score: 34.9 vs. 30.7; p = 0.013.	“Although the short-term complication rate and clinical outcome were less good with the Oxford prosthesis, it would seem highly likely that for both groups, prostheses that had a good result at 2 years will function satisfactorily for several years and that beyond 10 years, the fixed bearing prostheses will fail at a greater rate.”	Two-year follow-up. Data suggest high pain and more reoperation with Oxford.
Kim 2005 RCT	6.5	N = 50 (2 males, 48 females with a mean age 68)	Standard fixed-bearing (NexGen LPS) prosthesis vs. high-flexion fixed-bearing (NexGen LPS-Flex) prosthesis in consecutive primary bilateral total knee arthroplasties.	Mean ROM for knees with standard prosthesis was 135.8° (range, 105° to 150°) vs. those with a high-flexion prosthesis had a mean ROM of 138.6° (range, 105° to 150°) (p = 0.41).	“After a minimum duration of follow-up of two years, we found no significant differences between the groups with regard to range of motion or clinical and radiographic parameters, except for posterior femoral condylar offset.”	Data suggest comparable outcomes except greater in NexGen LPS Flex group.

Henricson 2006 RCT	6.5	N = 47 (52 knees, average age 72, range 62-84)	NexGen cruciate-retaining fixed-bearing cemented TKA vs. MBK mobile bearing cemented TKA.	From 3-24 months maximum subsidence larger ($p = 0.05$) for MBK implants, and maximum lift-off significantly larger ($p = 0.02$) for NexGen implants. Clinical result did not differ between 2 groups.	“The hypothesis that mobile-bearing implants of this design would result in improved fixation of the tibial implant could not be confirmed. In no way did these mobile-bearing implants perform better than the fixed-bearing ones.”	Two-year follow-up. Outcomes not different. However, subsidence and lift-off favored fixed bearing over mobile.
Harrington 2009 RCT	6.0	N = 132 (72 fixed-bearing or FB and 68 rotating platform or RP)	Fixed bearing (FB) vs. rotating platform (RP) prostheses in unilateral total knee arthroplasty.	At 6 weeks ROM $96.5^{\circ} \pm 2.1^{\circ}$ and $102.1^{\circ} \pm 1.7^{\circ}$ for FB and RP groups, respectively; $p = 0.039$. At 1 year, ROM for FB was $114.5^{\circ} \pm 1.9^{\circ}$ and RP was $119.8^{\circ} \pm 1.6^{\circ}$; $p = 0.032$.	“This study supports the conclusion of several other studies that there is no clinically significant difference in the early functional outcomes between FB and mobile-bearing total knee arthroplasties. Longer-term follow-up is needed to determine if there are changes in the functional results or if the mobile-bearing designs will live up to their potential advantages in terms of wear and longevity.”	Two-year follow-up. Data suggest comparable outcomes.
Gioe 2009 RCT	6.0	N = 358 age 60-85 (400 joints) to start; 273 followed up with 312 arthroplasties	Cruciate-substituting rotating-platform design vs. fixed-bearing design with all-polyethylene tibial component.	No significant improvements or differences in both groups with regard to mean post-op ROM; mean KSS clinical score; mean KSS pain score.	“The two designs functioned equivalently at the time of early follow-up in this low-to-moderate-demand patient group. The rotating-platform design had no significant clinical advantage over the design with the all-polyethylene tibial component.”	Data suggest comparable outcomes.
Lädermann 2008 RCT	6.0	N = 102 (104 knees); 12 lost to follow-up with 92 in mid-term results; average age 70	FB (fixed-bearing) vs. MB (mobile-bearing) posterior-stabilized prostheses.	No significant differences of FB over MB design could be demonstrated with respect to American Knee Society score; pain score, a questionnaire of general health (SF-12 score), ROM, or complication rates.	“In conclusion, our study does not show any clear advantage in terms of function, pain, range of motion, general health, and radiological signs of loosening of the fixed-bearing or mobile-bearing total knee arthroplasty at a mean follow-up of 7.1 years.”	Average 7.1 year follow-up. Data suggest comparability.

Seon 2009 RCT	5.5	N = 100 (50 in each group); initially 104 in study group but 4 lost to follow-up	High-flexion group (6 males, 44 females, average age 69.2 years, range 50-85) vs. standard group in unilateral primary TKA (10 males, 40 females with an average age of 67.5 years, range 54-82).	No significant differences found between groups regarding weight-bearing flexion and number of knees that allowed kneeling and sitting cross-legged.	"In conclusion, although short-term clinical outcomes were satisfactory, the high-flexion cruciate-retaining knees did not have greater knee flexion compared with those that had the standard cruciate-retaining design. We conclude that maximal flexion after total knee arthroplasty is probably dictated more by patient characteristics and surgical technique than by differences between the designs of the implant used."	Mean 26 month follow-up. Data suggest comparable results.
Confalonieri 2004 RCT	5.5	N = 40 (20 in each group); with medial compartment knee arthritis; average age 69	Group A, UKR with a fixed tibial bearing vs. Group B, UKR with a mobile tibial bearing.	No statistically significant difference in outcome observed between 2 groups.	"In conclusion, despite its widespread use, no advantage could be detected for a UKR with a mobile bearing over a fixed bearing design in terms of clinical performance and longevity in this prospective randomized study."	Mean 5.7 year follow-up. Comparable outcomes.
Kim 2001 RCT	5.0	N = 116; (80 females, 36 males, average age 65), and 110 patients with OA and 6 with RA	Fixed bearing total knee prosthesis (AMK) in 116 knees (58 in each of right and left sides) vs. mobile meniscal-bearing total knee prosthesis (LCS) in 116 knees (58 in each of right and left sides).	No statistical significance for any clinical results in either group. For radiographic results, patella component angle AMK Group: 5.4° (range 0-16°, SD 4.55) vs. LCS Group: 8.8° (range 0-28°, SD 7.04), p = 0.017. In both groups, mean ROM 118° (SD, 20.78) in knees with a post-op joint line change more than 5mm compared with pre-op joint line, 123° (SD, 11.66) in knees with a post-op joint line change <5mm compared with pre-op joint line, p = 0.002. Prevalence of radiolucent lines: overall-AMK Group 33.6% vs. 25% LCS Group; Tibial Side - Zone 1 (<1mm) AMK Group 29% vs. 17% LCS Group, Zones 1 and 2 (<1mm) AMK Group 0.9% vs. 0.0%	"The results of mobile-bearing total knee replacements after a minimum followup of 6 years are favorable and comparable with fixed-bearing designs in terms of total knee score, pain score, functional score, ROM, polyethylene wear, aseptic loosening, and periprosthetic osteolysis. However, there is no evidence to prove the superiority of the mobile-bearing total knee designs."	Unclear if side randomized. Data suggest comparable outcomes.

				LCS Group, Zone 4 (<1mm) 0.0% AMK Group vs. 0.9% LCS Group; Femoral Side - Zone 1 (<1mm) AMK Group 3.4% vs. 6.8% LCS. Lateral patella tilt – AMK Group 14% vs. LCS Group 17%.		
Hansson 2005 RCT	5.0	N = 52 (26 men and 26 women)	Rotaglide Total Knee System prosthesis (mobile polyethylene platform) vs. Nuffield Total Knee System prosthesis (fixed tibial bearing).	No difference in clinical outcome. Though ROM improved in both groups (107 -117 at 2 years). No p values or CIs reported.	“In conclusion we found that there were no differences between the mobile and the fixed bearings regarding the fixation measured as the migration over time; both designs showed only a small number of continuously migrating prosthesis. Also, inducible displacement was very low and similar between the two groups. For the mobile meniscal knee we found that there was motion between the polyethylene insert and the metal base=plate according to the design rationale even after 1 year.”	Two-year follow-up. Data suggest comparable outcomes.
Li 2006 RCT	5.0	N = 48 (58 knees), 34 males, 14 females, mean age 72	Fixed vs. mobile meniscal bearing knee prosthesis in unicompartmental knee arthroplasty for medial compartmental OA.	MB knees had larger incremental increase in tibial internal rotation than FB 4.3°, 7.5°, 9.5° vs 3.0°, 3.0°, 4.2° respectively (at 30, 60, and 90°); 90° difference significant (p = 0.043). Incidence of radiolucent lines at tibia implant interface higher in FB knee (p = 0.005). Knee society, WOMAC, and SF-36 scores increased in both groups, but did not differ from each other significantly in any area.	“In summary, a closer approximation of normal kinematics and a lower incidence of radiolucency was found in the mobile bearing UKA. However, these advantages have not translated into any improved clinical outcomes at 2 years follow-up.”	Function comparable, but less radiolucency at 2 yrst with mobile bearing.
Pagnano 2004 RCT	4.5	N = 240 with advanced OA who had a primary unilateral TKA	Single posterior-stabilized knee design with identical femoral and patellar components with different tibial components: rotating platform tibia group vs.	At 1-year follow-up, each of 3 groups had significant (p < 0.01) increase in respective stair climbing scores compared with pre-op scores. Post-op knee pain and function scores improved (p < 0.05) in each of the 3	“This study suggests that surgeons and patients should not expect a posterior stabilized rotating platform knee replacement to decrease the prevalence of lateral retinacular release	One-year follow-up. Some details sparse. Comparable results.

			all-PE tibia group vs. modular metal-backed tibia group.	treatment groups, but not different among 3 groups.	and patellar tilt or subluxation, nor increase knee flexion, nor improve stair climbing ability at 3 months or 1 year postoperatively when compared with a posterior-stabilized fixed-bearing knee replacement.”	
Aglietti 2005 RCT	4.5	N = 197 (210 knees) with primary TKA; 17 underwent staged bilateral TKA with LPS on 1 side, MBK on other	Fixed-bearing total knee prosthesis (LPS) vs. mobile-bearing total knee prosthesis (MBK).	No difference between LPS and MBK TKAs with respect to Knee Society functional score pre-op or at 36 months follow-up (p = 0.40 and p = 0 .71).	“Our study has shown that using a fixed-bearing or mobile-bearing design, when all the other variables are controlled, did not seem to influence the outcome in short-term FU.”	Mean 3 years follow-up. High dropouts. Data suggest comparability.
Garling 2005 RCT	4.0	N = 33 and 42 TKPs	Fixed-bearing posterior stabilized (PS) prosthesis vs. mobile-bearing (MB) prosthesis in primary cemented total knee prostheses.	No significant differences in scores at any follow-up between groups. No significantly different radiographic results. No significant differences in translations and rotations between groups. “PS group had higher variability in subsidence (p = 0.04) and rotation about the transverse axis (p = 0.05).”	“The low variability of the data in the MB knee prosthesis group suggests that this design is more predictable and forgiving with respect to micro-motion of the tibial component.”	Two year follow-up. Mostly RA patients. Outcomes did not significantly differ.
Wohlrab 2009 RCT	4.0	N = 60 (30 in each group) Follow-up at 3 months and 3 and 5 years	High flex knee (NexGen LPS Flex mobile) vs. regular PS knee (NexGen LPS).	At 3 months: high flex group favored significantly in ROM (15.25±1.34 vs. 13.5±1.64), pain (29.0±2.03 vs. 27.17±4.29, and total HSS score (87.21±3.89 vs. 82.68±6.8). High flex group had significant better knee flexion (122.5°±12.78°). No significant differences at 3 and 5 years.	“Up to 5 years after the surgery, the theoretical advantages of the mobile bearing knee system are not reflected in the clinical results of the presented study.”	High dropouts at 5 years. Data suggest comparable results at 5 years.
Saari 2003 RCT	4.0	N = 22 (5 males, 17 females) median age 69 (range 59-80)	Standard Design (7 patients) vs. Spherical design (8 patients) vs. Mobile design bearing (7 patients).	Relative tibial and femoral motions: tibial rotations (degrees) abduction: mobile 1.3 (range 7.2-2.2) vs. spherical 5.2 (range 8.2-0.2), p = 0.03. Antero-posterior displacement of midpoint of tibial component, more anterior position	“The short-term clinical results in the current study were equal to results of studies of other designs of total knee replacements without any difference among the three groups. The pattern of motion also were similar concerning most of	Small sample sizes. Minimal patient data. Follow-up time unclear. Data mostly stereometric and suggest some differences.

				observed in mobile bearing vs. other groups (p = 0.02 mobile bearing vs. standard, p = 0.01 mobile bearing vs. spherical). Displacements of circular center of medial femoral condyle.	the kinematic parameters evaluated. There were, however, some differences, which can be of importance for the stability and long-term results.”	
Saw Blade						
Toksvig-Larsen 1994 RCT	5.0	N = 33 (15 males, 18 females (mean age 73, range 60-87)	Non-cemented knee arthroplasties with tibial bone cut via a standard 3M Maxi Driver oscillating L 122 saw blade vs. an internally-cooled saw blade.	At 1 year, all tibial components migrated 1.2 (0.6-2.0)mm in standard saw group and 1.7 (0.5-4.1) mm in cooled saw group. At 2 years, tibial components migrated 1.4 (0.8-2.6) mm for standard and 2.0 (0.4-4.5) mm for cooled saw group. At 6 months, difference in MTPM between 2 saw blades with 0.7 for standard and 1.2 for cooled. At 2 years, tendency towards less migration in cooled saw group. Significant difference between saw blade positions 2 and 5, 0.4mm and 0.5mm (MTPM), favoring cooled saw group.	“Our study showed greater stiffness in the bone-prosthesis interface when using an internally cooled saw blade, and a tendency to less continuous migration, when using the PCA bossed tibia component with screw fixation. This may indicate a positive effect of the cooled saw blade on prosthetic fixation.”	Two year follow-up. Data suggest more migration total point motion in cooled blade.
Polyethylene vs. Metal-backed Components						
Hyldahl 2005 RCT	6.0	N = 40 with Ahlbäck Grade III-V primary arthrosis, with bilateral disease with or without surgery and previous meniscectomy	All-polyethylene (AP, n = 20) vs. metal-backed (MB, n = 20). Participants also stratified by age, less than 65 or greater than/equal to 65; 2 years follow-up.	Tendency for higher rotation of MB than AP components. Significant difference at 3 months for anterior/posterior and varus/valgus tilt in favor of AP. MB components showed more lift off at 3 months, p = 0.001.	“[A]P components had better fixation than MB tibial components using 8 mm plateaus and only proximal cementing. Based on these findings, we believe that AP components should be used more frequently, especially in the standard patient with thin components are to be inserted.”	Second report of trial. Small sample sizes in each group.
Hyldahl 2005 RCT 2nd report of Hyldahl 2005 above	6.0	N = 39 (40 knees). Ahlbäck Grade III-V primary arthrosis, with bilateral disease with or without surgery and	All-polyethylene (APCC) or metal-backed (MBCC). Outcomes were assessed at 3, 12 and 24 months.	No statistically significant difference between groups.	“Our findings indicate that there was equal initial fixation of the AP and MB stemmed monobloc components when they were cemented beneath the tibial plateau and around the stem.”	Data suggest comparable results

		previous meniscectomy				
Norgren 2004 RCT	6.0	N = 21 (23 knees) with Ahlbäck Grade III-V primary gonarthrosis, >60 years, body weight <120kg	All-polyethylene vs. metal-backed tibial prosthesis. Outcomes were assessed at 3, 12, and 24 months.	Median migration of AP implants tended to be slightly lower than MP and statistically significant at 24 months for internal/external rotation, maximum subsidence and maximum migration. Five out of 11 MB implants classified as unstable at 12 and 24 months.	"[T]here appears to be little evidence to support any advantage of metal backing over an AP component in patients over 60 years of age. This conclusion also appears to be valid irrespective of the design of the tibio-femoral articulation. Moreover, using an AP implant eliminates the risk of backside wear, inherent in the MB component."	Data suggest metal backed components migrated more.
Muller 2006 RCT	6.0	N = 51 primary OA or RA, ≥65 years randomized but 10 did not receive allocated intervention ; analyses on 40 participants	All-polyethylene vs. metal-backed tibial prosthesis. Outcomes assessed at 6, 12, and 24 months.	No statistically significant differences in translation in x, y, or z planes between 2 groups at 24 months. No statistically significant difference in SF-12 scores between 2 groups. No statistically significant differences between 2 groups at any point in time for Oxford Knee Score and varus-valgus tibial alignment after operation.	"In an uncomplicated primary total knee replacement the all-polyethylene PFC-Σ tibial prosthesis showed no statistical difference in migration from that of the metal-backed counterpart."	Data suggest comparable outcomes between polyethylene and metal.
Adalberth 2001 RCT	6.0	N = 40 (40 knees) with Ahlbäck Grade III-V primary OA, over age 50, weight below 100kg	All-polyethylene tibial components (n = 20) vs. stemmed metal-backed tibial components. Outcome assessments conducted at 4, 12 and 24 months.	Most AP components classified as stable. Half of MB components migrated continuously between 1 and 2 years. Median Knee Society knee and function scores increased significantly in both group up to 12 months, p <0.001.	"[T]here is little evidence to support the possible advantages of metal backing over an AP cemented tibial component. Migration of AP implants was equivalent to that of MB implants, which suggests a good long-term prognosis."	Second report of Adalberth 2000.
Adalberth 2000 RCT	6.0	N = 34 (40 knees) with Ahlbäck Grade III-V primary OA	All-polyethylene tibial components (n = 17) vs. stemmed metal-backed tibial components (n = 17). Outcome assessments conducted at 4, 12 and 24 months.	Maximum lift-off of the tibial component from the tibia was significantly larger in the MB group compared to AP at all times, p = 0.02-0.03.	"In this study, no negative consequences regarding the quality of fixation using an all-polyethylene tibial component with unconstrained articulation surfaces could be identified."	Data suggest comparable results.

Bettinson 2009 RCT	5.5	N = 510 (566 knees) with OA or RA	All-polyethylene vs. metal-backed components. All received Kinemax Plus prostheses; 10 years follow-up. Follow-ups at 3 months, 1, 3, 5, 8, and 10 years, with mean follow- up duration of 6.5 years.	The 10 year survivorship for entire group 95.3%. Subgroup analyses of revision reasons and component type between 94.5% and 97%. No statistically significant differences between groups for survivorship at any timepoint; 28 knees received revision, (19 for aseptic failure). Patients undergoing revision for aseptic failure nearly statistically significantly younger ($p = 0.051$) for all-polyethylene group.	“Our results demonstrate excellent survivorship at 10 years, with no significant difference between the 2 designs.”	High dropouts. However, 10 year follow-up data. Data suggest comparable outcomes. 28/293 (9.6%) TKAs had been revised.
Hyldahl 2001 RCT	5.0	N = 42 (45 knees) with primary Stage I to III medial arthrosis, no previous knee surgery except meniscectomy, intact ACL, no tibial translation, ROM 10- 90° and clinical symptoms and primary pain which indicated surgical treatment	All-polyethylene vs. metal-backed tibial prosthesis, Miller Galante. Outcomes were assessed at 6, 12, and 24 months.	Weak positive correlation between varus leg alignment and MTPM at 1 year after surgery, $p =$ 0.011.	“Our findings do not support better fixation with MBT. Because of these findings, we advocate APT in UKA. These components provide optimal biomechanical strength at a given height of the tibial component. Possible problems of modularity would be avoided, and the amount of interfaces would be minimized. These potential advantages would be achieved at a lower cost.”	Data suggest comparable outcomes over this duration and authors suggest preference for all polyethylene components to metal.
Cement vs. Hydroxyapatite Fixation						
Önsten 1998 RCT	7.5	N = 116 (146 knees) with primary knee OA; unilateral in 56, bilateral in 30	Hydroxyapatite- augmented porous coating (HAPC) ($n = 78$) vs. plain porous coating ($n = 73$) vs. cemented fixation ($n = 76$). Outcome assessments at 3, 12, 24, 36 months.		“We conclude that hydroxyapatite augmentation may offer a clinically relevant advantage over a simple porous coating for tibial component fixation, but is no better than cemented fixation.”	Data suggest least motion over 24 months with cement, although gap narrowed with time.
Carlsson 2005 2 RCTs	7.0	N = Series I: 90 undergoing unilateral TKR; Series II: 30 undergoing	Each series randomized to cemented fixation (CF) vs. uncemented porous fixation (UC-F) vs. uncemented		“At the 2-year follow- up, we concluded that hydroxyapatite- coated porous (UCHA-F) implants were more stable than porous implants without an	Femoral components cemented and uncemented. Data suggest least rotation and motion with cement.

		bilateral, simultaneous TKR	hydroxyapatite-augmented fixation (UCHA-F). Outcome assessments conducted at 12, 24, 36 and 60 months.		hydroxyapatite coating between 12 and 24 months postoperatively. After 5 years, there was a small but statistically non-significant difference in migration between hydroxyapatite-coated and porous implants.”	
Nilsson 2006 RCT	6.5	N = 85 (97 knees) with OA inflammatory arthritis who underwent TKA	TKA with fixation of tibial components cemented (n = 34) vs. uncemented (HA coating) with screws (n = 28) vs. uncemented (HA coating) without screws (n = 35). Outcome measurements assessed at 6 weeks, 3, 6, 12, and 24 months.		“In conclusion, for patients younger than 65 years, an uncemented HA-coated tibial component of the present design without additional screw fixation seems to be the design with the highest probability for long-term survival regarding fixation.”	Cemented fixation had less motion at 3 months, but difference gone at 2 yrs. Cemented trended towards lower knee society median scores at 24 months (p = 0.06). Included age < 65 only.
Nelissen 1998 RCT	6.0	N = 23 (31 knees) for total knee arthroplasty	Fixation with cement vs. fixation without cement vs. hydroxyapatite coating fixation without cement. Outcome measures were assessed at 1, 3, 6 weeks, 3, 6, 12 months.	Surgery time (minutes) for cementing tibial component vs. hydroxyapatite coated-coating vs. noncoated component without cement: 134±10.2 vs. 120±9.0 vs. 120±13.8, p <0.05. Noncoated subsided more than hydroxyapatite-coated components and cemented components, p <0.05. Micromotion along sagittal axis statistically different between noncoated and cemented components (p = 0.01) and between noncoated and hydroxyapatite-coated components (p = 0.03). Micromotion along transverse axis significantly lower for cemented and hydroxyapatite-coated than noncoated components, p <0.01.	“In conclusion, tibial components fixed with cement and hydroxyapatite-coated tibial components fixed without cement have far less micromotion along the three orthogonal axes than do noncoated tibial components fixed without cement.”	Blinding not well described. Mostly RA. Data suggest more micromotion in uncoated than cemented or HA coated which were similar.
Beaupré 2007 RCT	6.0	N = 81 undergoing primary total knee arthroplasty to treat	Total knee arthroplasty with hydroxyapatite-coated tibial component (n = 40) vs. with	No significant differences between groups. WOMAC pain scores (baseline/6 months/1 year/5 years): HA	“In summary, we cannot recommend or discourage the use of cementless tibial fixation with hydroxyapatite	Randomization methods not well specified but groups appear well randomized. Data suggest

		non-inflammatory arthritis	cemented tibial fixation (n = 41). Outcome measures assessed at 6 months and 1 and 5 years.	(42.7/72.2/81.5/79.0) vs. cement (45.0/81.3/79.7/80.6).	instead of cemented tibial fixation, as patients reported similar five-year clinical outcomes and similar results were seen on plain radiographs.”	equivalent outcomes at 5 years.
Uvehammer 2007 RCT	5.5	N = 50 with non-inflammatory arthritis of Ahlbäck Grade 2 to 5	Cemented or uncemented implants with either standard components, rotating platform, or FS 100 for total knee replacement.	At 2 years, rotating platform more posteriorly tilted than FS 100: 0.25 (-0.71° to +1.78°) vs. 0.15° (-1.28° to +1.31°), p = 0.04. Standard more anteriorly tilted vs. rotating platform: -0.16° (-1.65° to +1.35°), p = 0.04.	“At two years we found no differences when the fixation of the cemented and uncemented, HA-coated, femoral components were compared.”	Small numbers per group. Sparse description of groups. Data suggest modest difference between groups at 2 years.
Nilsson 1999 RCT	5.0	N = 56 (60 knees) with Ahlbäck OA Grade III to V and/or rheumatoid arthritis	Insertion with hydroxyapatite coated (n = 29) vs. cemented tibial components (n = 28).	MTPM larger in HA group than cemented group at 6 weeks (p = 0.02) and 3 months (p = 0.04). Maximum subsidence larger in HA group up to 12 months (p = 0.001-0.04). Absolute mean (SD) internal/external rotation at 3 months between HA vs. cemented: 0.34 (0.33) vs. 0.09 (0.07), p <0.05. Absolute mean (SD) varus/valgus rotation at 6 months: 0.31 (0.27) vs. 0.14 (0.11), p <0.05. Knee Society score and function score increased significantly between 6 weeks and 2 years for both groups, p = 0.001. After 2 years, cemented group significantly decreased in functional score, p = 0.03.	“At 5 years, there were no differences between cemented and HA-coated tibial components as regards fixation.”	High dropouts at 5 years. Data suggest HA coated migrates more in first 30 months, then by 5 years, cemented has migrated equivalent amount.
Hansson 2008 RCT	5.0	N = 60 knees with gonarthrosis undergoing total knee replacement	Hydroxyapatite coating vs. porous coating only. Clinical analysis done at 6 weeks, 3, 6, 12, and 24 months.	Y-translation migration significantly lower in hydroxyapatite coating group at 6-months to at least 2 years, p <0.05. Major clinical improvement achieved at 6 weeks.	“Addition of a solution-deposited HA coating appears to provide better early stable fixation in a porous coated knee prothesis.”	Unequal groups due to “decision to change to cement fixation.” Numbers of those protocol violations somewhat unclear. Patients not well described. HA coating reduced subsidence though not maximum total point rotation

Regnér 2000 RCT	4.5	N = 45 (51 knees) with Grade III to V OA	Uncemented implant of Freeman Samuelson Hydroxyapatite (FS HA) vs. Miller-Galante II (MG II) design. Outcome assessments at 1, 3, 5 years.	MG II group had more migration in terms of MTPM ($p = 0.028$) and maximum ($p = 0.01$) subsidence. FS HA components only subsided during first 6 months, and then stabilized.	"The stability of the implants obtained is equal to or better than cemented implants after 5 years."	Appears to be 3rd report of Regner 1998. Data suggest HA coated had better maximum total point scores, subsidence and tilt.
Petersen 2005 RCT	4.5	N = 18 with primary OA who underwent unilateral total knee arthroplasty using posterior cruciate ligament-retaining total condylar knee	Tibial components with a cast-mesh ingrowth surface with hydroxyapatite coating vs. without. Outcome measurements assessed at 2 weeks and 3, 6, 12, 24 months.	Mean (range) percent change in bone mineral density from 0 to 24 months at lateral measuring site for no coating vs. coating: 6.1 (2.1 to 16.3) vs. -4.3 (-16.9 to 6.7), $p = 0.005$.	"[O]ur study showed that the Interax tibial component with a cast-mesh ingrowth surface, with or without HA coating, induced a very beneficial bone remodeling pattern without loss of bone mineral."	Small groups (8 each). Data suggest more bone mass density loss in 1 measure (lateral) in HA coated group.
Regnér 1998 RCT	4.0	N = 36 (40 knees) with Ahlbäck Grade III to V osteoarthrosis undergoing total knee arthroplasty with uncemented Miller Galante II prostheses	Tibial components with hydroxyapatite and tricalcium phosphate (HA/TCP) vs. without. Outcome measurements assessed at 1 week, 2, 12, and 24 months.	Less anterior or posterior tilt for HA/TCP group over 2 years, $p = 0.02$. Maximal subsidence in lateral plan less in uncoated group over 2 years, $p = 0.03$. Knee society Scores less in HA/TCP group at 2 years compared to cemented, $p < 0.02$.	"We have found no adverse effects of HA/TCP, and the stable fixation of the coated components is promising. The long-term effects of ceramic coating are still not completely known."	Patients not well described. Data suggest outcomes comparable. Subsidence and motion appeared greater in uncoated.
Fixation with or without Cement						
Gao 2009 RCT	5.5	N = 41 who underwent total knee arthroplasty due to primary OA or OA secondary to trauma	Cobalt-chrome NexGen CR femoral component with titanium fibre mesh with cement ($n = 19$) vs. uncemented ($n = 22$) trabecular metal cruciate retaining tibial component. Clinical evaluations conducted pre-op at 6 weeks, 3, 12, and 24 months.	Median (range) KS knee score at 3 months for cemented vs. uncemented: 72 (44-95) vs. 81 (53-95), $p = 0.03$. Median (range) KS pain score at 3 months: 40 (20-50) vs. 45 (10-50), $p = 0.03$.	"In patients under the age of 60 years using the NexGen cruciate-retaining TKA there were no significant differences in outcome both clinically or radiologically or on radiostereometric analysis when comparing a cemented with an uncemented femoral component. The RSA findings suggest that an uncemented and non HA-coated femoral component may behave equally as well as a cemented one in the long-term."	Baseline data somewhat better in cemented group. Tibial components changed half way through trial. Most data suggest comparable outcome at 2 years. Included ages under 60 only.

Dalén 2005 RCT	5.5	N = 59 (61 knees) with primary gonarthrosi s underwent TKR with metal-backed Profix®	VersaBond (VB, n = 32) cement vs. Palacos (PC, n = 29) cement. Outcome assessments conducted at 3, 6, 12 and 24 months.	No significant differences between groups.	"In conclusion, the result of this study indicates that VersaBond bone cement will perform at least equally as well as Palacos R in the tibial components of total knee replacement as far as aseptic loosening is concerned."	Baseline data not well described. Data suggest comparable results.
Hilding 2000 RCT	5.5	N = 49 with Ahlbäck stage 3-5 gonarthrosi s undergoing total knee arthroplasty	Cemented NexGen implants with 400mg clodronate (Bonafos) vs. with placebo. Outcome assessments post-op at 6 weeks, 6 months, 1 year.	MTMP mm (SD) between clodronate vs. control at 1 year: 0.29 (0.11) vs. 0.40 (0.16), p = 0.01.	"Since early migration is related to late loosening, 6 months of clodronate medication might reduce the risk of loosening."	Patients not well described. Data suggest clodronate reduces migration at 1 year. No long term outcomes.
Dunbar 2009 RCT	4.5	N = 70 randomized to 2 groups (36 and 34) with 8 and 13 loss to follow up respectively	Trabecular metal uncemented implant vs. cemented tibial implant; 24 months follow-up.	Pre-op WOMAC score between 2 groups trending toward statistical significance (p = 0.152). Trabecular metal group statistically significantly higher variability in maximum total point motion at all follow-up points (p = 0.019). Between 12 and 24 month follow-ups, statistically significantly different maximum total point motion (p <0.000), lateral/medial translation (p <0.001), and internal/external rotation (p <0.001). Upon radiosterometric analysis, statistically significant differences between lateral/medial translation (p <0.0001 for valgus vs high varus) and valgus/varus tilt (p <0.0001 for valgus/neutral vs. varsu/high varus. All other analyses statistically negative.	"This study suggests that Trabecular Metal component may be an effective alternative to the standard cemented tibial component."	Biomechanical/ stereo analyses. Not powered for more typical measures of function which did not differ statistically.
Toksvig-Larsen 1998 RCT	4.5	N = 25 (26 knees) with knee OA	Insertion of tibial component with cement (n = 11) vs. without cement (n = 15).	Y-translation between cement vs. uncemented: -0.11±0.03mm vs. 0.05±0.04, p = 0.008. Maximum total point motion for cement vs. uncemented at 6-week follow up: 0.7±0.3mm	"[W]hen there is little inducible displacement of a prosthesis after six weeks there will be little inducible displacement after one year and little	Baseline differences suggest trend to better pre-op function in uncemented group. Data suggest more maximum total

				vs. 0.9±0.1mm; 6 months: 1.0±0.2mm vs. 1.4±0.2mm; 1-year evaluation: 1.0±0.2mm vs. 1.4±0.2mm; 2-year evaluation: 1.0±0.1mm vs. 1.5±0.2mm, p = 0.061, repeated-measures analysis of variance all time periods. Proportion of continuously migrating prostheses same between groups. Prosthesis subsided 0.0±0.1 mm in cement vs. 0.5±0.1mm in uncemented, p = 0.008.	migration after two years.”	point motion scores in uncemented, though stable from 6 months to 2 years.
van der Linde 2006 RCT	4.5	N = 21 (26 knees) with RA undergoing primary cementless TKA	Uncoated Duracon implant vs. Duracon implant coated with calcium phosphate (PA). Outcome measurements assessed at 1 week and 3, 6, 12, and 24 months.	Uncoated components had higher variance in subsidence compared to PA coated components, p = 0.007.	“Although we noted no differences in migration between uncoated and PA-coated implants, we saw a trend for less subsidence and anterior tilting in patients with PA-coated implants. We observed lower variance in migration when PA-coated implants were used.”	All RA patients; small sample size. Data suggest comparable results for main health outcomes.
Albrektsson 1992 RCT	4.0	N = 36 (37 knees) with stage IV-V OA/RA with complete destruction of cartilage in 1 or more compartments	Cement (18 knees) vs. uncemented (19 knees).	Cemented vs. uncemented mean±SD MTPM during 1 year: 0.5mm±0.3/1.5mm±1.1 /Mann Whitney's U test p <0.01. Direction of migration: 0.02mm±0.3/0.7mm±1/ p <0.01	“[A] proximally placed layer of PMMA under the tibial component enhances its security, presumably by increasing the contact area and increasing the shear and tensile strengths of the interface as compared with a press-fit.”	High dropouts. data suggest comparable results clinically but more migration at 1 year.
Clarke 1998 RCT	4.0	N = 117 with primary, unilateral TKR or THR	Cemented TKR (n = 61) vs. uncemented TKR (n = 56); cemented THR (n = 111). Venography taken at Day 5, 6, and 7 after operation.	Experienced DVT in 32 of 58 (55%) of cemented TKR venograms compared to 42 of 52 (81%) for uncemented TKR, p = 0.004. Cemented THR, DVT in 32 of 101 (32%) venograms. Median length (range) of thrombus in cemented TKR vs. uncemented TKR vs. cemented THP: 26.5 cm (7-59 cm) vs. 11cm (2-41 cm) vs. 7 cm (0.5-33 cm), p <0.001 for both knee groups compared to hip, p = 0.032 for uncemented	“[T]he use of cement does not increase the incidence of DVT after TKR, but that it does appear to increase the amount of thrombus which is formed.”	Demographic data not well described. Data suggest high DVT risk with uncemented THA.

				TKR compared to cemented THR.		
McCaskie 1998 RCT	4.0	N = 113 (139 knees) who underwent knee replacement with press-fit Condylar Knee Replacement System	Cemented (81 knees) vs. uncemented (58 knees). Assessments done at 5 years.	Cemented group experienced 20 positive venograms, uncemented had 13 positive venograms. Anteroposterior tibial scores at 5 years different: cemented 2.19 (SD 1.83) vs. uncemented 1.41 (SD 1.67), p = 0.02. Anteriorposterior tibial score for cemented vs. uncemented at 5 years: 1.58 (SD 1.73) vs. 0.96 (SD 1.38), p = 0.03. Anteroposterior femur score at 5 years: 0.71 (SD 1.18) vs. 0.21 (SD 1.03), p = 0.03.	"We found no difference in the clinical outcome of the cemented and cementless knees. Both gave improvement in pain, function and joint movement and were equally effective."	High dropouts. Patients not well described. Data suggest more radiolucent lines at 5 years among cemented.
Bonoloc Bone Cement vs. Conventional Treatment						
Nilsson 1998 RCT	4.0	N = 23 (23 knees) with Ahlbäck gonarthrosis stage III-V	Fixation of tibial component with Boneloc I (n = 8) vs. Boneloc II (n = 4) vs. Palacos cum Gentamicin (n = 11). Outcome assessments conducted at 6 weeks; 3, 6, 12, and 24 months; and 5 years.	Boneloc migrated more than Palacos at 3 months and was statistically significant from 12 months onward. Fixation component subsided in boneloc vs. Palacos at 2 years.	"We conclude that, even in total knee arthroplasty, there is a substantial risk that Boneloc leads to inferior clinical results, but later than in hip replacements."	Data Suggest Boneloc inferior. Product is off the market.
Full vs. Partial Cement						
Saari 2009 RCT	4.0	N = 38 who underwent primary TKR using cemented PROFIX total knee system	Complete (both under baseplate and around stem) cementing vs. horizontal (only under baseplate) cementing. Outcome measures assessed at 2 years.	Tibial baseplate external rotation for uncemented vs. cemented: 0.23° vs. 0.18°, p = 0.01. Tibial baseplate subsided 0.14 mm in cemented vs. none in uncemented, p = 0.02.	"The differences in migration were small and probably without clinical significance. The findings do not favour either of the cementing techniques in TKR."	Higher KSKS total score in uncemented at baseline (51 vs. 37). Data suggest comparability.
Computer Aided Systems						
Confalonieri 2007 RCT	7.5	N = 74 undergoing TKR	Mini-incision system MIS (n = 37) vs. mini-incision and computer-assisted system MICA (n = 37); 8 month follow-up.		"The MICA group showed both a significant fewer number of outliers and a significant higher number of implants with all five radiological parameters ideally aligned. The operative time was statistically longer in	All mini-incisions. Data suggest better alignment with computer-assist.

					the computer assisted group.”	
Choong 2009 RCT	7.0	N = 115 scheduled for primary TKA	Computer guidance system CAS (n = 60) vs. conventional approach CONV (n = 55); 1 year follow-up.		“[T]his is the first randomized controlled study to demonstrate that computer assisted knee arthroplasty affords greater accuracy in achieving a desired prosthetic alignment than a conventional jig system and to correlate this improvement in accuracy with enhanced knee function and patient quality of life.”	Detailed data to compare between group outcomes not provided. Some data are provided that suggest better design led to better function.
Cobb 2006 RCT	6.5	N = 27 scheduled for medial UKA	Conventional surgery (n = 14) vs. acrobot system (n = 13); 18 weeks follow-up.	Conventional vs. acrobot mean±SD (median) WOMAC change in pain score, stiffness, physical function score: 6±2 (7)/8±3 (8), 2±2 (3)/3±2 (3), 17±11 (18)/24±10 (23). WOMAC change in scores insignificant, p = 0.06. Tibiofemoral alignment mean°±SD (range°) in coronal plane (≤2° angles): -0.84±2.75 (-4.2-+4.2)/0.65±0.59 (-1.6-0.3)/Fisher exact test p = 0.001.	“[C]computer assistance improves the accuracy and consistency of placement of the implant in UKA. ... The operations took longer but the clinical outcome as shown by the functional scores at six and 18 weeks did not reveal any detrimental effect.”	Groups not well described. Data trend in favor of robotic system.
Stöckl 2004 RCT	5.5	N = 64 (64 knees) requiring primary TKA, diagnosed with OA or AVN, and no OA of knee ≤12 months prior	Conventional surgical technique (n = 32) vs. navigation-guided surgical technique (n = 32). Patella resurfaced in only one.	Conventional vs. navigation post-op mean°±SD°(range°) radiographic measurement mechanical axis(-=valgus, +=varus), femoral flexion angles(-=flexion, +=extension), tibial slope(=posterior slope, +=anterior slope), femoral rotation angle(=external, +=internal), component rotation angle(-=external, +=internal), and insall-salvati index: 0±3.19(-11-8)/0.3±2.35(-5-3), 3.34±5.33 (-22-4)/0.04± 2.3 (-4-6), 5.11±2.95 (-10-1)/3.78±2.7 (-9-2), 1.09± 2.81 (-2-12)/-0.41±2.44 (-7-4), 2.52	“[T]he Knee Navigation System allowed for significant improvement of rotational and flexion angle alignment for the femoral component. A more consistent combined rotational alignment of tibial and femoral components was achieved by avoiding excessive internal rotation.”	Follow-up times unclear. Data suggest better alignment with navigation system.

				± 6.77 (-17-18)/ 1.27 ± 3.27 (-5-7), 1.01 ± 0.14 (0.78-1.30)/ 1.05 ± 0.18 (0.75-1.65).		
Kalairajah 2006 RCT	5.5	N = 24 undergoing unilateral TKA for OA	Computer-assisted navigated TKA (n = 14) vs. conventional TKA using intramedullary alignment guides (n = 10). All cemented Scorpio. All cemented patellar buttons. Transcranial Doppler used in both groups to monitor blood flow continuously, detecting emboli intra-operatively, and quantifying cerebral micro-emboli. No additional follow-up.	Computer assisted vs. conventional detection of emboli: $0.64 \pm 0.74 / 10.7 \pm 13.5 / p = 0.0003$. Day 1 mean mental score: $8.9 / 7.9 / p = 0.29$.	"[T]here was a highly significant reduction in the number of cranial emboli as detected by automated transcranial Doppler ultrasonography in the computer-assisted group when compared with the non-navigated group."	Small numbers of subjects. Data suggest computer-assisted resulted in substantially fewer Doppler-detected emboli.
Dutton 2008 RCT	5.5	N = 108 scheduled for TKA	Conventional TKA (n = 56) vs. computer-assisted minimally invasive TKA (n = 52). A cemented posterior cruciate-retaining total knee prosthesis system with patellar resurfacing was used in all operations; 6 months follow-up.		"Although specific clinical parameters reflect an early increased rate of functional recovery in association with computer-assisted minimally invasive total knee arthroplasty within the first postoperative month, the main advantage of this technique over conventional total knee arthroplasty is improved postoperative radiographic alignment without increased short-term complications."	Data suggest improved alignment.
Kim 2008 RCT	5.5	N = 320 (420 knees) scheduled for primary TKA	Bilateral arthroplasty (n = 60), 1 knee navigated and 1 non-navigated (same patient). vs. bilateral arthroplasty (n = 50) both knees (same patient navigated vs. bilateral	Navigated vs. non-navigated overall prevalence for ≥ 1 fat globule, and ≥ 1 bone-marrow-cell: $102(49\%) / 109(52\%) / p = 0.2674$, $36(17\%) / 31(15\%) / p = 0.2591$.	"The prevalence of fat and/or bone-marrow-cell embolization was not significantly different between the patients who underwent total knee arthroplasty with navigation and those who underwent it without navigation."	No differences in fat embolization between navigated and non-navigated.

			arthroplasty (n = 50) both knees (same patient non-navigated. vs. (n = 50) unilateral arthroplasty both knees (same patient) navigated. vs. (n = 50) unilateral arthroplasty both knees (same patient) non-navigated.			
van Strien 2009 RCT	5.5	N = 40 cemented Nexgen total knee prostheses	CT-based (n = 17) vs. CT-free (n = 19) vs. (control group) conventional operated TK group (n = 21); 2 years follow-up.		“No Clinical significant difference in alignment was found between CAOS and conventionally operated TK. More subsidence of the tibial component was seen in the conventional groups at two year follow-up. A significant difference in micromotion in caudal–cranial direction between the groups at two years was found, with more micromotion in the conventional group. CT-free CAOS showed a significantly better performance in FFC than CT-based CAOS, though clinically similar results for limb and TK alignment were found.”	CT-free vs. CT-based plus conventional control. More micromotion in conventional; however, study not randomized on that.
Weinrauch 2006 RCT	5.0	N = 70 who underwent TKA	TKA with computer navigation (n = 39) vs. TKA with conventional instrumentation using intramedullary femoral and extramedullary tibial alignment guides (n = 31).	Standard instrumentation vs. computer navigation for medial parapatellar approach, subvastus approach, low contact stress, rotating platform, both components cemented, regional anaesthesia, reinfusion drain, days in hospital, transfusion(units), and post-op haemoglobin level(g/l): 21/21, 10/18, 31(100%)/39(100%), 31(100%)/36(92.3%), 28 (90.3%)/32(84.6%), 25 (80.6%)/33(84.6%), 6.94/7.23, 0.54/0.36,	“The subvastus approach is recommended for computer-assisted TKA as it reduces the incidence and duration of early postoperative quadriceps dysfunction.”	Very short duration trial, 8 day follow-up. Data suggest very short term delayed recovery in computer group attributed to required quadriceps dissection.

				105.7/103.2. Pre-op condition for varus, maxial flexion, fixed flexion deformity, and haemoglobin level (g/l): 0.5°/3.4°, 108.1°/109.6°, 4.8°/6.8°, 137.0/137.6. Medial parapatellar vs. subvastus pre-op condition: 0.8°/2.4°, 108.6°/109.6°, 6.1°/5.7°, 137.0/137.9. Medial parapatellar vs. subvastus for low contact stress, rotating platform, both components cemented, regional anaesthesia, and reinfusion drain: 42(100%)/28(100%), 42(100%)/25(89.3%), 37(88.1%)/23(82.1%), 42(100%)/16(57.1%).		
Oberst 2008 RCT	4.5	N = 69 admitted for primary TKA	Navigated implantation (n = 34) vs. conventional implantation (n = 35).	Navigated vs. conventional internal rotation IR and external rotation ER of distal femur at pre-op, post-op, and delta rotation (°): 6.5±8.6IR (range 24 IR 16 ER)/9.1±8.6 IR (range 29IR 9 ER), 5.0±8.0 IR (range 18Ir 13 ER)/8.3± 9.4 IR (range 27 IR 13 ER), 2.2±6.2 ER (range 12 IR 13 ER)/0.7±4.1 ER (range 9 IR 8 ER). No significant change between groups, p >0.05.	"[N]o difference between conventional technique and the navigated operation was found concerning the rotational position of the femoral component."	Patients not well described. Data suggest better alignment with computer system.
Chin 2005 RCT	4.5	N = 90 who underwent primary TKA	Conventional technique using EM tibia guides vs. conventional technique using IM tibia guides vs. VectorVision knee computer navigation CAS. Follow-up time unclear.		"[C]omputer-navigated TKA helps increase accuracy and reduce outliers for implant placement. This is significant in placement of tibial and femoral components in the coronal plane and placement of the femoral component in the sagittal plane. Hence, the overall alignment tends to be better using CAS. In addition, significantly more patients in the CAS have good collective outcomes."	Follow-up time unclear. High dropouts not well explained. Computer navigation required more time to perform (118 vs. 90 vs. 83.5 minutes); however, also less drainage and better alignment.

Sparmann 2003 RCT	4.5	N = 240 scheduled for primary TKA, and suitable for a condylar prostheses	Navigation guided system (Stryker) (n = 120) vs. conventional hand-guided technique (n = 120). All Duracon condylar RKA, all patellae replaced and all components cemented.	Mechanical axis major malalignment up to 6° and 7° significant, p <0.0001/ χ^2 = 26.8. Frontal femoral axis deviation of 0° significant, p <0.0001/ χ^2 = 38.3. Femoral axis (sagittal plane) extension or flexion malalignment up to 6° significant, p <0.0001/ χ^2 = 62.8. Alignment of tibial component in tibial axis (frontal plane) significant, p <0.05/ χ^2 = 14.53. Navigated vs. hand-guided number of subjects for deep infection, thrombosis, delayed wound healing, and manipulation under anaesthesia: 1/0, 1/1, 3/1, 1/4.	“The results revealed a highly significant difference between the two groups in favour of navigation with regard to the mechanical axis, the frontal and sagittal femoral axis and the frontal tibial axis (p < 0.0001). The use of a navigation system was therefore shown to improve the alignment of the implant.”	Quasi-randomized. Randomization process limited by equipment availability, causing unequal group sizes. Data suggest superior alignment of implants with navigation system.
Unicompartmental Disease						
Pandit 2009 RCT	6.5	N = 61 (62 knees) with primary anteromedial osteoarthritis undergoing unicompartmental knee replacement	Unicompartmental knee replacement with cement (n = 32) vs. cementless (n = 30). Clinical assessments done at pre-op, 6 months, and 1 year.	Thin radiolucent lines around cemented components appeared in 24 knees (75%). Lines were complete in 11 knees (32%) and partial in 13 (43%). Partial radiolucencies found in 7% of cementless implants, complete radiolucencies in none, p <0.0001.	“At one year there was no difference in clinical outcome between the two groups.”	Unicompartmental KR. Data suggest more radiolucencies develop in cemented than uncemented at 1 year.
Newman 1998 RCT	5.5	N = 100 (110 knees) suitable for unicompartmental replacement	Unicompartmental UKR (n = 45) vs. posterior-cruciate preserving TKR (n = 46). Patella resurfaced in all TKR. In both groups, all components fixed using Palacos cement with gentamicin.	Five in TKR group had clinical evidence of deep-venous thrombosis vs. 1 in UKR group. UKR vs. TKR pre-op knee score and pre-op ROM (°): 54.7/57.2, 101/102. Bristol knee score number (%) at 5 years for excellent, good, fair, poor/revision: 34 (75.6)/26 (56.5), 5 (11.1)/12 (26.1), 3 (6)/5 (10.9), 3 (6)/3 (6.5). Pain relief at 5 years for excellent, good, poor: 40 (88.9)/38 (82.6), 3 (6.7)/5 (10.9), 2 (4.4)/3 (6.5). UKR ROM comparison for pre-op ROM \geq 120° and 5 years ROM \geq 120°: 7/50 (14.0), 31/45 (68.8).	“In our trial, if the good and excellent results are combined, there is no difference between the groups but a higher proportion of the UKR group has a knee rated as excellent. Since pain relief was satisfactory in both groups this must relate to the greater range of movement achieved and possibly to the more normal feel of the joint. UKR gives better results than TKR and that this superiority is maintained for at least 5 years.”	Data suggest unicompartmental replacement has some demonstrable superiority to TKA at 5 years for unicompartmental disease as assessed by both ROM and percentage excellent (75.6 vs. 56.5%).

				TKR: 10/52 (19.2), 8/46 (17.3).		
Newman 2009 RCT	4.5	N = 94 (102 knees) suitable for unicompartmental replacement	ST Georg Sled UKR (n = 52 knees) vs. Kinematic modular TKR (n = 50 knees).	UKR vs. TKR 5 year results for deceased, lost to follow-up, and follow-up available: 52/50, 5/4, 1/1, 46/45; 15-year results for deceased, failed, revised, failure (not revised), surviving, scored, known alive with intact knees, lost to follow-up: 24/21, 4/6, 3/4, 1/2, 24/23, 21/19, 2/2, 1/2. Data for pre-op knee score (range), and pre-op ROM (°): 54.7 (37- 75)/57.2 (31-76), 101 (80-130)/102 (75-120); 15 year Bristol knee score number (%) for excellent, good, fair, poor: 15 (71.4)/10 (52.6), 1 (4.8)/3 (15.8), 1 (4.8)/1 (5.2.), 4 (19.0)/5 (26.4).	“The better early results with UKR are maintained at 15 years with no greater failure rate. The median Bristol knee score of the UKR group was 91.1 at five years and 92 at 15 years, suggesting little functional deterioration in either the prosthesis or the remainder of the joint. These results justify the increased use of UKR.”	Follow-up at 15- years with results of superiority of unicompartmental replacement maintained.
Stukenborg -Colsman 2001 RCT	4.0	N = 60 (62 knees) with medial unicompartmental OA	High tibial osteotomy HTO (n = 32 subjects, 32 knees) vs. unicompartmental arthroplasty UKA (n = 28 subjects, 30 knees).	More intra- and post- op complications observed after HTO. HTO vs. UKA mean functional score, and ROM (°) at last follow- up: 71 (0-100)/59 (0- 100)/p = 0.220, 117 (85-135)/103 (35-140). Post-op revision (years): 3.7 (0.9- 7.8)/4.5 (2.4-6.2). Cox regression analysis for relation between age of subject and revision [p (95%CI)]: p = 0.90 (0.087-1.13)/p = 0.44 (0.91-1.24). Using Knee Society Score, 71% (15) of patients after osteotomy and 65% (13) after replacements had knee score of excellent or good 7-10 years post-op.	“[T]he advanced design of unicompartmental prosthesis today, UKA offers better long-term success.”	Seven to 10 year follow-up. High dropouts. Baseline gender difference with more females in UKA.
Intramedullary vs. Extramedullary Guides						
Reed 2002	5.0	N = 126 (135 knees) who	Intramedullary (n = 54) vs. extramedullary	Intramedullary vs. extramedullary TCA results for radiographs	“Our findings have shown that in tibiae suitable for the	Sparse results. Data suggest intramedullary

RCT		underwent cemented AGC TKR	(n = 46) guides for preparation of proximal tibia.	assessed, mean TCA (°), and number (%) with correct TCA: 54/46, 90.8/91.3, 46 (85)/30 (65). Correct tibial alignment: 85%/65%/p = 0.019.	technique, intramedullary tibial alignment guides passed to the distal epiphyseal scar are more likely to provide correct alignment of tibial prostheses than extramedullary devices.”	superior to extramedullary.
Patellar Resurfacing vs. Retention						
Myles 2006 RCT	8.0	N = 50 with knee OA undergoing unilateral TKA	Patella resurfacing (n = 25) vs. non-resurfacing (n = 25).	American Knee Society Function score at 18-24 months comparing resurfaced vs. non-resurfaced: 63.6 vs. 79.2; p = 0.008. Repeated measures ANOVAs indicate changes within group performance over 3 time periods for 9 of 11 functions: level walking, slope ascent and descent, and into and out of low chair, standard chair, bath; p <0.05.	“Routine patella resurfacing in a typical knee arthroplasty population does not result in an increase in the functional range of movement used after knee replacement.”	Limited demographic data by groups at baseline. Data suggest comparable results.
Smith 2008 RCT/Cross-over trial	7.5	N = 142 (181 knees) underwent primary total knee replacement with inflammatory arthritis; history of patellar fracture, patellectomy, patellofemoral instability or prior unicondylar knee replacement excluded	Patella resurfacing (n = 87) vs. patella non-resurfacing (n = 94). Patients received either right with and left without, or left with and right without patellar resurfacing.	No benefit shown for TKR with patellar resurfacing over without resurfacing with respect to any measured outcomes. Anterior knee pain at latest follow-up: 22 of 73 knees with patellar resurfacing (30.1%; 95% CI 19.6 to 40.7); 18 of 86 without resurfacing (20.9%; 95% CI 12.3 to 29.5), p = 0.182. Knee pain scale at minimum 3 year follow-up (pre-op/post-op/change): resurfacing (36.2±16.6/100.0±37.0 / 47.7±25.0) vs. no resurfacing (40.0±15.0/100.0±23.6 /48.7±23.2), p = 0.797. Knee Society score: (39.7±18.9/92.0±12.0/ 46.2±20.1) vs. (39.0±13.8/ 93.0±11.0/50.0±16.8), p = 0.202. Knee Society function score: (51.9±17.1/60.0±30.0/ 14.4±19.3) vs. (51.7±16.4/ 70.0±46.0/18.6±19.5),	“The results of our study indicate no superiority of patellar resurfacing over patelloplasty in a TKR system with an anatomical femoral component and a domed patellar component. They contrast strongly with those of our previous study, suggesting that the design of both the femoral and patellar components may be an important consideration in the decision as to whether or not to resurface the patella.”	Data trend against resurfacing at 3 plus years follow-up.

				p = 0.184. Satisfaction: 19 of 71 (26.8%) TKRs with patellar resurfacing, 15 of 86 (17.4%) TKRs without patellar resurfacing had satisfaction score less than 100, p = 0.158.		
Wood 2002 RCT	7.5	N = 201 with OA (220 knees) scheduled to undergo a primary TKA	Patella retention vs. patella resurfacing. Miller-Galante II prosthesis implanted in all patients and all components cemented. Mean 48 months follow-up.	Retention group showed worse anterior knee pain compared to resurfacing, with 31% vs. 16%, p = 0.005. Risk of revisions and other procedures for anterior knee pain in 15/128 (12%) of non-resurfaced vs. 9/92 (10%) resurfaced. No differences in knee scores, function scores, or satisfaction.	"Patients who underwent patellar resurfacing had superior clinical results in terms of anterior knee pain and stair descent. However, anterior knee pain still occurred in patients with patellar resurfacing, and nine (10%) of the ninety-two patients in that group underwent a revision or another type of reoperation involving the patellofemoral joint."	Large sample size. Long follow-up. Data suggest patellar resurfacing modestly reduces rate of anterior knee pain.
Campbell 2006 RCT	7.0	N = 100 with OA undergoing TKR using Miller-Galante II prosthesis having failed conservative treatment	Miller-Galante II TKR with vs. without cemented polyethylene patellar component with posterior cruciate ligament retained in all.	No differences in outcomes found between both groups. WOMAC scores: function 8 years (resurfaced 35.9 vs. not resurfaced 36.1), p = NS, function 10 years (31.7 vs. 37.5), p = NS, pain 8 years, 10 years NS; stiffness 8 years, 10 years, NS. Anterior pain (%) pre-op/4 years/8 years/10 years: resurfaced vs. not resurfaced (52 vs. 43, NS/35 vs. 28, NS/29 vs. 33, NS/47 vs. 43, NS).	"We are unable to recommend routine patellar resurfacing in osteoarthritic patients undergoing total knee replacement on the basis of our findings."	High dropouts (42%). Data suggest comparable results at 10 years.
Burnett 2004 RCT Follow-up report of Bourne 1995	7.0	N = 90 (100 knees) with OA	Patella resurfacing vs. retention at time of TKA. All knees cruciate-retaining with a cemented tibial baseplate and cementless femoral component; 10 plus years follow-up.	Mean pre-op pain score for nonresurfaced patellas improved: 14.9±9.5 to 43.7±8.7; p <0.001. Resurfaced patellas improved 16.6±10.5 to 45.3±7.5; p <0.001). Mean pre-op total function score for nonresurfaced patellas improved: 42.4±14.4 to 59.5±25.3; p <0.001).	"The current practice and recommendation of the two senior authors is generally to elect to resurface the patella, but to be comfortable with and to continue to leave the patella unresurfaced in younger patients, patients with thin patellas (< 15 mm) or poor bone quality, and in patients with well-preserved articular cartilage and normal patellar	Blinding attempted. Data suggest no meaningful differences in outcomes at 10 plus years of follow-up, although study reported more stairs combined in nonresurfaced group than resurfaced in 30s (31 vs. 20, p = 0.043); 39% deceased.

					tracking and anatomy who do not complain of anterior knee pain preoperatively.”	
Burnett 2007 RCT	7.0	N = 32 (64 knees) who underwent primary bilateral single-stage TKA for OA	Patella resurfacing vs. nonresurfacing for the first TKA; second knee received the opposite treatment. Follow-up minimum of 10 years.	No differences found on pain scores for either group, including global, anterior, and VAS scores.	“Our randomized study at 10 years after single-stage bilateral TKA identified no differences in operative procedure, anterior knee pain, global knee pain, KSCRS, function, revision rates, radiographs, or patient satisfaction between the two groups. The surgeon may expect similar clinical results whether the patella is resurfaced or nonresurfaced in bilateral TKA.”	Data suggest comparable results at 10 years.
Burnett 2009 RCT	7.0	N = 86 (118 knees) who underwent primary total knee replacement	Patella resurfacing (n = 58) vs. patella non-resurfacing (n = 60). All received same cemented posterior cruciate-sparing prosthesis.	No differences in Knee Society clinical rating scores or ROM between both groups were found; p >0.05.	“[W]ith the type of total knee arthroplasty used in our patients, similar results may be achieved with and without patellar resurfacing.”	Follow-up report in series on 1 RCT. Data suggest no significant differences in outcomes.
Bourne 1995 RCT	7.0	N = 100 with knee OA undergoing TKR	Patella resurfacing (n = 50) vs. non-resurfacing (n = 50) using prosthesis that featured an anatomic patellofemoral joint.	Mean±SD knee flexion torque at 2 year follow-up comparing resurfaced vs. non-resurfaced: 41±12 vs. 49±17; p <0.001.	“These results suggest that longer-term followup is required, but that one should keep an open mind regarding patellar resurfacing during total knee replacement.”	Initial report of RCT. Data trend in favor of resurfacing with less pain.
Barrack 1997 RCT	6.0	N = 89 scheduled to have TKA for treatment of degenerative OA after an adequate trial of non-operative therapy	Resurfacing vs. retention of patella in which all patients received the same posterior cruciate-sparing prosthesis.	No differences found between both groups in regards to mean Knee Society score; patient satisfaction or responses to questions involving function of patellofemoral joint.	“The prevalence of anterior pain after total knee arthroplasty was not influenced by whether or not the patella had been resurfaced. The postoperative clinical scores, the postoperative development of anterior pain, and the need for subsequent resurfacing were not predicted by the presence of preoperative anterior pain, obesity, or the grade of chondromalacia	All Miller Galant II prosthesis. Data suggest comparable results for patellar resurfacing vs. not; however, operated on 10% of those without resurfacing.

					observed intraoperatively.”	
Barrack 2001 RCT	6.0	N = 80 (118 knees) undergoing primary total knee arthroplasty for OA severe enough to warrant TKA after adequate trial of non-operative therapy	Patella resurfacing vs. non-resurfacing. All received same posterior-cruciate-sparing prosthetic components (Miller-Galante II).	No differences in both groups were observed.	“The occurrence of anterior knee pain could not be predicted with any clinical or radiographic parameter studied. On the basis of these results, it seems likely that postoperative anterior knee pain is related either to the component design or to the details of the surgical technique, such as component rotation, rather than to whether or not the patella is resurfaced.”	Second report of Barrack 1997. Data suggest patellar resurfacing not predictable.
Newman 2000 RCT 2nd report of Karachalios	6.0	N = 125 with OA suitable for a posterior cruciate sparing replacement undergoing TKR	Group A all patellae resurfaced vs. Group B no patellae resurfaced vs. Group C decision about resurfacing patella left to discretion of surgeon who based decision on patients’ pre-op symptoms and state of patellar articular cartilage.	Results after 5 years for need of a secondary procedure comparing resurfaced vs. non-resurfaced vs. selected: 0 vs. 6 vs. 1; p = 0.05.	“[W]e feel this study supports a policy of always resurfacing the patella when doing a total knee replacement as this gives the most reliable results. Assessment methods which focus on the patella show a resurfaced patella to be more comfortable and to tolerate minor degrees of malalignment much better than when left unresurfaced.”	Data suggest patellar resurfacing produced less need for re-operations.
Kajino 1997 RCT	5.0	N = 35 with Stage II-IV OA	Patellar replacement in 1 knee vs. no patella replacement in other knee.	No differences in groups. No p-values reported. Hospital for Special Surgery Knee Scores: Over-all mean score (yes – pre-op/post-op; no – pre-op/post-op): 48/81; 47/80. Pain: 13/28; 13/28. Function: 7/15, 7/15. ROM: 12/13; 12/13. Muscle strength: 5/8; 5/8. Flexion contracture: 3/7; 3/6. Instability: 7/9; 6/9.	“In conclusion, these findings suggest that, in order to alleviate pain and to prevent erosive changes of the patella, it is advisable to perform a patellar replacement as part of total knee arthroplasty in patients who have rheumatoid arthritis.”	No p-values reported. All RA. Generalizability to OA uncertain. High dropouts. Nearly all outcomes suggest comparable results. At least 6 years follow-up.
Keblish 1994 RCT	5.0	N = 52 (104 knees) who underwent bilateral arthroplasty; pre-op diagnosis: OA in 44, RA in 6, post-	Patella resurfacing vs. non-resurfacing.	No differences in both groups observed. Pain (patella retained vs. patella resurfaced): 28.7 vs. 28.0. Total score: 89.2 vs. 90.1.	“If the prosthesis is suitable, and if technical and radiological criteria are met, the non-resurfaced patella performs as well as the resurfaced patella.”	At least 2 years follow-up (mean 5 years). Data suggest comparable results.

		traumatic arthritis in 2; 5 knees had previously high tibial osteotomy, 4 in bi-compartmental and 1 in tri-compartmental group				
Waters 2003 RCT	5.0	N = 431 (514 knees) undergoing primary press-fit condylar total knee replacements	Resurfacing vs. retention undergoing trimming of osteophytes. Patients randomized to cruciate-substituting or cruciate-retaining prosthesis as part of a separate trial. Press-Fit Condylar prostheses.	Prevalence of anterior knee pain in non-resurfacing group higher than resurfacing group; $p < 0.0001$. Higher rate of anterior knee pain both in osteoarthritic non-resurfaced knees ($p < 0.0001$) and rheumatoid non-resurfaced knees ($p < 0.0001$).	“As the present study showed a significantly higher rate of anterior knee pain following arthroplasty without patellar resurfacing, we recommend patellar resurfacing at the time of total knee replacement when technically possible.”	Data suggest more anterior knee pain if patella not resurfaced (prevalence 25.1% vs. 5.3%, $p < 0.0001$).
Partio 1995 RCT	5.0	N = 100 knees undergoing knee arthroplasty	Patella resurfacing (n = 50) vs. non-resurfacing (n = 50).	Mild patella pain reported by resurfaced group vs. non-resurfaced: 11(23%) vs. 1(2%); $p < 0.001$. Compression and grinding was painful in: 22(46%) vs. 4(8%); $p < 0.001$. Satisfaction ratings equivalent.	“The results of this prospective study indicate that there was no significant difference in knee function after total whether or not the patella had been resurfaced at the time of operation, but that resurfacing guarantees a pain-free knee in most cases.”	Data suggests no differences in function with patellar resurfacing.
Feller 1996 RCT	4.5	N = 40 undergoing primary TKA for OA by 1 surgeon using 1 type of prosthesis and whose patella was not severely deformed	Retention vs. resurfacing with cemented, all-polyethylene component regardless of state of patellar articular cartilage.	No differences between both groups for review HSS and patellar scores. Resurfacing group showed worse scores for stair climbing; $p < 0.05$.	“We had no complications at three years after patellar resurfacing, but despite this consider that our study and those previously published provide adequate evidence for retention: we do not now resurface the patella as a matter of routine for patients having a primary TKA for osteoarthritis.”	Patients without severe PF DJD. Data suggest comparable results at 3 years.

Schroeder-Boersch 1998 RCT	4.0	N = 40 with knee OA, age 50-79 undergoing TKA; RA, avascular necrosis, post-traumatic arthritis, tumor patients excluded	A: Patella replacement (n = 20) vs. B: non-replacement (n = 20); 2 year follow-up.	Twenty-two had severe Grade 4 OA (11 patients from each group) and showed differences between 12- and 24-month scores: 24-month knee score A: 84.4; B: 70.1; p <0.05. Climbing stairs A: 40.0, B: 33.6; p <0.025. Function score A: 83.2, B: 70.9; p <0.05.	“The superior functional results are arguments for patellar resurfacing, at least in knees with advanced osteoarthritis.”	Small sample sizes. Data suggest resurfacing superior.
Mayman 2003 RCT	4.0	N = 90 (100 OA knees) excluded if inflammatory arthritis or procedure being performed primarily to treat patellofemoral symptoms	Patella resurfacing (n = 50) vs. patella non-resurfacing (n = 50). Assessment at baseline, at 3 and 6 months, and 1 and 2 years.	Knee Society Clinical Rating Score at 2 years resurfaced groups vs. non-resurfaced: 147.7 vs. 163.7; p = 0.01. Patient questionnaire for pain at climbing stairs: 10% vs. 47%; p = 0.042. Pain walking: 0% vs. 33%; p = 0.039. Patients extremely satisfied: 80% vs. 48%; p = 0.023.	“[T]otal knee arthroplasty with or without patellar resurfacing dramatically relieves pain and improves function. It has shown better subjective results with patellar resurfacing.”	Data suggest mostly comparable results at 9 years.
Total Joint Arthroplasty: Randomized Comparative Studies						
Hilding 1995 RCT	5.5	N = 45 with Ahlbäck arthrosis Stage III to V treated with total knee arthroplasty	Tricon-M vs. Tricon Stem vs. PCA resurfacing. Outcome measurements were assessed at 10 days, 6 weeks, 6, 12, and 24 months.	Mean (SD) inducible displacement around the sagittal axis at position 1-3 for PCA vs. Tricon stem vs. Tricon-M: 0.03 (0.26) vs. -0.19 (0.25) vs. -0.24 (0.24), p = 0.02; position 3-4: -0.06 (0.33) vs. 0.25 (0.39) vs. 0.40 (0.40), p = 0.03. Mean (SD) inducible displacement as MTPM in stable vs. unstable at position 1-3: 0.36 (0.13) vs. 0.47 (0.19), p = 0.03; at position 3-4: 0.43 (0.19) vs. 0.61 (0.03), p = 0.03.	“The series was divided into one group of continuously migrating prostheses with a poor prognosis (unstable, one third) and another group of prostheses in which migration stopped after 1 year (stable, two thirds). With this classification, no differences between the prostheses design groups were revealed. However, the unstable group showed a larger inducible displacement by provocation, an association hitherto not established.”	PCA group trended towards higher Hospital for Special Surgery Scores at baseline. Data suggest most migration occurs initially, and then stabilizes.
Hilding 1997 RCT 3rd report of Hilding 1993, 1995	5.5	N = 45 with Ahlbäck arthrosis Stage III to V treated with total knee arthroplasty	Tricon-M vs. Tricon Stem vs. PCA resurfacing. Outcome measurements assessed at 10 days, 6 weeks, 6, 12, and 24 months.	No differences in post-operative activity levels. In sub-analyses, higher activity not associated with more migration.	“We conclude that the Nottingham Health Profile is a sensitive, relevant and simple measure of outcome after knee arthroplasty.”	Data suggest no significant differences, although main thrust of paper is measurement tool and quality of life.

Hall 2008 RCT	4.0	N = 100 who underwent TKA	Single sagittal radius femoral design (n = 50) vs. multi-radius femoral design (n = 50).	Multi vs. single mean(°) flexion values ±1 SD at pre-op, 4-6 weeks, 3 months, 1 year: 115.6/114.1, 98.1/96.9, 110.0/108.1, 111.7/109.5. Knee society score mean±SD at pre-op, 1 year: 43.0±15.5/45.0±17.4, 83.4±17.1/85.7±14.7. Knee society function score: 55.3±18.1/52.4±15.7, 67.8±18.4/67.1±17.2. Extension difference at 4-6 weeks postop, and 1 year (°): -2.7±3.5/-4.3±4.0/p = 0.01, 0.8±2.7/0.7±1.9/p = 0.9. Mean weight at time of surgery: single-radius design (83.5±17.6) vs. multi-radius design (8.14±16.9).	"Knee extensor mechanism function after TKA with either a single sagittal radius or multiradius implant was comparable in contemporary posterior cruciate ligament-retaining TKA designs."	Data suggest comparable outcomes at 1 year.
Transfusions, Erythropoietin, Autologous Blood Salvage and Reinfusion Systems						
Faris 1996 RCT	5.5	N = 200 scheduled for a major elective orthopaedic operation	Group 1 (n = 60) recombinant human erythropoietin, 300 international units/kg/ day vs. Group 2 (n = 71) recombinant human erythropoietin, 100 international units/kg/day vs. Group 3 (n = 61) placebo.	Mean±SD transfused for each patient: 0.37±0.96 in Group 1; 0.58±1.15 in Group 2; 1.42±1.67 in Group 3; p <0.01 between 2 groups managed with recombinant human erythropoietin and group that received placebo.	"These data suggest that recombinant human erythropoietin, administered before and after major orthopaedic operations, can minimize the need for homologous red blood cell transfusion."	Higher rate of transfusions if placebo and baseline hemoglobin of 10.0-13.0g/dL (78%) than >13.0 g/dL (36%). Data suggest erythropoietin may prevent some transfusions in select patients, especially if low Hgb and/or did not store blood.
Majkowski 1991 RCT	5.0	N = 40 undergoing primary unilateral TKA performed under tourniquet and wounds drained by 2 intra-articular Redivac drains and 1 subcutaneous Redivac drain	Two deep intra-articular drains connected to Solcotrans reservoir and suction pressure 80mmHg applied for initial period of 10 minutes (study, n = 20) vs. drains attached to Redivac bottles (control, n = 20); 8 days follow-up.	Study vs. control post-op wound drainage (ml) for 1st Solcotrans reservoir deep drain, 2nd Solcotrans reservoir deep drain, Redivac bottles deep drain, superficial drains, total drainage: 37/-, 211/-, 333/1050, 104/88, 1020±540/1140±513. Blood transfusions for autologous transfer/subjects transfer, autologous transfer/mean volume (ml), homologous transfer/subjects	"The use of postoperative salvage in unilateral total knee arthroplasty has not only proved to be safe but has also resulted in a reduction in both the number of patients requiring homologous blood transfusion and the quantity of homologous blood required."	Data suggest blood salvage system reduces need for transfusion.

				transfer, and homologous transfer/mean volume (units): 18/-, 520±245/-, 7/19, 18/50, 0.9/2.5. Mean serum haemoglobin (g/dl) measured at pre-op, intra-op, Day 1 post-op, 4, and 8: 13.2/12.7, 11.4/11.3, 10.7/11.5, 11.1/11.2, 11.4/11.6.		
Gannon 1991 RCT	5.0	N = 239 (105 males, 134 females); 142 total knee arthroplasties (100 patients) and 151 total hip arthroplasties (151 patients)	Control Group (standard drainage system) vs. Study Group (Solcotrans blood salvage canister)	Control group required average 245mL of blood per patient compared to 67 in study group (p <0.0001). More required homologous blood in control group (39%) compared to study group (13%) (p <0.0001).	“Our study has shown that postoperative blood salvage following total hip and knee arthroplasty can significantly reduce the volume of homologous blood required. In addition, these patients also tended to maintain a higher postoperative hemoglobin level. We have found this system to be safe, effective, and reasonably easy to use without adding significant cost. We now use postoperative blood salvage routinely in eligible patients undergoing total hip and knee arthroplasty.”	Three day follow-up. Patients not well described. Blood salvage markedly reduced transfusion needs.
Kristensen 1992 RCT	4.5	N = 56 (34 hip/22 knee replacements) undergoing elective primary arthroplasties	Autologous (n = 31) vs. homologous (n = 25) transfusion with 3 days of follow-up.	No significant differences between groups.	“A reduction in the use of homologous blood of 72 percent in hip arthroplasty and 91 percent in knee arthroplasty was achieved in our study.”	Data suggest autotransfusion reduced need for transfusion.
Healy 1994 RCT	4.5	N = 128 undergoing either THA, TKA, or spine fusion	Autologous shed blood reinfusion collected by: Orthevac device (n = 44, TKA = 16, bilateral knee arthroplasty = 16, revision knee arthroplasty = 3) vs. Solcotrans device (n = 40, TKA = 14, bilateral knee arthroplasty = 10, revision		“[R]einfusion of autologous, unwashed, filtered, postoperative drainage blood from orthopaedic wounds is an acceptable alternative to the transfusion of liquid-preserved red blood cells.”	Short, 1-day follow-up. Heterogeneous patients that included spine fusion. Data suggest cell savers comparable with each other and superior to control.

			knee arthroplasty = 3) vs. control (n = 44, TKA = 19, bilateral knee arthroplasty = 7, revision knee arthroplasty = 1). Subjects in control group transfused with pre-deposited autologous or homologous liquid-preserved blood; 1 day follow-up.			
Simpson 1994 RCT	4.0	N = 24 scheduled for elective primary total joint arthroplasty ; all enrolled in pre-op autologous blood program	Solcotrans Orthopaedic Drainage Reinfusion System for post-op blood salvage (n = 12) vs. control (n = 12).	Solcotrans vs. control mean (range) for operative blood loss (ml), post-op blood loss, total blood loss, post-op hemoglobin (g/dl), post-op hematocrit (%), post-op PT, post-op PTT, final hemoglobin(g/dl), and final hematocrit(%): 250 (50-750)/360 (75-750), 1087 (490-2284)/551 (190-850)/p <0.005, 1337 (713-2474)/911 (475-1600)/p <0.005, 10.8 (8.2-12.3)/10.7 (9-12.6), 32.9 (25.7-36.2)/31.3 (26.3-35.9), 11.8 (10.3-13.7)/11.9 (10.5-14.1), 30.4 (23.3-36)/29.6 (23.6-45.2), 10.5 (8-11.9)/10.8 (8.8-13.4), 31.3 (24.5-34.5)/31.9 (26.3-40.4). Incidence of post-op transfusion for number (%) subjects requiring transfusions, number of units transfused, number (%) TKA subjects transfused, total number units transfused: 3 (25)/10 (83), 8/21, 1 (11)/7 (78), 2/14.	"Postoperative blood salvage is an effective means of preserving red cell mass in post-arthroplasty patients. Despite the proven effectiveness of postoperative salvage, we continue to request that our arthroplasty patients donate autologous blood preoperatively."	Procedures uncontrolled. Data suggest efficacy to reduce transfusion needs.
Newman 1997 RCT	4.0	N = 70 with osteoarthritic unilateral total knee replacement with a cruciate-sparing Kinmax Plus prosthesis	Homologous transfusion (bank blood, n = 35) vs. re-infusion (unwashed blood salvaged after operation, n = 35). Both groups had tourniquet which	Hematological assessment (mean ± SD) of homologous vs. reinfusion. Pre-op Hb (g/dl): 13.2±1.4 vs. 13.4±1.2; 1-week Hb (g/dl): 10.9±1.4 vs. 11.4±1.4. Mean blood loss (ml): 891±401 vs. 896±545. Mean volume reinfused (ml):	"The use of reinfusion technique after TKR (total knee replacement) can reduce costs by shortening the hospital stay as a result of less febrile and infective episodes."	No VTE prophylaxis other than TED. Patients not well described. Data suggest autologous transfusion superior.

			was released after application of pressure dressings. All received 3 peri-op doses (1g) cephmandole. All wore TED stockings. Hemoglobin level measured on 1st, 3rd, and 7th post-op days.	682±360. Median homologous transfusion (units, range): 2 (0 to 4) vs. 0 (0 to 3). Post-op clinical observation in both groups. Temperature > 38.5°C, re-infusion vs. homologous: 4 vs. 16, p <0.05. Antibiotic usage: 2 vs. 12, p <0.05. Proven infection: 1 (chest) vs. 3 (urinary tract). Mean length of stay in days: 12.6±3.8 vs. 15.2±5.3		
Drains						
Seo 2010 RCT	6.5	N = 111 (111 knees) with OA undergoing unilateral TKA, Genesis II posterior-stabilized prosthesis fixed with cement	Subcutaneous indwelling group (n = 54) vs. intraarticular indwelling group (n = 57) with follow-up 12 months post-op.	Hemovac drainage (ml): subcutaneous 139.8±118.4 vs. intraarticular 352.1±204.3, p <0.001. NS between groups for allogenic blood transfusion, hypotension episode, hemoglobin drop after 2 days, hemoglobin drop after 5 days, hemoglobin recovery after 2 weeks, hemoglobin recovery after 6 weeks, hemoglobin recovery after 12 weeks. Pre-op and post-op functional outcomes: NS between groups.	"[S]ubcutaneous indwelling closed-suction drainage is a reasonable alternative to intraarticular indwelling closed-suction drainage and to no suction drainage."	Data suggest comparability. No non-drain control group.
Confalonieri 2004 RCT	6.5	N = 78 who underwent UKR	Post-op closed-suction drain for 48 hours after surgery (n = 39) vs. drain (n = 39). All UKR prostheses, cemented.	Closed suction vs. drain post-op mean±SD for haemoglobin Day 1, 1 week, haematocrit day 3, 1 week, analogue pain score 3 days, 1 week, 1 month, 4 months, analgesia requests (time) 1 day, 2 days, 3 days, knee flexion(°) 1 month, 4 months, hospital stay(days), and total complications.	"[T]he increased equipment costs associated with post-operative closed suction drainage cannot be justified on the basis of the results of this study."	Small groups for detecting infrequent outcomes, thus likely underpowered. Data suggest no differences in outcomes. Trend towards higher complications in drained group (p = 0.058).
Ovadia 1997 RCT	5.5	N = 88 undergoing primary arthroplasties; 58 TKA 32 of who had suction drains, and 30 THA, 18 with suction drains;	THA vs. TKA. Drains vs. no drains. THA drains (n = 18). THA no drains (n = 12). TKA drains (n = 32). TKA no drains (n = 26); 6 days follow-up.	Hemoglobin levels and blood transfusions. THA with drains pre-op vs. post-op Day 2: 13.5±1.6 vs. 9.9±1.28. Without drains: 13.5±0.8 vs. 10.2±1.58. Post-op Day 2 drain vs. no drain: 9.9±1.28 vs. 10.2±1.58, p = 0.06. TKA with drains	"As in other previous studies, our results support the view that drains are not needed following THA; however, we suggest continuing the use of suction drainage systems following TKA to reduce the	Some details sparse. Appears underpowered. Data trend towards more transfusions in drain groups, longer hospitalization in drained THA group but more

		same cemented prostheses in all; drains for 48 hours; all Heparin 5,000 U SQ BID post-op		pre-op vs. post-op Day 2 with drains: 13.4±0.9 vs. 9.5±1.15. Without drains: 13.3±1.2 vs. 10±1.2. Drain vs. no drain on post-op Day 6: 9.6±0.8 vs. 9.8±1, p = 0.005.	possibility of serious wound leakage".	serious drainage in non-drained TKA group.
Amin 2008 RCT	5.0	N = 178 osteoarthritis/inflammatory arthritis/awaiting knee replacement, age range of 55 years.	Condylar knee replacements in both groups. Standard vacuum drain with -100mgHg (Control group, n = 86) vs. autologous retransfusion drain (Bellovac system) with -90mmHg connected to transfusion bag with 40mm filter (Study group, n = 92). All drains removed 24 hours post-op. Hemoglobin measured at 24, 48, and 72 hours.	No differences between 2 groups in mean drainage volume (p = 0.468) and hemoglobin levels (p = 0.354).	"[T]he study confirms the safety, but casts doubt over the efficacy, of retransfusion drains in reducing the need for allogenic transfusion compared with standard suction drainage after TKR."	Few baseline data with multiple surgical technique differences. Study found no differences.
Berman 1990 RCT	4.5	N = 126 consecutive operative wounds which required suction drainage; inclusion criteria need for routine post-op wound suction drainage; 24 of 126 total knee replacements. 37 of 126 total hip replacements (total hip replacements and bipolar hemiarthroplasty chosen as	Group 1 (received a VariDyne continuous vacuum system, n = 16) vs. Group 2 (Hemovac spring-type vacuum units, n = 25). Standard polyvinyl chloride drainage tubing with internal diameter of 1/4 inch used when drain placed deep to fascia, and 1/8 inch internal diameter drain used for placement at bone graft site. All drains pulled at 24 hours if drainage for last 8-hour shift less than 50cc or at	Comparison of continuous vacuum and hemovac groups. Group 1 vs. Group 2, Drainage after operation: (ml) Recovery room (1-3 hours): 339±185 vs. 193±157, p <0.025. After 8 hours: 304±183 vs. 185±112, p <0.015. Total drainage (ml): 826±349 vs. 514±304, p <0.015. Days wound drained 1.4±1.7 vs. 3.4±4.3, p <0.07.	"[A]ll wounds which utilized continuous vacuum drained less serosanguinous or serous fluid than those wounds utilizing the intermittent system following drain removal. A clear advantage to using a continuous vacuum suction device over an intermittent spring-loaded device is seen with respect to hematoma evacuation, wound drainage, wound healing, and possible complications."	Quasi-randomized on SSN (even/odd). Modest to small group sizes. Data suggest continuous suction at 200mmHg increases total drainage and decreased days of drainage in THA and TKA patients compared to intermittent spring-loaded suction.

		independent variables)	48 hours regardless of last shift.			
Tourniquet Issues						
Barwell 1997 RCT	8.0	N = 88 who underwent TKA randomly selected to have operation under a tourniquet which was released after wound closure and compression bandaging; patients excluded if diabetic or previous open knee surgery	Group A (tourniquet release after wound closure and bandaging, n = 44) vs. Group B (tourniquet release before quadriceps layer closed allowing control of bleeding before suture, n = 44); 30 of 44 in each group had spinal anesthesia. Pain control post-op with IM morphine 7.5 to 10mg.	Early postoperative progress. Median pain score at 4 hours (range) Group A vs. Group B.: 4 (0 to 8) vs. 1 (0 to 7), p = 0.001. Median analgesic injection in 24 hours: 1 (0 to 4) vs. 1 (0 to 4). Mean time to straight-leg raise (days): 5 (1 to 18) vs. 2.8 (1 to 7), p < 0.00001. Mean days in hospital: 16.3 (7 to 37) vs. 13.8 (5 to 25).	“There were no significant differences between the two groups in operating time, or the decrease in haemoglobin concentration at 48 hours postoperatively. Some of the adverse effects of the use of a tourniquet for knee surgery can be significantly reduced by early tourniquet release, with haemostasis before the quadriceps mechanism and the wound is closed.”	More complications in late tourniquet group. Better early function and pain relief in early release group. Data suggest early tourniquet release superior.
Abdel-Salam 1995 RCT	8.0	N = 80 admitted for total knee replacements	Surgery with pneumatic tourniquet around thigh vs. surgery without a tourniquet.	No significant differences between groups in operating time or blood loss. All able to fully extend knee, but group without tourniquet performed straight-leg raising earlier (mean of 2.4 days and 4.6 days; p < 0.05). Pain scores significantly lower in Group B (without tourniquet), and time interval between intramuscular injections greater in Group B (p < 0.05).	“We conclude that total knee arthroplasty can be safely and effectively performed without the use of the tourniquet, avoiding the potential adverse effects associated with its use.”	Data suggest comparable results although earlier SLR achieved in non-tourniquet group.
Christodoulou 2004 RCT	5.0	N = 80 who underwent TKR for OA; excluded if previous knee surgery, bleeding diathesis, peripheral vascular disease, or steroid or anti-coagulant therapy	Group A (tourniquet release and homeostasis before wound closure, n = 40) vs. Group B (tourniquet release after skin closure and application of compressive bandaging, n = 40). Tourniquet inflated to 125-150mm Hg above systolic BP. Anticoagulant therapy with LMWH begun	Hb day 1 post-op (gr/dl) (mean and SD), Group A vs. Group B: 9.1±0.8 vs. 9.8±0.9. Hb Day 3 post-op (gr/dl): 11.3±0.9 vs. 11.9±1.0. Number of transfusions per patient (1 unit = 300 ml): 4.7± 1.4 vs. 4.0±1.0, p < 0.05. Operating time (minutes): 79±12 vs. 66±10, p < 0.001.	“Postoperative tourniquet release seems to offer better conditions of haemostasis probably due to the better controlled fibrolytic activity.”	Stratified enrollment on cement use. No short or longer term outcomes reported in detail. Trend towards higher complications in late group. Data trend in favor of intra-operative tourniquet release.

			pre-op, then for 30 days. Discharged on 8th post-op day. Follow-up 1 year.			
Ishii 2005 RCT	5.0	N = 57 (60 knees) who underwent TKA with New Jersey LCS total knee systems analyzed for study; also diagnosed with OA or RA; those diagnosed with peripheral vascular diseases or neurological problems excluded	350mmHg tourniquet pressure (OA n = 25, 27 knees. RA n = 3, 3 knees) vs. systolic blood pressure (SBP) plus 100mmHg tourniquet pressure (OA n = 28, 29 RA n = 1, knee 1). In 3 patients who underwent bilateral TKA, surgery was on each knee on 2 separate operations over 6 months. Tourniquet was MT-720 with cuff of 86cm long and 10cm wide.	Measured and calculated blood loss due to total knee arthroplasty. Total amount of blood loss, 350mm Hg vs. SBP plus 100mm Hg: 897±307 vs. 906±238, p = 0.751. Calculated blood loss: 1065 ±331 vs. 1066±341, p = 0.610.	"In conclusion, we recommend using a TP of 100 mm Hg above SBP during TKA, rather than using the conventional TP of 350 mm Hg."	Data suggest no differences in blood loss.
Wakankar 1999 RCT	5.0	N = 77 who underwent TKR; excluded if diabetes, RA, previous thromboembolism, active malignancy, or 1-stage bilateral procedures	Group A (used tourniquet in operation, n = 37) vs. Group B (no tourniquet, n = 40). All had identical anesthesia which included pre-medication with temazepam. All had "patient-controlled analgesia" with an infusion of morphine sulfate.	Mean change in pain score, 1 week after surgery, Group A vs. Group B: -1.62 vs. -1.48, p = 0.85. 6 weeks: -4.41 vs. -3.95, p = 0.46. 4 months: -5.25 vs. -5.12, p = 0.81. Mean change in circumference (cm) knee, 1 week: 4.1 vs. 3.6, p = 0.36; 6 weeks: 2.4 vs. 2.36, p = 0.96; 4 months: 1.7 vs. 1.36, p = 0.57. Mean change in knee flexion (degrees), 1 week: -41.76 vs. -32.28, p = 0.03. 6 weeks: -13.65 vs. -10.73, p = 0.49. 4 months: -4.51 vs. -1.03, p = 0.37.	"We conclude that the use of a tourniquet is safe and that current practice can be continued."	Moderate to heavy bleeding in 6/40 without tourniquet. Study not powered for typical adverse effects.
Jorn 1999 RCT	4.0	N = 75 with OA of knee; excluded if on anti-coagulants or steroids for a long time; 77 primary knee replacement	Group 1 (tourniquet released for hemostasis before wound closed, n = 42) vs. Group 2 (tourniquet released after wound closed and	Blood loss in mL, number of transfusions required and difference in hemoglobin, mean and SD. Group 1 vs. Group 2 intra-operative blood loss: 221±147 vs. 0. Post-op blood loss: 637±414 vs. 589±347. Total intra- and post-op blood	"Our findings speak against the efficacy of tourniquet release for hemostasis in knee replacement surgery."	Data suggest modestly higher blood loss in early release group. No adverse outcomes reported.

		t operations completed on 75 patients	compressive dressing applied, n = 35). All enoxaparin 40mg SQ QD 1 week. Pneumatic tourniquet inflated to 300mm Hg.	losses p = 0.01. Total blood loss: 858±443 vs. 5898±347. Number of transfusions: 1.0±1.3 vs. 0.6±1.0. Hemoglobin reduction: 28±13 vs. 30±17.		
Rehabilitation: Urinary						
Carpiniello 1988 RCT	4.0	N = 77 elderly female patients undergoing THA or TKA	Straight catheterization performed in recovery room (n = 31) vs. no catheterization in recovery room (n = 23) vs. Foley catheter inserted pre-op and removed 24 hours post-op (n = 23).	No statistical differences between straight catheterization and no catheterization in recovery room. Foley catheter group had 1 patient with a positive urine culture and 1 required straight catheterization. Did not reach significance.	"[P]eroperative twenty-four-hour bladder drainage is recommended in light of the decreased incidence of urinary tract infections and urinary retention with this regimen."	Many details sparse. Data suggest 4-10% incidence of post-operative UTIs in arthroplasty patients.
Drugs						
Hansson 2009 RCT	7.5	N = 60 (60 knees) with gonarthrosis Stage 3-5, age 50-80 scheduled for TKR	Bisphosphonate (alendronate) (n = 30) vs. placebo treatment (n = 30). Treatment started post-op and continued on weekly basis for 6 months.	No differences in migration of implants between groups.	"With uncemented fixation of knee implants, no benefit of once-weekly treatment with alendronate, starting postoperatively, could be seen during a 2-year follow-up period."	Sparse baseline data. Data interpreted as no difference however, graphs suggest trends toward differences, suggesting possible underpowering.
Surgical Considerations						
Usichenko 2008 RCT	9.5	N = 80 scheduled for TKA under standardized general anesthesia	Millimeter wave therapy MWT (n = 42) vs. sham (n = 38); 6 sessions of 30 minutes duration. During each session, knee wound exposed to electromagnetic waves with frequency 50-75 GHz and power density 4.2 mW/cm ² .	MWT vs. sham postop mean±SD; median(IQR) for duration of surgery (minutes), duration of tourniquets application (minutes), piritramide requirement 3 (mg), total piritramide requirement after surgery (mg), duration of PCA with piritramide (days), total ibuprofen requirement after surgery (g), duration of hospital stay (days), frequency of tramadol rescue med, and patients satisfaction with pain relief (NRS-6): 114±27/117±23, 84±28/84±36, 101±45/101±48, 106±46/105±54, 3.5±0.6/3.5±0.9, 5.4 (4.8-9.6)/7.6 (4.8-9.6), 16±4/16±3, 19/21, 1	"This study shows that millimetre waves (MW) with total power 8.7 mW distributed in frequency range 50–75 GHz applied to the wound area do not reduce postoperative opioid analgesic requirement compared to sham procedure in patients after TKA."	Data suggest lack of efficacy.

				(1-2)/1 (1-2). Incidence of analgesia related side effects number of patients (%) for drowsiness, nausea/vomiting, pruitus: 2 (6)/2 (5), 2 (6)/3 (7), 0/2 (5). MWT related for paresthesia, and fatigue: 14 (33)/18 (47), 0/2 (5).	
Compression Designs vs. Other Treatments					
Levy 1993 RCT	6.0	N = 80 undergoing unilateral TKA	Post-op dressing: cold compression (Aircast Cryo/Cuff, n = 40) vs. standard compression (n = 40).		“Cold compression provides significant benefits to the patient undergoing TKA. These include decreased blood loss, diminished swelling, lessened pain, and improved early range of motion. The Aircast Cryo/Cuff is an efficacious vehicle for the application of cold compression.” Data suggest somewhat lower blood loss with cryotherapy over 1 week.
Andersen 2008 RCT	5.5	N = 48 scheduled for unilateral TKA and local infiltration analgesia	Compression bandage (n = 24) vs. non-compression bandage (soft absorptive padding only) (n = 24). Both treatments administered post-op.	Median/IQR 8 hour post-op pain at rest: compression = 2/1-4, non-compression = 4/2-6, p = 0.03. 5 hour post-op 90° flexion of knee pain: compression = 2/0-3.75, non-compression = 4.5/1.25-7, p <0.02; 6 hours post-op pain: compression = 2.5/1-5, non-compression = 5/3.25-7, p <0.01; 8 hours post-op: compression = 3.5/1-5.75, non-compression = 5/3.25-7.75, p <0.02; 6 hour post-op 45° elevated straight-leg pain: compression = 2/0.25-3, non-compression = 4/2-6, p <0.02. Compression vs. non-compression mean mg (SD) for supplementary administration of oxycodone: 11 (10)/12 (10)/p = 0.6; no between groups. Mean hospital stay: 2.8/3.3/p = 0.7.	“A compression bandage is recommended to improve analgesia after high-volume local infiltration analgesia in total knee arthroplasty.” Data suggest efficacy over first day.

Webb 1998 RCT	5.0	N = 40 undergoing TKR, 31 subjects for unilateral TKR, 9 for bilateral TKR	Cold compressive (Aircast Cryo/Cuff) vs. wool and crepe dressing (control). Posterior cruciate ligament (PCL) retaining cement Press Fit Condylar prosthesis used in all cases, with plugging of distal femur and without patella resurfacing.	Control vs. cryo/cuff mean (range) volume of suction drainage, analgesia requirements, undergoing bilateral TKR pain, and combined results of TKR: 982ml (500- 2200ml)/768ml (379- 1180ml)/p <0.05, 0.71mg/kg-48 hours (0.17-1.33)/0.57mg/kg- 48 hours (0.24-0.99)/p <0.01, 68 (38-100)/52 (5-95)/p <0.02, 58 (30- 100)/ 45 (5-95)/p <0.05. ROM for pre-op, 3 months: 91°/97°, 89°/98°.	“The use of the Cryo/Cuff in this study demonstrated an improvement in postoperative blood loss and pain control but did not influence swelling or return of motion following TKR.”	Data suggest primary advantage appears to be opioid use; 3 month follow-up.
Miscellaneous						
Berti 1997 RCT	5.5	N = 30 undergoing TKA or THA	Insulated blanket covering head, trunk, upper limbs; unoperated lower limbs added to low- flow anesthesia system (n = 10) vs. active forced-air warming covering trunk, upper limbs, at 38°C added to low-flow anesthesia system (n = 10) vs. low-flow anesthesia control (n = 10).	Control vs. blanket vs. forced air mean±SD for duration of surgery (hours), fluid infused (L), and urine output (L): 2.8±0.6/2.4±0.4/2.6±0. 3, 2.26±0.48/2.57±0.53/2. 30±0.44, 0.33±0.125/ 0.29±0.148/0.30±0.134 . Change of tympanic temperature at end of surgery p = 0.0016. Change 30 minutes after anesthesia induction p = 0.01.	“During combined epidural-general anesthesia for elective hip and knee arthroplasty, passive heat retention by means of low-flow anesthesia alone and in combination with reflective blankets is ineffective in maintaining intraoperative normothermia and definitely inferior to active forced-air warming.”	Short study of intra-operative management. Active forced air warming maintained higher core temperatures, of uncertain clinical significance.
Hester 1992 RCT	4.0	N = 75 undergoing total joint arthroplasty	Surgeons and assistants wore 2 pairs of latex gloves changed hourly, inner gloves Perry orthopaedic gloves 150% thickness of standard latex gloves, outer gloves standard latex gloves (Group I, n = 25) vs. orthopaedic gloves covered by 1 pair cotton gloves, not changed unless perforation (Group II, n = 25) vs. Perry	No significant differences between groups.	“Our study showed no significant correlation of time with perforation; however, in the latex/latex group there was a tendency toward perforation in longer cases, and this tends toward the finding of Sanders et al. of 100% perforation of gloves in cases lasting 3 hours or longer.”	Quasi-randomised for patients by hospital admission date. Patients and surgeons not well described. Data suggest lowest rates for triple gloves.

			ortho gloves, covered by cotton gloves, covered by standard latex gloves, not changed unless perforation (Group III, n = 25).			
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BISPHOSPHONATES AND CALCITONIN

Bisphosphonates have been used to attempt to reduce periprosthetic bone resorption in the immediate peri-operative period.(1730, 1784, 1785) Calcitonin has been used to attempt to develop better healing after hip fracture fixation.(1786)

1. Recommendation: Routine Peri-operative Use of Bisphosphonates

There is no recommendation for or against the routine peri-operative use of bisphosphonates.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

2. Recommendation: Routine Post-operative Use of Calcitonin

There is no recommendation for or against the routine post-operative use of calcitonin.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

Multiple studies have shown less bone loss with cemented prostheses.(1787-1790) A high-quality trial of intranasal calcitonin also found better healing after internal fixation of hip fractures compared to placebo.(1786) However, these studies are of short-term duration and there is no long-term follow-up. Thus, the utility of these medications for this purpose is unclear. Among those patients with osteoporosis however, these medications may be indicated.

Evidence for the Use of Bisphosphonates and Calcitonin

There is 1 high- and 4 moderate-quality RCTs incorporated in this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Bisphosphonates						
Hilding 2007 RCT	7.5	N = 50 with gonarthrosis, arthrosis Stages 3-5	All NexGen cemented prostheses. Before cementation, ibandronate 1mg vs. saline applied to tibial bone surface; 24 months follow-up.	No aseptic loosening observed. Migration reduced from 0.45mm to 0.32mm at 6 months; at 12 months from 0.47 to 0.36mm; at 24 months from 0.47 to 0.40mm.	"This is the first study to show improvement of prosthesis fixation by local pharmacological treatment in humans. The treatment appears to be safe, cheap, and easy to perform. However, the improvement in postoperative stability was not greater than with systemic clodronate treatment."	Groups not well described. Data suggest local application of bisphosphonate may reduce aseptic loosening, although study only powered to address migration.
Hilding 2000 RCT	5.5	N = 49 with Ahlbäck Stage 3-5 gonarthrosis	Cemented NexGen implants with 400mg clodronate (Bonafos) vs. with placebo. Outcome	MTMP mm (SD) between clodronate vs. control at 1 year: 0.29 (0.11) vs. 0.40 (0.16), p = 0.01.	"Since early migration is related to late loosening, 6 months of clodronate medication might	Patients not well described. Data suggest clodronate reduces migration at 1 year.

		undergoing TKA	assessments post-op at 6 weeks, 6 months, 1 year.		reduce the risk of loosening.”	
Venesmaa 2001 RCT	5.0	N = 13 HA-coated uncemented THA	Alendronate 10mg plus calcium carbonate 500mg vs. calcium 500mg only for 6 months	Periprosthetic bone mass all Gruen zones (post-op/3 months/6 months): calcium (1.58±0.12/1.43±0.22/1.43±0.19) p = 0.022 vs. alendronate plus CaCO3 (1.60±0.25/1.55±0.27/1.56±0.25), NS. Between-group differences, p <0.05.	“[A]lendronate seems to be a potent drug to inhibit the periprosthetic bone loss that occurs after primary uncemented THA. . .the follow-up time was too short and the study population too small to make firm conclusions.”	Small sample sizes. Data suggest alendronate may be effective, but study underpowered.
Wilkinson 2001 RCT	5.0	N = 47 THA	Single-dose infusion pamidronate 90mg vs. placebo	Pamidronate significantly reduced bone loss compared with placebo (p< 0.01). Pamidronate associated with suppressing multiple biochemical markers of bone turnover (p <0.05).	“Pamidronate significantly reduces the acute bone loss of proximal femur and pelvis over the first 6 months after total hip arthroplasty. The most protective effect of pamidronate was seen in the medial periprosthetic bone of the femur, the site is where femoral bone typically is most severe.”	Single-dose study. No long-term follow-up. No significant differences in clinical outcomes.
Calcitonin						
Huusko 2002 RCT	8.5	N = 260 with acute hip fracture	Intranasal salmon calcitonin 200 IU daily vs. placebo nasal spray for 3 months.	At 3-months, median pain intensity VAS scale 0mm in calcitonin group vs. 4mm in placebo (p = 0.15). Median change in IADL score from baseline to 3 months: -1 calcitonin vs. -2 placebo (p = 0.74). “The mean change in calcaneal bone mineral density from baseline to 3 months was not statistically significant between the groups.”	“Intranasal calcitonin might be useful for hip fracture patients but the clinical significance of this finding needs to be confirmed by studies with more participants, a longer treatment period, a longer follow-up, and perhaps a higher dose of calcitonin.”	Data trend towards suggesting weak efficacy.

ANTIBIOTICS

Antibiotics have been utilized systemically and added to cement for many years.(1791-1814)

Recommendation: One-day Use of Systemic Antibiotics for Knee Surgery

One-day use of systemic antibiotics is moderately recommended for patients undergoing surgical knee procedures. Antibiotic-impregnated cement also appears effective compared

with cement without antibiotics with evidence particularly in the hip and by inference assumed likely to be true of the knee as well.

Strength of Evidence – Moderately Recommended, Evidence (B)

Rationale for Recommendation

There are trials comparing multiple doses with a single day of antibiotics, (1815) finding no differences in outcomes. This is a similar finding to the hip as there is evidence from a non-randomized registry data of 10,905 hip prostheses that the risk of revision due to infection was reduced 75 to 78% with a systemic antibiotic combined with antibiotic-impregnated cement compared with either systemic antibiotic administration or antibiotic-impregnated cement alone.(1816) The risk, if there was only antibiotic in the cement, was 6.3-fold higher, and, if the antibiotic was only systemic risk, was 4.3-fold greater. There is a belief that some cases of aseptic loosening are undiagnosed infections(1796) as there were lower rates of aseptic loosening among those with both routes of antibiotic administration compared with either alone(1816) and those with gentamicin cement appear to have lower rates of aseptic loosening compare with systemic antibiotics.(1817, 1818) Thus, there is quality evidence that a combination of systemic and antibiotic-impregnated cement is important to prevent infections.

Evidence for the Use of Antibiotics

There are 2 high-quality and 10 moderate-quality RCTs incorporated into this analysis. There are 4 low-quality RCTs in Appendix 1(1778, 1819-1821) (see Hip and Groin Disorders guideline for additional studies).

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Antibiotics (Systemic and/or within Cement)						
Gatell 1984 RCT	8.0	N = 284 with any metal device inserted to be eligible (plates, screws, wires); no open fracture; no joint replacements	Cefamandole 2gm IV 30 minutes before, 2gm 2 hours after start of operation, 1gm IV or IM 8, 14, and 20 hours later vs. placebo.	Superficial wound infections in 0/134 (0%) patients given cefamandole vs. 7/150 (4.7%), p <0.05. Two deep-wound infections developed in cefamandole group vs. 4 controls (p >0.05).	“Cefamandole (five doses) reduced the rate of wound infection in patients undergoing clean orthopaedic surgery that required an internal fixation device.”	Varied diagnoses. Does not apply to hip. Cefamandole appears prevent superficial wounds, but not deep infections. Mortality higher in Cefamandole group unrelated to infection, although did not reach statistical significance.
McQueen 1987 RCT	4.5	N = 295 hip or knee arthroplasties	Cefuroxime in bone cement (1.5g mixed in 40gm CMW cement powder) vs. cefuroxime 1.5gm IV at induction; 750mg Q6 hour x 2.	Twenty-one infections in 3 month period (6.8%), 11 (7.5%) in cement vs. 6.7% parenteral (NS); 3 deep infections, 1 in cement (0.7%) vs. 2 in parenteral (1.3%), (NS).	“Both methods of administering Cefuroxime appear to be satisfactory in the prevention of early infection after total joint replacement.”	Data suggest equivalent efficacy for IV vs. antibiotic in cement for prevention of infections.
Antibiotics, Antibiotic cement and Infection Issues (See also Hip and Groin Disorders chapter)						
Bryan 1988 RCT	8.0	N = 97 undergoing initial or revision of	Cefazolin 1g before surgery followed by 500mg every 8	Mean±SD for intra-operative concentrations comparing cefazolin vs.	“Cefazolin given at one-half the dose of cefamandole appeared to be equally safe and	Data suggest no long-term differences in outcomes

		total hip or knee arthroplasty , ages >18 years, free of infection at arthroplasty site	hours for 6 doses vs. 2g cefamandole before surgery followed by 1g every 8 hours for 6 doses; 2-3 years follow-up.	cefamandole for knee arthroplasty: Time of sampling: 106.5±39.1 vs. 66.1±41.0; p = 0.046. Bone concentration: 0.64±0.57 vs. 3.8±3.4; p <0.01.	effective but resulted in lower bone concentrations of antibiotic."	however, likely underpowered.
Mauerhan 1994 RCT	7.0	N = 1,354 scheduled for elective primary or revision THA or TKA	Cefuroxime 1.5g plus 750mg 6/16 hours later (n = 669) vs. 1 g cefazolin/8 hours for 9 doses (n = 685); 1 year follow-up.	Cefuroxime vs. ceftazolin number (%) for primary TKA (cefuroxime n = 178, ceftazolin n = 207) deep infection, superficial infection, revision of TKA (cefuroxime n = 16, ceftazolin n = 16) deep infection, and superficial infection: 1 (1)/3 (1), 6 (3)/4 (2), 0/0, 0/1(6).	"[T]he results of the present study indicate that there was no significant difference in the prevalence of wound infections between patients who had received a one-day regimen of cefuroxime and those who had received a three-day regimen of ceftazolin for prophylaxis against infection after primary or revision total hip or knee arthroplasty."	Large sample size. High dropouts. No statistical differences in injections although trend towards fewer in ceftazolin group suggest may be underpowered despite sample size.
Periti 1999 RCT	7.0	N = 860 from orthopedic centers in Italy undergoing primary prosthetic replacement of hip or knee	Teicoplanin 400mg IV (n = 427) vs. ceftazolin 2g IV Q 6hours for 24 hours (n = 433).	Teicoplanin (n = 410) vs. ceftazolin (n = 416) incidence of early infectious complications number (%) for wound infection, fever>38°C, asymptomatic bacteriuria, UTI, lower respiratory tract infection, decubitus, antibiotic therapy, and total infected patients: 6 (1.5)/7 (1.7), 36 (8.8)/41 (9.8), 2 (0.5)/2 (0.5), 3 (0.7)/9 (2.2), 4 (1.0)/2 (0.5), 4 (1.0)/1 (0.2), 2 (0.5)/-, 7 (1.7)/3 (0.7), 63(15.4)/64 (15.4). Incidence of late deep wound infections infected patients/evaluable patients (%) 3 and 12 months post- op: Teicoplanin 3 months = 3/375(0.8), 12 months =1/340(0.3), ceftazolin 3 months = 3/364(0.8), 12 months = 1/343(0.3), total 3 months = 6/739(0.8), 12 months =2/683(0.3). Teicoplanin vs. ceftazolin number and incidence of adverse effects for gastric pyrosis, nausea, itch, erythema, cutaneous rash, diarrhea, and total: 0/1 (0.2), 1 (0.2)/3	"[T]eicoplanin has a good spectrum of antimicrobial activity against primary pathogens responsible for wound infection in orthopedic surgery. In particular, it is highly active against staphylococci, both methicillin-sensitive and methicillin-resistant strains, which are the most common pathogens in prosthetic orthopedic surgery. Teicoplanin also has excellent tissue penetration and low toxicity. Its elimination half-life is exceptionally long, outlasting the mean operating times in orthopedic implant surgery, thus making it suitable for preoperative prophylaxis."	Data suggest equivalency. However, fewer injections with teicoplanin.

				(0.7), 0/2 (0.5), 2 (0.5)/1 (0.2), 0/1 (0.2), 0/1 (0.2), 3 (0.7)/9 (2.1)/p = 0.083.		
DeBenedictis 1984 RCT	5.0	N = 76 undergoing total hip or knee replacement	Cefonicid 1g administered IM or IV 30 minutes before incision once daily for 3 days vs. 1g of cefazolin 30 minutes before incision and every 8 hours for 72 hours post-surgery.	No superiority of one drug over the other	"We were unable to show with early follow-up of cases (four months to one year) a significant difference in the rate of infection between the group administered cefazolin and the group administered cefonicid, which has a broader spectrum of activity. Nevertheless, in view of the relatively small number of patients in each of the drug groups and the even smaller number of patients in the possible high-risk groups, it is impossible to draw any conclusion about superiority of the study drug."	Varying follow-ups of 4-12 months. Many details sparse. Data suggest underpowered for adverse effects.
Vainionpää 1988 RCT	4.5	N = 58 undergoing total hip or knee arthroplasty for osteoarthritis	Cefamandole intravenously before operation then 1g every 6 hours parenterally for 3 days vs. 29 cloxacillin IV every 8 hours for 1 day and 29 dicloxacillin orally every 8 hours for 2 days.	No differences found between groups. No p-values provided.	"[C]efamandole seems to be more recommendable as antibiotic prophylaxis in total hip and knee replacements. The CRP level decreased to below 60 mg/l in all 16 patients on the 6th postoperative day."	No clinical outcomes. Cefamandole for 3 days vs. cloxacillin for 2nd. No data to determine which is superior treatment.
Soave 1986 RCT	4.5	N = 101 undergoing total hip or knee arthroplasty	Ceforanide (1gm pre-op plus 1gm 12 hours later) vs. cephalothin (2gm pre-op, 2gm intra-operatively plus 1gm every 6 hours for 3 additional doses); 1.5 year follow-up.	Ceforanide plasma and bone levels remained sustained over 6 hours. No p-values given.	"[C]ephalothin were equally efficacious in preventing implant infections for at least one-year following total joint arthroplasty."	One and one-half years follow-up. Data suggest comparable outcomes however, likely underpowered.
McQueen 1987	4.5	See Antibiotics (Systemic and/or with Cement) above.				
Wymenga 1991	4.5	N = 3,013 who	Single-dose group 1,500mg	No significant between group differences.	"[W]ith the DDD method, no relevant	Excluded gentamicin-

RCT		underwent hip replacement, hemiarthroplasty of hip or total knee arthroplasty	cefuroxime administered intravenously at induction of anesthesia (n = 1,327 hips and 362 knees) vs. 3 dose group 750mg cefuroxime intravenously after 8 and 16 hours (n = 1,324 hips, 187 knees).		differences were found between a single dose and three doses of perioperative cefuroxime in hip and knee replacements, with respect to the amount, type, indication, and duration of additional antibiotic therapy."	impregnated cement. Data suggest 3 doses not more effective than 1.
Chiu 2001 RCT	4.0	N = 78 primary TKAs in subjects with diabetes	Group 1 (n = 41 knees) cefuroxime-impregnated cement (2g of cefuroxime in 40g of simplex P cement) vs. Group 2 (n = 37 knees) Simplex P cement without cefuroxime. Mean 50 month follow-up.	Without infection (n = 73) vs. infection (n = 5) mean (SD) details measured at tourniquet time (minutes), operation time, volume of blood transfusion, pre-op ac blood sugar (mg/dl), pre-op pc blood sugar, post-op ac blood sugar, post-op pc blood sugar, pre-op knee scores (HSS), NIDDM/IDDM (%), and type of treatment (OHA/insulin/diet).	"We conclude that cefuroxime impregnated cement is effective in the prevention of deep infection at primary TKA in patients with diabetes mellitus."	Quasi-randomized on MRN, however groups appear reasonably equivalent. Data suggest cefuroxime impregnated cement prevents deep infections, but not superficial infections.
Chiu 2002 RCT	4.0	N = 285 (340 knees) undergoing primary TKA	Cefuroxime-impregnated cement (Group 1, n = 178 knees) vs. pure Simplex P cement without cefuroxime (Group 2, n = 162 knees). Mean 49 months follow-up.	No deep infection in Group 1; 5 deep infections in Group 2 (3.1%), p = 0.02.	"In conclusion, this prospective, randomized study strongly supports the efficacy of antibiotic (cefuroxime) impregnation in cement in the prevention of early and intermediate deep infection after primary total knee arthroplasty. On the basis of these data, we recommend the use of antibiotic-impregnated cement in primary total knee arthroplasty when the procedure is performed in an operative environment that does not include so-called clean-air measures."	Blinding not described. Quasi-randomized on MRN. Data suggest cefuroxime-impregnated cement prevents deep but not superficial infections when added to an IV antibiotic regimen.
Josefsson 1981 RCT	4.0	N = 1,685 with 85% OA, 6.8% fracture, 4.1% RA	Prophylaxis with systematic antibiotics (not standardized) vs. gentamicin bone cement.	Systemic antibiotic: 49 (5.9%) vs. 71(8.3%) gentamicin cement with superficial infections. Difference statistically significant (p <0.05). Deep infections favored gentamicin cement (0.4% vs. 1.6%, p <0.01).	"The difference in deep infection frequency between the antibiotic and gentamicin group was statistically significant."	First of 3 publications on same group. Sparse methodological description weakens score. Systemic antibiotics not standardized.

						More superficial infections in cement group, but fewer deep infections.
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GLUCOCORTICOSTEROID INJECTIONS AFTER ARTHROSCOPY AND MENISCECTOMY

Intra-articular glucocorticosteroid injections are frequently performed after arthroscopy and meniscectomy.(1485)

Recommendation: Glucocorticosteroid Injections after Arthroscopy

Intraarticular glucocorticosteroid injections are recommended for select patients after arthroscopy and meniscectomy.

Indications – Patients undergoing arthroscopy, particularly if osteoarthritis is identified and patient is believed to potentially benefit from glucocorticoid injection, although there may be no long-term benefit.(1485)

Frequency/Dose/Duration – Injection performed at end of procedure.

Strength of Evidence – **Recommended, Evidence (C)**

Rationale for Recommendation

Two moderate-quality trials suggest superior short-term results from injection with glucocorticosteroid if chondromalacia is identified,(1485) or compared with placebo among patients with osteoarthritis.(1486) There is generally no additional invasiveness of this adjunctive procedure and the complication rate (primarily due to infection) is believed to be quite low. As there is evidence of efficacy,(1325) these injections are recommended.

Evidence for the Use of Glucocorticosteroid Injections after Arthroscopy and Meniscectomy

There are 3 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Corticosteroid Injection vs. Placebo						
Wang 1999 RCT	7.0	N = 60 with ASA physical Status I-III, age 35-65, with OA (chronic degenerative arthritis) of knee and scheduled for elective arthroscopic knee surgery	Group 1 (n = 30) with triamcinolone acetonide 10mg plus 1mL NS vs. Group 2 (n = 30) with 20mL NS. Instilled end of arthroscopic procedure. Post-op pain assessed. Pain assessed by VAS for 2 hour intervals for 24 hours after surgery except when sleeping.	From 6 to 24 hours, Group 1 had lower pain scores, p <0.05 to p <0.01. Survival curve different from Group 2 p <0.01. In Group 1 and 2, 6/29 (21%) vs. 17/28 (61%) required rescue analgesia 0-24 hours post-op, p <0.01. From 6 to 24 hours, 0% vs. 15/28 (53%) in Group 2 requested rescue analgesia, p <0.001.	"[I]ntraarticular triamcinolone acetonide provides a valuable local therapy for acute joint pain after arthroscopic knee surgery. Patients who received triamcinolone acetonide reported less pain and requested less rescue analgesia."	Blinding not well described. Short study of 24 hours. All arthroscopic knee surgery, but procedures not well described. Data suggest less rescue analgesics required for steroid group.
Koyonos 2009 RCT	6.5	N = 58 (59 knees) age 18-65 with meniscectomy and OA (chondromalacia, Outerbridge Grade 2+) confirmed by arthroscopy.	Group 1 (n = 30 knees, with injection of 1 mL 0.9% normal saline plus 9 mL 1% lidocaine) vs. Group 2 Depomedrol 40mg plus 9mL 1% lidocaine. Evaluations	Steroid group's Knee Injury and Osteoarthritis Outcome Score (KOOS) at 6 weeks: steroid 29±24 vs. placebo 50±26, p = 0.005. KOOS Quality of Life scores also favored steroid at 6 weeks: 41±19 vs. 55±	"In patients with OA of the knee, who are inherently at greater risk for poorer outcomes following meniscectomy, adding an intra-articular corticosteroid injection to	Data suggest short-term benefit of intraarticular glucocorticoid after meniscectomy if chondromalacia present,

			preoperatively, 6 weeks, 6, 9, 12 months.	24, p = 0.035.), and International Knee Documentation Committee scores at 6 weeks: 49±16 vs. 59±20, p = 0.01. At 6, 9, 12 months no differences.	postoperative care is safe and effective at decreasing pain and improving function for the first 6 weeks after surgery.”	but no long-term benefits.
Young 2001 RCT	5.0	N = 40 (41 knees) with symptomatic knee OA, assessed at time of initial arthroscopy and 2nd arthroscopy	Methylprednisolone acetate 120mg intra-articularly (n = 20) vs. NS placebo (n = 20). Assessments arthroscopic ally at initial and 1 month; 1 month follow-up.	Pre-treatment: no difference between methylprednisolone acetate and placebo. Post-treatment: small reduction in CD68+ in methylprednisolone acetate (30%) vs. placebo group (p = 0.048). Data also support efficacy of injection by WOMAC scores.	“[T]he administration of intraarticular glucocorticoids was associated with a small reduction in CD68+ macrophage infiltration in the synovial lining but not the synovial sublining layers in human OA synovial membranes. There was no effect on the expression of MCP-1, MIP-1α, MMP-1, MMP-3, TIMP-1, or TIMP-2. The observations from this study suggest that intraarticular glucocorticoids do not influence the expression of some of the important mediators of cartilage destruction in OA.”	Data provide histological evidence to support efficacy of glucocorticoid injections.

PERIARTICULAR GLUCOCORTICOSTEROID INJECTIONS FOR ARTHROPLASTY PATIENTS

Periarticular glucocorticoid injections have been used for arthroplasty patients.(1488)

Recommendation: Periarticular Glucocorticosteroid Injections for Arthroplasty Patients

There is no recommendation for or against the use of periarticular glucocorticosteroid injections for arthroplasty patients.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There is one moderate-quality trial comparing a mixture of pharmaceuticals with and without a glucocorticosteroid.(1488) While most outcomes including pain scores and narcotics consumed were negative, the length of hospital stay was inexplicably shorter in the steroid group and produced a mixed picture regarding efficacy of this intervention. Thus, there is no recommendation for or against these injections.

Evidence for the Use of Periarticular Glucocorticosteroid Injections for Arthroplasty Patients

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
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Christensen 2009 RCT	6.5	N = 76 males and non-pregnant females scheduled to undergo unilateral primary knee arthroplasty ; age 18-95	Periarticular injection of 80mg bupivacaine hydrochloride, 4mg morphine, 300µg epinephrine, 100µg clonidine, 750mg cefuroxime, and normal saline vs. same combination plus methylprednisolone acetate 40mg (n = 37); 12 weeks follow-up.	Knee Society function scores (baseline/6 weeks/12 weeks): No steroid (29.6±15.9/38.3±23.1/48.2±28.2) vs. steroid (34.7 ±20.4/42.0±27.1/56.5±27.7). No differences in other measures including narcotic consumption, pain scores. Length of stay favored steroid (2.6±0.7 vs. 3.5±1.9, p = 0.01).	"[T]he results of this study suggest that the addition of a corticosteroid to intraoperative periarticular injections does not provide benefit when compared with injections that do not contain a corticosteroid."	Mixed results with no reduction in pain, narcotics, other measures, but shortened hospital stay. As other measures not significant, raises question of validity of single measure favoring steroid.
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PRE-OPERATIVE EDUCATION

Educational interventions have been utilized for rehabilitation of arthroplasty patients, particularly for pre-operative preparation.(1822-1824) These interventions may include various combinations of procedural, sensory information, cognitive coping strategies, reassurance, and relaxation and hypnosis training.(1825, 1826) Multiple modes of instruction are frequently incorporated, including oral, written, and video.

Recommendation: Pre-operative Educational Program Prior to Arthroplasty

A pre-operative educational program is moderately recommended prior to arthroplasty.

Components should include procedural and recovery information and use at least two modes of teaching (e.g., oral and written).

Strength of Evidence – Moderately Recommended, Evidence (B)

Rationale for Recommendation

Most studies of educational interventions involved hip and not knee patients and have demonstrated benefits.(565, 1827-1829) Lengths of contact have ranged widely, although most studies do not report educational contact time. Some programs encourage involvement of family members and other care givers. Better post-operative compliance with rehabilitation has been shown in patients who have participated in educational interventions.(1830) Numerous studies have combined exercises and other interventions with educational interventions. However, nearly all studies reporting length of hospital stay have shown earlier hospital discharge after hip arthroplasty with educational interventions.(1822-1824, 1831, 1832) Other studies have shown earlier performance of activities such as stair climbing(1833) and reductions in pain and anxiety.(1834)

Evidence for the Use of Pre-operative Education Prior to Arthroplasty

There are 12 moderate-quality RCTs incorporated in this analysis. There are 5 low-quality RCTs in Appendix 1.(1822, 1835-1838)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Giraudet-Le Quintrec 2003 RCT	6.5	N = 100 undergoing THR	Group 1 attended ½ day collective multidisciplinary information session 2 to 6 weeks before surgery vs. controls who did not attend.	Patients receiving education significantly less anxious just before surgery than control (- 4.98; 95% CI, -8.62 to - 1.34, p = 0.01), in linear regression after adjustment for gender, trait, state anxiety at baseline, depression	"The current study showed the value of developing alternative information approaches for informing patients and answering their questions. Group discussion	Suggests education effective to reduce anxiety and pain especially pre- operatively.

				score, and health assessment questionnaire score. Intervention group had less pain before surgery ($p = 0.04$), and borderline after surgery ($p = 0.07$).	with the care team seems to be useful.”	
Siggeirsdottir 2005 RCT	5.5	N = 50 undergoing THR	“Conventional” rehab augmented by stay at rehab center (control group, CG) vs. pre-op and post-op education program and home visits from outpatient team.	Mean hospital stay SG 6.4 days vs. CG 10 days, $p < 0.001$. During 6-month study, non-fatal complications not different (9 in SG vs. 12 in CG, $p = 0.3$). Oxford Hip Scores better for SG at 2 months ($p = 0.03$); difference remained throughout study.	“Our preoperative education program, followed by postoperative home-based rehabilitation, appears to be safer and more effective in improving function and QOL after THR than conventional treatment.”	Suggests educational program and home visits superior to rehabilitation stay. Hospital stays longer than in U.S.
Mancuso 2008 RCT	5.5	N = 177 undergoing THR N = 143 undergoing TKR	Two RCTs for patients undergoing THA or TKA. Controls received standard class vs. intervention (standard class plus additional information focusing on expectations of recovery during 12 months after surgery).	Main outcome was within-patient change in pre-op expectation scores (maximum increase, +100; maximum decrease, -100) before and after class. Mean changes in hip scores: 3.3 ± 8 for intervention patients (range, -22 ± 32) and 4.9 ± 8 for controls (range, -13 ± 29).	“[E]xpectations of patients undergoing THA and patients undergoing TKA can be modified by classes administered before surgery.”	More controls retired at baseline (69% vs. 54%, $p = 0.05$).
Gocen 2004 RCT	5.0	N = 60 Undergoing THR, all thrust plate prostheses	Pre-op physiotherapy (strengthen limbs and hip ROM for 8 weeks) plus educational program vs. no intervention prior to surgery.	First day for activity (exercise vs. controls): walking 2.1 ± 0.2 vs. 2.2 ± 0.41 , $p = 0.14$; climbing stairs 6.2 ± 1.7 vs. 7.4 ± 1.0 , $p = 0.01$; bed transfer 2.9 ± 0.6 vs. 3.3 ± 0.7 , $p = 0.02$. Improvements in Harris Hip scores not significant at 3 months or 2 years ($p > 0.05$).	“[T]he routine use of preoperative physiotherapy and education programme is not useful in total hip replacement surgery.”	Baseline differences present with exercise group younger ($p = 0.01$) and lower BMI ($p = 0.06$), Harris Hip scores ($p = 0.13$) suggest randomization failure. Study reported as negative based on Harris Hip score, all 5 functional post-op measures favor exercise.
Wong 1985 RCT	5.0	N = 98 undergoing THR	Intervention group (pre-op teaching that combined educational and behavioral strategies by a research	Significant difference between experimental and controls in regularity, willingness, accuracy with which they performed prescribed post-op exercises.	“The findings suggest that an approach to preoperative teaching that combines educational and behavioral	Four day study, no long-term follow-up. No outcome data such as length of stay, performance benchmarks or

			assistant) vs. control group.	Experimental patients significantly more satisfied with approach to pre-op teaching than controls.	strategies significantly improves patients' adherence to the prescribed postoperative activities."	long-term complications.
Daltroy 1998 RCT	5.0	N = 222 undergoing THR or TKR (47% THR; 53% TKR)	Slide-tape with post-op inpatient rehab (Information) vs. Benson's Relaxation Response with bedside audiotape (Relaxation) vs. both vs. neither.	Relaxation response did not influence post-operative outcomes, but information reduced length of stay (data not described in detail). Main outcomes not analyzed or reported. Instead, sub-analyses performed. Sub-analyses suggested those in denial and with anxiety may benefit from educational interventions.	"Patients who exhibit most denial and highest anxiety may benefit from educational interventions, but patients directly expressing desire for information may be a poor guide in deciding which patients would benefit, compared with more formal psychological testing for denial and anxiety."	Conclusion does not directly follow study's primary hypothesis and design. Due to problems with inadequate time to practice relaxation, primary hypothesis was either not tested (or possibly was negative for differences between groups).
Vukomanovic 2008 RCT	4.5	N = 45 undergoing THR	Study group vs. control group (with and without pre-op education and physical therapy).	Groups started walking at same time, but study group walked up and down stairs (3.7 ± 1.66 vs. 5.37 ± 1.46 , $p = 0.002$), used toilet (2.3 ± 0.92 vs. 3.2 ± 1.24 , $p = 0.02$) and chair (2.2 ± 1.01 vs. 3.25 ± 1.21 , $p = 0.006$) significantly earlier than control group.	"The short-term preoperative program of education with the elements of physical therapy accelerated early functional recovery of patients (younger than 70) immediately after THA and we recommend it for routine use."	Program components not described. Frequency of activities not described.
Butler 1996 RCT	4.5	N = 132 undergoing THR	Total hip replacement educational booklet vs. no booklet.	Length of stays higher for women (12.2 vs. 8.2 days). Less anxiety reported in booklet group. Booklet group engaged in deep breathing, coughing, log rolling and leg exercises more than controls ($p < 0.001$). Booklet group used less PT (32.7 vs. 45.6, $p = 0.001$).	"Compared to the No-Booklet patients, patients who had received the booklet were less anxious at the time of hospital admission and at discharge, were more likely to have practised physiotherapy exercises prior to hospitalization, and required significantly less occupational therapy and physiotherapy while in hospital."	Study included first time as well as other THR patients; 32 or 80 first timers received booklet and 48 did not, resulting in a potential significant confounding.
Pour 2007	4.5	N = 100 undergoing THR,	Group A standard incision	Hospital lengths of stay (standard vs. accelerated rehab): 4.2	"This study highlights the importance of	Due to multiple interventions, effects of any

RCT		uncemented, proximally coated tapered stem (Accolade) and plasma-sprayed acetabular component (Trident)	(>10cm), standard pre-op/ post-op care (2-3 days PCA analgesia). Group-B small incision (≤10cm), standard pre-op/ post-op protocols. Group-C standard incision but pre-op counseling, accelerated rehab, altered pain control regimen (OxyContin 5mg Q4-6 hours. PRN plus celecoxib 200mg a day. Group-D small incision, pre-op counseling, accelerated rehab, altered pain control regimen.	days (range 3-8) vs. 3.5 (range 2-5) (p = 0.001). Walking independently or supervised at discharge 60.4% vs. 84.8%, p = 0.009. Walking distance at discharge: 24.3m (range 3.5-91.5) vs. 35m (range 7-91.5), p = 0.008. Equianalgesic requirement (mg): 26.8(2.4-113.7) vs. 41.2 (2.4-120); p = 0.01. No benefits of short incision shown.	factors such as family education, patient preconditioning, preemptive analgesia, and accelerated preoperative and postoperative rehabilitation in influencing the outcome of total hip arthroplasty.”	single intervention unclear. Suggests combination of education, pre-op gait training and exercise, assistive walking day of surgery, and oral narcotics plus celecoxib are more effective. No benefit shown of small incision. Overall equianalgesic opioid dose higher in accelerated rehabilitation.
Gammon 1996 RCT	4.0	N = 82 pre-surgery THA patients	Educational program (procedural, sensory and coping information) vs. usual education (usual advice by ward, medical and nursing staff).	Length of hospitalization 14 vs. 17 days (p <0.001). Intramuscular analgesia doses favored intervention (2 vs. 4, p <0.001). Mobilization, breathing exercise frequency, exercise frequencies all favored intervention (p <0.05). No differences in post-op complications or oral analgesic doses. Patient assessments of ability to cope favored intervention (6.6 vs. 4.1, p <0.001).	“[P]reparatory information, given pre-operatively, post-operatively and pre-discharge had positive effects on the physical recovery and coping outcomes measured.”	Quasi-randomized every other patient. Suggested benefits of more focused information on arthroplasty and recovery processes.
Gammon 1996 RCT	4.0	N = 82 pre-surgery THA patients	Educational program (procedural, sensory and coping information) vs. usual education (usual advice by ward, medical and nursing staff).	Anxiety scores for information group mean 4.2 vs. 4.4, p <0.001. Sense of control scores 19.9 vs. 11.2, p <0.01. Patient sense of coping 6.6 vs. 4.3, p <0.001.	“[P]reparatory information of various types and in different forms appears to have positive effects on psychological coping outcomes for THR patients, which may have influenced postoperative recovery.”	Differences in anxiety (mean 4.2, range 0-11 vs. mean 4.4, range 0-16) stated statistically significant, but biological significance appears questionable. Sense of

						control appears significant.
Hopman-Rock 2000 RCT	4.0	N = 105 with hip or knee OA	Group receiving program, "Living with osteoarthritis of the hip or knee" consisted of 6 weekly sessions of 2 hours, including health education by a peer and physical exercise taught by physical therapist vs. group without intervention.	Significant MANOVA group x time effects (p < 0.05, 1-sided) found for pain, quality of life, strength of left M. quadriceps, knowledge, self-efficacy, BMI, physically active lifestyle, and visits to physical therapist. Most effects negative; those positive were moderate at post-test assessment and smaller at follow-up. No effects for ROM and functional tasks.	"[T]his self-management program was reasonably effective in terms of the educational and exercise components. However, future interventions should pay more attention to proactive follow up interventions such as telephone follow up."	Stratification by hip or knee OA not performed. Most results negative and those that were positive were mild.

PRE- AND POST-OPERATIVE REHABILITATION FOR KNEE ARTHROPLASTY

Numerous studies have evaluated post-operative rehabilitation and activity levels that appear important for recovery from knee procedures, especially for arthroplasty.(1839, 1840) Considerations have included pre-operative exercise programs, post-operative activity limitations, post-operative rehabilitation programs and late rehabilitation programs several months after surgery.(1841, 1842) Compliance is noted to be problematic.

PRE-OPERATIVE REHABILITATION

Pre-operative exercise programs have been prescribed to attempt to improve arthroplasty results and reduce complications.(1828, 1833, 1843-1849)

Recommendation: Pre-operative Exercise Program

A pre-operative exercise program particularly emphasizing cardiovascular fitness and strengthening prior to knee arthroplasty is recommended for a select, fairly small minority of patients who exhibit evidence of considerable weakness, debility or unsteady gait. Flexibility components may be reasonable in those without fixed deficits.(1833, 1846, 1848)

Indications – Highly select pre-operative arthroplasty patients who have considerable muscle weakness and/or debility, particularly sufficient weakness to have impairments such as unsteady gait or difficulty with ADLs.

Frequency/Duration – Most program elements require an initial appointment to teach exercises followed by a home exercise program prescription. Two or 3 follow-up appointments for adherence and additional exercise instruction may be needed. Patients with severe deficits may require 2 to 3 appointments a week for 4 to 6 weeks in advance of arthroplasty.(1848) Patients

with minimal deficits may benefit from a single appointment to teach programmatic elements for a self-directed program.

Indications for Discontinuation – Achievement of program goals, resolution of strength or gait deficits, intolerance or other adverse effects.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendation

There are few quality trials that evaluate pre-operative exercise programs for the treatment of knee arthroplasty, and there is no consistent evidence of benefits in either knee or hip arthroplasty patients.(1850, 1851) One trial has suggested benefits, but most have not.(588, 1852) One moderate-quality study demonstrated there were benefits from a 6-week pre-operative exercise program that consisted of several elements broadly including cardiovascular, strengthening and flexibility exercises with 30 to 60-minute sessions 3 times a week.(1848) The benefits included reduced post-operative complications, earlier discharge and higher probability to be discharged directly to the patient’s home. A second moderate-quality study demonstrated benefits of a peri-operative exercise program and also demonstrated benefits lasting 6 months after surgery.(1846) Another moderate-quality study was reported as negative using the author’s main outcome of changes in Harris Hip Scores. However, all 5 post-operative milestones (e.g., walking, chair transfer, stair climbing) statistically favored the exercise group.(1833) Pre-operative rehabilitation may be useful as a component of pre-operative education and exercise programs for selected high risk, deconditioned patients. However, most typical patients do not require preoperative programs.

Evidence for the Use of a Pre-operative Exercise Program

There are 4 moderate-quality RCT incorporated in this analysis. There is 1 low-quality RCT in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Pre-Operative Exercise and Education						
Beaupre 2004 RCT	6.0	N = 131 undergoing TKA	Control vs. treatment (exercise and education); 6 weeks pre-op treatment; 1 year follow-up.	No differences found at any time between groups.	“The exercise/ education intervention did not alter functional recovery or HRQOL following TKA.”	Data suggest pre-op exercise and education ineffective.
Rooks 2006 RCT	5.0	N = 108 scheduled to undergo hip (n = 63) or knee (n = 45) arthroplasty	Six-week pre-op program of exercise (water and land-based exercise, cardiovascular, strength and flexibility, 30-60 minute sessions, 3 times a week) vs. education controls.	WOMAC scores (baseline/ pre-op/8 weeks) for THA patients improved at pre-op measure (exercise 29.1±12.9/26.9±11.9/12.8 ±9.0 vs. education 29.8±11.2/ 33.7±10.9/ 12.9±8.0) pre-op p = 0.02. SF-36 scores -0.4 vs. -14.3, at pre-op assessment p = 0.003. Differences not present at 8 weeks. Fewer complications in exercise group (0 vs. 4, p = 0.04). Exercise	“A 6-week presurgical exercise program can safely improve preoperative functional status and muscle strength levels in persons undergoing THA. Additionally, exercise participation prior to total joint arthroplasty dramatically reduces the odds of inpatient rehabilitation.”	Results more favorable for hip than knee arthroplasty patients. Education controls 3.7 times more likely to be discharged to rehabilitation facility compared with exercise group. High dropout rate. Study suggests pre-op exercise effective for

				group more likely to walk 50 feet on post-op Day 3 (76% vs. 61%). Exercise group more likely discharged to home 65% vs. 44%.		improving functional status and preventing inpatient rehab.
D'Lima 1996 RCT	4.5	N = 30 undergoing primary total knee replacement, age greater than 55 and diagnosis of OA	Control vs. experimental physical therapy vs. experimental cardiovascular conditioning after total knee replacement.	No significant differences between groups.	"While it seems reasonable to believe that patients undergoing total knee replacement would benefit from preoperative strengthening exercises, there is no evidence to support this assumption. Preoperative physical therapy is not an effective method of improving outcome or shortening hospital stay in patients undergoing total knee replacement."	Small groups. Data suggest preoperative exercises largely ineffective.
Weidenhielm 1993 RCT	4.0	N = 40 with moderate-medial knee OA scheduled for unicompartmental knee replacement with cemented endoprosthesis	Preoperative physiotherapy (n = 20) vs. control (n = 20).		"[T]his study did not disclose any major benefit from the program of preoperative physiotherapy tested."	Data suggest comparable outcomes at 3 months.

POST-OPERATIVE REHABILITATION

Exercise, physical therapy and rehabilitation have been used pre-operatively as well as post-operatively for rehabilitation of arthroplasty patients.(580, 1850, 1851, 1853-1858) Continuous passive-motion machines have also been used in rehabilitation of arthroplasty patients.(1859, 1860)

1. Recommendation: Post-Operative Rehabilitation of Knee Arthroplasty Patients

Post-operative rehabilitation is recommended for knee arthroplasty patients.

Indications – Patients having undergone knee arthroplasty.

Duration – Treatment may need individualization based on factors including pre-operative conditioning and immediate post-operative results. Treatment is often daily while hospitalized, then 2 to 3 sessions a week. One trial suggested an educational kneeling intervention had demonstrable long-term benefits.(1854) Three trials have suggested benefits of accelerated and/or early rehabilitation.(1839, 1855, 1861)

Indications for Discontinuation – Achievement of goals, non-compliance with clinic or home-based exercises or intolerance.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. *Recommendation: Continuous Passive Motion for Knee Arthroplasty Patients*
Continuous passive motion is not recommended for routine use for arthroplasty patients. It may be useful for select, substantially physically inactive patients post-operatively.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendations

Most of the available quality trials concern continuous passive-motion (CPM) devices in the immediate post-operative period.(1862-1867) This literature base has many older, lower quality trials(1307, 1860, 1868-1878) (see Appendix 1). Trials comparing CPM with splinting have suggested efficacy.(1879) However, over the past 25 years, patients have gradually been ambulated earlier and are now generally placed on immediate weight bearing status, which appears a likely reason that both of the more recent and higher quality studies have failed to show benefits from use of CPM.(1862, 1863) This device is likely preferable to no activity; however, for most patients, active exercise appears superior. Thus, CPM is not recommended for most patients, but it may retain some utility for selected, relatively inactive patients in the immediate postoperative period.

Accelerated rehabilitation programs have been assessed and appear to be superior to usual care(1839, 1855, 1861) or CPM.(1880) There is no demonstrable difference between clinic- and home-based rehabilitation programs or between home and hospital-based care after arthroplasty.(1881, 1882) One trial has suggested neuromuscular electrical stimulation was not of significant additive benefits.(1883) Exercise and rehabilitation are not invasive, have low adverse effects, and are moderately costly, depending on numbers of appointments required; thus, they are recommended for select patients who have functional deficits.

Evidence for the Use of Post-operative Rehabilitation

There is 1 high- and 12 moderate-quality RCTs incorporated into this analysis. There are 13 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Exercise and Education						
Jenkins 2008 RCT	7.5	N = 60 scheduled for primary medial PKR	Kneeling intervention (30 minute session with advice to kneel, written information, demonstration, n = 30) vs. routine intervention (n = 30); 1 year follow-up.	Kneeling/routine/both groups preop knee Oxford knee score OKS (0-48) median, IQ, range, Mann- Whitney U test for OKS, range of flexion (°) mean, SD, range, and Mann-Whitney U test for range of flexion.	“The results of this study suggest that advice and instruction in kneeling should form part of a postoperative rehabilitation program after PKR. The results can be applied only to patients following PKR.”	Data suggest kneeling education and intervention effective with longer term results at 1 year present.

Reilly 2005 RCT	7.0	N = 41 with medial compartmental OA undergoing UKA	Accelerated recovery (mobilization 2 hours after surgery, progressive walking and aim to discharge at 24 hours, n = 21) vs. standard care (n = 20); 6 months follow-up.		“In terms of effectiveness and acceptability, this study indicates that accelerated discharge for UKA is feasible, acceptable to patients and has potential value to the NHS. The new protocol appears safe although conclusions regarding safety and complications are moderated in view of the trial size.”	Data suggest accelerated rehabilitation results in earlier discharge (1.5±0.7 vs. 4.3±1.3 days) and lower costs (£3391 vs. £4634) with same high satisfaction.
Liebs 2010 RCT	5.5	N = 159 with knee replacements, 203 with hip replacements for OA or ON	Ergometer cycling group using standard bicycle ergometer (minimum resistance) 3 times a week for at least 3 weeks vs. control with no ergometer cycling. All treated with standard post-op program of daily PT (ROM, strengthening, balance, coordination, gait, ADL instructions, stairs; TKA patients also treated with CPM until suction drain removal); 2 year follow-up.		“Ergometer cycling after total hip arthroplasty is an effective means of achieving significant and clinically important improvement in patients’ early and late health-related quality of life and satisfaction. However, this study does not support the use of ergometer cycling after knee arthroplasty.”	Data suggest cycling by ergometer successful for rehabilitation of hip arthroplasty, but not knee arthroplasty patients as adjunctive treatment to a standard program.
Frost 2002 RCT	4.5	N = 47 unilateral knee OA undergoing arthroplasty, ages 65-80	Home-based traditional exercise group (TEG, mobilizing, strengthening exercises, gait reeducation, active flexion with sliding board, isometric quadriceps, straight leg raises, inner range quadriceps exercises, 3-4 times a day for 10-15 minutes) vs. home-based functional exercise group (FEG, progressive walking and document amount of walking/day, warmup exercise, chair rise, leg lifts, daily exercise log) following discharge from hospital; 12 month follow-up.	Mean±SD pain comparing baseline/3, 6, 12 months: TEG (completers): 4.2±1.16/2.6±0.9/1.9±1.14/1.5±0.93. FEG (completers): 4.2±0.54/2.6±1.0/2.0±0.8/1.6±0.8; p <0.0001.MANOVA for within-subject change. Trend towards faster walking speed in FEG (mean change 0.42m/s vs. 0.23, p = 0.21).	“There were trends in favour of the FEG that were of clinical relevance. A definitive study would need a sample size of at least 100 patients in each arm. It is essential to develop strategies to combat loss to follow-up.”	Underpowered and high dropouts. Data suggest functional exercise may have better outcomes compared to traditional exercises. Functional exercise included progressive walking and exercise logs.

Nielsen 1988 RCT	4.0	N = 50 who underwent primary uncemented total knee arthroplasty (TKA) for arthritis	Active physical therapy vs. active physical therapy plus 2 hours passive knee motion twice daily.	No difference between groups 14th post-op in regards to flexion, extension, and total ROM.	“As a consequence of our results, we no longer use continuous passive motion after primary knee arthroplasty.”	Sparse methods and results. Data suggest CPM ineffective.
Passive Range of Motion						
Denis 2006 RCT	8.0	N = 82 with knee OA diagnosis, expecting TKA, and were ambulatory	Conventional PT intervention (CTL) without continuous passive motion (CPM) vs. CTL with CPM for 35 minutes daily vs. CTL with CPM for 2 hours daily after total knee arthroplasty.	No significant differences between 3 groups.	“[A]dding CPM applications to conventional physical therapy interventions does not favor better knee flexion ROM. Furthermore, the results indicate that CPM applications do not have any additional effect on knee extension ROM, functional ability, or LOS. Therefore, we believe that CPM should not be routinely used during in-hospital rehabilitation programs after primary TKA for people with osteoarthritis.”	Data suggest CPM ineffective.
Beaupré 2001 RCT	6.5	N = 120 receiving primary TKA with a mean age of 68.4 years with a knee OA diagnosis.	Three 2-hour CPM sessions a day with ROM increased as tolerated (CPM group, n = 40) vs. a minimum of 2 10-minute sessions of slider board (SB) a day and standard exercises (SE) (SB group, n = 40) vs. control group of SE (n = 40) with 6 months follow-up.	No significant between-group differences.	“When postoperative rehabilitation regimens that focus on early mobilization of the patient are used, adjunct ROM therapies (CPM and SB) that are added to daily SE sessions are not required. Six months after TKA, patients attain a satisfactory level of knee ROM and function.”	Data suggest CPM and sliding boards are of no additive benefit in addition to an early mobilization regimen over 6 months.
McInnes 1992 RCT	5.5	N = 102 with OA and RA undergoing primary TKA.	CPM plus standardized rehabilitation vs. standard rehabilitation.		“[T]he use of CPM plus standard rehabilitation avoids the need for manipulation, improves early active flexion, decreases swelling, and lowers cost compared with standard rehabilitation alone but does not affect pain, active and passive extension, strength, length of	Rehab protocols and lengths of stay very long for current time, suggesting value of trial limited. Data suggest CPM effective.

					stay, or overall function or ROM at 6 weeks after the operation.”	
Davies 2003 RCT	5.0	N = 120 underwent TKA	Continuous passive motion (n = 40) vs. slider board (n = 40) vs. standardized exercise (n = 40) for 6 months.	Average cost of health services not significant among study groups.	“No difference in the quantity or cost of health services was seen among the 3 treatment groups in the subacute recovery phase after a TKA.”	Study focused on health care cost and utilization and not outcomes.
Montgomery 1996 RCT	4.5	N = 68 with uncemented porous-coated anatomic prosthesis, n = 25 tri-compartmental and n = 43 uni-compartmental	Continuous passive motion CPM (n = 34) vs. active PT APT (active and passive motion knee exercises, 30 minutes BID, 5 days a week, n = 34). All uncemented PCA prostheses.	CPM vs. APT mean±SD or mean (range) for hospitalization (days), post-op pain (VAS) for day 1, 3, 5, mid-patellar effusion (cm) preop, patellar effusion at discharge, patellar effusion individual diff pre/post, knee flexion at discharge (°), and ROM 70°(days): 9±3/10±4, 7(1-10)/8(1-10), 4(1-8)/5(1-10), 5(1-10)/5(2-8), 43±5/41±3, 44±4/44±3, 1.3±2/4.6±8/p <0.05, 77±8/76±6, 5±2/7±3/p≤0.01.	“[C]PM provided an improvement in early knee motion. However, this did not affect hospitalization or postoperative pain.”	Some details sparse.
Chen 2000 RCT	4.5	N = 51 with TKA who were tolerant of a CPM machine	Standard program of physical therapy as well as CPM for 5 hours a day (n = 29) vs. physical therapy only (n = 35).	No significant between-group differences.	“[T]he use of CPM in the rehabilitation hospital is likely of no added benefit to patients admitted after single total-knee replacement.”	Data suggest CPM of no post-op rehabilitation additive benefit.
Johnson 1990 RCT	4.0	N = 102 who had primary knee replacement	Immediate CPM passive motion (n = 50) vs. immobilization of knee in splint (n = 52) for 7 days post surgery; 14 days follow-up.	Length of stay less in CPM group vs. immobilization, p <0.01. Fix flexion deformity not significant between groups. CPM had greater range of flexion at 7, 10, 14 days, 6 weeks, 1 year vs. immobilization. Transcutaneous oxygen tension significantly reduce in both medial edge of wound (p <0.02) and lateral edge of wound (p <0.01) in patients in CPM group vs. to	“On the basis of these results, a protocol for continuous passive motion was designed to minimize the detrimental effects on viability of the wound.”	Subjects not well described. Data suggest CPM may be helpful, however comparison group was immobilization.

				immobilization group with 0-60° range.		
Ritter 1989 RCT	4.0	N = 50 with bilateral TKA with pre-op flexion range greater than 90°	CPM vs. PT (isometric quadriceps, gluteal sets, ankle dorsiflexion, plantar flexion, assisted SLR, ambulation with walker and weight bearing as tolerated). All received anatomically graduated component.	No significant difference in ROM between CPM machine and controls.	"[T]he CPM machine is an inefficient and expensive adjunct to physical therapy and is not indicated in the treatment of patients with total knee arthroplasties."	Demographics and baseline data not described. Crossover with each knee assigned to one or other group. Data suggest CPM ineffective compared with PT.

POST-OPERATIVE ACTIVITIES AND SPORTS

There is a greater volume and quality of literature on post-operative hip arthroplasty patients than knee arthroplasty patients(1797) (see Hip and Groin Disorders guideline). Researchers summarizing this literature have concluded there is somewhat less return to sports in knee than hip arthroplasty patients.(1884, 1885) There are three primary methods to assess appropriate sports or activities for knee arthroplasty patients: epidemiological studies, biomechanical models, and experimental studies. While there are more hip data, the available studies for the knee also produce conflicts that are not readily resolved. Since the evidence conflicts and the epidemiological studies are the gold standard for the development of quality guidance,(1886-1888) this review emphasizes epidemiological studies.

There are many studies suggesting sizable proportions of individuals successfully returning to sports and manual labor, including high impact sports that have not been generally recommended for these patients. One study has suggested 91% of knee arthroplasty patients return to low impact sports compared with 20% to high impact activities.(1889) A small case series reported no apparent complications with high impact sports, including jogging, downhill skiing, tennis, racquetball, squash and basketball, although it may be underpowered for adverse effects.(1890) One study found 16% of arthroplasty patients were involved in heavy manual labor or sports that were "not recommended" by the Knee Society.(1891, 1892) Yet, there are neither randomized controlled trials of returning to sports,^{xv} nor are there large prospective cohort studies that have used return to sports as a primary indicator, thus the overall quality of this literature from which to draw conclusions is quite limited. Data for hip arthroplasty patients is similarly conflicted (see Hip and Groin Disorders guideline).

One concern has been increased wear rates for prosthetic joints subjected to sports or manual labor. While joint use has been thought to be an important factor, the evidence is primarily derived from biomechanical studies and not quality epidemiological studies with large sample sizes. Wear rates for knee arthroplasties are reportedly worse with activity reported in a small necropsy study.(1893) However, that study which also evaluated multiple factors found body mass index as the most important factor, which creates a conflict between physical activity and body mass index. Another large case series reported worse outcomes with increased body mass index, higher Deyo-Charlson index, female gender, age over 80 years and

^{xv}Almost no RCTs have addressed return to activity other than a number of post-operative rehabilitation studies such as a study of ergometer cycling that found it ineffective in contrast with hip rehabilitation (see Hip and Groin Disorders guideline).

comorbidities.(1894) Younger patients are presumed to be more active on average than older patients, yet such a cohort of younger active patients reported a 94% 18-year arthroplasty survival rate.(1895) Thus, the importance of activity for joint survival is somewhat unclear.

Among unicondylar knee arthroplasty patients, one report noted 93 to 95% of patients returned to sports.(1896, 1897) Others have similarly found more patients with unicondylar arthroplasties return to sports compared with total knee arthroplasty patients,(1898) although these studies could be confounded by other factors.

A related issue is lack of use after arthroplasty from fear of use or fear of excessive wear, which could worsen outcomes and incur worse health outcomes associated with inactivity. For example, one descriptive study found few golfers walked the course after arthroplasty and suggested education to increase exercise is needed.(1899) Among the determinants of post-operative activity levels, pre-operative condition is thought to be an important, if not the most important factor.

Operative approaches in relation to return to sports have not been well studied, although evidence suggests minimal differences in return to usual functions (see Arthroplasty above). Minimally invasive approaches have been hypothesized to potentially be better for return to sports activity, particularly in the early phases. No differences by type of operation have been found.

The Knee Society survey of opinions on returning to sports(1900) included the following sports recommendations by category: recommended allowed sports were low impact aerobics, stationary bicycling, bowling, golfing, dancing, horseback riding, croquet, walking, swimming, shooting, shuffleboard, and horseshoes. Sports allowed with experience were road bicycling, canoeing, hiking, rowing, cross country skiing, speed walking, tennis, weight machines and ice skating. Sports not recommended were racquetball, squash, rock climbing, soccer, singles tennis, volleyball, football, gymnastics, lacrosse, hockey, basketball, jogging, and handball. Sports with no conclusion were fencing, roller blading/in-line skating, downhill skiing, and weight lifting. However, these recommendations do not necessarily conform with epidemiological evidence (see above).

Studies on prosthetic wear rates have been used to imply appropriate work limitations for the post-arthroplasty patient. However, no quality studies have been reported that address the appropriateness of work limitations. Additionally, the avocational studies reviewed above do not provide quality evidence in support of activity limitations. Thus, although reduced return-to-work status has been reported among patients with more physically demanding work, there is not a strong rationale for work restrictions in the post-surgical knee population.

Recommendation: Post Operative Vocational or Avocational Activities

There is no recommendation for or against specific vocational or avocational pursuits post-operatively.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

Quality evidence does not sufficiently support evidence-based guidance and therefore there is no recommendation for or against specific vocational or avocational activities.

Evidence for the Use of Vocational or Avocational Activities

There are no quality studies evaluating the use of vocational or avocational activities.

PSYCHOLOGICAL SERVICES

Psychological issues appear to be substantially less prevalent among patients with osteoarthritis compared with spine disorders for unclear reasons. Thus, psychological services are rarely needed for knee pain patients (see Chronic Pain guideline for further discussion of psychological evaluation).

1. Recommendation: Psychological Evaluation for Chronic Knee Pain

A psychological evaluation is recommended as part of the evaluation and management of patients with chronic knee pain with any of the below indications in order to assess whether psychological factors will need to be considered and treated as part of the overall treatment plan.

Indications – 1) Knee pain or dysfunction that persists longer than typical for the condition; 2) disability or impairments thought to be disproportionate to usual or expected findings; 3) demonstration or suspicion of significant psychosocial dysfunction; 4) medication issues and/or drug problems(1901-1904); 5) current or premorbid major psychiatric symptoms or disorder thought to be impacting disorder; 6) non-compliance with the prescribed treatment regimen; or 7) experiencing delayed functional recovery.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. Recommendation: Cognitive Behavioral Therapy (CBT) for Patients with Subacute or Chronic Knee Pain

Cognitive-behavioral therapy is recommended as an adjunct to an interdisciplinary program for treatment of subacute or chronic knee pain.

Indications – Specific indications for CBT in chronic pain conditions are:

1. Management of clinically significant behavioral aberrations and/or anxiety during opiate weaning or detoxification;
2. A component therapy integrated into an interdisciplinary or other functional restoration program;
3. Clinically significant problems of noncompliance or non-adherence to prescribed medical or physical regimens;
4. Vocational counseling for resolution of psychosocial barriers in return to work (requires a current or imminent medical release to return to work);
5. Resolution of interpersonal, behavioral, or occupational self-management problems in the workplace, during/after return to work, where such problems are risk factors for loss of work or are impeding resumption of full duty or work consistent with permanent restrictions.

Frequency/Duration – Therapy provided for the above indications should be limited to 6 sessions or less. When therapy is provided as a component of an interdisciplinary or functional restoration program, the number of sessions is based on the needs of the program to provide relevant treatment objectives.

Indications for Discontinuation – Noncompliance, failure to obtain functional or behavioral improvement, or resolution of problems.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

There are no quality studies specifically addressing knee pain as nearly all studies evaluated low back pain patients (see Chronic Pain and Low Back Disorders guidelines). Psychological assessments are routinely accomplished for the purposes given above, including treatments for which various levels of evidence are provided herein, e.g., functional rehabilitation or interdisciplinary pain programs, candidacy for certain procedures, or chronic use of opioid medications. Evaluations are moderate cost and, when done appropriately, present little risk of harm.

Evidence for the Use of Psychological Evaluations/Cognitive-Behavioral Therapy

There are no quality studies evaluating the use of psychological evaluations for patients with chronic knee pain. However, there are quality studies evaluating spine patients (see Low Back Disorders and Chronic Pain guidelines).

REHABILITATION FOR DELAYED RECOVERY BIOFEEDBACK

Biofeedback is a behavioral medicine method providing automated information and training to improve control of certain physiologic processes which are normally inaccessible to a subject's perception. Biofeedback most commonly involves surface EMG input to a monitor with audible or visual feedback of the degree to which there is muscle activity. (1905) Through this feedback, the patient may learn to control the degree of muscle contraction.

Recommendation: Biofeedback for Chronic Knee Pain

There is no recommendation for or against the use of biofeedback for chronic knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

Biofeedback is not invasive, has no complications, and is moderately costly. However, there are other efficacious treatment strategies.

Evidence for the Use of Biofeedback

There are no quality studies for use of biofeedback for treatment of knee pain patients.

FUNCTIONAL RESTORATION

Functional restoration is both a type of interdisciplinary pain management and rehabilitation program and a general approach to medical care. Fundamental elements of a functional restoration approach include assessment of the patient's dynamic physical and functional status including traditional tests for strength, sensation, and range of motion. Psychosocial strengths and stressors must also be assessed including the patient's support system, evidence of mood disorders, medication use, presence of litigation, work capacity, and assessment of education and skills. Following this evaluation, the emphasis is on expectation management, directed conditioning and exercise, cognitive behavioral therapy, setting functional goals and decreased medication use. An ongoing assessment of patient participation and compliance (with documentation of complicating problems and progress toward specific goals, including reduction in disability and medical utilization) is needed.

In functional restoration, the treatment team members are educators. Passive therapies and invasive interventions are de-emphasized while home exercise/self-management efforts are stressed. There should be a shift of health, function, and well-being responsibility (locus of control) from physicians and therapists to the patient. A functional restoration approach may include the limited/adjunctive use of medications and interventional measures (where specifically indicated) however, these should not be viewed as ongoing solutions. It may also

involve institution of preventive measures, education for relapse prevention, proper activity and work pacing, ergonomic accommodation, and when appropriate, transitional return to employment.

Functional restoration's goals are returning to a productive life despite having a chronic pain problem and mitigation of a patient's suffering. If an individual fails to recover within the appropriate biological healing time frame, the acute care paradigms of specific diagnosis and treatment change to biopsychosocial approaches that address pain, function, work, and psychological factors impeding progress. Treatment programs focus on restoration of work-related function. These programs include work conditioning and work hardening, interdisciplinary pain rehabilitation programs and functional rehabilitation. Because functional restoration is an approach, not just a specific program, the approaches taken both overlap on a continuum.

WORK CONDITIONING, WORK HARDENING, AND EARLY INTERVENTION PROGRAMS

Work conditioning and work hardening programs are often recommended for patients who are not able to return to work because of persistent symptoms and functional limitations following acute care and rehabilitation. Early intervention functional restoration programs are sometimes recommended during the first 3 to 6 months if the injured worker is noted to have increased risk factors and evidence of delayed recovery. These risks and delays suggest that a more coordinated functional restoration approach with a psychosocial emphasis is needed beyond conditioning or hardening alone.

Work Conditioning and Work Hardening Programs

Differentiating work conditioning from work hardening is problematic as the terms are sometimes used interchangeably. The American Physical Therapy Association (APTA) defines work conditioning as "an intensive, work-related, goal-oriented conditioning program designed specifically to restore systemic neuromusculoskeletal functions (e.g., joint integrity and mobility, muscle performance (including strength, power, and endurance), motor function (motor control and motor learning), range of motion (including muscle length), and cardiovascular/ pulmonary functions (e.g., aerobic capacity/endurance, circulation, and ventilation and respiration/gas exchange)." (1906) APTA classifies work conditioning as a single-discipline program and work hardening program as interdisciplinary. The Commission on Accreditation of Rehabilitation Facilities (CARF) defines occupational rehabilitation as work conditioning, and comprehensive occupational rehabilitation as work hardening. Although not universally accepted, some physicians consider work conditioning as a generalized endurance and strengthening program that includes work simulation activities, whereas work hardening is a program where a specific job has been identified and stresses involvement in sets of occupationally-related tasks and functional activities that are directly related to a patient's work. Work conditioning and work hardening programs in the U.S. are heterogeneous and are often provided by a single-therapy discipline, either physical or occupational therapy. (1907-1909)

Work conditioning and work hardening programs generally involve structured programs of gradually increased levels of exertion to bridge a significant gap between the patient's current physical or perceived capabilities and the requirements needed to return to everyday activities and work. Regardless of the terminology used, the most successful programs involve a detailed appreciation of the worker's capabilities, a detailed knowledge of the job physical requirements (if possible, obtained from on-site analysis or familiarity), and individualization of the program to address specific deficits that are barriers to return to work. These programs can be somewhat

heterogeneous with varying components and there is some overlap with multidisciplinary programs.

Work conditioning and work hardening programs focus on increasing physical efforts, using fear avoidance belief training if necessary. These programs may also use a cognitive-behavioral model and overlap with early intervention programs. In the majority of return-to-work situations, work conditioning or work hardening programs are not required as the gap between worker abilities and capabilities are not sufficiently large to justify either the time or expense. These programs are generally utilized for workers involved in significant demanding jobs for the knees that may include materials handling tasks that commonly involve high-force expenditures or highly repetitious activities. Not infrequently, work conditioning or work hardening programs are the next step after conventional physical or occupational therapy is exhausted and a gap remains to return the patient back to work, particularly in the subacute pain setting. These programs are also utilized for patients who have tried to return to work but failed due to either the gap between abilities and capacities or the lack of modified duty in physically demanding occupations. These programs are not invasive and have low adverse effects, but are moderate to high cost depending on program length.

Patients who may benefit from work conditioning or hardening include those who: 1) remain completely off work or are on modified duty for 6 to 12 weeks; 2) have not responded to less costly interventions including a 4 to 6 week physical or occupational therapy program or a graded therapy program of at least 6 to 8 weeks that includes aerobic and knee strengthening exercise components; 3) have a stated strong interest and expectation to return to work; 4) involve cooperation of the employer; 5) are supervised by a qualified physical or occupational therapist; 6) have had a careful assessment of their occupational demands; 7) have a FCE that indicated appropriate performance effort and consistency at a level of work lower than that to which they need or wish to return; and 8) are in a program that includes a cognitive-behavioral approach with a focus on function rather than pain, a conditioning or aerobic exercise component and simulated graded work tasks, and is tailored to their needs and identifies gaps between current capabilities and job demands.

Early Intervention (Functional Restoration) Programs

Early identification and appropriate management of patients exhibiting signs of delayed recovery is believed to decrease the likelihood that they will go on to develop chronic pain.⁽¹⁹¹⁰⁾ These patients may benefit from a limited but intense program of physical restoration with a strong emphasis on education that identifies barriers to recovery and return to work. They may require an abbreviated early intervention interdisciplinary rehabilitation program (IPRP), preferably using functional restoration principles, rather than a longer program utilized for more complex cases. Early intervention programs are an alternative to work conditioning and work hardening programs for subacute or patients with early chronic pain who have evidence for delayed recovery with an increased need for education and psychological assessment and intervention. These programs are usually appropriate in cases of work incapacity lasting 3 to 6 months. The interdisciplinary functional restoration program used for early intervention contains the features of a functional restoration IPRP, but involves lower intensity and duration of services than a program for patients with greater chronicity of disability. The type, intensity, and duration of services is dictated by the patient's unique rehabilitation needs and may be used for those who fail work conditioning and work hardening programs, usually within 6 months of onset of disability post-injury. The time frame of 3 to 6 months post-injury is vital for intervening with the most effective treatment possible in order to avoid the negative sequelae that come with increasing duration of disability. During this time, normal musculoskeletal healing generally

occurs, eliminating any remaining physical barriers to intensive rehabilitation. Such programs are appropriate for prevention, before the patient is entrenched in a chronic pain syndrome or before severe pain and illness behavior evolves.

Recommendation: Work Conditioning, Work Hardening, or Early Intervention Programs for Chronic Knee Pain Syndromes

Work conditioning, work hardening, and early intervention programs are recommended for treatment of chronic knee pain syndromes.

Frequency/Duration – Three (3) to 5 times a week for work conditioning and early intervention programs; daily for work hardening. Weekly evaluations demonstrating sufficient levels of physical effort and consistency, compliance with the plan of care, and functionally significant progress toward the return-to-work goal must be documented to justify continuation. Program length and intensity is dictated by each patient's unique rehabilitation needs.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

There are no quality studies of knee pain patients and limited evidence that work conditioning, work hardening, or early intervention programs are effective for chronic spinal pain, nevertheless there is a longstanding belief and experience that they are highly effective. While there is potential for overlap, work conditioning, work hardening, and early intervention are distinct programs and are not intended for sequential use, although this might be appropriate in certain situations depending on program components. In acute cases, where delayed recovery is not an issue, these programs are inappropriate. In more chronic cases, particularly with pain and illness behavior and a high level of reported dysfunction, a more intense IPRP should be considered. Although less costly, work conditioning, work-hardening, and early intervention programs do not need to be attempted before moving to an IPRP as long as a quality interdisciplinary program with proven outcomes is accessible to the patient. Program choice depends on availability and matching patient needs to the services offered to provide the most cost-effective and beneficial outcome. Hence, these programs might provide the greatest potential impact when used to manage patients during the subacute phases of injury, although they might also be appropriate for use in those with chronic pain who do not, after evaluation, have significant psychosocial factors contributing to their clinical presentation.

Evidence for the Use of Work Conditioning, Work Hardening, and Early Intervention Programs

There are no quality studies evaluating the use of work conditioning, work hardening, and early intervention programs for chronic knee pain.

INTERDISCIPLINARY PAIN REHABILITATION PROGRAMS

An interdisciplinary pain rehabilitation program (IPRP) is a type of chronic pain management program that uses a biopsychosocial paradigm (preferably employing a functional restoration approach), that can enhance function, reduce pain and illness behavior, and mitigate chronic pain associated disability. These programs are intended to manage psychological, social, physical and occupational factors and are discussed in detail in the Chronic Pain guideline. All IPRP programs involve an integrated team of professionals who provide intensive, coordinated care. This team may include physical and occupational therapists, psychologists, vocational counselors, nurses, and case managers. Quality programs emphasize functional recovery and active, progressive physical activity and generally involve intensive 5-days-a-week treatment regimens that should be individualized. **All medical and therapy services must be supervised by a physician who is directly involved with the program and regularly interviews and**

examines the patient for relevant parameters. For reasons that are unclear, there appear to be few lower extremity pain patients, including knee pain patients who require these programs. Nevertheless, a minority of patients may derive benefits (see Chronic Pain guideline).

Recommendation: IPRPs for Chronic Knee Pain

A multidisciplinary or interdisciplinary program (IPRP) with a focus on behavioral or cognitive-behavioral approaches combined with conditioning exercise is recommended for patients who due to chronic knee pain demonstrate partial/total work incapacity.

Indications – Chronic knee pain in patients who are not working, or unable to return to full duty, and have significant, pain-related limitations in activities of daily living. Patients should have failed other standard approaches (e.g., physical therapy, occupational therapy, interventions, medication) and have reasonable probability of recovery.

Frequency/Duration – Median 20 days, with trial of the first 10 days to assess patient compliance, attendance, and progress. Program duration is variable due to the patient's needs, the rehabilitation strategies used, and the demonstrated program outcomes. IPRP treatment is generally provided 5 full days per week, though slightly fewer hours and longer calendar durations are utilized in some programs. Complicating problems involving activities of daily living (such as coordinating part-time employment, transportation, or child care needs) or limitations imposed by co-morbid medical conditions which preclude the patient from participating in the program full-time (thus preventing them an assessment at 10 days) are considerations that might necessitate program modification.

Indications for Discontinuation – Failure to improve, noncompliance, resolution of symptoms and disability, exhaustion of reasonable program duration for a specific condition.

***Strength of Evidence* – Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

Participation in an IPRP to treat chronic knee pain patients has not been evaluated in quality studies. These programs may be helpful if there is medical need to wean the patient from opioids or other medications and/or if the patient has shown demonstrable clinical progress with less intense rehabilitation but “pain limitation” has impeded adequate recovery. Development of entrenched psychosocial barriers to recovery and a chronic pain syndrome as sequelae of the original physical components of the injury may be associated with this group of patients. Functional restoration might be appropriate, as well as vocational re-entry in positions not requiring the same job physical characteristics when all previous treatments have failed. With the possible exception of workplace-based interventions, most successful multidisciplinary programs appear to utilize either a cognitive-behavioral approach or involve psychologists.(1911-1914) While exercise is a major focus in many of these successful programs that primarily treat spine pain,(1911-1915) the one trial that compared a graded exercise approach with a participatory ergonomics approach found exercise inferior.(1916) This suggests that of the options available, the participatory ergonomics approach may be superior to other approaches.(1917) These heterogeneous studies also suggest that multidisciplinary programs that focus on functional improvements are superior.

IPRPs of the types described in the literature are not invasive, have few adverse effects, but are high cost. Some U.S.-based programs involve significant interventions, but there is no documentation of superior outcomes from such programs which can cost \$20,000 to \$50,000. IPRPs are indicated for select, more severely affected patients, including those who have failed appropriate conservative management (e.g., appropriate medications, specific exercises, etc.).

Generally, these referrals are most indicated in the early chronic pain management timeframe (3 to 6 months). However, there are times when earlier referral in the mid- to late-subacute interval is indicated. (Physicians should be aware that there is a belief that earlier referral results in higher probability of successful treatment, but that supposition has not been rigorously tested and is prone to a strong spectrum bias whereby all patients tend to do worse the longer they have a acute, subacute, or chronic pain condition.) Referrals beyond 6 months might also be indicated if there has been failure to progress with numerous interventions and there is reasonable expectation for potential benefits. Referrals during the subacute phase best occur when there is a quality program with proven outcome efficacy is available, the patient has documented delayed recovery, yet there is interdisciplinary assessment that the patient is likely to benefit from the program.

PREVENTION OF VENOUS THROMBOEMBOLIC DISEASE

Venous thromboembolic disease (VTED) is a high-risk complication among post-operative knee and hip arthroplasty patients resulting in morbidity and mortality. This topic is extensively reviewed in the Hip and Groin Disorders guideline. Only the recommendations are reviewed here, and the reader is referred to the Hip and Groin Disorders guideline for further details.

Reported risk factors in these post-operative patients include age, general anesthesia, and obesity. There has been some review of risk of VTED from cement; however, the evidence conflicts.(1735, 1918) Treatments have included early ambulation (discussed elsewhere), compression boots or stockings(1919) and other methods,(1920) and medications.(1921-1929) There are currently four classes of medications used to prevent VTED: warfarin/coumadin,(1930, 1931) low molecular weight heparin,(1932-1942) Factor Xa inhibitors,(1943) and direct thrombin inhibitors. (670) Of these options, all are currently available in the U.S. with the exception of oral direct thrombin inhibitors. While initially believed to be a complication of hospitalization, post-hospital discharge surveillance data suggest high risks of thromboembolism continue well after discharge,(1944) with many studies treating patients for 30 days for longer.

1. Recommendation: Prevention of Venous Thromboembolic Disease

Prevention of venous thromboembolic disease is strongly recommended for post-operative knee patients, particularly arthroplasty patients or other post-operative patients with prolonged reductions in activity. Early ambulation is recommended.

Strength of Evidence – Strongly Recommended, Evidence (A)

2. Recommendation: Compressions Stockings for Prevention of Venous Thromboembolic Disease

The use of post-operative graded compression stockings is moderately recommended for the prevention of venous thromboembolic disease.(1945, 1946)

Indications – All post-operative major knee surgical patients (e.g., knee fractures, knee arthroplasties, or any other patients thought at increased risk of VTED in the post-operative period).

Duration – Duration unclear and longer use does not add expense. As risk of VTED is high, particularly for these major procedures, threshold for use of 2 weeks or longer should be generally low.

Strength of Evidence – Moderately Recommended, Evidence (B)

3. Recommendation: Lower Extremity Pumps for Prevention of Venous Thromboembolic Disease

The use of lower extremity pump devices is moderately recommended for the prevention of venous thromboembolic disease.(1947-1950)

Indications – All post-operative major knee surgical patients (e.g., knee fractures, knee arthroplasties, or any other patients thought at increased risk of VTED in the post-operative period).

Devices – Devices include foot pumps, foot plus calf pumps, entire lower extremity intermittent compression devices and various other combinations. As there are no quality comparative trials, there is no recommendation for a particular device.

Duration – Duration unclear. Most have utilized devices for the duration of hospitalization. As risk of VTED is high, particularly for these major procedures, threshold for use of 2 weeks or longer should be generally low, including while at home.

Indications for Discontinuation – Discontinuation is generally recommended by 14 days unless there are continuing ongoing issues, such as delayed rehabilitation and ambulation that result in a judgment of increased risk. Some patients are also unable to tolerate devices.(1951)

Strength of Evidence – **Moderately Recommended, Evidence (B)**

4. *Recommendation: Low-molecular Weight Heparin for Prevention of Venous Thromboembolic Disease*

Low-molecular weight heparin is strongly recommended for prevention of venous thromboembolic disease.

Indications – Post-operative arthroplasty, knee fracture, and other major knee surgery patients, particularly those with either prolonged inactivity or prolonged reduced or sedentary activity levels.(1941, 1945, 1952-1962) There is some evidence LMWH is generally preferable to warfarin for VTED prophylaxis. Patients with prior reactions to LMWH should generally receive other treatments first.

Dose/Frequency – Subcutaneous injections of enoxaparin (Lovenox) 4,000 IU or 40mg SC QD(1945, 1952-1954, 1956, 1963-1968) for variable durations ranging from 5 to 9 post-operative days(1965-1967) to 8 to 14 days(1964) to 10 to 14 days,(1963) 21 days,(1952, 1953) 30 days,(1956) to 12 weeks.(1954) There is no consensus on duration of treatment, and individualization based on activity level appears indicated.

Duration – Duration unclear. Available quality studies utilized treatment courses ranging from 4 days(1960) to 12 weeks.(1954) A plurality of studies utilized a course of 30 to 35 days.(1955-1957, 1961) There is quality evidence that treatment is generally required beyond hospitalization; there is evidence of deep venous thromboses many months later (reviewed above). One quality trial suggested no benefits from extending 4 to 10 days treatment out to 12 weeks.(1958) In the absence of substantive quality data comparing various durations of treatment, it is suggested that approximately 30 days of treatment after surgery may be required for average patients (a single trial suggested 30 to 42 days after arthroplasty).(1944) Patients with prior histories of venous thrombi, prolonged inactivity, delayed recovery or recurrences of thromboses, or family histories of venous thrombi likely require longer courses. Those with major risk of bleeding may warrant individualized shorter courses. Patients who regain activity rapidly may be appropriate candidates for shorter courses of treatment.

Indications for Discontinuation – Completion of course of treatment, development of major complication (e.g., major bleeding) or other adverse effect.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

5. *Recommendation: Factor Xa Inhibitors for Prevention of Venous Thromboembolic Disease*
Factor Xa inhibitors are strongly recommended for the prevention of venous thromboembolic disease.

Indications – Post-operative arthroplasty, knee fracture, or other major knee surgery patients, particularly those with prolonged inactivity or prolonged reduced or sedentary activity levels.(1918, 1969-1972) Patients with prior reactions should generally receive other treatments first. Patients with renal failure or renal insufficiency should generally receive a different medication due to renal excretion of this compound.

Dose/Frequency – Subcutaneous injections of Fondaparinux (Arixtra) 2.5mg SC QD. Currently Rivaroxaban (Xarelto) is investigational in the U.S.

Duration – Duration unclear. Literature suggests duration be individualized based on factors such as prolonged inactivity, delayed recovery or thrombotic recurrences, prior history, and risks of bleeding.

Indications for Discontinuation – Completion of course of treatment, development of major complication (e.g., major bleeding) or other adverse effect.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

6. *Recommendation: Warfarin and Heparin for Prevention of Venous Thromboembolic Disease*
Warfarin and heparin are moderately recommended for prevention of venous thromboembolic disease.

Indications – Post-operative arthroplasty, knee fracture, other major knee surgery.(1973, 1974) Patients with adverse reactions to warfarin may be maintained on heparin throughout the treatment course. Patients with reactions to heparin, but at increased risk of thrombosis may be started on the other agents and switched to warfarin.

Dose/Frequency – Subcutaneous injections of Heparin, which can be titrated to the activated partial thromboplastin time (aPTT). Warfarin dose titrated to International Normalized Ratio (INR). Magnitude of anticoagulation is recommended to be individualized, and include risks of thrombi versus risks of bleeding and it is notable that the quality studies utilized a range of INRs.

Duration – Duration unclear. Literature suggests duration be individualized based on factors such as prolonged inactivity, delayed recovery or thrombotic recurrences, prior history, and risks of bleeding.

Indications for Discontinuation – Completion of course of treatment, development of major complication (e.g., major bleeding) or other adverse effect.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

7. *Recommendation: Prevention of Venous Thromboembolic Disease*

Aspirin is moderately recommended for the prevention of deep venous thrombosis.

Indications – Post-operative arthroplasty, knee fracture, and other major knee surgery patients, particularly after cessation of other treatments such as LMWH, heparin, or other anticoagulants.(1975)

Dose/Frequency – Aspirin 160mg per day was used in PEP trial. Other studies have found 85mg/day sufficient for heart attack prevention.

Duration – Duration unclear; 1 month is suggested, however due to other risk factors, prolonged or indefinite treatment may be recommended.

Indications for Discontinuation – Completion of course of treatment, development of major complication (e.g., major bleeding) or other adverse effect.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Evidence for the Prevention of Venous Thromboembolic Disease

There are 9 high- and 23 moderate-quality RCTs incorporated into this analysis. There are 3 low-quality RCTs in Appendix 1.(1976-1978)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Compression Stockings vs. No Stockings						
Robinson 1997 RCT	9.0	N = 1,024 with total hip or knee replacement	Bilateral screening compression ultrasonography vs. sham ultrasonography.	518 screening compression ultrasonography; 19 (3.7%) positive result; 6/19 proximal DVT excluded by venography; 4 (0.8%) developed symptomatic proximal DVT. All 4 normal results on screening compression ultrasonography. Of 506 randomly assigned to sham ultrasonography, 3 developed symptomatic DVT, 2 non-fatal symptomatic PE. Total primary outcome cluster event rate 1% (CI, 0.3-2.2%).	“Our results suggest that continuing warfarin prophylaxis beyond an average of 9 days after total hip or knee arthroplasty would be of little value, given the low rate of symptomatic venous thromboembolic complications.”	Unusual blinding: techs had blank screen so not to affect results. Followed all excluded patients who gave informed consent. Co-interventions mentioned but not accounted for.
Kaempffe 1991 RCT	5.0	N = 149 with total hip or knee arthroplasty	Coumadin 10mg night before surgery, 5mg night after, then dose keeping PT = 15s vs. thigh-length intermittent pneumatic compression (IPC). Treatment duration unclear, appears to be during hospitalization.	13/52 (25%) had roentgenographic DVT evidence 5/21 (24%) total hip arthroplasty patients developed DVT. Overall DVT incidence with IPC 12/48 (25%) vs. 13/52 (25%) on coumadin. Following total hip arthroplasty, the IPC group was more effective at preventing DVT (16% vs. 24% in coumadin).	“36% of patients (5/14) who were treated with revision surgery developed DVT despite prophylaxis (4/10 in the Coumadin group and ¼ in the IPC group). These figures may indicate that neither Coumadin nor IPC are effective in the prevention of thrombi in this group of patients.”	Relatively small numbers of subjects. Different clotting risk in revision THA. Data suggest equivalency.
Hui 1996 RCT	4.0 (5.0 for TKA patients)	N = 177 with total hip or knee arthroplasties	Above vs. below-knee graded compression stocking vs. controls.	DVT on venograms in 27% controls vs. 22% above-knee vs. 50% below-knee stockings among THR patients. Knee rates 78% vs. 65% vs. 68%. THR patients wearing below-knee stocking had higher rates of proximal or major calf DVT (p = 0.03).	“[W]ith the exception of below-knee stockings in knee replacement patients, graded compression stockings were ineffective in preventing DVT after hip or knee replacement surgery.”	Two studies done together analyzed differently. Included lower risk patients. THA groups less comparable.
AV Impulse System						

Wilson 1992 RCT	5.5	N = 59 undergoing 60 elective TKR with: Biomet AGC prosthesis, Insall- Burstein protheses , or standard technique	No prophylaxis (n = 31) vs. A-V Impulse System (n = 28).	No pump vs. A-V venographic findings in knee replacements for normal (n), major calf DVT [n (%)], and proximal DVT (n): 10/14, 13 (59.4)/5 (17.8)/p = 0.014/ $\chi^2=8.508$, 6/0.	“We have shown, however, that the A- V Impulse System is an effective means of prophylaxis for deep-vein thrombosis against which pharmacological methods should be evaluated.”	Data suggest efficacy.
Low Molecular Weight Heparin vs. Placebo						
Heit 2000 RCT	11.0	N = 1,195 with total hip or knee arthroplast y	All received open label treatment for 4 to 10 days. Then randomized to extended treatment with daily subcutaneous ardepain (100 anti-X _a IU/kg vs placebo for total hip or knee replacement from hospital discharge to 6 weeks after surgery.	Incidence of 9 (1.5%) with extended treatment vs. 12 (2.0%) for placebo, OR = 0.7 (0.3- 1.7), p >0.2.	“The low rate of symptomatic venous thromboembolism in the part B placebo is consistent with the hypothesis that most cases of asymptomatic deep venous thrombosis that occur despite in-hospital low- molecular-weight heparin prophylaxis are not clinically important. Our findings call into question the need for extended out-of- hospital prophylaxis in all patients undergoing elective hip replacement.”	Low number of higher risk patients, thus article primarily addresses low risk. Study primarily addresses benefit of extended treatment as all initially were actively treated.
Comp 2001 RCT	10.0	N = 873 with total hip or knee replaceme nt	Enoxaparin 40mg QD vs. placebo for 12 weeks.	Prevalence of venous thromboembolism in enoxaparin 8% (18/224) vs. 23.2% (49/211) for placebo (p <0.001). OR = 3.62 (95% CI 2.00- 6.55), Relative risk reduction 65.5%.	“[T]he recommended seven to ten-day postoperative thromboprophylactic regimen of 30mg of enoxaparin twice daily for patients treated with total hip replacement is suboptimal and that a substantial therapeutic benefit is gained, without compromising safety, by prolonging the enoxaparin treatment (at a dose of 40mg once daily) for an additional three weeks postoperatively (resulting in a total of four weeks of enoxaparin treatment)”	Suggests efficacy. Includes younger patients. Stratified analyses suggest no effect in males with knee replacement. Suggests treatment for 4 weeks.

RD Heparin Arthroplasty Group 1994 RCT	7.5	N = 1173 with total hip or knee arthroplasty	Anti-factor-Xa 50U of RD heparin/kg SC BID vs. anti-factor-Xa ()U of RD heparin/kg body weight SC QD vs. warfarin 5mg QD and adjustments to PTT 1.2-1.5 for total hip replacement.	VT disease among 8% (14 patients). RD bid heparin 3% (n = 5/178) had proximal DVT vs. 14% (24/171) QD heparin vs. 14% (24/174) on warfarin. No difference between heparin BID and warfarin efficacy – p = 0.07 for BID vs. warfarin and p = 0.82 for QD vs. warfarin.	“For patients who had a total hip arthroplasty, a fixed dose of anti-factor-Xa units of RD heparin per kilogram of body weight, administered unmonitored twice daily, beginning postoperatively, and low-dose warfarin were equally effective and safe.”	Accounted for medications & physical exams. Suggests comparable efficacy, although trend towards BID heparin dosing.
Low Molecular Weight Heparin vs. Other LMWH Doses or Other Treatments						
Hull 1993 RCT	8.5	N = 795 hip surgery patients N = 641 knee arthroplasty patients	Warfarin sodium initial dose 10mg post-op evening of surgery and QD with dose adjusted to INR 2.0-3.0 vs. low molecular weight heparin fixed dose of 75 IU/kg body weight SC QD. Treatments until 14th post-op day or hospital discharge.	Of warfarin group, 37.4% vs. 31.4% of low molecular weight heparin group developed DVT, p = 0.03; 1.2% of warfarin group vs. 2.8% low molecular weight heparin group with major bleeding, p = 0.04.	“[L]ow-molecular-weight heparin given in a single subcutaneous injection per day is effective, as compared with warfarin sodium prophylaxis, and that it avoids the need to monitor the level of anticoagulation. The reduction in the rate of venous thrombosis with low-molecular-weight heparin, as compared with warfarin, is offset by an increase in the number of bleeding complications and wound hematomas.”	Dropouts unclear. Appears to be ITT. Data suggest modest reduced risk for DVT with LMWH.
Heit 1997 RCT	6.5	N = 860 who underwent primary unilateral, simultaneous bilateral, or unilateral revision of total knee replacement surgery	Subcutaneous low molecular weight heparin doses administered BIC. Ardeparin sodium 25 U/kg vs. ardeparin sodium 35 U/kg vs. 50 anti-X U/kg vs. warfarin.	Ardeparin (n = 232) venous thromboembolism prevalence total n (%), proximal n (%), OE n, DVT or PE n(%), p value, and risk reduction: 62 (27%), 15 (6%), 1, 63 (27%), 0.019, 27%. Warfarin: 85 (38%), 15 (7%), 0, 85 (38%). Ardeparin 50 vs. 35 vs. 25 vs. warfarin venous thromboembolism prevalence total n, DVT n, PE n, total venous thromboembolism prevalence n (%): 232/116/110/222, 62/32/40/85, 1/0/1/0, 63 (27)/32 (28)/41 (37)/85 (38). Over bleeding n(%) at operative site, remote from operative site, withdrawn from study	“Postoperative, unmonitored, fixed-dose ardeparin 50 anti-Xa U/kg SC BID is significantly more effective than adjusted-dose warfarin for this indication. Although overt bleeding among warfarin and ardeparin 50 BID patients did not differ significantly, ardeparin 50 BID patients had significantly greater blood loss. Ardeparin 35 anti-X U/kg SC BID may provide efficacy similar to ardeparin 50 anti-X U/kg SC BID but with reduced bleeding.”	High dropouts. Follow-up: venography 5-14 days post-op. Double dummy. Data suggest ardeparin superior to warfarin for VTE prophylaxis.

				because of bleeding, invasive diagnostic or therapeutic procedure because of bleeding, and total: 13 (5)/4 (3)/4 (3)/10 (4), 7 (3)/3 (2)/3 (2)/2 (1), 3 (1)/1 (<1)/1 (<1)/0 (0), 6 (2)/1 (<1)/1 (<1)/1 (<1), 22 (7.9)/7 (5.0)/7 (5.2)/12 (4.4).		
Enoxaparin vs. Placebo						
Marlovits 2007 RCT	6.5	N = 175 scheduled for arthroscopic ACL surgery, age 19-55 years, either maximum weight of 100kg or admitted to hospital for arthroscopic ACL surgery	Patients received subcutaneous enoxaparin 40mg once daily 12 to 18 hours pre-surgery and 3 to 8 days post-surgery during hospitalization. After discharge, patients randomized to 40mg enoxaparin (n = 87) vs. placebo (n = 88) self-administered once daily subcutaneously for 20 days.	Post-discharge thromboprophylaxis and risk factors for DVT in patients undergoing ACL reconstruction in the ITT population. Enoxaparin vs. placebo 0.0017 (Odds Ratio), 0.003-0.106 (95% CI), p <0.001.	“Extended-duration postdischarge thromboprophylaxis for 20 days with enoxaparin in the outpatient setting significantly reduced the incidence of DVT in ACL surgery patients compared with enoxaparin limited to in-hospital thromboprophylaxis without increasing major or minor bleeding. LEVEL OF EVIDENCE: Level I, high-quality randomized controlled trial.”	Study 23-28 days. Randomization and blinding not well described. Data suggest efficacy.
Ofosu 1992 RCT	4.5	N = 129 age 40 and older who underwent knee replacement surgery at high risk for DVT	Enoxaparin 30mg vs. 0.4ml of saline every 12 hours for 14 days.	Endogenous thrombin-antithrombin III increased in each post-surgical plasma with it being significantly higher in placebo vs. enoxaparin group, p <0.05. Higher factor VII zymogen concentrations seen in all post enoxaparin plasma vs. post placebo plasmas, p <0.05 for days 1, 2, 5, 6, 7.	“[I]nhibition of <i>in vivo</i> prothrombin activation appears to be an important action for the antithrombotic effect of this LMW heparin after knee surgery.”	Follow-up: 14 days. Some details including blinding sparse. Patients not well described.
Enoxaparin vs. Other Treatments						
Lassen 2008 RCT	7.5	N = 2,531 who underwent TKR	Rivaroxaban 10mg PO QD beginning 6-8hr after surgery vs. enoxaparin 40mg SQ QD beginning 12 hr after surgery. 10-14 days treatment.	Primary efficacy outcome (DVT, PE, death from any cause): rivaroxaban 79/824 (9.6%) vs. enoxaparin 166/878 (18.9%), p<0.001. PE difference p = 0.06. DVTs differed.	“Rivaroxaban was superior to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding.”	High dropouts. Data suggest rivaroxaban superior.
Fauno 1994 RCT	6.5	N = 185 who underwent TKR	Unfractionated heparin 5000U TID vs. enoxaparin 40mg pre-op then QD. 6 to 9 days treatment to venography or 8 days treatment if no venogram.	DVT by venography in 25/93 (27%) heparin vs. 21/92 (23%) enoxaparin, p = 0.60. Proximal DVT in 5% vs. 3% (NS). Clinical symptoms of PE in 2 vs. 1 patient.	“[W]e believe that enoxaparin is safe and efficient as prophylaxis against venous thromboembolism after total knee arthroplasty.”	Data suggest equivalency.
Turpie 2009	5.0	N = 215 who	Betrixaban 15mg BID vs. betrixaban	DVT incidences: betrixaban 15mg 14/70	“A dose- and concentration-	Blinded for betrixaban,

RCT		underwent TKR	40mg BID vs. enoxaparin 30mg SQ Q12 hours. 10-14 days follow-up.	(20%) vs. 40mg 10/65 (15%) vs. enoxaparin 4/40 (10%) (NS). Proximal DVTs in 2 vs. 1 vs. 0. Distal only DVTs in 10 vs. 8 vs. 2.	dependent effect of betrixaban on inhibition of thrombin generation and anti-Xa levels was observed. Betrixaban demonstrated antithrombotic activity and appeared well tolerated in knee replacement patients at the doses studied."	not enoxaparin. Scored for enoxaparin comparison.
Colwell 1995 RCT	4.0	N = 453 who underwent TKR	Enoxaparin 30mg Q12 hour vs. unfractionated heparin 5000U Q 8 hour for 4 to 14 days. follow-up approximately 3 weeks after last dose. Venography within 24 hours of last dose.	DVT (proximal and distal deep) in enoxaparin 56/228 (24.6%) vs. heparin 77/225 (34.2%). No differences in major hemorrhage (3 each).	"[E]noxaparin administered postoperatively 30 mg every 12 hours is more effective and as safe as unfractionated heparin prophylaxis to prevent deep venous thrombosis in patients having elective total knee arthroplasty."	Some details sparse. High dropout rate. Data suggest enoxaparin superior to unfractionated heparin.
Factor Xa Inhibitor vs. Other Treatments						
Agnelli 2007 RCT	10.5	N = 511 with total hip or knee replacements	Dose escalation study. Oral LY517717 (Difumarate) 25, 50, or 75mg or later doses of 100, 125, or 150mg 6-8 hours after wound closure then every morning after overnight fasting at 7am±1 hour vs. enoxaparin 40mg SC on evening before surgery, then every evening at 8pm±2 hours; both treatments continued for 6 to 10 doses.	Difumarate resulted in dose-dependent decrease in incidence of thromboembolic events (p = 0.0001). Doses between 25-75mg ineffective. Incidences of VTE with 100, 125, and 150mg of 19%, 19% and 16% vs. 21% enoxaparin (NS).	"In conclusion, this phase II proof-of-concept study demonstrated the safety and efficacy of LY517717 for the prevention of VTE following THR or TKR in comparison to enoxaparin."	Suggests comparable efficacy with enoxaparin.
Aprotinin						
Thorpe 1994 RCT	4.5	N = 17 who underwent elective TKR and had no history of clinical coagulation abnormality	Group A (aprotinin 5000 000 KIU (kallikrein inhibiting units) over 20 minutes immediately before inflation of tourniquet, n = 8)) vs. Group B (5000 000 KIU over 20 minutes before deflation of tourniquet followed by infusion of 1000 000 KIU over next	Blood loss (ml) in aprotinin vs. control group patients. Median: 663 vs. 960. Range: 320-1180 vs. 460-1755. Interquartile range: 452-903 vs. 677-1288. Blood transfused. Number of patients transfused: 1 vs. 6. Units transfused: 2 vs. 14. Median 0 vs. 2, p< 0.05. Range: 0-2 vs. 0-4.	"The results from this curtailed study indicated that aprotinin appears to reduce blood transfusion requirements in patients undergoing total knee replacement. The authors' opinion is that the patient's peripheral vascular disease was sufficient to account	Small groups. Patients not well described. Data suggest fewer transfusions needed in aprotinin group.

			2 hours, n = 9). Four in aprotinin group and 5 in control receiving non-steroidal inflammatory drugs. All patients premedicated with temazepam.		for his ischaemic leg. However, it is not possible to determine if aprotinin was a contributing factor. Given the current level of knowledge on aprotinin we would recommend caution in its use in surgical patients with peripheral vascular disease where surgery is to be performed under tourniquet control.”	
Aprotinin vs. Placebo						
Eriksson 2003 RCT	9.0	N = 2,835 who underwent THR or TKR	Melagatran/ximelagatran 2mg SC immediately before surgery and 3mg melagatran evening after surgery followed by 24mg ximelagatran orally vs. enoxaparin 40mg SC QD 12 hours before surgery. Both treatments 8-11 days.	2,316 patients assessed for first stage and 2326 for second stage. VTE in 2.3% of ximelagatran vs. 6.3% enoxaparin (p = 0.000018). Relative risk reduction 23.7%. Rate in THR group lower (1.8% vs. 5.5% enoxaparin, 0.6% of ximelagatran and 0.9% enoxaparin had confirmed symptomatic VTE. More transfusions (66.8% vs. 61.7%), somewhat higher blood loss (geometric mean 1,014mL vs. 913mL) with ximelagatran.	“In patients undergoing total hip or knee replacement, preoperatively initiated s.c. melagatran followed by oral ximelagatran was significantly more effective in preventing VTE than preoperatively initiated s.c. enoxaparin.”	Data suggest melagatran/xi melagatran superior.
Durations and Doses of Warfarin						
Wilson 1994 RCT	6.0	N = 96 orthopedic patients who underwent fixation of a hip fracture or hip/knee reconstruction	Dose of 2mg a day warfarin vs. an adjusted higher dose of warfarin for 1 month after discharge. Dose of 5-10mg warfarin given prior to surgery; 6 weeks follow-up.	No differences found between groups regarding efficacy and safety.	“Fixed, low-dose warfarin appears to be a promising, cost-effective approach to home prophylaxis. Additionally, the convenience of a fixed 2mg/d regimen may encourage more widespread utilization of posthospital discharge prophylaxis following orthopedic surgery.”	Pilot study. Data suggest comparable results.
Vives 2001 RCT	5.5	N = 245 undergoing THA or TKA	Fixed minidose warfarin 2mg a day vs. adjusted higher dose warfarin with target PT range of 14 to 16 seconds (INR 1.4 - 1.8);	Twenty-three patients eliminated; 7.1% of adjusted low-dose group vs..4.6% fixed minidose group developed symptomatic DVT, p = 0.02; 8.0% of THA patients and 6.0% TKA	“We found no difference in efficacy between the fixed 2-mg dose and the adjusted higher dose warfarin groups. The rates of symptomatic DVT	Study thrust to reduce warfarin to obviate need for testing. Conclude that need to monitor on

			both taken for 6 weeks.	patients in adjusted dose group developed symptomatic DVT, p = 0.03; 6.0% THA patients vs. 4.0% TKA patients on fixed dose developed symptomatic DVT, p = 0.01. No major bleeds.	were not significantly different with the numbers available." "[W]arfarin has a low rate of major and minor complications when maintained properly on an adjusted low-dose or a fixed minidose regimen. Fixed minidose warfarin holds promise as a streamlined approach to outpatient thromboembolic prophylaxis after total joint arthroplasty. The efficacy of the fixed minidose regimen appears similar to that of adjusted-dose warfarin."	low dose as well.
Heparin						
Francis 1990 RCT	5.0	N = 83 scheduled for TKA, >18 years of age	Antithrombin III (3000 units 2 hours before operation and 2000 units, over 20 minutes, each day for first 5 post-op days) plus heparin (n = 42) vs. treatment with 10ml/kg dextran (n = 41) infused over 12 hours.	Venous thrombosis developed in 35% in those who received anti-thrombin III plus heparin vs. 80% in those received dextran; p <0.001.	"Our findings indicated that the combination of antithrombin III and heparin effectively reduced the risk of venous thrombosis after total knee arthroplasty. A high incidence of thrombosis and a risk of congestive heart failure are major disadvantages to the use of dextran."	Confusing p values. Abstracts states thrombosis development was significantly different but the text states a p-value >0.001. Patients not well described. Data suggest dextran inferior to A T III plus heparin for VTE.
Heparin Arthroplasty Group 1994 RCT	4.0	N = 969 undergoing elective unilateral total hip or knee arthroplasty between 1986-1991	50 anti-factor X units of RD heparin per kg beginning evening of operation vs. 50 anti-factor X units of RD heparin per kg administered subcutaneously night of operation plus 90 anti-factor X units per kg once each morning vs. 5mg warfarin administered orally either night before or morning of	Mean (95% CI) blood loss index for total knee arthroplasty for patients taking RD heparin twice daily: 4.24 (3.97-4.51); p = 0.004. RD heparin once daily: 4.15 (3.88-4.42); p = 0.01.	"[F]or patients who had a total hip arthroplasty, a fixed dose of fifty anti-factor X units of RD heparin per kilogram of body weight, administered unmonitored twice daily, beginning postoperatively, and low dose warfarin were equally effective and safe. Although there was no difference	Data trended towards fewer VTE in RD Heparin BID.

			operation plus a 2nd 5mg dose in evening.		between the RD heparin prophylaxis and the warfarin regimen with regard to the rate of clinically important bleeding events, the blood loss index was significantly higher in the patients who received RD heparin twice daily by approximately 0.5 gram per deciliter of hemoglobin.”	
Defibrinating Enzyme vs. Placebo						
Perhonieni 1996 RCT	7.0	N = 165 with hip or knee replacement	Enoxaparin 40mg SC QD vs. dihydroergotamine 0.5mg and heparin 5,000 IU SC for 7 days. First dose of enoxaparin 12 hours before operation and heparin-dihydroergotamine (HDHE) 2 hours before operation	One case of DVT in enoxaparin vs. 0 in HDHE group. 2 cases of PE in HDHE group and 0 in enoxaparin (NS). No differences in blood loss.	“[E]noxaparin is as effective as HDHE in thromboprophylaxis of patients undergoing orthopaedic surgery.”	Higher risk patients. Dropouts not mentioned. Appears underpowered. Suggests comparable efficacy.
Hamulyak 1995 RCT	6.5	N = 672 who underwent THR or TKR	Oral anticoagulant (OAC, acenocoumarol) 4mg day before surgery, 2mg evening of surgery day, then adjusted to maintain INR 2.0-3.0 for 10 days vs. LMWH, nadroparine SC Q24 hour (about 60 IU of antifactor Xa (AXa)/kg), 0.3ml for patients weighing less than 60kg, 0.4ml for patients weighing 60-80kg, 0.6ml for patients weighing more than 80kg for 10 days.	50/257 (20%) OAC vs. 43/260 (17%) nadroparine with DVTs (p = 0.45). No differences in bleeding, transfusions.	“[F]ixed-dose subcutaneous nadroparine is at least as effective and safe as adjusted-dose OAC for prophylaxis against DVT after hip or knee implantation, but more convenient to administer.”	Blinded assessor mentioned only in abstract. Stockings not mentioned as co-interventions. Data suggest comparable efficacy.
Schmidt 2003 RCT	6.0	N = 346 with 1 ^o or 2 ^o THR and TKR	Prolonged prophylaxis nadroparine 2500-4000 IU between Day 11 and Day 35 vs. sonographic screening for DVT before Day 10.	36.8% of patients in ultrasound group had asymptomatic thrombosis. Combined endpoint of proximal DVT, symptomatic PE or death by PE diagnosed in 15 (8.7%) U/S screening group vs. 7 patients (4.3%) under prolonged prophylaxis (p = 0.12). Any	“[U]ltrasound screening for distal thrombosis after hip or knee replacement surgery with termination of heparin prophylaxis after exclusion of in-hospital thrombosis does not reduce the incidence of proximal DVT or symptomatic	Study terminated early because of higher DVTs in ultrasound group, though not statistically significant. Co-interventions

				symptomatic event of VTE in 4 (2.3%) in U/S screening (1 PE, 3 thrombosis) vs. 7 (4.3%) under prolonged prophylaxis (2 PE, 5 thrombosis; p = 0.37).	PE over five weeks postoperatively when compared to prolonged prophylaxis with LMWH. [Study indicates] efficacy of nadroparin calcium in preventing post-operative DVT in patients under going elective total hip replacement.”	not mentioned.
Desmopressin						
Karnezis 1994 RCT	7.5	N = 92 hemostatically normal subjects scheduled for primary THA or TKA	Desmopressin (n = 17) vs. placebo (n = 19); 6 days follow-up.		“[A]administration of desmopressin during orthopedic operations was not found to reduce postoperative blood loss either in the current study or in previous ones. Although desmopressin has been shown to increase thrombogenicity and to induce hyponatremia, we found no evidence of this.”	Co-interventions, compliance, and dropouts unclear. Data suggest lack of efficacy.
Aspirin						
McKenna 1980 RCT	4.5	N = 46 aged >40 years, admitted for TKR	Group 1 placebo, 1 tablet twice daily vs. Group 2 aspirin 325mg twice daily vs. Group 3 aspirin (Enseals, each capsule 650 mg) 1300 mg twice daily vs. Group 4 used an IPCD.	Highest incidences of DVT were in Groups 1 (9/12) and 2 (7/9). Incidence of DVT reduced in Groups 3 (1/12) and 4 (1/10); p = 0.001 Group 1 vs. 3; p = 0.004 Group 1 vs. 4; p = 0.002 Group 2 vs. 3; p = 0.005 Group 2 vs. 4.	“We have therefore established the clinical efficacy of a new IPCD and of large doses of aspirin in preventing venous TE in patients, primarily women, undergoing total knee replacement. We are continuing our studies to accumulate a larger group of patients to avoid the pitfalls inherent in small samples. The controversy over the suppressive effect of large doses of aspirin on prostaglandin I ₁ synthesis and the efficacy of larger doses of aspirin in preventing TE in man can only be resolved by further studies.”	Small group sizes. Data suggest high dose ASA and compression device superior.
Tranexamic Acid						

Hiippala 1997 RCT	8.5	N = 77 who underwent TKA instructed to cease use of any acetylsalicylic acid or any drugs containing ASA 1 week before surgery; all given 40mg enoxaparin subcutaneously once a day to prevent thromboembolic complications	15 mg/kg tranexamic acid (TA, n = 39) vs. 15mg/kg NS control (n = 38). Both serums injected IV just before tourniquet deflated. Two additional doses of 10mg/kg given during surgery day, first in recovery room 3-4 hours after initial dose, second 6-7 hours after initial dose. Blood loss replaced with RBCs if hemoglobin decreased <10 g/dL. Pneumatic tourniquet around thigh inflated to 350-400 mm Hg after elevating and draining extremity with sterile rubber bandage.	Replacement solution used by end of 1st day and number of red cell units transfused during hospital stay TA vs. NS. Crystalloids (mL): 4295±425 vs. 4842±669, p <0.0001. HES (mL): 205±297 vs. 605±371, p <0.0001. RC units: 1.0±1.2 vs. 3.1±1.6, p <0.0001.	“We conclude that short-term TA therapy significantly reduces TKA-associated blood loss and transfusion requirements without increasing thromboembolic complications.”	Duration somewhat unclear. Data suggest tranexamic acid reduced blood loss and transfusions.
Hiippala 1995 RCT	8.5	N = 29 scheduled to undergo total knee arthroplasty instructed to stop taking medication containing acetylsalicylic acid 1 week before operation	Tranexamic acid 15mg (received a few minutes before tourniquet deflated, n = 15) vs. placebo (equal volume and also received a few minutes before tourniquet deflated, n = 13). Hemoglobin concentration, platelet count and packed cell volume measured when patient entered and left recovery on day of operation at 20:00, and 1st and 2nd mornings after operation.	Pre-op haemostatic status (mean ±SD)). Platelet count (10 ⁹ litre-1), tranexamic acid vs. placebo group: 307 (101) vs. 307 (119). Bleeding time (s): 327 (105) vs. 393 (203). Activated partial thromboplastin time (s): 35 (4) vs. 32 (4). Prothrombin time %: 108 (21) vs. 106 (23). Duration of tourniquet inflation (minutes): 83 (18) vs. 76 (16).	“[T]ranexamic acid reduced perioperative blood loss and transfusion requirements associated with total knee arthroplasty.”	Very short-term study of 2 days. Data suggest efficacy to reduce blood loss. Not powered for VTE outcomes. 2 post-op days follow-up.
Benon 1996 RCT	8.0	N = 86 who underwent total knee prosthesis (PFC) if no history of	10 mL tranexamic acid (Cyklokapron 100mg/ml, n = 43) vs. 10mL placebo	Mean and SD postoperative blood loss in ml at 24 hours and the effect of tranexamic acid prophylaxis and of the use of bone cement.	“Both the number of patients receiving blood transfusion and the number of blood units transfused were	Likely not powered for VTE. Data suggest reduced blood loss.

		bleeding disorders or warfarin medication, diagnosis of OA or aseptic bone necrosis, but not RA, had primary, unilateral, bicompartme ntal knee arthroplasty, either both or no components cemented, ceased taking NSAIDs 1 week before surgery	(physiological saline, n = 43) ampoules. All received low-molecular-weight heparin, as thromboprophylaxis, either dalteparinsodium 5000 units (n = 49), or enoxaparin 40mg (n = 37) as a daily subcutaneous injection for 7 to 10 days starting evening before surgery.	Cemented vs. uncemented, tranexamic acid: 470±210 (n = 16) vs. 500±240 (n = 19). Placebo: 990±360 (n = 19) vs. 1290±500 (n = 20), p = 0.04. Cemented: p < 0.001; uncemented: p < 0.001.	reduced to one-third in the treated group, and mean postoperative Hb concentrations were significantly higher after prophylaxis. The number of thromboembolic complication was the same in both groups. Tranexamic acid should be given prophylactically in order to be effective.”	
Orpen 2006 RCT	7.5	N = 30 undergoing TKA asked to discontinue use of NSAIDs 1 week prior to TKA	15mg/kg of tranexamic acid (n = 14) vs. saline control (n = 15). Both treatments given at time of cementing of prosthesis.	Tranexamic acid vs. control mean(95% CI) blood losses (ml) observed at intra-operative, recover period, 12 hours, 24 hours, and total: 220(132-308)/169(14-225), 95(56-133)/218(129-295), 170(124-217)/237(136-339), 130(72-187)/77(26-128), 660(496-824)/726(548-904)/p = 0.55. Drop in Hb (g/dl) at Day 1, and Day 3: 2.23 (0.1-4.5)/2.97 (0-4.5), 2.49 (1.0-4.9)/3.27 (1.3-5.7).	“One injection of 15 mg/kg of tranexamic given at the time of cementing the prosthesis in total knee arthroplasty, before deflation of the tourniquet, significantly decreases the amount of blood loss in the early post-operative period. The use of tranexamic acid was not associated with an increase in thromboembolic complications.”	Small sample size. Not powered for VTE. Surgeries not standardized. Only 1day follow-up. Data suggest modest differences of unclear significance.
Garneti 2004 RCT	5.5	N = 50 with OA	Bolus 10mg/kg of intravenous tranexamic acid vs. normal saline at anesthesia.	No significant difference in blood loss from femoral canal, peri-operative bleeding, and post-op hemoglobin. Tranexamic acid group required more transfusions.	“The results of this study do not support the routine use of tranexamic acid in primary total hip arthroplasty.”	Tranexamic acid appears unhelpful. Blinding not well described.
Engel 2001 RCT	5.0	N = 36 undergoing TKA	One million KIE aprotinin immediately before deflating tourniquet, followed by infusion of 500,000 KIE per hour for 4 hours (n = 12) vs. 15mg/kg tranexamic acid followed by repeated dose of 10mg/kg after 3	Patients receiving RBC: 1 unit (control 0 vs. tranexamic acid 0 vs. aprotinin 3), 2 units (control 2 vs. tranexamic acid 0 vs. aprotinin 2).	“Therefore, primarily these methods should be used because there is no increased risk of adverse drug effects.”	Many details sparse. Data suggest tranexamic acid generally superior to aprotinin and controls by coagulation parameters.

			hours (n = 12) vs. no medication (controls, n = 12); 6 days follow-up.			
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HAMSTRING AND HIP FLEXOR STRAINS

See Hip and Groin Disorders guideline.

ILIOTIBIAL BAND SYNDROME

Iliotibial band syndrome is believed to occur in susceptible individuals with exposure to forceful, repeated movement of the iliotibial band over the lateral femoral condyle with resultant friction.(129, 141, 177, 183, 187, 189, 190) This disorder has been reported mostly in discrete, physically active populations, including runners, military recruits, weight lifters, bicyclers, and downhill skiers.(127, 175, 176, 178-184, 189, 191-196, 1979, 1980) Quality epidemiological studies are absent, but purported risk factors include increased activity, genu varus, leg length discrepancies, running surface and shoe wear.(141, 1981, 1982) The results are thought to include tendinopathy-like changes involving the iliotibial tract with accompanying inflammation of the lateral synovial recess.(131, 132, 141, 183, 189, 1983-1987)

The diagnosis is mostly clinical, although MRI has been used for evaluation of IT band syndrome.(131, 132, 1988) Treatment has largely been empiric, as quality evidence has been notably sparse.(130) Conservative treatment has been thought to be successful.(1984, 1985, 1989) Treatments have predominantly included: reducing the exposure factor(s) and rest,(177, 185, 191, 192, 1984, 1989-1991) NSAIDs, gradual return to activity, ice,(141, 192, 196, 1980, 1992) massage,(1980, 1992, 1993) physical therapy, stretching of the IT band,(192, 194, 1994) and local injections.

NSAIDs

Anti-inflammatory medications have been used for treatment of IT band syndrome.(141, 177, 189, 191-193, 1980, 1984, 1989, 1990, 1995, 1996)

Recommendation: NSAIDs for Iliotibial Band Syndrome

NSAIDs are recommended for the treatment of iliotibial band syndrome.

Indications – Iliotibial band syndrome patients with sufficient symptoms to require treatment.

Frequency/Dose/Duration – Per manufacturers’ recommendations.

Indications for Discontinuation – Sufficient clinical results (NSAIDs no longer required), resolution of symptoms, intolerance, adverse effects. A trial with a different class of NSAID is reasonable for treatment failures.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendation

There is one moderate-quality placebo-controlled trial; however, it did not document improvements compared to placebo.(1980) That trial included patients with acute symptoms and baseline differences that may have impacted the results. It also involved very short follow-up of 1 week with continued treadmill exercise in athletes resulting in difficulty extrapolating to working populations. The use of acute patients may have resulted in underpowering due to favorable

prognoses in all treatment groups. NSAIDs are thought to be helpful, are not invasive, have few adverse effects especially in young patients, are of low cost, and are thus recommended.

Evidence for the Use of NSAIDs

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
NSAID vs. Placebo						
Schwellnus 1991 RCT	7.0	N = 49 with Iliotibial band friction syndrome (lateral knee pain during running, tenderness over lateral femoral condyle, tenderness aggravated at 30° knee flexion, other knee exam normal)	Diclofenac 50mg TID (n = 14) vs. Ibuprofen 400mg plus paracetamol 500mg plus 20mg codeine 20mg TID (n = 16) vs. placebo TID (n = 13). All treated rest, ice BID and same physiotherapy (IT stretching, US, transverse frictions on days 3, 5, 7) from Days 3 to 7. 7 day trial duration and no additional follow-up.	Overall daily pain reduced to Day 2 in all groups equally (graphic data), then increased Day 3, then decreased remaining days. Only group 3 increased running distance significantly over trial.	“All three treatment modalities are effective in the early treatment of ITBFS but physiotherapy in combination with analgesic/anti-inflammatory medication is superior.”	Very short, 7-day trial in acute patients. Some baseline differences in outcome measures (e.g., pain experienced during running ranged 35-46; mean daily pain ranged 2.5-3.5, graphic interpretations) that may have impacted results. No superiority to placebo shown.

KNEE IMMOBILIZATION

Knee immobilization has been used for treatment of IT band syndrome.(1997)

Recommendation: Knee Immobilization for Iliotibial Band Syndrome

Knee immobilization is not recommended for treatment of Iliotibial band syndrome.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

There are no placebo-controlled trials that evaluate knee immobilization for treatment of IT band syndrome. There are also no quality trials comparing knee immobilization with an intervention with known efficacy. There is one moderate-quality trial comparing knee immobilization with phonophoresis that found the phonophoresis superior.(1997) While that study is likely biased in favor of phonophoresis, it does suggest that knee immobilization is not effective, and knee immobilization is thus not recommended.

Evidence for Knee Immobilization

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Bischoff 1995 RCT	4.0	N = 25 Navy SEALs (26 knees) with iliotibial band friction syndrome (lateral knee pain, tenderness over lateral femoral condyle, Ober's positive)	Phonophoresis (1MHz) with 10% hydrocortisone QD (maximum 10 treatments) vs.3-panel knee immobilization. Both groups treated with rest, ice massage TID,	Phonophoresis resulted in pain free exam sooner (2 vs. 8 days, p<0.001). Percentage recovering by 10 days 100% in phonophoresis vs. 62% immobilization.	“A greater (p<0.005) proportion of subjects from group (phonophoresis) (100%) recovered in less than 10 days than from group	No placebo group. Small sample sizes. Sparse details. Population of SEALs is highly unique, unusually motivated and may limit generalizability. Comparison group was immobilization, which is generally ineffective for treatment of MSDs, thus study design likely

			stretching, ibuprofen 800mg.		(Immobilization) (62%).”	biased in favor of phonophoresis.
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TRANSVERSE FRICTION MASSAGE

Transverse friction massage has been used for treatment of IT band syndrome.(1980, 1992, 1993)

Recommendation: Transverse Friction Massage for Iliotibial Band Syndrome

There is no recommendation for or against the use of transverse friction massage for the treatment of iliotibial band syndrome.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There is one moderate-quality trial assessing additive benefit in addition to stretching, ice and ultrasound.(197) It failed to show improvement, although it may have been underpowered. Thus, there is no recommendation for or against the use of transverse friction massage for treatment of iliotibial band syndrome.

Evidence for the Use of Transverse Friction Massage

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Design	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Schwellnus 1992 RCT	4.0	N = 17 iliotibial band friction syndrome (lateral knee pain during running, tenderness over lateral femoral condyle, tenderness aggravated at 30° knee flexion, other knee exam normal)	Transverse friction massage vs. no massage as additive treatment. All treated with daily stretching ice BID, ultrasound and stretching from days 3 to 14. 14 day follow-up.	Mostly graphic data. No differences between groups in mean daily pain recall, total pain, percentage maximum pain during running.	“[T]here were no differences observed between the two groups. The addition of deep transverse frictions to an established baseline physiotherapy programme of rest, ice, stretches and ultrasound is not recommended in the management of iliotibial band syndrome.”	Small sample sizes. Likely underpowered. Baseline differences with shorter symptom duration in massage group (23 vs. 74 weeks), presumably biased in favor of massage. Data suggest friction massage not of additive benefit.

PHONOPHORESIS

Phonophoresis has been used for treatment of IT band syndrome.(1997)

Recommendation: Phonophoresis for Iliotibial Band Syndrome

There is no recommendation for or against the use of phonophoresis for the treatment of iliotibial band syndrome.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are no placebo-controlled trials that evaluate phonophoresis for treatment of IT band syndrome. There are also no quality trials comparing phonophoresis with an intervention with known efficacy. There is one moderate-quality trial comparing phonophoresis with knee immobilization that found phonophoresis superior.(1997) However, the study was likely biased in favor of phonophoresis. Therefore, there is no recommendation for or against the use of phonophoresis.

Evidence for the Use of Phonophoresis

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Bischoff 1995 RCT	4.0	N = 25 Navy SEALs (26 knees) with iliotibial band friction syndrome (lateral knee pain, tenderness over lateral femoral condyle, Ober's positive)	Phonophoresis (1MHz) with 10% hydrocortisone QD (max. 10 treatments) vs. 3-panel knee immobilization. Both groups treated with rest, ice massage TID, stretching, ibuprofen 800mg.	Phonophoresis resulted in pain free examination sooner (2 vs. 8 days, $p \leq 0.001$). Percentage recovering by 10 days was 100% in phonophoresis vs. 62% immobilization.	"A greater ($p \leq 0.005$) proportion of subjects from group (phonophoresis) (100%) recovered in less than 10 days than from group (Immobilization) (62%)."	No placebo group. Small sample sizes. Sparse details. Population of SEALs is highly unique, unusually motivated and may limit generalizability. Comparison group was immobilization, which is generally ineffective for treatment of MSDs, thus study design likely biased in favor of phonophoresis.

GLUCOCORTICOSTEROID INJECTIONS FOR ILIOTIBIAL BAND SYNDROME

Glucocorticoid injections have been used for treatment of IT band syndrome.(1998)

Recommendation: Glucocorticosteroid Injections for Iliotibial Band Syndrome

Glucocorticosteroid injections are recommended for the treatment of iliotibial band syndrome in a subset of patients with insufficient results from other treatments.

Indications – Iliotibial band syndrome patients with insufficient results from activity modification, relative rest, NSAIDs, and local applications of ice or heat.

Frequency/Dose/Duration – One quality trial used methylprednisolone acetate 40mg mixed with 1% lidocaine, injected between the IT band and lateral femoral condyle.(1998) If there is insufficient response, consideration may be given to a second injection, often with a modestly higher dose.

Indications for Discontinuation – A second glucocorticosteroid injection is not recommended if the first has resulted in significant reduction or resolution of symptoms. If there has not been any response to a first injection, there is also less indication for a second. If the interventionalist believes the medication was not well placed and/or if the underlying condition is so severe that one steroid bolus could not be expected to adequately treat the condition, a second injection may be indicated. In patients who respond with several weeks of pharmacologically appropriate, temporary, partial relief of pain, but then have worsening pain and function and are not (yet) interested in surgical intervention, a repeat steroid injection is an option. There is unlikely to be benefit with greater than about 3 injections per year.

Strength of Evidence – **Recommended, Evidence (C)**

Rationale for Recommendation

There is one moderate-quality placebo-controlled trial that suggested benefits of injection with glucocorticoid compared with placebo anesthetic for treatment of iliotibial band syndrome.(1998) Although the trial was small, the results were statistically significant, thus meeting minimum criteria for an evidence-based recommendation. These injections are mildly invasive, have adverse effects, are moderately costly, and appear effective and are therefore recommended.

Evidence for the Use of Glucocorticosteroid Injections

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Title Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Injection vs. Injection and Corticosteroid						
Gunter 2004 RCT	5.0	N = 18 with iliotibial band friction syndrome (localized, sudden-onset, sharp lateral femoral condylar pain, usually after specific time or distance of running), more intense pain at stage when foot comes into contact with ground during deceleration, worse during downhill running, relieved by walking with knee in full extension.	Methylprednisolone acetate 40mg plus 10mg (1mL) 1% lignocaine hydrochloride vs. 20mg (2mL) 1% lignocaine hydrochloride injections between IT band and lateral femoral condyle. Told to not run for 14 days, to keep continuing work related activities, and self-apply ice. 14 days follow-up.	Data mostly graphic. Steroid group had lower pain during running treadmill test at Day 14 (interpretation of graphic data: 95 vs. 160, p = 0.010).	"[T]he results of this study show that the infiltration of the lateral femoral condyle area deep to the iliotibial tract with corticosteroid decreased pain during running after 14 days. Therefore the practical recommendation for treating runners is that local corticosteroid infiltration is effective and safe in the early (first 14 days) treatment of recent onset ITBFS."	Short-term trial, no intermediate or longer follow-up. Small sample sizes. Data suggest efficacy of glucocorticoid injection for ITBFS.

SURGERY

Surgical procedures have been used for treatment of iliotibial band syndrome, which have included x-lengthening.(192, 1990)

Recommendation: Surgery for Iliotibial Band Syndrome

There is no recommendation for or against surgery for treatment of iliotibial band syndrome.

Indications – Iliotibial band syndrome patients with insufficient results from activity modification, relative rest, NSAIDs, local applications of ice or heat, and 2 glucocorticoid injections.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Rationale for Recommendation

There are no quality trials comparing surgery with sham surgery for treatment of iliotibial band syndrome. There are also no quality trials comparing surgery with a non-interventional control group. There also are no quality comparative trials for different operative approaches. Therefore, surgery would be a last resort for the small minority of patients with unsatisfactory results from other treatments that generally include at least 2 glucocorticoid injections. Surgery is invasive, has adverse effects, and is highly costly. Therefore, there is no recommendation for or against its use in this small group of patients as data are insufficient and inconclusive.

QUADRICEPS, GASTROCNEMIUS, AND SOLEUS STRAINS

Quadriceps, gastrocnemius and soleus strains are thought to be true muscular strains (i.e., disrupted myotendinous junctions). These problems are usually precipitated by a high-force maneuver, including sports injuries in sprinting, football or soccer,(1999-2001) with near maximum voluntary contraction capabilities. Prior injury is likely the greatest predictor of future risk. Patients have pain exacerbated by use, stiffness and weakness.

X-RAYS and MRI

Recommendation: X-ray and/or MRI for Severe Quadriceps, Gastrocnemius, or Soleus Strains

In the more severe cases of quadriceps, gastrocnemius, and soleus strains, evaluation with x-ray and/or MRI are recommended for evaluation of the underlying bony structure as well as the degree of muscle tear.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendation

The examination findings for these types of strains are tenderness, usually at either the muscle origin or insertion (e.g., high vs. low hamstring strains), with swelling or large ecchymoses in more severe cases. Some cases involve complete ruptures and require surgical repair. Clinical tests are generally not necessary, although in the more severe cases, evaluation with x-ray and/or MRI are recommended for evaluation of the underlying bony structure as well as the degree of muscle tear, as severe cases may require surgery.

WORK LIMITATIONS

1. *Recommendation: Work Limitations for Select Cases of Quadriceps, Gastrocnemius, or Soleus Strains*

Work limitations are recommended for those with quadriceps, gastrocnemius, or soleus strains performing high physical demand tasks or those who have no ability to avoid repeating physically demanding job tasks thought to have resulted in the condition.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. *Recommendation: Work Limitations for Other Cases of Quadriceps, Gastrocnemius, or Soleus Strains*

There is no recommendation for or against work limitations for other cases of quadriceps, gastrocnemius, or soleus strains.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

Work limitations may be necessary depending on the severity of the condition and the required job demands.

BED REST

Recommendation: Bed Rest for Quadriceps, Gastrocnemius, or Soleus Strains

Bed rest is not recommended for treatment quadriceps, gastrocnemius, or soleus strains, although relative rest may be required for many patients.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

NSAIDs

Recommendation: NSAIDs for Quadriceps, Gastrocnemius, and Soleus Strains

Nonsteroidal anti-inflammatory medications are recommended for quadriceps, gastrocnemius, and soleus strains.

Dose/Duration – See NSAID section for dose, frequency, discontinuation information.

Strength of Evidence – Recommended, Insufficient Evidence (I)

ICE/HEAT

Recommendation: Ice/Heat for Quadriceps, Gastrocnemius, or Soleus Strains

Ice and/or heat are recommended for treatment of quadriceps, gastrocnemius, or soleus strains.

Strength of Evidence – Recommended, Insufficient Evidence (I)

WRAPS

Recommendation: Ace Wraps for Quadriceps, Gastrocnemius, or Soleus Strains

Ace wraps are recommended for treatment of quadriceps, gastrocnemius, or soleus strains.

Strength of Evidence – Recommended, Insufficient Evidence (I)

REHABILITATION THERAPY

Recommendation: Rehabilitation Therapy for Quadriceps, Gastrocnemius, or Soleus Strains

A course of rehabilitation therapy is recommended for patients with persisting pain from quadriceps, gastrocnemius, or soleus strains.

Strength of Evidence – Recommended, Insufficient Evidence (I)

PROGRESSIVE AGILITY, TRUNK STABILIZATION AND ICING (PATS)

Recommendation: PATS for Quadriceps, Gastrocnemius, or Soleus Strains

PATS is recommended for quadriceps, gastrocnemius, or soleus strains.

Dose/Duration – See Exercise section for exercise dose, frequency, discontinuation information.

Strength of Evidence – Recommended, Evidence (C)

Rationale for Recommendations

There is one quality study of treatment options, however, it only addressed exercise(2002); thus nearly all treatment recommendations are empiric.(2003-2005) Bed rest is not recommended due to concern regarding deep venous thrombosis and other adverse effects of bed rest. A course of rehabilitation therapy is recommended for those with persisting pain, although long term compliance is a noted problem.(2003) Quality evidence suggests stretching and isolated progressive resistance training are not successful compared with progressive agility, trunk stabilization and icing (PATS)(2002); thus PATS is recommended.

Evidence for the Use of PATS for Hamstring Strains

There is 1 moderate-quality RCT incorporated in this analysis. There are 2 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
STST vs. PATS						
Sherry 2004 RCT	5.0	N = 24 athletes with acute hamstring strains	STST (static stretching, isolated progressive hamstring resistance exercise, icing) vs. PATS (progressive agility, trunk stabilization and icing)	Time to return to sports: STST 37.4±27.6 days vs. PATS 22.2±8.3 days (p = 0.25). First 2 weeks after return to sports, re-injury rate significantly greater (p = 0.0034) in STST [6/11 (54.5%) vs. 0/13 (0%)]. After 1 year return to sports, re-injury rate also higher among completers in STST [7/10(70%)] vs. PATS [1/13(7.7%)], p = 0.0059.	“A rehabilitation program consisting of progressive agility and trunk stabilization exercises is more effective than a program emphasizing isolated hamstring stretching and strengthening in promoting return to sports and preventing injury recurrence in athletes suffering an acute hamstring strain.”	Small sample size. Data suggest agility and trunk stabilization exercises superior. Re-injury rate also lower in that group both short and long term.

KNEE SPRAINS (INCLUDING MEDIAL AND LATERAL COLLATERAL LIGAMENTS; ANTERIOR AND POSTERIOR CRUCIATE LIGAMENTS)

Knee sprains are partial or complete disruptions of ligaments.(104, 2006, 2007) Thus, these injuries are usually a result of high force events, particularly including sporting injuries, slips, trips, falls, motor vehicle accidents and work injuries.(104, 2006, 2008, 2009) The 4 major ligaments of the knee are all susceptible to knee sprains.(104, 2006) These are the medial and lateral collateral ligaments, along with the anterior and posterior cruciate ligaments. Sprains are typically graded from I to III ranging from an intact ligament without laxity but with fiber disruption (I) to complete disruption (III).(104, 2006, 2007) Low grade sprains are considered to have excellent prognoses.(2006, 2010-2012) Grade III sprains are more susceptible to concomitant injuries such as the ACL and menisci.(2006) A careful history will usually result in a presumptive diagnosis that is confirmed on physical examination (see History and Physical Examination sections). Patients have pain exacerbated by use and ligament stretching. The examination findings are focal tenderness over the collateral ligament and pain augmentation with ligamentous stressing for collateral ligament sprains. Examination findings may be normal for Grade I cruciate ligament sprains or include laxity with complete disruptions. Some cases involve complete ruptures and may require surgical repair (see ACL section). Combined ruptures (e.g., MCL plus ACL) are beyond the scope of this guideline as there are few quality studies to define treatment options and both operative and non-operative care has been attempted with successes.

X-RAY AND MRI

Recommendation: X-rays and MRI for Evaluation of Knee Sprains

X-ray and/or MRI are recommended for the evaluation of knee sprains, particularly to rule out fracture.

Strength of Evidence – Recommended, Insufficient Evidence (I)

ULTRASOUND

Recommendation: Ultrasound for Evaluation of Knee Sprains

There is no recommendation for or against the use of diagnostic ultrasound for the evaluation of knee sprains.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

Clinical tests are generally not necessary for mild sprains, although in more severe cases, evaluation with x-ray and/or MRI are recommended, particularly to rule out fracture, and MRI is helpful for defining cruciate ligament tears. There is no recommendation for or against the use of diagnostic ultrasound to evaluate knee sprains.

WORK LIMITATIONS

1. *Recommendation: Work Limitations for Select Knee Sprains*

Work limitations are recommended for those with knee sprains performing high physical demand tasks or those who have no ability to avoid repeating physically demanding job tasks thought to have resulted in the condition.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. *Recommendation: Work Limitations for Other Cases of Knee Sprains*

There is no recommendation for or against the use of work limitations for other cases of knee sprains.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

BED REST AND KNEE IMMOBILIZATION

Recommendation: Bed Rest and Knee Immobilization for Knee Sprains

Bed rest and knee immobilization are not recommended for treatment of knee sprains, although relative rest may be required for many patients.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

NSAIDs

Recommendation: NSAIDs for Knee Sprains

Nonsteroidal anti-inflammatory medications are recommended for treatment of knee sprains.

Dose/Duration – See NSAID section for dose, frequency, discontinuation information.

Strength of Evidence – Recommended, Insufficient Evidence (I)

ICE/HEAT

Recommendation: Ice/Heat for Knee Sprains

Ice and/or heat are recommended for treatment of knee sprains.

Strength of Evidence – Recommended, Insufficient Evidence (I)

WRAPS AND KNEE BRACES

Recommendation: Ace Wraps and Knee Braces for Knee Sprains

Ace wraps and knee braces are recommended for treatment of knee sprains.

Strength of Evidence – Recommended, Insufficient Evidence (I)

REHABILITATION THERAPY

Recommendation: Rehabilitation Therapy for Knee Sprains

A course of rehabilitation therapy is recommended for those with persisting pain from a knee sprain.

Dose/Duration – See exercise section for dose, frequency and discontinuation.

Strength of Evidence – Recommended, Insufficient Evidence (I)

OTHER PHYSICAL MODALITIES/INJECTIONS

Recommendation: Other Modalities/Injections for Knee Sprains

There is no recommendation for or against the use of therapeutic ultrasound, diathermy, electrical stimulation, iontophoresis, low-level laser therapy, phonophoresis, acupuncture, manipulation, mobilization or manual therapy, autologous blood injections, plasma rich platelet injections, glucocorticosteroid injections, and hyaluronic acid injections for knee sprains.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

SURGERY

1. *Recommendation: Surgery for Grade III LCL Tears*

Surgery is recommended in isolated Grade III LCL tears, recognizing that they are rare.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. *Recommendation: Surgery for Select Cases of Grade III MCL Tears*

Surgery in isolated Grade III MCL tears is usually not necessary because of the documented excellent healing potential of this ligament with closed (i.e., non-operative) treatment. Surgery is only recommended in those rare select cases of failure of non-operative management.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendations

There are no quality studies of treatment options aside from surgery and rehabilitation for complete ACL tears (see next section) and one trial comparing NSAIDs(719) and one with DHEP gel.(2013) Of necessity, guidance for treatment relies upon ankle sprains for analogy as there are considerable quality trials for ankle sprains(2014, 2015) (evidence ratings are all “Insufficient Evidence” due to the analogy with the ankle). Work limitations may be necessary depending on the severity of the condition and the required job demands.(2016) Those performing high physical demand tasks or those who have no ability to avoid repeating physically demanding job tasks thought to have resulted in the condition are recommended to have work limitations.

Bed rest and knee immobilization are not recommended due to risks of venous thromboembolisms and other adverse effects of bed rest, although relative rest may be required for many patients. NSAIDs, ice and/or heat, Ace wraps, and knee braces are recommended. A low-quality trial suggested a less bulky elastic support bandage was superior to a Robert Jones bandage.(2017) Those with persisting pain are recommended to have a course of rehabilitation therapy. There is no recommendation for or against autologous blood injections, plasma rich platelet injections, glucocorticosteroid injections, hyaluronic acid injections, therapeutic ultrasound, diathermy, electrical stimulation, iontophoresis, low level laser therapy, phonophoresis, acupuncture, manipulation, and mobilization or manual therapy. RCTs and a systematic review suggested neuromuscular training for sports injury prevention was effective.(2018-2021) However, this topic is beyond the scope of these *Guidelines* but may be of interest to some readers. Warm-up stretching has been shown to increase flexibility(2022); however, its relationship to preventing injury is unclear. Surgery is recommended in isolated Grade III LCL tears, recognizing that they are rare. Surgery in isolated Grade III MCL tears is usually not necessary because of the documented excellent healing potential of this ligament with closed (i.e., non-operative) treatment. Surgery is only recommended in those rare select cases of failure of non-operative management.

Evidence for Knee Sprains

There are 5 moderate-quality RCTs incorporated into this analysis. There are 3 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Work Disability						
Abásolo 2007 RCT	4.0	N = 13,077 workers who began sick leave due to a musculoskeletal disorder (MSD) not secondary to trauma, surgery, or work accidents	Standard care provided by primary care physicians who could give specialized care at any time (control group, n = 7,805) vs. specific care program: education, pharmacologic and nonpharmacologic treatment, and timing of diagnostic tests (intervention group, n = 5272) until work disability resolved or recovery unrealistic.	NS between groups for knee pain for all outcomes. Efficacy of programs was lowest in the knee pain population.	“The implementation of this type of specialist-run, protocol-based early intervention program would be very beneficial in the treatment of patients with work disability related to MSDs, except for those with knee pain (excluding osteoarthritis).”	Study from Spain and applicability to U.S. unclear as lost time likely considerably higher in Europe and WC much different. Study data suggests early implementation effective. Scored for CTS patients within trial. Overall participation rate 62.8%.
NSAIDs						

Mahler 2003 RCT	6.0	N = 100 with 1st-degree ankle (57%) and knee joint sprains (26%), 1st-degree muscle strains or mild-to-moderate muscle contusions (16%)	DHEP lecithin gel (65mg of diclofenac 5g TID (n = 52) vs. DHEP gel for 10 days. All treated with ice in first 48 hours. No bandages, no partial immobilization.	Absolute decrease for VAS pain on movement for lecithin vs. gel at 3 days: -24.7mm vs. -16.8mm, p = 0.025; at end of treatment: -48.3mm vs. -41.3mm, p = 0.036. Mean±SD spontaneous pain VAS baseline/3 days for lecithin vs. gel: 39.9 ±20.8/21.5±16.5 vs. 38.4±21.7/28.5±20.7, p = 0.014. Mean±SD Pain on pressure VAS baseline/10 days for lecithin vs. gel: 71.7 ±16.6/21.5±20.8 vs. 71.9±16.4/29.8±20.9, p = 0.019.	“Compared with the reference gel formulation, containing the same active substance but without lecithin, DHEP lecithin gel displayed a therapeutic action that was significantly more marked throughout the study period, with faster onset of the analgesic/antiinflammatory activity.”	No placebo group. Heterogeneous mix of disorders with first degree sprains and 1st or 2nd degree contusions. Data suggest DHEP lecithin gel superior to DHEP gel.
Duncan 1988 RCT	6.0	N = 139 age 18-70 with acute sprain/strain of knee or ankle within previous 36 hours while participating in athletics; mostly ankle sprains.	Diclofenac 75mg BID (n = 69) vs. aspirin 1.2g TID (n = 70) for 10 days	ROM between groups not significant. Swelling less in diclofenac group vs. aspirin p = 0.003. No significant difference between groups for time to return to sports by Day 10.	“[D]iclofenac is useful in treating sport-related injuries and may allow an earlier return to playing fitness.”	Double dummy. Data trend in favor of diclofenac for pain on active motion. Playing fitness at 10 days did not differ.
Mcllwain 1988 RCT	4.5	N = 34 with acute symptoms from sprains to ankle, acromioclavicular joint, and interphalangeal joint of hand or acute soft-tissue injury to shoulder, knee, or about hip	Piroxicam 40mg daily for 2 days and then 20mg once daily vs. naproxen 500mg twice daily for 2 days, then 375mg twice daily.	Mean change from baseline to visit 2 in spontaneous pain comparing piroxicam vs. naproxen: 7.3 vs. 4.6. Change to visit 3: 11.9 vs. 11.5. Changes in swelling at visit 2: 1.1 vs. 0.7; Changes in tenderness at visit 2: 1.6 vs. 1.1.	“[P]iroxicam and naproxen are effective and well-tolerated short-term treatments for acute musculoskeletal injuries in athletes.”	Heterogeneity in disorders treated (e.g., sprains of ankle, AC, hand IP, soft tissue injuries of shoulder, knee or hip). No placebo group. Data suggest piroxicam superior to naproxen.
Topical Treatment						
Frahm 1993 RCT	6.0	N = 156 age 18-65 suffering from pain and swelling due to acute sprains to ankle (n = 117) or collateral knee ligaments (n = 39)	Two tubes of cream containing MPS 0/2% and salicylic acid 2% (n = 78) vs. 2 tubes of placebo cream (cream base) (n = 78) applied twice daily with follow-ups on days 2, 4, 9, and 11.	Decrease in pain on movement significantly better in active treatment group (24.87±26.00) vs. control group (38.73±30.42) at 9 days, p = 0.0065; NS between groups for all other parameters.	“The results of this double-blind study appear to provide proof of the clinical efficacy and good tolerability of the cream for acute sprains.”	Double blinding details sparse. Study suggests topical Movelat cream has limited analgesic efficacy as only significant on Day 9. No differences demonstrated for pain at rest, edema, or subjective

						efficacy. Data suggests no to minimal efficacy. Mostly ankle patients so applicability to knee patients also unclear.
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ANTERIOR AND POSTERIOR CRUCIATE LIGAMENT TEARS

This section addresses complete disruptions of the cruciate ligaments. These injuries are most commonly experienced in athletics, as well as acute discrete, forceful traumatic events.(2, 4, 1061, 1064-1066, 1068, 1069, 1072-1075, 2023-2031) The history and physical examination findings have been previously discussed (see History and Physical Examination and Knee Sprain sections). There are concerns regarding subsequent development of osteoarthritis, and a positive pivot shift after surgical repair has been reported to predict osteoarthritis.(2032)

The anterior cruciate ligament (ACL) is considered the most important stabilizing knee ligament. Thus, this section will primarily address ACL tears. Posterior cruciate ligament tears are uncommon, and rarely require surgery in non-professional athletes. PCL ligament tears are thought to be best rehabilitated with progressive exercises which are **Recommended, Insufficient Evidence (I)** (see ACL exercise section above).

Whereas ACL tears were once universally thought to require surgical repair, there is now quality evidence of successful non-operative rehabilitation in well selected patients (see below). This has somewhat increased the complexity of patient management. For many interventions, there is not quality evidence, and either inference from treatment of other body parts, consensus, and/or expert opinion guide treatments.

X-RAYS

Recommendation: X-ray for Evaluation of ACL Tears

X-ray is recommended for many cases of ACL tears, particularly accompanying trauma, to rule out fractures.

Strength of Evidence – Recommended, Insufficient Evidence (I)

MRI

Recommendation: MRI for the Evaluation of ACL Tears

MRI is recommended for ACL tears, particularly if there are concerns for other soft tissue damage including meniscal tears and other sprains. However, some cases also may be managed clinically without MRI.

Strength of Evidence – Recommended, Insufficient Evidence (I)

ULTRASOUND

Recommendation: Ultrasound for the Evaluation of ACL Tears

There is no recommendation for or against the use of diagnostic ultrasound for evaluation of ACL tears.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

Clinical tests may or may not be necessary depending on the mechanism of severity, physical examination findings and potential for complicating injuries. X-ray is recommended particularly in cases with accompanying trauma to rule out fractures. MRI is helpful, particularly if there are concerns for other soft tissue damage including meniscal tears and other sprains. However, some cases also may be managed clinically without MRI. There is no recommendation for or against the use of diagnostic ultrasound to evaluate ACL tears.

INITIAL CARE

Rest, splints, ice and heat have been utilized for treatment of ACL injuries.(1066, 1068, 1072, 1074, 2023, 2033, 2034) Functional bracing has been used to prevent and treat ACL injuries; they have also been used post-operatively as part of the rehabilitation program.(1064, 1065, 1069) There are no quality studies of treatment options aside from exercise, rehabilitation, braces and surgical treatment.

BRACING

Knee bracing is commonly performed for ACL tears.(1061, 1064-1066, 1068, 1069, 1072-1077, 2023-2031, 2033, 2035, 2036) Most often, hinged braces are used, although there are different models in use.

1. Recommendation: Functional Bracing for Treatment of Non-Operative Anterior Cruciate Ligament Injuries

There is no recommendation for or against the use of functional bracing for treatment of non-operative ACL injuries.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

2. Recommendation: Functional Bracing for Anterior Cruciate Ligament Injuries Post-operatively

Functional bracing is not recommended for ACL injuries post-operatively.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendations

There are many RCTs that evaluate the use of braces to treat and rehabilitate post-operative and non-operative patients with ACL tears. However, nearly all of the trials for non-operative treatment are of low quality. Thus, there is no recommendation for or against the use of braces for non-operative treatment of ACL tears. Use of braces in these patients must balance theoretical stabilization against disuse and delayed progression. If braces are prescribed it is suggested patients be monitored for progress and generally be engaged in an active exercise program.

There are four moderate-quality trials that evaluated post-operative patients. Three of these studies suggested no differences in outcome,(1076, 2035, 2036) and the other suggested modestly less reduction in range of motion in a post-operative group.(1077) Bracing is not invasive, has low adverse effects, and is low to moderately costly. However, available evidence does not suggest significant benefits; therefore bracing is generally not recommended. Exceptions may include suboptimal surgical repairs and other extenuating factors.

Evidence for the Use of Bracing for ACL Tears

There are 5 moderate-quality RCTs incorporated into this analysis. There are 8 low-quality RCTs in Appendix 1.(2037-2044)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Hiemstra 2009 RCT	5.5	N = 88 aged 18-40 with ACL deficient knee	Knee-immobilization brace (n = 44) vs. no knee-immobilization brace (n = 44) for 14 days.	Significant surgeon effect for immobilized group, p = 0.033.	"No differences in pain or any of the secondary outcomes were detected between immobilized and nonimmobilized patients at any point during the first 14 days after anterior cruciate ligament reconstruction."	No blinding. No differences found up to 14 days post-op.
Mikkelsen 2003 RCT	4.5	N = 44 undergoing arthroscopic ACL-reconstruction with a bone patellar tendon bone graft	Straight post-op brace (straight brace group, n = 22) vs. brace set at -5° of knee extension (hyperextension brace group, n = 22) for at least 3 weeks.	No straight knees in group with straight post-op brace. Still some knee flexion in hyperextension brace group.	"[T]he use of a Hypex brace set in hyperextension for at least three weeks after ACL-reconstruction seems to be an easy way of preventing a cumbersome extension deficit of the knee joint."	No mention of activities that may influence extension. Data suggest extension setting resulted in fewer cases of reduced extension.
Birmingham 2008 RCT	4.5	N = 150 aged 14-45 with unilateral ACL tears undergoing reconstruction	DonJoy Legend functional knee brace (n = 76) vs. neoprene knee sleeve (n = 74) for 12 months.	No significant differences between groups for outcome measures.	"A functional knee brace does not result in superior outcomes compared with a neoprene sleeve after ACL reconstruction."	No control group used to compare. Data suggest comparable (in)efficacy.
Möller 2001 RCT	4.5	N = 62 with unilateral ACL injuries undergoing ACL reconstruction	No brace (Group A, n = 30) vs. rehabilitative brace (Group B, n = 32) for 6 weeks post surgery.	No significant difference between groups for knee laxity, muscle and functional performance, ROM, or knee circumference. Tegner activity score significant after 6 months in favor of Group A.	"In conclusion, we found no beneficial effect of this knee brace on either subjective or objective knee function up to 2 years after surgery."	Lack of blinding lowered score. No differences reported at set times and none after 2 years of follow-up
Brandsson 2001 RCT	4.5	N = 50 with unilateral isolated ACL rupture scheduled for reconstruction surgery	DonJoy knee brace (Group A, n = 25) for first 3 weeks after surgery vs. no knee brace (Group B, n = 25).	At 2-year follow-up, no significant differences between groups for Lysholm scores, Tegner activity levels, 1-leg hop test, IKDC evaluation system, and KT-1000 measurements. Two weeks post surgery, brace group lower VAS score vs. controls, p = 0.04.	"[T]he overall function, ROM, muscle strength and activity level two years after ACL reconstruction were similar in both groups, regardless of whether a brace was used during the early postoperative period."	Baseline difference in Lysholm score. Data suggest comparable results over 2 years.

REHABILITATION AFTER ACL INJURY WITH OR WITHOUT RECONSTRUCTION

Exercise, physical therapy, and rehabilitation have been used for treatment of ACL tears either instead of surgery or post-operatively.(224, 2008, 2009, 2045-2054) The early objectives of rehabilitation include restoration of knee range of motion, pain management, reduction of swelling, early ambulation and increasing muscle strength.(2047, 2051)

1. Recommendation: Post ACL Injury Rehabilitation with or without Surgical Repair

Rehabilitation is recommended after ACL injury with or without surgical reconstruction.

Indications – ACL injury with or without surgery.

Duration – One to 6 weeks, 2 to 3 sessions a week, decreasing over time with active treatment up to 12 weeks.(2009, 2055) There is quality evidence that a home-based program is as effective as a therapy based program for motivated post-operative patients(2047, 2056) (see Table 6).

Indications for Discontinuation – Achievement of goals, non-compliance with clinic or home based exercises or intolerance.

Strength of Evidence – Recommended, Evidence (C)

Table 6. Post-operative Rehabilitation after ACL Injury

		0-4 weeks	5-8 weeks	9-12 weeks	13-16 weeks	17-24 weeks
Unloaded ROM		As tolerated	As tolerated	Normal	Normal	Normal
Muscle Function	<i>Quadriceps</i>	Unloaded, full control	Loaded, non-weight bearing in 40-120°; weight-bearing exercises in 0-80°	Closed chain exercises without limitations		
	<i>Hamstrings</i>	Loaded exercises	No limitations	No limitations	No limitations	No limitations
	<i>All other lower limb muscles</i>	Initiated	No limitations	No limitations	No limitations	No limitations
Symptoms	<i>Pain</i>	As tolerated; treat if necessary	As tolerated; treat if necessary	No pain	No pain	No pain
	<i>Swelling</i>	As tolerated; treat if necessary	As tolerated; treat if necessary	Occasional activity-related swelling, no treatment	Occasional activity-related swelling, no treatment	Occasional activity-related swelling, no treatment
Walking		As tolerated; may use crutches until walk backwards without limping	Full weight bearing. Daily walking without restriction	Slow and fast walking on treadmill	Running on treadmill/even surface. Non-surgical: unrestricted running	Surgical: unrestricted running
Balance/Coordination	<i>One-leg standing</i>	Stand in functional positions	Stand in functional positions on soft ground and Babs-board	More demanding surfaces	Two legged bounces, easy sport-specific movements. Easy agility exercises	One-legged bounces. Provoked sport-specific movement. Provoked agility exercises.
Activities		Unloaded and loaded biking on stationary bike backwards and forwards	Stationary biking without restrictions. Water based running. Non-surgical: outdoor biking with restrictions.	Slide-board training	Non-surgical: introduction of sport-specific exercises. Surgical: Outdoor biking without restrictions	Surgical: introduction of sport-specific exercises.

Adapted from Frobell, et al. 2007.

2. *Recommendation: Home-Based Physical Therapy for Post-ACL Operative Repair Patients*
Home-based physical therapy is recommended for post-ACL operative repair patients.

Indications – ACL post-operative patients.(2047, 2056, 2057)

Duration – From 3 to 5 supervised physical therapy visits focusing on a home-based exercise program that lasts up to a total of 3 months post-operatively.(2047, 2056, 2057) The idea is to develop a continual exercise program indefinitely.

Indications for Discontinuation: Discontinuation of intermittent supervision based on achievement of goals, non-compliance or intolerance.

Strength of Evidence – **Recommended, Evidence (C)**

Rationale for Recommendations

A moderate-quality trial has shown equivalent results whether treatment is surgical or non-surgical (see Surgical section below).(2009) There are no quality studies comparing post ACL-injury with rehabilitation compared with no rehabilitation. Two moderate-quality studies evaluated home exercises after 0 to 4 supervised physical therapy sessions compared with a total of 17 or more sessions and reported no differences in several objective and subjective outcomes.(2047, 2056) A low-quality study evaluated home therapy after supervised physical therapy to supervised physical therapy and reported no significant differences in favor of a fully-supervised physical therapy program.(2057) A second low-quality study evaluated a home exercise program versus clinic-based exercises and found no significant differences.(2058) Another low-quality study evaluated a supervised home exercise program versus a knee exercise class for a minimum of 6 months after ACL reconstruction and concluded there was no difference between groups.(2059) Physical therapy appears beneficial in ACL-injured patients with no reported significant adverse events. One trial suggested supervised training to be superior to self-monitoring; however, the trial appears to have instructed the self-monitored group to avoid use, thus biasing against that treatment.(2060) Home based exercises programs appear as efficient as supervised programs, cost less, and are recommended for most motivated post-operative patients.(2058) It is recommended that several types of exercises be included in the post injury rehabilitation program (see above).(1275, 1292, 2009, 2049, 2061-2065) Rehabilitation is not invasive, has few adverse effects and is moderately costly using the regimen noted above. Given the evidence of efficacy, rehabilitation is recommended.

3. *Recommendation: Perturbation Training As Part of a Rehabilitation Program for ACL Injured Patients*

Perturbation training is recommended as part of a comprehensive exercise program in patients with injured ACL with or without surgery.

Indications – ACL injured patients who choose to undergo ACL reconstruction surgery, or patients who opt for nonsurgical management. To be done as part of a comprehensive exercise therapy program that includes strength training exercises.(2066, 2067)

Duration – As part of a therapy program, both supervised and unsupervised. Available studies have examined up to 10 sessions of therapy with perturbation as a part of the therapy program.(2066, 2067)

Indications for Discontinuation – Achievement of goals, non-compliance, or lack of benefits.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

A low-quality study evaluated ACL-injured patients who opted to be treated non-operatively. The study compared physical therapy with or without perturbation training and reported slightly better

improvements in the perturbation group.(2066) Perturbation training can be included in a therapy program. A low-quality study evaluated perturbation and strength training versus strength training alone prior to ACL surgery. Both groups increased strength post-operatively, but the group that included perturbation training had better gait mechanics results 6 months after surgery.(2067) It appears to have low adverse events and encourages physical activity. One trial has suggested that patients, classified as non-copers performed better with perturbation training and quadriceps strength training than quadriceps strength training.(2068)

4. Recommendation: Early Post-operative Rehabilitation After ACL Reconstruction Surgery
Early post-operative rehabilitation after ACL reconstruction surgery is recommended.

Indications – ACL reconstruction patients starting as early as the first post-operative day.(2051, 2061, 2069)

Duration – Two to 3 times a week for up to 6 weeks for guided therapy.(2062, 2070)

Indications for Discontinuation – Complications causing a need for further intervention and/or surgery.

Strength of Evidence – Recommended, Evidence (C)

Rationale for Recommendation

A moderate-quality study evaluated isokinetic hamstring exercises as part of a post-operative rehabilitation program. One group started the exercises 3 weeks post-operatively, the other 9 weeks post-operatively. They reported benefits of starting exercises earlier in an athletic cohort.(2071) A moderate-quality study compared patients who started quadriceps exercises on post-operative day 2 with patients who started therapy 1 to 2 weeks following surgery. They reported no increase in adverse events and faster recovery of knee range of motion and stability in the group that started therapy earlier.(2051) Earlier rehabilitation has not been reported to increase adverse events, and it has been reported to increase benefits.(2061) A low-quality study evaluated knee continuous passive range of motion starting post-operative day two to range of motion on post-operative day seven. They reported no increase in adverse events with starting therapy earlier.(2069) Early rehabilitation is not invasive, has low adverse effects, is low cost, has documented efficacy, and is therefore recommended.

Evidence for Post ACL Injury Rehabilitation

There are 9 moderate-quality RCTs incorporated into this analysis. There are 5 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Exercise						
Grant 2005 RCT	7.5	N = 152 with ACL deficiency, over age 16 and surgery at least 6 weeks after injury	Home based rehabilitation with 4 PT sessions (group HB, n = 73) vs. supervised physical therapy with 17 PT sessions from any therapist at any clinic (group PT, n = 72) for 12 weeks.	No differences between ROM during walking, ligament laxity, and strength. Home-based group had significantly higher acceptable outcomes in flexion (p = 0.03) and extension (p = 0.02) ROM. Percentage of acceptable patients: extension ROM (home 96.8 vs. PT 83.3, p = 0.02), flexion ROM (66.7	“A structured, minimally supervised rehabilitation program was more effective in achieving acceptable knee range of motion in the first 3 months after anterior cruciate ligament reconstruction than a standard physical therapy-based program.”	Patient outcomes dichotomized to acceptable vs. unacceptable. No mention of co-interventions. Less compliance with PT visits in PT group. Data suggest home based therapy as

				vs. 47.0, p = 0.03), video extension ROM (57.1 vs. 48.5, p = 0.38), video flexion ROM (94.5 vs. 85.2, p = 0.13), KT arthrometer side to side difference (88.9 vs. 93.8, p = 0.36), quadriceps strength (83.9 vs. 78.1, p = 0.50), hamstrings strength (93.5 vs. 87.5, p = 0.36).		effective for young post-op ACL patients.
Risberg 2007 RCT	7.0	N = 74 scheduled for arthroscopic ACL repair with autogenous bone-patellar tendon-bone graft	Muscle strength training (quadriceps, hamstrings, gluteus medius, gastrocnemius) vs. neuromuscular training (balance, dynamic joint stability, plyometric, agility, sport-specific exercises) after ACL repair both begun in 2nd week postop, 2-3 times a week for 6 months. All received rehabilitation program including ROM, swelling reduction. 6 months follow-up.	Difference for Cincinnati knee scores (pre-op/3 months/6 months mean±SD) for strength training 65.3±13.0/61.4±11.7/73.4±9.6 vs. neuromuscular training 65.2±17.0/64.3±11.5/80.5±12.3, p = 0.05. Difference in VAS for knee function (pre-op/3 months/6 months mean mm±SD) for strength training 33.9±25.3/51.7±26.0/59.3±23.1 vs. neuromuscular training 39.1±25.5/50.1±23.8/72.4±22.1, p = 0.02.	“[A]lthough there were small differences between the [neuromuscular training] program and the [strength training] program, the [neuromuscular training] program was superior to the [strength training] program in improving knee function after ACL reconstruction.”	Data suggest neuromuscular training in addition to rehabilitation program more effective than muscle strength training.
Bynum 1995 RCT	6.0	N = 100 with arthroscopically assisted ACL reconstruction with middle third of patellar tendon autograft for isolated ACL tears; surgeries mostly more than 1 year after injury	Open kinetic chain exercise (OKC, conventional PT equipment) vs. closed kinetic chain exercise (CKC, with elastic Sport Cord). Numbers and frequencies of appointments not specified. All treated with post-op hinged knee brace. At least 1 year follow-up.	Very satisfied in 53% open vs. 55% closed (p = 0.57). Excellent results in 50% open vs. 55% closed with 20% vs. 3% fair, p = 0.13. Return to normal activities later than expected in 20% vs. 3%, p = 0.007. Return to sports later than expected in 40% vs. 21%, p = 0.118. No differences in Lysholm scores, Tender activity level, subjective rating. Mean KT-max side-to-side difference was 1.6 and 3.3mm in CKC and OKC, p =	“The results of this study support the premise that closed kinetic chain exercises, when used as part of an accelerated protocol, are a safe and effective means of rehabilitating the knee in the early stages after ACL reconstruction. The results also suggest that closed kinetic chain exercises may offer additional advantages of less stress on the maturing graft and the patellofemoral joint, cost	Frequency and numbers of appointments not specified. Co-interventions unclear. Most results favored closed chain exercises.

				0.02. At 9 months, patellofemoral pain severe enough to restrict activities 15 % in CKC vs. 38% Open, p = 0.046.	effectiveness and convenience, and excellent patient acceptance and satisfaction.”	
Shaw 2005 RCT	5.5	N = 103 who underwent unilateral, arthroscopically-assisted ACL reconstruction with either bone-patellar tendon-bone or semitendinosus-hamstring graft	No quadriceps exercise group vs. quadriceps exercise group before anterior cruciate ligament reconstruction.	Statistically significant differences found at 1 month post-op for active flexion for no quadriceps exercise (122.3°±14.5) vs. quadriceps exercise (128.2°±12.7), p = 0.05, and for active extension ROM (-14.8°±6.4 vs. -12.1°±4.8), p = 0.05. Statistically significant differences in Cincinnati knee rating system for quadriceps exercise (7.5±1.2) vs. no quadriceps exercise (6.8±1.1), p = 0.005, and sport score (66.4±14.4 vs. 61.±15.2), p = 0.05.	“[I]sometric quadriceps exercises and straight leg raises can be safely prescribed during the first two postoperative weeks, and inclusion of such a regimen results in small but statistically significant improvements in recovery of range of motion and the frequency of knee stability.”	No mention of co-interventions or compliance with exercises. Early quad exercise was not reported to increase adverse events or ligamentous laxity. Subjectively patients had better outcomes with quad exercises.
Beard 1998 RCT	5.0	N = 31 undergoing ACL reconstruction surgery	Group H, n = 13 (performed all exercises at home or using alternative commercial/private facilities) vs. group S, n = 13 (same exercises as group H and supervision by a physical therapist 2 times a week) for 6 months.	No significant differences between groups.	“No demonstrable benefit, in terms of functional outcome and muscle strength, was derived by ACL-reconstructed patients attending supervised exercise sessions which were supplemental to a home-based program. It is suggested that home-based regimens of rehabilitation, with regular physical therapy outpatient assessment, provide an adequate and appropriate format for rehabilitation following anterior cruciate ligament reconstruction.”	Small numbers. VAS questions created by authors for this study. Data suggest no significant differences.

Heijne 2007 RCT	4.5	N = 68 age 16-50 with ACL injuries; 34 repaired with patellar tendon-bone grafts and 34 hamstring grafts (not randomized for surgical procedure)	All supervised PT 2-3 times a week begun <1 week post-op. Open kinetic chain exercises (OKC) at 4 weeks post operative for patellar tendon grafts (seated knee extension with ROM 90-40°, P4) vs. OKC at 12 weeks post- op for patellar tendon grafts (P12) vs. OKC exercises at 4 weeks for hamstring tendon grafts (H4) vs. OKC exercises at 12 weeks postoperatively for hamstring tendon grafts (H12). 7 months follow-up.	Statistically significant difference for anterior knee laxity between all groups, $p = 0.02$; H4 showed higher mean difference of 1.0 mm compared to P4 ($p = 0.04$) and 1.2 mm compared to H12 ($p = 0.02$). Higher rotational instability for H4 vs. P4 at 3 months ($p = 0.04$) and at 7 months ($p = 0.04$). Significant trend differences for changes over time between 4 groups for quadriceps ($p < 0.001$) and hamstrings ($p < 0.001$). Quadriceps muscle torques had general treatment effects ($p = 0.004$). Hamstring muscle torque had general treatment effects ($p < 0.0001$).	"[E]arly start of OKC quadriceps exercises results in greater anterior knee laxity than late start in patients with hamstring ACL reconstructed knees as well as those with patellar tendon ACL reconstructed knees. The early introduction of OKC quadriceps exercises did not influence quadriceps muscle torques in any of the four different groups. Furthermore, no differences in terms of postural sway and anterior knee pain... suggest that the rehabilitation for patients with hamstring ACL reconstructed knees should not include early start of OKC quadriceps."	Highly intensive regimens with median 37-45 sessions (range 9-61). Data suggest more anterior knee laxity in hamstring reconstructed knees undergoing early open kinetic chain exercises, but no differences between early vs. late exercises in patellar tendon grafts.
Morrissey 2002 RCT	4.5	N = 43 having had ACL reconstruction for less than 20 days	Open kinetic chain exercise (hip/knee extensor exercises with ankle weights or machines) vs. closed kinetic chain exercises (hip/knee extensor resistance training, supine with hip/knee in 90° flexion at start) 3 times a week for 4-weeks; 6 weeks follow-up.	Decrease in pain mean±SD for pre test/post test of Hughston Clinic Questionnaire questions 1, 2, 25 for closed chain: 5.1±3.3/4.0±3.9, 6.0±2.9/4.0±3.1, 4.8±3.4/3.4±3.0; open chain: 4.5±3.3/2.9±3.0, 4.6±3.3/2.7±2.3, 4.7±3.5/2.9±3.1. Whole group analysis of question 1 ($p < 0.01$), question 2 ($p < 0.001$), question 25 ($p < 0.001$).	"The results of our study indicate that knee pain, especially in the anterior portion of the knee, is not affected differently by exercises of the leg extensors with the lower extremity distally fixated or not fixated in the early period of rehabilitation following ACL reconstruction surgery."	Allocation to 2 sites for therapy differed between groups (67% vs. 36%) of unclear significance, but potentially fatal study flaw. Data suggest no meaningful differences between groups.
Zätterström 2000 RCT	4.0	N = 100 age 15-45 with acute ACL tear, with or without associated lesions of other structures of knee, previously normal knee and uninjured	Supervised training (SV) with education and active movement, 2x50-60 min sessions/week for 5-8 months (fewer sessions towards end) vs. self-monitored (SM) training instructions on joint mobilization	Mean±SD isometric muscle strength extension at 3 months comparing SV vs. SM: 159±72.0 vs. 135.8±55.7; $p = 0.07$. Isometric flexion at 3 months: 78.6±36.6 vs. 67.4±51.1; $p = 0.006$. Isokinetic muscle extension at 3 months: 3153±992	"[D]espite the transfer of nearly 50% of the patients in the self-monitored (SM) group to the supervised (SV) program after the first 6 weeks' follow-up, the intention-to-treat analysis showed significantly better results in nearly all muscle tests and in the hop	Patients not well described at baseline. Many details sparse. Half of patients in self-monitored group transferred to supervised training at 6 weeks due to ROM restrictions

		contralateral extremity	and knee muscle training to regain mobility and muscle strength. After 6-week scheduled daily training period patients were to continue training until follow-up controls after 3 and 12 months.	vs. 2580±649; p = 0.002.	test of the original SV group at 12 months. However, these results were valid only with regard to the male patients.”	and/or atrophy. Appears instruction to self-monitored group to “not to force mobility, in order to allow healing” may have produced differences in results and failures in self-monitored group who then transferred to active treatment group.
Sekir 2010 RCT	4.0	N = 48 age 17-44 with their 1st unilateral ACL injury and a healthy contralateral leg	Early hamstring exercise, instructed to perform specific isokinetic hamstring exercises daily at beginning of 3rd week (Group I, n = 26) vs. perform isokinetic hamstring exercises daily starting at 9th week after surgery (Group II, n = 22) assessed for 12 months.	Hamstring strengths at 30° of flexion in both isokinetic and isometric measures greater in early group, p = 0.45 at 12 months. Cincinnati knee scores higher in Group I for all measures expect pain. Cincinnati knee scores at 12 months: pain (Group I 9.0±1.1 vs. Group II 8.3±1.6, p = 0.235), swelling (9.0±1.1 vs. 7.6±1.9, p = 0.042), partial giving way (9.2±1.0 vs. 8.0±1.6, p = 0.037), full giving way (9.3±1.0 vs. 8.3±1.5, p = 0.047), symptom average (9.1±0.8 vs. 8.1±1.2, p = 0.021).	“The results of the present study suggest that it is possible to improve knee stability and functional capacity and to decrease the symptoms in ACL-reconstructed patients using hamstring-strengthening exercise during the early phase of rehabilitation. Therefore, we strongly recommend the isokinetic hamstring-strengthening exercises used in this study for patients who have undergone ACL surgery.”	Sports related cohort. Exercises 5 times a week for 4 months. In an athletic group, earlier hamstring exercises as part of a rehab programmed suggested to show beneficial results.

WORK LIMITATIONS

1. Recommendation: Work Limitations for Select Cases of ACL Tears

Work limitations for ACL tears are usually necessary, especially in the acute phase, although required job demands must be incorporated. Severe cases may be unable to perform any work for a few days. Those performing high physical demand tasks or those who cannot avoid repeating physically demanding job tasks similar to those that resulted in the condition are especially recommended to have work limitations.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. Recommendation: Work Limitations for Other Cases of ACL Tears

There is no recommendation for or against work limitations in other cases of ACL tears, particularly where the worker has the ability to modulate work tasks.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

BED REST AND KNEE IMMOBILIZATION

Recommendation: Bed Rest and Knee Immobilization for ACL Tears

Bed rest and knee immobilization are not recommended for ACL tears, although relative rest may be required for most patients.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

NSAIDs

Recommendation: NSAIDs for ACL Tears

Nonsteroidal anti-inflammatory medications are recommended for ACL tears. (See NSAID section for dose, frequency, discontinuation information.)

Strength of Evidence – Recommended, Insufficient Evidence (I)

ICE/HEAT

Recommendation: Ice/Heat for ACL Tears

Ice and/or heat are recommended for ACL tears.

Strength of Evidence – Recommended, Insufficient Evidence (I)

OTHER MODALITIES/INJECTIONS

Recommendation: Other Modalities/Injections for ACL Tears

There is no recommendation for or against therapeutic ultrasound, diathermy, electrical stimulation, iontophoresis, low-level laser therapy, phonophoresis, acupuncture, manipulation and mobilization or manual therapy, autologous blood injections, plasma rich platelet injections, glucocorticosteroid injections, and hyaluronic acid injections.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

There are no quality trials specifically addressing patients with ACL and PCL tears. Work limitations are usually necessary, especially in the acute phase, although required job demands must be incorporated. Those performing high physical demand tasks or those who cannot avoid repeating physically demanding job tasks similar to those that resulted in the condition are especially recommended to have work limitations. In other cases, particularly where the worker has the ability to modulate work tasks, there is no recommendation for or against work limitations. Bed rest and knee immobilization are not recommended due to risks of venous thromboembolisms and other adverse effects of bed rest, although relative rest may be required for most patients. Nonsteroidal anti-inflammatory medications and ice/heat are recommended. There is no recommendation for or against the use of therapeutic ultrasound, diathermy, electrical stimulation, iontophoresis, low-level laser therapy, phonophoresis, acupuncture, manipulation and mobilization or manual therapy, autologous blood injections, plasma-rich platelet injections, glucocorticosteroid injections, or hyaluronic acid injections for treatment of ACL tears.

SURGERY FOR ACL TEARS

Surgery has been utilized for reconstruction of torn ACLs.(1, 581, 1538, 1555, 1557, 1559, 1560, 1562, 1566-1570, 2008, 2009, 2045, 2048, 2072-2107) Recently, studies have documented equivalent success with non-operative management of ACL tears.(2009) The crossover rate to surgery from the non-operative arm was 37% (23 of 59), potentially signaling that significant numbers of patients may still require surgery for successful outcomes from ACL tears. There also are some concerns that meniscal injuries may occur more readily in cruciate deficient knees, and subsequent surgical repairs may be less successful.(2108-2112)

Recommendation: Surgery for ACL Reconstruction

Surgical reconstruction of ACL tears is recommended for treatment of select patients with ACL tears.

Indications – Patients should generally have attempted non-operative treatment that included progressive exercise implemented after the acute phase of swelling, if any, has subsided. Duration of a non-operative treatment plan to determine success or failure is unclear and likely requires individualization. A study evaluated grafting at 2 weeks versus 8 to 12 weeks and reported no significant differences after 52 weeks of follow up.(2113) Most patients who fail non-operative treatment appear to require surgery within 3 months of the ACL tear.(2009) Some patients, particularly those with high demand jobs or high performance athletes, may be candidates for early surgical reconstruction, as they are believed to more frequently fail non-operative rehabilitation.(1, 2113) There is moderate-quality evidence that delay in surgical reconstruction does not impair outcomes,(2009, 2113) thus there is no rush to operate that has been shown in quality studies.

***Strength of Evidence* – Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

There is one moderate-quality trial comparing rehabilitation with surgical reconstruction of ACLs and which found no differences over time intervals up to 2 years.(2009) Four low-quality trials comparing surgical ACL reconstruction with non-operative care have also been published, with one trial suggesting mostly comparable results but more instability in the non-surgical group,(2045) one suggesting fewer subsequent meniscal tears after surgical ACL reconstruction,(2048) one suggesting comparable functional outcomes,(2008) and one suggesting superior stability with surgery.(2109)

There are numerous quality trials comparing different surgical approaches, most commonly a patellar tendon autograft or hamstring tendon autograft (see evidence table). Most RCTs have participants that are actively participating in various levels of sports, which may somewhat limit generalizability, although presumably less active patients may derive comparable benefits.

Patellar tendon autografts have been associated with fewer graft failures and less knee laxity. Hamstring tendon autografts have been associated with less anterior knee pain and less extension deficit.(2114-2116) Use of hamstring autograft compared to patellar reportedly results in less anterior knee pain up to 3 years post-operatively,(2117-2122) and other studies reported no differences up to 7 years post-operatively.(2114, 2123-2126)

Different hamstring autograft techniques have been used. There are studies evaluating the double-bundle technique versus the single-bundle technique.(378, 2127-2132) The argument for the more technically demanding anatomic double-bundle technique is that the results are more anatomical compared to the single-bundle technique.(2115, 2133, 2134) Two moderate-quality studies comparing hamstring autograft double-bundle to single-bundle techniques reported superior anterior and rotational stability, but no subjective difference.(2115, 2133) One study evaluated the double bundle hamstring autograft done with 4 strands versus 8, and reported superior outcomes in terms of laxity and subjective results in the 8-strand double-bundle group.(2134) There is no clear evidence supporting one surgical treatment over another; thus there is no recommendation regarding specific autologous tendon harvest sites or surgical techniques.

Thus, currently available quality evidence suggests autologous grafting may be superior to prosthetics or allografts,(2135-2138) although individual patient factors should be considered. This precludes a formal recommendation for or against prosthetics and allografts. Surgical

reconstruction is invasive, has adverse effects, and is highly costly, but appears necessary for selected patients and is thus recommended.

Evidence for Surgery for ACL Tears

There are 3 high- and 50 moderate-quality RCTs incorporated into this analysis. There are 19 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Rehabilitation vs. ACL Surgical Reconstruction						
Frobell 2010 RCT	6.5	N = 141 age 18-35 presenting to ER with rotational knee trauma in prior 4 weeks, Tegner Activity Scale scores 5-9 pre-injury (equivalent to participation in recreational sports to competitive non-professional sports); all received MRI (excluded total collateral ligament or full-thickness cartilage tears.	Immediate ACL repair (patellar tendon or hamstring tendon) and Rehabilitation vs. Rehabilitation with option for delayed surgical repair. 2 year follow-up.	See figure above for Knee Injury and Osteoarthritis Outcome Scores (KOOS) by time intervals. At 2 years, no differences in KOOS scores (total KOOS AUC immediate surgery 1638±406 vs. 1662±349, p = 1.0), SF36, Tegner Activity scores, or percent returning to prior activity level or higher (44% surgical vs. 36% rehab, p = 0.37). Weak trend towards more treatment failures at 2 years in non-operative group, [severely decreased knee-related quality of life in 11/62 (18%) vs. 16/59 (27%) p = 0.22]. Adverse events differed between groups. Instability more common in non-operated knees (19/59 vs. 2/62) and meniscal signs/symptoms (13/59 vs. 1/62). Somewhat more pain/swelling (6/62 vs. 3/59) and decreased ROM (4/62 vs. 1/59) in operated group.	“In young, active adults with acute ACL tears, a strategy of rehabilitation plus early ACL reconstruction was not superior to a strategy of rehabilitations plus optional delayed ACL reconstruction.”	Some baseline differences of uncertain significance. No blinded assessor. Co-interventions not well controlled and compliance with rehabilitation program unclear, which may have biased against rehabilitation. Data suggest 61.0% of ACL tears in young active patients may be successfully rehabilitated without surgery. Data suggest delayed surgical group with comparable outcomes to early surgical group.
ACL Reconstruction						

Muneta 2007 RCT	5.0	N = 68 with unilateral ACL injury	Single-bundle reconstruction group (n = 34) vs. double-bundle reconstruction group (n = 34), with mean follow-up periods of 25.4 months (range, 18 to 41 months) and 25.2 months (range, 18 to 40 months), respectively.	No significant differences between 2 groups with regard to ROM, thigh girth, muscle strength, and Lysholm score.	“This randomized controlled trial indicated that DB ACL reconstruction via 4-strand ST is superior to the SB technique with regard to anterior and rotational stability; however, it fails to show any subjective difference.”	Differences in menisci surgery between groups; 1 surgeon. Assessor blinded. After 1st year, follow-up appointment ranged differently between groups. No mention of co-interventions other than post-op rehab. Both groups used 4-strand hamstring tendon. Double bundle reported greater stability.
Rigid Fix vs. Bioscrew						
Harilainen 2009 RCT	8.5	N = 120 with a fresh or chronic ACL injury	Group 1: femoral Rigidfix cross-pins and a tibial expansion sheath and a tapered expansion screw (Intrafix, n = 30) vs. Group 2: femoral Rigidfix and tibial interference screw fixation (BioScrew, n = 30) vs. Group 3: femoral BioScrew and tibial Intrafix fixation (n = 30) vs. Group 4: BioScrew Fixation into both tunnels (n = 30). Assessments were at baseline, 1 and 2 years after treatment.	No significant difference in ROM, clinical stability, Tegner activity level, Lysholm knee score, IKDC score, Kujala patellofemoral score, at 1 and 2 years. Pre-op, significant difference in isokinetic peak muscle torque with Group 3 and Group 4 having a higher 180 deg/s flexion torque (p = 0.0316)	“There was no statistically or clinically relevant difference in the results 1 or 2 years postoperatively, and all 4 techniques improved patient function. It is important to evaluate the performance of the new fixation methods in prospective randomized studies comparing them with standard methods.”	No mention of what groups were compared for pre-op isokinetic peak muscle torque; 2 surgeons. Baseline differences present in outcome variables between groups. Patients and PT's were blinded. Overall no significant differences found.
Anderson 2001 RCT	4.0	N = 267 with unilateral ACL tears	Group 1: intra-articular ACL reconstruction using an autologous bone-patellar tendon bone graft (n = 35) vs. Group 2: intra-articular ACL reconstructions with semitendinous and gracilis tendon autografts combined with a Losee extraarticular iliotibial band tendesis (n = 35) vs. Group 3: intra-articular ACL	No significant difference in ROM, incidence of patellofemoral creptitation, mean quadriceps/hamstring muscle strength, roentgenographic evaluation between groups. Group 1 significantly better than Group 3 (1: 2.1±2.0mm, 3: 3.1±2. mm, p < 0.05). Pathologic Laxity: Group 1 significantly less than Group 3 (p < 0.05). Final IKDC Rating: Group 1 more incidences normal or near normal results	“In summary, ACL reconstruction with a semitendinosus and gracilis tendon autograft or a patellar tendon autograft yields similar patient-reported outcomes, although the patellar tendon autograft may provide better objective stability at a minimum follow-up of 2 years. In addition, there appears to be no benefit to combining an intraarticular ACL reconstruction with an extraarticular	Most injuries were from sports. No blinding. Co-interventions not well described. Subjectively both procedures are similar. Objectively patellar tendon has less laxity. Data suggest overall good results despite tendon harvest site.

			reconstructions with semitendinosus and gracilis tendon autografts without an extraarticular procedure (n = 35). Assessments at minimum 24 months post-treatment.	than Group 2 and 3 (1: 34, 2: 23, 3: 24, p = 0.02).	iliotibial band tenodesis."	
EndoFix Screw vs. Metal Screw						
Benedetto 2000 RCT	5.5	N = 124 with unilateral ACL repair, age 15-50	Endo-Fix screw (n = 67) vs. Control (metal) screw (n = 57).	No significant differences between groups with respect to any of IKDC problem areas at 1 year. IKDC final evaluation normal or nearly normal in 92% of polyglyconate patients, 90% of controls.	"This study shows that the polyglyconate screw is an effective alternative to metal in endoscopic reconstruction of the ACL."	Five different sites used. Randomization was for screw on femoral side. On tibial side some of each group had metal screws/staple. No differences noted.
EndoPearl and Bioscrew vs. Bioscrew						
Arneja 2004 RCT	5.0	N = 35 with ACL insufficiency who chose to proceed with ACL reconstruction	Patients were divided equally into 2 groups: (n = 18) Study group (EndoPearl and Bioscrew) vs. (n = 17) Control group (Bioscrew). Patients analyzed pre-op, 3, 6, and 18 months.	Statistically significant differences (2-tailed student's t-test).	"The application of the EndoPearl in conjunction with a bioscrew in the femoral tunnel in autogenous ACL reconstruction using semitendinosus and gracilis tendon grafts provides a significantly decreased laxity up to 18 months postoperatively in terms of KT-1000 side-to-side differences."	Two surgeons. Both groups had stability and confidence in their knee at 18 months. While there was objective difference reported, no functional difference found.
Double Bundle vs. Single Bundle						
Sastre 2010 RCT	7.0	N = 40 with initial ACL injury to surgery time ≤ 2 years, no previous surgery	Single-bundle group (SB, n = 20) vs. double-bundle group (DB, n = 20). Follow up of no less than 1 year.	No significant differences pre-op subjective IKDC score. Post-op, no significant differences in IKDC score or pivot shift test.	"Both the SB and DB techniques showed excellent results in the IKDC objective and subjective test, with no significant differences between the two groups of patients."	All done by single surgeon. No differences reported between groups.
Järvelä 2008 RCT	6.0	N = 60 (17 females, 43 males) with an ACL injury diagnosed by clinical exam and MRI	Double-bundle technique with bioabsorbable screw fixation (DB group, n = 35) vs. single-bundle technique with bioabsorbable screw fixation (SB group, n = 25).	No significant differences in tunnel enlargement of femoral side found between groups. Tunnel enlargement for tibial side significantly less for DP group than SB group (DP: 2.6±1.2mm, SB: 3.4±1.6mm, p = 0.051). At 27 month assessment, no significant difference between groups in	"This prospective, randomized study showed that our double-bundle ACL reconstruction technique results in less tunnel enlargement in each tunnel on the tibial side than the single-bundle technique with similar fixation methods, graft material, and rehabilitation."	Baseline characteristics had significant differences in age and operative time. No subjective or clinical difference reported.

				IKDC score, Lysholm score, and rotational stability.		
Kanaya 2009 RCT	6.0	N = 26 with antero-posterior (AP) laxity of knee from ACL tear.	Single-bundle ACL reconstruction (SB group, n = 13) vs. double-bundle ACL reconstruction (DB group, n = 13).	AP displacement not significant. Range of tibial ROM not significant.	"This study showed that a lower tunnel place single-bundle reconstruction reproduced AP and rotational stability as well as double-bundle reconstruction after reconstruction, intraoperatively."	One surgeon did all surgeries. Assessment done intra-operatively. No clinical outcomes measured. No differences reported.
Streich 2008 RCT	5.5	N = 50 males needing ACL reconstruction surgery without a previous surgery in same knee	Four-stranded single-bundle reconstruction with ST graft (SB, n = 25) vs. 2-stranded ST graft with double-bundle, 4-tunnel technique (DB, n = 24). Follow-up at 2 years post op.	Two-year follow-up: no significant difference in side-to-side anterior laxity-measurement with KT-1000, Pivot Shift test, ROM, IKDC subjective, Lysholm score, and Tegner activity score.	"On basis of our investigation, we conclude that the reconstruction of the ACL by a double-bundle ST graft with an extracortical anchorage, can achieve excellent clinical results. But in contrast to our initial hypothesis, we could not quote any significant advantages by creating two independent bundles."	One surgeon. Assessor blinded. Male athletes only. No differences reported.
Siebold 2008 RCT	5.0	N = 70 with ACL ruptures without additional knee ligament injuries, no previous knee ligament surgeries or no arthritic changes	Arthroscopic 4-tunnel double-bundle ACL reconstruction (DB, n = 35) vs. single-bundle ACL reconstruction with autologous hamstrings (SB, n = 35).	Objective IKDC 2000: DB (Normal = 79%, Nearly Normal = 21%, Abnormal = 0%, Severely Abnormal = 3%) vs. SB (Normal = 25%, Nearly Normal = 69%, Abnormal = 6%, Severely Abnormal = 0%) [p < 0.000, χ^2 -squared test]. KT-1000 side-to-side difference: not significant. Pivot Test: DB (97% neg., 3% 1+) vs. SB (70% neg., 0% 1+) [p = 0.01]. ROM, Subjective IKDC 2000, Cincinnati knee score, Lysholm score: all not significant.	"Our study shows a significant advantage in anterior and rotational stability as well as objective IKDC for four-tunnel DB ACL reconstruction compared to SB ACL reconstruction. The subjective Cincinnati knee score, the Lysholm score, and the subjective IKDC 2000 did not show any statistical difference for one or the other technique."	One surgeon. Assessor blinded to status but patients were not. Double bundle technique reported better anterior and rotational stability objective IKDC score.
Metal Inference Screws vs. Absorbable Screws						
Myers 2008 RCT	7.0	N = 100 awaiting ACL reconstruction	Titanium interference screws (Titanium, n = 50) vs. bioabsorbable interference screws (HA-PLLA, n = 50). Assessments at 2, 6, 12, and 24 months post-op.	IKDC: not significant at any time. Lysholm Score: not significant at any time. Pivot shift test: not significant at any time. Middle femoral tunnel measurement was different in 2 groups, with HA-PLLA being wider in both anteroposterior (p < 0.05) and lateral (p <	"Our study has convincingly demonstrated the success of identically shaped bioabsorbable and titanium interference screws using hamstring autograft for ACL reconstruction up to 2 years. The shape of the RCI screws worked very successfully in our	Screws of identical dimensions. Similar tourniquet time and tunnel diameter at surgery. No differences in clinical outcomes reported.

				0.003) films (no data given, just graphs).	series in providing graft-tunnel fixation."	
Moisala 2008 RCT	5.0	N = 62 who met criteria of primary ACL reconstruction, closed growth plates, absence of injury in contralateral knee	Bioabsorbable screw fixation (B-Group, n = 31) vs. metal screw fixation (M-Group, n = 31). Follow-up minimum 2 years (range: 24-36 months).	Femur AP diameter: B-Group vs. M-Group (10.9±2.0 vs. 9.2±1.9, p = 0.01). IDKC: not significant. Lachman test: not significant. KT-1000 (6mm side to side difference): not significant.	"In conclusion, the use of bioabsorbable screws resulted in more AP femoral tunnel widening, which did not correlate with the clinical outcome at 2-year follow-up. The AP tibial tunnel diameter was smaller when the arthrometric knee laxity was normal compared to abnormal. There were more graft failures in the bioabsorbable screw group compared to the metal group."	Three surgeons performed procedures. Blinding of assessors. Metal screws had less graft failure & tunnel widening. No mention of any need to remove metal screws.
Drogset 2006 RCT	4.5	N = 41 (22 females, 19 males) with isolated ACL-deficient knees or ACL rupture with minor meniscal lesions and cartilage lesions	Metal interference screws (n = 20) vs. biologic resorbable PLLA screws (n = 21). Assessments pre-op, 6 weeks, and 1 year after operation.	No significant difference in knee function or any measured parameter pre-op in groups. No significant difference in C5a and TCC during follow-ups.	"In the present study, no difference was observed between the 2 groups in terms of in vitro C5a generation when a metal screw or BioScrew was incubated in serum... No statistical significant difference was observed between the BioScrew and metal screw groups concern C5a, TCC, and IL-8 formation. Therefore, in this study, we have not been able to demonstrate a general bioincompatibility of the materials used. However, some patients in the BioScrew group showed elevated levels."	Inflammatory parameters evaluated, but no anti-inflammatory use measured between or within groups. No blinding. No significant differences reported.
Patellar Tendon Graft vs. Hamstring Graft						
Webster 2001 RCT	5.0	N = 61 (43 males, 18 females) with an ACL rupture that occurred more than 3 weeks and less than 12 months prior	Hamstring graft (n = 33) vs. patellar graft (n = 28). Assessments at 4 months, 1 and 2 years post-surgery.	Radiographic tunnel widths: Anteroposterior View: Hamstring vs. Patellar (4 months: 49.5±19.8 vs. 16.2±17.4, p <0.0001; 1 year: 47.9±18.8 vs. 15.8±21.1, p < 0.0001; 2 years: 47.4±18.3, 15.6 ±17.4, p <0.0001); Lateral view: hamstring vs. patellar (4 months: 42.8±18.5 vs. 11.3±23.9, p < 0.0001; 1 year: 36.3±18.6 vs. 11.9±22.4, p < 0.001; 2 year: 35.9±16.3 vs. 10.5±26.6,	"In this study femoral bone tunnel enlargement following ACL reconstruction was shown to be more frequent and greater with hamstring grafts than in patellar tendon grafts."	No blinding. No mention of co-interventions after rehabilitation. No clinical correlates given with the results.

				p < 0.001). KT-1000 side to side difference (Average [range]) - 15 lbs: Hamstring vs. Patellar (1.4 [0 to 3.5] vs. 0.7 [-1 to 2.5], p < 0.01). Extension deficit (mean [range] - in degrees): Hamstring vs. Patellar (-1.7 [-8 to 0] vs. -3.1 [-9 to 0], p < 0.05).		
Patellar Tendon vs. Semitendinosus/Gracilis vs. Semitendinosus						
Carter 1999 RCT	4.0	N = 120 scheduled for ACL reconstruction	(n = 38) Patellar tendon (PT) vs. (n = 33) semitendinosus (ST) vs. (n = 35) vs. semitendinosus/Gracilis (ST/G). Hamstring and quadriceps isokinetic strength assessed at 180°/second and 300°/second with results of operatively treated leg expressed as a percent vs. non-operative leg.	Mean results for knee extension at 180°/sec: 68.3%, 74.3%, 78.1%; and at 300°/sec: 70.7%, 76.7%, 81.7% for PT, ST, ST/G, respectively. Mean results for knee flexion at 180°/sec: 86.1%, 80.6%, 81.7%; and at 300°/sec: 77.6%, 79.1%, 75.6% for PT, ST, ST/G, respectively. No statistically significant differences in regard to knee extension or flexion strength when evaluating different tissue sources.	"[N]o evidence was found in regard to leg strength as a basis for selecting either PT, ST, or ST/G tendons as the optimal graft."	One surgeon for all patients. Workers' comp excluded. Many more competitive athletes in patellar tendon group. Performed meniscal repair on some patients. Different number of PT visits between patients. No differences reported.
4-strand vs. 8-strand Hamstring Graft						
Zhao 2007 RCT	4.5	N = 76 (44 males, 32 females) with chronic ACL rupture	Double-bundle ACL reconstruction via 4-strand hamstring graft (4SHG, n = 38) vs. 8-strand hamstring graft (8SHG, n = 38). Follow-up for more than 2 years.	Laxity: 4SHG (2.8±0.5mm) vs. 8SHG (1.3±0.4mm) [p = 0.0003]. IKDC Score: 4SHG (86.4±4.2mm) vs. 8SHG (96.3±2.8mm) [p = 0.007]. Lysholm Score: 4SHG (89.6±3.7mm) vs. 8SHG (96.5±2.9mm) [p = 0.0006]. Tegner Score: 4SHG (5.9±1.2mm) vs. 8SHG (6.7±0.8mm) [p = 0.002]. Side-to-side difference according to KT-1000, <3 mm: 4SHG (25) vs. 8SHG (33) [p = 0.004].	"On the basis of KT-1000 examination and clinical measures, double-bundle ACL reconstruction with 8SHG yields significantly better results than double-bundle ACL reconstruction with 4SHG, with a mean side-to-side difference in anterior knee laxity of 1.3 ± 0.4 mm versus 2.8 ± 0.5 mm (p = .0003), IKDC subjective result of 96.3 ± 2.8 mm versus 86.4 ± 4.2 mm (p = .0007), and Lysholm score of 96.5 ± 2.9 mm versus 89.6 ± 3.7 mm (p = .0006)."	No blinding done. Similar past. Operative rehab program. Randomized by odd/even MRNs. The 4-strand performed worse than 8-strand. No mention at any adverse events.
BTB vs. ST Grafts						
Eriksson 2001 RCT	4.5	N = 107 (69 males, 38 females) with anterior cruciate ligament	ACL reconstruction with BTB graft (BTB, n = 50) vs. ACL reconstruction	No significant differences pre-op. Lachman test (0,+1): BTB vs. ST (0 = 36, +1 = 6 vs. 0 = 28, +1 = 19; p < 0.05). One Leg Hop	"In summary, there is a difference in one-leg hop performance, indication that ST affects the quadriceps muscle	Follow-up period ranged from 20-35 weeks. No blinding. At 6 months either

		insufficiency with trauma lasting at least 2 months	with ST graft (ST, n = 57). Assessments 6 months after surgery.	(≥90%,89-76%,75-50%,<50%): BTB vs. ST (≥90% = 6,89-76% = 18,75-50% = 3, <50% = 1 vs. ≥90% = 21,89-76% = 8,75-50% = 4,<50% = 1; p < 0.01). No other variables significantly different.	strength or proprioception less than BTB in the early postoperative period.”	technique had similar outcomes.
Bone-Patellar Tendon-Bone Graft vs. 4-strand Hamstring Tendon vs. 2-strand Hamstring Graft						
Yasuda 2006 RCT	5.0	N = 72 (42 males, 30 females) consecutive patients with chronic ACL deficiency in unilateral knee	Group S: Single-bundle ACL reconstruction using a 6-strand hamstring tendon graft (n = 24) vs. Group N-AD: nonanatomic double-blind reconstruction using 4-strand and 2-strand hamstring tendon grafts (n = 24) vs. Group AD: anatomic double-blind reconstruction using 4-strand and 2-strand hamstring tendon grafts (n = 24). Assessments before surgery and 2 years after.	Side to Side Anterior Laxity: Group S (2.8 ± 1.9 mm) vs. Group N-AD (2.2 ± 1.5) vs. Group AD (1.1 ± 0.9) [ANOVA: p = 0.006, χ-squared: p = 0.049]. Significant difference between Group S and Group AD (p = 0.002). Pivot-Shift Test: Group S (+: 9, ++: 3) vs. Group AD (+: 3, ++: 0) [χ-squared: p = 0.025]. No significant difference between groups in KT-2000 measurement, post-op loss of motion, and torque values.	“On the basis of the KT-2000 measurement, the side-to-side anterior laxity of our anatomic double-bundle ACL reconstruction was significantly better than that of the single-bundle reconstruction with the hamstring tendon graft, although there were no significant differences in the other clinical measure among any of the 3 procedures.”	One surgeon performed all operations. They performed surgery on injured meniscus. All either recreational or competitive athletes before injury. One area was reported superior, but all patients were able to return to their spots by 12 months.
Bone-Patellar Tendon-Bone Autograft vs. Irradiated Allograft						
Sun 2009 RCT	4.5	N = 68 with acute or chronic ACL ruptures (2 found to be ineligible after arthroscopy, 1 lost to follow-up, of remaining 65, 46 males, 19 females)	BPTB autograft group (Auto group, n = 34) vs. Irradiated autograft group (Ir-Auto group, n = 34). Assessments pre and post-op (mean post-op follow-up at 31 months).	Post-op: overall IKDC: No significant difference between groups. Subjective IKDC, Cincinnati knee score, Lysholm score, Tegner score: all no significant difference.	“The short term clinical outcomes of the ACL reconstruction with irradiated BPTB allograft were adversely affected. The less than satisfactory results led the senior authors to discontinue the use of irradiated BPTB allograft in ACL surgery and not to advocate the use of gamma irradiation as a secondary sterilized method. Further research into alternatives to gamma irradiation is needed.”	Data suggest irradiated autografts inferior.

Sun 2009 RCT	4.0	N = 102 with acute or chronic ACL ruptures	Bone-patellar tendon-bone autograph (Auto Group, n = 33) vs. Irradiated allograft (Ir-Allo group, n = 34) vs. non-irradiated allograft (non-Ir-Allo, n = 32).	No significant better rating for overall IKDC rating between groups. Auto vs. Non-Ir-Allo not significant. Side to side difference: Auto (2.4±0.6) vs. Ir-Allo (5.5±3.6) [p <0.05], Non-Ir-Allo (2.6±0.9) vs. Ir-Allo (5.5±3.6) [p <0.05], auto vs. non-Ir-Allo not significant.	“Patient undergoing ACL reconstruction with non-irradiated BPTB allograft or autograft had similar clinical outcomes. Non-irradiated BPTB allograft is a reasonable alternative to autograft for ACL reconstruction. While the short term clinical outcomes of the ACL reconstruction with irradiated BPTB allograft were adversely affected.”	Same surgical technique used. No blinding. Irradiation of allografted resulted in poorer clinical and functional outcome.
BPTB Autograft vs. BPTB Allograft						
Sun 2009 RCT	5.5	N = 172 who needed primary unilateral reconstruction of ACL in contralateral knee	BPTB autograft group (n = 86) vs. BPTB allograft group (n = 86). Mean follow-up post surgery 5.6 years.	Objective IKDC: not significant. ROM: not significant. Harner's Vertical Jump: not significant. Daniel's 1-leg hop test: not significant. Anterior Tibial Displacement: not significant. Subjective IKDC: not significant. Lysholm score: not significant. Tegner score: not significant. Cincinnati score: not significant.	“Both groups of patients achieved almost the same satisfactory outcomes after a mean of 5.6 years of follow-up. Allograft is a reasonable alternative to autograft for ACL reconstruction.”	Randomization process unclear. Data suggest comparable outcome.
Patellar Tendon Graft vs. Leeds-Keio Graft						
Engström 1993 RCT	4.0	N = 60 (35 males, 25 females) with unilateral chronic ACL ruptures	Patellar Tendon Graft (PT, n = 30) vs. Leeds-Keio Graft (LK, n = 30).	Laxity Test (Negative = N, Glide = GI, Positive = P, Gross = Gr): PT vs. LK (N = 20, GI = 5, P = 1, Gr = 0 vs. N = 5, GI = 9, P = 14, Gr = 1; p < 0.001). Lysholm score, IKDC, Tegner Activity Level: all not significant.	“Despite the fact that the period of observation was only intermediate, the Leeds-Keio ligament did not fulfill the requirements for a satisfactory result in ACL reconstructive surgery with regard to knee joint stability.”	Treated medial meniscus tears at surgery if present. No blinding. Different surgical techniques also evaluated: arthroplasty vs. arthroscopy. Complication interpretation.
Bone-Patellar Tendon-Bone Graft vs. Quadricep Tendon Graft						
Petruskevicius 2002 RCT	4.5	N = 20 (10 males, 10 females) who had total ACL lesion suitable for reconstruction with bone-patella tendon-bone graft	Osteoset group (n = 10) vs. control Group (n = 10). Assessments at 6 weeks, 3 and 6 months. (Osteoset manufacturing process creates uniform crystalline structure with results in controlled resorption rate said to be similar to that of a new bone formation.)	No significant difference found in new bone formation between groups.	“[T]he Osteoset resorption rate seems too rapid for bone formation in humans even during optimal conditions with no micromovement. Nadkarni et al. (2000) reported better bone formation on calcium sulfate composites augmented with calcium phosphate, which reduced the resorption rate. Bone substitutes with less rapid resorption than	Lack of details for baseline characteristics, blinding and co-interventions lowered score. No differences noted, yet increased cost for Osteoset. Use not supported.

					Osteoset may be better in men.”	
Pigozzi 2004 RCT	4.0	N = 48 (12 females, 36 males) who needed ACL reconstruction	ACL reconstruction with patellar tendon bone graft (patellar, n = 48) vs. ACL reconstruction with quadriceps tendon graft (quadriceps, n = 24). Assessments 6 months after surgery.	Counter Movement Jump: Patellar vs. Quadriceps (24±3.2% vs. 11.4±1.8%, p <0.01). Leg press 3 reps: quadriceps vs. patellar (peak torque: 8.4±2.1 vs. 15.2±3.4, p <0.05, total work: 8.9±2.4 vs. 14.4±4.1, p <0.05). Leg press 12 repetitions: not significant. Knee extensions 3 reps: quadriceps vs. patellar (peak torque: 17.6±3.5 vs. 30.3±5.1, p <0.05, Total Work: 16.5±2.9 vs. 26.4±4.5, p < 0.05) [Analogous significance found with Knee Extension 12 reps (no data given)]. Knee flexion 3 reps: quadriceps vs. patellar (peak torque: 8.6±2.4 vs. 14.1±3.1, p < 0.05, Total Work: 9.4±2.8 vs. 11.6±2.1, p <0.05). A similar difference (p < 0.05, no data given) found between knee flexion 12 reps. Anterior-posterior knee laxity: NS.	“Our data showed a significant improvement of the lower limb strength deficit using quadriceps tendon as a graft. There are many possible explanations for this evidence other than graft type like stiffness, giving way, swelling, patello-femoral symptoms, proprioceptive deficits, but these data are difficult to evaluate at the 6th month mark. Moreover donor site problems after patellar tendon harvest are well-documented.”	Single surgeon. All competitive athletes (soccer). No mention of dropout rate. Quadriceps tendon graft was reported to have better strength. All patients recovered well despite group allocation.
Patellar Tendon Graft vs. Hamstring Graft						
Feller 2001 RCT	6.0	N = 65 (18 females, 47 males) undergoing primary ACL reconstruction.	Patellar tendon graft (PT, n = 31) vs. hamstring graft (HS, n = 34). Assessments at 2 weeks, 8 weeks, and 4 months post-op.	Location of General Pain: Anterior (%): 2 weeks, HS (51%) vs. PT (87%), p <0.01; not significant at 8 weeks or 4 months), Posterior (%): not significant at any time assessment. Anterior Knee Pain (Yes %): at 2 weeks, HS (68%) vs. PT (97%); p <0.01; not significant at 8 weeks	“We observed less morbidity with the HS graft, primarily due to pain measurements rather than range of motion or strength variables. However, the severity of reported pain was relatively low in both groups, and the differences between the groups did not	All done by the same surgeon. Same post-op rehabilitation protocol but compliance for rehabilitation was not addressed. By 4 months the groups were similar although there was evidence that the

				<p>or 4 months. Pain on Kneeling (Yes %): 4 months - HS (62%) vs. PT (90%), $p < 0.05$. Severity of General Pain (median): 4 months - HS (2.0) vs. PT (4.0), $p < 0.01$; not significant at any other time. Severity anterior knee pain (mean +/- sd): 2 weeks - HS (3.7 +/- 2.3) vs. PT (5.2 +/- 2.7), $p < 0.05$; not significant at any other time. Severity pain on kneeling, extension deficit, active flexion deficit, passive flexion deficit, effusion, all not significant at any time. Quadricep deficit at 240°/s (mean +/- sd): HS (21.6 +/- 23.3) vs. PT (33.1 +/- 16.8), $p < 0.05$. Quadricep deficit at 60°/s and hamstring deficit at 60 and 240°/s not significant. KT-1000 15 pounds (mean +/- sd): HS (1.2 +/- 1.1) vs. PT (0.5 +/- 1.1), $p < 0.05$. KT-1000 30 pounds: not significant. IKDC category (Normal, Nearly Normal, Abnormal, Severely Abnormal): HS (0, 15, 35, 50) vs. PT (0, 3, 19, 78), $p < 0.05$. Sports Activity Level (L1, L2, L3, L4): HS (24, 35, 9, 32) vs. PT (42, 45, 3, 10), $p < 0.05$.</p>	<p>appear to be of great clinical relevance since the use of PT grafts associated with an increased sports activity level after 4 months postoperatively. As has been previously established, the longer term functional outcome of the two graft types is similar. From an early postoperative point of view, and perhaps contrary to popular assumptions, there also does not appear to be much evidence to indicate that one graft type is preferable to the other.”</p>	<p>PT group had more pain throughout rehab and generally less strength, but more sport activity at 4 months.</p>
TransFix Screws vs. Bioscrew						
Rose 2006 RCT	4.5	N = 68 (42 males, 26 females) with acute or chronic anterior instability of knee joint	ACL reconstruction with Transfix (TF group, n = 38) vs. ACL reconstruction with Bioscrew (BS group, n = 30). Assessments at 3, 6, and 12 months post-op.	Time for procedure, and time in hospital: not significant. Knee Joint Laxity not significant at any time. Femoral Tunnel Placement: not significant at any time. Knee Joint Mobility: not significant at any time. IKDC rating: not significant at any time. Average OAK-scores: not significant at any time. Lysholm score: not significant at any time. Similar sport level after 12 months not significant.	“In conclusion, this is the first prospective randomized clinical outcome study about the bioresorbable trasfixation technique for ACL-reconstruction using hamstrings. We disproved our hypothesis that the ACL-reconstruction using the transfixation device at the femoral side leads to less knee laxity and therefore to a better clinical outcome for the patient. The clinical	Same surgeon for all surgeries. All active is sport including professional athlete. Either technique gave similar results.

					results in this study clarified that this technique is an effective and safe method for femoral hamstring fixation in ACL-reconstruction.”	
Bioabsorbable Screws vs. Titanium Screw						
Fink 2000 RCT	4.5	N = 40 (11 females, 29 males) who underwent endoscopic ACL reconstruction	Group A: femoral bone block fixation with bioabsorbable interference screw and tibial bone block fixation with titanium screw (n = 20) vs. Group B: fixation of both femoral and tibial bone blocks with titanium interference screws (n = 20). Assessments were at 3, 6, 12, and 24 months.	Lysholm, Tegner, and IKDC scores, as well as instrumented laxity measurements did not show any significant differences between groups at any time period.	“In our study, polyglyconate interference screw fixation for patellar tendon grafts has not been found to be associated with increased clinical complications or major bony reactions. It provided equivalent fixation and clinical results compared with titanium screws.”	No mention of blinding or co-interventions other than post-operative rehabilitation. Only 17/40 had CT scans done at 24-months. No differences noted in this study.
TransFix vs. Metal interface Screw						
Harilainen 2005 RCT	9.0	N = 62 with fresh or chronic ACL tear age 15-56	Patients randomized into either TransFix cross-pin (Arthrex, Naples, FL) (TransFix group, n = 31) or metal interference screw femoral fixation (screw group, n = 31) in ACL reconstruction with hamstring tendons.	No difference between groups with respect to ROM at 1- or 2-year follow-up. No statistical differences between groups with respect to clinical stability evaluation either post-op or at 1- or 2-year follow-up. No differences between groups in 1- or 2-year follow-up exams with respect to Tenger activity level. No differences between groups in the pre-op IKDC Classification.	“There were no statistically or clinically relevant differences in the results 1 or 2 years postoperatively and both techniques seemed to improve patients’ performance.”	No differences between groups reported. No mention of adverse events.
Bone-Patellar Tendon-Bone Autograft vs. 4-strand Hamstring Autograft						

Pinczewski 2007 RCT	4.5	N = 180 (95 males, 85 females) with endoscopic ACL reconstruction with either patellar tendon or hamstring tendon autograft	Bone-patellar tendon-bone autograph (PT, n = 90) vs. 4-Strand semitendinosus and gracilis hamstring autograph (HT, n = 90). Assessments were 1, 2, 3, 4, 5, 7, and 10 years after surgery.	Data reported of HT vs. PT, ACL graft rupture rate not different. Contralateral ACL Injury - Mean Time to Injury: 32 months vs. 59 months, p = 0.02; Number of Injuries: 9 vs. 20, p = 0.02. Complications and further surgery at 10 years. Strenuous activity without pain: 57/74 vs. 45/75, p = 0.05. Strenuous activity without pain at 10 years: not significant. Lysholm score NS. Activity level after 10 years NS. Harvest Site Symptoms (Scale for variable: A = no tenderness, irritation, or numbness, B = mild, C = moderate, D = severe): (A = 70, B = 4, C = 0, D = 0) vs. (A = 49, B = 22, C = 3, D = 1), p = 0.001. Kneeling pain: At all time periods PT < HT, p < 0.01. Side to Side difference of <3 mm: at 2 years - 69 vs. 90, p = .004; NS at any other time. Overall IKDC, Lachman, Pivot shift, single-Legged Hop Test, ROM not different. "Ideal" Outcome: 69% vs. 47%, p = 0.03.	"Both HT and PT autograft ACL reconstructions have excellent 10-year results in knees without significant chondral or meniscal injury. The incidence of mild radiographic osteoarthritis in PT-reconstructed knees is greater at 10 years and appears to be gradually increasing in knees with both graft types. Kneeling pain is greater in PT-reconstructed knees. Ten-year survivorship and subjective function is no difference between graft types. Factors associated with the best outcomes in the study were the use of HT grafts, 2-year KT-1000 arthrometer scores <3 mm, and no need for subsequent surgery on the operative knee."	Single surgeon. Follow-up for 10 years. Both groups recovered well with PT group reported to have more graft site discomfort.
Tourniquet during Surgery vs. No Tourniquet during Surgery						
Nicholas 2001 RCT	4.0	N = 48 with an ACL tear	Tourniquet during surgery (T, n = 25) vs. no tourniquet during surgery (NT, n = 23). Assessments 2 weeks before surgery, 3 weeks, and 6 months after surgery.	Strength loss not significant at any time. Girth measurements (median cm [range]): T vs. NT (6 months: 2.5 [1.3 to 3.7] vs. 1.1 [0.4 to 1.8], p < 0.05; all other times not significant).	"The results of this prospective randomized study show that tourniquet compression around proximal neural structures does not affect lower extremity strength following ACL reconstruction."	Lack of details lowered score. Tourniquet use had no reported adverse events or benefits. No evaluation of duration of surgery presented.
Early vs. Delayed ACL Reconstruction						
Meighan 2003 RCT	6.0	N = 31 with acute ACL tears, athletic background	Early reconstruction [within 2 weeks of randomization] (Group 1, n = 13) vs. delayed reconstruction [between 8 to 12 weeks] (Group 2, n = 18). Assessments before operation, 2, 6, 12, 24, and 52 weeks.	ROM [in degrees]: Group 1 vs. Group 2 (2 weeks: 11 to 76 vs. 8 to 93, p < 0.05; not significant at any other time). Muscle Function - Work: Group 1 vs. Group 2 (12 weeks: 36 vs. 22, p = 0.05; not significant at any other time); Power: Group 1 vs. Group 2 (12 weeks: 36 vs. 23, p < 0.05; not significant at any other	"We therefore conclude that there is no advantage in early reconstruction for isolated tears of the ACL and that this is associated with an increased rate of complications. Delayed surgery is associated with a more rapid return of movement and muscle function. In addition, a	All patients active in sports. Early vs. late had similar outcomes at 52 weeks. Late had higher strength at 12 weeks, lack of detail lowered score.

				time). Torque, IKDC, Tegner Score: all not significant.	delay in surgical intervention allows the surgeon time to assess more carefully a patient's suitability for reconstruction of the ACL."	
Endoscopic vs. Transcondylar Technique						
Mariani 2001 RCT	8.0	N = 55 undergoing ACL reconstruction	Endoscopic Technique (Group A, n = 24) vs. Transcondylar Technique (Group B, n = 31).	Pre-op: not significant. Activity level: not significant. KT-2000 Maximum Manual Side-to-Side Measurement: Group A vs. Group B (3.68±1.71 vs. 1.64±2.05, p <0.0001). KT-2000 Maximum Manual Absolute Measurement: Group A vs. Group B (12.25±2.92 vs. 9.7±3.1, p = 0.003).	"In conclusion, the transcondylar screw allows stable and durable fixation of bone-patellar tendon-bone graft in ACL reconstruction."	All done by one surgeon. No difference in outcomes noted. Transcondylar fixation was new without many clinical studies evaluating it.
BPTB Graft vs. 3-strand ST Graft vs. 4-strand ST/G Graft						
Laxdal 2005 RCT	6.5	N = 134 patients (only 118 at follow up) with unilateral chronic ACL rupture	Bone-Patellar Tendon-Bone graft (BPTB group, n = 40) vs. 3-strand ST graft (ST group, n = 39) vs. 4-strand ST/G graft (ST/G group, n = 39). Assessments at 2 to 3 years.	Data reported as median [range]. Lysholm score: not significant. Tegner Activity Level: not significant. KT-1000 anterior and total side-to-side differences: not significant. Disturbance in anterior knee sensitivity: not significant. Loss of Motion: not significant. 1 leg-hop test: ST vs. ST/G (93[39-120] % vs. 99[79-120] %, p = 0.006); ST/G vs. BPTB (93[39-120] % vs. 91[52-108] %, p = 0.003); ST vs. BPTB (not significant).	"We were able to verify our hypothesis and, therefore, conclude that at the 2- to 3-year follow-up, both 3-strand ST grafts and 4-strand ST/G grafts produced results that were just as good as those produced by BPTB grafts in terms of functional parameters and laxity."	6 surgeons performed surgery. Less pain with semitendinosis group grafting, lack of details lowered score, Co-interventions only partially accounted for.
Ipsilateral BTB Graft vs. Ipsilateral Triple/Quadruple ST Graft						
Lidén 2007 RCT	6.0	N = 71 (22 females, 49 males) with unilateral ACL rupture	Ipsilateral BTB graft (BTB group, n = 34) vs. Ipsilateral triple/quadruple ST graft (ST group, n = 37). Median follow up was 86 months.	Data reported as median [range]. Lysholm score: not significant. Tegner Activity Level: not significant. 1-Legged Hop test: not significant. KT-1000 arthrometer anterior side-to-side difference: not significant. Disturbance in anterior knee sensitivity, kneeling, ROM all not significant.	"On the basis of the present study, we conclude that the results were acceptable using both types of graft at 7 years after surgery. No clear advantage for either technique was demonstrated. Both techniques are reliable when it comes to improving patient performance, allowing a return to a higher level of activity that before surgery, and are	Long-term follow-up. No differences reported. No increase in adverse events.

					therefore equally valid choices for ACL reconstructions even in the long term.”	
Ipsilateral Hamstring Autograft vs. Ipsilateral Hamstring Autograft with the Addition of a Bone Plug						
Hollis 2009 RCT	4.5	N = 36 (27 made it to follow up) with acute or subacute ACL tears	ACL reconstruction using Ipsilateral Hamstring autograft (Standard group, n = 12) vs. ACL reconstruction using Ipsilateral Hamstring autograft with addition of bone plug (Plug group, n = 15). Mean follow-up time 8 months.	Tunnel Enlargement: not significant. IKDC: not significant. KT-1000 manual maximum: not significant.	“Use of an autologous bone plug placed adjacent to the hamstring graft during ACL reconstruction does not reduce femoral tunnel widening, compared with a group without a bone plug, as determined by evaluation of post-operative digital radiographs.”	Large drop-out rate lowered powered. More than one surgeon. No difference reported to justify the additional procedure of a bone plug.
Preconditioned Patellar Tendon vs. No Preconditioning Patellar Tendon						
Ejerhead 2001 RCT	6.0	N = 53 unilateral ACL rupture	Pre-conditioned patellar tendon (Group P) n = 25 vs. non-pre-conditioned patellar tendon (Group NP) n = 28.	Data at 2-year follow-up. Follow-up exams (months): Group P 26 (23 to 29), Group NP 25 (23 to 30) p = n.s. KT-1000, total side-to-side difference (mm): Group P 2.5 (-1.5 to +8.5), Group NP 3.0 (-7 to +6.5) p = 0.3. KT-1000, anterior side-to-side difference (mm): Group P 3.0 (-1 to 10), Group 2.0 (-6.0 to +6.0) p = 0.3. Lysholm Score (points): Group P 86 (47 to 100), Group NP 94 (44 to 100), p = 0.4. Tenger activity level: Group P 6 (2 to 9), Group NP 7 (3 to 9) p = 0.6.	“Patients who underwent ACL reconstruction using a preconditioned patellar tendon autograft had no advantages in terms of restoration of laxity or clinical outcome at 2-year follow-up.”	One surgeon for all. No dropouts reported. All had same post-op rehab. No differences reported.
LAD Technique vs. Patellar Tendon Technique						

Grøndvedt 1995 RCT	6.5	N = 48 acute proximal ACL ruptures	(N = 26) Patellar tendon technique vs. (n = 22) LAD technique; 1 and 2 year follow-ups done.	Pivot shift sign: differences between groups significant at both 1 (p <0.01) and 2 years (p <0.0005). Lachman test (exhibited anterior instability): LAD group, 7 patients (32%) had 2 + or 3 + at 1 year that increased to 10 patients (46%) at 2 years. Differences significant, p <0.005. Laxity differences not significant at 1-year follow up, but were at 2-year follow-up.	“Because of the unacceptable high incidence of reruptures in the LAD group, we concluded that the augmentation technique with the LAD is unacceptable.”	No differences in pain noted. LAD technique had more ruptured and the authors concluded it shouldn't be used.
Semitendinosus Graft vs. Semitendinosus and Gracilis Graft						
Gobbi 2005 RCT	6.0	N = 97 underwent reconstruction	ST graft (n = 50) vs. STG graft (n = 47).	No difference between groups in standard knee scores, self-evaluation score, clinical findings, computerized knee laxity analysis, flexion, extension, and external rotation strengths, or functional tests. Internal rotation torque deficit higher in STG group (p = 0.039). External-to-internal rotation ratio greater in the STG group (p = 0.006)	“Although there is not much clinical difference when using the ST alone versus the STG construct, internal rotation weakness following harvest of 2 tendons may need to be evaluated further. We suggest that, whenever possible, only 1 tendon should be used when performing anterior cruciate ligament reconstruction with hamstring tendons.”	Both patients and assessors blinded. One surgeon performed surgery. No significant differences reported in function. Technique that uses Gracilis had increased internal rotation weakness.
Normal Debridement vs. Minimal Debridement						
Gohil 2007 RCT	6.5	N = 49 undergoing primary ACL reconstruction	(N = 25) normal debridement group vs. (n = 24) minimal debridement group.	An interesting finding was that signal/noise quotient values consistently higher in lowest part of graft in tibial tunnel (mean signal/noise quotient normal group, 4.56 (0.96 to 7.46); minimal debridement group, 7.12 (2.6 to 15.41), compared with near femoral insertion (mean signal/noise quotient normal group, 2.71 (0.79 to 6.99); and in minimal debridement group. Mid-substance of ACL graft, significant differences between groups at 2 and 6 months, but not at 1 year. Mid-substance PCL signal intensity showed significant	“No statistically significant differences were found in tunnel placement, incidence of Cyclops lesions, blood loss, IKDC scores, range of movement or Lachman test between the two groups.”	MRI scans at 2, 6, and 12 months. One surgeon. Debridement increase vascularisation at 2-months. No difference reported in clinical outcomes. No mention of co-interventions.

				differences at 2, 6, and 12 months.		
Low Tunnel Position vs. High Tunnel Position						
Jepson 2007 RCT	7.5	N = 60 (at follow up - 30 males, 21 females) with an isolated unilateral ACL injury	Low-Positioned ACL (Low, n = 30) vs. High-Positioned ACL (High, n = 30).	No significant differences in pre- and intra-operative data between groups. Post-op tibial angle: Low (58.63 +/- 7.43) vs. High (63.36 +/- 7.82); p < 0.05. At follow up: Tibial angle: Low (58.52 +/- 7.37) vs. High (63.77 +/- 7.05), p < 0.05; Femoral angle: not significant. Subjective IKDC score: Low (82.80 +/- 9.96) vs. High (70.39 +/- 15.30), p < 0.05. Knee Laxity and IKDC Objective score not significant.	"We conclude that it is possible to improve the clinical result in 1-bundle ACL reconstruction by lowering the tibial tunnel angle and thereby lowering the femoral tunnel toward the 2-o'clock position."	Three surgeons. Patients and assessors were blinded. Low position had subjective by better laxity.
Primary Repair vs. Patellar Tendon Technique vs. Kennedy LAD Technique						
Engebretsen 1990 RCT	5.5	N = 150 consecutive patients who had ACL ruptures	Primary Repair Technique (Repair, n = 50) vs. Patellar Tendon Technique (Patellar, n = 50) vs. Kennedy LAD Technique (LAD, n = 50). Assessments were at 6 months, 1 and 2 years after operation.		"In this 2 year, prospective, randomized study, the patellar tendon augmented repair was found to be superior to direct repair and augmentation with the Kennedy Ligament Augmentation Device. This judgement was made based on the Lachman test, pivot shift test, and KT-1000 testing."	Post-op rehab was 2 weeks cast, 6 weeks non-weight bearing brace. Patellar tendon superior in most all outcomes.
Patellar Tendon Graft with Augmentation vs. Patellar Tendon Graft without Augmentation						
Thureson 1996 RCT	4.0	N = 82 (59 males, 23 females) with chronic ACL insufficiency and severe symptoms of instability who had not improved after at least 3 months of supervised training	Patellar tendon graft with augmentation with a polypropylene band (LAD augmented, n = 45) vs. patellar tendon graft without augmentation with a polypropylene band (non-augments, n = 37). Assessments at pre-op, 2 weeks, 1, 2, 3, 6	Maximal extension of injured knee: non-augmented vs. LAD-augmented (1 month: 11±8 vs. 15±7, p = 0.026; 2 years: 3±4 vs. 0.6±3; p = 0.016; all other times not significant). Mid-patellar circumference in cm: non-augmented vs. LAD-augmented (pre-op: 0.6±0.7 vs. 0.2±0.6, p = 0.021; 2 weeks: 2.2±1.3 vs. 3.0±0.9, p = 0.011; 1 month: 1.9±0.9	"There seems to be no difference between using a full or less than full thickness patellar tendon graft in combination with the LAD augmentation, as seen by measuring extension block or sagittal instability."	More extension deficit in augmented group. Kennedy augmentation reported to increase cost, but not improve outcomes.

			months, 1 and 2 years after surgery.	vs. 2.5 ± 0.8 , $p = 0.018$; all other times not significant.) Lysholm Score (median [range]): non-augmented vs. LAD-augmented (pre-op: 3 [0-8] vs. 4 [0-7], $p = 0.029$; 1 year: 4 [2-9] vs. 4 [2-8], $p = 0.025$; 2 years: 4.5 [0-9] vs. 6 [2-10], $p = 0.034$; all other times not significant.) KT-1000 not significant at any time.		
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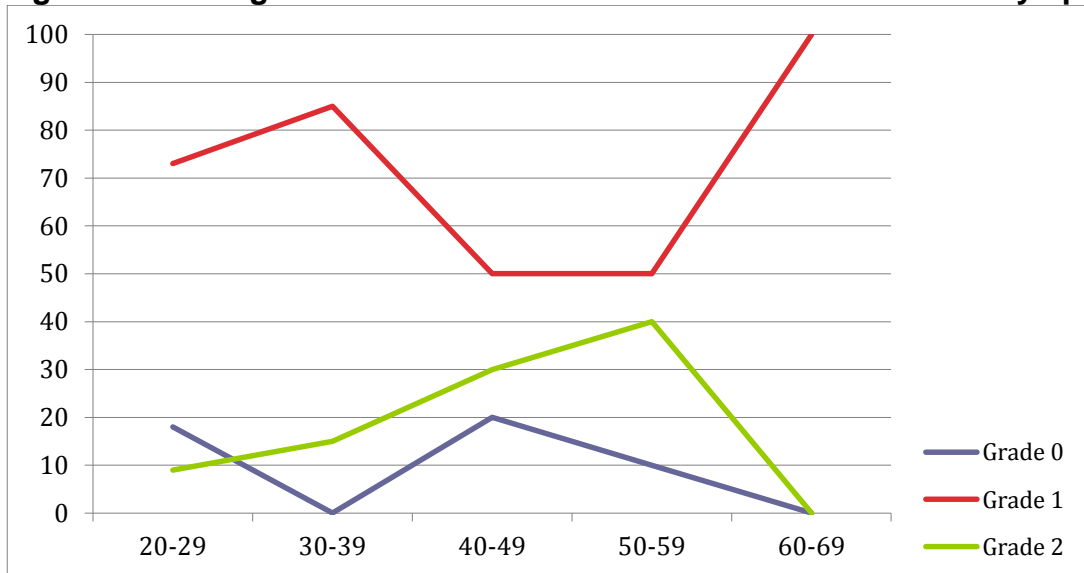
POST-OPERATIVE REHABILITATION FOR ACL TEARS

See above.

MENISCAL TEARS

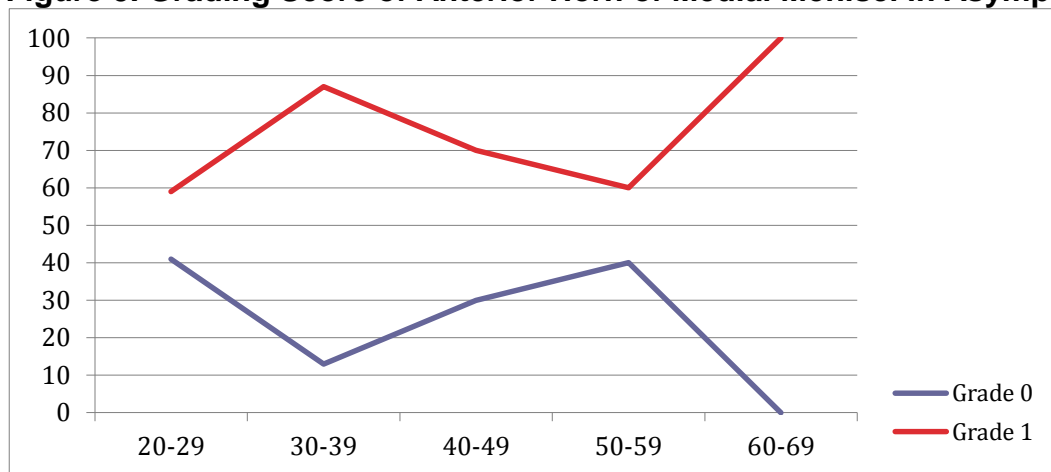
Magnetic resonance imaging of asymptomatic individuals has shown that among those 60 to 69 years of age, the anterior horns were normal in only 20% of the lateral menisci, and all medial menisci were abnormal.(2139) Similarly, all of the posterior horns were also showing some degenerative changes among the elderly with strong trends towards increased degeneration with age (see Figures 4, 5, and 6).(2139) Another study reported severity of changes and also found a strong correlation between increased degenerative changes and age.(2140) Thus, tears of the medial or lateral knee menisci are quite common. They have often been classified as trauma-related or degenerative.(2139-2141) However, due to the high prevalence of tears on MRI, designations of trauma-related tears may be a somewhat arbitrary distinction in many cases, particularly when the inciting event involves normal use or minimal exertion, rather than sporting events.

Figure 4. Grading Scores of Posterior Horn of Medial Menisci in Asymptomatic Patients



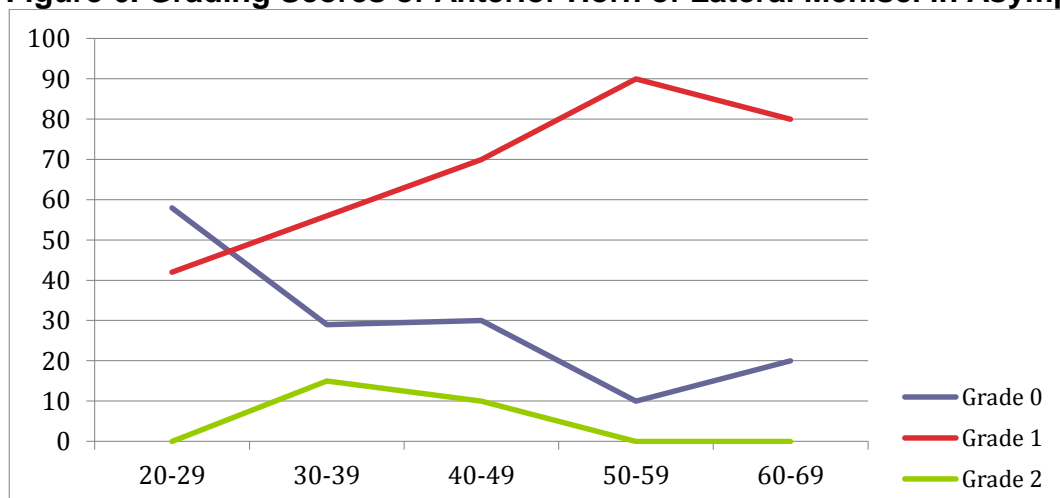
Adapted from Beattie KA, Boulos P, Pui M, et al. Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. *Osteoarthritis Cartilage*. 2005;13(3):181-6.

Figure 5. Grading Score of Anterior Horn of Medial Menisci in Asymptomatic Patients



Adapted from Beattie KA, Boulos P, Pui M, et al. Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. *Osteoarthritis Cartilage*. 2005;13(3):181-6.

Figure 6. Grading Scores of Anterior Horn of Lateral Menisci in Asymptomatic Patients



Adapted from Beattie KA, Boulos P, Pui M, et al. Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. *Osteoarthritis Cartilage*. 2005;13(3):181-6.

A careful history will usually result in a presumptive diagnosis that may be confirmed with physical examination (see History and Physical Examination sections above). Patients tend to have pain that lateralizes to the affected compartment and tends to not radiate and may or may not have swelling, presumably depending on factors such as the acuity and magnitude of the tear. Quality of physical examination tests has been called “poor to fair,”(138, 2142) and many examination maneuvers have relatively poor operant characteristics.(74, 75, 80, 83, 137, 2143-2146) A composite of physical examination maneuvers has been thought to be more helpful.(108) As there is a high prevalence rate of asymptomatic tears, the examination also may be normal, but an MRI may be abnormal.(2139, 2140) Clinical tests are generally not necessary for initial presentation and evaluation of mild meniscal tears as they do not tend to affect management.

X-RAY AND MRI

Recommendation: X-ray and MRI for Evaluation of Meniscal Tears

X-ray and MRI are recommended in more severe cases of meniscal tears, including cases involving significant trauma, particularly to rule out fracture. MRI is also helpful for defining other injuries that may accompany tears such as cruciate and other ligament tears.

Strength of Evidence – Recommended, Insufficient Evidence (I)

ULTRASOUND

Recommendation: Ultrasound for Evaluation of Meniscal Tears

There is no recommendation for or against the use of diagnostic ultrasound for the evaluation of meniscal tears.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

MRI has been commonly performed to evaluate meniscal tears.(430, 433, 2147-2177) However, MRIs have been thought to be able to be reserved for complicated and confusing cases,(2178) as they do not usually contribute to management.(2179, 2180) There also are concerns that have been raised regarding increasing unnecessary surgery by over-reliance on MRI findings(2181); although a clinical trial suggested this may not be the case.(2180) Ultrasound,(2182-2186) CT, CT arthrography, spiral CT,(2187-2190) SPECT,(2191-2193) and SPET(2194) have all been used for diagnostic purposes. There are no quality studies of treatment options aside from surgery and rehabilitation for meniscal tears (see next section). Out of necessity, guidance for treatment relies by analogy upon ankle sprains, as there are considerable quality trials for ankle sprains.

Evidence for the Use of MRI for Meniscal Tears

There are 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Utility of MRI for Meniscal Tear Management						
Brealey/DAMASK Team 2007 RCT	6.5	N = 553 age 18-55 inclusive (n = 279 allocated to MRI; n = 274 allocated to orthopaedic specialist) presenting in GP and whose GPs were considering referral to an orthopaedic specialist for suspected internal derangement of knee	Direct access to MRI vs. no MRI on assessment of GP diagnosis and treatment plans (UK National Health System)	Change in diagnostic confidence (%) for the MRI referral vs. Orthopaedic referral: Increased: 64 vs. 32; No effect: 29 vs. 52; Decreased: 7 vs. 16; p-between group change <0.001. Significant increase in within-group changes in diagnostic and therapeutic confidence.	“Access to MRI did not significantly alter GP’s diagnoses or treatment plans compared with direct referral to an orthopedic specialist, but access to MRI significantly increased their confidence in these decisions.”	Differences in length between randomization and allocation of intervention related to waiting lists. Although no specific co-intervention, natural history of improvement may have been a co-intervention for those waiting longer periods between randomization and allocation.

INITIAL CARE

Rest, splints, ice and heat have been utilized for treatment of meniscal tears.

WORK LIMITATIONS

1. *Recommendation: Work Limitations for Select Cases of Meniscal Tears*

Work limitations are recommended for those with meniscal tears performing high physical demand tasks or those who have no ability to avoid repeating physically demanding job tasks that may have resulted in the condition.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. *Recommendation: Work Limitations for Other Cases of Meniscal Tears*

There is no recommendation for or against work limitations in other cases of meniscal tears.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

BED REST AND KNEE IMMOBILIZATION

Recommendation: Bed Rest and Knee Immobilization for Meniscal Tears

Bed rest and knee immobilization are not recommended for meniscal tears, although relative rest may be required for some patients, particularly those more severely affected.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

NSAIDs

Recommendation: NSAIDs for Meniscal Tears

Nonsteroidal anti-inflammatory medications are recommended for meniscal tears. (See NSAIDs section for dose, frequency, discontinuation information).

Strength of Evidence – Recommended, Insufficient Evidence (I)

ICE/HEAT

Recommendation: Ice/Heat for Meniscal Tears

Ice and/or heat are recommended for meniscal tears.

Strength of Evidence – Recommended, Insufficient Evidence (I)

WRAPS/SUPPORTS/SLEEVES

Recommendation: Ace Wraps, Supports or Sleeves for Meniscal Tears

Ace wraps, supports, or sleeves are recommended for meniscal tears.

Strength of Evidence – Recommended, Insufficient Evidence (I)

REHABILITATION THERAPY

Recommendation: Rehabilitation Therapy for Meniscal Tears

A course of rehabilitation therapy is recommended for those with meniscal tears with persisting pain thought to not be clearly surgical.

Dose – See exercise section for dose, frequency and discontinuation.

Strength of Evidence – Recommended, Insufficient Evidence (I)

OTHER MODALITIES/INJECTIONS

Recommendation: Other Modalities and Injections for Meniscal Tears

There is no recommendation for or against therapeutic ultrasound, diathermy, electrical stimulation, iontophoresis, low-level laser therapy, phonophoresis, acupuncture, manipulation and mobilization or manual therapy, autologous blood injections, plasma rich platelet injections, glucocorticosteroid injections, and hyaluronic acid injections for meniscal tears.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

Work limitations may be necessary depending on the severity of the condition and the required job demands. Those performing high physical demand tasks or those who have no ability to avoid repeating physically demanding job tasks that may have resulted in the condition are recommended to have work limitations. In other cases, there is no recommendation for or against work limitations. Bed rest and knee immobilization are not recommended due to risks of venous thromboembolisms and other adverse effects of bed rest, although relative rest may be required for some patients, particularly those more severely affected. Nonsteroidal anti-inflammatory medications, ice, heat, Ace wraps, supports or sleeves are recommended. Those with persisting pain thought to not be clearly surgical are recommended to have a course of rehabilitation therapy. There is no recommendation for or against therapeutic ultrasound, diathermy, electrical stimulation, iontophoresis, low-level laser therapy, phonophoresis, acupuncture, manipulation and mobilization or manual therapy, autologous blood injections, plasma rich platelet injections, glucocorticosteroid injections, and hyaluronic acid injections. Hyaluronic acid injections have been used to treat knee osteoarthritis,(1424) and have been reported to have additive benefit for arthroscopy patients found to have arthrosis at the time of meniscal surgery.(2195)

Evidence for the Use of Hyaluronate Injections for Meniscal Tears

There are 2 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Dougados 1993 RCT	7.5	N = 110 diagnosed with knee OA	Intra-articular injections of hyalectin 20mg (H) vs. vehicle (C) once a week for 3 weeks.	Slight significant difference between groups in functional impairment at Week 49 (p = 0.046) favoring hyalectin.	"This study confirms the short-term efficacy and lack of toxicity of a course of four intra-articular injections of hyalectin in the treatment of osteoarthritis of the knee and suggests that this treatment might have a long- term beneficial effect."	Data suggest efficacy with Lequesne's index suggesting benefits at 1 year though VAS was not significant at 1 year.
Westrich 2009 RCT	4.0	N = 50 age 40 and older with symptoma tic MRI confirmed meniscus tears needing knee arthroscop y with Kellgren- Lawrence Stage II or III	Sodium hyaluronate injections vs. control with 1st injection immediately after surgery, 2nd injection 10-14 days later, and final injection 17- 21 days after surgery with follow-up at these times and 3 and 6 months after surgery.	Three month follow up: VAS (control 2.33±2.311 vs. injection 0.76 ±1.490). Swelling (control 80% vs. injection 13%); tenderness (control 85% vs. injection 9%) pain on motion (65% vs. 9%) effusion (60% vs. 4%) bulge sign (35% vs. 0%) patellar ballotement (20% vs. 0%) crepitus (75% vs. 22%); 6 month follow up: flexion in treated knee (°) (123.53± 7.1999 vs. 128.37±6.465, p = 0.036) Tenderness (53% vs. 16%). Pain on motion (53% vs. 5%); Crepitus (84% vs.	"[3] soduim hyaluronate injections given after arthroscopy (with the first intra-articular injection given at the end of the arthroscopic procedure) are more effective than arthroscopy alone for alleviating pain and restoring motion and function to patients with early- stage osteoarthritis and meniscal tears."	Patients not well described. Data suggest HA injections of additive benefit for meniscal surgery when occurring in a DJD setting.

				37%. NS between groups for 50 foot walk test time at 3 and 6 months.		
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REHABILITATION OF MENISCAL TEARS WITH OR WITHOUT SURGICAL REPAIR

Exercise, physical therapy, and rehabilitation have been used for treatment of meniscal tears.(2196-2198) Inferential current therapy has also been used.(1267)

1. Recommendation: Meniscal Tear Rehabilitation without Surgical Repair

Rehabilitation for select patients after meniscal tears without surgical repair is recommended.

Indications – Select patients with meniscal tears resolving without surgery, but particularly those with functional deficits, such as residual muscle weakness.

Duration – One to 4 weeks, 2 to 3 sessions a week.

Indications for Discontinuation – Achievement of goals, non-compliance with clinic or home based exercises or intolerance.

Strength of Evidence – **Recommended, Evidence (C)**

2. Recommendation: Meniscal Tear Rehabilitation after Surgical Repair

Meniscal tear rehabilitation for select patients after surgical repair is recommended.

Indications – Patients with meniscal tears having undergone surgical repair, particularly with functional deficits such as residual muscle weakness.

Duration – One to 6 weeks, 2 to 3 sessions a week.

Indications for Discontinuation – Achievement of goals, non-compliance with clinic or home based exercises or intolerance.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

There is one moderate-quality trial comparing surgery plus exercise with exercise alone suggesting equivalency.(2199) This provides some evidence for successful non-operative rehabilitation. Most trials of exercise and rehabilitation enrolled post-menisectomy patients.(2200) Most of these trials compared supervised therapy with either a home exercise program or advice compared to a home program,(2201) physiotherapy with oral and written advice,(2202) and stationary bicycling with no treatment.(2203) One trial found functional strengthening exercises superior to a control for post-operative rehabilitation.(2204) Thus, the balance of studies implies the post-operative results are good and many patients do not appear to require formal post-operative therapy aside from advice and education. Nevertheless, exercise is thought to be helpful for select patients with weakness or other functional limitations who were not the main enrollment criteria for the available evidence-base. Some may require few appointments for teaching while others require more supervision and assistance with advancement of the program towards independence in the presence of significant deficits. One trial evaluated early rehabilitation and its suggested superiority; however, baseline differences negate the ability to utilize the trial for the development of evidence-based guidance.(1861) Exercise is not invasive, has low adverse effects and is moderately costly, depending on numbers of appointments required, and is recommended for select patients with functional deficits.

Evidence for the Use of Rehabilitation for Meniscal Tears

There are 7 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Exercise vs. Surgery plus Exercise						
Herrlin 2007 RCT	4.5	N = 90 age 45-64 with no traumatic knee pain during last 2-6 months	Arthroscopic partial meniscectomy followed by supervised exercise (n = 47) vs. supervised exercise alone (n = 43).	No significant differences between groups.	"In conclusion, a combination of arthroscopic partial meniscectomy and supervised exercise does not necessarily lead to greater improvements of knee function compared to supervised exercise alone in middle-aged patients with non-traumatic medial meniscal tears."	Only nontraumatic patients included. Crossovers to surgery not high. Data show equal efficacy over 6 months, suggesting surgery for non-traumatic medial meniscal tear is not likely to produce benefits above exercise alone for these patients.
Post-operative Rehabilitation						
Vervest 1999 RCT	6.5	N = 20 who underwent partial arthroscopic meniscectomy for a solitary meniscus injury	Physiotherapy 9 sessions over 3 weeks vs. oral and written advice.	Sports activity rating scale statistically different between 2 groups comparing measurements 7 days vs. 28 days after arthroscopy (mean±SD): 30.0±10.54 vs. 48.3±24.11; p = 0.04.	"Standard exercise therapy under the supervision of a physiotherapist improved the functional recovery of the knee after partial arthroscopic meniscectomy."	Function improvement may not be clinically significant and no difference in satisfaction or pain scores.
Kelln 2009 RCT	6.0	N = 31 age 18-64 undergoing partial meniscectomy surgery	Stationary bike 6 sessions over 2 weeks vs. no treatment after partial arthroscopic meniscectomy.	No significant differences in IKDC scores, various girth measures, or knee ROM up to 3 months. Antalgic gait (#subjects per group with limp: Pre-op: 13 vs. 6, Day 1-15 vs. 14, Week 1: 13 vs. 6, Week 2-11 vs. 3, Month 1 9 vs. 3*, Month 3: 3 vs. 3 = (p <0.05)	"Early, protected active ROM on a bicycle ergometer equipped with an adjustable pedal arm system demonstrates promising results in the treatment of patients recovering from partial meniscectomy."	No differences in functional outcomes except antalgic gait, but there were differences in that measure at baseline, suggesting no differences overall.
Ericsson 2009 RCT	6.0	N = 45 age 35-45 who had undergone arthroscopic meniscectomy	Four years post meniscectomy-postural stability and functional strength training 3 days a week for 4 months vs. no treatment.	Exercise vs. control at 4 months: 1-leg hop (cm) 8 vs 2 (p <0.040), Quadriceps strength (PT E60) 3 vs. 2 (p <0.831), quadriceps endurance (TW E180) 155 vs. -40 (p <0.001), Hamstrings strength (PT F60) 8 vs. 1 (p <0.033). Number of PT sessions attended moderately correlated with 1-leg hop distance and quadriceps, hamstring endurance.	"We have presented a functional exercise concept that we have applied to a post-meniscectomy group, and found to be efficient and suitable for these patients. As the exercises require little equipment, the program can easily be adopted to clinical settings."	Despite functional improvements, study appears not powered to correlate improvement with clinical or other quality of life measures.
Jarit 2003 RCT	5.5	N = 87 over age 18 with no history of back injuries causing pain	Home inferential current therapy (IFC) vs. placebo.	All IFC subjects experienced less pain at all time points after time 0. Meniscectomy IFC subjects at time 0	"We recommend that physicians performing knee surgery consider using IFC	Randomization, allocation into 3 groups. Methods unclear. Baseline differences in

		or impairment of the extremities		reported 297% less pain than placebo group.	immediately after the surgery and then supplying home IFC for the patient. In this study we have not compared IFC to other modalities and we do not claim that IFC is preferred over those modalities.”	some measures. Data suggest efficacy of IF.
Moffet 1994 RCT	5.0	N = 31 age 20-55, scheduled for partial medial meniscectomy by arthroscopy	Early and intensive physiotherapy (EXP) vs. Control group (CTL)	EXP group better extension work recovery than CTL group at 30° (p = 0.0001) and 180°/sec (p = 0.0008). CTL group (n = 8) about 40% deficit at post-test whereas patients in EXP group (n = 8) had residual deficit of only 15%, at both speeds of movement. Results of statistical analysis not conclusive because power of these statistical tests (ANCOVA) to detect 8% (50% of mean post-op residual deficit without treatment) difference between groups estimated at 22%.	“...the results of the present study convincingly support the institution of an early intensive and supervised rehabilitation program postmeniscectomy by arthroscopy.”	Lack of randomization, allocation defects. Baseline differences in primary outcome measures concerning for randomization failure.
Karumo 1977 RCT	4.5	N = 56 with meniscectomies	Routine physiotherapy (quads setting and active straight-leg raising exercises, walking on crutches starting 1st day, then active flexion exercises 2nd day, then training in walking on stairs after 2 weeks (Group A, n = 27) vs. same routine but twice daily (Group B, n = 29) 15 minute sessions for 7 days.	Four weeks post surgery, knee ROM significantly less compared to healthy knee (Group A, p <0.01; Group B, p <0.001). Four weeks post surgery, knee flexion strength improved to that of healthy limb in Group A but not Group B, p <0.001. Flexion power better Group A vs. Group B, p <0.05; 14 patients in Group B still using crutches after 2 weeks, p <0.025 vs. Group A.	“[S]pecial postoperative physiotherapy does not accelerate the recovery of the patients. Excessive exercise may lead to swelling of the knee and thus to reflex inhibition of the muscles.”	Compliance and dropouts unclear. Data suggest comparable results over 1 month.

SURGERY FOR MENISCAL TEARS

Surgical partial meniscectomy has been used for treatment of meniscal tears,(2205-2213) particularly by arthroscopic means.(2214-2236) The short-term prognosis(2237, 2238) as well as the degree of subsequent arthrosis has been correlated with the amount of meniscus removed.(207, 2214, 2239-2241) Meniscal repairs have a higher operation rate than partial meniscectomies; however, reportedly more likely result in better long-term outcomes.(2242) All-inside repair has been utilized as a surgical technique.(2243-2245) There also are concerns that a lateral meniscus tear may have a worse prognosis.(2217) However, a Cochrane review

concluded the lack of RCTs impaired the ability to draw conclusions regarding surgical versus non-surgical management as well as repair versus excision of torn menisci.

There also are investigational techniques, including use of stem cells to attempt to regenerate menisci.(2246-2248) Allograft transplantation,(2249-2274) collagen implants(1678, 2275) , and synthetic materials(2276) (van Tienen 09) have also been utilized.

Recommendation: Surgery for Meniscal Tears

Arthroscopic partial meniscectomy and/or meniscal repairs for symptomatic, torn menisci is recommended for highly select patients.

Indications – Relatively few patients with meniscal tears appear to be candidates for this surgery. Possible expectations include those with locking symptoms, severe tears, and/or frank traumatic onset that does not generally include onset after “exercise,” “hard work,” or “twisting” events.(2277) Thus, patients should be highly selected and have attempted non-operative treatment that generally included passage of at least a few weeks, NSAIDs, and activity modulation, and also may have included formal therapy.(2199) Patients with marked mechanical symptoms (e.g., mechanical locking with effusions) are candidates for early operative intervention. Patients trending towards improvement generally warrant longer periods of non-operative management, while patients failing to trend towards improvement over at least 3 to 4 weeks are candidates for earlier surgical treatment.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

There is one high-quality trial comparing partial meniscectomy with sham in knees without osteoarthritis and found a lack of efficacy.(2277) There is one moderate-quality trial comparing meniscectomy with versus without exercise that suggested no differences in outcomes.(2199) As noted above, meniscal degenerative tears become universal with age. These data suggest that there are many cases of meniscal tears that do not require meniscectomy. Additionally, surgical indications have not been clearly defined. Those with marked mechanical symptoms have not been evaluated in randomized, quality trials and are believed to require operative treatment. Meniscal repairs have a higher re-operation rate than partial meniscectomies; however, reportedly more likely result in better long-term outcomes.(2242) One moderate-quality trial suggested a radiofrequency device was superior to a mechanical shaver to accomplish the meniscectomy.(2278) Surgery is invasive, has adverse effects, and is costly, but is thought to be required for treatment of selected meniscal tears, particularly those including significant mechanical symptoms. Surgery is thus recommended.

Available evidence suggests that preservation of more meniscal tissue is superior to removal of greater quantities of the menisci for both short- to intermediate-term function,(2205, 2206, 2275, 2279-2281) as well as for reduction in subsequent risk of osteoarthritis.(207, 2214, 2239-2241) There is no quality evidence to address utility of meniscectomy by peripheral/vascular vs. avascular zone involvement, although there are opinions about these tears.(2282-2285)

Evidence for Surgery for Meniscal Tears

There are 2 high-(2210, 2277) and 16 moderate-quality(2180, 2199, 2205-2209, 2211, 2212, 2221, 2275, 2278-2281, 2286) RCTs incorporated into this analysis. There are 4 low-quality RCTs in Appendix 1.(2287-2290)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
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Partial Meniscectomy vs. Sham for Meniscal Tear Management						
Sihvonen 2013 RCT	8.5	N = 146 ages 35-65 years with symptomatic degenerative knee meniscal tear, but no OA. Failure of non-operative treatment.	Partial medial meniscectomy (n = 70) vs. sham surgical procedure (n = 76).	Lysholm knee scores improved in surgical group 21.7 (95% CI 17.6-25.8) vs. sham 23.3 (19.5-27.2), NS. WOMET scores, score for knee pain after exercise, 15D score, score of knee pain at rest also all did not differ significantly.	"[T]he outcomes after arthroscopic partial meniscectomy were no better than those after a sham surgical procedure."	Data suggest meniscectomy for degenerative tears not effective. Whether there is a minor subgroup with efficacy is unclear. Study represents both excluded locking or painful snapping symptoms, but 46-49% enrolled had locking. Does not appear to apply to severe tears.
Exercise with vs. without Meniscectomy						
Herrlin 2007 RCT	4.5	N = 90 middle-aged patients 45-64 with no traumatic knee pain during last 2-6 months	Arthroscopic partial meniscectomy followed by supervised exercise (n = 47) vs. supervised exercise alone (n = 43).	No significant differences between groups.	"In conclusion, a combination of arthroscopic partial meniscectomy and supervised exercise does not necessarily lead to greater improvements of knee function compared to supervised exercise alone in middle-aged patients with non-traumatic medial meniscal tears."	Only nontraumatic patients included. Crossovers to surgery not high. Data show equal efficacy over 6 months, suggesting surgery for non-traumatic medial meniscal tear is not likely to produce benefits above exercise alone.
Partial vs. Total Meniscectomy						
Rodkey 2008 RCT	7.0	N = 311 age 18-60 with irreparable injury to or previous partial loss of 1 medial meniscus, with an intact rim, involved knees in neutral alignment with weight-bearing axis falling within limits of tibial eminences on a standing anteroposterior radiograph	Collagen meniscus implant vs. controls. Controls underwent appropriate partial meniscectomy and joint debridement (if indicated). Patients randomized to receive collagen meniscus implant underwent the identical treatment plus implantation of collagen meniscus implant. All procedures performed arthroscopically.	After 1 year, 84 of 92 partial meniscectomy patients and 72 of 90 total meniscectomy patients were symptom free, p = 0.029.	"[M]eniscectomy should only be undertaken after the demonstration of a meniscal tear, which must be assumed to be the cause of the patient's symptoms. Partial meniscectomy affords advantages over total, as a significantly larger number of patients were free of symptoms one year after partial meniscectomy."	Two arms of trial (acute: no prior surgery and chronic: 1 plus prior meniscal surgeries). Data suggest efficacy in chronic but not acute groups.
Hede 1992	5.5	N = 189 meniscus lesion	Partial meniscectomy (n = 97) vs. total	Larger areas of meniscus removed in those who had partial	"[P]artial meniscectomy gives better, or	Mean 7.8y follow-up. No non-surgical

RCT		undergoing meniscectomy; if tear in central 3/4 of meniscus seen and no other abnormality	meniscectomy (n = 92)	meniscectomy for bucket handle tears vs. anterior and posterior horn tears. Lysholm scores higher in anterior tear knee after partial compared to after total meniscectomy. Functional group according to Lysholm anterior horn: fair-poor (partial 3 vs. total 6), excellent (partial 13 vs. total 6). Bucket-handle: fair-poor (partial 1 vs. total 5), excellent (partial 26 vs. total 16). Posterior horn: fair-poor (partial 3 v. total 6), excellent (partial 7 vs. total 10).	equal, long term results, depending on the type of tear, compared to total meniscectomy. When more than 30% of the meniscus is removed during partial meniscectomy, preservation of the peripheral rim of the meniscus is essential to obtain the best long term results.”	comparison group. Long term study. Patients not well described. Data suggest trend towards higher functional score if less meniscus removed.
Hede 1992 RCT	5.5	N = 192 tear in central 3/4 of meniscus undergoing meniscectomy	Partial meniscectomy vs. total meniscectomy.	Patients in partial meniscectomy group had higher Lysholm scores, after 1 year. Overall, patients with a medial meniscectomy had higher Lysholm scores than those with lateral lesions. At long-term follow-up, more knee stable in partial meniscectomy group compared to total meniscectomy group.	“A higher level of knee function was achieved after partial meniscectomy than after total meniscectomy. Partial meniscectomy produced less joint instability but did not prevent progressive decline in knee function.”	Second report. Data suggest better outcomes with partial meniscectomy.
Hede 1986 RCT	4.5	N = 200 undergoing operation primarily on suspicion of meniscal injury (if operation showed a tear in central 3/4 of meniscus and absence of any other knee disorders)	Partial meniscectomy (n = 98) vs. total meniscectomy (n = 94) with follow-up at 2 and 12 months.	After 1 year, 84 of 92 partial meniscectomy patients and 72 of 90 total meniscectomy patients symptom free, p = 0.029.	“[M]eniscectomy should only be undertaken after the demonstration of a meniscal tear, which must be assumed to be the cause of the patient's symptoms. Partial meniscectomy affords advantages over total, as a significantly larger number of patients were free of symptoms one year after partial meniscectomy.”	Study of open surgeries. Data suggest partial meniscectomy tended towards better results than total meniscectomy.
Petersen 1996 RCT	4.5	N = 33 isolated tear of medial meniscus treated with partial or total meniscectomy by open joint surgery	Partial meniscectomy (n = 14) vs. total meniscectomy (n = 19).	No significant differences between groups for adaptive bone remodeling at either cortical or trabecular measuring sites.	“No significant differences in the distribution of bone mineral density, at either cortical or trabecular measuring sites, were found between totally	Third report of Hede 86, 92. Data suggest no differences.

					and partially meniscectomized knees.”	
Hamberg 1984 RCT	4.0	N = 40 degenerative tears of medial meniscus	Arthroscopic partial meniscectomy (n = 10) vs. arthroscopic total meniscectomy (n = 10) vs. open partial meniscectomy (n = 10) vs. open total meniscectomy (n = 10).	Patients in arthroscopic partial meniscectomy group had shorter sick leave periods compared to other groups, p<0.05. Mean sick leave (weeks): arthroscopic partial 1.5 vs. arthroscopic total 3.4 vs. open partial 2.6 vs. open total 3.4.	“The arthroscopic partial meniscectomy group gave the best results, with a significantly shorter operating time, a shorter period of sick leave and a smoother postoperative course.”	Eight week follow-up. Small numbers per group. Data suggest equal efficacy. Least lost time if partial meniscectomy by arthroscopy.
Surgical Techniques						
Spahn 2008 RCT	6.5	N = 60 medial meniscus tear and idiopathic Grade III cartilage defect	Use of bipolar radiofrequency-based instrument vs. mechanical shaver for partial meniscectomy	RFC patients less post-op bleeding than MSD (20.8 ±23.7 vs. 70.0±50.6 ml). Both groups used crutches and thrombosis for similar time. MSD group more units PT than RFC (9.8±0.6 vs. 6.4±1.6 units. At 6 weeks 50.0% of MSD vs. 60% of RFC taking medication. MSD reported longer time to return to work and/or professional activities. At 1 year, significantly fewer RFC (2%) than MSD patients (23%) used non-steroidal anti-inflammatory medications. Normalized KOOS Score 6 weeks MSD 29.3±4.3 vs. RFC 35.9±4.6; p <0.001. Normalized KOOS Score 1 year MSD 57.3±8.9 vs. RFC 81.2±6.9; p<0.001. Tegner scores tended higher (better) in RFC than MSD patients at 6 weeks but did not differ significantly; RFC patients had significantly higher score at 1 year (p <0.001). Patients with higher BMI tended to have worse outcome	“[T]reating Grade III medial femoral chondral lesions concomitantly with meniscectomy using RFC rather than MSD may provide overall clinical results. The RFC patients demonstrated earlier recovery from the arthroscopy than MSD patients and had significantly superior outcomes, which were assessed using several different measures, at both 6 weeks and 1 year postoperatively.”	Patients blinded. Follow-up unclear at 1 year. Data suggest RF superior to mechanical shaver.

				as measured using KOOS assessment. Smokers had significantly worse KOOS than non-smokers.		
Barber 2006 RCT	5.5	N = 60 age 18 and older with single Outbridge Grade III femoral condyle lesion 1.5-3.0cm in diameter	Mechanical shaving alone (n = 30) vs. mechanical shaving plus monopolar radiofrequency (MRF) (n = 30) with follow ups at 12 and 24 months after treatment.	No significant differences between groups.	“The use of monopolar radiofrequency as an adjuvant to mechanical chondroplasty with a shaver for the treatment of grade III chondral lesions did not affect MRI findings or pain and function outcomes when compared with mechanical chondroplasty by use of a shaver only.”	Patients not well described. No nonintervention or sham group. Data suggest RF not of additive benefit.
Jarvela 2010 RCT	6.5	N = 42 with (1) traumatic longitudinal unstable meniscal tear in a red-red zone or in the red-white zone of meniscus seen on arthroscopy during surgery, (2) less than 6 months' time delay between injury and operation.	<p>Patients were randomized with closed envelopes into 2 different groups of meniscal repair.</p> <p>Meniscal repair with bioabsorbable meniscal screws (screw group) (n = 21) vs. meniscal repair with bioabsorbable meniscus arrows (arrow group) (n = 21).</p> <p>Of patients, 28 had isolated meniscal tears (12 in screw group/16 in arrow group) and 14 had meniscal tears with anterior cruciate ligament (ACL) rupture (9 in screw group/5 in arrow group; difference not significant. Right</p>	<p>No differences between study groups pre-operatively. All 42 patients (100%) available for follow-up. However, during the follow-up, 11 patients had clinical failure, confirmed at second-look arthroscopy, of repair leading to partial meniscal resection. Four failures (all on medial meniscus) observed with use of meniscal screw fixation (17%), and 7 (4 on medial meniscus, and 3 on lateral meniscus) with use of meniscus arrow fixation (30%) (p = 0.242). Six patients with meniscus arrows (29%) had chondral damage on femoral condyles evaluated by MRA (magnetic resonance arthrography) or at second-look arthroscopy, while no patients with meniscal screws had same (p =</p>	<p>“In conclusion, this prospective, randomized study showed that all-inside meniscal repair with bioabsorbable meniscus arrows resulted in the same amount of failures on the medial meniscus, more failures on the lateral meniscus, and significantly more chondral damage than all inside meniscal repair with bioabsorbable meniscal screws at 2-year follow-up. However, in the patients with clinically healed meniscal repairs, the functional results were good and equal in both groups.”</p>	Data suggest comparable results but report more chondral damage with arrows. High refusal to MRA at follow-up limits conclusion.

			knee involved in 23 patients (12 in screw group/11 in arrow group) and left knee in 19 patients (9 in screw group/10 in arrow group; NS).	.018). However, Lysholm and IKDC (International Knee Documentation Committee) scores were similar in both groups at follow-up.		
Tourniquet Issues						
Graf 1996 RCT	4.5	N = 34 between ages of 16-55 undergoing arthroscopic partial meniscectomy.	Pneumatic tourniquet during surgery (n = 11) vs. no tourniquet during surgery (n = 23) with assessments preoperatively and at 1 week and 4 weeks post surgery.	There were no significant differences between groups.	“[T]he use of a pneumatic tourniquet during arthroscopic meniscectomy did not adversely affect recovery of quadriceps strength when tourniquet pressures were normalized for thigh circumferences and blood pressure.”	Used coin toss for randomization caused markedly different group sizes (23 vs. 11). Patients not well described. Data suggest no adverse effects on strength.
Thorblad 1985 RCT	4.0	N = 19 isolated meniscus lesions	Effect of tourniquet vs. no tourniquet use in arthroscopic meniscectomy and effect on muscle rehabilitation.	Mean CK rose significantly in both groups, but did not pass upper normal serum level of 2.6 kat/l. Isokinetic quadriceps torque significantly lowered in both groups 1 week after operation. In non-tourniquet group still lower than non-operated leg 4 weeks after operation. At 4 weeks tourniquet group reached initial quadriceps torque, whereas non-tourniquet group had mean loss of 20%.	“The decrease in muscle torque was, thus, probably an effect of pain inhibition... it can be concluded that short-time ischemia during arthroscopic meniscectomy does not cause any adverse effect on muscle torque, and does not cause any adverse effect on muscle torque influence the speed of rehabilitation. If meniscectomy is undertaken without tourniquet control it may be better to inflate the tourniquet in case of bleeding instead of increasing fluid pressure and flow.”	Small sample size. Lack of study details.

Dobner 1982 RCT	4.0	N = 48 male active military duty age 18-34 undergoing medial or lateral meniscectomy	Meniscectomy performed with a pneumatic tourniquet (n = 24) vs. without a pneumatic tourniquet (n = 24).	Seventeen patients in tourniquet group demonstrated abnormal EMG findings vs. 0 without tourniquet. Greater mean inches jumped by operated leg in group without tourniquet vs. group with tourniquet.	"[T]he idea of early return to functional activity after knee surgery can best be realized by avoiding use of pneumatic tourniquet."	Patients not well described. Data suggest EMG differences; 6 weeks strength difference present suggesting modestly worse results with tourniquet.
Suture Techniques						
Bryant 2007 RCT	8.0	N = 100 undergoing ACL reconstruction or knee arthroscopy with likely meniscal tear	Arrows vs. inside-out suturing for vertical meniscal lesions.	Mean time to complete repair suture group vs. arrows group: 41.9±21.0 minutes; p <0.0001.	"Inside-out suturing and bioabsorbable arrows offer comparable success rates for meniscal repair, although tear location may dictate which method is more appropriate. Longer follow-up is required to determine whether there is a greater incidence of damage to the surface of the articular cartilage in patients whose meniscal tear was repaired using arrows."	No differences in outcomes.
Hantes 2006 RCT	6.5	N = 57 longitudinal full thickness tears greater than 10mm in length	Outside-in (A) vs. inside-in (B) vs. all-inside (C) arthroscopic meniscal repair technique.	Healing rates at ≥12 months: A vs. B vs. C 17/17 vs. 19/20 vs. 13/20 (65%) A vs. C p = 0.009, B vs. C p = 0.044	"There were no significant differences among the three groups concerning complications. According to our results, arthroscopic meniscal repair with the inside-out technique seems to be superior to comparison with other methods because it offers a high rate of meniscus healing without prolonged operation time."	Baseline differences in ACL repair. Possible cointerventions of surgical procedure not described. Data suggest repair with outside-in technique superior for healing and all inside technique worst.
Albrecht-Olsen 1999 RCT	4.5	N = 68 results of inside-out horizontal meniscus suturing vs. meniscus repair using meniscus arrow; 96% underwent re-	Patients treated with a hinged brace for 9 weeks; 30 patients had isolated bucket-handle lesion. In 19 cases, repair done in conjunction with an ACL	Of 65 re-arthroscopies, 91% of patients had healed or partially healed in arrow group compared to 75% in suture group (p = 0.11).	"Short-term results with meniscus arrows, based on healing and evaluated by second-look arthroscopy, seem promising."	Uncertain method for allocation, randomization, control for co-interventions. No clear advantage other than operating time.

		arthroscopy after 3-4 months; only lesions in red/red or red/white areas included	reconstruction, and in 19 cases, repair performed in an ACL-insufficient knee.			
Utility of MRI for Meniscal Tear Management						
Brealey 2007 RCT	6.5	N = 279 18-55 years inclusive, presenting in general practice and whose GPs were considering referral to an orthopaedic specialist for suspected internal derangement of knee.	Direct access to MRI vs. no MRI on the assessment of GP diagnosis and treatment plans (UK National Health System).	Change in diagnostic confidence (%) for MRI referral vs. Orthopaedic referral: Increased: 64 vs. 32; No effect: 29 vs. 52; Decreased: 7 vs. 16; p-between group change <0.001. There was a significant increase in within-group changes in diagnostic and therapeutic confidence.	“Access to MRI did not significantly alter GP’s diagnoses or treatment plans compared with direct referral to an orthopedic specialist, but access to MRI significantly increased their confidence in these decisions.”	Differences in length between randomization and allocation of intervention related to waiting lists. Although no specific co-intervention, natural history of improvement may have been a co-intervention for those waiting longer periods between randomization and allocation.

POST-OPERATIVE REHABILITATION FOR MENISCAL TEARS

See above.

KNEE BURSITIS

Knee bursitis is usually associated with a painless effusion of one or more of the knee bursae. (2291-2294) Acute knee bursitis may be slightly warm, but is generally non-tender or minimally tender. Septic (infected) bursitis is either a complication of aseptic knee bursitis or a direct consequence of trauma. (96, 2291, 2295, 2296) Generally, to be a complication of aseptic knee, bursitis also requires introduction of organisms through the skin, such as via abraded skin or an injection, although systemic seeding may also occur. Signs include swelling, pain, tenderness, and pain on range of motion. (2291, 2292, 2294, 2297) Bursitis due to crystal arthropathies also tends to present with findings similar to those of septic bursitis. (2292, 2298)

SPECIAL STUDIES AND DIAGNOSTIC AND TREATMENT CONSIDERATIONS

There are no recommended special studies for most cases of knee bursitis. If the bursa is thought to be infected, aspiration of the fluid and analyses including Gram stain and culture and sensitivity are recommended.

1. *Recommendation: Fluid Aspiration and Analyses for Knee Bursitis*

Aspiration of the fluid and analyses including Gram stain and culture and sensitivity are recommended to evaluate for septic bursitis in patients with suspected infection.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. *Recommendation: X-ray for Bursitis*

X-ray is recommended to rule out osteomyelitis or joint effusion in cases of significant septic knee bursitis.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

INITIAL CARE AND ACTIVITY MODIFICATION

Most patients with knee bursitis are treated with soft knee padding or an ace wrap, are instructed to avoid kneeling, and require no further care other than monitoring to assure resolution.

1. *Recommendation: Soft Knee Padding and Ace Wraps for Knee Bursitis*

Soft padding of the knee and ace wraps are recommended for treatment of knee bursitis.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

There are no quality trials evaluating these modifications for treatment of knee bursitis. Most cases of bursitis appear to resolve with non-invasive options. Soft padding and ace wraps are not invasive, have few adverse effects, are low cost, thus they are recommended.

Evidence for the Use of Soft Padding and Ace Wraps for Knee Bursitis

There are no quality studies evaluating the use of soft padding or ace wraps for knee bursitis.

2. *Recommendation: Modifying Activities to Avoid Kneeling or other Pressure Over the Knee*

Modifying activities to avoid kneeling or pressure over the knee and allowing time to reabsorb the fluid are recommended for treatment of knee bursitis.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

There are no quality trials evaluating modification of activities for treatment of knee bursitis. Most cases appear to resolve with non-invasive options including avoiding kneeling and pressure on the knee. Activity modification is not invasive, has low or no adverse effects, is low cost and is recommended.

Evidence for the Use of Modifying Activities

There are no quality studies evaluating the use of modifying activities for knee bursitis.

MEDICATIONS

NON-STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

Some patients with knee bursitis have been treated with NSAIDs, particularly if there is some accompanying discomfort.

Recommendation: NSAIDs for Knee Bursitis

There is no recommendation for or against the use of NSAIDs for the treatment of knee bursitis.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Rationale for Recommendation

There is no quality evidence that NSAIDs alter the clinical course, thus there is no recommendation for or against their use for knee bursitis. The threshold for a trial of these medications should generally be low.

Evidence for the Use of NSAIDs for Knee Bursitis

There are no quality studies evaluating the use of NSAIDs for knee bursitis.

INJECTION THERAPIES

ASPIRATION

Aspiration of the swollen bursa has been used for diagnosing septic knee bursitis, or if it is thought to be potentially infected. (2292, 2294, 2299)

Recommendation: Aspiration for Infected Bursa

Aspiration of a clinically infected or questionably infected bursa is recommended.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Rationale for Recommendation

Aspiration has been used for diagnosis, particularly when combined with Gram stain, culture and sensitivity, and complete cell count of the aspirated fluid are performed. Crystal examination (light polarizing microscopy) should also be performed at least once on the aspirated fluid. Aspiration of a bursa is invasive, has relatively low adverse effects, although it can introduce an infection, and is low to moderately costly, but is recommended for diagnosis and planning of treatment.

GLUCOCORTICOSTEROID INJECTIONS

Injection with a glucocorticosteroid (typically doses of methylprednisolone approximately 20 to 40mg or equivalent), often accompanied by aspiration, is widely used for aseptic knee bursitis.(2299)

Recommendation: Glucocorticosteroid Injections for Knee Bursitis

There is no recommendation for or against the use of glucocorticosteroid injections for the treatment of knee bursitis. This may be a reasonable option for patients who are failing to resolve prior to consideration of surgery.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are no quality studies evaluating the use of glucocorticosteroid injections to treat knee bursitis. These injections sometimes appear to help speed resolution in cases not trending towards resolution. However, these injections potentially introduce bacteria, thus the one drawback is the potential to create a septic bursitis, which then often requires surgical drainage. If attempted, these injections appear to be reserved for patients thought to not be infected and/or who are not resolving with activity modifications and observation. If attempted, generally only 1 aspiration/injection is performed followed by careful observation. Some physicians aspirate and then inject, while others only inject the steroid. If the bursitis is not satisfactorily resolved, a second aspiration/injection is often attempted, although usually not sooner than 3 to 4 weeks later. Doses of steroid are approximately, e.g., methylprednisolone 20 to 40mg or equivalent. Aspirated fluid should be sent at least once for studies including crystals (light polarizing microscopy), Gram stain, culture, and sensitivity and complete cell count. Glucocorticosteroid injection is invasive, has relatively low adverse effects, although it can introduce an infection, and is moderately costly; thus, it is recommended in those cases not trending towards resolution.

Surgical Considerations

Surgery has been used to treat knee bursitis that has not responded to activity modifications and injections or if infection is believed to be present.(2300-2304)

1. Recommendation: Surgical Drainage for Knee Bursitis

Surgical drainage is recommended for treatment of knee bursitis.

Indications – Knee bursitis that is either infected, clinically thought to be infected, or not infected but present for at least approximately 6 to 8 weeks without trending towards resolution despite being treated with soft padding and activity modifications.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

2. Recommendation: Surgical Resection for Chronic Knee Bursitis

Surgical resection of the bursa is recommended for chronic knee bursitis with recurrent drainage.

Indications – Knee bursitis with recurrent drainage.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendations

There are no quality trials addressing surgery for the treatment of knee bursitis. Surgical drainage of a swollen knee bursa has been successfully used for treatment. As it is not without potential complications, it is recommended to be reserved for selected cases either involving infection or failure to respond to an adequate trial of non-operative measures. Surgical drainage is invasive, has modest adverse effects, and is moderately to highly cost, but is recommended in those cases not trending towards resolution or which are thought to be infected.

PATELLAR TENDINOSIS, PATELLAR TENDINOPATHY (“JUMPER’S KNEE”), AND ANTERIOR KNEE PAIN

Anterior knee pain is caused by several different entities that include patellar tendinosis as well as patellofemoral joint-related pain.(101, 159, 2305, 2306) The diagnosis is primarily clinical (see History and Physical Examination), and a careful history will usually result in a presumptive diagnosis that may be confirmed with physical examination. Patients have anterior knee pain, and those with patellar tendinosis have pain localized to the affected area of the patellar tendon. Those with patellofemoral joint disorders tend to have peripatellar knee pain that often is worse with use of stairs.(2305, 2307)

X-RAY

X-ray is commonly utilized, especially for evaluation of pain felt to be attributable to the patellofemoral joint.

Recommendation: X-ray for Evaluation of Patellofemoral Joint Pain

X-ray is recommended to evaluate patellofemoral joint pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

ULTRASOUND AND MRI

Recommendation: Ultrasound or MRI for the Evaluation of Patellofemoral Joint Pain

There is no recommendation for or against the use of diagnostic ultrasound or MRI to evaluate patellofemoral joint pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

INITIAL CARE

Rest, splints, ice, and heat have been utilized for treatment of tendinoses, as well as for patellofemoral joint disorders. There are no quality studies of treatment options, aside from surgery and rehabilitation for patellofemoral pain or tendinosis (see next section). Out of necessity, guidance for treatment relies upon other musculoskeletal disorders for inferences on projected treatment efficacy.

WORK LIMITATIONS

1. Recommendation: Work Limitations for Select Cases of Patellofemoral Joint Pain

Work limitations are recommended for patients with patellofemoral joint pain who perform physically demanding tasks or who have no ability to avoid repeating physically demanding job tasks that have resulted in the condition, especially jumping for patellar tendinosis and stair use for patellofemoral joint pain.

Strength of Evidence – Recommended, Insufficient Evidence (I)

2. Recommendation: Work Limitations for Other Cases of Patellofemoral Joint Pain

There is no recommendation for or against the use of work limitations for treatment of other cases of patellofemoral joint pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

BED REST AND KNEE IMMOBILIZATION

Recommendation: Bed Rest and Knee Immobilization for Patellofemoral Joint Pain

Bed rest and knee immobilization are not recommended for treatment of patellofemoral joint pain, although relative rest may be required for some patients, particularly those more severely affected.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

NSAIDs

Recommendation: NSAIDs for Patellofemoral Joint Pain

Nonsteroidal anti-inflammatory medications are recommended for treatment of patellofemoral joint pain.

Strength of Evidence – Recommended, Insufficient Evidence (I)

ICE/HEAT

Recommendation: Ice/Heat for Patellofemoral Joint Pain

Ice and/or heat are recommended for treatment of patellofemoral joint pain.

Strength of Evidence – Recommended, Insufficient Evidence (I)

WRAPS, SUPPORTS, AND SLEEVES

Recommendation: Wraps, Supports, or Sleeves for Patellofemoral Joint Pain

Ace wraps, supports, or sleeves are recommended for treatment patellofemoral joint pain.

Strength of Evidence – Recommended, Insufficient Evidence (I)

REHABILITATION THERAPY

Recommendation: Rehabilitation Therapy for Patellofemoral Joint Pain

A course of rehabilitation therapy is recommended for treatment of patellofemoral joint pain in patients with persisting pain thought to not be clearly surgical.

Dose/Duration – See exercise section for dose, frequency, and discontinuation.

Strength of Evidence – Recommended, Insufficient Evidence (I)

OTHER MODALITIES/INJECTIONS

Recommendation: Other Modalities/Injections for Patellofemoral Joint Pain

There is no recommendation for or against the use of therapeutic ultrasound, diathermy, iontophoresis, low-level laser therapy, phonophoresis, autologous blood injections, or hyaluronic acid injections for treatment of patellofemoral joint pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

Work limitations may be necessary depending on the severity of the condition and the required job demands. Those performing physically demanding tasks or those who have no ability to avoid repeating physically demanding job tasks that have resulted in the condition are recommended to have work limitations. In other cases, there is no recommendation for or against work limitations. Bed rest and knee immobilization are not recommended due to risks of venous thromboembolisms and other adverse effects of bed rest, although relative rest may be required for some patients, particularly those more severely affected. NSAIDs, ice, heat, Ace wraps, supports, and sleeves are recommended. Those with persisting pain thought to not be clearly surgical are recommended to have a course of rehabilitation therapy. There is no recommendation for or against therapeutic ultrasound, diathermy, iontophoresis, low-level laser therapy, phonophoresis, autologous blood injections, or hyaluronic acid injections for treatment of patellofemoral joint pain.

EXERCISE

Exercise, physical therapy, and rehabilitation have been used for treatment of anterior knee pain.(2308-2331) However, evidence to support physical interventions has been labeled “limited.”(2332)

Recommendation: Exercise for Patellofemoral Joint Pain

Exercise is moderately recommended for patellofemoral joint pain.

Indications – Patients with patellofemoral joint pain, especially if insufficiently responsive to treatment with NSAIDs and activity modification.

Duration – One to 4 weeks, 2 to 3 sessions a week; additional appointments based on continuing objective improvements.

Indications for Discontinuation – Achievement of goals, non-compliance with clinic or home-based exercises, intolerance.

Strength of Evidence – Moderately Recommended, Evidence (B)

Rationale for Recommendation

Two moderate-quality trials compared exercise therapy with no treatment and found exercise of modest efficacy.(2333-2335) Results from another trial of specific exercise approaches, including static, dynamic, vastus medialis obliquis selective activation (VMO), is unclear,(2335) and there is no recommendation for a specific exercise approach. There also is one trial suggesting a patellar brace is of equal efficacy.(2336) One high-quality trial with two reports included multiple co-interventions and suggested benefit, but an assessment of which intervention was effective is not possible.(2310, 2337) Exercises are not invasive, have low adverse effects, are low to moderately costly depending on numbers of appointments, and thus are recommended.

Evidence for the Use of Exercise for Anterior Knee Pain

There are 2 high- and 20 moderate-quality (one with two reports) RCTs incorporated into this analysis. There are 3 low-quality RCTs in Appendix 1.(594, 2338, 2339)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Crossley 2002 RCT	8.5	N = 71 patellofemoral pain (anterior or retro patellar knee pain with prolonged sitting, stair-climbing, squatting, running, kneeling, hopping/jumping) ≥1 month duration	Individual physiotherapy (quadriceps muscle retraining, patellofemoral joint mobilization, EMG biofeedback, patellar taping, daily HEP) once weekly, 30 to 60 minutes for 6 weeks then routine home PT practice with patellar taping vs. placebo taping, gluteal muscle strengthening, sham ultrasound, and light application of a nontherapeutic gel; 6 weeks treatment.	Physical therapy (PT) group with improvement in mean worst pain (3.0 vs. 5.0, p <0.05), mean usual pain (1.0 vs. 2.5, p <0.05), and mean AKPS (86 vs. 78, p <0.05) vs. sham. PT with more step ups (p = 0.01), step-downs (p = 0.03), and squats (p = 0.04) before onset of pain.	“[T]his randomized, double-blinded, placebo controlled trial provided evidence to support the use of a physical therapy regimen in the short-term management of patellofemoral pain.”	Attempted patient blinding, although somewhat higher beliefs in receipt of sham among sham group and no active exercise in sham. Data suggest active therapy superior to placebo, but heterogeneous mix of interventions precludes assessing which were effective.
Cowan 2002 RCT 2nd Report of Crossley	8.5	N = 65 described above	Described above.	PT group greater change in both average and worst pain in past week. Improved worst pain in last week ascending stairs; no differences worst pain in last week descending stairs. AKP greater improvement in PT group.	“[A] ‘McConnell’-based physical therapy treatment regime for PFPS alters the motor control of VMO relative to VL in a functional task and this is associated with a positive clinical outcome.”	Data suggest active therapy superior.
Quilty 2003 RCT	7.5	N = 87 patellofemoral joint OA	Experimental group (physiotherapy 9 30-minute sessions over 10 weeks with quadriceps exercises, patellar taping, postural/footwear/weight reduction advice) vs. controls; 1 year follow-up.	VAS pain (baseline/5 months/12 months): treatment (51.0/42.8/48.1) vs. controls (53.4/50.5/54.1). WOMAC function scale: treatment (27.4/26.5/29.7) vs. controls (27.8/27.5/28.3).	“The treatment package produced small improvements in knee pain scores and quadriceps muscle strength 10 weeks after the end of the treatment period. There was no difference between the 2 groups at 12 months.”	Multiple co-interventions, not well controlled. Data show no benefit other than MVC, suggests short-term benefit for that measure and not long-term benefit of this combination of treatments.
Song 2009 RCT	7.0	N = 89 patellofemoral pain syndrome, age <50; duration >1 month	Hip abduction (50N force hip abduction force to distal 1/3 of thigh, otherwise similar to leg press exercise) plus leg-press exercise vs. leg-press exercise (5 sets of 10 reps at 60% MVC, adjusted	VAS worst pain (pre/post): LPHA (4.80±2.26/2.62±2.51) vs. LP (4.85±2.49/2.26±2.20) vs. control (4.99±2.18/4.81±2.55), p = 0.72. Other measures also all	“Similar changes in pain reduction, functional improvement, and VMO hypertrophy were observed in both exercise groups.”	Symptom duration shorter in control group (p = 0.056). Data suggest comparable efficacy.

			over time for increased MVC) vs. no exercise. 3 sessions a week for 8 weeks.	negative between groups.		
Van Linschoten 2006 RCT	7.0	N = 131 patellofemoral pain syndrome of 2 months to 2 years duration	Supervised exercise therapy (9 visits in 6 weeks; static and dynamic quadriceps, balance and flexibility exercise plus HEP) vs. wait and see (education and advice regarding complaints) for 3 months; 12 months follow-up.	Recovery 3, 12 months: exercise [26/62 (41.9%)/36/58 (62.1%) vs. controls [21/60 (35.0%)/30/59 (50.8%)], OR 1.34/1.60 (NS). Function scores (pre, 3, 12 months): exercise (64.4/78.8/83.2) vs. controls (65.9/74.9/79.8), adjusted differences 4.92 (0.14-9.72) vs. 4.52 (-0.73-9.76).	“Supervised exercise therapy resulted in less pain and better function at short term and long term follow-up compared with usual care in patients with patellofemoral pain syndrome in general practice. Exercise therapy did not produce a significant difference in the rate of self reported recovery.”	Data suggest exercise program of modest short term benefit. Prognosis of all patients appears fair.
van Linschoten 2009 RCT	7.0	N = 131 patients 14-40 years of age with patellofemoral knee pain with symptoms longer than 2 months but less than 2 years	Exercise therapy intervention (n = 65) vs. usual care (n = 66) for 3 months.	Pain at rest 3 months compared to baseline (baseline/3 months): exercise therapy vs. control favored exercise. Pain at rest at 12 months compared to baseline: exercise therapy vs. control favored exercise. Pain on activity at 3 months compared to baseline (baseline/3 months): exercise therapy vs. control favored exercise. Pain on activity at 12 months compared to baseline: exercise therapy vs. control favored exercise.	“Supervised exercise therapy resulted in less pain and better function at short term and long term follow-up compared with usual care in patients with patellofemoral pain syndrome in general practice. Exercise therapy did not produce a significant difference in the rate of self reported recovery.”	Data suggest exercise program of modest short term benefit. Prognosis of all patients appears fair.
Bahr 2006 RCT	7.0	N = 40 patellar tendinopathy with a history of exercise-related pain in proximal part of the patellar tendon or patellar insertion and tenderness to palpation corresponding to painful area	Surgical treatment group vs. eccentric training group vs. secondary surgical treatment group for patellar tendinopathy	VISA scores not different among groups at all follow-ups, p = 0.87. No difference between groups for global evaluation score, jump height, or overall treatment satisfaction.	“[A]lthough surgical treatment and eccentric strength training can produce significant improvement in terms of pain and function scores, it appears that only about half of all patients will be able to return to sport within one year after treatment with each option, and	Data suggest no differences.

					fewer still will have relief of all symptoms. In the absence of other validated treatment options, we believe that eccentric training, a low-risk and low-cost option, should be tried before surgery is considered.”	
Syme 2009 RCT	6.0	N = 69 chronic patellofemoral pain syndrome	Vastus medialis obliquus selective activation treatment (selective) vs. quadriceps femoris strengthening group (general) vs. no treatment control for patellofemoral pain syndrome for 8 weeks.	Mean (SD) baseline/post treatment selective vs. general vs. control, body function and structures measures NRS-101 average pain intensity previous month: (pre/post) Selective (47.7/21.4) vs. General (51.3/28.1) vs. control (59.6/49.3), p = 0.001.	“[T]he study demonstrated that physiotherapy involving either selective VMO retraining exercises or a general quadriceps femoris strengthening program reduced pain, improved function and Quality of Life in PFPS patients. This study did not demonstrate that rehabilitation with selective VMO exercise significantly improves outcome above that provided by general open and closed chain strengthening exercises.”	Study has many co-interventions and unclear which were implemented. Data do not support advantage to VMO approach or general exercise. Both superior to controls over 8 weeks follow-up.
Visnes 2005 RCT	6.0	N = 29 volleyball players age 18-35 with patellar tendinopathy, at least 3 months duration, VISA <80	Training group (squats on 25°decline board as HEP, 3x15 reps BID) vs. control group (trained as usual) for 3 months treatment. 6 months follow-up.	No differences between groups in VISA scores at 6 weeks (p = 0.71) or 6 months (p = 0.99). Global knee function scores also not different (p = 0.44).	“There was no effect on knee function from a 12-week program with eccentric training among a group of volleyball players with patellar tendinopathy who continued to train and compete during the treatment period.”	Data suggest lack of efficacy.
Lun 2005 RCT	6.0	N = 129 at least 18 years of age with patellofemoral pain syndrome (PFPS)	Structured home rehab program (E group, n = 34) vs. patellar brace (B group, n = 32) vs. structured home rehabilitation program and patellar brace (EB group, n = 32) vs. structured home rehabilitation	No significant differences between groups although improvements seen in each group from baseline to 12 weeks. VAS pain ratings (0/12 weeks): exercise (4.4/2.9) vs. brace (4.4/2.7) vs.	“Symptoms of PFPS improved over time in terms of pain and knee function regardless of the treatment group.”	No placebo or sham group. Data suggest equal efficacy and no additive benefit of adding structured home rehabilitation program to

			and knee sleeve (ES group, n = 31) for 12 weeks	exercise plus brace (4.2/2.7) vs. exercise plus sleeve (4.4/2.8).		patellar brace or vice versa.
Nakagawa 2008 RCT	6.0	N = 14 age 17-40 with a clinical diagnosis of patellofemoral pain syndrome	Control group exercise (n = 7) vs. intervention group exercise consisting of training of the transversus abdominis muscle, hip abductors, and lateral rotator muscles (n = 7) for 6 weeks.	Significant differences from baseline to final assessment for intervention for 5 of 6 VAS scores: p <0.05; NS for control. Eccentric isokinetic knee extensor peak torque improved from baseline to final assessments for intervention and control. Significant increase in gluteus medius electromyographic signal during maximal isometric voluntary contraction in intervention group, p = 0.03, NS for control.	"[S]ix-week home exercise programme based on quadriceps strengthening supplemented by strengthening and functional training focused on the transversus abdominis muscle, hip abductors and lateral rotators muscles provided additional benefits with respect to the pain perceived symptoms during functional activities in patients with patellofemoral pain syndrome."	Small sample sizes. Data suggest strengthening in addition to other exercises more effective.
Crossley 2005 RCT	5.5	N = 40 anterior or retropatellar knee pain while sitting, stairs, squatting, running, or kneeling and presence of pain on palpation of patellar facets; subjects included in Crossley 2002	Physical therapy, n = 21 (patellar taping, retraining of vasti, exercises designed to provide progressive load to patellofemoral joint using surface EMG biofeedback, maximize vastus medialis obliquus (VMO) gluteal strengthening, isometric hip abduction/external rotation in standing) vs. placebo, n = 19 (placebo taping, sham ultrasound, and light application of nontherapeutic gel) once weekly for 6 weeks; assessed at baseline and 6 weeks.	Descending stairs knee flexion at heel strike (°) (baseline/final): PT (13±5/17±5) vs. placebo (13±4/4±4) mean difference 5 (95% CI: 2 to 7), p = 0.000. Descending stairs peak knee flexion (°): physical therapy (31±7/39±6) vs. placebo (34±7/32±5) mean difference 9 (95% CI: 5 to 12), p = 0.000. NS between groups for ascending stairs knee flexion at heel strike, peak knee flexion, time to peak, and descending stairs time to peak.	"Physical therapy intervention resulted in significantly greater changes in knee joint motion than a placebo treatment, and these changes in knee motion were partly related to changes in pain and changes in onset timing of the vasti."	Baseline differences including in symptoms duration (41 vs. 24mo) concerning for randomization failure, although likely bias in favor of placebo. Functional measures not different, though may be underpowered.
Herrington 2007 RCT	5.5	N = 45 males age 18-35 with diagnosis of anterior knee pain, patellofemoral joint syndrome, or patellar maltracking with symptoms for at least 1 month	No exercise (control group, n = 15) vs. non-weight-bearing single-joint exercises (SJNWBE, n = 15) vs. weight-bearing multiple-joint exercises (MJWBE, n = 15) 3 times per week for 6 weeks	Mostly graphic data. NS post-intervention between exercise groups for modified Kujala score. SJNWBE and MJWBE significantly improved modified Kujala scores vs. controls post-intervention. Knee extension strength:	"[B]oth weight-bearing and non-weight-bearing quadriceps exercises can significantly improve subjective and clinical outcomes in patients with PFPS."	Detailed baseline data not provided. Data suggest exercise superior to controls and mostly no differences between groups.

				NS between exercise groups post-intervention; greater in both exercise groups post-intervention vs. control. Pain during knee extension strength test: NS between exercise groups post-intervention; significantly lower level of pain in both exercise groups vs. controls. Pain during step-up and step-down test: NS between exercise groups post-intervention; lower pain level in both exercise groups vs. controls.		
Cannell 2001 RCT	5.0	N = 19 jumper's knee, mostly unilateral and a few bilateral; no orthotics; subacute or chronic symptoms	Drop squat exercises (3 sets of 20 drops once a day, 5 day a week) vs. leg extension/leg curl exercises (3 sets of 10 lifts each leg extension/leg curl, once a day, 5 days a week) for 12 week program. Both groups treated with ice, NSAIDs and relative rest for first 2 weeks; 12 weeks follow-up.	Mean±SD hamstring moment of force at baseline vs. 6 weeks vs. 12 weeks: Injured leg/drop squats: 271± 123 vs. 286±114 vs. 309±122; p <0.001 difference from baseline. Non-injured leg/drop squats: 282± 111 vs. 293±107 vs. 312±108; p <0.001. Injured leg/ext/curls: 287±98 vs. 320±93 vs. 338±91; p <0.001.	“Progressive drop squats and leg extension/curl exercises can reduce the pain of jumper's knee in a 12 week period and permit a high proportion of patients to return to sport. Not all patients, however, return to sport by that time.”	Longer symptom duration in leg extension group at baseline. No placebo/sham control as both groups active exercise. Small sample size and likely underpowered.
Bakhtiary 2008 RCT	4.5	N = 32 female university students with patellar chondromalacia	Open kinetic chain exercise (OKC): straight leg raise (SLR) (n = 16) vs. closed kinetic chain exercise (CKC) – semi-squats (n = 16) 20 times BID for 3 weeks.	Q angle reduced significantly more in semi-squat group (1.6±0.4) vs. SLR group (0.7±0.3), p = 0.016. Crepitation reduced by 55.6% in SLR vs. 36 in semi-squat group after 3 weeks. Semi-squat had increased muscle force (55.9 N±20.2) vs. SLR (40.1 N±28.5), p = 0.01. Thigh circumference increase in semi-squat at 5cm (p = 0.002) and 10cm (p = 0.01) above patella vs. SLR. NS	“[S]emi-squat exercises (closed kinetic chain) are more effective than SLR exercise (open kinetic chain) in the treatment of patellar chondromalacia.”	Co-interventions not controlled. Compliance and dropouts unclear. Relatively few data provided, mostly suggesting improvements in squat group; however, VAS pain score did not achieve significance (p = 0.13).

				between group for improvement in VAS.		
Young 2005 RCT	4.5	N = 17 elite volleyball players 18-35 years old with proximal patellar tendon pain that limited sports function	Decline exercises (25° decline board) vs. step exercises (10cm) 3x15 reps BID for 12 weeks. Exercises at 60° knee flexion and with progressive weight in backpacks. 12 months follow-up.	VISA scores increased in both groups (graphic data, with trend in favor of decline over step, but not significant (graphic data). VAS pain scores also favored decline; but initial scores 30 vs. 46.	“Both exercise protocols improved pain and sporting function in volleyball players over 12 months.”	Small sample sizes. Baseline differences. Underpowered. Co-interventions not controlled. Limited ability to rely on these data.
Witvrouw 2000 RCT	4.5	N = 60 unilateral or bilateral patellofemoral pain for ≥6 months	Open chain kinetic exercise (maximal static quadriceps contractions knee in full extension; supine SLRs; short-arc knee flexion from 10° to terminal extension; leg adduction exercises in lateral decubitus) vs. closed chain kinetic exercise (seated leg presses, 1/3 knee bends on 1 leg and both legs; stationary bicycling; rowing machine; step-up and step-down and progressive jumping exercises) for patellofemoral pain. 30-45 minutes per session, 3 times a week for 5 weeks; 3 months follow-up	Most results not different at 5 weeks or 3 months, including VAS, Kujala scores, VAS during tests. Frequency of locking (p = 0.03), clicking sensation (p = 0.041) pain during isokinetic testing (p = -0.28 and pain at night (p = 0.024) all favored closed chain exercises.	“The few significantly better functional results for some of the tested parameters in the closed kinetic chain group suggest that this type of treatment is a little more effective than the open kinetic chain program in the treatment of these patients.”	Several details sparse. Data suggest closed chain exercise superior.
Avraham 2007 RCT	4.5	N = 42 patellofemoral pain syndrome	Group 1: conventional rehab with quadriceps strengthening (7.5 minutes SLR and single-leg squats) plus TENS (15 minutes to peri-patella) vs. Group 2: hip orientated rehab (3 minute ITB stretch, 3 minute hamstring stretch, 9 minute hip external rotators strengthening plus TENS) vs. Group 3: combination of other 2 groups (15 minutes total exercise plus 15 minutes TENS). All treated 30 minute	Sparse results presented graphically.	“[T]he explored different rehabilitation programs showed a similar beneficial effect.”	Pilot study. No baseline demographic data by groups. Programs balance contact/treatment time. Data suggest comparable efficacy.

			sessions, 2 times a week for 3 weeks; 3 weeks follow-up.			
Roush 2000 RCT	4.5	N = 63 anterior knee pain (patellar tendinitis, quadriceps tendinitis, patellofemoral syndrome, chondromalacia patella, idiopathic knee pain, Osgood-Schlatter disease, plica syndrome)	Twice daily traditional home therapy vs. physical therapy 3 times a week for 6 weeks vs. home therapy with modified VMO exercise BID. 12 weeks follow-up.	Maximum isokinetic flexion peak torque was significantly different for modified therapy with VMO exercises compared to other groups. Cost for physical therapy group ranged from \$1,261.00 to \$1,711.00 compared to \$291.00 for other groups.	“[H]ome rehabilitation using the modified, VMO specific straight leg raise (Muncie method) appears to result in decreased impairment due to pain during activity compared with traditional home therapy programs and formal physical therapy. This improvement also occurs at a lower cost to the patient than other forms of therapy.”	Many disorders included and no block randomization. Baseline differences present (e.g., mean age 22.3 vs. 32.6; 23.8% vs. 50.0% male), results in low quality study. Data suggest VMO may be more effective.
Witvrouw 2003 2nd report of RCT	4.5	N = 60 unilateral or bilateral patellofemoral pain for ≥6 months	Open chain kinetic exercise vs. closed chain kinetic exercise for patellofemoral pain; 3 months follow-up.	No differences in reflex reaction times or pain scores.	“Only small and not statistically supported differences in anterior knee pain were found between the two groups... knee pain decreased significantly in both groups.”	Report primarily targeted reflex response times.
Witvrouw 2004 3rd report of RCT	4.5	N = 60 unilateral or bilateral patellofemoral pain for ≥6 months	Open chain kinetic exercise vs. closed chain kinetic exercise for patellofemoral pain	Open kinetic chain exercise group participated in more sports activity than closed chain (92% vs. 60%, p<0.05) after 5 years; 35% of open kinetic chain vs. 65% of closed chain participated in home exercise programs. More participants in open kinetic chain complained of knee joint swelling (p = 0.04), pain with descending knee pain (p = 0.01), and pain at night (p = 0.04).	“The 5-year results for patients with patellofemoral pain randomized to OKCE or CKCE were similar, and the improvements that were shown after 3 months were generally maintained.”	Data suggest comparability.
Jonsson 2005 RCT	4.0	N = 15 with 19 patellar tendons with pain, mean duration of 17.4 months (range 8-72 months). Proximal patellar tendon pain during or after patellar	Eccentric quadriceps training with standing on a decline board vs. concentric quadriceps training while standing on a decline board consisting of 3 sets of 15 repetitions,	VAS score at baseline/12 week follow up for eccentric training: 72.7±16.6/ 22.5±26.4, p <0.005 vs. concentric training: 74.3±16.6/68±18.5, p <0.34. VISA score	“In the short term, treatment with painful eccentric quadriceps training, but not with painful concentric quadriceps training, while standing on a	Small sample size. High dropouts in concentric group. Data suggest eccentric training exercise superior to concentric.

		tendon loading activity, proximal patellar tendon tenderness, or structural tendon changes together with proximal patellar tendon neovascularisation	BID, 7 days/week, for 12 weeks	for eccentric training: 41.1±17.9/83.3±23.4, p <0.005; concentric training: 40.7±16.3/37.0±4.6, p <0.34.	decline board, significantly reduced tendon pain during activity and improved function in athletes with chronic painful jumper's knee."	
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TAPING

Patellar taping has been used to treat anterior knee pain.(2340-2342) There is experimental evidence supporting the idea that taping and bracing provide coronal plane and torsional control of the knee in eccentric stair step descent.(1071)

Recommendation: Taping for Anterior Knee Pain

Taping is not recommended for anterior knee pain.

Strength of Evidence- Not Recommended, Evidence (C)

Rationale for Recommendation

One moderate-quality trial attempted sham taping and found no efficacy of taping(2343); two other trials also suggested that taping is ineffective.(2344, 2345) While one trial suggested taping may be superior,(2346) the balance of studies suggest that it is not effective. There were two crossover trials, but both were of very short duration, precluding their use in guidance.(2347, 2348) Taping is not invasive, but is not tolerated by some patients and compliance is reportedly problematic. Taping is low cost for one application, but rapidly becomes costly over time. As most quality evidence suggests a lack of efficacy, taping is not recommended for treating anterior knee pain.

Evidence for the Use of Taping for Anterior Knee Pain

There are 6 moderate-quality RCTs or crossover trials incorporated into this analysis. There are 1 low-quality RCTs or crossover trials in Appendix 1.(2349)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Hinman 2003 RCT	7.5	N = 87 meeting clinical and radiological classification criteria of American College of Rheumatology (presence of osteophytes, age over 50 years, pain in knee)	Therapeutic tape (provided medial glide, medial tilt, and anteroposterior or tilt to patella) (n = 29) vs. control tape aimed to provide sensory input only (n = 29) vs. no tape intervention (n = 29) with tape worn 3 weeks and reapplied	Pain on movement at 3 weeks (mean difference and 95% CI): no tape vs. control tape 0.8 (0.0 to 1.6), no tape vs. therapeutic tape 2.1 (1.2 to 3.0), control vs. therapeutic 1.3 (0.3 to 2.4). Pain on movement at 6 weeks: no tape vs. control tape 1.0 (0.0 to 2.0), no tape vs. therapeutic 1.7 (0.6 to 2.8), control vs. therapeutic 0.7 (-0.6 to 1.9). Pain on worst activity at 3 weeks: no tape vs. control NS, no tape vs. therapeutic 2.0 (1.0 to 3.1), control vs.	"Therapeutic knee taping is an efficacious treatment for the management of pain and disability in patients with knee osteoarthritis."	Patients not well described. Data suggest no difference between sham tape and treatment tape over 6 weeks.

			<p>weekly with assessments at baseline, 3 weeks, and 6 weeks.</p>	<p>therapeutic tape 1.5 (0.3 to 2.7). Pain on worst activity at 6 weeks: no tape vs. control (NS), no tape vs. therapeutic 2.4 (1.1 to 3.7), control vs. therapeutic tape 1.6 (0.1 to 3.0). Restriction of activity (WOMAC) at 3 weeks: no tape vs. control 1.6 (0.5 to 2.6), no tape vs. therapeutic 1.0 (0.2 to 1.9), control vs. therapeutic (NS). Restriction of activity at 6 weeks: no tape vs. control 1.9 (0.5 to 3.2), no tape vs. therapeutic 1.6 (0.3 to 2.9), control vs. therapeutic (NS). Pain (WOMAC) at 3 weeks: no tape vs. control (NS), no tape vs. therapeutic 1.7 (0.6 to 2.9), control vs. therapeutic (NS). Pain at 6 weeks: no tape vs. control 2.1 (0.6 to 3.6), no tape vs. therapeutic 2.1 (0.5 to 3.6), control vs. therapeutic (NS). Physical function (WOMAC) at 3 weeks: no tape vs. control (NS), no tape vs. therapeutic 5.1 (1.9 to 8.4), control vs. therapeutic 1.8 (-2.3 to 6.0). Physical function at 6 weeks: no tape vs. control 6.7 (3.1 to 10.3), no tape vs. therapeutic 4.7 (0.6 to 8.9), control vs. therapeutic (NS). Severity (knee pain scale) at 3 weeks: no tape vs. control (NS), no tape vs. therapeutic 2.2 (0.4 to 4.0), control vs. therapeutic (NS). Severity at 6 weeks: no tape vs. control tape 3.0 (1.0 to 4.9), no tape vs. therapeutic 2.6 (0.7 to 4.4), control vs. therapeutic (NS). Frequency (knee pain scale) at 3 weeks: no tape vs. control (NS), no tape vs. therapeutic 2.1 (1.0 to 3.3), control vs. therapeutic (NS). Frequency at 6 weeks: no tape vs. control 3.0 (1.0 to 4.9), no tape vs. therapeutic 2.5 (0.7 to 4.3), control vs. therapeutic (NS). NS SF-</p>		
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				36 bodily pain, physical function, and physical role.		
Whittingham 2004 RCT	7.0	N = 30 army recruits age 17-25 referred for physiotherapy with acute patellofemoral pain syndrome; pain on ascending/descending stairs, squatting, sitting for extended periods of time or associated with increase in physical activity	Patella taping and standardized exercise program (n = 10) vs. placebo taping and exercise program (n = 10) vs. exercises alone (n = 10) for 4 weeks	Twenty-four hour pain scores (mean±SD) initial/Week 1/Week 2/Week 3/Week 4: taping and exercise (7.5±1.0/4.4/2.4/0.8/0.0) vs. placebo taping and exercise (7.5±0.8/5.6/4.1/2.3/0.9) vs. exercise alone (7.5±0.8/5.0/3.9/3.1/1.8).	"[O]ver a period of 4 weeks a combination of daily patella taping and exercises was successful in improving pain and function in individuals with patellofemoral pain syndrome. The combination of patella taping and exercise was superior to the use of exercise alone."	Military population. Results suggest taping plus exercise may be superior to placebo taping plus exercise or exercise alone.
Cowan 2002 RCT/ Crossover Trial	6.5	N = 10 diagnosed with PFPS by clinical exam and 12 asymptomatic controls	Therapeutic tape vs. placebo tape vs. no tape during a stair stepping task with a 5 minute break between each taping condition.	Stair stepper task for patients with PRPS without tape: onset of vastus lateralis (VL) EMG occurred before vastus medialis obliquus (VMO) by 16.58 months for concentric, 19.71 months for eccentric phase, p <0.05 concentric and p <0.01 eccentric. Participants with no history of PFPS: VMO onset occurred before VL for concentric phase by 15.92ms (p <0.01), onsets simultaneous for eccentric phase (p = 0.11). NS between no tape and placebo tape in PFPS groups. No tape vs. therapeutic tape: p <0.003 concentric and p <0.005 eccentric. Placebo tape and therapeutic tape: p <0.002 concentric, NS for eccentric. Patella taped in PFPS group: EMG onset of VMO occurred before VL for concentric phase of stair stepping task (p <0.001) and simultaneous for eccentric phase (p = 0.091). NS between taping procedures of onset of VMO and VL. Pain measures PFPS group: less in therapeutic taped group vs. placebo (p <0.0001) and no tape (p <0.001), NS between no tape and placebo.	"The present study provides important information demonstrating that the application of therapeutic patellar tape is capable of changing both EMG onset timing of the vasti and pain in participants with PFPS."	Sample size very small. Experimental study of very short duration.

Cushnaghan 1994 RCT/ Crossover Trial	5.5	N = 14 knee OA (ACR), anterior knee pain, difficulty walking and with steps and stairs, mean age of 70.4, mean duration of knee symptoms of 8.3 years	Neutral taping (tape applied directly over front of patella without any pressure) vs. medial taping (tape pulled patella to medial side of knee joint) vs. lateral taping (taped pulled patella to lateral side) for 4 days.	VAS pain mean difference (Day 1/Day 2/Day 3/Day 4): neutral vs. medial taping. Medial taping had more "better" scores compared to neutral or lateral taping, p <0.05.	"The data indicate that tape applied with a force pulling the patella medially reduced knee pain and was preferred to taping in the lateral or neutral positions."	Very short crossover trial of 4-days duration. Sparse description and results. No sufficient follow-up results in inability to use for guidance.
Clark 2000 RCT	5.0	N = 81 age 16-40 with anterior knee pain lasting longer than 3 months.	Exercise, taping and education vs. taping and education vs. exercise and education vs. education alone for 6 treatments over 3 months for patients with anterior knee pain or patellofemoral pain syndrome.	At 3 months and 1 year, WOMAC and VAS scales improved significantly in all groups. At 1 year, exercise group had significantly lower scores than groups without exercise (p = 0.03). At 3 months Hospital Anxiety and Depression Scale (HAD) scores improved for all groups (anxiety p = 0.0005, depression p = 0.0001). At 1 year, HAD anxiety (p = 0.02) improved in all patients. Quadriceps power in affected leg improved in all (p <0.001).	"The proprioceptive muscle stretching and strengthening aspects of physiotherapy have a beneficial effect at three months sufficient to permit discharge from physiotherapy. These benefits are maintained at one year. Taping does not influence the outcome."	High dropouts. Data suggest best outcome with exercise and taping ineffective and of no additive benefit.
Kowall 1996 RCT	4.0	N = 25 ages 14-40 with unilateral or bilateral patellofemoral pain (35 knees) for ≥1 month, no history of patellofemoral dislocation.	PT (stretch, quadriceps strengthen, isometric, isotonic, isokinetic, twice a week) plus home exercise randomized to with patellar taping (n = 12) vs. without patellar taping (n = 12) for 4 weeks.	No tape group had a decrease in pain severity and effect on athletic activities vs. tape group, p <0.05. NS between groups for cybex data. NS between groups for EMG data.	"Results indicate that in similar groups of patients with patellofemoral pain, there is no beneficial effect of adding a patellar taping program to a standard physical therapy program."	Data suggest no additive benefits of taping.

ORTHOTICS AND KNEE SPLINTS

Orthotics has been used for treatment of patellofemoral joint pain.(594, 1118, 2336, 2350, 2351)

1. Recommendation: Orthotics or Knee Splints for Patellofemoral Knee Pain

There is no recommendation for or against the use of orthotics or knee splints for patellofemoral joint pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

2. Recommendation: Functional Bracing for Prevention of Anterior Knee Pain

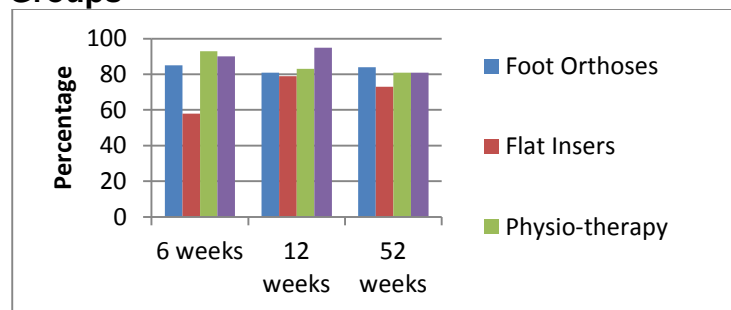
There is no recommendation for or against the use of functional bracing for prevention of anterior knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

There are no quality studies addressing the use of knee splints, orthotics, or bracing for treatment of patellofemoral knee pain. There is one moderate-quality study comparing bracing with no bracing in prevention of anterior knee pain in military recruits and that study reported a significant decrease in the development of anterior knee pain after 6 weeks.(2352) There is one high-quality trial comparing foot orthoses, flat inserts, physiotherapy and a combination of foot orthoses plus physiotherapy and found minimal differences(2308); (see Figure 7). Braces may be helpful for those with high-demand positions, particularly if they are not acclimated to the demands of the position. These devices are not invasive, have few adverse effects, are low cost, but absent evidence of efficacy, there is no recommendation regarding their use.

Figure 7. Percentage of Moderately or Markedly Improvement among Four Treatment Groups



Adapted from Collins N, Crossley K, Beller E, Darnell R, McPoil T, Vicenzino B. Foot orthoses and physiotherapy in the treatment of patellofemoral pain syndrome: randomized clinical trial. *BMJ*. 2008;337a1735.

Evidence for the Use of Orthotics and Knee Splints

There is 1 high- and 3 moderate-quality RCTs or crossover trials incorporated into this analysis. There are 4 low-quality RCTs in Appendix 1.(594, 2353-2355)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Collins 2008 RCT	8.0	N = 179 with patellofemoral pain over 6 weeks duration, ages 18-40	Foot orthoses (Vasyl) plus physiotherapy vs. physiotherapy alone vs. foot orthoses alone vs. flat inserts for 6 weeks intervention; 52 week follow-up.	Moderate or marked improvements (6/12/52 weeks): foot orthoses (85/81/84) vs. flat inserts (58/79/73) vs. physiotherapy (93/81/83) vs. orthoses plus physiotherapy (90/95/81). NNT foot orthoses vs. flat inserts	“While foot orthoses are superior to flat inserts...they are similar to physiotherapy and do not improve outcomes when added to physiotherapy in the short term	Minimal differences between groups. Data suggest foot orthosis superior to flat inserts and comparable to physiotherapy.

				4/50/9. NNT physiotherapy vs. foot orthoses 14/51/-29. Combination vs. physiotherapy - 45/8/226.	management of patellofemoral pain.”	
Lun 2005 RCT	6.0	N = 129 at least 18 years of age with patellofemoral pain syndrome (PFPS)	Structured home rehab program (E group, n = 34) vs. patellar brace (B group, n = 32) vs. structured home rehab program and patellar brace (EB group, n = 32) vs. structured home rehab and knee sleeve (ES group, n = 31), 12 weeks.	No significant differences between groups although improvements seen in each group from baseline to 12 weeks. VAS pain ratings (0/12 weeks): exercise (4.4/2.9) vs. brace (4.4/2.7) vs. exercise plus brace (4.2/2.7) vs. exercise plus sleeve (4.4/2.8).	“Symptoms of PFPS improved over time in terms of pain and knee function regardless of the treatment group.”	No placebo or sham group. Data suggest equal efficacy and no additive benefit of adding structured home rehabilitation program to patellar brace or vice versa.
Van Tiggelen 2004 RCT	4.0	N = 167 military recruits, no history of knee pain randomized into 2 groups prior to 6-week basic military training (BMT) program	Worn for all activities – On-Track dynamic patellofemoral brace (n = 54) vs. no brace (n = 113) for 6 weeks.	Number of recruits developing anterior knee pain during BMT: Brace group: Anterior knee pain 10, Total 54, % = 18.5. Control group: Anterior knee pain 42, Total 113, % = 37. Less recruits in brace group developed anterior knee pain compared to controls, p = 0.020.	“[T]he use of a patellofemoral brace is an effective way to prevent AKPS in subjects undergoing a strenuous training program.”	Dropouts in braced group 7/61; however controls were 26/139. Lack of study details lowered score.
Trotter 2008 Crossover Trial	4.0	N = 40 aged 18 or older with an active lifestyle and current musculoskeletal complaints of low extremity during activity including patellofemoral tracking dysfunction	Custom made orthoses (n = 27) vs. prefabricated inserts (n = 13) for 4 weeks each.	Prefab-custom and custom-prefab groups had different path length ratio scores at 2nd baseline, p <0.001. Prefab-custom group had significant improvement in path length ratio between baseline 1 and insertion of prefabricated insert at Week 2, p = 0.02.	“For patients with lower-extremity musculoskeletal pain, immediate improvements in economy of gait can be expected on wearing prefabricated inserts and full-contact custom-made foot orthoses. It seems, however, that this effect is maintained for at least 1 month for only the custom-made foot orthoses.”	Compliance unclear. No intermediate or longer term data reported.

ELECTRICAL STIMULATION

Electrical stimulation has been used for treatment of anterior knee pain.(1269)

Recommendation: Electrical Stimulation for Anterior Knee Pain

Electrical stimulation is not recommended for treatment of anterior knee pain.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

There are no quality placebo- or sham-controlled clinical trials evaluating electrical stimulation for anterior knee pain. One trial found electrical stimulation to be of no added benefit in addition

to exercises.(2356) Another moderate-quality trial that used two different active treatments failed to find differences.(1269) Electrical stimulation is not invasive, has low adverse effects, and is moderately costly. It appears ineffective in treating anterior knee pain and thus, is not recommended.

Evidence for the Use of Electrical Stimulation for Anterior Knee Pain

There are 2 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Callaghan 2004 RCT	6.5	N = 80 patellofemoral pain, 6 months to 10 years duration	Electrical stimulation with uniform constant 35Hz vs. 5 simultaneous stimuli (125, 83, 50, 2.5, 2Hz) to quadriceps 1 hour a day for 6 weeks (total 42 treatments).	Constant (pre/post) vs. experimental (pre/post) isometric strength (117.8/120.9Nm) vs. experimental (107.6/118.1). Pain 3/2 vs. 3/2 (NS).	“One form of stimulation was just as efficacious as the other in improving subjective and objective measures.”	No sham group. Home treatment device. Suggests devices appear different, thus unclear if truly double-blinded. Data suggest comparable (in)efficacy.
Bily 2008 RCT	5.0	N = 38 bilateral anterior knee pain for 6 to 120 months	Physiotherapy training vs. physiotherapy training and home based EMS for 12-weeks for bilateral patellofemoral pain syndrome.	Three-month VAS measurements mean decrease±SD: -2.84±3.50 (p = 0.003) for PT group and -3.39±3.43 (p <0.001) for PT plus EMS group; 3-month KSP scores improved from baseline 8.4±7.9 (p <0.001) in PT group and 12.1±11.9 (p <0.001) in PT plus EMS group.	“[A] supervised PT training program over a period of 3 months can decrease pain and improve function in patients with PFPS. Both groups, PT as well as PT and EMS, showed significant and clinically relevant treatment effects.”	Data suggest electrical muscle stimulation of no additive benefit.

MANIPULATION AND MOBILIZATION

Manipulation and mobilization and have been used to treat anterior knee pain, often in conjunction with axial joints.(1223, 1235, 1240, 1242, 2357)

Recommendation: Mobilization and Manipulation for Anterior Knee Pain

There is no recommendation for or against the use of manipulation and mobilization for treatment of anterior knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are no quality trials comparing manipulation or mobilization with sham or no treatment controls to treat anterior knee pain. The few, small available studies comparing active treatments have methodological flaws. Thus, there is no recommendation for or against the use of mobilization or manipulation to treat anterior knee pain.

Evidence for the Use of Manipulation and Mobilization for Anterior Knee Pain

There are 2 moderate-quality RCTs incorporated into this analysis. There are 2 low-quality RCTs in Appendix 1.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Brantingham	4.5	N = 31 patellofemoral	Chiropractic manipulative	NS between groups at baseline, after 6th	“A feasibility study investigating the	Feasibility study to plan for fully

2009 RCT		l pain syndrome >3months duration	therapy (CMT) to knee joints only, exercise and Graston Technique or Graston Instrument-assisted Soft Tissue Mobilization (GISTM) (Group A, n = 25) vs. CMT to full kinetic chain (FKC) including manipulative therapy to lumbosacral, sacroiliac, all lower extremity joints including knee, exercise, soft tissue (GISTM) treatment (Group B, n = 22) 1-3 times a week for 2-6 weeks, total 6 treatments. All treated with exercise; 2 months follow-up.	treatment, at 2 month follow-up for VAS (usual or worst), AKPS, or PSS. AKPS at 2 months change from baseline to follow-up: Group A increased 13.23 points, Group B 13.05 points. VAS usual decrease from baseline to 2 month follow-up: Group A 1.48, Group B 0.76cm. VAS worst decrease from baseline to 2 month follow-up: Group A 2.04, Group B 2.73cm. AKPS (baseline/change after 6th treatment): local 71.85±9.75/9.46 vs. extended 75.83±9.02/6.05.	ability to conduct a (RCT) of a manipulative therapy protocol of PFPS using available chiropractic college infrastructure was accomplished.”	powered RCT. As study compares 2 chiropractic protocols, it cannot in isolation address utility of either treatment compared with no treatment or other treatment. Multiple co-interventions.
Taylor 2003 RCT	4.5	N = 15 patellofemora l pain syndrome at least 1 month duration	Patella mobilization/ manipulation 2 times a week for 4 weeks vs. mobilization/ manipulation plus exercise 2 times a week for 4 weeks. Approximately 5 weeks of follow-up.	Graphic data presented. Some results favored combination group (e.g., SMPQ, p = 0.009 post-treatment; NPRS-101 p = 0.037 at 2nd treatment).	“[T]he design and results of the present study cautiously suggest that there is a possibility that combined mobilization/ manipulation and exercise may produce a marginally better outcome than patella mobilization/manipulation alone in the short-term treatment of PFPS.”	Follow-up of Rowlands’ pilot study (however that study design was different). Under enrollment of 12 instead of 30. Population not described. Many details sparse. Study would address additive value of exercise if powered. Groups too small for evidence-based guidance; results in low quality study.

ACUPUNCTURE

Acupuncture has been used for treatment of anterior knee and patellofemoral pain.(1208, 2358)

Recommendation: Acupuncture for Anterior Knee Pain

There is no recommendation for or against the use of acupuncture for anterior knee pain.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are two moderate-quality trials with somewhat conflicting results. One trial compared electroacupuncture with minimal superficial acupuncture and failed to find evidence of

efficacy,(1208) while the other suggested slight benefits compared with no treatment controls.(2358) Thus, there is no recommendation for or against the use of acupuncture to treat anterior knee pain.

Evidence for the Use of Acupuncture for Anterior Knee Pain

There are 2 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Jensen 1999 RCT	6.0	N = 75 patellofemoral pain	Acupuncture (20-25 minute session, 2 times a week, 4 weeks; ST34, SP10; either LE5 and ST35 or SP9 and ST36; others included BL17, 18, 20, 23; LI4; CV4; de qi) vs. no treatment; 12 months follow-up.	At 12 months assuming dropouts represented worse case, Cincinnati Rating System scores acupuncture 68.1 vs. 54.4, p = 0.03. CRS global scores (baseline/6 weeks/5 months/12 months): acupuncture (58.0/69.9/71.9/75.2) vs. controls (56.1/66.1/61.7).	"[A]cupuncture may be an alternative treatment for patellofemoral pain syndrome."	No treatment controls biases in favor of the active treatment. Individualized acupuncture results in difficulty replicating.
Näslund 2002 RCT	4.5	N = 58 activity induced pain for >6 months in at least 2 of climbing stairs, squatting, and prolonged sitting	Electro-acupuncture (n = 30) 2 Hz at 6 acupuncture points vs. minimal superficial acupuncture (n = 28) inserted subcutaneously with no de Qi sensation. Acupuncture points: ST34, ST36, ST38, SP9, SP10, GB34. Outcome measures assessed at 3 and 6 months.	VAS pain score for EA vs. minimal acupuncture median (range) for baseline/after treatments/3 months/6 months: 25 (0-66)/10 (0-30)/12.5 (0-50)/10 (0-35) vs. 30 (0-60)/10 (0-30)/5 (0-20)/5 (0-30).	"Our study shows that patients with idiopathic anterior knee pain benefit from both electro-acupuncture treatment and subcutaneous needling. The pain-relieving effect remains for at least half a year. As the pain reduction was not significantly better in patients receiving deep acupuncture compared with the control group, central pain inhibition, caused by either afferent stimulation or by non-specific therapeutic effects, is a plausible explanation underlying the treatment effects."	Attempted sham/minimal acupuncture suggesting comparable results; 6 month follow up.

BIOFEEDBACK

Biofeedback has been used for treatment of patellofemoral pain.(2359, 2360)

Recommendation: Biofeedback for Patellofemoral Pain

Biofeedback is not recommended for the treatment of patellofemoral pain.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

Biofeedback has been evaluated in two moderate-quality trials for treatment of patellofemoral pain syndrome.(2359, 2360) In both trials, there was no additive benefit for biofeedback in addition to exercise. Biofeedback is not invasive, has few adverse effects, and is low cost, but it is ineffective and thus is not recommended.

Evidence for the Use of Biofeedback

There are 2 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT in Appendix 1.(2361)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Yip 2006 RCT	5.0	N = 26 clinically diagnosed patellofemoral pain for >6 months	EMG biofeedback plus exercise vs. exercise only; 8 weeks follow-up.	Significant reduction in lateral patellar gliding (p = 0.014), lateral patellar gliding (p = 0.014), and lateral patellar rotation (p <0.001). Significant increases in overall isokinetic peak torque (p = 0.005) and total work per body weight (p = 0.037). However, no between group differences.	"In patients with patellofemoral pain, the addition of EMG biofeedback to the exercise programme on vastus medialis obliquus activation had no measurable effect at eight weeks."	No sham or non-interventional control group. No baseline demographic data. Claims of double blinding seem implausible. Data suggest biofeedback as additive treatment to exercise ineffective.
Dursun 2001 RCT	4.5	N = 60 unilateral patellofemoral pain syndrome	EMG biofeedback training plus conventional exercise program (quadriceps strengthening, vastus medialis, flexibility, bicycling) vs. conventional exercise program alone.	Vastus medialis 1st month contraction values biofeedback vs. control, 140.4 (83.4) vs. 102.4 (58.9), p = 0.046. Vastus lateralis 1st-month contraction values, 148.4 (86.7) vs. 96.1 (52.7), p = 0.007. Vastus medialis 2nd month contraction values, 150.8 (88.2) vs. 109.4 (63.8), p = 0.042. Vastus medialis 3rd month contraction values, 147.2 (82.2) vs. 106.4 (63.2), p = 0.036. VAS and FIQ significant improvement in both groups (p = 0.000).	"[C]onventional exercise program results in no additional gains. This study shows that the added expense and time required for electromyographic biofeedback is not warranted."	Data suggest biofeedback as additive treatment ineffective.

GLUCOCORTICOSTEROID INJECTIONS

Glucocorticosteroid injections have been utilized for treatment of patellar tendinopathy.

Recommendation: Glucocorticosteroid Injections for Select Patients with Patellar Tendinopathy

Glucocorticosteroid injections are recommended for select patients to treat patellar tendinopathy.

Indications – Chronic patellar tendinopathy that is unresponsive to other treatments including NSAID(s), activity modification and exercises.(1326, 2362)

Strength of Evidence – **Recommended, Insufficient Evidence (C)**

Rationale for Recommendation

There is one moderate-quality placebo-controlled trial that evaluated the use of glucocorticosteroid injections for the treatment of patellar tendinopathy and found some evidence of efficacy, although somewhat less than with aprotinin.(2362) There is also one moderate-quality trial comparing glucocorticosteroid injections with two different exercise regimens that suggested that the steroid injections are inferior to heavy slow-resistance training exercises.(1326) These injections are mildly invasive, have adverse effects, are moderately costly, and have some evidence of efficacy, thus they are recommended for those select patients who fail a quality exercise program.

Evidence for the Use of Glucocorticosteroid Injections for Patellar Tendinopathy

There are 2 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Glucocorticosteroid Injections						
Capasso 1997 RCT	7.5	N = 116 athletes suffering from pain at or around patellar tendon	Injection of aprotinin (n = 38) vs. methylprednisolone acetate (n = 39) vs. 0.9%NaCL (n = 39).	Overall results at 1 year follow-up Group 1 vs. Group 2 vs. Group 3: Excellent: 40.64% vs. 25.8% vs. 9.3%. Good: 46.8% vs. 35.4% vs. 18.7%.	“This study suggests that paratendinous injections of aprotinin may have a lasting beneficial effect in patients suffering from patellar tendinopathy.”	All athletes; 25 failed prior steroid injection, biasing somewhat against those injections. Blinding not well described. Variable findings and numbers of injections. Data suggest aprotinin superior to steroid and both superior to placebo.
Kongsgaard 2009 RCT	6.0	N = 37 pain duration of >3 months, a 4-week wash-out period for prior treatments ; 6 months follow-up	Peritendinous corticosteroid injections (CORT, n = 12) with methylprednisolone 40mg in 0.5mL lidocaine (1%) into peritendinous tissue posterior to hypoechoic area of patellar tendon vs. eccentric decline squat training (ECC, n = 12) vs. heavy slow resistance training (HSR, n = 13) (3 sessions a week with 3 movements with 4 sets of each movement with 2-3 minutes of rest between sets. Loads: 15 rep maximum (RM) week 1, 12 RM weeks 2-3, 10 RM weeks 4-5, 8 RM weeks 6-8 and 6 RM weeks 9-12. 6 months follow-up.	VISA-p score and VAS improved similarly in all groups from baseline (VISA-p: CORT: 64±14, ECC: 53±13, HSR: 56± 13, VAS: CORT: 58±17, ECC: 59±20, HSR: 61± 15) to 12 weeks (VISP-p: CORT: 82±19, ECC: 75± 3, HSR: 78±18. VAS: CORT: 18±21, ECC: 31± 26, HSR: 19±15) (p <0.01). Only CORT had a decrease in scores of VISA-p AND VAS scores from 12 weeks to 1/2 year follow-up (VISA-p: CORT: 64±22, ECC: 76±16, HSR: 86±12. VAS: CORT: 31±29, ECC: 22±17, HSR: 13±16) (p <0.05)	“The main findings of the present study were that the different treatment regimens had similar short-term clinical effects and clinical patient satisfaction, but these parameters differed on a long-term basis. Specifically, ECC and HSR maintained their clinical improvements whereas they deteriorated in CORT at the half-year follow up.”	Data suggest heavy slow resistance training exercise superior to eccentric exercise and injection for longer term management of patellar tendinopathy.

PLATELET RICH PLASMA AND AUTOLOGOUS BLOOD INJECTIONS

Platelet rich plasma, as well as autologous blood injections, have been used to treat several tendinopathies including lateral epicondylalgia,(2363, 2364) Achilles’ tendinopathies,(2365, 2366) and patellar tendinopathy. (2367, 2368) These injections have also been used for treatment of osteoarthritis.(1346-1349, 2369-2371)

Recommendation: Platelet Rich Plasma or Autologous Blood Injections for Patellar Tendinopathy

There is no recommendation for or against platelet rich plasma or autologous blood injections for treatment of patellar tendinopathy.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale for Recommendation

There are no placebo or sham-controlled trials for patellar tendinopathy. There is one moderate-quality study suggesting efficacy of PRP over dry-needling.(2372) There are two moderate-quality trials suggesting PRP is superior to extracorporeal shockwave therapy.(2373, 2374) PRP injections are invasive, have adverse effects and are costly. The Evidence-base Practice Knee Panel concluded there is insufficient evidence to conclude either for or against a recommendation (40% agree, 40% disagree, and 20% neutral) for PRP or autologous blood injections for patellar tendinopathy based on the lack of quality trials regarding the overall efficacy of these injections.

Evidence for use of Platelet Rich Plasma and Autologous Blood Injections

There are 4 moderate-quality RCTs incorporated into this analysis.(2372, 2374-2376)

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: platelet rich plasma injection(s), platelet rich plasma, PRP injections, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 56 articles, and considered 7 for inclusion. In Scopus, we found and reviewed 213 articles, and considered 2 for inclusion. In CINAHL, we found and reviewed 12 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 3 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 10 articles considered for inclusion, 7 randomized trials and 3 systematic studies met the inclusion criteria.*

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
PRP injections: Cell plus plasma vs. Plasma alone						
Clarke 2011 RCT	6.5	N = 46 patellar tendinopathy patients with mean age of 36 years, range of 20 and 51 years, and 60 tendons	Cell and plasma intervention (n = 33 tendons) vs. Plasma intervention only (n = 27 tendons). Both groups received physiotherapy and assessed with repeat outcome measures plus US at 6 weeks, 3 months, and 6 months. Subjects prohibited from using NSAIDs and any pain-provoking activities.	Improvement in VISA scores before treatment in both groups (cell/plasma) (44±15 to 75±17/50±18 to 70±14) at 6 months. Mean difference in VISA between groups 8.1 (95%CI, 2.4 to 13.7; p = 0.006. Significant difference between groups in effect of treatment estimated as 2.5 /U increase in 1/√time (95% CI, 0.9 to 4.1; p = .002).	“Ultrasound-guided injection of autologous skin-derived tendon-like cells can be safely used to treat patellar tendinopathy with, in the short term, faster response of treatment and significantly greater improvement in pain and function than injection of plasma alone.”	No sham/ placebo group. No baseline data. Cell groups modestly better than plasma groups in increasing function and decreasing pain associated with patellar tendinopathy.
PRP injections vs. Extracorporeal shock wave therapy						

Vetrano 2013 RCT	6.5	N = 46 athletes with chronic unilateral tendinopathy at lower pole of patellar tendon insertion for >6 months prior to treatment, ages 18-50 years.	2 autologous platelet rich plasma US-guided injections (n = 23) vs. 3 sessions of extracorporeal shock wave therapy (2.400 impulses at 0.17-0.25mJ/mm ² per session) (n = 23). Both groups had muscle strengthening and stretching for 2 weeks, follow-up at 2, 6 and 12 months.	Improved VISA-P scores and VAS from baseline to 6 and 12 month follow-up (mean (SD): VISA-P 6 month (PRP- 86.7 (14.2), ESWT- 73.7 (19.9)) p = 0.014, VISA-P 12 month (PRP- 91.3 (9.9), ESWT- 77.6 (19.9)) p = 0.026, VAS 6 month (PRP- 2.4 (1.9), ESWT- 3.9 (2.3)) p = 0.028, VAS 12 month (PRP-1.5 (1.7), ESWT- 3.2 (2.4)) p = 0.009. Post-treatment PRP injection group had satisfaction improvements and improved blazina scale scores vs. ESWT group at 12 months (p = 0.035 and p = 0.015).	“Therapeutic injections of PRP lead to better midterm clinical results compared with focused ESWT in the treatment of jumper’s knee in athletes.”	No placebo. Data suggest PRP superior to ESWT at 12 months.
Ultrasound PRP vs. Ultrasound Dry Needling						
Dragoo 2014 RCT	6.0	N = 23 diagnosed with patellar tendinopathy verified by MRI, symptoms lasting longer than 6 weeks, mean age 35.	US-guided 6 mL of leukocyte-rich platelet rich plasma (n = 10) vs. US-guided dry needling (n = 13). Both groups got eccentric exercise plan, follow-up at 3, 6, 9, 12, and ≥26 weeks.	Significant difference in VISA (mean±SD) scores between DN and PRP group (p = 0.02) from baseline at 12 weeks: DN- 5.2±12.5 (p = 0.2), PRP- 25.4 ± 23.2 (p = 0.01). Baseline to ≥26 weeks follow up analysis with significance (p = 0.006) for Lysholm scores: DN- 45.4 ± 18.8 (p = 0.0001), PRP- 14.7 ± 19.1 (p = 0.09).	“A therapeutic regimen of standardized eccentric exercise and ultrasound-guided leukocyte-rich PRP injection with DN accelerates the recovery from patellar tendinopathy relative to exercise and ultrasound-guided DN alone, but the apparent benefit of PRP dissipates over time.”	Small sample size. Blinded assessor but only reporting questionnaire data. Baseline difference in age (28 vs 40 years) concerning for randomization failure. Data suggest efficacy of PRP that is mostly shorter term.
Miscellaneous						
de Almeida 2012 RCT	6.0	N = 27 undergoing ACL reconstruction with patellar tendon harvesting	Received (n = 12) vs. not received (n = 15) PRP in patellar tendon harvest during ACL reconstruction.	Patellar tendon gap area smaller in PRP group (4.9±5.3mm ²); 95% CI, 1.1-8.8) vs. controls (9.4 ±4.4mm ²); 95% CI, 6.6-12.2; p = 0.046). VAS pain score lower in PRP group immediately post-op (3.8±1.0; 95% CI, 3.18-4.49) vs. controls (5.1±1.4; 95% CI, 4.24-5.90; p = 0.02).	“...PRP had a positive effect on patellar tendon harvest site healing on MRI after 6 months and also reduced pain in the immediate postoperative period. Questionnaire and isokinetic testing results	Small numbers. Data suggest PRP improves evidence of healing.

				No differences at 6 months in questionnaire and isokinetic testing results.	were not different between the groups at 6 months.”	
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APROTININ INJECTIONS

Aprotinin injections have been utilized for treatment of patellar tendinopathy as an anti-inflammatory treatment.(2362)

Recommendation: Aprotinin Injections for Patellar Tendinopathy

Aprotinin injections are recommended for select patients to treat patellar tendinopathy.

Indications – Chronic patellar tendinopathy that is unresponsive to other treatments including NSAID(s), exercise, and activity modification.

Strength of Evidence – **Recommended, Evidence (C)**

Rationale for Recommendation

There is one moderate-quality placebo-controlled trial that evaluated the use of paratendon, bursal, and tendinous insertion area aprotinin injections for the treatment of patellar tendinopathy and found suggested some efficacy.(2362) This trial did not utilize ultrasound, thus there is no recommendation for or against imaging to accomplish the injections. These injections are invasive, have adverse effects, and are moderately costly. They are recommended for use in highly select cases.

Evidence for the Use of Aprotinin Injections for Patellar Tendinopathy

There is 1 moderate-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Capasso 1997 RCT	7.5	N = 116 athletes suffering from pain at or around patellar tendon	Injection of aprotinin (n = 38) vs. methylprednisolone acetate (n = 39) vs. 0.9%NaCL (n = 39).	Overall results at 1 year follow-up Group 1 vs. Group 2 vs. Group 3: Excellent: 40.64% vs. 25.8% vs. 9.3%. Good: 46.8% vs. 35.4% vs. 18.7%.	“This study suggests that paratendinous injections of aprotinin may have a lasting beneficial effect in patients suffering from patellar tendinopathy.”	All athletes. 25 failed prior steroid injection, biasing somewhat against those injections. Blinding not well described. Variable findings and numbers of injections. Data suggest aprotinin superior to steroid and both superior to placebo.

PROLOTHERAPY, INCLUDING POLIDOCANOL AND HYPERTONIC GLUCOSE INJECTIONS

Prolotherapy is performed with various sclerosing agents, including polidocanol and hypertonic saline. These have been used to treat chronic patellar tendinopathy.

1. Recommendation: Prolotherapy Injections for Chronic Patellar Tendinopathy

Prolotherapy injections are recommended for select patients to treat chronic patellar tendinopathy.

Indications – Athletes with chronic patellar tendinopathy with neovascularization corresponding to the painful area that is unresponsive to other treatments including NSAID(s) and activity modification. Whether these injections are appropriate for others, including workers, is unclear. Ultrasound guidance is recommended for accomplishing the injections.

Strength of Evidence – **Recommended, Evidence (I)**

2. *Recommendation: Polidocanol Injection for Acute, Subacute, or Post-operative Patellar Tendinopathy*

There is no recommendation for or against the use of polidocanol injection for acute, subacute, or post-operative patellar tendinopathy.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendations

There is one high-quality trial among athletes suggesting efficacy of a sclerosing agent (polidocanol) for chronic patellar tendinopathy although there are some weaknesses in the trial.(2377) These injections are invasive, have adverse effects, and are moderately costly. They are recommended for use in highly select cases.

Evidence for the Use of Polidocanol Injections

There is 1 high-quality RCT incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Prolotherapy vs. Placebo Injections						
Hoksrud 2006 RCT	8.5	N = 33 (42 tendons), mainly from Norwegian elite divisions in basketball, team handball, and volleyball	Treatment group (n = 33) polidocanol injections in area of neovascularization vs. control group (n = 16) similar injections with lidocaine/epinephrine.	For both groups taken together, VISA score improved from 54 (95% CI, 50–58) at baseline to 75 (95% CI, 68–82) at 8-month follow-up after end of treatment period 2 (p <0.0001). Treatment group more satisfied with treatment compared with control group (p <0.001).	“Sclerosing injections with polidocanol resulted in a significant improvement in knee function and reduced pain in patients with patellar tendinopathy.”	Small numbers. All athletes. Baseline data on jump training appear to have error(s). Ultrasound-guided injections. Variable number of injections. Data suggest efficacy.

GLYCOSAMINOGLYCAN INJECTIONS

Glycosaminoglycan injections have been used for treatment of patellar tendinosis.

Recommendation: Glycosaminoglycan Injections for Patellar Tendinosis

Glycosaminoglycan injections are not recommended for treatment of patellar tendinosis.

Strength of Evidence – Not Recommended, Evidence (C)

Rationale for Recommendation

One moderate-quality trial has suggested a lack of efficacy.(2378) Thus, these injections are not recommended.

Evidence for the Use of Glycosaminoglycan Injections for Patellar Tendinopathy

There is 1 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Kannus 1992 RCT	4.5/5.5	N = 53 with chronic patellofemoral pain syndrome; mean	All treated with 6 weeks of quadriceps muscle exercise, cease symptom producing activities plus piroxicam 20mg QAM. Plus 5 weekly	Return to full physical activity at 6 weeks/6 months: conservative 56/63 vs. saline injection 53/65 vs. active injections 75/88%. Subjective	“Neither the GAGPS injections nor the physiologic saline injections are more effective	Score 4.5 for exercise only and 5.5 for double blind study of injections. Data suggest

		duration 16 months	injections of glycosaminoglycan polysulfate 50mg vs. placebo vs. no injections; 6 months follow-up.	overall excellent assessments: 50/69 vs. 53/53 vs. 50/75%. No differences in VAS pain data or Tegner scores.	than conservative therapy in the treatment of chronic PFPS.”	lack of efficacy.
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PERCUTANEOUS NEEDLE TENOTOMY

Percutaneous needle tenotomy has been attempted to treat chronic tendinoses.(1327-1330, 2379)

Recommendation: Percutaneous Needle Tenotomy for Chronic Tendinosis

There is no recommendation for or against the use of percutaneous needle tenotomy for treatment of chronic tendinosis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are no quality studies of percutaneous needle tenotomy as a treatment for chronic tendinosis. This procedure is invasive, has adverse effects, and is moderate to highly costly; thus, there is no recommendation.

Evidence for Percutaneous Needle Tenotomy

There are no quality studies evaluating the use of percutaneous needle tenotomy.

EXTRACORPOREAL SHOCKWAVE THERAPY (“Shockwave”)

Extracorporeal shockwave therapy (ESWT) has been utilized for treatment of tendinoses, especially in the shoulder and ankle. It has been documented to have efficacy for treatment of calcific tendinitis in the shoulder (see Shoulder Disorders guideline).(2380-2385)

Recommendation: Extracorporeal Shockwave Therapy for Patellar Tendinosis

There is no recommendation for or against the use of extracorporeal shockwave therapy for treatment of patellar tendinosis.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Rationale for Recommendation

There are no quality trials evaluating shockwave therapy for treatment of patellar tendinosis. There is one low-quality trial comparing extracorporeal shockwave therapy with either sham or low-energy treatment for patellar tendinosis.(2386) There are two trials suggesting ESWT is inferior to platelet-rich plasma injections (see above). For most body parts, there is evidence that ESWT is ineffective (see Elbow Disorders, Shoulder Disorders, and Ankle and Foot Disorders guidelines). Yet, there is evidence of efficacy for treatment of rotator cuff calcific tendinosis. ESWT is minimally invasive, is often performed with an injected anesthetic, has some adverse effects, and is moderate to highly costly depending on numbers of treatments. However, without evidence of efficacy, there is no recommendation for or against its use to treat patellar tendinosis.

Evidence for the Use of Extracorporeal Shockwave Therapy for Tendinosis

There is 1 low-quality RCT in Appendix 1.

SURGERY FOR ANTERIOR KNEE PAIN AND PATELLOFEMORAL SYNDROME

Several surgical procedures have been performed for anterior knee pain and patellofemoral pain syndrome. These have included chondroplasty and patellar shaving and resurfacing. Lateral retinacular release or lengthening and arthroscopic lateral retinacular release has been

performed for recurrent subluxation, and surgical realignment of the extensor mechanism has been used for some patients.(2387-2398) Lateral release has been performed without,(1245, 2399-2404) as well as in conjunction with, medial soft-tissue realignment for recurrent patellar instability.(2405-2411) Although, there are no RCTs, a comparison of these procedures concluded that medial soft-tissue realignment is superior.(2408)

Recommendation: Surgery for Anterior Knee Pain

Surgery is recommended in patients with anterior knee pain after a 6 month period of failed non-operative treatment provided the patient also has one or more of the below indications.

Indications – Moderate to severe anterior knee pain of at least 6 months duration with failed non-operative treatment (including 2 to 3 months of supervised exercises and home-exercise program components with which the patient has been compliant) and one or more of the following: 1) clinical and radiographical evidence of patellar malalignment; 2) clinically and/or radiographically proven subluxation; and/or 3) repeated episodes of patellar dislocation.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Rationale for Recommendation

One trial has suggested arthroscopic surgery for patellofemoral syndrome was of no additive benefit to a home exercise program, although it included techniques that are no longer recommended such as chondroplasty.(2315) Other trials have compared operative techniques,(2412) including one suggesting no differences between open and arthroscopic lateral release.(2413) Thus, there is one trial comparing operative with non-operative management,(2414) but no trials available that include optimal techniques. Patients who have failed non-operative management are very difficult to treat, and surgery should be carefully weighed against potential failure to improve. For select patients who have significant functional impairment due to patellar malalignment, subluxation, or recurrent dislocation and have failed exercises and non-operative management with which they have been compliant, an attempt at surgical intervention is recommended.

Evidence for the Use of Surgery for Anterior Knee Pain

There are 4 moderate-quality RCTs incorporated into this analysis.

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Kettunen 2007 RCT	7.5	N = 56 with PFPS (patellofemoral pain during knee loading physical activity and when knee kept in flexion for prolonged period, with relief on extension), duration ≥6 months)	Arthroscopy (n = 28, systematic protocol, plicae resection, stage cartilage, abrade chondral lesions, shave excessive/inflamed synovium), plus 8-week home exercise program (lower extremity strengthening and stretching, QD for 4 weeks, resisted knee flex/extend, rubber sling around ankle for exercises QD) vs. HEP alone	Mean±SD Kujala score comparing arthroscopy group vs. control group at baseline/9-month follow-up: 69±10.7/ 81.9±14.1 vs. 71.1±13.0/82.5±15.3; p <0.001 improvement in arthroscopy and control group. No differences between groups in Kujala score, VAS pain descending stairs, VAS pain ascending stairs, VAS pain standing up from sitting.	“In this controlled trial involving patients with chronic PFPS, the outcome when arthroscopy was used in addition to a home exercise program was no better than when the home exercise program was used alone.”	Trial appears to include chondroplasty, which is no longer generally indicated. Costs 3-fold higher in arthroscopy group (£1315.60 vs. 414.80). Data suggest arthroscopy not of additive benefit in addition to home exercise program.

			(n = 28); 24 months follow-up.			
Fernandez-Fairen 2010 RCT	7.5	N = 101 (108 knees) anterior knee pain for >6 months not responding to non-operative treatment that was secondary to degenerative changes of patellofemoral cartilage in age range of 22-65	Autograft tibial tubercle advancement (TTA) surgery (group 1, n = 48) vs. tantalum TTA surgery (group 2, n = 53). At least 5 years follow-up.	“At the last followup, clinical scores, fusion rates, and maintenance of the anteriorization either were better or similar for the TTA using the tantalum implant depending on the respective parameter. The operative technique was easier and shorter with the tantalum device. Complication and failure rates were greater using bone graft.”	“[A] porous tantalum device is a good bone graft substitute in TTA for treating degenerative chondral lesions of the patellofemoral joint.”	Dropout rate given as 0.0% over 5 years of follow-up which is highly unusual. Data suggest tantalum implants superior for pain, KOOS, and satisfaction.
Camanho 2009 RCT	5.0	N = 33 with first episode of patellofemoral dislocation and no previous knee surgery	Open repair of medial patellofemoral ligament (MPFL, n = 17) vs. conservative treatment for 3 weeks (n = 16). At least 25 months follow-up.	Eight recurrences in conservative group vs. none after surgery. Kujala questionnaire mean scores 69 in conservative group vs. 92 in surgical group.	“[S]urgical treatment afforded better results.”	Data suggest surgery superior to non-operative management after a first dislocation.
O’Neill 1997 RCT	4.0	N = 91 with anterior knee pain believed to be secondary to lateral patellar tilting	Arthroscopic lateral retinacular release (Group I, n = 44) vs. open lateral retinacular lengthening (Group II, n = 47); 2 to 6 years follow-up.	Rate of arthroscopically demonstrable chondromalacia patellae was greater in group I (1.3 mean) compared to group II (0.5 mean), p = 0.005. NS between groups for time to return to sports activity, group I (93%) vs. group II (100%) p = 0.08. NS between groups for closed-chain testing at 10 (p = 0.37), 20 (p = 0.97), and 30 inches per second (p = 0.99). NS between groups for loss of motion (p = 0.75), Group I (0.84°) vs. group II (1.1°). NS between groups for change in circumference of thigh, p = 0.31 (Group I = 3mm vs. Group II = 2 mm). Group I had less medialization compared to Group II, p = 0.02.	“Although there seemed to be a definite trend toward improved function of the knee in association with a longer duration of follow-up, no significant association could be detected between the duration of follow-up and improvement in the outcome measure of either group.”	Quasi-randomized (even/odd birth year). Most data suggest no differences between groups.

APPENDIX 1: LOW-QUALITY RANDOMIZED CONTROLLED TRIALS AND NON-RANDOMIZED STUDIES

The following low-quality randomized controlled studies (RCTs) and other non-randomized studies were reviewed by the Evidence-based Practice Knee Panel to be all inclusive, but were not relied upon for purpose of developing this document's guidance on treatments because they were not of high quality due to one or more errors (e.g., lack of defined methodology, incomplete database searches, selective use of the studies and inadequate or incorrect interpretation of the studies' results, etc.), which may render the conclusions invalid. ACOEM's Methodology requires that only moderate- to high-quality literature be used in making recommendations.(2415)

KNEE ARTHROSCOPY

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Ingram 1986 RCT	3.5	N = 105 undergoing double-contrast arthrography of knee; 2 days follow-up.	loxaglate (3 ml of Hexabrix 320, n = 44) vs. iohalamate (3 ml of Conray 280, n = 45).	More patients reported pain in Hexabrix group, 20 vs. 10 in Conray group. NS between groups for pain after 48 hours, degree of swelling. Delayed films showed better delayed coating (p = 0.0007) and less imbibition (p = 0.008) for Hexabrix group compared with Conray group. Hexabrix group had better quality of coating for patients with effusions than Conray group, p = 0.04.	"[H]exabrix has been shown to produce good photographic contrast as an arthrographic agent."	Quasi-randomized on DOB. High dropouts.

KNEE PAIN AND OSTEOARTHRISIS

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Orthoses						
Toda 2001 RCT	3.5	N = 90 females age 45 and older with knee OA	Traditional insole (n = 44) vs. lateral wedge plus subtalar strapping (n = 46), 3-6 hours a day for 8 weeks. All treated with indomethacin 30mg BID.	Comparison of radiographic angles with and without insoles: strapped insole group talocalcaneal angle (p <0.0001), femorotibial angle (p <0.0001), talar tilt angle (p = 0.003). Inserted insole group talocalcaneal angle (p <0.0001).	"[U]sing the insole with subtalar strapping for initial treatment, will benefit patients with knee OA with genu varum and medial compartment knee OA."	Pseudo-randomization on date of birth (even/odd). Many details sparse. Study combination of wedge plus strapping.
Toda 2006 RCT	2.5	N = 42 females with medial compartment OA of knee	Urethane wedges elevation of 12mm fixed to ankle sprain support (strapped insole group, n = 21) vs. traditional shoe inserted insole 6.35mm	Femorotibial angles in strapped insole group lower at 2 years compared to baseline, p = 0.015 vs. inserted insole group p = 0.27. Strapped group took less NSAIDs over 2 years (50.8±36.1 vs. 79.0±42.2 days, p = 0.025).	"Only those participants using the subtalar strapped insole demonstrated significant change in the FTA in comparison with the baseline assessments. If the insole with a subtalar strap maintains FTA for more than 2	Pseudo-randomization on date of birth (divisible by 4). Many details sparse. High dropout rate (36%), affecting both groups. No differences in x-ray changes.

			elevation (inserted insole group, n = 21) for 6 month study		years, it may restrict the progression of degenerative articular cartilage lesions of knee OA.”	
Toda 2004 RCT	2.5	N = 62 with knee OA	Lateral wedged insoles with subtalar strapping, elevations of 8, 12 or 16mm for 2 weeks.	Lequesne index of disease severity scores remissions: 8mm - 2.2±2.8 vs. 12mm - 4.1±4.8 vs. 16mm - 1.5±3.5.	“The degree of change in femorotibial angle with the insole with subtalar strapping was affected by the tilt of the lateral wedge. For constant routine use, the 8- or 12-mm elevation wedged insoles with subtalar strapping may be more comfortable and effective than the 16-mm elevation wedge.”	Pseudo-randomization by date of birth. Details sparse. Baseline differences in disease duration (medians 1.3-3y), raise concern about randomization failure. Short term follow-up.
Toda 2002 RCT	2.5	N = 88 female outpatients with knee OA	Lateral urethane wedges elevation 6.35mm fixed to ankle strap (n = 42) vs. sock-type ankle supporter with lateral rubber heel wedge insert (n = 46). All treated with acetaminophen 30mg BID for 8 weeks.	Femorotibial angle (FTA) significantly reduced more in subtalar strapping group vs. sock type group (-3.1°±2.5° vs. -0.4°±1.1°), p <0.0001.	“The lateral wedged insole with subtalar strapping induces correction of the femorotibial angle and symptomatic relief in patients with varus-deformity knee OA.”	Study of strapping vs. ankle supporter. Pseudo-randomization on date of birth (even/odd). Many details sparse. Baseline longer disease duration in strapping group (median 3 vs. 1.5 years).
Rodrigues 2008 RCT	2.5	N = 30 females with knee OA with bilateral valgus deformity ≥8°	Medial wedge insoles (8mm high) for rearfoot (medial insole group n = 16) vs. insole resembling other group but without raised wedges (neutral insole group n = 14) for 3-6 hours a day, for 8 weeks. Both wore ankle supports. Supplied standard shoes.	VAS at rest (pre/post): medial insole (5.1±2.3/2.7±2.4) vs. neutral (3.3±2.2/3.1±2.5), p = 0.056. VAS on movement favored medial insole (p = 0.001). Lequesne score declined significantly in medial group vs. neutral, p = 0.002. Medial group had significantly decreased WOMAC scores compared to neutral group, p = 0.001. Femorotibial angles improved significantly in medial group compared to neutral group, p <0.0001.	“The use of medial-wedge insoles was highly effective in reducing pain at rest and on movement and promoted a functional improvement of valgus knee OA.”	Baseline differences with more severe x-rays in medial insole at baseline (31.3% vs. 7.1% neutral). VAS ratings at baseline also higher in medial insole group, suggest possible randomization failure.
Toda 2005 RCT	2.0	N = 81 females older than 45 years of age with medical	Ankle sprain support without urethane wedges with 12mm elevation	Significant difference between placebo group and insole groups for femorotibial angle in favor of insole, p <0.0001. At final	“An optimal duration of insole with subtalar strapping wear for patients with varus deformity knee OA may be	Pseudo-randomization on date of birth (even/odd). Some baseline differences in

		compartment knee OA	(placebo, n = 22) vs. urethane wedges with elevations of 12mm fixed to ankle sprain support for <5 hours a day (short group, n = 21) vs. 5-10 hours a day (medium group, n = 20) vs. >10 hours a day (long group, n = 18) for 2 weeks	assessment, Lequesne index scores had greater improvement in medium group compared to placebo (p = 0.001) and long groups (p = 0.001).	between 5 and 10 h each day.”	disease duration (median 0.7-4.5 years). Many details sparse. Wedge replaced weekly. Short term study. Medium group did best, but also had lowest disease duration suggesting possible fatal randomization study flaw.
Exercise						
Keefe 2004 RCT	3.5	N = 72 married OA patients and their spouses with persistent knee pain	Spouse-assisted pain coping skills training (SA-CST; 12x 2-hour group sessions on pain coping and couples' skills) vs. spouse-assisted CST plus exercise training (SA-CST+ET) vs. exercise training (ET, 3 group sessions/week 12 weeks; cardio endurance training, strength training, flexibility/ROM) vs. standard care (ST).	Both exercise groups improved peak VO ₂ K vs. non-exercise. Leg extension and flexion strength improved for both exercise groups vs. non-exercise groups. Both spouse-assisted pain coping skills group significantly improved patient self-efficacy compared to standard treatment. Spouse assisted coping skills training plus exercise improved self-efficacy compared to exercise training alone (SA-CST + ET vs. ET, p = 0.006). Both spouse-assisted pain coping skills training group improved pain coping vs. exercise alone and standard treatment.	“[I]ntervention combining spouse-assisted coping skills training and exercise can improve physical fitness, pain coping and self-efficacy in patients suffering from OA of the knees.”	Many details sparse.
Yip 2007 RCT	3.5	N = 182 with knee OA (ACR)	Arthritis self management programme of six 2-hour small group classes (self-efficacy, behavior change; stretch, walk, Tai Chi exercises) for 16 weeks plus conventional orthopaedic treatment vs. conventional orthopaedic treatment alone; 16 weeks follow-up.	Arthritis self-efficacy scale for pain improved 6.89±12.64 points for intervention group vs. 1.54±6.05 for controls, p = 0.0001. Current pain VAS decreased 11.88±18.91 points for intervention vs. 1.74 for controls, p = 0.0001. Intervention group increased duration of weekly light exercise by 2.11±3.78 hours/week vs. 0.34±2.23 for controls, p = 0.0001. Mean change±SD pain rating for intervention group and control group: -11.88±18.91 vs. -1.76± 13.47, p =	“[T]he combined self management programme with an exercise protocol has a positive effect in enhancing arthritis self-efficacy, use of self management skills, reducing pain and improving daily activities for OA knee sufferers in 16 weeks.”	Two reports, one apparently partial data. High dropouts. Baseline data not detailed, but some data suggest less severe symptoms in controls.

				0.0001. Fatigue rating: -7.73±19.69 -2.23 ±11.72, p = 0.008. Duration weekly exercise: 2.11±3.78 vs. 0.34±2.23, p = 0.0001. Right knee flexion (degrees): 2.26±9.64 vs. -0.26±6.06, p = 0.004.		
Schilke 1996 RCT	3.5	N = 20 with knee OA	Training session (6 sets 5MVCs on Cybex) 3 times a week for 8 weeks, minimum 36 hours vs. control with usual activity.	ROM improved both groups (p = 0.002) pre-test/post-test for experimental vs. control: 95.9°/104.5° vs. 98.0°/107.1°. Pain and stiffness decreased and mobility increased in exercise but not controls.	"Subjects in the experimental group reported decreased pain, decreased stiffness, increased mobility, and decreased arthritis activity."	Small sample size. Many details sparse. Data suggest support for exercise intervention.
Topp 2009 RCT	3.5	N = 54 over age 50, scheduled for unilateral TKA	Usual care vs. prehabilitation (resistance training, flexibility, step training 3 times a week) for five months.	Mean±SEM sit-to-stand repetitions in 30 seconds prehab vs. control at baseline/3 months: 10.39±0.72/12.87±0.82 vs. 9.79±0.69/11.25±0.79. Sit-to-stand pain: 3.96±0.45/1.62 ±0.29 vs. 4.13±0.44/1.06±0.28; 6-minute walk distance (m): 1254±64/1337±58 vs. 1237±62/1365±56; 6-minute walk pain: 4.22±0.43/1.53±0.34 vs. 5.20±0.41/1.38±0.33. Descend stair pain: 4.64±0.47/1.42±0.37 vs. 5.26±0.44/1.45±0.35.	"These findings demonstrate preliminary support for the efficacy of prehabilitation but also demonstrate the need for further study and should be tempered by a number of limitations."	Many details sparse. Non-structured final visits (3 to 6 months post-op). Numbers of pre-op sessions varied (13.04±7.5) and to degree unclear based on description of study methods (methods suggest should have been approximately 60 appointments each). Most between-group data suggest minimal differences.
Gür 2002 RCT	3.5	N = 23 with bilateral grade 2 or 3 knee OA (K-L), age 41-75 who had not undergone any orthopedic procedures	Concentric training, 12 extension and flexion movements vs. concentric-eccentric training, 6 concentric extension, eccentric extension and flexion movements vs. nontreatment bilaterally 3 days a week for 8 weeks; 8 weeks follow-up.		"Our results showed that with the training programs used in this study, it is possible to improve functional capacity and to decrease pain in the patients with knee OA 2 to 3 times better than those reported in the similar studies... The results indicated that concentric-eccentric-coupled isokinetic training has a slightly better influence on the functional capacity of the patients, especially stair climbing and	Small sample sizes (n = 9, 8, 6).

					descending, compared with concentric isokinetic training.”	
Peterson 1993 RCT	3.5	N = 102 with knee OA with antalgic gaits	Intervention group of hospital-based educational and walking program.	Six minute walk (pre/post): Intervention (390/449m) vs. controls (357/338).	“[T]he walking and educational program was effective in improving gait function in patients with osteoarthritis of the knee.”	Co-interventions not controlled. Compliance unclear. Data suggest efficacy of walking and educational program.
Talbot 2003 RCT	3.5	N = 34 community-dwelling adults, ≥60 years with symptomatic knee OA and self-reported functional impairment.	All 12 hours of Arthritis Self-Management program over 12 weeks with follow-up. Walk + group also had pedometer instructions, with goal to increase step count by 30% over baseline; 24 weeks follow-up.	Mean±SD muscle strength comparing home-based pedometer group vs. arthritis self-management group at pre-test/post-test/follow-up. Pain rating indices (pre/post/follow-up): home based pedometer (14.65/12.41/12.95) vs. arthritis self-management group (13.94/10.12/10.90).	“In older adults with symptomatic knee OA, Walk + appears to increase walking, with improvements in muscle strength and walking performance. The use of a home-based pedometer-driven program to increase physical activity, strength, and function in this population warrants further research.”	Low compliance. No advantage in pain management identified.
Mikesky 2006 RCT	3.0	N = 221 over age 55 with moderate to severe knee OA	Strength training: month 1-3 train once a week at National Institute for Fitness and Sport (NIFS) and once at home; months 4-6 once a week at NIFS, twice weekly at home; months 7-9 2-months training at NIFS, 3 weekly at home training; months 10-12, once a month at NIFS, remaining workouts at home of 3 sets of 8-10 repetitions vs. ROM exercises not involving external loads 45 minutes a session; 30 months follow-up.	Isotonic hamstring strength 12 month improvement for women/men in strength training vs. ROM: 6.3%/11.8% vs. -0.7%/8.5%, p = 0.021; no significant difference at 18, 24, 30 months between groups. Joint space narrowing >0.50mm, number (percentages) for KL grade 2-3 for strength training vs. ROM: 19 (42%) vs. 24 (41), p = 0.858; KL criteria 0-1: 36 (34%) vs. 17 (19%), p = 0.038. WOMAC pain scores significant for treatment group X OA X time interaction, p = 0.033. Mean change in WOMAC pain score not significant between groups. SF-36 Mental Component Scale 30-months change for strength training vs. ROM: -0.4±1.1 vs. -1.6±1.0, p = 0.042;	“The [strength training] group retained more strength and exhibited less frequent progressive [joint space narrowing] over 30 months than the [range of motion] group. The increase in incident [joint space narrowing] >0.50 mm in [strength training] is unexplained and requires confirmation.”	Many weaknesses. Dropout rate high. Data suggest strength training superior.

				participants without knee OA at baseline: -5.0 ± 1.2 vs. -0.4±1.3, p = 0.004.		
Schneider 2001 RCT	3.0	N = 40 with persistent unilateral retropatella r pain for more than 6 months with unsuccessful conservative therapy using NSAIDs and analgesic agents	Sixteen round of physiotherapy vs. unsupported use of knee splint for 15 minutes, 3 times daily combined with exercise for patellofemoral pain syndrome for 8 weeks.	Mean±SD electromyographic measurements at Week 8 for vastus medialis: 456± 11.4 (p = 0.003) for physiotherapy vs. 532±8.1 (p = 0.001) for splint; vastus lateralis 240 ± 13.9 (p = 0.003) for physiotherapy vs. 292±10.2 (p = 0.001) for splint; Vastus lateralis/vastus lateralis 1.8 ± 1.3 (p = 0.003) for splint. Week 8 VAS score at rest 3.1±1.2 (p <0.05) for splint and after exposure 3.3 ± 1.1 (p <0.05).	“[T]his study show better the individually perceived therapeutic results to be better following knee splint use than those from physiotherapeutic exercises. The knee splint used here is thus confirmed as an effective therapeutic concept for coping with [patellofemoral pain syndrome] and for achieving early pain relief. The knee splint also enables patients to undertake sustainable self-therapy independently of scheduled therapy deadlines.”	Many details sparse. Dropouts unclear. Heterogeneous co-interventions not controlled.
Jan 2008 RCT	2.5	N = 49 with knee OA (ACR), K-L ≤III, 50+ years old	Target-matching foot-stepping exercise (TMFSE) in sitting, 3 sessions weekly for 6 weeks vs. no exercise intervention.	Interaction effect for walking time on ground level and stairs for TMFSE, p <0.001. All walking time (seconds) outcome measures decreased in TMFSE. Ground level: pre intervention: 44.1±2.9 post intervention: 38.6±2.5 p <0.0125. Stairs: 34.2±2.1 vs. 26.5±2.3 p <0.0125. Figure eight 51.3±6.7 vs. 29.1±3.6, p <0.0125.	“TMSFSE in sitting appears to be an option for exercise in patients with mild to moderate knee OA. This may be an especially attractive option for patients who may have pain with weight-bearing exercise. A longitudinal study with a larger sample size is needed to confirm the potential use of TMFSE for patients with knee OA.”	Quasi-randomized (every other). Baseline differences in outcomes measure(s).
Kovar 1992 RCT	2.5	N = 102 age >40 with knee OA and history of at least 4 months symptomatic knee pain during weight-	Eight week, hospital-based program of 24x90-minute indoor supervised fitness walking and patient education vs. routine care.	Intervention group had overall improvement of 18.4% (95% CI, 9.8%-27.0%) compared to controls. Those in walking program at post intervention improved 39% (CI, 15.6% to 60.4%), p <0.001 in Arthritis Impact Measurement Scale (AIMS) subscale.	“[O]ur results show a strong and what we judge to be a clinically significant effect of supervised fitness walking and patient education on independent measures of the functional status of patients with osteoarthritis of the	Some baseline differences. Many methods details sparse. Data suggest efficacy of fitness walking program.

		bearing activities		Walking group had decrease in arthritis pain of 27% (CI, 9.6% to 41.4%) (p = 0.003)	knee; this effect was achieved without exacerbating pain or triggering flares.”	
Callaghan 1995 RCT	2.0	N = 27 with x-ray appearance of knee OA	Control: sham electrical stimulation, 20 minutes twice a week vs. supervised 20-minute sessions of exercises (inner range quad exercises over wooden block, straight-leg raise to 18cm, isometric quad exercises) twice a week vs. 1 instruction session plus a functional home exercise regime (functional, weight bearing, sit to stand to sit, mini-squat wall slides; step-downs; 10 times each BID). Total appointments unclear.	Median change in pain pre-and post-treatment comparing control groups vs. exercise group vs. home regimen group: 0 vs. 18 (p = 0.04) vs. -21. ROM: -6 vs. 2 (p = 0.02) vs. 13.5.	“[P]atients with OA knee [sic] can be helped most economically by one session of advice and a functional home exercise regime. This can be done in a group setting under supervision of one physiotherapist.”	Many details sparse. Small sample sizes. Dropouts and compliance unknown. Data suggest functional, home-based exercise program superior.
Cochrane 2005 RCT	1.5	N = 106 with hip and/or knee OA	Water exercises vs. usual care for 1 year of treatment.	53.5% complied at 1-year. Estimated effect sizes 0.44 on WOMAC pain to 0.76 on WOMAC physical function.	“Group-based exercise in water over 1 year can produce significant reduction in pain and improvement in physical function in older adults with lower limb OA, and may be useful adjunct in the management to hip and/or knee OA.”	Abstract only. Compliance low, and dropped in subsequent 6 month period to 18%.
Sullivan 1998 RCT 1-year follow-up of Kovar 1992	1.0	N = 102 with knee OA described above	Eight week supervised fitness walking and supportive patient education program vs. routine medical control for knee OA.	Intervention group AIMS physical activity subscale scores returned to baseline levels after 1 year and not different from controls.	“There were no statistically significant differences between the intervention and control groups on measures of functional outcome or walking behavior as indicated by self-reported estimates	High dropouts and low compliance in addition to other weaknesses noted in Kovar 1992. Data suggest longer term compliance beyond an 8-week trial problematic.

					of distance walked at one year.”	
Hecht 1983 RCT	1.0	N = 36 undergoing total knee arthroplasty for OA.	Control group received exercise therapy alone vs. group 2 with local heat at arthroplasty site then exercise vs. group 3 with local cold then exercise.	Mean±SE in leg circumference (cm) after ten physical therapy sessions comparing exercise vs. heat plus exercise vs. cold plus exercise: Midpatella: -0.43±0.40 vs. 0.58±0.47 vs. -1.43±0.30; p <0.05.	“[T]hermal therapy provides no objective benefit in the postoperative rehabilitation of the total knee arthroplasty patient. Hypothermia does provide some subjective diminution in the pain associated with rehabilitation.”	Small sample sizes. Many details missing. ROM began 14 days after arthroplasty and is out of date.
Exercise vs. non-Exercise Control for Osteoarthritis						
Hurley 2007 Quasi-RCT	3.0	N = 418 who reported to their primary care practice mild, moderate, or severe knee pain for more than 6 months	Usual care vs. usual care plus individual rehabilitation vs. usual care plus group rehabilitation.	Mean (95% CI) WOMAC-function for usual care vs. rehabilitation (individual and group): 25.0 (22.9, 27.1) vs. 21.6 (20.2, 23.1), p = 0.010. WOMAC-pain: 6.7 (6.1, 7.4) vs. 5.7 (5.3, 6.2), p = 0.016. WOMAC-total: 35.0 (32.0, 38.0) vs. 30.4 (28.3, 32.6), p = 0.015. Aggregated functional performance time of 4 common activities of daily living: 61.0 (57.2, 64.9) vs. 57.6 (54.9, 60.2), p = 0.019.	“For individuals with chronic knee pain, supplementing usual primary care with a personalized progressive rehabilitation program integrating exercise, education, and active coping strategies (ESCAPE-knee pain) improved functioning for up to 6 months after completion of rehabilitation, regardless of whether it was delivered to individuals or small groups of patients.”	Study randomized by practice not patients. Large sample size. Many details sparse.
Hurley 2007 Quasi-RCT	3.0	N = 418 who reported to their primary care practice mild, moderate, or severe knee pain for more than 6 months	Usual care vs. usual care plus individual rehab vs. usual care plus group rehab.	Individual rehab mean costs £49 a session per person. Group rehab mean £23 a session per person. Participation in rehab £361 (95% CI \$297-423) more than usual care. Individual rehab £305 (95% CI 271-336) more than group rehab per person.	“Rehabilitation had cost implications, but at modest levels of investment was more likely to be cost-effective than usual primary care: investing £1,900 (or more) provided a 90% (or greater) change of rehabilitation being more cost-effective than usual primary care. Administering ESCAPE-knee pain to small groups of individuals reduced its costs without	This rehab program added costs to usual care, although total costs relatively modest.

					compromising clinical effectiveness, increasing the probability of cost-effectiveness.”	
Yip 2008 RCT	3.5	N = 95 with knee OA	ASMP (arthritis self-management program with goal direct exercise program) vs. control for 12 months.	According to ASE scale intervention group improved significantly as compared to controls in following areas (p value, mean change +- SD): Pain (p = 0.02) intervention 10.27 +- 7.99, control 5.20+- 9.38. Other Symptoms (p = 0.01) intervention 12.92 +- 10.04, control 6.33+- 10.70. Current Pain Rating (p = 0.0001) intervention - 33.50 +-23.65, control - 11.97+- 24.68. Pain rating at night (p = 0.001) intervention -34.50 +- 29.00, control -14.08+- 26.26. Pain rating during walking (p = 0.013) intervention - 23.88+-25.98, control - 9.85+-26.58.	“Our findings add to the evidence that the modified arthritis empowering programme improved perception of control of osteoarthritis and three health outcomes after 12 months of treatment.”	Some baseline differences with worse pain in intervention group (55.8 vs. 42.2, p = 0.002). Many details sparse. High dropouts by end of study (44.2%).
Exercise for Rheumatoid Arthritis						
Häkkinen 2003 RCT	3.5	N = 70 with recent onset RA	Strength training group performed strength training for 24 months (n = 35) vs. control group instructed to perform ROM exercises. (n = 35).	Mean muscle strength trunk extension change from baseline to month 24: Experimental group vs. control group: 8 vs. - 1; p <0.001. Knee extension: 33 vs. 15; p <0.001.	“As expected, strength training led to increased muscle strength, but this increase did not correlate with improved physical function as assessed by the Valpar 9 work sample test. The increased muscle performance did not prevent a substantial proportion of patients from retiring preterm. The 2 items from the Valpar 9 test that were applied were not sensitive enough to differentiate the patients according to their working status.”	Baseline differences in Ritchie’s index (11.8 vs. 16.7). High retirement rates both groups. Data suggest minimal differences in functional outcomes.
Häkkinen 2004 RCT	3.5	N = 70 with recent onset RA	Five- year follow-up of Häkkinen 2003 (see above).	Mean (SD) maximum muscle strength outcome increased from baseline to 2 years-in EG from 212 (78) kg by a mean (95% CI) of 68 (55 to 80) and in CG from 195 (72) kg by 35 (13 to 60) kg and	“The patients’ exercise induced muscle strength gains during a 2 year training period were maintained throughout a subsequent self monitored training	Data suggest many changes in medical management over 5 years providing a potentially potent co-intervention.

				remained at that level for next 3 years.	period of 3 years. Despite substantial training effects in muscle strength, BMD values remained relatively constant. Radiographic damage remained low even at 5 years.”	Data suggest better strength in exercise group.
Häkkinen 1999 RCT	3.0	N = 70 with recent onset RA	Training group (EG) (n = 32) vs. control group (CG, n = 33) for 12 months.	No differences were observed in pain outcomes (VAS) between the groups.	“Minimally supervised strength training resulted in significant improvements in muscle strength without detrimental effects on disease activity. The detected annual changes in central BMD were minor and statistically insignificant in both groups. Special attention should be focused on those patients with RA with high disease activity and concomitant glucocorticoid treatment.”	Some baseline differences. Cointervention with DMARDs precludes assessment of exercise.
Glucosamine						
Kawasaki 2008 RCT	3.0	N = 142 post-menopausal females with untreated OA of medial	Glucosamine 1500mg vs. Risedronate 2.5mg vs. no medication. All groups did home exercises	No significant differences in pain or overall functional scores between the three groups. Risedronate group had lower urine NTX. In subcategories of WOMAC and JOA, ROM better in glucosamine group (p = 0.042), joint stiffness was better in glucosamine and risedronate (p = 0.000013 and p = 0.000017 respectively).	“When glucosamine and risedronate were administered to OA patients who were performing knee exercise, improvement of range of motion and objective symptoms such as joint stiffness was observed which was not observed in the control group, however no statistically significant difference was observed.”	All women. Lack of study details lowered score. No blinding done.
Dietary Supplements						
Oben 2009 RCT	3.5	N = 45 who met following criteria: age 25-60 diagnosed with primary OA of target knee using ACR criteria and BMI 25-40kg/m ² or	Group 1 OT (overweight treatment group) (370mg formula per capsule. Capsule consisted of Phellodendron amurense. Tree bark extract standardized to minimum of 50% berberine		“[N]P 06-1 had beneficial effects on symptoms of osteoarthritis of the knee as measured using LAI scores and had anti-inflammatory effects as measured using CRP. Administration of NP 06-1 was also associated with weight loss, which may have been a	Eight weeks follow-up. Pilot study. Patients not well described and differences present at baseline in some outcome variables. Very high dropouts.

		18.9-24.9 kg/m ²	and citrus sinensis. Osbeck peel extract standardized to a minimum of 30% polymethoxylated flavones) vs. Group 2 OP (overweight placebo group) (placebo: identical red 2-piece hard shell capsule) vs. Group 3 NP (normal weight placebo group) vs. Group 4 NT (normal weight treatment group). Took capsules with food in morning and night (4 a day) with food for 8 weeks. Subjects had analgesic washout period 5 days prior to enrollment.		contributing factor to the other benefits.”	
Colker 2002 RCT	3.0	N = 31 who met following criteria: age 35 or older, osteoarthritis diagnosed by a physician in at least one knee, daily pain and stiffness, and subjects willing to avoid other dietary supplements.	Group A (fruit flavored, refrigerated drink formulated with proprietary milk protein concentrate and fortified with vitamins B12, C and E, iron and zinc, n = 16) vs. Group B (placebo, refrigerated grape juice isocaloric but no protein or added vitamins, iron, or zinc, n = 15). Each subject drank 355mL a day for 6 weeks.		“[D]aily consumption of the nutritional beverage containing milk-based micronutrients, vitamins, and minerals was beneficial in alleviating symptoms and dysfunction in subjects with osteoarthritis.”	6 weeks follow-up. Attempted blind but drinks dissimilar. High dropouts. Many details sparse.
Rose Hips						
Warholm 2003 RCT	3.0	N = 100 with hip or knee OA	Rose-hip powder 5g a day vs. placebo for 4 months.	Pain declined in active treatment group compared with placebo, p<0.035 (no data provided).	“Hyben Vital... reduces osteoarthritic pain in the hip and also reported a statistically significant improvement in energy, motivation	Conference abstract with limited data.

					for their daily activities and sleep during active therapy.”	
Herbal and Alternative Treatment						
Grube 2007 RCT	3.5	N = 220 with knee OA with 40mm on VAS scale	Comfrey root extract vs. placebo for 3 weeks.	Both groups declined in pain, but treatment group saw statistically significant decline in total VAS score (p <0.001). Pain at rest also achieved significance in treatment group (p <0.001). Clinical Global Impression on severity of disease significant in treatment group (p <0.001) compared to placebo. Global assessment of efficacy (FAS collective): physician's judgment no effect (verum 14 patients vs. placebo 100 patients), patient's judgment (symptom-free 8 vs. 1, no effect 17 vs. 94).	“At the end of the trial, pain in the verum group had, on an average, reduced five times more than in the placebo group. The primary target value (VAS total score) improved by 54.7% in the verum group, but only by 10.7% in the placebo group.”	Some details sparse. Patients not described. Data suggest efficacy; 3 weeks follow-up.
Kuptniratsai kul 2009 RCT	3.0	N = 107 with primary knee OA (ARA), over 50 years, pain score ≥5/10	Ibuprofen 400mg BID vs. C. domestica extracts 500mg QID for 6 weeks.	Pain improved in both groups after 6 weeks. No difference between groups in pain scores improvement in walking (p = 0.20) and pain on stairs (p = 0.92) after 6 weeks. No difference in patient satisfaction (p = 0.15) No difference in adverse events between groups (p = 0.36).	“[C.] domestica extracts might be as effective as ibuprofen in alleviating knee pain and improving knee functions.”	Many details sparse. Some baseline differences in outcome measures. E.g., mean of pain on stairs at baseline 5.6 vs. 6.4 and at end of trial 3.1 vs. 3.9 reported as significant, but data suggest possible randomization failure; thus a low-quality trial.
Tilwe 2001 RCT	2.5	N = 50 age 40-75 with active arthrosis of knee joint	Phlogenzym 3 tablets then reduced to 2/day vs. 50mg diclofenac BID for 3 weeks. 7 weeks follow-up.	Global evaluation by physicians was very good in 12% enzymes vs. 28% diclofenac. Study group showed significant improvement in joint tenderness at end of therapy and follow up period (p<0.05). Both groups did not change in knee ROM.	“[P]hlogenzym reduces the symptoms of active osteoarthritis as well as diclofenac sodium does...Both patients and doctor found the drugs to be comparable in efficacy and safety.”	Patients with “active osteoarthritis” and unclear if inflammatory arthritis included. Many details sparse. Claims of blinding unclear as dose changed and

						blinding of patients not apparently possible. If patients unblinded and treated with known NSAID 'more of the same' then biased in favor of phlogenzym.
Ultrasound						
Tsumaki 2004 RCT	2.5	N = 21 patients undergoing bilateral 1-stage opening-wedge high tibial osteotomy by hemicallotasis	Low intensity pulsed ultrasound vs. no ultrasound for 4 weeks	Bone mineral density increased significantly in ultrasound group compared to the control group during 4 weeks, p = 0.02.	"[L]ow-intensity pulsed ultrasound applied during the consolidation phase of distraction osteogenesis accelerates callus maturation after open-wedge high tibial osteotomy by hemicallotasis in elderly patients."	Lack of study details. Cost-benefit and functional outcomes need to be addressed to make clinical recommendations.
Acupuncture						
Different Types of Acupuncture						
Erqing 2005 RCT	1.5	N = 559 with ankle, knee, shoulder, or wrist joint issues	Blood-letting acupuncture with plum-blossom needle and cupping once every other day for 3 times (treatment group, n = 186) vs. TDP irradiation (control group, n = 373) once a day, 6 times.	Therapeutic effect on knee joint lower than other joints, p <0.01.	"Blood letting puncture with plum-blossom needle and cupping is effective in treating acute articular soft tissue injury and its therapeutic effect is probably brought about through accelerating blood circulation, promoting elimination of swelling and inflammatory substances, alleviating inflammatory reaction and relieving spasm of muscles and ligaments as well."	Many details sparse. Heterogeneous, unclear blinding not well described. Quality of controls unclear.
Electroacupuncture						
Yurtkuran 1999 RCT	3.5	N = 100 suffering from knee pain ≥6 months, and diagnosed with OA of knee	TENS (n = 25) vs. EA (n = 25) vs. ice massage with piece of wood 10cm long with frozen cube-shaped sponge used on same acupuncture points for 20 minutes (n = 25) vs. placebo (n = 25).	TENS pretreatment/TENS post-treatment/EA pre/EA post/ice pre/ice post/placebo pre/placebo post evaluation of parameters for pain, stiffness, 50 ft walking time (quads), muscle strength (quads), and knee flexion (quads). TENS vs. EA vs. ice vs. placebo percent	"Electroacupuncture may be an important modality in relieving pain and related symptoms such as stiffness, long walking time, quadriceps weakness in the treatment of knee osteoarthritis. Larger, prospective, randomized and long-term studies	Possible baseline differences. Trial too short to provide quality evidence on efficacy; 2-week follow-up.

			Acupuncture locations used: SP-9, GB-34, ST-34, ST-35; 2 weeks follow-up.	improved for pain at rest, stiffness, 50 ft walking time (quads), muscle strength (quads), and knee flexion (quads).	are needed to further explore the differences between EA, TENS, and ice massage.”	
Ng 2003 RCT	3.0	N = 24 diagnosed with OA of knee	Low frequency EA (2 Hz) on 2 acupuncture points for 20 minutes (n = 8) vs. low-frequency TENS 2 Hz and pulse width 200µs on same points for 20 minutes (n = 8) vs. education-only (n = 8).	Sparse data, mostly provided graphically. Data suggest both electroacupuncture and TENS reduces pain more than control	“[B]oth EA and TENS treatments demonstrated a significant pain reduction effect on patients with OA-induced knee pain. Therefore, both treatments are recommended for treating OA knee pain.”	Small groups. Follow-up too small to gauge efficacy.
Ahsin 2009 RCT	2.5	N = 84 who fulfilled ACR criteria for OA	Electro-acupuncture (n = 26) vs. sham acupuncture (n = 58) for 10 sessions, each sessions 20-25 minutes. Acupuncture points: ST35, EX-LE5, EX-LE2.	Mean reduction in WOMAC scores for sham were 0.7% compared to electro-acupuncture of 72%, p <0.001. Mean reduction in VAS pain scores for sham did not change compared to 72% decrease for electro-acupuncture, p <0.0001.	“It can be concluded that electro-acupuncture may be incorporated in conventional treatment of osteoarthritis of knee or other musculoskeletal disorders, and provides relief clearly beyond that of placebo effects.”	Very high dropouts, especially sham group make data difficult to interpret.
Manipulation or Mobilization						
Stakes 2006 RCT	3.0	N = 60 with patella-femoral pain syndrome	Patella mobilization only vs. patella mobilization plus spinal manipulative therapy. 6 treatments in 4 weeks.	Pressure pain threshold for algometry (treatment 1/treatment 6): patellar mobilization (3.64/5.22) vs. pat. plus spinal manipulation (3.63/5.36). Other between group differences not tested, but do not appear significant.	“Although there appeared to be promising effects suggesting either protocol may provide short-term relief for PFPS, use of a small convenience sample, lack of a blind observer or scales solely validated for PFPS additionally make tentative conclusions regarding this trial.”	Population not described. Many details sparse. Results not compared between groups. Data do not appear to support adding spinal manipulative therapy.
Rowlands 1999 RCT	1.5	N = 30+ with patella-femoral pain syndrome	Patella mobilization vs. placebo ultrasound.	Mostly graphic data presented. Unclear whether baseline differences present in outcomes data or trends at 1st follow-up after intervention begun.	“[P]atella mobilization was superior to placebo in the treatment of patellofemoral pain syndrome.”	Pilot study. No descriptive data. Dropouts replaced, but number dropping out not specified.
Low-level Laser Therapy						
Simunovic 2000 RCT	1.5	N = 126 with operated mechanic or overloading soft tissue injuries	Low level laser therapy (LLLT, n = 52) vs. placebo (n = 74) for 18 days.	Those treated with LLLT had passive and active movements earlier than placebo group, p <0.05. Patients 60 years and older had longer delay in healing and functional recovery, p <0.05.	“This animal and clinical study proved that LLLT applied as monotherapy can significantly improve wound healing and subsequently accelerate the	Lack of details and low-quality study. Need to repeat study with better randomization and blinding in

					functional recovery process on operated patients suffering from sport-and traffic-related injuries of soft tissue.”	order to evaluate effects.
Electrical Stimulation for Patellofemoral Pain						
Callaghan 2001 RCT	3.5	N = 16 with patellofemoral pain syndrome	Mixed frequency stimulation from standard device vs. simultaneous mixed frequency from experimental device.	Paired t-tests showed that improvement from pre to post test was statistically significant for the standard device (p = 0.019), but not for the experimental (p = 0.059).	“[T]he results from the repeated measures ANOVA (Table 3) are not significant.”	Pilot study. Small sample size. No placebo group. Patients not well described. Data suggest comparable results.
Electrical Stimulation for Post-surgical Patients						
Delitto 1988 RCT	3.0	N = 20	Voluntary exercise (n = 10) vs. EMS (n = 10). All had undergone ACL reconstruction.	Mean percentage of flexion and extension torque ratios differed between ES and VE groups (p <0.05).	“We found significantly greater isometric strength gains of both knee extensor and flexor muscles of patients in the ES group compared with patients in the VE group.”	Small samples and groups not well described. Some data suggest baseline differences. Programs not begun at uniform time. Data suggest electrical stimulation may be superior to exercise, but methods used problematic.
Synder-Mackler 1995 RCT	3.0	N = 110 who underwent ACL reconstruction	High-intensity neuromuscular electrical stimulation (n = 31) vs. high-level volitional exercise (n = 34) vs. low-intensity neuromuscular electrical stimulation (n = 25) vs. combined high and low-intensity neuromuscular stimulation (n = 20) for 4 weeks.	Significant difference between 2 groups that received high-intensity stimulation vs. those that did not in regards to recovery of quadriceps femoris (p = 0.001) and flexion-excursion of knee (p = 0.006).	“Our results indicate that there was no significant difference between the group treated with high-intensity neuromuscular electrical stimulation and the group treated with both high and low-intensity stimulation (statistical power >0.8).”	Patients not well described and included different procedures noted to have affected results (e.g. graft) but not stratified randomization that results in difficulty interpreting results.
Wigerstad-Lossing 1988 RCT	3.0	N = 23 undergoing ACL reconstruction	Electrical stimulation at 30Hz (n = 13) vs. no stimulation (n = 10) for 3 weeks post-surgery.	Quadriceps cross-sectional showed experiment group had a significantly less decrease (p <0.05) during immobilization period. No significant difference in muscle fiber distribution between legs.	“[T]he group with electrical stimulation demonstrated less reduction of the isometric muscle strength after the immobilization period than the control group and also significantly small reduction in	Small sample. Scant description but some apparent baseline differences. High dropout in controls due to non-compliance. Data suggest

					the cross-sectional area of the quadriceps muscles.”	electrical stimulation plus exercise superior to exercise alone.
Snyder-Mackler 1991 RCT	3.0	N = 10 who underwent ACL reconstruction	Neuromuscular electrical stimulation and volitional exercise (n = 5) vs. volitional exercise alone (n = 5) for 4 weeks.	There was only usable kinetic data for 6 patients. Neuromuscular group showed a significantly higher isokinetic torque and peak at 90 (p <0.05) and 210 (p <0.01) degrees per second compared to volitional group.	“...Our results suggest that the use of neuromuscular electrical stimulation translates, at least in the immediate postoperative period, not only into an increase in muscle strength but also into an improvement in the functional use of muscles.”	Very small samples. Patients not well described. No dropouts but 40% of kinetic data unusable. Data suggest electrical stimulation of additive benefit to exercise.
Draper 1991 RCT	2.5	N = 30 who suffered ACL acute tears and undergone autograft surgical reconstruction	Electrical stimulation with quadriceps exercises (n = 15) vs. EMG biofeedback to monitor muscle activity during quadriceps exercises (n = 15) for 6 weeks post-op.	EMG biofeedback group showed a significantly greater percentage of recovered nonoperative limb peak torque than electrical stimulation group (p = 0.044).	“[T]he results indicate that there was greater recovery of isometric peak torque by use of biofeedback than by use of ES and that there was no difference in the recovery of active knee extension when each of these modalities was used.”	Small groups. Baseline differences. No non-exercise group. Data suggest minimal difference between groups.
Electrical Stimulation for Improving Athletic Performance						
Hortobagyi 1998 RCT	3.5	N = 22 all females	Eccentric contraction via electrical stimulation (n = 8) vs. voluntary contraction (n = 8) vs. control (n = 8).	Current need for contraction increased over study from 39-65 mA (p = 0.0001). From pre- to post-training, voluntary group improved force production by 136 N (p <0.5) over EMS contractions on further voluntary contractions. EMS group improved force production by 229 N (p<0.05) over voluntary contractions on further EMS contractions (p <0.05).	“(T)raining with EMS-evoked eccentric forces resulted in a 1.2 EMS to voluntary ratio, suggesting incomplete muscle activation following EMS training. Even if individuals are trained, an inhibitory mechanism may protect muscles and joints from excessive forces during eccentric contractions.”	All healthy subjects. Small samples. Subjects not well described. Data suggest minimal change on force and increased electromyostimulation-associated strength.
Fahey 1985 RCT	3.5	N = 55 females (n = 27, and males (n = 28)	EMS at 65° knee flexion vs. EMS at full extension vs. control.	Males received greater electrical stimulus (p <0.05). No differences within sexes (p >0.05). Both treatment groups improved significantly over controls in several areas (p <0.05). Knee flexion groups performed better than full extension group in some measures (p <0.05).	“(T)hese data suggest that electrical stimulation of the quadriceps is effective in improving isometric and isokinetic strength in males and females and that it may be more effective... if the treatment is administered with	All healthy. Small groups. Subjects not well described. Data suggest electrical stimulation increased strength.

					the knee flexed rather than fully extended.”	
Romero 1982 RCT	3.0	N = 18 females	EMS treatment (n = 9) vs. control (n = 9).	Treatment group improved significantly over controls in terms of pre- to post-test knee extensor strength (p <0.05). No other measures reached significance.	“(T)he results of this study indicated that faradic electrical stimulation can produce a significant increase in isometric strength and perhaps strength at slow slow speeds of motion in young, untrained females.”	Small sample size. Experiment in uninjured athletes. Data suggest modest change in strength.
Currier 1983 RCT	3.0	N = 34	Isometric exercise via voluntary contraction (n = 8) vs. EMS only (n = 8) vs. a combination of both (n = 9).	No differences between groups. Although all groups improved on pre-training strength values (p <0.01).	“(H)igh intensity electrical stimulation... does augment torque when subjects train with isometric contractions... no increase in muscle (girth) is produced after 5 weeks of training by isometric exercise... resistance training methods used in this study produced torque gains, but no statistical differences.”	Small samples. All healthy. Subjects not well described. Data suggest trends of exercise superior to stimulation superior to controls and stimulation not of additive benefit.
Kubiak 1987 RCT	2.5	N = 29	Isometric exercise via voluntary contraction (n = 10) vs. EMS contraction (n = 10) vs. control (n = 9).	Both treatment groups improved significantly as compared to controls (p <0.05). Voluntary group showed greater strength increase 43% than EMS group (33%) but difference not significant.	“This study shows that an isometric exercise program is a more effective means of increasing isometric strength in healthy muscle, when compared to a program of electrical stimulation.”	Small samples. All healthy. Subjects not well described. Data suggest exercise superior to stimulation superior to control.
Maffiuletti 2000 RCT	2.5	N = 20 all males; all experienced athletes but novice weightlifters	Exercise via electrical stimulation (n = 10) vs. controls (n = 10).	In treatment group isokinetic strength increased significantly under eccentric conditions (p <0.05). Isometric strength increased only at angle adjacent to those trained (p <0.01). No change in concentric. Treatment groups increased squat jump significantly (p <0.01).	“(T)his study demonstrated that an increase in the eccentric, isometric, and concentric strength of the knee extensors and vertical jump performance without SSC can be achieved in a relatively short period after a 4-week EMS training program.”	RCT in uninjured athletes. Small groups and subjects not well described. Data suggest modest benefits although no true control/blind.
Balogun 1993 RCT	2.5	N = 30 all males	EMS stimulation at 20pps (n = 10) vs. 45pps (n = 10) vs. 80pps (n = 10). Left limbs used as control on all subjects.	Both lower limbs on subjects produced similar force pre-training (p >0.05). But at 2, 4, and 6 weeks, right limb on all subjects showed improved strength (p	“Our present findings suggest the NMES may be useful in the rehabilitation of patients where active exercise is not feasible due to	All healthy. Small samples. No placebo group. No differences between groups.

				<0.05). Isometric contraction used.	protective pain, immobilization, or weakness of the affected muscles.”	
Caggiano 1994 RCT	2.5	N = 18 all males age >65	Traditional contraction (n = 7) vs. EMS contraction (n = 11).	Pulse rate decrease in both groups from pre to post-training (p <0.05). No significant differences between peak torque produced on isometric contraction. So values assessed on individual basis with respect to activity level. Correlation with activity level and torque produced was found (r = 0.57, p = 0.01)	“The results of this study suggest that it is important to assess the prior physical activities of patients to ensure that the strength training program adequately stresses the muscle to ensure strength gains.”	Small samples. All healthy. Subjects not described well.
Mohr 1985 RCT	2.0	N = 17	Isometric exercise via voluntary contraction (n = 5) vs. EMS (n = 6) vs. control.	No measures reached significance. Although voluntary contraction group improved most (14.7%) while other 2 groups saw improvement of <1%.	“This study indicated that HVG stimulation was not as effective as isometric exercise in increasing isometric strength in healthy muscle.”	Very small samples. Subjects not well described. Data suggest exercise superior to electrical stimulation or control and electrical stimulation not effective.
Percutaneous Electric Therapy						
Eriksson 1979 RCT	2.5	N = 8 with chronic ruptures of knee ligaments	Isometric quadriceps training (n = 4) vs. isometric quadriceps training and percutaneous electrical stimulation (n = 4) for 4 weeks.	Patients who received electrical stimulation had less muscle atrophy compared to exercise alone, p <0.01.	“[P]ercutaneous electrical stimulation may be a way of preventing muscle atrophy after major knee ligament surgery in athletes.”	Small numbers. Lack of study details. Need additional follow-up to evaluate if reported muscle bulk affects functional recovery after cast removal.
TENS						
Cheing 2003 RCT	3.5	N = 38 with knee OA age 50-80	TENS for 20 minutes (n = 10) vs. TENS for 40 minutes (n = 10) vs. TENS for 60 minutes (n = 10) vs. placebo TENS (n = 8) 5 days a week for 2 weeks.	VAS scores between groups significant in favor of 3 active TENS groups, p <0.003.	“40 minutes is the optimal treatment duration of TENS, in terms of both the magnitude (VAS scores) of pain reduction and the duration of post-stimulation analgesia for knee osteoarthritis.”	TENS compared to placebo not completely blinded. No effect on pain. No measure of function done.
Cheing 2002 RCT	3.5	N = 62 with knee OA age 50-75	TENS for 60 minutes (n = 16) vs. placebo stimulation (n = 16) vs. exercise (n = 15) vs. TENS and	After 1st session, VAS scores improved. Differences seen when comparing TENS group and exercise group (p = 0.011) and TENS and exercise group with	“A single treatment session of TENS or TENS and Ex produced significantly greater pain reduction than the exercise group.	Exercise was as effective as TENS in chronic knee OA. Lack of study details lowered score, no blinding.

			exercise (n = 15) for 4 weeks.	exercise group, p = 0.008.	Over the four-week treatment period, various degree of pain reduction was found in the different groups, but the four treatment protocols did not show significant between-group difference at the end of the treatment period.”	
Jensen 1991 RCT	3.0	N = 20 knee OA and exercise-induced pain for at least 6 months	Low frequency TENS 2 Hz (group A, n = 10) vs. high frequency TENS 80 Hz (group B, n = 10) 1 treatment a day for 5 days	No significant differences between groups for pain, pain at rest, or consumption of analgesics/NSAIDs during study period.	“[T]he study does not indicate a short-term, clinically relevant difference between these two types of electrical afferent stimulation.”	Small numbers, no blinding, lack of details reported.
Fargas-Babjak 1989 RCT	2.5	N = 37 hip and knee OA for longer than 6 months	Codetron (n = 19) vs. placebo (n = 18) for 6 weeks.	VAS scores improved in Codetron group compared to placebo group, p <0.02.	“This is highly suggestive of beneficial effect of nonhabituating Codetron as a complementary modality in the therapy of chronic pain conditions such as osteoarthritis.”	Excluded workers’ comp patients. VAS improved, otherwise no significant difference noted. Not compared to a regular TENS unit.
Walker 1991 RCT	2.5	N = 22 in CPM study; 48 patients in TENS study; 30 patients in continuous cooling pad	Continuous passive motion vs. no continuous passive motion TENS vs. placebo TENS vs. control continuous cooling pad vs. no continuous cooling pad.	CPM trial- no difference in length of hospitalization, post-op drain blood loss, or knee flexion TENS trial. No difference in length of hospitalization and knee flexion CCP trial; no difference reported in length of hospitalization, post-op blood loss, and in knee flexion. Decrease in mean used post-op analgesia use (p <0.004).	“...during postoperative UTKA recovery, the use of CPM vs. no CPM and CPM with CCP vs. CPM without CCP can diminish postoperative hospitalization analgesia consumption. Decreased postoperative analgesia consumption implies potentially improved patient comfort and diminished risk of analgesia-related complications. CPM with TENS does not appear to offer this advantage over CPM without TENS.”	Small numbers in each trial. Multiple different trials reported in trial. Lack of study details lowered score. TENS did not have any reported effect. CPM and cooling reported to decrease in hospital analgesia consumption but placebo effect could be involved.
Smith 1983 RCT	2.5	N = 100 post knee surgery	TENS vs. no TENS; arthrotomy patients (Group A had TENS, n = 25; Group B had no TENS, n = 25); total knee patients (Group	Hospital stay: Group A 3.84 days vs. Group B 5.40 days; Group C 14.92 days vs. Group D 17.88 days. Days until straight leg raise: Group A 1.72 days vs. Group B 2.44 days; Group C 4.92 days vs. Group D	“[T]ENS is an effective electronic pain control. It is a noninvasive technique that significantly improves knee patients’ postoperatively	Lack of details lowered score. No statistical comparisons run to know if differences are significant.

			C had TENS, n = 25; Group D no TENS, n = 25)	7.54 days. Days until ambulation: Group A 1.40 days vs. Group B 2.44 days; Group C 4.96 days vs. Group D 4.96 days.	rehabilitation performance as well as shorts the hospital stay.”	
Anderson 1989 RCT	2.0	N = 100 after ACL reconstruction	Group 1 (maximum support knee immobilizer in extension 12 weeks, n = 20) vs. Group 2 (immobilization and TENS, n = 20) vs. Group 3 (hinged knee brace at 60° of flexion, n = 20) vs. Group 4 (hinged knee brace and pre-op muscle stimulator, n = 20) vs. Group 5 (hinged knee brace and continuous passive motion, n = 20).	At 18 months, instrumented Lachman test showed an average laxity of 3.48mm in Group 1 and 1.70mm in Group 2, p = 0.045. Compliance index +0.5mm in Group 1 and -0.14mm in Group 3, p = 0.050. Active drawer test showed 1.83mm of laxity in Group 2 and 0.44mm of laxity in Group 2, p = 0.050. Groups 3 and 4 showed Group 3 lost an average of 11.8° flexion and Group 4 lost 5.6° flexion, p = 0.028. Lachman test greater in Group 1 than Group 4, p = 0.037.	“TENS did not significantly reduce the number of injections of milligrams of pain medicine required... Comparison of treatment in extension to early limited range of motion in flexion revealed no clear difference in stability... EMS did not reduce atrophy but it was effective in minimizing the strength decreases that occur with immobilization...CPM reduced the need for manipulation compared to immobilization in extension, but was not as effective as early limited range of motion...The optimal rehabilitation program included EMS and immobilization in flexion with early limited range of motion.”	Lack of study details lowered score.
Alcidi 2007 RCT	1.5	N = 40 with knee OA in a single knee	Lower power RF vs. TENS 50 Hz for 5 days.	A decrease of mean values of pain intensity and Lequesne’s index observed in both groups. Decrease in pain and LI only significant in RF group (p <0.01)	“A therapeutic effect of RF was demonstrated on pain and disability due to knee OA this effect was better than the effect of TENS.”	Lack of details lowered the score. Unable to draw treatment conclusions.
Viscosupplementation Injections						
Grecomoro 1992 RCT No mention of sponsorship or COI.	2.5	N = 40 with knee OA (13 males, 27 females)	Sodium hyaluronate 20mg in 2ml phosphate buffer weekly injections for 5 weeks (n = 20) vs. same regimen plus dexamethasone phosphate 0.4mg added to 1st injection (n = 20).	HA vs. HA+dexamethasone mean daytime pain rating at baseline, Day 7, 14, 21, 28, 35, and 60: 2.1/2.7, 1.6/1.4, 1.3/0.8, 0.8/0.6, 0.4/0.3, 0.3/0.2, 0.3/0.0. Night time pain: 1.7/2.6, 1.4/1.5, 0.9/0.9, 0.6/0.7, 0.3/0.3, 0.3/0.2, 0.3/0.1. Severity of weight-bearing pain mean scores: 2.6/3.4, 2.3/2.6,	“These data suggest a very effective therapeutic synergism between hyaluronic acid and the steroid but further studies are needed to confirm the preliminary findings.”	“[P]reliminary” study. Study suggests modest synergistic effect from steroid; however study only to 60 days and most study details missing.

				1.7/2.1, 1.2/1.6, 1.0/1.2, 0.6/0.9, 0.7/0.8.		
Dose-Ranging and High vs. Low Dose Studies of Viscosupplementation						
Bragantini 1987 RCT No mention of sponsorship or COI.	3.5	N = 55 with knee osteoarthritis rated grade II to IV on Kellgren-Lawrence scale verified via radiograph; mean age 57 years	40mg Hyaluronic acid injection group (n = 20) vs. 20mg Hyaluronic acid injection group (n = 18) vs. Saline placebo group (n = 17). Assessments at baseline, 7, 14, 21, and 60 days.	Both treatment groups showed significantly better improvement scores for walking pain and pain under load vs. placebo group at 21 and 60 days analyses: walking pain -- 21 days, (p <0.05); 60 days, (p <0.01); pain under load -- 21 days, (p <0.01); 60 days, (p <0.01). No significant differences between two doses.	"We can conclude that even when HA is injected intra-articularly at a low dose (20 mg/week), it is an active agent and could have a useful role in the treatment of OA of the knee."	Sparse methodological details. Both treatment groups better than placebo.
Viscosupplementation vs. Platelet Rich Plasma Injections						
Filardo 2012 RCT Sponsored by RICERCA FINALIZZA TA, Health Department. COI, Filardo is affiliated with Nano-Biotechnology Laboratory, Italy. However, all authors mention no COI.	3.5	N = 109 patients with history of chronic (at least 4 months) pain or swelling of knee and imaging findings of degenerative changes of the joint (Kellgren-Lawrence Score up to 3); mean age PRP group was 54 years; HA group 55 years.	3 autologous platelet rich plasma (PRP) intra-articular injections (n = 54) vs. 3 Hyaluronic Acid (HA (>1500 KDa; HyalubrixW, Fidia, Abano Terme (PD), Italy) injections (n = 55). 150ml venous blood sample for every knee treated. 12 months of follow-up.	Post injective pain reaction (n. of days * level 1-10): PRP 16.87 vs. HA 9.2; p=0.039.	"Results suggest that PRP injections offer a significant clinical improvement up to one year of follow-up. However, conversely to what was shown by the current literature, for middle-aged patients with moderate signs of OA, PRP results were not better than those obtained with HA injections, and thus it should not be considered as first line treatment. More promising results are shown for its use in low grade degeneration, but they still have to be confirmed."	No significant differences between HA and PRP groups but both showed clinical improvement at 1 year post injection.
Spakova 2012 RCT No mention of sponsorship. No COI.	2.5	N = 120 with osteoarthritis of the knee joint; mean age 53 years for both groups.	Platelet-rich plasma group (PRP) -- 3 injections of PRP (n = 60) vs. Hyaluronic Acid group - 3 injections of HA. (HA) (n = 60). Follow-up assessments were made at 3 and 6 months.	At 3-month follow-up, mean WOMAC-pain score for PRP vs. HA was 14.35 vs. 26.17 (p <0.05). There was also a significant difference found at 6 month follow-up; 18.85 vs. 30.90 (p <0.05). Both groups showed significant differences when compared to baseline values of WOMAC pain scores.	"The clinical results of our pilot study are encouraging and suggest that this method may be successfully used for the treatment of initial stages of knee OA."	Sparse methodological details. PRP "may" be effective in early stages of knee OA as demonstrated by increased platelet concentration.
Viscosupplementation vs. Glucocorticosteroid						
Tasciottaoglu 2002 RCT	3.5	N = 60 female patients with Grade II and III	Intra-articular HA treatment: 3 weekly injections of 2ml sodium (n = 30)	Mean±SD VAS score for rest pain improved from baseline vs. month 3: HA group (30.43±9.78 vs.	"[B]oth intra-articular hyaluronic acid and 6-MPA treatments provide clinically significant	At 3 months, HA group did better in all pain scores but at 6 months, no

No mention of sponsorship or COI.		knee osteoarthritis and pain under weight-bearing >40mm VAS score. Mean±SD age: sodium hyaluronate (HA) was 57.4±6.5 years, 6-methylprednisole acetate (6-MPA) 60.1±8.6 years.	vs. 1ml 6-methylprednisolone acetate (40mg/ml) by intra-articular injection for 3 weeks (n = 30). Follow-up at baseline, weeks 1, 2, 3, 4 and month 3 and 6.	12.00±10.15; p <0.001). 6-MPA group (29.90±10.15 vs. 19.70±11.72; p <0.001).	improvement and demonstrated that Na HA has a long-term beneficial effect in patients with knee osteoarthritis.”	significant differences between groups.
Viscosupplementation Injections vs. Placebo						
Grecomoro 1987 RCT No mention of sponsorship or COI.	3.5	N = 34 patients (40 knees) with gonarthrosis; mean age 64.88±10.94 years.	Hyaluronic acid (Hyalgan®) with molecular weight between 500,000-750,000 daltons; 3 intra-articular injections at 20mg sodium hyaluronate in 2ml phosphate buffer (n = 20) vs. Placebo 3 injections of 2ml phosphate buffer (n = 20). Injections received at baseline, 1 week, and 2 weeks. Assessment at weekly injections, 7 days after third injection, and 60 days after baseline.	Improvements in favor of hyaluronic acid: pain on touch (p <0.025), pain under load (p <0.005), and pain while walking (p <0.01).	“The results showed a significant difference between treatments for all the variables assessed. In the sodium hyaluronate group, pain relief was not only rapid but also long lasting.”	Small sample size, short follow-up time although HA group showed promise for rapid pain relief when compared to placebo both short and long term.
Tashiro 2012 RCT Double-blind No mention of sponsorship or COI.	3.5	N = 60 with OA of Kellgren-Lawrence (K/L) Grade 2 or Grade 3. age 50 or older.	Oral hyaluronic acid or HA 200mg once a day every day (n = 30) vs. placebo received 4 hard capsules which contained only cornstarch (n = 30).	Pain and stiffness in knees; at 2/and 12 months; 77.9±3.6 vs 84.6±4.6 placebo, p <0.05 against / and 66.8±4.4 vs. 72.5±8.0, p <0.05 against baseline.	“Oral administration of HA may improve the symptoms of knee OA in patients aged 70 years or younger when combined with the quadriceps strengthening exercise.”	Randomization and blinding not well described. High dropout rate and poor compliance. Study compared HA+exercise to placebo+exercise. Both groups showed improvement.

			Follow-up for 12 months.			
Tamir 2001 RCT No mention of sponsorship or COI.	3.5	N = 49 with knee osteoarthritis rated Grade 2 or 3 osteoarthritis on Kellgren and Lawrence scale via radiograph meeting Altman criteria, ages 60-85, mean age 71 for BioHy group and 70 for placebo group.	20mg sodium hyaluronate, "BioHy" (MW 3.0±0.6 MDa), injection group (n = 25) vs. Placebo control group (n = 24). Both groups received 5 weekly injections. Assessments at baseline, 1 week, 2, 3, 4, 6, 12, and 20 weeks.	No significant p-value results reported between the BioHy and placebo groups.	"[H]A products such as BioHy, which consistently contain high molecular weight HA, may be beneficial for patients with various inflammatory joint disorders without causing serious side effects. BioHy will be examined in further studies involving greater numbers of patients in order to show statistically significant clinical effectiveness."	An open label trial. Title says double blind but study design is single blind. BioHy showed some improvement at week 20 for pain relief.
Wu 1997 RCT No mention of sponsorship or COI.	3.5	N = 90 with 116 knees diagnosed as early osteoarthritis (mild to moderate). Mean±SD age: ARTZ group 68.9±9.4 years, Placebo group 69.2±8.1 years.	2.5ml drugs sodium hyaluronate (ARTZ) intraarticularly once a week for 5 consecutive weeks without use of local anesthetic drugs (n = 60) vs. placebo (2.5ml solvent for ARTZ: sodium chloride phosphate solution (n = 51). Follow up at 1, 13, and 26 weeks.	Mean value of clinical symptoms and daily activities were relieved after week 5. No p-values given. Usefulness (p < 0.05) and effectiveness (p < 0.05) were better in the ARTZ group at the 5-week and 3-month interval. No additional data provided.	"Based on clinical results here, SPH is a safe drug for administration as an alternative approach to treat the osteoarthritis knee."	Pragmatic study with high dropout rate.
Jubb 2003 RCT Supported by Fidia SpA, Abano Terme, Italy. No mention of COI.	3.0	N = 408 with osteoarthritis (OA) of knee; mean age: Placebo/HA groups; 65.0±9.1/63.5±9.5	Intra-articular knee injections of 20mg/2ml HA (n = 208) vs. Intra-articular knee injection of 2ml vehicle placebo (saline) for 3 weeks (n = 200). Follow-up at 3 weeks and 1 year.	For analysis, patients divided into greater joint space (JSW ≥4.6mm) and smaller joint space (JSW <4.6mm). Change in JSN (joint space narrowing) in greater JSN subgroups significantly less at 1 year in HA group compared to control; 0.13mm vs. 0.55mm (p = 0.02). In subgroup with smaller JSN, no significant difference; 0.06mm vs. -0.2mm (p >0.05).	"In patients with radiologically more severe disease there was no difference in JSN between the two treatments."	No differences observed between groups but baseline joint space width (JSW) may be a factor in treatment response.

Çubukçu 2005 RCT No mention of sponsorship or COI.	3.0	N = 30 with clinical and radiological signs of osteoarthritis of knee joint. Mean±SD age: HA group 52.6±7.16; Saline group 57.6±2.77.	Treatment group receiving 3 weekly injections of HA (hylan G-F 20, Synvisc) into one or both knees (30 knees, 20 patients) vs. Control group receiving 3 intra-articular injections of 2ml saline at same intervals (10 knees, 10 patients).	HA group had a greater reduction in the WOMAC pain score beginning in the 3rd week (40.9±1.11) and the improvement continued through week 8 (35.9±1.04) (p <0.05) compared to the placebo group.	"[I]ntraarticular injections of HA is an effective choice of treatment in patients with knee osteoarthritis."	Apparent 2:1 allocation for unknown reasons. Small sample size.
Sezgin 2005 RCT No mention of sponsorship or COI.	3.0	N = 41 with Grade II or III disease on plain x-ray of knee and pain score ≥15 on WOMAC index, effusion in painful and swollen knee. Mean age: study group 59.9±9.8 years, control group 59.4±10.2 years.	Study group: Effusion was evacuated and 2ml HA (15mg/ml) administered 3 times at 1-week intervals (n = 22) vs. Control group: effusion evacuated and 2ml 0.9% NaCl administered with same frequency (n = 19). Follow-up not specified.	Effusion decreased in study group (from 19.0±5.3 to 7.6±2.6; p = 0.001). WOMAC pain score decreased in both groups after treatment (18.9±0.5 to 8.9±0.7 in study group and 17.3±0.6 to 11.1±0.8 in control group, p = 0.0001).	"[H]yaluronan considerably decreased IL-6 levels, which correlated with clinical improvement, but had no effect on IL-8 and TNF-α levels in synovial fluid."	Sparse methodological details. No mention of blinding of patient, treated or assessor. Dropout rate cannot be determined.
Formiguera Sala 1995 RCT No mention of sponsorship or COI.	3.0	N = 36 patients (40 knees) with mono or bilateral knee OA and painful limitation of movement, narrowing femoro-tibial space and osteophytes. Mean age: HA 63±8 years, placebo 61±9 years.	1% hyaluronic acid (HA, Hyalgan®) one injection of 20 mg/2 ml every 7 days (n = 20) vs. Saline one injection of 2 ml every 7 days (n = 20). One week washout period for those who took NSAIDs, 2 weeks for systemic corticosteroids, and 12 weeks for intra-articular corticosteroid treatment before study started. Assessments at	Evolution of pain between Day 0 and Day 90: better for HA for spontaneous pain (p <0.05), pain on load (p <0.05), and pain on movement (p <0.005).	"The results of this short-term study, during which patients were followed for 2 months after the end of treatment enable us to conclude that 1% hyaluronic acid, administered intra-articularly, is safe and more effective than placebo in the treatment of patients with unilateral or bilateral osteoarthritis of the knee."	Study says, "compliance was excellent and no dropouts" but there are no details to demonstrate what that means. Methodology is sparse.

			baseline, days 7, 14, 21, 28, 35, 60, 90 after start of study.			
Frampton 2010 RCT No sponsorship. Potential COI. During peer review process, manufacturer of agent under review offered an opportunity to comment on this article. Changes resulting from comments received were made on basis of scientific and editorial merit.	2.5	N = 253 with diagnosis of osteoarthritis in primary knee	Hylan G-F 20 (in 6mL of phosphate-buffered saline) (n = 124) vs. Placebo group (6mL of phosphate-buffered saline) (n = 129). Follow-up assessments made of 26 weeks and at 26 weeks from baseline.	The mean difference between Hylan group and Placebo for WOMAC score was (-0.15) over 26 weeks (p = 0.047). At 26 weeks, this difference was not statistically significant; -0.18 (p = 0.064).	“In the 26-week study,[37] a single intra-articular injection of hylan G-F 20 was moderately effective in providing pain relief over a 6-month period in patients with symptomatic OA of the knee. Hylan G-F 20 therapy was generally well tolerated”	Sparse methodological details in study.
Creamer 1994 RCT No mention of sponsorship or COI.	2.5	N = 12 women with bilateral knee OA, use-related pain, no steroid injection for at least 3 months prior to study, OA evidence on x-ray. Mean age: 72.2±8.7 years.	Hyaluronic acid (HA) 20mg sodium hyaluronate in 2ml saline into one knee (n = 12) vs. placebo (2ml saline) into other. Each patient served as own control. Assessments 1 week before study, weekly at week 0-5, and at week 9 (study completion) (n = 12). Follow-up for 5 weeks.	Change in 5D4 cartilage marker (ng/ml, mean±SD) significant in placebo knee from baseline to week 5, 15734±5064 vs, 16803±4835 (p <0.05) but was not significant in treatment group (18047±4205 vs. 15777±4394). No other significant differences between treatments for study outcomes (no p-values reported).	“[A]ssessment of cartilage markers may be of value when studying novel therapies in OA. MRI appearances remain remarkable stable over a 6 week period.”	Small sample size and short follow-up time.
Corrado 1995 RCT No mention of sponsorship or COI.	2.5	N = 40 with mono or bilateral osteoarthritis of the knee for at least 6 months with at least	Group A: 20mg sodium hyaluronate in 2ml phosphate buffer Hyalgan®, molecular weight 500,000-730,000	Pain on movement (mean±SD) at day 60: Group A 29.7±22.9mm vs. Group B 43.2±22.3mm (p = 0.0246). Pain at rest (mean±SD) at day 60: Group A 5.1±12.3mm vs. Group B 12.2±13.4mm (p =	“The results of our study indicate that HA plays a major role in the maintenance of homeostasis in the joint environment and that variations in its concentration and	Sparse methodological details. Short follow-up time of 2 months.

		3ml joint effusion; mean age 61.30±11.1 4 years.	Daltons) intra-articularly at baseline and days 7, 14, 21, and 28 (n = 21) vs. Group B: placebo – 2ml water containing 17mg sodium chloride, 0.1mg monobasic sodium phosphate, 1.2mg bibasic sodium phosphate intra-articularly at baseline and days 7, 14, 21, and 28 (n = 19). Assessments at each injection and on days 35 and 60.	0.0562). Flexion (mean±SD) at day 60: Group A 125.5±9.9 degrees vs. Group B 117.9±11.4 degrees (p = 0.0221). Joint effusion volume reduction (mean±SD) at day 60: Group A 2.3±6.2ml vs. Group B 10.4±13.7ml (p = 0.0033).	molecular weight can modulate the behaviour of inflammatory cells as shown by various experimental studies.”	
Viscosupplementation Injections vs. Other Treatments						
Karatay 2004 RCT No mention of sponsorship . No COI.	3.5	N = 40 patients with knee OA; mean age 62 years (range 57-75) Group I; 61 years (range 55-75) Group II.	Group I: Native sodium hyaluronate (Orthovisc®, Anika Therapeutics, 2ml, 30mg) vs. Group II: cross-linked hylan G-F 20 (Synvisc®, Wyeth, 2ml, 16mg). Each group received injections once each week for 3 weeks.	Mean±SD synovial fluid ICAM-1 levels: baseline (19.2±11.1), week 1 (14.1±7.0), week 2 (12.6±7.6), and week 3 (12.0±7.5); p <0.05 from baseline to week 1; p <0.001 from baseline to week 3.	“Intra-articular HA treatment is effective in reducing pain perception, alleviating functional impairment, and decreasing synovial fluid ICAM-1 and VCAM-1 levels in patients with knee OA.”	ICAM-1 vs VCAM-1 showed similar results in decreasing WOMAC pain scores as well as physical function and stiffness at weeks 1 and 3.
Iannitti 2012 Pilot Study RCT No mention of sponsorship. No COI.	3.5	N = 20 with bilateral knee osteoarthritis rated grade II or III on Kellgren-Lawrence scale verified via MRI, VAS pain score ≥30 for both knees, mean age 53.7 for both groups	Hylan G-F 20, “Synvisc” group (n = 10) vs. Sodium hyaluronate, “Variofill” group (n = 10). Both groups received two 2mL injections 15 days apart. Assessments at baseline, 3 and 6 months.	No significant differences reported between the two groups for WOMAC pain, WOMAC stiffness, WOMAC physical activity, and VAS pain.	“The results of our study can support Variofill potential clinical use in patients affected not only by knee OA, but also in other different joints where the persistence of cross-linked HA is required notwithstanding the high pressure of the body weight over the cartilage, either at rest or while performing daily activities.”	A pilot study comparing Synvisc to Variofill which showed no significant differences between the two groups except at 6 months the Variofill group showed better VAS pain reduction.
Atamaz 2006 RCT	3.0	N= 40 with clinical and radiological knee osteoarthritis	2mL Intra-articular Sodium Hyaluronic Acid (Na HA -- 30mg sodium	Although there were significant improvements within groups for follow-up comparisons, no	“[T]he results of this study support the PTA to be useful, safe and well-tolerated treatment	Possible randomization failure (baseline 9.6 v 6.5 and ROM 119 v

No mention of sponsorship or COI.		s lasting >6 months, grade 2 or 3 osteoarthritis on the Kellgren and Lawrence scale rated via radiograph, ages 40-80 years; Mean (±SD) age 62.4 (±9.0) for Na HA group, 60.4 (±9.3) for Hylan group and 58.7 (±8.3) for PTA group	hyaluronate and 18mg sodium chloride) group receiving 4 injections (baseline, 1 week, 2 weeks and 6 months) (n = 20) vs. 2mL Intra-articular Hylan G-F 20 (16mg Hylan, 0.32mg sodium chloride and 0.08mg sodium dihydrogen phosphate hydrate) group receiving 4 injections (baseline, 1 week, 2 weeks and 6 months) (n = 20) vs. Physical Therapy Agents (i.e. NSAIDs, analgesics, IA injections, deep heat exercises, electrotherapies, etc.) Group (n = 42). Assessments at baseline, 1 month, 3, 6, 9, and 12 months.	significant differences reported between groups for 15m walk time, WOMAC-total, night pain, pain on movement, VAS-pain, SF-36 physical functioning, physical role, vitality/energy, general health, social functioning, and emotional role subscales. At 1, 3 and 6 months evaluations, physical therapy agents exhibited significantly greater results over other two groups for pain at rest, pain on touch and SF-36 pain subscale, (p <0.05).	for patients with knee OA, as well as hyaluronan therapy. Compared with Neha, Hylan seems to be a more appropriate agent with its high molecular weight for some of the symptoms such as pain. However, evidences from controlled clinical trials are needed to demonstrate the superiority of Hylan for analgesic efficacy in patients Of knee OA.”	123). Single blind study comparing 2 forms of HA to each other.
Different forms of Viscosupplementation: Viscosupplementation Injection vs. Viscosupplementation Injection						
Zoboli 2013 RCT No mention of industry sponsorship or COI. TRB Pharma laboratory donated the medications used in this study.	2.5	N = 108 with knee osteoarthritis; mean age not provided.	Single Group -- application of one 6mL injection of Sodium Hyaluronate and 1mL triamcinolone hexacetonide (n = 54) vs. Weekly Group -- 3 applications of 2mL of Sodium Hyaluronate within a week interval of each other (n = 54). Follow-up assessments made at 1 and 3 months.	Weekly group showed a significant improvement compared to baseline for WOMAC score at 1 month (p <0.001). Weekly group also showed significant improvement in VAS score at 1 month (p <0.001) and 1-3 months (p = 0.01). No significant differences for WOMAC scores or VAS scores between groups at any time interval. The single group did not show any significant improvements from baseline, (p >0.05).	“Our results suggest that both application regimes improve function, but the regime of 3 weekly applications of 2 ml was more efficient at improving pain.”	Drug study with short follow-up time. More frequent applications of HA was better as pain reduction. Sparse methodological details.
Pasqualit Ronchetti 2001	2.0	N = 99 patients with knee osteoarthritis	HY (2 ml of 500-730 000 MW hyaluronan, 10 mg/ml in saline,	Synoviocytes appeared larger and more spherical in OA than in controls (p <0.03); after	“At least in the medium term, both HY and MP modified a number of	High dropout rate and sparse methodological description.

RCT Sponsored by Fidia SpA for scholarships and partial financial support. COI, E. Genoni helped with experimental design. S. Piva helped with statistical analysis.		s; mean age 50.0±12.8 years.	one injection per week for 5 weeks) vs. MP (1 ml of methylprednisolone acetate, 40 mg/ml, one injection per week for 3 weeks). Number of patients in primary OA HY = 25; MP = 25). Number of patients in secondary OA (HY = 25; MP = 24). Injections given for 3 weeks. Follow-up on days 7, 14, 21, 28, 35, 60, 120 and 180.	both treatments, in both primary and secondary OA. MP more active than HY in reducing necrosis in primary OA (p <0.01).	structural variables of the synovial membrane of the osteoarthritic human knee towards the appearance of that of normal synovium. The effect was more evident in primary OA than in OA secondary to a traumatic event. This is the first evidence that local hyaluronan injections modify the structural organization of the human knee synovium in OA.”	
Román 2000 RCT No mention of sponsorship or COI.	2.0	N = 49 patients with gonarthrosis following clinical and radiological criteria (states II and III according to Kellgren and Lawrence); mean±SD age 65.14±9.77 years.	Adant: 5 injections of 25mg (2.5ml), 1% sodic hyaluronate solution (n = 30) vs. Hyalgan: 5 injections of 20mg (2 ml), 1% sodic hyaluronate solution (n = 19). Follow-up at week 1 after 5 th infiltration, and months 3 and 6.	Painful infiltrations: n = 6 with Adant (16.3%) vs. n = 2 with Hyalgan (10.5%); p <0.001). Excellent and good results according to the assessment of efficacy at 3 months: 50% cases with Adant vs. 21.1% cases with Hyalgan; p <0.05.	“The efficacy with Adant at 3 months (50%) after treatment was greater than with Hyalgan (21.1%), probably because its greater viscosity increases its half-life in the joint.”	Far more females in study than men and high degree of bias in article. Groups not equally randomized. Not clear if a 2:3 randomization?
Karatay 2005 RCT No mention of sponsorship or COI.	1.5	N = 40 with knee OA. All patients had radiographic changes of knee OA of Kellgren-Lawrence Grade 2 or 3. No use of NSAIDs. Or prior surgeries (6 months); mean age - Group 1: 61, range (57-75), Group 2:	Group 1 treated with intra-articular injections of native sodium hyaluronate (n = 20) vs. Group 2 treated with intra-articular with cross-linked hylan G-F 20 (n = 20). Follow-up at Baseline (1st injection), second injections (weeks 1) third injections (week 2) and a week	No significant differences between group 1 and group 2 when comparing NO levels, GSHPx activity, WOMAC pain scores, WOMAC stiffness scores, and WOMAC physical fxn scores. However, comparing baseline to end of study results in group 1 WOMAC stiffness (p < 0.05). Group 2 WOMAC stiffness between baseline and week 1 (p < 0.05) and end of study (p < 0.01).	“In conclusion, exogenous hyaluronic acid treatments may reduce the NO levels but not the GSHPx activities in synovial fluid.”	Sparse methodology. No significant differences between different HA products varying in terms of molecular weights.

		62, range (55-75).	after third injections (week 3).			
Bayramoğlu 2003 RCT No mention of sponsorship or COI.	1.5	N=37 patients with symptomatic OA of the knee; mean age 61.5±10.9 years.	Weekly hyaluronan (Orthovisc) injections (hyaluronan [HN] Group, n = 16) vs. weekly hylan (Synvisc) injections (hylan-GF 20 [HL] group, n = 15) vs. PT with no additional treatment (n = 15).	Index of severity score for OA of knee at baseline ranged from 6.5 to 17 (mean±SD 12.4±2.7) in HN group; from 7 to 16.5 (mean±SD 12.8±2.7) in the HL group; and from 5 to 17 (mean±SD 11.6±3.8) in the PT group; p = 0.72).	"[N]o difference in terms of reduction in ISK scores between patients treated with intraarticular HA injections+PT and those treated with PT alone."	No significant differences between groups at 3 months. Sparse methodological details.
Onel 2008 RCT Sponsored by Ferring Pharmaceuticals, Inc. COI, Drs Erol Onel and Kathleen Kolsun are employed by Ferring Pharmaceuticals, Inc. and Dr Kauffman serves as an occasional speaker for Ferring Pharmaceuticals, Inc.	1.0 Cannot accurately score this.	N = 321 with unilateral or bilateral knee osteoarthritis exhibiting osteophytes with or without joint space narrowing, symptoms >1 year, WOMAC index score in moderate to severe range, ages 50-80 years; Mean (SD) age 63.7 (7.3) for Hylan G-F 20 group and 62.7 (7.5) for Bio-HA group	Hylan G-F 20 "Synvisc" group (n = 161) vs. Bio-Hyaluronic Acid "Euflexxa" group (n = 160). Both groups received 3 mL injections once weekly for 3 weeks. Assessments at baseline, 1 week, 2, 3, 6 and 12 weeks.	During 12 week assessment, BIO-HA group had significantly more patients reporting less than 20mm, or pain free, WOMAC pain scores than Hylan G-F 20 group; 63% vs. 52%, (p = 0.038). BIO-HA group also reported significantly less paracetamol use vs. Hylan G-F 20 group; 61% vs. 73%, (p = 0.013).	"The current secondary analysis, which is one of the first to use the modified OMERACT-OARSI criteria, has confirmed that the efficacy of BIO-HA is non-inferior to that of hylan G-F 20. In addition to a high rate of response to both forms of intra-articular hyaluronic acid, we found a lower risk of effusions with Bio-HA. Taken together with our long-term follow-up results, these data indicate that Bio-HA has an improved risk-benefit profile compared with Hylan G-F 20."	No significant difference between groups. This is a post-hoc analysis.
Autologous Blood Donation and Blood Transfusion						
Tsumara 2006 Quasirandomized RCT	3.5	N = 212 total knee arthroplasty (TKA) patients	30 ml NS with 1:500 000 adrenaline injected after wound closure. (Drain clamping, n = 106) vs. Consta Vac blood conservation system 2 application. (Blood salvage, n = 106).	No differences between groups in post-operative reduction in hemoglobin. Mean post-op drained blood volume for drain clamping vs. blood salvage (352.1 ml (SD 130.7; 100 to 770) vs. 662.3ml (SD 333.6; 15 to 1540), p <0.0001. Hemoglobin levels decreased to 82% of pre-op level in drain clamping vs. 83% for blood salvage.	"[D]rain clamping with intra-articular injection of saline with adrenaline is more effective than post-operative autologous blood transfusion in reducing blood loss during total knee arthroplasty."	Quasi-randomized (every other). Study suggests significant decrease in blood loss using clamping versus blood salvage. Many sparse details.

			In both groups, all TKAs unilateral. Drains removed at 48 hours.			
Knee Arthroplasty						
Posterior Stabilized and Cruciate Retention						
Maruyama 2004 RCT/Cross-over trial	3.5	N = 20 with bilateral OA knees, bilateral TKAs ≤2 years prior, and correction with retention of PCL	Posterior cruciate-retaining PCR vs. posterior stabilized PS TKAs. Approximately 30 months follow-up.	PCR vs. PS data pre-op femoro-tibial angle, pre-op knee score, post-op knee score, pre-op extension angle, post-op extension angle, pre-op flexion angle, postop flexion angle, pre-op ROM, post-op ROM, pre-op mean joint line (mm), and post-op mean joint line (mm).	"[T]he present study compared the clinical outcome between the PCR and PS TKAs and showed a superior postoperative range of motion in the PS knee. It is thought that one of the factors associated with flexion limitation in the PCR knee is unphysiologic tension of the PCL causing abnormal knee kinematics in flexion."	Small groups. Randomization of knees is unclear. Data suggest comparable outcomes, but improvement in ROM favored posterior stabilization.
Ishii 2005 RCT	2.0	N = 95 (115 knees)	Genesis total knee arthroplasty with PCL retaining (PCLR) vs. substituting (PCLS). Cemented femoral and metal-backed tibial components in 70 knees and all-cementless components in 12 knees.	ROM increased from 82° (15-140°) to 108° (90-140°); 63 (77%) knees rated excellent, 14 (17%) rated good, 4 (5%) fair, 1 (1%) poor. Femoral bone cement radiolucencies in 4 knees (5%); all in zone 1.	"Even in this mid-term clinical comparison, we found no differences between the two groups."	Quasi-randomized. First 30 all PCLR, then randomized. Unequal group sizes. HSS scores differed at baseline (48 vs. 39). Follow-up duration unclear (5-10 years).
Mobile vs. Fixed						
Higuchi 2009 RCT	3.0	N = 68 with OA of knee who underwent TKA using PFC	Mobile (n = 31 joints) vs. fixed platform (n = 45 joints).	Mobile vs. fixed extension ROM of the knee mean±SD for pre-op, post-op, flexion pre-op, and post-op: -11.7±15.2/-10.8±10.8, 0.3±3.2/-1.6±4.5, 113.5±19.1/109.6±21.9, 115.8±13.6/110.8±15.6.	"The postoperative extension angle of the knee was significantly improved after TKA using a mobile bearing type compared with that employing a fixed bearing type. In mobile bearing TKA, the intraoperative gap difference was not related to the postoperative flexion angle of the knee. However, they were related in TKA using a fixed bearing type, with a positive correlation regarding the flexion group."	Group sizes differed (31 vs. 45) and demographic data not provided by groups raising concerns regarding randomization.
Polyethylene vs. Metal-backed Components						

Gioe 2006 RCT	3.5	N = 147 with minimum 8-year follow-up; age 60 or over having TKAs not necessitating bone grafting, modular stems or augments, or more constrained design	Cemented posterior cruciate ligament-retaining APT or MBT component with identical articulating surfaces vs. cemented femoral components vs. cemented polyethylene patellae.	Latest follow-up showed modest gain in functional KSS for APT compared to MBT, $p = 0.04$. Complications necessitating revision of one or more components occurred in 10 metal-backed and 12 all-polyethylene TKAs.	"Our findings support continued use of appropriately designed congruent APT components as an attractive and cost-effective alternative to MBT components in patients who do not require modular augmentation."	Approximately 10-years data. High dropouts. Many details sparse. Data suggest comparable outcomes.
Gioe 2000 RCT	3.5	N = 324 with TKA performed on 296 (285 males) randomized into 2 groups; all age 60+ (28 died, and 7 lost to follow-up); in final analyses 213 joints (111 all-polyethylene vs. 102 metal-backed) in 195 patients	All-polyethylene tibial components vs. metal-backed tibial components. All arthroplasties had "identical articulating surfaces, cemented femoral components and cemented polyethylene patellas." Follow-up data was collected at 1 year, 3 years, and 5 years.	No statistically significant differences between 2 implant groups for clinical or functional knee society scores ($p = 0.52$ and 0.45 respectively). No statistically significant difference in post-op ROM ($p = 0.52$). Radiographic results demonstrated no statistically significant difference between implant types when evaluating femoral coronal position, tibial coronal position, change in joint line, patellar height, and posterior tibial slope in sagittal plane ($p = 0.30$ to 0.80). Statistically significant difference between post-op radiolucent lines when comparing metal-backed tibia (23%) with all-polyethylene tibia (4%, $p \leq 0.0001$). No statistically significant difference between 2 treatment arms for outcomes of pain of physical function scores. Statistically significant difference between role physical functioning at 1 and 5 years.	"Total knee arthroplasty with a well-designed, contemporary congruent all-polyethylene tibial component functions equivalently to its metal-backed counterpart at 3- to 5-year followup in this patient population, and is less costly (\$675)."	Patient groups not well described. Sparse methods.
Cement vs. Hydroxyapatite Fixation						
Toksvig-Larsen 2000 RCT	3.5	N = 60 (62 knees) with arthrosis Grades II to V	Group 1 (n = 15) porous-coated Osteonics 7000 tibial tray using internally cooled oscillating saw blade vs. Group 2 (n = 15)	Subsidence less in hydroxyapatite groups vs. porous coated groups, $p = 0.014$. Maximum total point motion for Group 1 vs. Group 2 vs. Group 3 vs. Group 4 at 1 year: 1.7 ± 0.8 mm vs. 1.9 ± 1.7 mm	"The hydroxyapatite coating had a strong positive effect on the tibial component fixation. No prosthesis in the hydroxyapatite groups showed	Most baseline demographic data no reported. Many details sparse.

			porous-coated Osteonics 7000 tibial tray using standard oscillating saw blade vs. Group 3 (n = 16) Osteonic hydroxyapatite tibial tray using cooled saw blade vs. Group 4 (n = 16) Duracon cruciform hydroxyapatite coated tibial tray using cooled saw blade. Assessments at 1 and 2 years post-op.	vs. 1.3±0.7mm vs. 1.0±0.7mm, p<0.05 for Group 2 vs. Group 4; at 2 years: 1.8± 0.9mm vs. 1.5±0.5mm vs. 1.4±0.7mm vs. 1.0±0.7, p <0.05 for Group 1 vs. Group 4. Maximum total point motion for hydroxyapatite group vs. porous-coated group at 1 year: 1.2±0.7mm vs. 1.7± 0.8mm, p = 0.02.	continuous migration.”	
Regnér 1999 RCT	3.0	N = 33 (38 knees) with Ahlbäck Grade III to V OA	Uncemented implant of Freeman Samuelson Hydroxyapatite (FS HA) vs. Miller-Galante II (MG II) design. Outcome assessments conducted post-op at 1 year and again at 5 years.	Tibial components has condensation of trabecular bone in 72 % (13 of 18) of FS HA group vs. 11% (2 of 18) for MG II group, p <0.001. BMD decrease between FS HA vs. MG II at 1 year: 29% vs. 15%; 4-5 years: 36% vs. 15%, p = 0.02. Migration regarding MTPM and maximum subsidence less in FS HA group at 5 years compared to MG II, p = 0.02 for MTPM, p = 0.01 for maximum subsidence.	“Clinically excellent results were recorded in both groups after 5 years.”	Another report from Regner 1998. Data appear to be incomplete dataset from trial.
Fixation with or without Cement						
Khaw 2002 RCT	3.5	N = 392 (501 knees) who underwent primary TKR using press-fit condylar knee replacement system	Press-fit condylar total knee replacements with cement (n = 277 knees, 219 patients) vs. cementless (n = 224 knees, 177 patients). Outcome assessments measured post-op at 6 months, 1, 5, and 10 years.	Seventy-eight (36%) of patients (87 TKR) in cemented group and 51 (29%, 67 TKR) in cementless group died by 10 year assessment. Mean change in ROM at 10 years: for cemented group 10.1±23.5, p = 0.03; cementless group 0.0±18.4; between groups p = 0.07.	“This randomised, controlled trial has failed to show significant differences in clinical outcome or ten-year rates of survival between cemented and cementless fixation using the press-fit condylar knee.”	High dropouts due to deaths. Quasi-randomized mostly on birth year. Most bilaterals had same treatment. Data suggest equivalent failure rates.
Baker 2007 RCT	3.5	N = 396 (501 knees) TKR	Modular prosthesis with cobalt-chrome femoral component articulation with polyethylene	Revision for infection for cemented vs. cementless group: 7 patients (2.5%) vs. 4 patients (1.8%). Revision for aseptic loosening: 14 patients	“[This study] demonstrates that the survival of the press-fit condylar TKR remains good at 15 years, irrespective of the	Fifteen year follow-up of Khaw 2002.

			insert with cement (277 knees, 219 patients) vs. cementless (224 knees, 177 patients); outcomes assessed over 15 years.	(5%) vs. 12 patients (5.4%).	method of fixation in this series where randomisation of fixation was delayed until the suitability of either method of fixation was confirmed after preparation of the bone.”	
Nilsson 1991 RCT	3.5	N = 43 (45 knees) with RA and primary OA	Cemented fixation (n = 14 with OA, n = 11 with RA) vs. uncemented (n = 11 with OA, n = 9 with RA) fixation. Outcome measurements assessed at 2 and 6 weeks, 3, 6, 12, and 24 months.	No significant differences between groups.	“There were no statistically significant differences between cemented and cementless prostheses in either the OA or the RA group. This fixation in the RA patients did not significantly differ from that of the OA patients, perhaps because the RA patients had lower weight and were living a more sedentary life.”	Quasirandomized on DOB. Stratified randomization on OA & RA. Small groups.
Nilsson 1993 RCT	3.0	N = 30 (35 knees) with OA of knee operated on with Miller-Galante knee prosthesis	Cement fixation (n = 15) vs. uncemented fixation (n = 14).	Uncemented vs. cemented median(range) post-op hospital for special surgery scores for knee at 6 months, 24, 6-24, pain while walking at 6 months, 24, 6-24, pain at rest at 6 months, 24, 6-24, extension lag 24 months(°), and knee flexion 24 months(°). Post-op radiographic results mean(range) for HKA angle(°), change in joint line position†(mm), thin components(8.5mm), thick components (>11 mm), tibial component alignment(°) for frontal plane‡, and tibial component alignment for sagittal planes.	“[T]he Miller-Galante prosthesis displayed rather small migration, and the fixation achieved seemed to be similar or slightly superior to other designs investigated with RSA. The uncemented components displayed magnitudes of migration compatible with bone in growth only at certain areas. Cement improved early fixation, seemingly reducing the influence of tibial component thickness and bone quality.”	Quasi-randomized on DOB. Appears to be another report of trial. Data suggest more rotations in uncemented at 2 years.
Nilsson 1995 RCT	3.0	N = 28 (33 knees) with Miller-Galante I knee replacements	Cemented fixation (n = 13) vs. uncemented fixation (n = 15) with assessments pre-op 6, 12, and 24 months after surgery.	No significant between group differences.	“This investigation revealed no differences in fixation between cemented and cementless fixation of the femoral component at 2 years, and the magnitudes of micromotion were as large as those reported for the tibial component of the	Quasi-randomized on DOB. Some baseline differences. Dropouts unclear. Data suggest mostly comparable results.

					Miller-Galante I knee replacement.”	
Computer Aided Systems						
Ensini 2007 RCT	3.0	N = 120 who underwent primary TKA	Navigated (n = 60) vs. conventional (n = 60).		“Postoperative radiographs showed better component alignment using navigation, particularly at the femur. However, clinical scoring systems showed this radiographic improvement did not necessarily result in a better clinical outcome at short-term follow-up.”	At least 24 months follow-up. Many details sparse.
Park 2007 RCT	3.0	N = 72 with OA of knee scheduled for TKA	Conventional manual implantation of a Zimmer LPS prosthesis (n = 30) vs. robotic-assisted implantation of a Zimmer LPS prosthesis (n = 32).		“Robotic-assisted technology had definite advantages in terms of preoperative planning, accuracy of the intraoperative procedure, and postoperative follow-up...But a disadvantage was the high complication rate in early stage.”	Limited data; follow-up unclear.
Intramedullary vs. Extramedullary Guides						
Stern 1994 RCT	3.5	N = 26 who underwent bilateral index cemented TKA	Group 1: intramedullary knees implanted with standard intramedullary fluted instruments (n = 13) vs. Group 2: extramedullary knees implanted with extramedullary tibial guide/ intramedullary femoral guide placed through vented femoral hole (n = 13).		“Results point to the continued use of fluted intramedullary rods and vented entrance holes as a reasonable surgical technique in patients undergoing knee arthroplasty.”	Although trial with bilateral TKA, did not randomize sides. Many details sparse.
Total Joint Arthroplasty: Randomized Comparative Studies						
Kirk 1994 RCT	3.5	N = 100 with primary OA of knee	Anatomic Modular Knee (n = 50) vs. Miller Galante I (n = 50).	AMK vs. MGI 2-year mean(range) Hospital for Special Surgery knee score/ ROM for overall, and average: 86(65-95)/87(68-97), 28(5-30)/29(20-30). Mean (range) 2 year average function score, and average ROM(°): 18(6-22)/18(12-22), 110(65-130)/112(75-135).	“We postulate that the major difference contributing to this complication is related to patellofemoral design and patellar tracking, with the more anatomic AMK femoral component having better patellar tracking and stability clinically.”	Data suggest comparable results at 2 years.

Laskin 2003 RCT	3.0	N = 73 TKRs using Genesis® II prosthesis	Co-Cr-mo femoral component vs. oxidized Zr femoral component; 2 year follow-up.	At 2 years, mean KS score 92 (79-100), mean functional score 74 (45-100). Oxidized Zr implants reached functional milestones 20% faster than Co-Cr-Mo implants, p = 0.04.	"At the 2-year followup, no adverse effects had been observed clinically or radiologically."	Data from apparent subset of RCT with 28 of unclear number. Many details sparse. Report also appears to (largely?) mix data with non-randomized study
Laskin 2000 RCT	3.0	N = 176 with severe OA undergoing unilateral primary TKR arthroplasty ; Genesis II implants used and all implants cemented to respective bones using Palacos acrylic cement	Posterior stabilized polyethylene component with intercondylar eminence inserted (Group I) vs. deep-dish congruent ultra-high molecular weight polyethylene component inserted (Group II) vs. component without a central cam housing used for femur and deep-dish implant used for tibial component (non randomized, Group III, n = 48).	No significant differences between groups.	"Using deep-dish implant obviates the need to rescet intercondylar femoral bone, decreasing the potential for fracture and maximizing bone volume should revision be necessary in the future."	Time frames of data provided unclear.
Transfusions, Erythropoietin, Autologous Blood Salvage and Reinfusion Systems						
Slagis 1991 RCT	3.5	N = 109 who underwent hip or knee arthroplasty ; excluded if needed transfusions pre-op or who refused to participate	Blood salvage group (wound drainage tubs connected in OR to sterile reservoir with 200ml heparin saline solution to prevent clotting, n = 51) vs. control (n = 51). Collection continued in post-anesthetic care unit and later on surgical ward for 4 hours. All had daily hematocrits for 3 days.	Mean total of banked blood transfused as units of packed cells control vs. salvage: total hip arthroplasty: 1.7 vs. 1.1, p = 0.32. Unilateral knee arthroplasty: 0.5 vs. 0.4, p = 0.8. Bilateral knee arthroplasty: 2.4 vs. 1.1, p = 0.04.	"By reducing the requirement for homologous transfusion, blood salvage diminishes the risks of transmission of HIV and hepatitis viruses. In those cases where the equivalent of two units of blood are reinfused, blood salvage saves money. However, due to the small amounts of blood collected in unilateral hip or knee arthroplasty, we do not recommend its routine application in these cases."	Many details sparse. Patients not well described. Data suggest salvage superior to controls for bilateral TKA (p <0.04) to reduce transfusions.
Mah 1995 RCT	3.0	N = 205 encouraged to predeposit	Intra/post-op autologous blood salvage ABS vs. no	Cemented THR-NO ABS/ABS/uncemented THR-NO ABS/ABS/TKR NO-ABS/ABS % of	"[B]lood salvage, when combined with three units of PABT, eliminated the need	Patients not well described. Many details sparse.

		autologous blood (PABT) prior to TKA; all offered oral iron. Cemented THR n = 44, uncemented THR n = 62, and TKR n = 99	intra/post-op autologous blood salvage NO-ABS.	subjects needing a homologous blood transfusion for no PABT, 1-2 units PABT, and 3 units PABT: 100/89/83/70/79/50, 50/29/58/57/50/0, 38/0/25/0/22/0. Cemented THR NO ABS vs. ABS Chi-square for subjects needing a homologous blood transfusion, p <0.005. Uncemented NO ABS vs. ABS, p<0.001. TKR NO ABS vs. ABS, p <0.001.	for HBT in all patients undergoing primary joint replacement surgery. A cost comparison analysis showed that blood salvage was more expensive than PABT, and therefore it should be limited to patients who had predeposited fewer than three units of autologous blood."	
Drains						
Willemsen 1991 RCT	3.5	N = 25 of whom 16 had bilateral TKA	Group 1 (closed suction drainage at 24 hours, n = 21) vs. Group 2 (closed suction drainage at 48 hours, n = 20). Flexion exercises were started depending on state of wound healing, which was assessed clinically at 14 and 21 days after surgery.	During 1st 24 hours of surgery, mean volumes of fluid drained were 286ml in Group 1 and 245ml in Group 2 (did not differ significantly). In Group 2, mean volume of fluid drained during 2nd 24-hour period was 50ml, significantly less than that drained during 1st 24-hour period, p <0.001; 14 days post-op, 37 cases completely healed. By 21 days, all wounds healed.	"Suction drainage is safe and effective during the 24 hours following TKA, but little is to be gained continuing thereafter. If drainage is continued, there may be an increased risk of contamination by bacteria."	Patients not well described. Variable tourniquet use. Data suggest drain colonization occurs frequently within 48 hours.
Ritter 1994 RCT	3.0	N = 415 managed consecutively who had been diagnosed with OA and had undergone THR or TKR	Group 1 (closed wound drains used for 24 hours post-op, n = 293 procedures) vs. Group 2 (no wound drain, n = 200 procedures). All followed intra-operative heparin protocol, used aspirin post-op for thromboembolitic prophylaxis.		"[P]ostoperative drainage systems offer little advantage in the outcome of primary total knee or total hip replacements. A savings of \$21,500 (215 drainage units per \$100 per unit) would have resulted if drains had not been used at all in this series. Our series was large; however, the findings should be considered preliminary."	Many details sparse. Drop out rate appears high. Groups not well described.
Ritter 1988 RCT	3.0	N = 45 who had undergone unilateral THR or TKR	Stryker Constavac drainage system (n = 24) vs. Snyder Hemovac drainage system (n = 21). No patients	When adjusted means for Hemovac and Constavac statistically compared, not a significant difference in volume and rate at 8 hours or in time and rate at 300ml. Constavac drained an average of 581.30ml vs. Hemovac	"This study demonstrated that the Stryker Constavac is an acceptable substitute for the Snyder Hemovac and its performance is at least as effective."	Very short trial, many details sparse. Patients not well described. Data suggest constant suction removes more fluid; however whether that

			received anticoagulants or any medication that might have influenced results.	average of 435.24ml. Revision surgery bled significantly more than primary surgery. Revision = 609ml vs. primary = 458ml, p <0.05. Stryker Constavac evacuated more total blood from wound, p <0.025, than Hemovac.		translates to superior outcomes is unclear.
Tourniquet Issues						
Steffin 2009 RCT	3.0	N = 37 diagnosed with OA of knee undergoing primary TKA; excluded if history of bleeding disorder, current chronic anticoagulation therapy, and refusal to consent to receive blood transfusion s.	Early tourniquet release (n = at least 16) vs. late tourniquet release (n = at least 16). All underwent cemented TKA with Zimmer Negev Legacy LPS implants, and daily hematocrits until discharge or stabilized on consecutive days. Drainage recorded until drain discontinued AM 2nd post-op day.	Hematocrit drip, hemoglobin level drop, wound drainage, blood volume salvaged after early vs. late tourniquet release (mean, SD). 24-hour hemaocrit drop: 7.6±2.34 vs. 7.0±3.11, p = 0.52. Maximum hematocrit drop: 11.74±3.03 vs. 11.72±3.34, p = 0.99; maximum hemoglobin level drop (mg/dL): 3.93±1.04 vs. 4.00±1.19, p = 0.86. Maximum drainage (mL): 582±392 vs. 532±540, p = 0.76. 24-hour drainage (mL): 455±288 vs. 397±407, p = 0.64. Autologous blood salvage (mL): 250±155 vs. 230±272.	“We conclude that the use of a blood salvage drain should not influence the surgeon's preference on timing of tourniquet release in total knee arthroplasty.”	Patients not well described. Sparse results.
Burkart 1994 RCT	3.5	N = 100 who underwent primary TKA	Group 1: tourniquet released for hemostasis before wound closure (n = 50) vs. Group 2: tourniquet not released until wound closed plus compressive dressing (n = 50).	Group 1 (n = 49) vs. 2 (n = 49) average blood loss for cemented fixation, hybrid, and cementless: 644/538/p <0.01, 898/817, 988/1007/p <0.02. Mean (g/L) ±SD (range, g/L) for decrease in hemoglobin level, and decrease in hematocrit level: 35.2±13.2 (5-69)/34±13 (9-60), 0.104 ±0.037 (0.024-0.199)/0.097±0.04 (0.02-0.179).	“Tourniquet release for hemostasis is not an effective means of limiting postoperative blood loss or reducing transfusion need after primary total knee arthroplasty.”	Unclear if truly randomized. Surgical procedures, prosthesis and cement varied. Data suggest no differences.
Rehabilitation: Urinary						
Michelson 1988 RCT	3.5	N = 100 undergoing total joint replacement	Indwelling Foley catheter placed before surgery vs. post-op intermittent catheter.	Less retention in Foley group (27 vs. 52%, p <0.01). No significant difference between groups in rate of post-op urinary tract infection.	“[S]hort-term use of an indwelling Foley catheter is superior to intermittent catheterization in preventing urinary bladder retention after total hip-replacement or knee-replacement surgery.”	Quasi-randomized on MRN. Unequal groups (n = 41 vs. 55). More retention in straight cath group, but more UTIs if long-term indwelling catheter used (35% vs. 6% for all others).
Brown 1996 RCT	2.5	N = 30 scheduled for THR or TKR	Usage of an unscrubbed, ungowned leg holder vs.	Mean air counts during skin preparation and draping unscrubbed, ungowned	“We recommend that the leg is held by a scrubbed and gowned member of	Demographic data not provided. Article's data

			scrubbed, gowned holder.	4.4 times greater than that during operation (95% CI 2.3 to 8.4, p < 0.001). With scrubbed, gowned leg holder: this difference reduced to 2.4 fold (95% CI 1.5 to 3.8, p = 0.001).	the team. More importantly, we consider that instrument packs should be opened only after skin preparation and draping have been completed.”	suggest potential randomization failure. However, data suggest precautions warranted to prevent infections while scrubbing.
Compression Designs vs. Other Treatments						
Healy 1994 RCT	2.5	N = 76 (105 knees) who underwent primary TKA with insertion of a Porous-Coated Anatomic Modular or a Duracon	Cold compressive dressing (Cryocuff, n = 50 knees) vs. control (ACE wrap +ice packs, n = 55 knees). Phase I: ice water in cryocuff replaced every 4 hours. Phase II: replacement every 1-2 hours.		“In patients undergoing unilateral TKA, no significant difference existed between the narcotic requirements of control patients and patients wearing the cold compressive dressing.”	Study either is of 2 RCTs or protocol changed part way through. Data suggest lack of efficacy.
Miscellaneous						
Parker 2001 RCT	3.5	N = 99 (100 knees) who underwent MGI total knee replacements	Cementless fixation (n = 52 knees) vs. hybrid fixation (n = 48 knees). Outcome measures assessed at 6 weeks, 3, 6, and 12 months, then yearly.	Seventeen cementless fixation required revision compared to 8 hybrid fixation, p = 0.036. Last follow-up of Knee Society scores 130.2 points for cementless fixation group vs. 158.3 points for hybrid fixation, p = 0.018.	“The current study shows that a durable result can be achieved with either a cementless or hybrid cruciate-retaining total knee arthroplasty with no significant differences between the outcomes of the two groups. A relatively high failure rate was related largely to problems with the patellofemoral articulation attributable to design faults that now have been largely eliminated. The findings support the authors' view that a correctly aligned impoant, with an all polyethylene patellar component and a modern design femoral implant, can provide a good result well beyond 10-years followup.”	Second report of Kirk 1994. High dropouts, mostly due to deaths. Most failures due to metal backed patellae.
Linke 2006 RCT	1.5	N = 60 with subtotal loss of the medial	Collagen implant vs. no implant after high tibial	Evaluation on the Lysholm Score, IKDC (International Knee Documentation	“It remains to be seen if the CMI offers a chondroprotective	Incomplete study - interim report. Data non-conclusive

		meniscus and varus morphotype	osteotomy (>50 meniscus absent).	Committee), and subjective pain data revealed only slight, nonsignificant differences for 39 patients after 24 months (CMI and correction n = 23; correction only n = 16).	effect and the continuously improved parameters of the Lysholm score, IKDC and pain will endure vs. the group with high tibial osteotomy.”	without full results.
Pre-Operative Education						
McGregor 2004 RCT	3.5	N = 35 with THR	Standard care (B) vs. standard care plus hip class 2 to 4 weeks before surgery and information booklet (A).	Pre-op class and booklet, had lower hospital stays by 3 days (15 vs. 18), significantly reducing costs. Group A reported prediction of surgical results with 93.9±8.9% accuracy at discharge, decreasing to 89.6±3.2% at 3 months. Group B had 79.1±19.2% success in predicting outcome at discharge, decreasing to 69.4±30.9% at 3 months.	“Patients attending the class reported higher levels of satisfaction (99% satisfied in the preoperative rehabilitation class compared with 80% in the control group 3 months postoperatively) and had more realistic expectations of surgery.”	Details sparse. Length of stay may not be generalizable beyond U.K. Exercise intervention apparently to ensure ability to perform exercises post-op, rather than perform pre-op exercises.
Lilja 1998 RCT	3.5	N = 101 included 55 with THR and 46 with breast cancer	Control group informed about pre- and post-op routines by ward nurse vs. intervention group given extended information by an anesthetic nurse (0.5 hours day before surgery)	No significant differences between intervention and control group for breast cancer patients or THR patients. Breast cancer patients in intervention group significantly more anxious than THR patients in intervention group (p < 0.01). Breast cancer patients in intervention group showed highest anxiety scores on Hospital Anxiety and Depression Scale (HADS) scale on day of surgery.	“[E]xtended preoperative information given by anaesthetic nurses will decrease anxiety, cortisol and pain in...THR patients, was not supported. The other assumption, that anxiety, cortisol and pain would decrease more for the THR patients than for breast cancer patients was confirmed.”	Baseline data not provided.
Wong 1990 RCT	2.5	N = 146 with THR	Group I (experimental) – early discharged, experimental program participants (pamphlet, videotape, home nurse visits); Group II (experimental) – conventional discharged, experimental program participants; and Group III (control) – conventional discharged, traditional program participants.	Lengths of stay: 8.8, 13.8 and 12.8 days, respectively. Patients in both experimental groups had higher score in Perceived Preparedness for Discharge Scale (p <0.01) and exercise compliance scores (p <0.05), but no significant difference between Groups I and III on Compliant behavior index (p <0.05).	“The findings suggest that a programme of after-care combines’ educational and follow-up home-visit strategies for the early discharged patients provides outcomes that are comparable to the traditional discharge planning for the conventionally discharged patients. It also points out that patients who have been adequately informed of their conditions are more likely to comply with prescribed treatment.”	Sparse details. Results suggest earlier discharge and education are effective. Interventions began 3 to 6 days after surgery, likely limiting utility of findings.

Santavirta 1994 RCT	2.5	N = 60 with primary THR	All received educational booklet. Trial was educational booklet vs. booklet plus intensive education (20-60 minute teaching session).	Knowledge of complications poor, with no differences between intensive education and control groups. Intensive educational group followed exercise program better (p = 0.02).	"[T]he experimental group showed greater interest in obtaining more information about their replaced hip. Patients in the experimental group showed significantly better adherence to the instructions for the postoperative rehabilitation programme."	Randomized, but compliance with assignments low in experimental group. Contact time varied significantly. 37% could not name a relevant complication.
Burns 1992 RCT	2.0	N = 108 (?) "Approximately 108 patients were included" females with hip fractures	Controls in acute orthopaedic ward (both therapists responsible for other wards) vs. trial group transferred to continuing care hospital with occupational therapy, kitchen, physiotherapy area.	"At discharge, significantly more patients in the treatment group were independent in terms of activities of daily living, than the control group: 41 v. 25. Their median stay was 24 days compared with 41 days in the control group."	"This trial confirms the effectiveness of rehabilitative aftercare for elderly woman with hip fracture. Without provision of such aftercare, these patients would occupy a rising, proportion of hospital beds and achieve a lesser degree of independence."	Sparse description of study and results.
Pre-Operative Exercise						
Topp 2009 RCT	3.5	N = 54 undergoing unilateral TKA for OA	Control (usual care) vs. prehab training (resistance training, flexibility, step training) 3 times a week before surgery; 3months follow-up.	At 3 months, prehab group had significant improvement in sit-to-stand; control group had significant increase in strength asymmetry. At 4 months, prehab group had significant improvements in all functional tasks except 6 minute walk and reported significant decreases in all knee pain measurements. Control group improved in sit-to-stand, 6 minute walk only, and reported decreased pain in all measurements. Control group increased quadriceps strength in non-surgical leg, increasing strength asymmetry.	"These findings appear to indicate the efficacy of prehabilitation among TKA patients and support the theory of prehabilitation."	Data suggest some advantages in strength and function in prehabilitation group up to 3 months follow-up. No long-term follow-up reported.
Post-operative Rehabilitation						
Passive Range of Motion						
Johnson 1992 RCT	3.5	N = 56 undergoing primary total condylar knee arthroplasty with Kinematic	Immediate post-op CPM (n = 16 with OA, n = 10 with RA) with machine 20 hours a day for 3 days, then 16 hours a day	Mean hospital stay for CPM vs. immobilised group: 15 vs. 20, p <0.01; 1 year range of knee flexion for CPM vs. immobilised group: 105° vs. 93°, p <0.05.	"Those patients who received the CPM regimen postoperatively regained functional knee flexion more rapidly than those who were immobilised."	Limited data describing groups. Patients not well described. Data suggest CPM superior to splint.

		total condylar knee prosthesis	for 4 days vs. immobilised in a splint (n = 20 with OA, n = 10 with RA) for 7 days with straight-leg raising exercises performed twice daily. Outcome measurements assessed at Day 7, 10, and 14, Week 6, Month 3, 6, and 12.			
Worland 1998 RCT	3.5	N = 80 with 103 TKR (23 bilateral)	Continuous passive motion (CPM, n = 37) machine used 3 hours a day on surgically treated knee for 10 days vs. physical therapy (n = 43) with therapist to patient's home 1 hour 3 times a week for 2 weeks. Outcome measurements assessed at 2 weeks, 3 and 6 months.	Mean (SD) flexion contracture at 2 weeks for CPM vs. PT: 4.2 (5.4) vs. 2.1 (3.3), p = 0.047.	"[T]he CPM machine after the hospital discharge of patients having total knee replacement is an adequate rehabilitation alternative with lower cost and with no difference in results compared with professional therapy."	Data suggest CPM of equal (in)efficacy with home PT after discharge with 6 month follow-up.
Harms 1991 RCT	3.5	N = 113 patients with OA or RA undergoing primary TKA.	CPM (n = 35 with OA, n = 20 with RA) vs. non-CPM groups (n = 37 with OA, n = 21 with RA).	CPM degree of flexion regained significantly greater at all time points. Ease score mean (SD) for CPM vs. non-CPM: 41 (24) vs. 54 (25), p <0.05.	"[A] regime incorporating CPM will produce an overall improvement in the speed and quality of recovery in TKA patients."	Data suggest CPM superior over 14 days; 14 day follow up.
May 1999 RCT	3.5	N = 21 undergoing primary total knee prostheses for OA	Continuous passive motion machine (CPM) (n = 12) vs. lower limb mobility board (LLiMB) (n = 7).	No statistically significant differences between groups at time of discharge in any of variables measured.	"[T]his pilot study with a small sample size was unable to demonstrate any statistically significant difference in final outcome between CPM or LLiMB treatment adjuncts..."	Pilot study. Small samples. Unclear why size and other difference in groups (12 vs. 7); concerning for potential randomization failure.
Vince 1987 RCT	3.0	N = 62 with posterior stabilized condylar knee prosthesis	Continuous passive motion (CPM, n = 42) vs. control (n = 20).	Hospital stay length for CPM vs. control: 15.3 days vs. 16.7 days, p = NS; Mean length time to achieve 90° of flexion for CPM vs. control: 9.1 days vs. 13.8 days, p <0.001.	"These data demonstrate that CPM after knee arthroplasty enables patients to recover motion more quickly and affords some protection against	Data suggest efficacy of CPM.

					deep vein thrombosis.”	
Lotke 1991 RCT	3.0	N = 121 scheduled for unilateral primary TKR with cement, average age 69.4 years	Tourniquet inflated throughout surgery with continuous passive motion after 3 days (Group I, n = 31) vs. tourniquet inflated throughout surgery with continuous passive motion immediately in recovery room (Group II, n = 36) vs. tourniquet released during surgery and continuous passive motion after 3 days (Group III, n = 25) vs. tourniquet released during surgery and continuous passive motion immediately in recovery (Group IV, n = 29).	Calculated blood loss (ml): Group I (1140±86) vs. Group II (1335±75) vs. Group III (1493±117) vs. Group IV (1793±106). Measured loss in suction drainage (ml): Group I (379±49) vs. Group II (497±58) vs. Group III (552±56) vs. Group IV (677±61).	“The greatest blood loss occurred in patients who had the tourniquet released intraoperatively and then had immediate continuous passive motion, and the least blood loss occurred in those who had the tourniquet released after the application of a compressive dressing and splint and in whom continuous passive motion was delayed for a few days.”	Quasi-randomized on MRN. Patients not well described. Data suggest more blood loss if Intra-operative tourniquet release plus CPM.
Gotlin 1994 RCT	3.0	N = 40 scheduled for TKR with cruciate substituting , Insall-Burstein, posterior stabilized prosthesis	Traditional physical therapy plus (electrical stimulation ESTIM, n = 21) vs. traditional PT only (n = 19). Continuous passive motion therapy administered to both experimental and control groups. Electrical stimulation applied to experimental group subjects twice daily for 1 hour. Electrodes placed above proximal femoral nerve	Prelag values not statistically different, however, after treatment, mean extensor lag for experimental group reduced to 5.67±1.93°, whereas control group increased to 8.32±2.52°. Differences in Postlag scores between groups had p-value of 0.01. Furthermore, experimental group subjects reached hospital discharge criteria after 6.71±1.23 days as compared to control group, 7.47±1.12, p <0.05.	“[E]STIM is effective in expediting recovery from surgery, as evidenced by a more rapid patient return to active daily living. Secondly, reduced hospital stay may decrease the overall cost of patient care, contributing further benefit to the patient”.	Co-interventions not well controlled. Study evaluated whether electrical stimulation of additive benefit to CPM. Treatment duration unclear. Data suggest e-stim may be helpful.

			and distal vastus medialis oblique. Frequency 35Hz with ramp time of 3 seconds beginning at 40° of extension and terminating at maximal passive extension.			
Lau 2001 RCT	3.0	N = 43 undergoing primary total knee arthroplasty	Immobilization vs. continuous passive motion for 1 week.	No significant difference in active ROM between 2 study groups (p = 0.28) on Day 14. By 1-year follow-up, still not significant (p = 0.38).	"We found that there was no significant difference between knees that had CPM and knees that were immobilized after unilateral primary TKA from postoperative day 14 onward."	Limited patient data. Data suggest CPM better than immobilization over 1st post-op week.
Kumar 1996 RCT	3.0	N = 40 (46 knees) with OA undergoing unilateral primary TKA	CPM machine and physical therapy vs. drop and dangle plus physical therapy. 6 months follow-up.	CPM/drop and dangle/p value passive flexion ROM (range°) for day 5 post-op, 6 weeks post-op, 3 months post-op (CPM n = 40, drop and dangle n = 34), and 6 months post-op (CPM n = 27, drop and dangle n = 14).	"Range of motion and hospital discharge can be achieved in a similar time interval with the drop and dangle technique as with using a continuous passive motion device, and that such a device is not required for postoperative knee rehabilitation."	Data trend towards worse CPM groups pre-op which may have biased results. High dropouts. Data suggest comparable results with therapy vs. CPM.
Pope 1997 RCT	3.0	N = 53 (57 knees) undergoing primary TKA	No CPM vs. CPM 0-40° vs. CPM 0-70°. All treated with PT.		"Our findings show that CPM had no significant advantage in terms of improving function or range of movement, and that its use increased blood loss and analgesic requirements."	Sparse details. Some differences in groups. CPM provided no demonstrable additive advantage.
Chiarello 1997 RCT	2.5	N = 45 with degenerative joint disease who underwent primary unilateral TKA	Short continuous passive motion CPM 3-5 hours a day with CPM ROM increased 5° twice a day vs. short CPM duration with CPM ROM increased daily to subject tolerance vs. long CPM duration 10-12 hours a day		"Based on the results of this study, CPM does not increase flexion or extension ROM in primary total knee arthroplasty patients with degenerative joint disease compared with a control group not using CPM."	Small groups. CPM groups did not comply with treatment parameters, nullifying randomization and limiting utility of study.

			with CPM ROM increased 5° twice a day vs. long CPM duration with CPM ROM increased daily to subject tolerance vs. control.			
Walker 1991 RCT	2.5	N = 22 index unilateral total knee arthroplasty (UTKA)	CPM (n = 12) vs. CPM with TENS (n = 18) vs. CPM with continuous cooling pad (n = 15) vs. control (n = 10 no CPM, n = 12 CPM with no TENS, n = 15 CPM with no CCP).	Mean (range) in-hospital postoperative analgesia consumption for CPM vs. no CPM: 96 (38-169) vs. 148 (65-322), p<0.05. Mean (range) analgesia IM/PO for CPM + CCP vs. CPM: 88/30 vs. 111/53, p<0.05. No significant difference between CPM + TENS and CPM.	"[D]uring postoperative UTKA recovery, the use of (1) CPM vs. no CPM and (2) CPM with CCP vs. CPM without CCP can diminish postoperative hospitalization analgesia consumption."	Report of 3 RCTs and none reported in detail. Data suggest equal (in)efficacy.
Ververeli 1995 RCT	2.0	N = 103 with degenerative OA who underwent primary TKA	CPM initiated at recovery room (n = 51) vs. no CPM (n = 52).	CPM vs. no CPM pre-op ROM mean \pm SD for extension and flexion: -5 \pm 5.6/-3 \pm 4/p = 0.3, 106 \pm 12.4/104 \pm 11.3/p = 0.4. Pre-op VAS score: 59.3 \pm 28.4/ 54.9 \pm 26/p = 0.41. Hospital for special surgery knee scores: 63.5 \pm 10.7/65 \pm 9.5/p = 0.47. At discharge active extension, flexion, and flexion contraction ($^{\circ}$): -12.5 \pm 4.9/-8.8 \pm 4.2/p = 0.0001, 81.3 \pm 13/71.2 \pm 9.5/p = 0.0001, 9.3 \pm 4.2/6.4 \pm 3.3/p = 0.0002. 2 year post-op: -2.2 \pm 3.7/-2.6 \pm 4.2/p = 0.65, 109.8 \pm 8/107.8 \pm 9.4/p = 0.27, 2.2 \pm 3.7/2.3 \pm 3.8/p = 0.95; 2-year knee scores: 84.5 \pm 12.1/81.3 \pm 11.1/p = 0.25. VAS p values for day 1, 3, 5, 7, and 10: 0.38, 0.77, 0.20, 0.87, 0.51. Length of hospitalization: Group 1, 12.1 days vs. 12 days Group 2, p = 0.092.	"Continuous passive motion is efficacious in increasing short term flexion and decreasing the need for knee manipulation without increasing costs."	Patients not well described. Comparison group did not use knee; maintained extension that may have biased in favor of CPM.
Antibiotics, Antibiotic Cement and Infection Issues						
Friedman 1990 RCT 2nd report is Friedman 1990	3.5	N = 24 undergoing TKA	Cefazolin 1g given 1 vs. 2 vs. 5 minutes after tourniquet inflation; 2 hours follow-up.	Percentages of soft-tissue and bone penetration (5 vs. 2 vs. 1min groups): soft tissue (14.5% vs. 6.7% vs. 5.9%). Bone penetrations were 4.6% vs. 3.0% vs. 4.6%.	"The standard of 1 g of cefazolin with a five-minute interval between administration and tourniquet inflation resulted in adequate mean soft-tissue and bone concentrations	Small groups. Pharmacological study without health outcomes.

					for prophylaxis during TKA with a tourniquet time less than two hours. Additional doses are not warranted after tourniquet time.”	
Nelson 1993 RCT	3.0	N = 28 with periprosthetic infections: 22 infected hips and 6 knees	Debridement and implantation of gentamicin-polymethylmethacrylate beads PMMA (n = 12 THA, 3 TKA) vs. debridement and conventional parenteral systemic antibiotic therapy (n = 10 THA, 3 TKA).	Comparable results whether using debridement, gentamicin-polymethylmethacrylate beads implanted and a 2-stage delayed reconstruction vs. debridement plus conventional systemic arthroplasty and 2-stage reconstruction.	“The outcome of treatment in patients with infected total joint arthroplasties using debridement, gentamicin-PMMA bead implantation, and a two-stage delayed reconstruction was similar to that of patients treated with debridement combined with conventional parenteral systemic arthroplasty and two-stage reconstruction.”	Patients not well described. Many details sparse. May be underpowered for all but major differences.
Richardson 1993 RCT	3.0	N = 32 with TKA	Cephmandole: (A) 1g 5 minutes before tourniquet inflation vs. (B) 2g 5 minutes before tourniquet inflation vs. (C) 1g 5 minutes before and 1g 5 minutes before tourniquet release; 6 hour follow-up.		“Concentrations of cepha-mandole in drain fluid were directly proportional to the serum concentration at the time of tourniquet release. A ‘tourniquet-release’ dose of antibiotic increased drain fluid concentration threefold.”	Very short-term study of 6 hours. No follow-up for outcomes. Small numbers, especially in control group (8 each). Patients not well described. Many details sparse.
Mollan 1992 RCT	2.5	N = 660 >14 years undergoing primary total hip or knee replacement (512 THR, 148 TKR)	Teicoplanin 400mg at induction of anaesthesia (n = 308) vs. cephamandole 2 g i.v., 1g subsequently at 6, 12, and 18 hours post-op (n = 352).	No significant between group differences.	“[S]ingle-dose teicoplanin is a safe and effective prophylactic agent in prosthetic joint implant surgery.”	Sparse methods. Patients not well described. Data suggest one dose of teicoplanin may be effective, but insufficient follow-up for adverse health outcomes.

PERI- AND POST-OPERATIVE CRYOTHERAPY

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Schröder 1994 RCT	3.5	N = 44 having undergone open ACL reconstruction with autologous patellar	Cryo/Cuff (continuous in hospital) vs. ice (TID ice bag). 12 weeks follow-up.	Drainage volume not different (ice 403±209 vs. CC 370±206mL). Greater ROM achieved with cryocuff group; that group also achieved earlier full extension.	“The results from our study document the advantages of continuous cold-compression therapy over cold alone following ACL reconstruction.”	Contact time differed between groups, biasing against ice. No baseline data on outcomes. Day 1 data

		tendon graft		Quadriceps strength did not differ.		differed, concerning for potential randomization failure.
Woolf 2008 RCT	3.5	N = 60 undergoing knee arthroscopy (many different procedures; excluded major ligament reconstruction)	Ice (Q2 hours for 20 minutes for 4 days, then PRN for 10 days) vs. continuous cryotherapy (Nocturnal use for 4 days, then prn for 10 days); 14 days follow-up.	Pain intensity scores (days 2/5/8/11/14): Ice (2.95/2.15/1.90/1.46/1.60) vs. continuous cryo (2.64/2.23/2.20/1.66/1.15). Continuous cryo produced more patients able to sleep soundly at 48 hours, p = 0.04.	"These findings support use of continuous temperature-controlled cold therapy devices for nighttime pain control and improved quality of life in the early period following routine knee arthroscopy."	Quasi-randomized by even/odd MRN. Groups not well described at baseline. Sparse outcomes data, mostly suggesting modest benefit.
Gibbons 2001 RCT	3.5	N = 60 undergoing TKA	Cryo/Cuff vs. modified Robert Jones bandage.	VAS pain scores did not differ, graphic data p >0.05. EBL cold compression 720mL vs. Robert Jones 1,200mL, p <0.05. Adjunctive analgesia did not differ.	"No difference was found between the 2 groups except for less blood loss in the surgical drains in the cold compression group."	Data suggest comparable efficacy.
Dervin 1998 RCT	3.0	N = 78 undergoing arthroscopic anterior cruciate ligament reconstruction	Cryo/Cuff with ice water vs. room temperature water. All treated with PCA morphine.	Total hemovac output with ice 335±177 vs. 348±148 (NS). Morphine infused with ice 0.37±0.23 vs. 0.35±0.21mg/kg. No differences in numbers of codeine tablets consumed. Pain score with ice 30±17 vs. 25±13. Length of stay with ice 60±16 vs. room temp 55±18 hours.	"The clinical effect of the Cryo/Cuff in this study was not influenced by the use of continuous ice water vs. room temperature water."	Quasi-randomized on even/odd birth month. Data suggest lack of efficacy.
Scarcella 1995 RCT	3.0	N = 74 (50 THA and 24 TKA patients)	Cryotherapy (Hot/Ice Blanket. THA patients treated at 70°F and TKA at 50°F) vs. no cryotherapy.	In TKA group, cryotherapy treated patients discharged average 1.5 days earlier (p = 0.186). ROM at discharge similar for groups.	"There were no statistically significant differences between the control groups or the test groups for both THA and TKA patients in narcotic usage, postoperative range-of-motion (ROM), or rate of progression of ROM."	Patient groups not well described. Data suggest study may have been underpowered.
Barber 1998 RCT	2.5	N = 100 undergoing outpatient arthroscopically assisted ACL reconstruction	Continuous cold therapy (constant for 3 days, then prn days 4-7; not well controlled as temp 35-50F) vs. noncold therapy. Both groups treated with CPM 6-8 hours a day (54 hours for cold vs. 41 hours for non-	VAS pain scores (1 hour/2 hours/8 hours/Days 2/3/4/5/6): cold (3.71/3.61/4.1/5.61/5.04/4.55/4.29/4.33) vs. non-cold (4.63/3.75/5.22/5.88/5.37/4.63/4.65/4.39), p = 0.059. No differences in failures to achieve full extension. No differences in swelling (p = 0.76).	"Continuous-flow cold therapy is safe and effective for outpatient ACL reconstruction reducing pain medication requirements."	Quasi-randomized (even/odd SSN). Results may have been confounded by CPM which differed between groups. VAS score at baseline not provided. VAS score at 1 hour differed (4.83 non-cold vs. 3.71 cold), Likert

			cold, p = 0.003). All used crutches.			pain, vicodin use all different, concerning for possible randomization failure.
Hecht 1983 RCT	2.5	N = 31 (36 knees) undergoing TKA	Local heat plus exercise (n = 13) vs. local cold plus exercise (n = 13) vs. exercise alone (n = 10).	No differences in ROM. At midpatella, more reductions in leg circumference for cold plus exercise or exercise alone than heat plus exercise (p<0.05).	"Results showed that temperature alteration does not augment passive range of motion after total knee arthroplasty. It was also shown that cold application decreases swelling as compared with heat."	Sparse details. Small samples. Demographics not described. Follow-up after 10 PT appointments.

QUADRICEPS, GASTROCNEMIUS and SOLEUS STRAINS

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
STST vs. PATS						
Engelbreton 2008 RCT	3.5	N = 388 soccer players with history of MSD of ankle, knee, hamstring or groin and high recurrence risk	Exercise program intervention (stepped increase in ankle, knee, groin, hamstring exercises up to 3 per week for 10 weeks) vs. control	505 injuries among 56% of players. Total injury incidence mean 3.2 (95% CI 2.5-3.9) in low-risk group, 5.3 (95% CI, 4.6-6.0) HR controls (p = 0.0001 vs LR controls), and 4.9 (95% CI, 4.3-5.6) HR intervention group (p = 0.50 vs. HR controls). For main outcome measure, sum of ankle, knee, hamstring, groin injuries, significantly lower injury risk in LR control vs. other 2 groups, no difference between HR intervention and HR controls. Compliance with training programs in HR intervention: 27.5% ankle, 29.2% knee, 21.1% hamstring, 19.4% groin.	"[P]layers with a significantly increased risk of injury were able to be identified through the use of a questionnaire, but player compliance with the training programs prescribed was low and any effect of the intervention on injury risk could not be detected."	Prevention study of soccer players and applicability to other patients unclear. Multiple injuries and exercises combined with inadequate reporting. Thus validity and utility for any one outcome unclear. Compliance so low (19-29%) that results appear without meaning.
Hartig 1999 RCT	3.5	N = 148 and 150 (2 infantry basic trainee companies)	Three hamstring stretching sessions plus usual training fitness program vs. no hamstring stretching exercises added to usual training fitness program	Intervention group's hamstring flexibility increased (baseline/post) 41.7±8.3/34.7 vs. controls 45.9±6.5/42.9. 43 injuries in controls group (incidence rate 29.1%) vs. 25 injuries in intervention (IR = 16.7%), p = 0.02.	"[T]he number of lower extremity overuse injuries was significantly lower in infantry basic trainees with increased hamstring flexibility."	Randomization by company. Baseline differences in hamstring flexibility (intervention more flexible 41.7±8.3 vs. 45.9±6.5, p <0.001), indicate randomization failure, potential fatal study flaw.

KNEE SPRAINS

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Prevention						
Ekstrand 1983 RCT	3.0	N = 180 male soccer players (12 teams)	Prophylactic program of no shooting before warm- up, warm-up 20 minutes excluding all calisthenics and dynamic stretching, 10 minutes of both passing ball and contract-relax stretching, 5 minute cool down; leg guards, prophylactic taping, controlled rehab; excluded players with knee instability; information; correction and supervision.	Prophylactic group had 75% less injuries compared to control group, p <0.001. Prophylactic group had 23 injuries vs. 93 in control group, p <0.001. Prophylactic group missed 111 practices and 48 games vs. 476 and 215 in control group, p <0.001. Prophylactic group had 2 operations vs. 11 in control group, p <0.05. NS between groups for injuries sustained during games. Prophylactic group experienced 6 strains vs. 23 strains in control group, p <0.001.	"It is concluded that the proposed prophylactic program, including close supervision and correction by doctors and physiotherapists, significantly reduces soccer injuries."	Cluster randomized by team. No data on prior injuries at baseline by group, which may be a critical variable. Data suggest program effective.
Caraffa 1996 Quasi-RCT	0.5	N = 600 soccer players on semi- professiona l and amateur teams in Italy (40 teams randomized)	Proprioceptive training plus standard program: 20 minutes a day in 5 phases consisting of balance training without a board (standing alternately on 1 leg 2.5 minutes 4 times a day, phase 1); training each leg alternately on rectangular balance board (phase 2); phase 3 round board; phase 5 training on BAPS board/ multiplanar board (group A, n = 20 teams) vs. training as usual (groups B, n = 20 teams) preseason	Group A had an incidence of 0.15 injuries per team/season vs. 1.15 injuries in group B, p <0.001.	"[P]roprioceptive training should become standard in preseason training as well as during the actual playing seasons."	Quasi- randomized by team not player. Most details quite sparse, although results suggest possible efficacy.

			training (at least 30 days).			
NSAIDs						
Hughes 1995 RCT	2.5	N = 40 with moderate or severe acute knee sprains of under 24 hours duration	Modified Robert Jones bandage vs. elastic support bandage (Tubiton). All treated with walking stick, analgesics, Cco-dydramol 2 QID PRN. Weekly follow-up until recovered.	No differences in VAS pain at all time intervals. Baseline range of movement data and subsequent data suggest randomization failure, as range of movements all higher in Modified Robert Jones bandage group. Patients preferred elastic bandage after 1st week; however, by then most patients had dropped out or recovered.	"[T]he two treatments were equally effective in treating knee sprains, and patients preferred the (elastic support bandage) in the early post-injury period."	Quasi-randomized on even/odd MRN. Substantially different group sizes (26 vs. 14) and patients not well described. Data suggest elastic support bandage superior to modified Robert Jones bandage. Study does not have a non-supported control group.

ACL TEARS

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Bracing						
Risberg 1999 RCT	3.5	N = 60 age 15-50 with ACL injury undergoing ACL reconstruction	Knee brace for 3 months and then whenever needed thereafter for sports (Group B, n = 30) vs. non-brace (Group NB, n	No significant differences between groups for knee laxity, ROM, isokinetic strength measurements, and functional knee tests at any of follow-up times. Group B had significant improvement in knee	"We found no evidence that bracing (DonJoy Gold Point brace) had an effect on knee joint laxity, range of motion, muscle strength, functional knee	Meniscus injury rates different between groups during follow-up, 33% in Group B and 60% Group NB. Patients who wore brace intermittently for

			= 30) for 2 years.	function at 3 months compared to Group NB, $p < 0.05$.	tests, patient satisfaction, or pain, in comparison to no brace after ACL reconstruction.”	up to 2 years had significantly decreased quadriceps muscle strength vs. those who wore brace for a shorter period of time.
Swirtun 2005 RCT	3.0	N = 95 age 18-50 with acute ACL tear (within past 5 weeks) included in study. (n = 22) dropped out due to surgery or (n = 10) personal reasons, leaving 42 remaining	SofTec Genu off the shelf brace (n = 22) vs. no brace (n = 20) for 12 weeks.	Brace group experienced less sense of instability from Week 6 to 12 compared to control group, $p = 0.047$. No significant difference between groups.	“Nonoperated acute ACL-deficient patients experienced a positive effect of the brace regarding sense of instability and rehabilitation. However, these findings were not supported by objective outcomes.”	Baseline difference in KOOS score, with brace group having more problems with ADLs ($p = 0.003$), concerning for randomization failure.
McDevitt 2004 RCT	3.0	N = 95 cadets and midshipmen with ACL injury having had surgical repair	DonJoy IROM brace for 6 weeks, then off self functional brace for 6 months to 1 year (brace group, n = 47) vs. knee immobilizer for 3 weeks; no brace after that (non-braced group, n = 48).	No statistically significant differences between groups for any outcome measures.	“In this young, active population, postoperative bracing does not appear to change the clinical outcomes after anterior cruciate ligament reconstruction.”	Lack of details lowered score. Bracing did not improve outcomes for up to 2 years after surgery.
Harilainen 2006 RCT	3.0	N = 60 with ACL tears after surgery	DonJoy COOL IROM (brace group, n = 30) vs. no brace (n = 30) for 12 weeks.	No significant differences between groups for any outcome measures.	“Thus it appears that knee braces are not needed in the post-operative rehabilitation after ACL reconstruction with the patellar tendon graft.”	Lack of details lowered score. No differences seen.
Ito 2007 RCT	2.5	N = 30 with unilateral chronic ACL insufficiency	Two week immobilization vs. 3-day immobilization for post-op knees.	No statistically significant difference between 2 groups in overall scores on Lysholm scale. Isokinetic muscle strength in knee extensions also showed no statistical difference.	“[O]ur study has shown no significant differences in the clinical outcome between the two groups in terms of the subjective knee function, joint stability, position sense, and thigh muscle strength.”	Lack of study details lowered score. Also lacks adequate control group.

Feller 1997 RCT	2.5	N = 40 undergoing primary ACL reconstruction more than 3 weeks after injury	No brace (control group, n = 20) vs. brace (n = 20) for 6 weeks.	No significant differences between groups.	"The overall lack of benefit of the brace in the restoration of extension following ACL reconstruction may well be a reflection of the apparently general decrease in frequency of a postoperative extension deficit following this type of surgery."	Small numbers. Lack of details lowered score. No mention of drop-out rate, cointerventions, or blinding. No differences reported.
Henriksson 2002 RCT	2.5	N = 50 with unilateral total ACL ruptures awaiting ACL reconstruction	Immobilization in a plaster cast (plaster group, n = 25) vs. early mobilization in a brace (brace group, n = 25) for 5 weeks.	Mean peak torque deficit at 24 months follow-up significant in hamstring muscles (p <0.01) and quadriceps muscle (p <0.001) but neither significant in plaster group. Significant difference between groups for strength deficient for hamstring muscles, p<0.05.	"It is suggested therefore that the rehabilitation protocol used with early ROM training should ideally be accompanied by tests to ascertain regainment of full muscle strength."	Plaster group needed more PT exercises to regain ROM than brace group. No strength testing done pre-operatively. Difference could be from inadequate randomization rather than from intervention.
Wu 2001 RCT	1.5	N = 31 who underwent ACL reconstruction with a semitendinosus tendon autograft	Test performed with a DonJoy Legend brace vs. mechanical placebo brace vs. no brace.	Significant difference for knee joint angle repositioning test, p = 0.000.	"[B]racing can enhance the proprioceptive function of the knee after ACL reconstruction at more than 5 months after surgery."	Lack of study details. Unable to draw conclusions without more details.
Post ACL Injury Rehabilitation						
Exercise						
Fitzgerald 2000 RCT	3.5	N = 26 with diagnosis of ACL rupture or rupture of an ACL graft	Standard rehab (resistive exercises for quadriceps femoris and hamstring muscle groups, cardiovascular endurance training, agility skill training, and sport specific skill training, n = 14) vs. perturbation (anteroposterior and mediolateral perturbations on a balance master motorized force platform, anteroposterior	Standard group had more unsuccessful rehabilitation vs. perturbation group, p <0.05. NS between groups for pre-treatment and post-treatment hop test scores and anterior knee laxity.	"Although both training programs used in this study allowed subjects with isolated ACL ruptures to return to high-level physical activities, subjects who received the perturbation training demonstrated greater long-term success than subjects who did not receive this training. The greater proportion of successful return to activity in both treatment groups compared with previously reported success rates indicates the	Includes patients only active in sports. Lack of details lowered score. Uncertain of co-interventions. Patients "selected" making generalizability difficult.

			and mediolateral rotary perturbations on tiltboard, multidirectional perturbations while standing with 1 lower extremity on roller board other on stationary platform, multidirectional perturbations while standing in single-limb support on roller board, n = 12) for 5 weeks.		screening examination enhanced treatment outcome by identifying patients with good potential to succeed with nonoperative management.”	
Fischer 1998 RCT	3.0	N = 54 older than 15 years with no previous repair or reconstruction of knee ligaments, underwent reconstruction of anterior cruciate ligament	Home-based exercise consisting of 6 supervised PT visits (at 1, 2, 3, 4, 6, 12 weeks), n = 27 vs. clinic based exercise consisting of 24 PT sessions in 1st 6 months (n = 27) for 6 months.	No significant differences between groups.	“[I]n a selected group of patients who had undergone anterior cruciate ligament reconstruction, a home based postoperative rehabilitation program is understandable, convenient, and reliable. Such a program can be instituted effectively for many of the anterior cruciate ligament reconstructions performed today.”	Range from injury to operation changed for 6 weeks to 18 years. Lack of details lowered score. Difference in age between groups with home based group may have changed outcomes.
Noyes 1987 RCT	2.0	N = 18 who underwent ACL reconstruction or acute repair with graft augmentation	“Motion” group, (10 hours daily continuous passive motion on 2nd post-op day) vs. “delayed” motion group, (using soft hinged knee brace with knee hinges locked at 10° of flexion on 2nd post-op day).	On 7th day after surgery, degrees of knee extension and flexion for motion group vs. delayed motion group: 11±8 extension/68±12flexion vs. 14±7/63±14.	“The initiation of intermittent passive motion on the 2nd postoperative day after major ligamentous reconstruction had no effect in increasing joint effusion and hemarthrosis or soft tissue swelling. Postoperative joint effusions were absent after the 14th day. There was no statistically significant difference in the degrees of knee extension or knee flexion related to initiation motion on the 2nd or 7th	Used “special suturing and fixation techniques.” ROM tested in experimental group was continuous passive range of motion for 10 hours a day. Late ROM group had different intervention.

					postoperative day, although there were trends for regaining more motion for patients who started mobilization on the 2nd postoperative day.”	
Perturbation vs. Strength Training						
Hartigan 2009 RCT	3.5	N = 19 (12 males, 8 females) with compete, acute, or isolated ACL rupture	Perturbation group (n = 9) vs. strengthening group (n = 10). Strengthening group received 10 sessions of progressive quadriceps strength training only. Perturbation group same 10 sessions and specialized neuromuscular exercises involving systematic translation of support surfaces; 6 months follow-up.	Quadricep Strength: Before surgery - Perturbation (87.2%) vs. Strength (75.8%), not significant; 6 months after Surgery - Perturbation (97.1%) vs. Strength (94.4%) (F = 16.5, observed power = 0.961, p = 0.002). Knee Excursions between Limbs: Before Surgery - Perturbation (mean = 5.9 degrees, 95% CI = 10.2 to 1.5) vs. Strength (mean = 5.6, 95% CI = 10.5 to 0.6) (F = 15.98, observed power = 0.96, p-value = 0.001); 6 Months after Surgery - Perturbation (mean = 3.5 degrees, 95% CI: 8.3 to -1.4) vs. Strength (mean = 7.0 degrees, 95% CI = 11.6 to 2.5) (F = 7.52, observed power = 0.73, p = 0.014).	“Despite symmetrical strength achieved by both of our groups, the strength group demonstrated differences in knee excursions between limbs during mid-stance 6 months after ACL reconstruction. This suggests that the neuromuscular system is not controlling the involved limb the same way as the uninvolved limb in both groups. Improved mid-stance excursion in the perturbation group is a promising first indication that neuromuscular training rehabilitation programs can improve movement patterns in the involved limb after ACL-reconstruction in non-copers.”	Small sample size. Many details sparse. Sparse outcomes data.
Hartigan 2010 RCT	2.5	N = 40 non-copers after ACL reconstruction	Progressive quadriceps strength training exercises vs. perturbation training; 1 year follow-up.	No difference found for functional groups except more patients in PERT group able to pass return-to-sports criteria at 6 and 12 months.	“Functional outcomes suggest that a subgroup of noncopers require additional supervised rehabilitation to pass stringent criteria to return to sports.”	Highly select patient population group non-copers well after ACL surgery prior to return to sports. Data suggest non-copers do better with more supervised therapy. Single arthroscopically assisted surgeon. No mention of co-interventions other than interventions. No differences reported.
Surgery						

Double Bundle vs. Single Bundle						
Wang 2009 RCT	3.5	N = 64 (49 males, 15 females) needing ACL reconstruction	Single-bundle ACL reconstruction (SB group, n = 32) vs. double-bundle ACL reconstruction (DB group, n = 32). Average follow-up for SB group 14.4± 3.4 months; average follow-up for DB group 17.7±4.3 months.	No significant differences between groups in KT 2000, muscle perimeter, ROM, Lysholm, Tegner, or IKDC scores.	"Double bundle ACL reconstruction has not shown significant advantages over single bundle reconstruction so far. But it is more close to the anatomy, and may restore the rotational stability of the knee more successfully. Long-term study with more reliable evaluation methods is needed. Comparison of single and double bundle ACL reconstruction still needs a lot of work."	Lack of details lowered score. No blinding. Double bundle test about 20 minutes longer to perform. No differences reported.
Yagi 2007 RCT	N/A (quasi-randomized)	N = 60 (42 male, 18 female) consecutive patients who underwent arthroscopically assisted ACL reconstruction and had unilateral ACL insufficiency and no previous ligament reconstruction	Double-bundle reconstruction (n = 20) vs. anteromedial single-bundle reconstruction (n = 20) vs. posterolateral single-bundle reconstruction (n = 20).	No significant difference between groups for Overall IKDC, Lachman Test, Pivot Shift Test, and KT-1000. Average acceleration of tibial motion during Pivot Shift Test showed anteromedial and posterolateral reconstruction groups significantly larger than double-bundle group (p < 0.05)	"Our results seem to agree with the results of previously published preliminary studies showing double-bundle ACL reconstruction provides better control of dynamic rotatory stability than single-bundle reconstruction in vivo without increasing complications of affecting postoperative recovery."	Quasi-randomized. Reported improved pivot shift test with double bundle technique. Clinical relevance not evaluated.
Arthroscopic vs. 2-Incision Technique						
Gerich 1997 RCT	3.0	N = 40 (19 females, 21 males) with acute knee instability	Arthroscopic procedure (Group 1, n = 20) vs. 2-incision technique (Group 2, n = 20). Follow-up at 6 and 12 months post op.	Difference of MMD: not significant at any time. Range of Motion: not significant at any time. Muscle circumference: not significant at any time. IKDC: not significant at any time. One Leg hop: pre-op, Group 1 < Group 2 (p = 0.046), not significant at any other point.)	"In summary, this prospective study could not provide significant data suggesting that one technique is superior to the other. In our analysis we could not prove unequivocally any difference between the two study groups caused by the different surgical approaches or graft positions."	Included both acute and Chronic ACL patients. Pre-op one-incision group had significantly lower muscle strength. Also conducted a trial of another technique during open surgery that increased surgery time.
ACI vs. Matric Induced ACI						
Bartlett 2006 RCT	3.0	N = 136 who underwent autologous	ACI-C (n = 73) vs. MACI (n = 63) tourniquet times.	MACI had significantly better mean tourniquet compared to ACI-C (p = 0.03).	"A significantly less tourniquet time for MACI technique makes it particularly	No follow-up beyond surgery, Sparse

		chondrocyte implantation (ACI)			suitable for cartilage resurfacing when performed in combination with other techniques such as posterior cruciate ligament reconstruction and high tibial osteotomy.”	details. Study design unclear.
Other Surgery						
Ahldén 2009 RCT	3.5	N = 71 with unilateral ACL injuries	ACL reconstruction using an ipsilateral bone-patellar-tendon-bone autograft (BPTB group, n = 22) vs. quadruple ST autograph (ST group, n = 25) [47/71 attended pre-op exam and all 4 post-op exams]. Assessments were pre operatively, 6 months, 1 year, 2 years, 7 years post-op.	No significant difference in cause of injury between groups. No significant difference in knee laxity found pre op or at follow-ups between groups.	“There was no significant differences in knee laxity measurements between the two study groups pre-operatively or at 7 years. A decrease in knee laxity over time was seen in both the BPTB and HS groups. There was no significant difference between the BPTB group and HS group regarding radiographically visible osteoarthritis at 7 years.”	Lack of study details lowered score. No blinding. No mention of co-interventions after port-op rehab. No differences reported at 7-year follow up. Argument that patellar tendon grafts have less laxity not supported by this study.
Cameron 1995 RCT	3.5	N = 45 with ACL deficiencies	Arthroscopic (n = 28) vs. Open (n = 17). Assessments done at 1, 3, and 6 months post-op.	Statistical significance achieved (p <0.05) in only 3 parameters; 1-month post-op ROM, 6-month post-op thigh atrophy, and Cybex II test (knee extension at 60°/sec) statistically different favoring arthroscopic method.	“[V]ery few differences in the arthroscopic and open ACL reconstruction groups could be identified except for the impact on the quadriceps strength.”	Most participants active army. Included both acute and chronic tears. Pseudo-randomization by social security number. No repairs of meniscal tears.
Zaffagnini 2006 RCT	3.5	N = 75 who needed ACL reconstruction	Group 1: bone patellar tendon bone graft (n = 25) vs. Group 2: ACL reconstruction via 4 strand hamstring tendon (n = 25) vs. Group 3: ACL reconstruction with two strand hamstring plus extraarticular		“In conclusion, the IKDC score showed similar results for these three groups suggesting that the graft choice is not influencing the final clinical outcome of ACL reconstruction. However analyzing in detail the results obtained, the technique with lateral plasty showed a significantly better subjective	All patients involved in cutting sports at competitive or master level. All surgeries done by same surgeon. All patients returned to same sport practice before trauma. Some differences seen, but all patients

			plasty (n = 25).		evaluation, a faster return to sports, less kneeling pain and a higher capacity of return to normal muscle trophism.”	returned to activities.
Harilainen 2006 RCT	3.5	N = 99 with a torn ACL	Patellar Tendon Group (BPTB, n = 51) vs. Hamstring Tendon Group (STG, n = 28). Assessments were pre-operatively, 1, 2, and 5 years after operation.	Pre-op: knee laxity test, Tegner Activity levels, Kujala patellofemoral scores, and isokinetic muscle torque values not significantly different between groups. Lysholm score: BPTB (74) vs. STB (68), p = 0.044. At 2 year follow-up: side-to-side difference, Lysholm Score, IKDC score, Kujala Patellofemoral score all not significant. AP femoral drill tunnel: BPTB (11.3 +/- 2.3) vs. STG (13.3 +/- 1.9); p = 0.0002. AP tibial drill tunnel and sagittal tibial drill tunnel not significant. At 5 year follow-up: ROM, Side to Side Difference, Isokinetic Peak Muscle Torque, Lysholm knee score, IKDC score, Kujala Patellofemoral score, Tegner Score, AP femoral drill tunnel all not significant. AP tibial drill tunnel: BPTB (11.0 +/- 2.2) vs. STG (12.3 +/- 2.1), p = 0.0180. Sagittal tibial drill tunnel width: BPTB (10.4 +/- 2.7) vs. STG (11.8 +/- 1.8), p + 0.0138.	“The results of the present study and of others do not confirm the superiority of either the patellar or hamstring tendon grafts in ACL reconstruction.”	Two surgeons performed surgeries. Birth year used to randomize. No mention of co-interventions other than initial rehab program. Study conducted with different tendons and different fixation techniques.
Andersson 1991 RCT 2nd report of Odensten 85	3.5	N = 167 with acute and complete rupture of ACL; follow-up 41-80 months after injury	Group 1: repair of all major injuries including suture, augmentation of ACL with strip of iliotibial band (n = 33 menisci in 28 patients) vs. Group 2: ACL repair without augmentation (n = 33 menisci in 31) vs. Group 3: non-surgical ACL treatment (n = 56 menisci in 53).	Lysholm Score at follow-up (distribution and mean±SD). Nonsurgical: 3(score 0-64), 23(score 65-83), 25(84-94), 21(95-100), mean ± SD (86±11). Repair: 1(score 0-64), 3(score 65-83), 8(84-94), 10(95-100), mean ± SD (90 ±10). Augmented Repair: 0(score 0-64), 8(score 65-83), 14(84-94), 23(95-100), mean ± SD (92±7).	“From this study, it could be concluded that patients with high functional demands should be treated by primary ACL augmentation in order to have the best chance to return competitive sports. A nonaugmented ACL repair cannot be recommended, since the prognosis for these patients was generally the same as for the patients who had nonsurgical treatment.”	Quasi-randomization on DOB. Many details sparse. Substantially uneven group sizes. Data suggest greater return to competitive sports in surgically repaired group.

Dahlstedt 1990 RCT	3.5	N = 41 undergoing ACL reconstruction	Gortex prosthesis group (n = 18) vs. Kennedy LAD group (n = 23).	Functional and activity scores. Pivot shift and thrometric values pre-op and at last follow-up in patients who had anterior cruciate ligament reconstruction with Gortex prosthetic ligament or Kennedy ligament augmentation device (LAD). Median SD (range). Lysholm score: Last: Gortex 89 (71-100), LAD 96 (75-100), p = 0.01. Pain Score: Last: Gortex 20 (15-25), LAD 25 (20-25), p = 0.01.	“Although many patients are satisfied, our short term results with the Gortex prosthetic ligament in its present form are unacceptable mainly because of effusions and increased occurrence of pain symptoms. Short term results with the use of a polypropylene braid as an augmentation to an autologous graft seem promising.”	Four surgeons. Athletes increased adverse events with use of Goretex. Lack of details lowered score. Absolute issue as no prostheses used regularly in practice.
Gobbi 2006 RCT	3.0	N = 100 (67 males, 33 females) non-professional athletes in competitive sports at regional or national level or participating in recreational sports 3 times a week, normal contralateral knee, partial meniscectomies	Patellar tendon graft (PT group, n = 50) vs. hamstring tendon graft (HT group, n = 50). Assessments at 3, 6, 12, and 24 months post-op.	Quadriceps strength tested at 60, 180, and 300 degree/s after 12 months revealed no significant differences between groups. No significant difference in Anterior laxity test between groups at any time. 53.3% of the 65 patients who returned to sports reported they did not have any difficulty doing the same activities (p < 0.001).	“Standard knee scales like IKDC, Lysholm, Noyes, and Tegner remain a valuable tool for evaluating the progression of knee recovery following ACL reconstruction. However, we believe that the additional use of the Marx knee activity rating scale and the psychovitality evaluation can provide additional data on the patient’s functional capabilities and psychological profile which could be useful in determining the capacity of athletes to resume pre-injury activity levels.”	Quasi-randomized (apparently every other). Patients not well described by group. Results primarily did not report comparison of outcomes by two techniques.
Meunier 2007 RCT 3rd report of Odensten 1985	3.0	N = 50 needing total knee replacements	Placebo vs. celecoxib (200mg) pre-op and then twice daily; 15 years follow-up.	No differences found in total, hidden, drainage blood loss, or pain between the groups. In celecoxib group, 30% lower pain scores during 1st 4 weeks after surgery and lower morphine consumption after surgery.	“Celecoxib does not increase perioperative blood loss but reduces pain during the postoperative period after TKR. It is not necessary to discontinue celecoxib before surgery. The postoperative use of celecoxib did not increase range of motion or subjective outcome 1 year after TKR.”	Co-interventions problematic as unevent rehab treatment in groups. Quasi-randomization on DOB. Many details sparse. Substantially uneven group sizes. Iliotibial used for ACL repairs; 31% crossed over to surgical repair. More meniscal surgeries in

						secondary ACL surgical group (50% vs. 28%).
Odensten 1985 RCT	3.0	N = 90 patients (65 males, 25 females) with total mid-structural tears of ACL; 1.5 years follow-up	Surgical treatment (n = 46) vs. conservative treatment (n = 44). Average assessment 18.2 ±6.7 months post-op. Score given at follow-up of a total of 100. Breakdown: limp (0-5 points), need for support (0-5 points), instability (0-25 points), pain (0-25 points), swelling (0-10 points) stair climbing (0-10 points), squatting (0-5 points), catching (0-15 points).	At follow-up, more than 76% of surgical group scored 84 or more compared to 53% that scored an 84 or more in conservative group (p < 0.05). Instability: surgical group 4/41 with instability compared to 10/35 in conservative group (p <0.05). Quadriceps strength: surgical vs. conservative (0.97±0.14 vs. 0.89±0.12, p <0.02). Jumping and running not significant. Stability: 39/41 in surgical group had stable knees vs. 4/35 in conservative group (p <0.001). Median activity level (median, 0-10): surgical vs. conservative (5 vs. 6, p <0.01 to 0.001).	“The present study suggests that early primary suture with augmentation may give the patient with an acutely torn ACL a better start than conservative treatment, although conservative treatment is sometimes followed by a good primary result.”	Timing of follow-ups may have been uneven. No data on populations provided. Data suggest comparable outcomes.
Cerullo 1995 RCT	3.0	N = 50 undergoing ACL patellar tendon reconstruction	Tendon defect was randomly closed in Group I (n = 25) vs. left open in Group II (n = 25).	No statistically significant differences between 2 groups. Ultrasonography showed in 68% of knees of Group I (defect closed) a thickened patellar tendon (PT), while in 60% of Group II it was of normal thickness. No patients of either group developed patella infera by x-ray evaluation 6 months post-op. CT scans at 6 months showed that 100% of knees of Group I had a thickened PT in toto (nearly twice as thick as normal).	“[O]ther studies are needed to definitely settle the enigma of whether the tendon defect has to be closed or not.”	Some patients (not all) had CT scan at 6-months. All involved in sports. No statistical significance calculated. Reported it is “probably” better to leave defect open.
Zeifang 2010 RCT	3.0	N = 21	First generation autologous chondrocyte implantation with periosteal flap (ACI-P, n = 11) vs. 3rd generation matrix-associated ACI (m-ACI, n	Lysholm and Gillquist score mean (SD) to m-ACI vs. ACI-P at 12 months: +4.9 (19.0) vs. +25.0 (22.8), p = 0.0449 (95% CI, 1.0 to 41.0); at 24 months: +1.2 (22.3) vs. +22.7 (25.9), p = 0.0487 (95% CI, 1.0 to 48.0).	“This RCT confirmed the efficacy of ACI and m-ACI based on polyglycolic acid scaffolds in the treatment of cartilage defects in the femoral condyle.”	Small numbers. Excluded obese patients. No women in the periosteal flap group. No mention or control of any co-interventions. 50% drop out

			= 10). Outcome measurements associated at 0, 3, 6, 12, and 24 months.			rate at 24 months.
Robert 2004 RCT	2.5	N = 41 (6 female, 35 male) with isolated rupture of ACL with normal contralateral knee with differential laxity inferior to 10mm as measured with KT-1000	Femoral fixation by transfix and resorbable screw (Group 1, n = 21) vs. femoral fixation by transfix and periosteal flap (Group 2, n = 20). Assessments at 1, 2, 3, 5, 8, 12, and 16 months post-op. X-rays taken at 10 weeks and 11 months post-op.	Anteroposterior view <3 months (Group 1 vs. Group 2, p-value): Tunnel Aperature: 29.83% vs. 10.28%, p = 0.001, +1 cm: 30.39% vs. 10.75%, p = 0.001. Lateral view <3 months: Tunnel Aperature: 27.23% vs. 13.71%, p = 0.009, +1 cm: not significant. Anteroposterior view after 6 months: Tunnel Aperature: 37.38% vs. 18.97%, p = 0.0003; +1 cm: 38.48% vs. 20.91%, p = 0.0002. Lateral view after 6 months: Tunnel Aperature: 31.79% vs. 20.91%, p = 0.0002; +1 cm: 35.31% vs. 19.27%, p = 0.0002. Laxity: not significant.	"At 2.5 months and 11 months postoperatively on average, there was a significant reduction of enlargement at the outlet of the tunnel with the use of a periosteal flap but widening was constant."	One surgeon did all surgeries. Tendon wrap technique developed by author. Low score make it difficult to assess outcome.
Basad 2010 RCT	2.5	N = 60 with post-traumatic, single, isolated, symptomatic chondral defects (4-10 cm ²)	Matrix induced autologous chondrocyte (n = 40) vs. microfracture (n = 20). Outcome measurements assessed at 0, 8-12, 22-26, and 50-54 weeks after surgery.	MACI significantly more effective over time than MF for improvement in Lysholm scores, p = 0.005. MACI significantly more effective over time than MF for improvement in median Tegner scores, p = 0.04. MACI significantly more effective than MF for ICRS scores, p = 0.03.	"MACI™ is superior to MF in the treatment of larger (>4cm ²), symptomatic articular defects over 2 years. MACI™ and MF are complementary procedures for the treatment of articular cartilage defects, depending on the size of the defect and symptom recurrence. As a third generation technique, MACI™ is not only superior to MF but also improves upon the first and second generation chondrocyte-based cartilage repair techniques in terms of reproducibility, safety, operative time, surgical simplicity and reduced invasiveness."	Included patients with BMI >30. Osteoarthritis changed study protocol to not include biopsy at 1 year after randomization. Matrix-induced group twice as large as microfracture group because of another protocol change. Lack of study details lowered score.
Andersson 1992	2.0	N = 107 consecutiv	Group A: Patients with	Hop ratio lower for Group D (0.94±0.06)	"Conservative treatment of the	All patients had surgical repair

RCT		e patients with acute ACL rupture assigned to groups according to birth year; 55 had anterior cruciate ligament rupture without associated meniscal or ligamentous injuries, all (n = 52) who had anterior cruciate ligament rupture combined with rupture and subsequent primary repair of medial collateral ligament	an isolated ACL tear that was repaired and augmented (n = 24) vs. Group B: Patients with an isolated tear that not augmented (n = 31) vs. Group C: patients with ACL tear combined with an MCL tear, where both ligaments repaired with ACL augmentation (n = 24) vs. Group D: Patients with a combined ACL and MCL tear, where only MCL repaired (n = 28).	that Group C (0.97±0.13); p <0.05.	anterior cruciate ligament with repair of the medial collateral ligament and other associated injuries, when present, resulted in an almost equally unfavorable outcome for patients with combined and isolated anterior cruciate ligament lesions."	of additional injuries to MCL, LCL regardless of gap randomization. Lack of blinding, mention of co-interventions and compliance. Surgical repair of ACL was reported to have better outcomes in this low-quality RCT.
Chouteau 2008 RCT	1.5	N = 73 with ACL injuries	Group 1: ACL reconstruction with Computer-assisted surgery (CAS) (n = 37) vs. Group 2: ACL reconstruction without CAS (n = 36). Assessments of operation were done at an average of 2.2 years after operation.	Linear distance between post-op femoral tunnel center and center indicated by Triangle method significantly less in Group 1 than Group 2 (1: 2.5±1.1mm, 2: 7±1.5mm, p <0.001). Group 1 also allowed for a more anterior graft placement than Group 2 in Aglietti and Howell's measurement method ([Aglietti] 1: 28.5±5.4%, 2: 34±6.8%, p <0.001, [Howell] 1: 38.4±4.8%, 2: 43.6±6.6%, p <0.001). IDKC scores, pre- and post-op KT -1000 scores, pre- and post-op radiographic differential laxity not significantly different between groups.	"The CAS Triangle method Benareau provided a more accurate and reproducible placement of tunnels in ACL reconstruction. Knee laxity seemed to be better controlled in CAS series but postoperative functional and clinical evaluations did not show statistically significant differences between both series. Longer follow-up is required to confirm these first results. Indeed, correct tunnels placement is a main factor for long-term results stability."	One surgeon. Use of computer added about 9.3 minutes to surgery time. Prevalence of medial meniscus tear different between groups. No significant difference. Lack of details lowered score.

MENISCAL TEARS

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
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Post-operative Rehabilitation						
Goodwin 2003 RCT	3.5	N = 84 undergoing arthroscopic partial meniscectomy	PT 3 times a week for 6 weeks vs. control for meniscal injuries.	No significant differences between the groups.	“[P]hysical therapist supervised intervention plus written and verbal instructions compared with written and verbal instructions alone in the early period after arthroscopic partial meniscectomy, no differences were found at 6 weeks after surgery for any of the outcomes examined. Both the intervention and control groups improved similarly overall, revealing no benefit in receiving a mean of 12 standardized treatment sessions postsurgery over written and verbal advice. We therefore conclude that for an uncomplicated arthroscopic partial meniscectomy, routine physical therapy intervention is not indicated.”	Large discrepancy in pre-op lost days (2 v. 64). May be driven by 1 outlier, but medians not provided. Data suggest PT after partial meniscectomy ineffective in addition to HEP.
Surgery						
Biedert 2000 RCT	3.0	N = 40 age 16-50 with isolated medial intrasubstance meniscal lesion	Conservative treatment (n = 12) vs. arthroscopic suture repair with access channels (n = 10) vs. arthroscopic minimal central resection, fibrin clot, suture repair (n = 7) vs. arthroscopic partial meniscectomy (n = 11).	Partial meniscectomy more beneficial than other treatment methods.	“Partial meniscectomy, according to our findings in the present study, offers the best short-term results for patients with intrasubstance meniscal lesions.”	Mean 26.5 month follow-up. Small sample sizes. Quasi- randomized on DOB (unclear how). Patients not well described. Data suggest best results with arthroscopic partial meniscectomy. Criteria unclear, as presumably a minimum symptom duration or severity present.
Grifka 1994 RCT	3.0	N = 108 with severe chondromalacia and simultaneous meniscus lesions	Excimer laser vs. mechanical debridement of meniscus.	A higher increase and better results are reported for the laser- treated group based on the Lysholm score (p<0.03).	“[A]rthrotic changes themselves determine further progress. Our results support data from the literature that lavage and debridement bring about temporary relief only. The xenon chloride excimer laser is the best treatment for	High dropouts. Randomization, allocation unclear. Outcomes modestly better with laser than mechanical shaver.

					chondromalacia II compared with the usual mechanical methods.”	
Kirnap 2005 RCT	3.0	N = 40 who had undergone arthroscopic meniscectomy	EMG-biofeedback vs. routine exercise program for post arthroscopic meniscectomy.	Operated extremity knee flexion angle values at baseline, 3rd and 14th day, and 6th week comparing EMG group vs. Control (mean±SD): 134.3±9.3 vs. 130.2±8.8; p>0.05; 99.7±17.8 vs. 98.2±13.6; p >0.05; 129±10.2 vs. 118.2±11.7; p <0.05; 137.1±6.5 vs. 129.2±7.4; p <0.001.	“[T]hese results show the effectiveness of EMG-B in the functional improvement of the knee, possibly provided by its positive effect on quadriceps muscle strength. Our results are consistent with other results in the literature, in that EMG-B was a very effective modality in increasing muscle strength.”	Randomization, allocation unclear. Population not well described. Co-interventions and compliance unclear.
Krebs 1981 RCT	1.0	N = 26 having undergone meniscectomy; enrolled 1-7 days after surgery	Traditional PT with vs. without EMG feedback.	No data provided on pain, or functional outcomes.	“Electromyographic feedback is demonstrated to be an efficacious and specific therapeutic modality for the patient who has had a meniscectomy.”	Subject numbers unclear (26 per abstract, methods; 59 per table 2). Data supportive of surface EMG for enhancing rehab; however trial does not have power to demonstrate meaningful clinical differences.

ANTERIOR KNEE PAIN

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Exercise						
Schneider 2001 RCT	2.0	N = 40 with persistent unilateral retropatellar pain for more than 6 months with unsuccessful conservative therapy using NSAIDs and analgesic agents	16 round of physiotherapy vs. unsupported use of knee splint for 15 minutes 3 times daily combined with exercise for patellofemoral pain syndrome for 8 weeks.	Mean±SD electromyographic measurements at Week 8 for vastus medialis: 456±11.4 (p = 0.003) for physiotherapy vs. 532±8.1 (p = 0.001) for splint; vastus lateralis 240±13.9 (p = 0.003) for physiotherapy vs. 292±10.2 (p = 0.001) for splint; Vastus lateralis/vastus lateralis 1.8±1.3 (p = 0.003) for splint. Week 8 VAS score at rest 3.1±1.2 (p <0.05) for splint and after exposure 3.3±1.1 (p <0.05).	“[T]his study show better the individually perceived therapeutic results to be better following knee splint use than those from physiotherapeutic exercises. The knee splint used here is thus confirmed as an effective therapeutic concept for coping with [patellofemoral pain syndrome] and for achieving early pain relief. The knee splint also enables patients to undertake sustainable self-therapy independently of	Study of persistent or resistant cases.

					scheduled therapy deadlines.”	
Thoméé 1997 RCT	3.5	N = 40 females age 15-28 with patellofemoral pain syndrome (3-4/4 of PFJ pain during or after activity, PFJ pain during/after sitting, PF joint pain with stair climbing, PFJ pain with squatting)	Isometric vs. eccentric muscle contraction; 1 year follow-up.	Isometric 60° (pre/3 months/12 months): isometric (130.6/147.6/154.1) vs. eccentric (151.6/161.5/175.1).	“The results indicate that the improvements shown in this study may be due to spontaneous recovery over time, the education given to the subjective, the pain monitoring system, the gradually progressing training program, and the adjusted physical activity.”	Some baseline differences. No baseline demographic data for comparisons.
Colón 1988 RCT	2.0	N = 29 age 15-24 with possible patellofemoral knee pain	Pogo stick up to 700-1,000 bounces BID for 6-8 weeks plus stretching (n = 16) vs. conservative exercise (SLRs, stretching) program BID for 6-8 weeks (n = 13).	Quadriceps strength increased in both legs by 71% in pogo group, 36% in conservative group. Pogo group 27% increase in quadriceps power compared to decrease of 8%+ in conservative group. Endurance 7% for quadriceps, 10% for hamstrings, both groups.	“[T]he pogo stick was shown to be of benefit in the rehabilitation of a small number of young adults with patellofemoral chondrosis.”	Most data suggest pogo stick group superior. This may suggest active, forceful exercises are superior.
Taping						
Ryan 2006 Crossover Trial	N/A	N = 25 asymptomatic college students (convenience sample)	Lateral glide taping vs. medial glide vs. neutral glide vs. no-tape/glide while performing squats.	Vastus medialis (VM)/vastus lateralis (VL) ratio for later taping: significantly greater than medial (p = 0.007) and neutral (p = 0.007). VM/VL ratio: greater for later than for no tape, NS. Lateral condition: greatest VM and smallest VL activity, NS.	“The magnitude of the change brought about by all taping conditions on the VM/VL ratio was small and of questionable clinical significance.”	Experimental study. No short or long term clinical outcomes. Data do not support patellar taping, however they also did not use clinical patients.
Orthotics						
Finestone 1993 RCT	3.5	N = 59 male military recruits with overuse patellofemoral pain	Elastic knee sleeve (Group 1, n = 22 knees) vs. elastic knee sleeve with silicone patellar ring (Group 2, n = 22 knees) vs. no treatment (Group 3, n = 40 knees) for 14 weeks.	Anterior knee pain was completely resolved in 74% of Group 1 and 43% of Group 2 two months after completing basic training, p = 0.013. 80% of Group 3 had completely resolved pain by 2 months after training complete.	“[I]t cannot be stated that treatment by a patellar brace is better than no treatment.”	Study includes basic description of prospective cohort study of military recruits. Cumulative incidence of “overuse anterior knee pain” 59/395(14%) over 14 weeks

						of training. Data suggest knee sleeves not efficacious.
Timm 1998 RCT	3.0	N = 100 with patellofemoral pain (PFP) during ascending and descending stairs, when rising from sitting, during squatting, and with prolonged sitting	No brace (Group 1) vs. protonics knee brace (Group 2) for 4 weeks.	No differences pre- and post-assessment for control group for patellofemoral congruence angle, Kujala patellofemoral score, and VAS. Significant gains in PFCA from lateral toward medial in brace group ($p < 0.001$), improvement in patellofemoral function (KPS, $p < 0.001$), and decrease and PFP by VAS scores ($p < 0.001$.)	"[T]he Protonics exercise program reduced PFP and improved PFC, as measured by PFCA, KPS, and VAS, when compared with the control group."	Quasi-randomized (every other), although groups appear comparable. Many methods details sparse. Data suggest Protonics effective.
Miller 1997 RCT	3.0	N = 59 Air Force Academy basic cadets who presented with anterior knee pain during initial phases of basic training	No brace (Group A, n = 20) vs. Palumbo Dynamic Patellar Brace (Group B, n = 18) vs. Cho-Pat (functions dynamically as knee bends and straightens and improves tracking and assist in spreading pressure uniformly over surface area.) Knee Strap (Group C, n = 13) for 6-8 weeks. All started PT with "closed chain" rehabilitation and NSAIDs.	No significant differences between treatment groups. Average change in pain from 1st to 2nd visit: Group A: average change -0.07. Group B: average change -0.47. Group C: average change -0.96. Average change in pain from 2nd to 3rd visit: Group A: average change -0.69. Group B: average change -2.04. Group C: average change -1.78.	"Despite manufacturer claims, these two orthotics do not appear to be effective in controlling anterior knee pain in this basic trainee population."	Study appears underpowered.
Schneider 2001 RCT	2.0	N = 40 with chronic patella-femoral pain syndrome, age 16-40	Sixteen rounds PT exercises based on proprioceptive neuromuscular facilitation (PNF) plus extension of tractus iliotibialis and quadriceps femoris muscles in 2x1-hour sessions a week (Group A, n = 20) vs. unsupported use of special knee splint for 15 minutes TID plus	No differences between groups except for post-loading improvement in VAS in group B, VAS with $p = 0.0065$, and score with $p = 0.0047$.	"[T]he findings of this study show better the individually perceived therapeutic results to be better following knee splint use than those from physiotherapeutic exercises. The knee splint used here is thus confirmed as an effective therapeutic concept for coping with PFS and for achieving early pain relief."	Excluded significant PF arthrosis. Study of persistent or resistant cases. Many details sparse. Data suggest knee splint superior to PNF.

			exercises performed according to instructions and knee flexion in both knees (Group B, n = 20) for 8 weeks.			
Manipulation and Mobilization						
Stakes 2006 RCT	3.5	N = 60 with patellofemoral pain syndrome	Patella mobilization only vs. patella mobilization plus spinal manipulative therapy. 6 treatments in 4 weeks.	Pressure pain threshold for algometry (treatment 1/treatment 6): patellar mobilization (3.64/5.22) vs. pat. plus spinal manipulation (3.63/5.36). Other differences not tested, but do not appear significant.	“Although there appeared to be promising effects suggesting either protocol may provide short-term relief for PFPS, use of a small convenience sample, lack of a blind observer or scales solely validated for PFPS additionally make tentative conclusions regarding this trial.”	Population not described. Many details sparse. Results not compared between groups. Data do not appear to support adding spinal manipulative therapy.
Rowlands 1999 RCT	2.0	N = 30+ with patellofemoral pain syndrome	Patella mobilization vs. placebo ultrasound.	Mostly graphic data presented. Unclear whether baseline differences present in outcomes data or trends at 1st follow-up after intervention begun.	“[P]atella mobilization was superior to placebo in the treatment of patellofemoral pain syndrome.”	Pilot study. No descriptive data. Dropouts replaced, but numbers dropping out not specified.
Biofeedback						
Ng 2008 RCT	2.5	N = 26 age 20-55 with PFPS; anterior knee pain for at least 6 months without physiotherapy	Exercise program (Group 1, n = 13) vs. EMG biofeedback and exercise program (Group 2, n = 13) for 8 weeks	Vastus medialis obliquus (VMO)/vastus lateralis (VL) EMG ratio during study: p = 0.335 Group 1 vs. p = 0.016 Group 2.	“[T]here was a significant difference in the VMO/VL EMG ratio over time in the subjects performing therapeutic exercise with the assistance of EMG biofeedback. This finding implies that EMG biofeedback is an effective adjunct to physiotherapy exercise for patients with PFPS in facilitating their VMO activity.”	Unclear how study could be double blinded. Many details sparse. Few data provided.
Extracorporeal Shockwave Therapy						
Wang 2007 RCT	3.5	N = 50 with chronic patellar tendinopathy	Shockwave therapy 1,500 impulses at 14 KV (n = 29) vs. control (n = 24).	Pain score, VISA score, and knee motion significantly different in favor of shockwave group after treatment, p <0.05. Subjective assessment for functional improvement after treatment favored shockwave group, p <0.001.	“Extracorporeal shockwave treatment appeared to be more effective and safer than traditional conservative treatment in the management of patients with chronic patellar tendinopathy.”	No blinding, good duration of follow-up (2-3 years). No significant adverse events reported. No mention of compliance in control group.

PREVENTION OF VENOUS THROMBOEMBOLIC DISEASE

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
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Low Molecular Weight Heparin vs. Other LMWH Doses or Other Treatments						
Stulberg 1989 RCT	3.5	N = 42 undergoing cemented TKA	3,000 units ATIII as loading dose followed post-op by 2,000 units daily combined with 5,000 units of LDH twice daily vs. LMWD (10ml/kg x 12 hours loading dose followed by 7ml/kg x 24 hours maintenance dose).	DVT identified in 25% of ATIII/LDH group vs. 82% of LMWD group; p<0.001.	"These findings indicate that the combination of ATIII and LDH may offer superior protection from DVT than does LMWD."	Many details sparse. Data suggest AT III plus low dose heparin effective over very short trial; 1 week follow-up.
Heparin						
Francis 1989 RCT	1.0	N = 21 undergoing total hip or knee replacement.	Dextran 40 with regimen of ATIII (1,500 units pre-op and 1,000 units daily for 5 days) vs. low-dose heparin. Two cohorts of patients undergoing total knee replacement studied using different doses of ATIII in combination with heparin.	Mean±SE for daily ATIII levels comparing ATII/heparin vs. dextran: chromogenic assay Day 1 after surgery: 88.5±2.4 vs. 72.9±3.0; p <0.001. Day 5 after surgery: 92.7±3.4 vs. 72.8±2.4; p <0.001. Immunologic assay Day 1 after surgery: 28.9±1.2 vs. 24.2±0.8; p <0.001. Day 7 after surgery: 32.5±2.0 vs. 27.3±0.9; p <0.01.	"[A]TIII replacement following total hip or knee replacement corrects the postoperative ATIII deficiency and that the combination of ATIII and low-dose heparin is an effective prophylactic regimen following total hip replacement."	Four trials with 2 RCTs. Multiple trials none of which are well reported.
Aspirin						
Westrich 1996 RCT	2.0	N = 122 (164 knees) scheduled for primary unilateral (n = 80) or 1stage bilateral (n = 42) TKA	Aspirin control (n = 61) vs. pulsatile pneumatic plantar-compression device PPC and aspirin (n = 61).	PPC vs. control prevalence of deep vein thrombosis for primary unilateral, 1 stage bilateral, and overall: 27%/67%/p <0.006, 28%/52%/p <0.03, 27%/59%/p <0.001. Prevalence of major deep venous thrombosis in calf: 15%/44%/p <0.006, 5%/34%/p <0.0009, 10%/39%/p <0.0001. PCC with absence of DVT vs. PCC with presence of DVT measured at hours, days, hours/days: 96/67/p <0.001, 5/5, 19.2/13.4.	"In conclusion, we found pulsatile pneumatic plantar compression and aspirin to be a safe and effective method of prophylaxis against thromboembolic disease in patients who had had a unilateral or a one-stage bilateral total knee arthroplasty. Furthermore, we demonstrated that effective prophylaxis with this device depends on compliance by the patient in the postoperative period."	Quasi-randomized on hospital number. Many details sparse. Some differences between groups at baseline.

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